Medisch Spectrum Twente

Medical School Twente

Wetenschappelijk onderzoek MST 2024

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een santeon ziekenhuis

Wetenschappelijk onderzoek in Medisch Spectrum Twente

2024

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Voorwoord

Voor u ligt de 16e editie van het jaarlijks overzicht van de wetenschappelijke publicaties van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2024. Dit jaaroverzicht wordt ook buiten MST verspreid onder huisartsen, apothekers, fysiotherapeuten en wetenschappelijke instellingen in de regio.

De publicaties zijn gegroepeerd op vakgroep op maatschap. Niet op volgorde van belangrijkheid maar alfabetisch. Hierbij is als criterium genomen dat de publicatie terug te vinden moet zijn op PubMed met publicatiedatum in 2024 ('print date'). De zogenaamde "Epub Ahead of Print" artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit geïndexeerde en peer-reviewed Nederlandstalige tijdschriften opgenomen.

In 2024 zijn 365 unieke publicaties verschenen in peer-reviewed tijdschriften. Ten opzichte van vorig jaar hebben we flink meer gepubliceerd. Een mogelijke verklaring hiervoor zou kunnen zijn dat we door COVID-19 in 2021 en 2022 een flinke piek in publicaties hadden en in 2023 juist te maken hadden met beperkte tijd voor wetenschap door 'in te halen zorg'. Dat effect is waarschijnlijk in 2024 weer verdwenen. We zitten nog steeds fors hoger dan pre-COVID.

De gemiddelde impact factor van de artikelen uit 2024 was net als voorgaande jaren weer zeer hoog met 8,8. De mediane impact was 4,4. We hebben dit jaar 9 keer in een toptijdschrift gepubliceerd: 2 keer in the Lancet, 5 keer in Nature Medicine en 3 keer in the New England Journal of Medicine.

In het overzicht wordt per publicatie ook weergeven in welk kwartiel het tijdschrift staat in de betreffende categorie. We publiceerden in 2024 veel meer in Q1 dan in voorgaande jaren: 66%! Verder 20% in Q2, 7,4% in Q3 en 1,6% in Q4. Bij 4,7% van de artikelen was geen indeling in kwartielen beschikbaar. Dit betrof dan relatief nieuwe tijdschriften, die nog geen Impact Factor hebben. Qua promoties was 2024 net als 2023 een matig jaar. Binnen MST waren maar 4 promoties.

In deze uitgave vindt u per gepubliceerd artikel de impact factor van het tijdschrift en per vakgroep of maatschap de totale en gemiddelde impact factor score van alle gepubliceerde artikelen. Om een indruk te krijgen van de bijdrage van eigen onderzoek is ook een overzicht gegeven van het aantal artikelen waarbij een onderzoeker uit MST 1e, 2e of laatste auteur is.

Om de ontwikkeling te kunnen volgen zijn de ranglijsten van 2024 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

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Overzicht publicaties en impact factors

Tabel 1. Statistieken unieke publicaties in peer-reviewed tijdschriften met medewerkers van MST als (co-)auteur

	2020	2021	2022	2023	2024
Unieke publicaties	239	334	383	282	365
Gemiddelde impact factor	5.8	6.5	9.9	8.9	8.8
Mediane impact factor	3.4	3.9	4.6	4.1	4.4

Tabel 2. Top 3 afdelingen MST met betrekking tot aantal publicaties, totale impact factor, gemiddelde impact factor van 2021 – 2024

2021		**2022**		**2023**		**2024**	
Aantal publicaties:							
1 Neurocentrum	52	1 Heelkunde	67	1 Neurocentrum	49	1 Heelkunde	64
2 Thoraxcentrum	47	2 Neurocentrum	52	2 Heelkunde	43	2 Neurocentrum	52
3 Heelkunde	43	3 Thoraxcentrum	47	3 Thoraxcentrum	35	3 Thoraxcentrum	50
Totale impact factor score:							
1 Neurocentrum	442	1 Neurocentrum	713	1 Neurocentrum	662	1 Thoraxcentrum	469
2 Thoraxcentrum	346	2 Intensive care	647	2 Intensive care	409	2 Heelkunde	468
3 Intensive care	307	3 Heelkunde	561	3 Interne gnkd	371	3 Interne gnkd	439
Gemiddelde impact factor score:							
1 Microbiologie	25	1 Intensive care	18	1 Radiotherapie	17	1 Klin. farmacie	32
2 Radiologie	18	2 Interne gnkd	17	2 Intensive care	15	2 Oogheelkunde	29
3 MDL	11	3 Radiologie	17	3 Interne gnkd	13	3 MDL	16
				3 Neurocentrum			
Aantal publicaties als 1e, 2e of laatste auteur:							
1 Neurocentrum	23	1 Heelkunde	18	1 Neurocentrum	12	1 Thoraxcentrum	19
2 Thoraxcentrum	14	2 Neurocentrum	15	2 Thoraxcentrum	10	2 Neurocentrum	17
3 Longgnkd	10	3 Thoraxcentrum	12	3 Heelkunde	8	3 MedST	11
				3 Plastische chir			
Totale impact factor score als 1e, 2e of laatste auteur:							
1 Neurocentrum	85	1 Heelkunde	85	1 Thoraxcentrum	120	1 Thoraxcentrum	165
2 Thoraxcentrum	44	2 Klin. farmacie	78	2 Neurocentrum	49	2 Longgnkd	84
3 Klin. chemie	33	3 Neurocentrum	75	3 Heelkunde	24	3 Epidemiologie	60
Gemiddelde impact factor score als 1e, 2e of laatste auteur:							
1 MDL	8	1 Klin. farmacie	10	1 Thoraxcentrum	12	1 Longgnkd	17
2 KNO	5	2 Klin. chemie	10	2 Anesthesie	9	2 Intensive care	15
				2 Radiotherapie			
3 MKA chirurgie	5	3 Anesthesie	8	3 Kindergeneesknd	7	3 Thoraxcentrum	9

Overzicht aantal publicaties per vakgroep

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
3D lab	-	-	-	-	-	-	-	-	-	7
Anesthesie	2	0	1	0	1	4	2	6	1	6
Dermatologie	0	0	0	0	1	0	1	1	0	0
Epidemiologie	-	-	-	-	-	-	-	-	-	21
Gynaecologie	6	4	13	7	6	6	5	8	3	8
Heelkunde	31	26	30	20	39	23	43	67	43	64
Intensive care	14	13	20	15	12	11	33	37	28	27
Interne geneeskunde	17	8	11	24	14	27	35	39	29	48
Kindergeneeskunde	11	6	6	8	3	11	8	7	6	5
Klinische chemie	7	5	5	7	4	8	12	12	3	9
Klinische farmacie	8	10	3	8	13	7	14	12	3	3
Klinische fysica	2	0	2	1	0	0	2	2	0	0
Klinische psychologie	1	0	1	2	1	0	0	1	1	0
KNO	1	1	0	0	0	0	1	1	3	1
Longgeneeskunde	16	19	24	28	14	17	22	20	17	10
MDL	5	9	10	5	14	14	16	19	11	19
Medical School Twente	35	33	26	24	24	29	19	35	23	24
Microbiologie	2	4	3	1	2	0	1	12	7	7
MKA chirurgie	0	1	0	1	0	0	1	3	3	2
Neurochirurgie	9	5	5	4	3	-	-	-	-	-
Neurologie	33	41	28	30	33	-	-	-	-	-
Neurocentrum	-	-	-	-	-	29	52	52	49	52
Nucleaire geneeskunde	2	0	0	0	0	0	0	0	0	0
Oogheelkunde	0	0	0	1	0	1	1	0	0	1
Orthopedie	7	5	4	2	5	3	13	16	8	13
Pathologie	8	4	9	3	4	0	0	1	0	3
Plastische chirurgie	2	4	4	13	12	11	16	23	16	20
Psychiatrie	1	0	4	0	0	1	0	0	0	0
Raad van Bestuur	0	0	0	0	9	10	7	8	10	7
Radiologie	14	10	4	11	2	4	9	20	21	14
Radiotherapie	12	10	4	5	4	5	6	13	9	18
Reumatologie	23	15	7	15	17	11	10	19	23	11
Revalidatiegeneeskunde	6	0	0	1	0	0	0	0	0	0
Spoedeisende hulp	-	-	-	-	-	-	-	-	-	1
Technische geneeskunde	-	-	-	-	-	-	-	-	-	13
Cardiologie	28	39	31	40	27	40	-	-	-	-
Thoraxchirurgie	2	4	5	4	3	8	-	-	-	-
Thoraxcentrum	-	-	-	-	-	-	47	47	35	50
Urologie	0	0	0	1	0	0	1	0	0	2
Waardegedreven zorg	-	-	-	-	-	-	4	1	1	1

Promoties
Heelkunde

TECHNICAL INNOVATIONS IN BREAST CANCER SURGERY

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
prof.dr.ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Wednesday the 26th of June 2024 at 16.45 hours

by

Anke Christenhusz
Born on the 24nd of August, 1987
In Oldenzaal, the Netherlands

Promotor:	Prof. Dr. Ir. B. ten Haken
Co-promotors:	Dr. Ir. L. Alic Dr. A.E. Dassen

Samenvatting

Borstkanker is wereldwijd de meest voorkomende kankersoort bij vrouwen en vereist vaak een chirurgische ingreep, waar nodig aangevuld met lokale of systemische therapie. Het verbeteren van de effectiviteit van de behandeling van borstkanker vereist voortdurend onderzoek en innovaties. Onder andere op het gebied van chirurgische technieken voor het behandelen van stadium 1 borstkanker, waar nauwkeurige stadiëring van de lymfeklieren en beeldgeleide lokalisatie van niet-palpabele tumoren essentieel zijn. Optimalisatie van chirurgische behandelingen, om patiënt uitkomsten te verbeteren, omvat daarnaast overwegingen zoals oncologische veiligheid, kosteneffectiviteit, workflow-efficiëntie, voorkeur van arts en patiënt, en gebruiksgemak. Hierbij speelt de transitie naar een stralingsvrije benadering voor tumorlokalisatie en lymfeklier stadiëring een belangrijke rol.
Nauwkeurige stadiëring van de ziekte tijdens de diagnostische fase is van groot belang, idealiter door gebruik te maken van niet-invasieve en zeer nauwkeurige methoden. De vervanging van een chirurgische schilwachtklier (SWK) biopsie, door middel van preoperatieve lymfeklier stadiëring zou een waardevolle toevoeging zijn in de diagnostische fase. Superparamagnetische ijzeroxide (SPIO)-versterkte MRI biedt mogelijk een nauwkeurig alternatief en vermindert de morbiditeit en zorgkosten. Onderzoek waarin histopathologische coupes en MR-beelden van magnetische (SPIO) lymfeklieren wordt vergeleken is veelbelovend, er is echter nog verdere ontwikkeling nodig om metastatische betrokkenheid nauwkeurig te kunnen kwantificeren. In de afgelopen jaren verkennen ziekenhuizen steeds meer stralingsvrije alternatieven voor beeldgeleide tumorlokalisatie, gedreven door logistieke voordelen, regelgevingsoverwegingen en duurzaamheidsdoelen. Innovaties zoals magnetische tumor lokalisatie laten vergelijkbare resultaten zien op het gebied van detectie en oncologische veiligheid, in verhouding tot de traditionele technieken. Transitie naar de magnetische markers laten op meerdere fronten voordelen zien door het wegvallen van regelgeving omtrent radioactief materiaal, het minimaliseren van re-excisies en hoge tevredenheid bij de medisch specialisten.
SPIO als magnetische tracer voor de SWK-biopsie vertoont een hoge overeenkomst met traditionele radioactieve methoden, maar kan leiden tot huidverkleuring en MRI-artefacten. Meta-analyses suggereren verbeterde detectiepercentages met behulp van een specifiek injectieprotocol, maar het risico op ijzerresidu dat achterblijft in de borst blijft een belemmering voor brede adaptatie. Een ander stralingsvrij alternatief voor detectie tijdens SWK-biopsie is indocyanine groen (ICG). Deze techniek zorgt voor een accurate visualisatie van de lymfeklieren tijdens de operatie, maar uitdagingen zoals lekken van de kleurstof in het operatiegebied, en het ontbreken van preoperatieve mapping kunnen de procedure compliceren. Het verkennen van gecombineerde tracers, zoals SPIO voor MRI-mapping en ICG voor intra-operatieve visualisatie, is wenselijk voor de toekomst.
Bij het overwegen van het combineren van magnetische tumorlokalisatie met de magnetische SWK-biopsie moeten uitdagingen zoals overlappende magnetische signalen en mogelijk ijzerresidu worden aangepakt. Magnetische tracers die tijdens de operatie worden gebruikt, kunnen MRI-artefacten veroorzaken tijdens postoperatieve beeldvorming. Dit kan de diagnostische nauwkeurigheid tijdens de follow-up van de ziekte beïnvloeden. De duur van deze artefacten na injectie is onzeker, maar een aangepast injectieprotocol of een overstap van postoperatieve MRI naar contrast versterkte mammografie (CEM) lijkt een potentieel alternatief na een magnetische SWK-biopsie. Concluderend richten recente technische innovaties in de diagnose en behandeling van borstkanker zich op het verbeteren van nauwkeurigheid, efficiëntie en patiënt veiligheid. Hoewel preoperatieve stadiëring met SPIO-versterkte MRI veelbelovend is voor de toekomst, is verdere verfijning van het protocol noodzakelijk. Magnetische markers voor tumorlokalisatie bieden een veilig en betrouwbaar alternatief voor conventionele technieken, terwijl gecombineerde ICG-SPIO-tracerbenaderingen potentieel tonen bij het optimaliseren van intraoperatieve SWK-detectie. Patiëntstratificatie is hierin van cruciaal belang, met de inzet van verschillende tracers die geschikt zijn voor uiteenlopende klinische scenario's.

Kindergeneeskunde

IMPROVING
THE MONITORING AND TREATMENT OF CHILDHOOD ASTMA

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. ir. A. Veldkamp,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op woensdag 11 december 2024 om 14.30 uur

door

Natasja Lammers
Geboren op 16 december 1990
In Hellendoorn, Nederland

Promotor:	Prof. Dr. J.A.M. van der Palen
Co-promotoren:	Dr. B.J. Thio Dr. R. Spenkelink-Visser

Samenvatting

Astma is wereldwijd de meest voorkomende chronische aandoening bij kinderen en heeft voor hen aanzienlijke fysieke en emotionele gevolgen. Astma wordt gekenmerkt door een chronische ontsteking van de luchtwegen en gaat gepaard met een toegenomen gevoeligheid voor verschillende prikkels. Deze bronchiale hyperreactiviteit (BHR) leidt tot aanvalsgewijze en reversibele bronchoconstrictie. De chronische luchtwegontsteking die ten grondslag ligt aan astma is complex en kan individueel verschillen wat betreft lokalisatie, onderliggende immuunreactie en mogelijke triggers. Astma heeft een dynamisch karakter en symptomen kunnen zowel intra- als interindividueel sterk variëren, wat een uitdaging vormt voor zorgprofessionals die deze ziekte monitoren en behandelen.

Bij het kritisch analyseren van de huidige astmazorg voor kinderen komen verschillende verbeterpunten naar voren, vooral op het gebied van gepersonaliseerde geneeskunde. Er is behoefte aan ondersteuning voor zorgprofessionals om de basisprincipes van astmazorg te optimaliseren; het kiezen van het juiste medicijn en inhalatortype en het objectief monitoren van de inhalatietechniek en therapietrouw. Dit proefschrift richt zich daarom op praktische alternatieve en innovatieve methoden om de monitoring en behandeling van astma bij kinderen te verbeteren, met als doel zorgprofessionals te helpen om meer onderbouwde klinische beslissingen te nemen in de dagelijkse praktijk.

Deel A van dit proefschrift richt zich op het analyseren van de huidige monitoring van astma bij kinderen en het aandragen en beoordelen van innovatieve methoden om deze monitoring te verbeteren. Bij astmatische kinderen is lichaamsbeweging een bekende trigger voor bronchiale hyperreactiviteit (BHR). De term ‘exercise-induced bronchoconstriction’ (EIB) beschrijft de vernauwing van de luchtwegen tijdens of na lichamelijke inspanning. De aanwezigheid van EIB weerspiegelt een actieve luchtwegontsteking en is een teken van onvoldoende astmacontrole. Een gestandaardiseerde inspanningstest (ECT) uitgevoerd in koude en droge lucht kan worden gebruikt als provocatietest om astma bij kinderen te diagnosticeren en te monitoren. In de dagelijkse praktijk worden ECT's echter niet vaak uitgevoerd en beoordelen kinderartsen EIB en astma controle meestal op basis van een anamnese (zelf- of oudergerapporteerd), een lichamelijk onderzoek en mogelijk een longfunctieonderzoek. In **hoofdstuk 2** bestudeerden we het vermogen van kinderartsen om de aanwezigheid en ernst van EIB bij astmatische kinderen te voorspellen op basis van informatie die routinematig beschikbaar is tijdens een polikliniekbezoek. Ze maakten een inschatting op basis van een anamnese (met specifieke focus op astmasymptomen), de resultaten van een lichamelijk onderzoek en video-opnames van de gehele beoordeling. De inschatting van kinderartsen ten aanzien van een positieve EIB diagnose (gedefinieerd als een daling van het geforceerd expiratoir volume in 1 seconde (FEV1) ≥10%) bleek sensitief (84%) maar weinig specifiek (24%). De overeenkomst tussen de voorspelde EIB classificaties en de gevalideerde classificaties na de ECT was gering [Kappa = 0,05 (95% CI 0,00–0,17)]. Deze voorspelling bleef gering nadat kinderartsen waren geïnformeerd over de longfunctie vóór de ECT [Kappa = 0,19 (95% CI 0,06–0,32)]. Er was een opmerkelijke onderschatting van de ernst van EIB bij kinderen met matige en ernstige EIB. Het is belangrijk dat kinderartsen zich realiseren dat het voorspellen van de ernst van EIB en daarmee astmacontrole onbetrouwbaar is, zonder een objectieve en gestandaardiseerde ECT.

In het dagelijks leven provoceren astmatische kinderen hun luchtwegen regelmatig tijdens fysieke activiteiten in de vorm van sport en spel. Tevens hebben kinderen regelmatig bovenste luchtweginfecties die zowel astma symptomen kunnen nabootsen als kunnen leiden tot bronchusobstructie bij kinderen met ongecontroleerd astma. Tegenwoordig kunnen ouders video's van deze gebeurtenissen in de thuissituatie opnemen en deze tonen

tijdens een geplande poli-afspraak, wanneer kinderen meestal asymptomatisch zijn. Dit kan mogelijk waardevolle informatie bieden aan zorgverleners, omdat een juiste beoordeling van deze video's een praktisch alternatief voor een ECT zou kunnen zijn. Een eerste stap in de validatie van zelfgemaakte video's is het onderzoeken van het vermogen van kinderartsen om bronchusobstructie te beoordelen aan de hand van video's die in een gestandaardiseerde omgeving zijn gemaakt. In **hoofdstuk 3** beoordeelden kinderartsen postinspanningsvideo's van astmatische kinderen die een gestandaardiseerde ECT ondergingen. Kinderartsen werden gevraagd om de ernst van EIB te beoordelen op een continue schaal en in classificaties met betrekking tot ernst. Ze beoordeelden ook de eventuele aanwezigheid van verschillende klinische symptomen van luchtwegobstructie. Kinderartsen bleken slechts matig goed (Kappa = 0,36) de ernst van EIB te kunnen beoordelen op basis van postinspanningsvideo's. Opmerkelijk was dat in 75% van de kinderen met ernstige EIB de ernst werd onderschat. Onafhankelijke voorspellende fysieke symptomen voor de daling van FEV1 waren een piepende ademhaling (−11%), supraclaviculaire intrekkingen (−8,4%) en een verlengd expirium (−8,8%). Opmerkelijk was dat slechts bij 22% van de kinderen met EI een piepende ademhaling werd waargenomen. Tevens had een piepende ademhaling de laagste sensitiviteit voor een EIB diagnose (ook 22%). In een praktische context betekent dit dat lang niet alle kinderen met EIB een piepende ademhaling vertonen. Clinici zouden zich ervan bewust moeten zijn dat focussen op een piepende ademhaling als enige indicator voor bronchusobstructie, een aanzienlijk risico met zich meebrengt om dit te missen. Concluderend toont deze studie aan dat kinderartsen hooguit redelijk de ernst van EIB kunnen beoordelen op basis van post-inspanningsvideo's gemaakt in een gestandaardiseerde omgeving. Het is te verwachten dat video's uit dagelijkse thuissituaties nog moeilijker te beoordelen zijn. Toekomstige studies die gericht zijn op het ontrafelen van de relatie tussen de ernst van inspanningsgeïnduceerde bronchusobstructie en verschillende fysieke symptomen in grotere onderzoeksgroepen, zouden de kwaliteit van het beoordelen van EIB-video's kunnen verbeteren en uiteindelijk ook het beoordelen van video's van astmatische kinderen thuis.

In ons streven om hulpmiddelen te bieden die het monitoren van astma bij kinderen vereenvoudigen en verbeteren, hebben we de Visuele Analoge Schaal (VAS) voor dyspneu geëvalueerd als een middel om EIB bij astmatische kinderen te detecteren. We beoordeelden tevens de waarde van het combineren van VAS-scores met de uitkomsten van twee veelgebruikte vragenlijsten met betrekking tot astma controle: de Childhood Asthma Control Test (C-ACT) en de Asthma Control Test (ACT). Deze gevalideerde vragenlijsten worden ingevuld door astmapatiënten en evalueren de astmacontrole over de afgelopen vier weken. Verschillende studies hebben echter aangetoond dat deze vragenlijsten de resultaten van longfunctietesten en EIB bij astmatische kinderen niet goed kunnen voorspellen. In **hoofdstuk 4** ondergingen 75 astmatische kinderen een gestandaardiseerde ECT en vulden kinderen en ouders VAS-dyspneu scores in vóór en na de ECT. Astmacontrole werd beoordeeld met de C-ACT en ACT. We ontdekten dat veranderingen in VAS-scores (ΔVAS), gerapporteerd door kinderen en ouders, redelijk goed correleerden met de daling in FEV1 (respectievelijk rs=0,57 (p<.001) en rs=0,58 (p<.001)). Een ΔVAS van ≥ 3 bij kinderen had een sensitiviteit van 80% en een specificiteit van 79% voor EIB (AUC 0,82). Het combineren van (C-)ACT-uitkomsten met VAS-scores had een sensitiviteit van 97% en een negatief voorspellende waarde van 96% voor EIB. Daarnaast vonden we dat de VAS effectief was in het detecteren van EIB bij kinderen met vals-negatieve (C-)ACT-uitkomsten. Al met al toont deze studie aan dat de VAS een effectief hulpmiddel kan zijn voor het stellen van een EIB diagnose bij kinderen.

Deel B van dit proefschrift richt zich op het exploreren van gepersonaliseerde behandelopties voor astma bij kinderen. Astma is een heterogene ziekte met sterk variabele

klinische fenotypes en uiteenlopende reacties op behandeling. Het is algemeen bekend dat inhalatiecorticosteroïden (ICS) de hoeksteen vormen van de onderhoudsbehandeling voor astma. Ze bieden langdurige bronchoprotectie door het verminderen van luchtweginflammatie en zijn zeer effectief in het voorkomen van exacerbaties. Het is echter bekend dat niet alle astmatische kinderen even goed reageren op een behandeling met ICS, wat kan leiden tot behandeling met hoge doses ICS om astmacontrole te bereiken. Dit kan onterecht zorgen voor blootstelling aan mogelijke bijwerkingen van ICS, zoals bijnierschorsinsufficiëntie en groeivertraging. Het effectief voorspellen van individuele reacties op ICS voordat een langdurige behandeling bij kinderen met astma wordt gestart, zou dit kunnen voorkomen. In **hoofdstuk 5** evalueerden we of de respons op een eenmalige dosis beclometasondipropionaat (BDP) de individuele reactie op een langdurige ICSbehandeling kan voorspellen. In deze prospectieve cohortstudie werden 32 steroïd-naïeve kinderen met EIB geïncludeerd. Ze voerden drie ECT's uit: een baseline-ECT, een ECT zes uur na een eenmalige dosis D (200 µg) en een ECT na 4 weken behandeling met D (100 µg tweemaal daags). Het beschermende effect van een eenmalige dosis BDP op de daling in FEV1 na inspanning toonde een significante correlatie met het effect van 4 weken behandeling ($r = .38$, $p = .004$). Een afname in daling van FEV1 na inspanning van meer dan 8% na een eenmalige dosis BDP kon de effectiviteit van BDP tegen EIB na 4 weken behandeling voorspellen met een positieve voorspellende waarde van 100% (CI: 86,1–100%) en een negatieve voorspellende waarde van 29,4% (CI: 11,7%–53,7%). Deze studie toont aan dat de individuele respons op een eenmalige dosis BDP tegen EIB een voorspellende waarde heeft voor de effectiviteit van langdurige behandeling met BDP. Dit zou clinici kunnen ondersteunen bij het geven van meer gepersonaliseerde en onderbouwde behandeladviezen voor kinderen met astma.

Naast het belang van een gepersonaliseerde benadering bij het selecteren van het juiste type medicatie, is de effectiviteit van astmatherapie ook afhankelijk van een juiste inhalatietechniek en consistente therapietrouw. Uit talrijke studies blijkt dat verkeerd gebruik van astma inhalatoren veel voorkomt, wat kan leiden tot suboptimale of slechte astmacontrole. In **hoofdstuk 6** beschrijven we een studie waarbij we de dagelijkse inhalatietechniek van kinderen thuis met twee frequent voorgeschreven inhalatoren evalueren: de Diskus en de Autohaler. Gedurende een studieperiode van 28 dagen werden inhalaties thuis gefilmd met beide inhalatoren en vervolgens gedemonstreerd in het ziekenhuis. De video's werden gecontroleerd op zeven kritieke inhalatiefouten. De meest voorkomende kritieke inhalatiefout bij dagelijks gebruik van de Diskus was een onjuiste positie van het apparaat tijdens het voorbereiden van de dosis. Bij de Autohaler betrof dit een te ondiepe inhalatie. De Diskus werd correct gebruikt tijdens 44% van de studiedagen, vergeleken met 96% van de studiedagen met de Autohaler ($p<0,001$). Opmerkelijk was dat de twee meest voorkomende kritieke fouten met de Diskus minstens twee keer zo vaak thuis werden gemaakt als tijdens de demonstratie in het ziekenhuis. Deze studie toont aan dat de inhalatietechniek van kinderen thuis beter was met de Autohaler dan met de Diskus. Zorgverleners zouden zich ervan bewust moeten zijn dat demonstraties in het ziekenhuis de dagelijkse inhalatietechniek thuis overschatten, vooral bij gebruik van de Diskus.

Een veelvoorkomende comorbiditeit bij kinderen met astma is allergische rhinitis; een aandoening van de neus die wordt gekenmerkt door rinorroe, congestie, jeuk en niezen. Allergische rhinitis heeft niet alleen een aanzienlijk negatief effect op de kwaliteit van leven van kinderen, maar wordt ook geassocieerd met verschillende negatieve astma-uitkomsten. Het is een risicofactor voor het ontstaan van astma, de ernst van astma en een verminderde kans op remissie. Richtlijnen en behandelalgoritmen voor (allergisch) astma bij kinderen bevatten momenteel geen expliciete adviezen voor de behandeling van allergische rhinitis. Nasale corticosteroïden, alleen of in combinatie met antihistaminica, vormen de

voornaamste behandeloptie voor allergische rinitis. Het potentiële effect van de combinatie van INCS en INA op verschillende astma uitkomsten bij kinderen is tot op heden nog onduidelijk. In **hoofdstuk 7** presenteren we een protocol om het gecombineerde effect van INCS en INA in de vorm van azelastine/fluticason-propionaat op EIB bij te bestuderen. Het betreft een dubbelblinde, gerandomiseerde, placebogecontroleerde studie bij astmatische kinderen met allergische rhinitis, in de leeftijd van 12-18 jaar. Longfunctie zal worden beoordeeld met spirometrie en geforceerde oscillatietechniek (FOT) tijdens een gestandaardiseerde inspanningstest. Twee vragenlijsten gericht op astmacontrole (de ACT en de Pediatric Asthma Quality of Life Questionnaire (PAQLQ)) zullen worden ingevuld. Deelnemers worden gerandomiseerd om gedurende een periode van drie weken tweemaal daags azelastine/fluticasonpropionaat of een placebo te gebruiken. Na deze periode worden longfunctie en vragenlijsten herhaald en vergeleken met elkaar. Deze studie heeft als doel het begrip van het beschermende effect van de behandeling van allergische rhinitis op astma uitkomsten bij kinderen te verbeteren, gemeten aan de hand van veranderingen in inspiratoire en expiratoire luchtstroombeperking, evenals luchtwegweerstand en reactantie. Het aantonen van een positief effect van deze therapie op astmacontrole kan pleiten voor een prominentere rol van de behandeling van allergische rhinitis in de huidige richtlijnen voor astmabehandeling.

Neurocentrum/Klinische farmacie

OPTIMIZING MEDICATION MANAGEMENT FOR PARKINSON'S PATIENTS IN PRIMARY CARE

CHALLENGES, OPPORTUNITIES AND FUTURE PERSPECTIVES

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
prof.dr.ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday the 26th of April 2024 at 14.45 hours

by

Nicol Geertruida Maria Oonk
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In Weerselo, the Netherlands

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Samenvatting

De ziekte van Parkinson is na de ziekte van Alzheimer de meest voorkomende neurodegeneratieve ziekte wereldwijd, en het aantal Parkinsonpatiënten zal de komende jaren verder stijgen. De ziekte kenmerkt zich door motorische symptomen: het trager worden van bewegingen (bradykinesie), trillen (tremor), stijfheid van de spieren (rigiditeit) en houdingsinstabiliteit. Daarnaast komt een scala aan nietmotorische symptomen voor, zoals autonome disfunctie (urine-incontinentie, obstipatie, orthostatische hypotensie), mentale klachten (depressie, angst, hallucinaties, cognitieve achteruitgang), reukstoornissen, pijn en slaapproblemen. De verscheidenheid aan symptomen en het progressieve karakter van de ziekte zijn van invloed op kwaliteit van leven. De ziekte van Parkinson is vooralsnog niet te genezen, en behandeling bestaat uit het zo goed mogelijk bestrijden van de symptomen. Een van de belangrijkste elementen hierin blijft farmacotherapie. Dit bestaat voor een groot deel uit dopaminerge medicijnen, die direct of indirect effect hebben op het tekort aan dopamine. Voor comorbiditeiten – al dan niet gerelateerd aan de ziekte van Parkinson – wordt daarnaast non-dopaminerge medicatie voorgeschreven. De hoeveelheid non-dopaminerge medicijnen is sterk gecorreleerd met het voorkomen van comorbiditeiten. Medicamenteuze behandeling is in het begin van de ziekte vaak effectief, echter bij voortschrijding van de ziekte verergeren symptomen en moeten verschillende medicijnen frequenter en hoger gedoseerd worden. Dit leidt dit al snel tot het gelijktijdig gebruik van meerdere geneesmiddelen (polyfarmacie) en complexe medicatieschema's, waarbij tijdige medicatie-inname nauw luistert. Het correct volgen van alle medicatievoorschriften blijkt een uitdaging; therapietrouw is bij significant percentage van de Parkinsonpatiënten suboptimaal. Dit draagt bij aan het ontstaan van farmacotherapie-gerelateerde problemen (FTP's), een suboptimaal behandeleffect, hogere zorgkosten en verminderde kwaliteit van leven.

Een medicatiebeoordeling (MBO) kan deze problemen mogelijk (deels) ondervangen. Dit betreft een beoordeling van de farmacotherapie door patiënt, apotheker en arts, waarbij er op kritische, gestructureerde wijze een evaluatie plaatsvindt van de medische-, farmaceutische-, en gebruiksinformatie. Betrokkenheid van de patiënt en zijn of haar individuele behoeften ten aanzien van het medicatiegebruik zijn hierin de leidraad. FTP's worden opgespoord en mogelijke verbeteringen worden aangedragen, waarop medicamenteuze therapie in samenspraak met de patiënt en betrokken zorgverleners kan worden aangepast. Het doel is het optimaliseren van de farmacotherapie, het bevorderen van zelfmanagement, en het tegengaan van verergering van gezondheidsproblemen of complicaties van ziekte(n) en medicatie.

Openbare apothekers in Nederland voeren deze MBO's frequent uit. Vooral patiënten met een hoog risico op FTP's lijken hier baat bij te hebben. Het selecteren van deze patiënten is echter moeizaam gebleken en de selectiecriteria hiervoor wisselden de afgelopen jaren. Het effect van MBO's is uitgebreid onderzocht in verschillende studies met verschillende patiëntengroepen, uitkomstmaten en uitgebreidheid. Dat maakt vergelijking lastig. Hoewel er positieve resultaten zijn gevonden ten aanzien van therapietrouw en FTP's, is het effect op kwaliteit van leven wisselend. Voor Parkinsonpatiënten zou een MBO specifiek van meerwaarde kunnen zijn, gezien de relatieve kwetsbaarheid van deze doelgroep op basis van zowel de progressieve ziekte als de ingestelde medicamenteuze therapie. Het optimaliseren van medicamenteuze therapie kan therapietrouw, behandeleffect en kwaliteit van leven mogelijk verbeteren. Dit vraagt om nadere verkenning van de rol van de openbare apotheker binnen de behandeling van de ziekte van Parkinson.

Het doel van dit proefschrift is het analyseren van verschillende aspecten van een MBO bij Parkinsonpatiënten, uitgevoerd door de openbare apotheker. We onderzochten in een gerandomiseerde studie de klinische effecten van een MBO, en beoordeelden de kosteneffectiviteit van deze interventie. Vanuit het perspectief van de apotheker verkregen we daarnaast inzichten in de

knelpunten en faciliterende factoren met betrekking tot de uitvoering van MBO's bij Parkinsonpatiënten.

Een beter begrip van de relatie tussen medicamenteuze factoren en kwaliteit van leven bij de ziekte van Parkinson kan aangrijpingspunten bieden voor verbetering van individuele farmacotherapeutische behandelopties in de toekomst. Daarom analyseerden we allereerst demografische, ziekte-specifieke en medicamenteuze factoren in relatie tot de kwaliteit van leven. Dit werd onderzocht in een cross-sectioneel onderzoek, waarin de kwaliteit van leven werd vastgesteld aan de hand van ziektespecifieke vragenlijsten. In **hoofdstuk 2** beschrijven we onze resultaten: we vonden een associatie tussen het gebruik van meer non-dopaminerge medicijnen, en specifiek het gebruik van anti-epileptica, en verminderde kwaliteit van leven. Anti-epileptica worden in het algemeen – naast behandeling voor epilepsie – frequent voorgeschreven voor het behandelen van andere aandoeningen, zoals neuropathische pijn, angst- en slaapstoornissen. Deze laatstgenoemde aandoeningen komen frequent voor bij de ziekte van Parkinson, en kunnen de kwaliteit van leven significant beïnvloeden. Ook treden frequent bijwerkingen op bij het gebruik van deze medicijnen. Op basis van huidige studie kunnen we niet onderscheiden waarop de associatie is gebaseerd; mogelijk op FTP's, of op de (onvoldoende behandelde) conditie waarvoor de medicatie is voorgeschreven. Het is echter van belang de impact van het gebruik van deze medicatie (en hun indicatie) mee te wegen in een MBO. Naast bovengenoemde factoren waren ook vrouwelijk geslacht, verder gevorderde ziektestadia en het ervaren van meer niet-motorische symptomen geassocieerd met een lagere kwaliteit van leven. Dit impliceert dat de directe impact van de ziekte van Parkinson zelf een significante factor is in de verlaagde kwaliteit van leven.

In **hoofdstuk 3** wordt het studieprotocol beschreven van de vervolgens uitgevoerde multicenter gerandomiseerde, gecontroleerde studie. Het doel van deze studie was het beoordelen van het klinische effect van een MBO bij Parkinsonpatiënten. De uitkomstmaten betroffen ziekte-specifieke en algemene kwaliteit van leven, het dagelijks functioneren, niet-motorische symptomen en, indien van toepassing, kwaliteit van leven van mantelzorgers. De MBO's werden uitgevoerd door de openbare apotheker, bij patiënten met het gebruik van ≥4 verschillende medicijnen per dag, en ≥4 verschillende medicatie innametijdstippen per dag.

De resultaten van deze studie zijn beschreven in **hoofdstuk 4**. In totaal werden 202 (semi-)zelfstandig wonende patiënten geïncludeerd, die voor de ziekte van Parkinson werden behandeld in de ziekenhuizen Medisch Spectrum Twente (Enschede), Ziekenhuis Groep Twente (Almelo/Hengelo) of Isala (Zwolle). De helft ontving een MBO van hun apotheker, de andere helft kreeg zorg zoals gebruikelijk. Apothekers van 82 openbare apotheken uit de omgeving van bovenstaande ziekenhuizen werkten mee aan deze studie, en kregen voorafgaand een training aangeboden over de ziekte van Parkinson, de verschillende behandelingen en ons studieprotocol. Patiënten (en eventueel hun mantelzorgers) vulden bij aanvang van de studie, en na 3 en 6 maanden een set vragenlijsten in.

Het kostte apothekers gemiddeld 101 minuten om een MBO uit te voeren. In de 99 uitgevoerde MBO's werden in totaal 260 potentiële FTP's gevonden (2.6 ±1.8 FTP's per patiënt), die in 62% van de gevallen leidde tot aanpassing van medicamenteuze behandeling. Er werd zes maanden na het ontvangen van een MBO geen verschil gevonden in Parkinson-specifieke kwaliteit van leven, dan wel in één van de andere secundaire uitkomsten. Aanvullende exploratieve analyses toonden geen specifieke patiëntkarakteristieken op basis waarvan in deze populatie een betere patiëntselectie zou kunnen worden uitgevoerd, zodat specifiek die patiënten geselecteerd zouden kunnen worden bij wie een MBO leidt tot relevante klinische verbetering.

We concluderen dat het standaard uitvoeren van een MBO niet van meerwaarde is met betrekking tot kwaliteit van leven of eerder genoemde klinische uitkomsten. Op basis van voortschrijdend inzicht zouden we een aantal elementen in de huidige setting optimaliseren, voor een mogelijk groter

klinisch effect van een MBO. Dit is ten eerste een striktere patiëntselectie, onder andere gebaseerd op gezondheidsklachten die mogelijk veroorzaakt worden door FTP's, ten tweede het verbeteren van (digitale) communicatie tussen betrokken zorgverleners, en tot slot nauwere betrokkenheid van de medisch specialisten in de tweede lijn.

Hoewel geen klinisch voordeel werd geobjectiveerd na een MBO, zou een MBO zorgkosten kunnen reduceren. Deze hypothese is gebaseerd op het feit dat geoptimaliseerde medicatieschema's en minder FTP's mogelijk leiden tot afname van de zorgvraag en (medicatie-geïnduceerde) ziekenhuisopnamen. Middels de kostenutiliteitsanalyse beschreven in **hoofdstuk 5** vergeleken we de gezondheidswinst na een MBO met de gemaakte kosten. De kans dat een MBO kosteneffectief is, bleek tussen de 18 en 30% te liggen. Wanneer we deze relatief lage kans afwegen tegen de tijdsinvestering van de apotheker, zou het voordeliger zijn deze tijd toe te wijzen aan interventies die effectiever en kostenefficiënter zijn.

Niet alle patiënten die initieel gerandomiseerd waren in de interventiegroep – en dus een MBO behoorden te krijgen – ontvingen deze uiteindelijk ook. Redenen hiervoor waren niet altijd duidelijk. Doordat patiënten in de interventiegroep pas daadwerkelijk geïncludeerd waren na het ontvangen van een MBO, had dit geen directe consequenties voor de analyses, doch roept dit vragen op over de uitvoerbaarheid. De verschillende fasen van een MBO, met betrokkenheid van verschillende personen per fase, lijkt een logistieke uitdaging, en de praktische uitvoering kan worden beïnvloed door verschillende factoren. In de kwalitatieve studie beschreven in **hoofdstuk 6** verkregen we inzicht in de al dan niet toegevoegde waarde van, en belemmerende en faciliterende factoren in, de uitvoering van MBO's bij Parkinsonpatiënten vanuit het perspectief van de apotheker. Dertien openbare apothekers werden geïnterviewd. De toegevoegde waarde van de MBO's werd vooral ervaren in het kunnen bieden van gepersonaliseerde behandeling met meer betrokkenheid van de patiënt, en in de mogelijk preventieve effecten op langere termijn. Er werden echter significante knelpunten ervaren, waarvan tijd, logistieke problemen en de samenwerking met de tweede lijn de belangrijksten waren.

Samenvattend is het standaard uitvoeren van MBO's door openbare apothekers bij Parkinsonpatiënten in de eerste lijn in de huidige setting niet van voldoende meerwaarde betreffende klinische effecten en kosten. Omdat we ervan overtuigd zijn dat (periodieke) medicatie-evaluatie en -optimalisatie belangrijk zijn bij kwetsbare patiënten met complexe ziekten en met een hoog risico op FTP's, zou de toekomstige focus moeten liggen in het verbeteren van de huidige setting, dan wel in het onderzoeken van alternatieve strategieën om optimale farmacotherapie te bereiken.

Op basis van onze bevindingen en resultaten beschreven in eerdere literatuur, pleiten we voor een patiëntselectie gebaseerd op de inschatting van betrokken zorgverleners, met aandacht voor gezondheidsklachten die mogelijk kunnen wijzen op FTP's, al dan niet in combinatie met aanwijzingen voor kwetsbaarheid, risicosituaties (zoals recente ziekenhuisopname) en het aantal medicijnen. Het gebruik van vragenlijsten kan behulpzaam zijn, evenals het stellen van individuele, realistische doelen. Daarnaast is up-to-date digitale documentatie en communicatie tussen betrokken zorgverleners van groot belang. De zorg voor Parkinsonpatiënten wordt steeds meer gecentraliseerd in Parkinsoncentra, en gespecialiseerde zorgverleners zijn aangesloten bij landelijke netwerken (ParkinsonNet). In het afgelopen decennium is daarnaast meer aandacht gekomen voor, en onderzoek gedaan naar, de rol van gespecialiseerde apothekers bij de behandeling van patiënten met die ziekte van Parkinson. Er zijn overtuigende aanwijzingen voor een positieve impact in het reduceren van FTP's en het verbeteren van therapietrouw. We bevelen aan dat openbare apothekers met expertise in de ziekte van Parkinson een meer zichtbare rol krijgen in het multidisciplinaire behandelteam, met secundair kortere communicatielijnen met overige betrokkenen. De uitgebreide MBO's voor een selectievere groep Parkinsonpatiënten kunnen vervolgens worden uitgevoerd door deze apothekers, dan wel door apothekers werkend binnen de Parkinsoncentra. Sinds enkele jaren

bestaan er daarnaast ‘Parkinson Farmabuddy zorgteams’, bestaande uit een in de ziekte van Parkinson geschoolde apothekersassistent of farmaceutisch consulent en apotheker. Door goede toegankelijkheid en regelmatig contact kunnen deze zorgteams waardevol bijdragen aan logistieke ondersteuning en continuïteit van optimale farmaceutische zorg.

Neurocentrum/Thoraxcentrum Twente

STRATEGIES FOR DETECTING CARDIAC SOURCES OF EMBOLISM AFTER ISCHEMIC STROKE

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
prof.dr.ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday the 12th of January 2024 at 14.45 hours

by

Geertje Hermalinde van der Maten
Born on the 22nd of January, 1989
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Samenvatting

Het belangrijkste doel van het aanvullend onderzoek na een herseninfarct is het vaststellen van de oorzaak. Voor de verschillende oorzaken van een herseninfarct bestaan specifieke behandelingen om de kans op het opnieuw krijgen van een herseninfarct te verkleinen. Er zijn verscheidene hartaandoeningen die een herseninfarct kunnen veroorzaken, de zogenaamde cardiale emboliebronnen. De onderzoeken die patiënten op de stroke unit ondergaan, zijn onder andere gericht op het vaststellen van een van deze hartaandoeningen. Bij ongeveer 25% van de patiënten wordt na deze eerste analyse geen oorzaak voor het herseninfarct gevonden. Zij ondergaan aanvullende monitoring van het hartritme en beeldvorming van het hart.

Dit proefschrift richt zich op deze cardiale oorzaken van het herseninfarct en heeft drie doelen:

- Ten eerste een evaluatie van de adviezen van de huidige Nederlandse richtlijnen voor het opsporen van een cardiale oorzaak van het herseninfarct.
- Ten tweede het integreren van deze resultaten met de kennis uit de literatuur.
- Ten derde het vinden van aanwijzingen hoe de bestaande opsporingsstrategieën kunnen worden verbeterd en bepalen van wat het effect van deze veranderingen zou zijn.

Hoofdstuk 1 geeft een algemene inleiding over het herseninfarct, en bespreekt het belang van het opsporen van de oorzaak. De term cardio-embolische oorzaak wordt geïntroduceerd, met de beschrijving van zijn verschillende verschijningsvormen en van de manier waarop een cardiale emboliebron (CEB) kan worden opgespoord. Ook worden de consequenties voor behandeling na detectie van een CEB besproken. Het hoofdstuk sluit af met het doel en de opzet van dit proefschrift.

Hoofdstuk 2 toont de resultaten van een prospectieve evaluatie van een geautomatiseerd detectie-algoritme voor atriumfibrilleren (AF) op de stroke unit. Klinische hartritme monitoring gegevens van 507 patiënten werden beoordeeld door personeel van de stroke unit. Tegelijkertijd was het “ST segment en aritmie monitoring (ST/AR)” algoritme actief, met uitgeschakelde AF-alarmen. Na 24 uur monitoring werden de detecties vergeleken met de beoordeling van professionals werkzaam op de stroke unit. Bij zes (2.1%) patiënten werd AF vastgesteld door het stroke unit team, en het algoritme suggereerde AF bij 26 (4.7%) patiënten. Na evaluatie bleek bij 13 (2.6%) patiënten AF correct gedetecteerd door het algoritme, en hadden 11 patiënten een foutieve AF detectie. Deze resultaten laten zien dat het gebruik van een algoritme de AF detectie op de stroke unit aanzienlijk verbetert, met als nadeel een toename van het aantal fout-positieven. Zodoende blijft zorgvuldige analyse van alle alarmen noodzakelijk.

Hoofdstuk 3 beschrijft de resultaten van AF detectie met ambulante hartritmemonitoring bij patiënten met een herseninfarct met onbekende oorzaak. Patiënten uit één van de deelnemende ziekenhuizen van de prospectieve ATTESTstudie (beschreven in Hoofdstuk 6) werden geïncludeerd wanneer ze ten minste drie dagen thuisregistratie van het hartritme hadden. De mediane duur van monitoring was 7 dagen, en de mediane duur vanaf het herseninfarct tot de start van monitoring was 36 dagen. AF werd gedetecteerd bij 17 (4.6%) patiënten. Na de eerste dag van monitoring was bij 50% van de patiënte AF gedetecteerd, desalniettemin werd nieuw AF werd gevonden tot op de laatste dag van monitoring. Patiënten met AF hadden significant meer cardiovasculaire risicofactoren dan patiënten zonder AF. Een belangrijke beperking van de studie was het relatief lange interval tot aan de start van monitoring. Toch kunnen deze resultaten van waarde zijn als referentie voor toekomstige studies en om te beslissen welke patiënten in aanmerking komen voor langdurige hartmonitoring met implanteerbare recorders.

Hoofdstuk 4 presenteert de resultaten van een systematische review en metaanalyse van cardiale beeldvorming bij patiënten met een herseninfarct met onbekende oorzaak. Uit vijf databases bleken

zes studies geschikt voor inclusie: één studie beschreef resultaten van transthoracale echocardiografie (TTE) vier studies beschreven resultaten van transoesofageale echocardiografie (TEE) en één studie beschreef zowel TTE- als TEE-resultaten. De zes studies rapporteerden totaal 1022 patiënten. Een majeure CEB werd gedetecteerd middels TTE bij 1.3% van de patiënten en middels TEE bij 5.9% van de patiënten. Het vaakst betrof dit een thrombus van het linker hartoor. Echter, vanwege het kleine aantal geïncludeerde studies en de substantiële heterogeniteit, moeten de resultaten van deze analyse met voorzichtigheid geïnterpreteerd worden en kunnen er geen zekere conclusies uit worden vertaald naar de klinische praktijk.

Hoofdstuk 5 bespreekt onze retrospectieve studie, uitgevoerd in één ziekenhuis, waarin de toepassing van TTE en thuisregistratie van het hartritme in een real-world setting werd geëvalueerd. Patiënten met een herseninfarct of TIA met onbekende oorzaak die een TTE ondergingen weden geïncludeerd. Een majeure CEB werd gevonden met TTE bij 9 (1.9%) van 484 patiënten, van wie er zeven patiënten ECG-afwijkingen of hartklachten hadden die reeds aanvullend onderzoek door de cardioloog rechtvaardigden. AF werd gevonden met thuisregistratie bij 10 (2.4%) van 411 patiënten. Deze resultaten tonen dat routinematig verrichten van TTE en thuisregistratie van het hartritme bij patiënten met een herseninfarct of TIA met onbekende oorzaak niet vaak leidt tot detectie van een majeure CEB. Bovendien was voor de meeste patiënten met een majeure CEB verwijzing naar een cardioloog aangewezen, ongeacht de stroke analyse, gezien de cardiale klachten en/of ECGafwijkingen. Deze resultaten suggereren dat TTE selectiever zou kunnen worden toegepast in deze specifieke patiëntengroep. Desalniettemin betrof dit een singlecenter, retrospectieve studie, en deze bevindingen vragen om bevestiging een grotere, multicenter studie.

Hoofdstuk 6 rapporteert de resultaten van het prospectieve ATTEST onderzoek uitgevoerd in zes Nederlandse ziekenhuizen. Deze studie had als doel om de prevalentie vast te stellen van majeure CEB gevonden met TTE bij 1.084 patiënten met een herseninfarct met onbekende oorzaak. Bij 11 (1.0%) patiënten detecteerde TTE een majeure CEB. In 10 gevallen betrof dit een linkerventrikel (LV) aneurysma, LV thrombus of een combinatie van beide. In al deze gevallen was er sprake van majeure ECG-afwijkingen. Slechts één patiënt (0.1%) met een majeure CEB had een normaal ECG, deze patiënt had een myxoom (een harttumor) van het linker atrium. De belangrijkste beperking van deze studie was dat niet alle geschikte patiënten ook een TTE ondergingen, in de meeste gevallen vanwege een gegronde reden. Concluderend suggereren deze resultaten dat routinematig een TTE verrichten bij patiënten met een herseninfarct met onbekende oorzaak niet efficiënt is. De huidige strategie kan worden verbeterd door selectie van patiënten afhankelijk van ECG-karakteristieken (hoewel de aanwezigheid van majeure ECG-afwijkingen niet vooraf was vastgelegd als uitkomstmaat). Losstaand van deze resultaten, blijft het belangrijk om een TTE met contrast te verrichten bij de kleine, geselecteerde groep van patiënten die in aanmerking zou komen voor de behandeling van een patent foramen ovale (PFO).

Hoofdstuk 7 evalueert de kosteneffectiviteit van drie TTE-strategieën met behulp van de resultaten van de ATTEST studie. We vergeleken de kosten en quality-adjusted life years (QALY) voor drie strategieën waarbij óf alle patiënten, óf enkel patiënten met majeure-ECG afwijkingen óf geen patiënten TTE ondergingen. Met behulp van een model met verschillende gezondheidstoestanden werd gesimuleerd hoe patiënten opnieuw een herseninfarct of bloedings-complicatie kregen afhankelijk van de risico's horende bij de TTE-strategie. Uit deze analyse bleek dat het uitvoeren van een TTE enkel bij patiënten met ECG-afwijkingen leidde tot 0.008 additionele QALYs en €108 additionele kosten per patiënt in vergelijking met het niet verrichten van een TTE (€ 12.987/QALY). Alhoewel dit een zeer kleine winst in QALYs betrof, was de strategie om TTE uit te voeren bij ECG-afwijkingen kosteneffectief in vergelijking met het niet verrichten van een TTE. Het uitvoeren van een TTE bij alle patiënten resulteerde in 0.0005 additionele QALYs en €422 additionele kosten per patiënt vergeleken met het verrichten van een TTE in geval van majeure ECG-afwijkingen (€805.336/QALY). Deze strategie was zodoende niet kosteneffectief. Hoewel er bij de ontwikkeling van het model

verscheidene aannames zijn gedaan, ondersteunen deze resultaten de strategie waarbij patiënten voor TTE worden geselecteerd op basis van majeure-ECG afwijkingen.

Hoofdstuk 8 geeft een algemene discussie en integratie van de resultaten van dit proefschrift en bespreekt mogelijke richtingen voor toekomstig onderzoek.

Conclusies
Het doel van dit proefschrift is het evalueren van routineonderzoeken voor het opsporen van majeure CEB bij patiënten met een herseninfarct of TIA met onbekende oorzaak. De resultaten tonen dat de huidige strategie in deze groep op verschillende manieren kan worden verbeterd.

We vonden dat een geautomatiseerd detectie-algoritme voor AF tijdens telemetrie de detectie van AF op de stroke unit verbetert. Na ontslag uit het ziekenhuis leidt thuisregistratie van het hartritme tot een verdere toename van AF detectie. Tevens leidt langer registeren tot meer detectie. Tijdens 7-daagse monitoring met een externe looprecorder werd tot op dag zeven nieuw AF vastgesteld. Deze bevindingen ondersteunen de verlenging van de huidige aanbevolen registratieduur naar ten minste zeven dagen. Daarnaast kan een korter tijdsinterval tot de start van de ritmeregistratie de AF detectie verbeteren. Nieuwe technieken zoals ECG-registratie met smartwatches vormen een veelbelovend alternatief, hoewel de toepasbaarheid bij patiënten met een herseninfarct nog bevestigd dient te worden. Op dit moment evalueren verschillende studies de effectiviteit van directe anticoagulantia en plaatjes-aggregatieremmers in het geval van kortdurend AF. Deze resultaten hebben mogelijk impact op de consequentie en dus ook de urgentie van het opsporen van subklinisch AF na een herseninfarct.

De resultaten van onze systematische review en meta-analyse, retrospectieve singlecenter studie en prospectieve multicenter studie optellend, kunnen we concluderen dat het routinematig verrichten van een TTE na een herseninfarct of TIA met onbekende oorzaak zelden leidt tot detectie van een majeure CEB. De meerderheid van patiënten met een majeure CEB, met name patiënten met een LV thrombus of LV aneurysma, had ook majeure ECG-afwijkingen. Het selecteren van patiënten voor TTE alleen in geval van dergelijke ECG-afwijkingen verbetert dus de efficiëntie aanzienlijk. Een strategie waarbij alleen patiënten worden geselecteerd met majeure ECG afwijkingen, naast patiënten die kandidaat zijn voor de behandeling van een eventueel PFO, zal het aantal noodzakelijke TTE's verminderen naar rond 27% van de huidige omvang.

Om de best onderbouwde aanbeveling voor de klinische praktijk te kunnen geven, is het belangrijk om de beschikbaarheid van middelen en kosten mee te wegen. De huidige beschikbaarheid van TTE in Nederland wordt beperkt door een tekort aan ervaren echo-laboranten. Het routinematig uitvoeren van een TTE in een specifieke patiëntengroep zal ten koste kunnen gaan van andere patiëntencategorieën, met mogelijk urgentere indicaties voor echografie. Inperking van het aantal benodigde TTE's door middel van selectie zal de druk op het zorgstelsel doen verminderen. De resultaten van onze kosteneffectiviteitsanalyse ondersteunen deze benadering.

Publicaties

3D lab

1. Three cases of posttraumatic wrist problems solved with 3D-printed patient-specific guides
Haandrikman S, Schröder FF, de Graaff F, Olde Heuvel J, Vochteloo AJH.

Symptomatic malunion of the wrist is one of the most common posttraumatic wrist problems. This study demonstrates three patients with complex malunions of the wrist who benefited from a corrective osteotomy using preplanned 3D-printed patient-specific guides, by experiencing improvement in their wrist function, grip strength and a reduction in pain.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2024;11(1):2311730.
Impact factor: 0.6 ; Q4

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2. Contrasting results in sacroiliac joint fusion studies: the role of bilateral complaints
Kampkuiper N, Schröder F, Brusse-Keizer M, Nellensteijn J.

Gepubliceerd: EClinicalMedicine. 2024;79:102978.
Impact factor: 10.0 ; Q1

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3. Sacroiliac joint fusion guided by intraoperatively superimposed virtual surgical planning using simulated fluoroscopic images
Lankheet S, Kampkuiper N, Nellensteijn J, Hekman E, Tuijthof G, Schröder F, Koenrades M.

INTRODUCTION: Sacroiliac joint fusion (SIJF) is a minimally invasive treatment for sacroiliac (SI) dysfunction. It involves placing implants through the SI joint under fluoroscopic guidance, requiring precise implant positioning to avoid nerve injury. Preoperative virtual surgical planning (VSP) aids in optimal positioning, but replicating it accurately in the operating room is challenging.
RESEARCH QUESTION: This study aims to assess the feasibility of superimposing VSP onto intraoperative fluoroscopic images to aid in optimal implant placement.
MATERIAL AND METHODS: A method for intraoperative guidance using 3D/2D registration was developed and tested during SIJF as an available and potentially efficient alternative for costly and more invasive navigation systems. Preoperatively, a VSP is performed and simulated fluoroscopic images are generated from a preoperative CT scan. During surgery, the simulated image that visually best matches the intraoperative fluoroscopic image is selected. Subsequently, the VSP is superimposed onto the intraoperative fluoroscopic image using a developed script-based workflow. The surgeon then places the implants accordingly. Postoperative implant placement accuracy was evaluated.
RESULTS: Five interventions were performed on five patients, resulting in a total of 15 placed implants. Minor complications without clinical consequences occurred in one case, primarily attributable to the patient's anatomy and pathological manifestations. Mean deviations at implant apex and 3D angle were 4.7 ± 1.6 mm and 3.5 ± 1.3°, respectively.
DISCUSSION AND CONCLUSIONS: The developed intraoperative workflow was feasible and resulted in implants placed with low deviations from the VSP. Further research is needed to automate and validate this method in a larger cohort.

Gepubliceerd: Brain Spine. 2024;4:102905.
Impact factor: 2.5 ; Q2

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4. A novel patient specific guide design to correct a complex multiplanar foot deformity.
Lankheet S, Schröder F, Kappert K, Ten Cate W, Hekman E, Asseln M, Koenrades M, Zeegers AVCM.

Surgical intervention is often indicated for complex multiplanar foot deformities (CMFDs). Addressing the 3D nature of these deformities proves challenging for achieving optimal foot alignment and reoperations are often necessary. Virtual surgical planning (VSP) can aid in the understanding of the multiplanar deformity and determine the osteotomies needed for correction. This study introduces a patient-specific guide (PSG) applied to a CMFD patient undergoing midfoot closing wedge osteotomy. The PSG design allowed for accurate reconstruction of the angular deformity, while allowing for intra-operative translational adjustments. Further improvement of the PSG design was proposed to ensure an even better fit in future applications.

Gepubliceerd: Proceedings of The 24th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery. 2024;7:107-11.
Impact factor: onbekend

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5. Three-Dimensional Heart Modeling of Hypertrophic Obstructive Cardiomyopathy for In Situ Patient-Specific Simulation to Optimize Septal Myectomy
Smits KC, Speekenbrink RGH, Hekman EEG, Koenrades MA, Heeringa TJP, Arens J, Halfwerk FR.

OBJECTIVE: Hypertrophic obstructive cardiomyopathy (HOCM) develops in at least 1 out of 715 young adults. Patients who are refractory to medical therapy qualify for septal myectomy. Due to anatomy, serious complications such as ventricular septal defect and heart block may occur. Establishing cardiovascular magnetic resonance (CMR)-based 3-dimensional (3D) models as part of preoperative planning and training has the potential to decrease procedure-related complications and improve results.
METHODS: CMR images were used to segment cardiac structures. Left ventricular wall thickness was calculated and projected on top of the in silico model. A 3D model was printed with a red layer indicating a wall thickness exceeding 15 mm and used for preoperative resection planning and patient counseling. To provide preoperative patient-specific in situ simulation, the planned resection volume was replaced with silicone in a second model. For perioperative quality control, resected silicone was compared with resected myocardial tissue. The impact of the models was evaluated descriptively through consultation of both the cardiothoracic surgeon and patients and through patient outcomes.
RESULTS: Three-dimensional in silico and 3D-printed heart models of 5 patients were established preoperatively. Since the introduction of the models in October 2020, the surgeon feels better prepared, more confident, and less difficulty with making decisions. In addition, patients feel better informed preoperatively.
CONCLUSIONS: Using 3D heart models optimized preoperative planning and training, intraoperative quality control, and patient consultation. Reduction of procedure-related complications and clinical outcome should be studied in larger cohorts.

Gepubliceerd: Innovations (Phila). 2024;19(5):532-40.
Impact factor: 1.6 ; Q2

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6. Instability Severity Index Score predicts recurrent shoulder instability after arthroscopic Bankart repair
van Blommestein MYH, Govaert LHM, van der Palen J, Verra WC, Koorevaar RCT, Schröder FF, Veen EJD.

PURPOSE: The Instability Severity Index (ISI) Score was developed to preoperatively assess the risk of recurrent shoulder instability after an arthroscopic Bankart repair. This study aims to validate the use of ISI Score for predicting the risk of recurrence after an arthroscopic Bankart repair in a heterogeneous population and proposes an appropriate cut-off point for treating patients with an arthroscopic Bankart repair or otherwise.
METHODS: This study analysed 99 shoulders after a traumatic dislocation that underwent arthroscopic Bankart repair with at least 3 years follow-up. Patients were divided into subcategories based on their respective ISI Score. Recurrence includes either a postoperative dislocation or perceived instability.
RESULTS: The overall recurrence rate was found to be 26.3%. A significant correlation was identified between ISI Score and the recurrence rate (odds ratio [OR]: 1.545, 95% confidence interval [CI]: 1.231-1.939, $p < 0.001$). Furthermore, ISI Score 4-6 (OR: 4.498, 95% CI: 1.866-10.842, $p < 0.001$) and ISI Score > 6 (OR: 7.076, 95% CI: 2.393-20.924, $p < 0.001$) both had a significantly higher risk of recurrence compared to ISI Score 0-3. In ISI Score subcategories 0-3, 4-6 and >6, the recurrence rate was, respectively, 15.4%, 40.7% and 71.4%.
CONCLUSION: ISI Score has predictive value in determining the recurrence risk of shoulder instability following an arthroscopic Bankart repair in a heterogeneous population. Based on the findings of this study, we recommend using arthroscopic Bankart repair in patients with ISI Score 0-3. Clinical and shared decision-making are essential in the group with ISI Score 4-6, since the recurrence rate is significantly higher than in patients with ISI Score 0-3. Arthroscopic Bankart repair is not suitable for patients with ISI Score > 6. LEVEL OF EVIDENCE: Level III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2024;32(8):2152-60.
Impact factor: 5.0 ; Q1

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7. Development of a virtual surgical plan for reverse shoulder arthroplasty as a treatment for complex proximal humerus fracture in an elderly patient
van Luit RJ, Rijntjes J, Hekman E, Govaert L, Hollman F, Schröder FF, Veen EJD.

Gepubliceerd: JSES Rev Rep Tech. 2024;5(1):92-6.
Impact factor: onbekend

Totale impact factor: 19.7
Gemiddelde impact factor: 2.8

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 13.1
Gemiddelde impact factor: 3.3

Anesthesie

1. The effect of enhanced recovery after surgery (ERAS) in renal surgery
Elferink SEM, Bretveld R, Kwast ABG, Asselman M, Essink JGJ, Potters JW, van der Palen J.

OBJECTIVE: To study the effect of ERAS on a textbook outcome (TO) after elective renal surgery.
PATIENTS AND METHODS: Retrospective study of all patients who underwent a robot-assisted laparoscopic partial or radical nephrectomy or robot-assisted laparoscopic radical nephroureterectomy in Medisch Spectrum Twente (MST), Enschede, the Netherlands. In total, 277 patients were included. 66 patients from 2018 to 2021 (pre-ERAS group) and 211 patients from 2021 to 2023 (ERAS group). TO is a maximum of two nights in the hospital after surgery, no severe complications during or after surgery ≥ grade IIIb, no blood transfusions, no intensive care, no readmissions, and no mortality within 30 days after surgery. Comparisons were made between the pre-ERAS and ERAS groups using unpaired t-test, Mann-Whitney U test, the chi-squared test or Fisher's exact test. Multivariate logistic regression was used to adjust for possible confounding.
RESULTS: TO was significantly (p = 0.005) better in the ERAS group (TO = 76.8%) compared to the pre-ERAS group (TO = 59.1%). Compared to a pre-ERAS patient, the adjusted odds ratio for achieving a TO as an ERAS patient is 2.1 (95% CI 1.15-3.78).
CONCLUSIONS: The implementation of ERAS showed a positive effect on the TO of elective renal surgery patients.

Gepubliceerd: World J Urol. 2024;42(1):490.
Impact factor: 2.9 ; Q2

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2. Driving pressure during general anesthesia for minimally invasive abdominal surgery (GENERATOR)-study protocol of a randomized clinical trial
Generator-investigators; Potters JW.

BACKGROUND: Intraoperative driving pressure (ΔP) has an independent association with the development of postoperative pulmonary complications (PPCs) in patients receiving ventilation during general anesthesia for major surgery. Ventilation with high intraoperative positive end-expiratory pressure (PEEP) with recruitment maneuvers (RMs) that result in a low ΔP has the potential to prevent PPCs. This trial tests the hypothesis that compared to standard low PEEP without RMs, an individualized high PEEP strategy, titrated to the lowest ΔP, with RMs prevents PPCs in patients receiving intraoperative protective ventilation during anesthesia for minimally invasive abdominal surgery.
METHODS: "DrivinG prEssure duriNg gEneRal AnesThesia fOr minimally invasive abdominal suRgery (GENERATOR)" is an international, multicenter, two-group, patient and outcome-assessor blinded randomized clinical trial. In total, 1806 adult patients scheduled for minimally invasive abdominal surgery and with an increased risk of PPCs based on (i) the ARISCAT risk score for PPCs (≥ 26 points) and/or (ii) a combination of age > 40 years and scheduled surgery lasting > 2 h and planned to receive an intra-arterial catheter for blood pressure monitoring during the surgery will be included. Patients are assigned to either an intraoperative ventilation strategy with individualized high PEEP, titrated to the lowest ΔP, with RMs or one with a standard low PEEP of 5 cm H(2)O without RMs. The primary outcome is a collapsed composite endpoint of PPCs until postoperative day 5.
DISCUSSION: GENERATOR will be the first adequately powered randomized clinical trial to compare the effects of individualized high PEEP with RMs versus standard low PEEP without RMs on the occurrence of PPCs after minimally invasive abdominal surgery. The results of the GENERATOR trial will support anesthesiologists in their decisions regarding PEEP settings during minimally invasive

abdominal surgery. TRIAL REGISTRATION: GENERATOR is registered at ClinicalTrials.gov (study identifier: NCT06101511) on 26 October 2023.

Gepubliceerd: Trials. 2024;25(1):719.
Impact factor: 2.0 ; Q3

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3. Effectiveness of intra-articular analgesia in reducing postoperative pain after minimally invasive sacroiliac joint fusion: a double-blind randomized controlled trial
Hermans SMM, Nellensteijn JM, Knoef R, van Santbrink H, Droeghaag R, Most J, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

During the first postoperative days following minimally invasive sacroiliac joint fusion (MISJF), patients often report serious pain, which contributes to high utilization of painkillers and prevention of early mobilization. This prospective, double-blind randomized controlled trial investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% versus placebo (NaCl 0.9%) in 42 patients in reducing postoperative pain after MISJF. The primary outcome was difference in pain between bupivacaine and placebo groups, assessed as fixed factor in a linear mixed model. Secondary outcomes were opioid consumption, patient satisfaction, adverse events, and length of hospital stay. We found that SIJ infiltration with bupivacaine did not affect postoperative pain scores in comparison with placebo, neither as group-effect ($p = 0.68$), nor dependent on time (group*time: $p = 0.87$). None of the secondary outcome parameters were affected in the postoperative period in comparison with placebo, including opioid consumption ($p = 0.81$). To conclude, intra-articular infiltration of the SIJ with bupivacaine at the end of MISJF surgery is not effective in reducing postoperative pain. Hence, we do not recommend routine use of intraoperative SIJ infiltration with analgesia in MISJF.

Gepubliceerd: Sci Rep. 2024;14(1):22647.
Impact factor: 3.9 ; Q1

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4. Hypotension Prediction Index Is Equally Effective in Predicting Intraoperative Hypotension during Noncardiac Surgery Compared to a Mean Arterial Pressure Threshold: A Prospective Observational Study
Mulder MP, Harmannij-Markusse M, Fresiello L, Donker DW, Potters JW.

BACKGROUND: The Hypotension Prediction Index is designed to predict intraoperative hypotension in a timely manner and is based on arterial waveform analysis using machine learning. It has recently been suggested that this algorithm is highly correlated with the mean arterial pressure itself. Therefore, the aim of this study was to compare the index with mean arterial pressure-based prediction methods, and it is hypothesized that their ability to predict hypotension is comparable.
METHODS: In this observational study, the Hypotension Prediction Index was used in addition to routine intraoperative monitoring during moderate- to high-risk elective noncardiac surgery. The agreement in time between the default Hypotension Prediction Index alarm (greater than 85) and different concurrent mean arterial pressure thresholds was evaluated. Additionally, the predictive performance of the index and different mean arterial pressure-based methods were assessed within 5, 10, and 15 min before hypotension occurred.
RESULTS: A total of 100 patients were included. A mean arterial pressure threshold of 73 mmHg agreed 97% of the time with the default index alarm, whereas a mean arterial pressure threshold of 72 mmHg had the most comparable predictive performance. The areas under the receiver operating characteristic curve of the Hypotension Prediction Index (0.89 [0.88 to 0.89]) and concurrent mean

arterial pressure (0.88 [0.88 to 0.89]) were almost identical for predicting hypotension within 5 min, outperforming both linearly extrapolated mean arterial pressure (0.85 [0.84 to 0.85]) and delta mean arterial pressure (0.66 [0.65 to 0.67]). The positive predictive value was 31.9 (31.3 to 32.6)% for the default index alarm and 32.9 (32.2 to 33.6)% for a mean arterial pressure threshold of 72 mmHg.
CONCLUSIONS: In clinical practice, the Hypotension Prediction Index alarms are highly similar to those derived from mean arterial pressure, which implies that the machine learning algorithm could be substituted by an alarm based on a mean arterial pressure threshold set at 72 or 73 mmHg. Further research on intraoperative hypotension prediction should therefore include comparison with mean arterial pressure-based alarms and related effects on patient outcome.

Gepubliceerd: Anesthesiology. 2024;141(3):453-62.
Impact factor: 9.1 ; Q1

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5. Do all sedatives promote biological sleep electroencephalogram patterns? A machine learning framework to identify biological sleep promoting sedatives using electroencephalogram
Ramaswamy SM, Kuizenga MH, Weerink MAS, Vereecke HEM, Nagaraj SB, Struys M.

BACKGROUND: Sedatives are commonly used to promote sleep in intensive care unit patients. However, it is not clear whether sedation-induced states are similar to the biological sleep. We explored if sedative-induced states resemble biological sleep using multichannel electroencephalogram (EEG) recordings.
METHODS: Multichannel EEG datasets from two different sources were used in this study: (1) sedation dataset consisting of 102 healthy volunteers receiving propofol (N = 36), sevoflurane (N = 36), or dexmedetomidine (N = 30), and (2) publicly available sleep EEG dataset (N = 994). Forty-four quantitative time, frequency and entropy features were extracted from EEG recordings and were used to train the machine learning algorithms on sleep dataset to predict sleep stages in the sedation dataset. The predicted sleep states were then compared with the Modified Observer's Assessment of Alertness/ Sedation (MOAA/S) scores.
RESULTS: The performance of the model was poor (AUC = 0.55-0.58) in differentiating sleep stages during propofol and sevoflurane sedation. In the case of dexmedetomidine, the AUC of the model increased in a sedation-dependent manner with NREM stages 2 and 3 highly correlating with deep sedation state reaching an AUC of 0.80.
CONCLUSIONS: We addressed an important clinical question to identify biological sleep promoting sedatives using EEG signals. We demonstrate that propofol and sevoflurane do not promote EEG patterns resembling natural sleep while dexmedetomidine promotes states resembling NREM stages 2 and 3 sleep, based on current sleep staging standards.

Gepubliceerd: PLoS One. 2024;19(7):e0304413.
Impact factor: 2.6 ; Q2

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6. Percutaneous left stellate ganglion block for refractory ventricular tachycardia in structural heart disease: our single-centre experience
van der Pas VR, van Opstal JM, Scholten MF, Monteiro de Oliveira NP, Speekenbrink RGH, van Dessel P.

INTRODUCTION: When electrical storm (ES) is amenable to neither antiarrhythmic drugs, nor deep sedation or catheter ablation, autonomic modulation may be considered. We report our experience with percutaneous left stellate ganglion block (PSGB) to temporarily suppress refractory ventricular arrhythmia (VA) in patients with structural heart disease.

METHODS: A retrospective analysis was performed at our institution of patients with structural heart disease and an implantable cardioverter defibrillator (ICD) who had undergone PSGB for refractory VA between January 2018 and October 2021. The number of times antitachycardia pacing (ATP) was delivered and the number of ICD shocks/external cardioversions performed in the week before and after PSGB were evaluated. Charts were checked for potential complications.
RESULTS: Twelve patients were identified who underwent a combined total of 15 PSGB and 5 surgical left cardiac sympathetic denervation procedures. Mean age was 73 ± 5.8 years and all patients were male. Nine of 12 (75%) had ischaemic cardiomyopathy, with the remainder having non-ischaemic dilated cardiomyopathy. Mean left ventricular ejection fraction was 35% (± 12.2%). Eight of 12 (66.7%) patients were already being treated with both amiodarone and beta-blockers. The reduction in ATP did not reach statistical significance (p =- 0.066); however, ICD shocks (p = 0.028) and ATP/shocks combined were significantly reduced (p = 0.04). At our follow-up electrophysiology meetings PSGB was deemed ineffective in 4 of 12 patients (33%). Temporary anisocoria was seen in 2 of 12 (17%) patients, and temporary hypotension and hoarseness were reported in a single patient.
DISCUSSION: In this limited series, PSGB showed promise as a method for temporarily stabilising refractory VA and ES in a cohort of male patients with structural heart disease. The side effects observed were mild and temporary.

Gepubliceerd: Neth Heart J. 2024;32(7-8):283-9.
Impact factor: 2.0 ; Q3

Totale impact factor: 22.5
Gemiddelde impact factor: 3.8

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 11.7
Gemiddelde impact factor: 5.9

Epidemiologie

1. The effect of dexamethasone on the incidence of delirium in patients hospitalized due COVID-19 infection: a retrospective cohort study
Boersma MN, Kamperman E, van der Palen J.

PURPOSE: Delirium has been suggested to be a complication associated with corticosteroid use. Therefore, the association between dexamethasone use and delirium in COVID-19 patients was studied herein.
METHODS: In this single-center retrospective cohort study, 412 patients who were hospitalized because of COVID-19 between March 2020 and January 2021 were included. Delirium was diagnosed using the Delirium Observation Screening Scale. The association between the daily use of dexamethasone 6 mg and delirium was measured via multivariable logistic regression analysis.
RESULTS: The incidence of delirium was 11.4% in patients treated with dexamethasone (n = 245) and 9.6% in patients not treated with dexamethasone (n = 167) (RR 1.19, CI 0.67-2.13, p = 0.55). After adjusting for age (mean 69 years) and comorbidity score, the odds ratio for developing delirium when using dexamethasone was 1.11 (CI 0.56-2.21, p = 0.76).
CONCLUSION: The use of dexamethasone in hospitalized COVID-19 patients did not affect the incidence of delirium.

Gepubliceerd: Eur Geriatr Med. 2024;15(4):971-5.
Impact factor: 3.6 ; Q2

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2. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms
Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group; Brusse-Keizer M, Haalboom M, van der Palen J.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

Gepubliceerd: Heliyon. 2024;10(10):e29591.
Impact factor: 3.6 ; Q1

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3. Adherence to single inhaler triple therapy and digital inhalers in Chronic Obstructive Pulmonary Disease: a literature review and protocol for a randomized controlled trial (TRICOLON study)
Cuperus LJA, van der Palen J, Aldenkamp A, van Huisstede A, Bischoff E, van Boven JFM, Brijker F, Dik S, van Excel J, Goosens M, van Hal PTW, Kuijvenhoven JC, Kunz LIZ, Vasbinder EC, Kerstjens HAM, In 't Veen J.

BACKGROUND: Medication non-adherence is a significant problem in patients with Chronic Obstructive Pulmonary Disease (COPD). Efforts to address this issue are receiving increased attention. Simplifying treatment by prescribing single-inhaler triple therapy (SITT) as an alternative to multi-inhaler triple therapy (MITT) or with smart inhalers are often considered potential solutions. However, the actual impact of these innovations on adherence and clinical outcomes is unclear.
METHODS: To address this knowledge gap we first conducted a literature review focusing on two research questions: 1) the difference in adherence between SITT and MITT users in COPD, and 2) the effect of smart inhalers on adherence in COPD. Separate searches were conducted in PubMed and two authors independently assessed the articles. In addition, we present a protocol for a study to acquire knowledge for the gaps identified.
RESULTS: To address the first research question, 8 trials were selected for further review. All trials were observational, i.e. randomized controlled trials were lacking. Seven of these trials showed higher adherence and/or persistence in patients on SITT compared with patients on MITT. In addition, four studies showed a positive effect of SITT on various clinical outcomes. For the second research question, 11 trials were selected for review. While most of the studies showed a positive effect of smart inhalers on adherence, there was considerable variation in the results regarding their effect on other clinical outcomes. The TRICOLON (TRIple therapy COnvenience by the use of one or multipLe Inhalers and digital support in ChrONic Obstructive Pulmonary Disease) trial aims to improve understanding regarding the effectiveness of SITT and smart inhalers in enhancing adherence. This open-label, randomized, multi-center study will enroll COPD patients requiring triple therapy at ten participating hospitals. In total, 300 patients will be randomized into three groups: 1) MITT; 2) SITT; 3) SITT with digital support through a smart inhaler and an e-health platform. The follow-up period will be one year, during which three methods of measuring adherence will be used: smart inhaler data, self-reported data using the Test of Adherence to Inhalers (TAI) questionnaire, and drug analysis in scalp hair samples. Finally, differences in clinical outcomes between the study groups will be compared.
DISCUSSION: Our review suggests promising results concerning the effect of SITT, as opposed to MITT, and smart inhalers on adherence. However, the quality of evidence is limited due to the absence of randomized controlled trials and/or the short duration of follow-up in many studies. Moreover, its impact on clinical outcomes shows considerable variation. The TRICOLON trial aims to provide solid data on these frequently mentioned solutions to non-adherence in COPD. Collecting data in a well-designed randomized controlled trial is challenging, but the design of this trial addresses both the usefulness of SITT and smart inhalers while ensuring minimal interference in participants' daily lives.
TRIAL REGISTRATION: NCT05495698 (Clinicaltrials.gov), registered at 08-08-2022. Protocol version: version 5, date 27-02-2023.

Gepubliceerd: BMC Pulm Med. 2024;24(1):317.
Impact factor: 2.8 ; Q2

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4. The effect of enhanced recovery after surgery (ERAS) in renal surgery
Elferink SEM, Bretveld R, Kwast ABG, Asselman M, Essink JGJ, Potters JW, van der Palen J.

OBJECTIVE: To study the effect of ERAS on a textbook outcome (TO) after elective renal surgery.
PATIENTS AND METHODS: Retrospective study of all patients who underwent a robot-assisted laparoscopic partial or radical nephrectomy or robot-assisted laparoscopic radical nephroureterectomy in Medisch Spectrum Twente (MST), Enschede, the Netherlands. In total, 277 patients were included. 66 patients from 2018 to 2021 (pre-ERAS group) and 211 patients from 2021 to 2023 (ERAS group). TO is a maximum of two nights in the hospital after surgery, no severe complications during or after surgery ≥ grade IIIb, no blood transfusions, no intensive care, no readmissions, and no mortality within 30 days after surgery. Comparisons were made between the pre-ERAS and ERAS groups using unpaired t-test, Mann-Whitney U test, the chi-squared test or Fisher's exact test. Multivariate logistic regression was used to adjust for possible confounding.
RESULTS: TO was significantly ($p = 0.005$) better in the ERAS group (TO = 76.8%) compared to the pre-ERAS group (TO = 59.1%). Compared to a pre-ERAS patient, the adjusted odds ratio for achieving a TO as an ERAS patient is 2.1 (95% CI 1.15-3.78).
CONCLUSIONS: The implementation of ERAS showed a positive effect on the TO of elective renal surgery patients.

Gepubliceerd: World J Urol. 2024;42(1):490.
Impact factor: 2.9 ; Q2

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5. Contrasting results in sacroiliac joint fusion studies: the role of bilateral complaints
Kampkuiper N, Schröder F, Brusse-Keizer M, Nellensteijn J.

Gepubliceerd: EClinicalMedicine. 2024;79:102978.
Impact factor: 10.0 ; Q1

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6. Effect of Physical Exercise on MRI-Assessed Brain Perfusion in Chemotherapy-Treated Breast Cancer Patients: A Randomized Controlled Trial
Koevoets EW, Petr J, Monninkhof EM, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, van der Palen J, Mutsaerts H, de Ruiter MB, May AM, Schagen SB.

BACKGROUND: Exercise is a promising intervention to alleviate cognitive problems in breast cancer patients, but studies on mechanisms underlying these effects are lacking.
PURPOSE: Investigating whether an exercise intervention can affect cerebral blood flow (CBF) in cognitively impaired breast cancer patients and to determine if CBF changes relate to memory function.
STUDY TYPE: Prospective.
POPULATION: A total of 181 chemotherapy-treated stage I-III breast cancer patients with cognitive problems and relatively low physical activity levels (≤150 minutes moderate to vigorous physical activity per week), divided into an exercise (N = 91) or control group (N = 90).
FIELD STRENGTH/SEQUENCE: Two-dimensional echo planar pseudo-continuous arterial spin labeling CBF sequence at 3 T.
ASSESSMENT: The 6-month long intervention consisted of (supervised) aerobic and strength training, 4 × 1 hour/week. Measurements at baseline (2-4 years post-diagnosis) and after 6 months included gray matter CBF in the whole brain, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. Physical fitness and memory function were also assessed. Subgroup analyses were performed in patients with high fatigue levels at baseline.

STATISTICAL TESTS: Multiple regression analyses with a two-sided alpha of 0.05 for all analyses.
RESULTS: There was a significant improvement in physical fitness (VO(2peak) in mL/minute/kg) in the intervention group (N = 53) compared to controls (N = 51, β = 1.47 mL/minute/kg, 95% CI: 0.44-2.50). However, no intervention effects on CBF were found (eg, whole brain: P = 0.565). Highly fatigued patients showed larger but insignificant treatment effects on CBF (eg, whole brain: P = 0.098). Additionally, irrespective of group, a change in physical fitness was positively associated with changes in CBF (eg, whole brain: β = 0.75, 95% CI: 0.07-1.43). There was no significant relation between CBF changes and changes in memory performance.
DATA CONCLUSION: The exercise intervention did not affect CBF of cognitively affected breast cancer patients. A change in physical fitness was associated with changes in CBF, but changes in CBF were not associated with memory functioning.
LEVEL OF EVIDENCE: 1
TECHNICAL EFFICACY STAGE: 5.

Gepubliceerd: J Magn Reson Imaging. 2024;59(5):1667-80.
Impact factor: 3.5 ; Q1

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7. A Critical Appraisal of the Whack-a-Mole and Swivel Chair Signs in the Diagnosis of Functional Movement Disorders
Lagrand TJ, Brusse-Keizer M, Charmley A, Edwards MJ, Tijssen MAJ, Lehn AC.

BACKGROUND: The demonstration of positive signs during neurological examination is a cornerstone of the diagnosis of functional movement disorders, however, the available data supporting the diagnostic value of some of these signs is limited.
OBJECTIVES: To determine the diagnostic value (sensitivity and specificity) of the "whack-a-mole" (WAM) and "swivel chair" (SC) tests in patients with functional movement disorders (FMD).
METHODS: We enrolled patients with functional and organic movements in the WAM test if they exhibited tremor, dystonia, myoclonus, chorea, or tics. For the SC test, patients with a gait disorder as their primary impairment were recruited. Two blinded movement disorder specialists rated the presence of these signs in edited videos.
RESULTS: Inclusion criteria were met by 42 patients with FMD and 65 patients with organic movement disorders. Both tests demonstrated high specificity (means, 78% and 96%), but their sensitivity was low (means, 52% and 37%). Interobserver agreement for the WAM sign was 0.77 in the FMD group, against 0.28 in patients with organic movement disorders, whereas Movement Disorders Clinical Practice for Review Only for the SC sign was 0.69 in both groups. CONCLUSIONS: The present study indicates that physicians must be cautious in the application and interpretation of these clinical signs in the diagnosis of functional movement disorders, and they should be carefully considered and used as necessary.

Gepubliceerd: Mov Disord Clin Pract. 2024;11(1):63-8.
Impact factor: 2.7 ; Q2

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8. Potential for personalised and biomarker-guided COPD self-treatment approaches
Lenferink A, Citgez E, van der Valk P, van der Palen J, Effing TW, Brusse-Keizer MGJ.

Gepubliceerd: Lancet Respir Med. 2024;12(8):e48-e9.
Impact factor: 32.8 ; Q1

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9. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; Brusse-Keizer M, Haalboom M, van der Palen J.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

Gepubliceerd: Sci Rep. 2024;14(1):16387.
Impact factor: 3.9 ; Q1

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10. Ghrelin for Neuroprotection in Post-Cardiac Arrest Coma: A Randomized Clinical Trial
Nutma S, Beishuizen A, van den Bergh WM, Foudraine NA, le Feber J, Filius PMG, Cornet AD, van der Palen J, van Putten M, Hofmeijer J.

IMPORTANCE: Out-of-hospital cardiac arrest survival rates have markedly risen in the last decades, but neurological outcome only improved marginally. Despite research on more than 20 neuroprotective strategies involving patients in comas after cardiac arrest, none have demonstrated unequivocal evidence of efficacy; however, treatment with acyl-ghrelin has shown improved functional and histological brain recovery in experimental models of cardiac arrest and was safe in a wide variety of human study populations.
OBJECTIVE: To determine safety and potential efficacy of intravenous acyl-ghrelin to improve neurological outcome in patients in a coma after cardiac arrest.
DESIGN, SETTING, AND PARTICIPANTS: A phase 2, double-blind, placebo-controlled, multicenter, randomized clinical trial, Ghrelin Treatment of Comatose Patients After Cardiac Arrest: A Clinical Trial to Promote Cerebral Recovery (GRECO), was conducted between January 18, 2019, and October 17, 2022. Adult patients 18 years or older who were in a comatose state after cardiac arrest were assessed for eligibility; patients were from 3 intensive care units in the Netherlands. Expected death within 48 hours or unfeasibility of treatment initiation within 12 hours were exclusion criteria.
INTERVENTIONS: Patients were randomized to receive intravenous acyl-ghrelin, 600 µg (intervention

group), or placebo (control group) within 12 hours after cardiac arrest, continued for 7 days, twice daily, in addition to standard care.
MAIN OUTCOMES AND MEASURES: Primary outcome was the score on the Cerebral Performance Categories (CPC) scale at 6 months. Safety outcomes included any serious adverse events. Secondary outcomes were mortality and neuron-specific enolase (NSE) levels on days 1 and 3. RESULTS: A total of 783 adult patients in a coma after cardiac arrest were assessed for eligibility, and 160 patients (median [IQR] age, 68 [57-75] years; 120 male [75%]) were enrolled. A total of 81 patients (51%) were assigned to the intervention group, and 79 (49%) were assigned to the control group. The common odds ratio (OR) for any CPC improvement in the intervention group was 1.78 (95% CI, 0.98-3.22; P = .06). This was consistent over all CPC categories. Mean (SD) NSE levels on day 1 after cardiac arrest were significantly lower in the intervention group (34 [6] µg/L vs 56 [13] µg/L; P = .04) and on day 3 (28 [6] µg/L vs 52 [14] µg/L; P = .08). Serious adverse events were comparable in incidence and type between the groups. Mortality was 37% (30 of 81) in the intervention group vs 51% (40 of 79) in the control group (absolute risk reduction, 14%; 95% CI, -2% to 29%; P = .08).
CONCLUSIONS AND RELEVANCE: In patients in a coma after cardiac arrest, intravenous treatment with acyl-ghrelin was safe and potentially effective to improve neurological outcome. Phase 3 trials are needed for conclusive evidence.
TRIAL REGISTRATION: Clinicaltrialsregister.eu: EUCTR2018-000005-23-NL.

Gepubliceerd: JAMA Neurol. 2024;81(6):603-10.
Impact factor: 21.4 ; Q1

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11. Structured medication reviews in Parkinson's disease: pharmacists' views, experiences and needs - a qualitative study
Oonk NGM, Dorresteijn LDA, Te Braake E, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Bode C.

BACKGROUND: Executing structured medication reviews (SMRs) in primary care to optimize drug treatment is considered standard care of community pharmacists in the Netherlands. Patients with Parkinson's disease (PD) often face complex drug regimens for their symptomatic treatment and might, therefore, benefit from an SMR. However, previously, no effect of an SMR on quality of life in PD was found. In trying to improve the case management of PD, it is interesting to understand if and to what extent SMRs in PD patients are of added value in the pharmacist's opinion and what are assumed facilitating and hindering factors.
OBJECTIVES: To analyse the process of executing SMRs in PD patients from a community pharmacist's point of view.
DESIGN: A cross-sectional, qualitative study was performed, consisting of face-to-face semi-structured in-depth interviews.
METHODS: The interviews were conducted with community pharmacists who executed at least one SMR in PD, till data saturation was reached. Interviews were transcribed verbatim, coded and analysed thematically using an iterative approach.
RESULTS: Thirteen pharmacists were interviewed. SMRs in PD were considered of added value, especially regarding patient contact and bonding, individualized care and its possible effect in the future, although PD treatment is found already well monitored in secondary care. Major constraints were time, logistics and collaboration with medical specialists.
CONCLUSION: Although community pharmacist-led SMRs are time-consuming and sometimes logistically challenging, they are of added value in primary care in general, and also in PD, of which treatment occurs mainly in secondary care. It emphasizes the pharmacist's role in PD treatment and might tackle future drug-related issues. Improvements concern multidisciplinary collaboration for optimized SMR execution and results.

Gepubliceerd: Ther Adv Drug Saf. 2024;15:20420986241237071.
Impact factor: 3.4 ; Q2

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12. Affect and post-COVID-19 symptoms in daily life: An exploratory experience sampling study
Schaap G, Wensink M, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

Insight into the daily life experiences of patients with post-COVID-19 syndrome is lacking. The current study explored temporal fluctuations of and associations between positive and negative affect and symptoms throughout the day in previously hospitalised post-COVID-19 patients using an experience sampling methodology. Ten participants (age: median = 60, interquartile range = 9 years; 50% women; 80% ≥1 comorbidity; 8-12 months since hospital discharge) filled out brief online questionnaires, six times a day for 14 consecutive days. Positive and negative affect, and self-reported symptoms (physical and mental fatigue, cognitive functioning, dyspnoea, and pain) were assessed in real-time. Primarily, graphs were analysed to assess the individual longitudinal courses of and (concurrent and time-lagged) associations between affect and symptoms. Secondly, correlations or multilevel linear regression models were used to support these interpretations. Visual assessment showed limited temporal fluctuation in affect and symptoms. All symptoms appeared to associate positively with each other (correlations between .26 and .85). Positive affect was associated with lower symptoms severity (β's between -.28 and -.67), and negative affect with higher symptoms severity (β's between .24 and .66). Time-lagged analyses showed that-adjusted for residual symptom severity of prior measurements-both types of affect predicted symptom severity two hours later (β's between -.09 and -.31 for positive affect; between .09 and .28 for negative affect). These findings suggest that positive and negative affect may play important roles in post-COVID-19 symptom experience and temporal fluctuation.

Gepubliceerd: PLoS One. 2024;19(10):e0295217.
Impact factor: 2.6 ; Q2

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13. Does adherence to exacerbation action plans matter? Insights from two COPD self-management studies
Schrijver J, Effing T, van Helden J, van der Palen J, van der Valk P, Brusse-Keizer M, Lenferink A.

INTRODUCTION: Patients' adherence is essential for COPD self-management, as beneficial effects can only be expected in adherent patients. We explored associations between patients' adherence to COPD exacerbation action plans and health outcomes.
MATERIALS AND METHODS: Pooled COPD self-treatment intervention group data from two RCTs were analysed, only including patients who had ≥1 COPD exacerbation or started ≥1 course of oral corticosteroids over one-year follow-up. Optimal adherence was defined as 'self-treatment initiated ≤1 day before or after exacerbation start', suboptimal adherence as 'self-treatment initiated 2 days before or after exacerbation start or no self-treatment initiated for a short (1-3 days) exacerbation', and significant delay or no treatment as 'self-treatment initiated >2 days after exacerbation start or no self-treatment initiated for a longer (>3 days) exacerbation'. Regression models were built for several health outcomes, with the number of COPD exacerbation days/patient/year being the primary outcome.
RESULTS: Patients with significant delay or no treatment (n = 46) had more exacerbation days/patient/year (33.3 (95 % CI 10.9; 55.6)) than optimal adherent patients (n = 38) (23.7 (95 % CI 1.7; 45.7)). The duration per COPD exacerbation was longer for patients with significant delay or no treatment (15.5 days) compared to optimal adherent patients (7.8 days). No differences in health outcomes were observed between optimal and suboptimal adherent patients.

CONCLUSIONS: Being adherent to action plans is associated with better health outcomes than significant delayed treatment or no treatment at all. Interestingly, suboptimal adherence demonstrated health benefits comparable to optimal adherence. COPD self-management interventions should prioritise strategies to optimise patients' adherence to action plans.

Gepubliceerd: Heliyon. 2024;10(20):e39070.
Impact factor: 3.6 ; Q1

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14. An alternative treatment for degenerative triangular fibrocartilage complex injuries with distal radioulnar joint instability: first experience with 48 patients
Shaer SA, van der Palen J, Teunissen J, Fink A, van der Heijden B, Zöphel O.

Treatment of ulnar impaction syndrome combined with distal radioulnar joint instability due to irreparable degenerative triangular fibrocartilage complex injuries can be complex. We describe the outcomes of a novel technique for restoring distal radioulnar stability due to ulnar impaction syndrome using a distally based extensor carpi ulnaris tendon strip combined with ulnar shortening osteotomy in 48 patients. Patients were assessed using standardized outcome measurements. The patient-rated wrist/hand evaluation total score improved from 66 (SD 15) at intake to 40 (SD 25) at 3 months, and 28 (SD 23) at 12 months postoperatively ($p < 0.001$). Wrist extension and flexion improved significantly at 12 months from 53° (SD 11) to 65° (SD 8) ($p < 0.001$) and from 45° (SD 10) to 56° (SD 12) ($p = 0.01$), respectively. Adding a distally based longitudinal extensor carpi ulnaris strip to ulnar shortening osteotomy for restoring distal radioulnar joint stability seems to be an effective treatment in patients with irreparable degenerative triangular fibrocartilage complex injuries due to ulnar impaction syndrome. Level of evidence: IV.

Gepubliceerd: J Hand Surg Eur Vol. 2024;49(2):240-9.
Impact factor: 1.7 ; Q2

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15. Comparing the Effectiveness of the Blended Delivery Mode With the Face-to-Face Delivery Mode of Smoking Cessation Treatment: Noninferiority Randomized Controlled Trial
Siemer L, Pieterse ME, Ben Allouch S, Postel MG, Brusse-Keizer MGJ.

BACKGROUND: Tobacco consumption is a leading cause of death and disease, killing >8 million people each year. Smoking cessation significantly reduces the risk of developing smoking-related diseases. Although combined treatment for addiction is promising, evidence of its effectiveness is still emerging. Currently, there is no published research comparing the effectiveness of blended smoking cessation treatments (BSCTs) with face-to-face (F2F) treatments, where web-based components replace 50% of the F2F components in blended treatment.
OBJECTIVE: The primary objective of this 2-arm noninferiority randomized controlled trial was to determine whether a BSCT is noninferior to an F2F treatment with identical ingredients in achieving abstinence rates.
METHODS: This study included 344 individuals who smoke (at least 1 cigarette per day) attending an outpatient smoking cessation clinic in the Netherlands. The participants received either a blended 50% F2F and 50% web-based BSCT or only F2F treatment with similar content and intensity. The primary outcome measure was cotinine-validated abstinence rates from all smoking products at 3 and 15 months after treatment initiation. Additional measures included carbon monoxide-validated point prevalence abstinence; self-reported point prevalence abstinence; and self-reported continuous abstinence rates at 3, 6, 9, and 15 months after treatment initiation.

RESULTS: None of the 13 outcomes showed statistically confirmed noninferiority of the BSCT, whereas 4 outcomes showed significantly (P<.001) inferior abstinence rates of the BSCT: cotinine-validated point prevalence abstinence rate at 3 months (difference 12.7, 95% CI 6.2-19.4), self-reported point prevalence abstinence rate at 6 months (difference 19.3, 95% CI 11.5-27.0) and at 15 months (difference 11.7, 95% CI 5.8-17.9), and self-reported continuous abstinence rate at 6 months (difference 13.8, 95% CI 6.8-20.8). The remaining 9 outcomes, including the cotinine-validated point prevalence abstinence rate at 15 months, were inconclusive.
CONCLUSIONS: In this high-intensity outpatient smoking cessation trial, the blended mode was predominantly less effective than the traditional F2F mode. The results contradict the widely assumed potential benefits of blended treatment and suggest that further research is needed to identify the critical factors in the design of blended interventions.
TRIAL REGISTRATION: Netherlands Trial Register 27150; https://onderzoekmetmensen.nl/nl/trial/27150.
INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): RR2-doi.org/10.1186/s12889-016-3851-x.

Gepubliceerd: J Med Internet Res. 2024;26:e47040.
Impact factor: 6.0 ; Q1

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16. A randomized crossover study assessing critical errors, preferences, and ease of use of two multidose powder inhalers
Tinke P, van Beurden W, Goosens M, van der Palen J.

BACKGROUND: The effectiveness of inhaled medications in asthma and COPD is significantly impacted by inhalation errors. Feedback mechanisms, built into the design of the inhaler might reduce the number of critical errors. This study compares critical errors, preferences, and ease of use of two dry powder inhalers, the Nexthaler, and the Turbuhaler.
RESEARCH DESIGN AND METHODS: In this multi-center, prospective, randomized, open-label, cross-over study, the proportions of asthma and COPD patients making critical errors were compared between the Nexthaler and Turbuhaler after 4 weeks of clinical use, after having been trained for the correct use of both inhalers.
RESULTS: Ninety and 49 patients with asthma and COPD, respectively, were assessed. No significant difference was found in the number of critical errors between the two inhalers (3 with Nexthaler and 5 with Turbuhaler). However, more patients preferred the Nexthaler (57.6%) over the Turbuhaler (34.5%) (p = 0.006), while 7.9% stated no preference.
CONCLUSIONS: The study found no significant differences in critical error rate between the Nexthaler and Turbuhaler but the Nexthaler was preferred over the Turbuhaler. This study highlights the importance of dedicating sufficient time to instructing patients on the correct inhalation technique, which can lead to long-term retention of the inhalation technique.
We compared two inhalers on critical use errors, 4 weeks after a thorough instruction, and asked for a preference for either inhaler. No difference in error rate was observed, but the Nexthaler was preferred over the Turbuhaler.

Gepubliceerd: Expert Opin Drug Deliv. 2024;21(12):1889-96.
Impact factor: 5.4 ; Q1

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17. Instability Severity Index Score predicts recurrent shoulder instability after arthroscopic Bankart repair
van Blommestein MYH, Govaert LHM, van der Palen J, Verra WC, Koorevaar RCT, Schröder FF, Veen EJD.

PURPOSE: The Instability Severity Index (ISI) Score was developed to preoperatively assess the risk of recurrent shoulder instability after an arthroscopic Bankart repair. This study aims to validate the use of ISI Score for predicting the risk of recurrence after an arthroscopic Bankart repair in a heterogeneous population and proposes an appropriate cut-off point for treating patients with an arthroscopic Bankart repair or otherwise.
METHODS: This study analysed 99 shoulders after a traumatic dislocation that underwent arthroscopic Bankart repair with at least 3 years follow-up. Patients were divided into subcategories based on their respective ISI Score. Recurrence includes either a postoperative dislocation or perceived instability.
RESULTS: The overall recurrence rate was found to be 26.3%. A significant correlation was identified between ISI Score and the recurrence rate (odds ratio [OR]: 1.545, 95% confidence interval [CI]: 1.231-1.939, $p < 0.001$). Furthermore, ISI Score 4-6 (OR: 4.498, 95% CI: 1.866-10.842, $p < 0.001$) and ISI Score > 6 (OR: 7.076, 95% CI: 2.393-20.924, $p < 0.001$) both had a significantly higher risk of recurrence compared to ISI Score 0-3. In ISI Score subcategories 0-3, 4-6 and >6, the recurrence rate was, respectively, 15.4%, 40.7% and 71.4%.
CONCLUSION: ISI Score has predictive value in determining the recurrence risk of shoulder instability following an arthroscopic Bankart repair in a heterogeneous population. Based on the findings of this study, we recommend using arthroscopic Bankart repair in patients with ISI Score 0-3. Clinical and shared decision-making are essential in the group with ISI Score 4-6, since the recurrence rate is significantly higher than in patients with ISI Score 0-3. Arthroscopic Bankart repair is not suitable for patients with ISI Score > 6.
LEVEL OF EVIDENCE: Level III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2024;32(8):2152-60.
Impact factor: 5.0 ; Q1

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18. Routine transthoracic echocardiography in ischaemic stroke or transient ischaemic attack of undetermined cause: a prospective multicentre study
van der Maten G, Meijs MFL, Timmer JR, Brouwers P, von Birgelen C, Coutinho JM, Bouma BJ, Kerkhoff H, Helming AM, van Tuijl JH, van der Meer NA, Saxena R, Ebink C, van der Palen J, den Hertog HM.

BACKGROUND: Guidelines recommend routine transthoracic echocardiography (TTE) after ischaemic stroke or transient ischaemic attack of undetermined cause; yet, only limited scientific evidence exists. Therefore, we aimed to determine in these patients the prevalence of TTE-detected major cardiac sources of embolism (CSE), which are abnormalities leading to therapeutic changes.
METHODS: Six Dutch hospitals conducted a prospective observational study that enrolled patients with ischaemic stroke or transient ischaemic attack of undetermined cause. Patients underwent TTE after comprehensive diagnostic evaluation on stroke units, including blood chemistry, 12-lead electrocardiogram (ECG), ≥ 24 h continuous ECG monitoring, brain imaging and cervical artery imaging. Primary outcome measure was the proportion of patients with TTE-detected major CSE.
RESULTS: From March 2018 to October 2020, 1084 patients, aged 66.6 ± 12.5 years, were enrolled; 456 (42.1%) patients were female and 869 (80.2%) had ischaemic stroke. TTE detected major CSE in only 11 (1.0%) patients. Ten (90.9%) of these patients also had major ECG abnormalities (previous infarction, major repolarisation abnormalities, or previously unknown left bundle branch block) that would have warranted TTE assessment regardless of stroke evaluation. Such ECG abnormalities were

present in 11.1% of the total study population. A single patient (0.1%) showed a major CSE despite having no ECG abnormality.
CONCLUSIONS: This multicentre cross-sectional study in patients who-after workup on contemporary stroke units-were diagnosed with ischaemic stroke or transient ischaemic attack of undetermined cause found TTE-detected major CSE in only 1% of all patients. Most of these patients also had major ECG abnormalities. These findings question the value of routine TTE assessment in this clinical setting.

Gepubliceerd: Neth Heart J. 2024;32(2):91-8.
Impact factor: 2.0 ; Q3

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19. Lack of Evidence Regarding Markers Identifying Acute Heart Failure in Patients with COPD: An AI-Supported Systematic Review
van Dijk SHB, Brusse-Keizer MGJ, Bucsán CC, Ploumen EH, van Beurden WJC, van der Palen J, Doggen CJM, Lenferink A.

BACKGROUND: Due to shared symptoms, acute heart failure (AHF) is difficult to differentiate from an acute exacerbation of COPD (AECOPD). This systematic review aimed to identify markers that can diagnose AHF underlying acute dyspnea in patients with COPD presenting at the hospital.
METHODS: All types of observational studies and clinical trials that investigated any marker's ability to diagnose AHF in acutely dyspneic COPD patients were considered eligible for inclusion. An AI tool (ASReview) supported the title and abstract screening of the articles obtained from PubMed, Scopus, Web of Science, the Cochrane Library, Embase, and CINAHL until April 2023. Full text screening was independently performed by two reviewers. Twenty percent of the data extraction was checked by a second reviewer and the risk of bias was assessed in duplicate using the QUADAS-2 tool. Markers' discriminative abilities were evaluated in terms of sensitivity, specificity, positive and negative predictive values, and the area under the curve when available.
RESULTS: The search identified 10,366 articles. After deduplication, title and abstract screening was performed on 5,386 articles, leaving 153 relevant, of which 82 could be screened full text. Ten distinct studies (reported in 16 articles) were included, of which 9 had a high risk of bias. Overall, these studies evaluated 12 distinct laboratory and 7 non-laboratory markers. BNP, NT-proBNP, MR-proANP, and inspiratory inferior vena cava diameter showed the highest diagnostic discrimination.
CONCLUSION: There is not much evidence for the use of markers to diagnose AHF in acutely dyspneic COPD patients in the hospital setting. BNPs seem most promising, but should be interpreted alongside imaging and clinical signs, as this may lead to improved diagnostic accuracy. Future validation studies are urgently needed before any AHF marker can be incorporated into treatment decision-making algorithms for patients with COPD.
PROTOCOL REGISTRATION: CRD42022283952.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2024;19:531-41.
Impact factor 3.1 ; Q2

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20. Feasibility study of the Digital Patient Benefit Assessment Scale (P-BAS): A Digital Tool to Assess Individual Patient Goals
van Erp RAL, de Rooij SE, Wymenga ANM, Zeegers A, van der Palen J.

The study objective was to assess the feasibility of the Patient Benefit Assessment Scale (P-BAS), a digital tool designed to enable older outpatients (≥70 years) to elucidate at home their individual goals regarding their current medical issue. Several digital tools are developed to assist older people

in identifying their goals, thereby facilitating the process of shared decision making. However, studies on the feasibility of these digital tools, especially in older patients, are limited. Data were collected from 36 older patients. The study comprised three stages. In stage I and II, cognitive interviews were conducted to strengthen the feasibility of the P-BAS. In stage III, 80% of the patients completed the P-BAS independently at home. The cognitive interviews provided insight into patients' interpretation and individual understanding of the digital visual P-BAS and associated opportunities for improvement, which were subsequently implemented. One conclusion is that the digital visual P-BAS might be of added value for patients and contributes to the process of shared decision making, assuring that the goals of the patient will be into account in treatment options. Findings are useful for researchers interested in technological tools that contribute to shared decision making.

Gepubliceerd: Gerontol Geriatr Med. 2024;10:23337214241230159.
Impact factor: 1.8 ; Q4

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21. 'Effects of a home-based bimodal lifestyle intervention in frail patients with end-stage liver disease awaiting orthotopic liver transplantation': study protocol of a non-randomised clinical trial
Wijma AG, Bongers BC, Annema C, Dekker R, Blokzijl H, van der Palen JAM, De Meijer VE, Cuperus FJ, Klaase JM.

INTRODUCTION: Patients with end-stage liver disease awaiting orthotopic liver transplantation (OLT) are generally classified as frail due to disease-related malnutrition and a progressive decline in musculoskeletal and aerobic fitness, which is associated with poor pre-OLT, peri-OLT and post-OLT outcomes. However, frailty in these patients may be reversable with adequate exercise and nutritional interventions.
METHODS AND ANALYSIS: Non-randomised clinical trial evaluating the effect of a home-based bimodal lifestyle programme in unfit patients with a preoperative oxygen uptake (VO(2)) at the ventilatory anaerobic threshold ≤13 mL/kg/min and/or VO(2) at peak exercise ≤18 mL/kg/min listed for OLT at the University Medical Center Groningen (UMCG). The programme is patient tailored and comprises high-intensity interval and endurance training, and functional exercises three times per week, combined with nutritional support. Patients will go through two training periods, each lasting 6 weeks.The primary outcome of this study is the impact of the programme on patients' aerobic fitness after the first study period. Secondary outcomes include aerobic capacity after the second study period, changes in sarcopenia, anthropometry, functional mobility, perceived quality of life and fatigue, incidence of hepatic encephalopathy and microbiome composition. Moreover, number and reasons of intercurrent hospitalisations during the study and postoperative outcomes up to 12 months post OLT will be recorded. Finally, feasibility of the programme will be assessed by monitoring the participation rate and reasons for non-participation, number and severity of adverse events, and dropout rate and reasons for dropout.
ETHICS AND DISSEMINATION: This study was approved by the Medical Research Ethics Committee of the UMCG (registration number NL83612.042.23, August 2023) and is registered in the Clinicaltrials.gov register (NCT05853484). Good Clinical Practice guidelines and the principles of the Declaration of Helsinki will be applied. Results of this study will be submitted for presentation at (inter)national congresses and publication in peer-reviewed journals.
TRIAL REGISTRATION NUMBER: NCT05853484.

Gepubliceerd: BMJ Open. 2024;14(1):e080430.
Impact factor: 2.3 ; Q2

Totale impact factor: 124.1
Gemiddelde impact factor: 5.9

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 59.9
Gemiddelde impact factor: 6.7

Gynaecologie

1. Cost-effectiveness of pessary therapy versus surgery for symptomatic pelvic organ prolapse: an economic evaluation alongside a randomised non-inferiority controlled trial
Ben Â J, van der Vaart LR, J EB, Roovers JWR, Lagro-Janssen ALM, van der Vaart CH, Vollebregt A, PEOPLE group; Massop-Helmink DS.

OBJECTIVE: To evaluate the cost-effectiveness of pessary therapy as an initial treatment option compared with surgery for moderate to severe pelvic organ prolapse (POP) symptoms in secondary care from a healthcare and a societal perspective. DESIGN: Economic evaluation alongside a multicentre randomised controlled non-inferiority trial with a 24-month follow-up.
SETTING: 21 hospitals in the Netherlands, recruitment conducted between 2015 and 2022.
PARTICIPANTS: 1605 women referred to secondary care with symptomatic prolapse stage ≥2 were requested to participate. Of them, 440 women gave informed consent and were randomised to pessary therapy (n=218) or to surgery (n=222) in a 1:1 ratio stratified by hospital.
INTERVENTIONS: Pessary therapy and surgery.
PRIMARY AND SECONDARY OUTCOME MEASURES: The Patient Global Impression of Improvement (PGI-I), a 7-point scale dichotomised into successful versus unsuccessful, with a non-inferiority margin of -10%; quality-adjusted life-years (QALYs) measured by the EQ-5D-3L; healthcare and societal costs were based on medical records and the institute for Medical Technology Assessment questionnaires. RESULTS: For the PGI-I, the mean difference between pessary therapy and surgery was -0.05 (95% CI -0.14; 0.03) and -0.03 (95% CI -0.07; 0.002) for QALYs. In total, 54.1% women randomised to pessary therapy crossed over to surgery, and 3.6% underwent recurrent surgery. Healthcare and societal costs were significantly lower in the pessary therapy (mean difference=-€1807, 95% CI -€2172; -€1446 and mean difference=-€1850, 95% CI -€2349; -€1341, respectively). The probability that pessary therapy is cost-effective compared with surgery was 1 at willingness-to-pay thresholds between €0 and €20 000/QALY gained from both perspectives.
CONCLUSIONS: Non-inferiority of pessary therapy regarding the PGI-I could not be shown and no statistically significant differences in QALYs between interventions were found. Due to significantly lower costs, pessary therapy is likely to be cost-effective compared with surgery as an initial treatment option for women with symptomatic POP treated in secondary care.
TRIAL REGISTRATION NUMBER: NTR4883.

Gepubliceerd: BMJ Open. 2024;14(5):e075016.
Impact factor: 2.3 ; Q2

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2. Management of an acute intracranial emergency in pregnancy
Brokkelkamp P, Baalman JH, Driesse MJ, Kho KH.

We report a case of a mid-20s primigravida at 37 weeks' gestation who presented with severe headache and acute neurological deterioration. The CT brain scan showed hydrocephalus caused by a colloid cyst in the third ventricle. The patient underwent emergency placement of an external ventricular drain for decompression of acute hydrocephalus. Four hours later, labour commenced spontaneously, and in view of her neurological status, a decision was taken to perform a caesarean section under general anaesthetics. Four days postpartum, the patient underwent an endoscopic removal of the cyst. Intracranial emergencies during pregnancy are rare and challenging to manage. The mortality rate can be significant. Diagnostic and surgical intervention should not be delayed because of pregnancy. An individualised treatment approach is required with multidisciplinary input. The collaborative efforts of our multidisciplinary team resulted in prompt diagnosis and surgical treatment in this case that resulted in both a healthy mother and child.

Gepubliceerd: BMJ Case Rep. 2024;17(3).
Impact factor: 0.5 ; Q3

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3. The web-based Pleasure&Pregnancy programme in the treatment of unexplained infertility: a randomized controlled trial

Dreischor F, Dancet EAF, Lambalk CB, van Lunsen HW, Besselink D, van Disseldorp J, Boxmeer J, Brinkhuis EA, Cohlen BJ, Hoek A, de Hundt M, Janssen CAH, Lambers M, Maas J, Nap A, Perquin D, Verberg M, Verhoeve HR, Visser J, van der Voet L, Mochtar MH, Goddijn M, Laan E, van Wely M, Custers IM.

STUDY QUESTION: Does offering the Pleasure&Pregnancy (P&P) programme rather than expectant management improve naturally conceived ongoing pregnancy rates in couples diagnosed with unexplained infertility?
SUMMARY ANSWER: The P&P programme had no effect on the ongoing pregnancy rates of couples with unexplained infertility.
WHAT IS KNOWN ALREADY: Underpowered studies suggested that face-to-face interventions targeting sexual health may increase pregnancy rates. The impact of an eHealth sexual health programme had yet to be evaluated by a large randomized controlled trial.
STUDY DESIGN, SIZE, DURATION: This is a nationwide multi-centre, unblinded, randomized controlled superiority trial (web-based randomization programme, 1:1 allocation ratio). This RCT intended to recruit 1164 couples within 3 years but was put on hold after having included 700 couples over 5 years (2016-2021). The web-based P&P programme contains psychosexual information and couple communication, mindfulness and sensate focus exercises aiming to help maintain or improve sexual health, mainly pleasure, and hence increase pregnancy rates. The P&P programme additionally offers information on the biology of conception and enables couples to interact online with peers and via email with coaches.
PARTICIPANTS/MATERIALS, SETTING, METHODS: Heterosexual couples with unexplained infertility and a Hunault-prognosis of at least 30% chance of naturally conceiving a live-born child within 12 months were included, after their diagnostic work-up in 41 Dutch secondary and tertiary fertility centres. The primary outcome was an ongoing pregnancy, defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed by an ultrasound scan, conceived naturally within 6 months after randomization. Secondary outcomes were time to pregnancy, live birth, sexual health, and personal and relational well-being at baseline and after 3 and 6 months. The primary analyses were according to intention-to-treat principles. We calculated relative risks (RRs, pregnancy rates) and a risk difference (RD, pregnancy rates), Kaplan-Meier survival curves (live birth over time), and time, group, and interactive effects with mixed models analyses (sexual health and well-being). MAIN **RESULTS AND THE ROLE OF CHANCE**: Totals of 352 (one withdrawal) and 348 (three withdrawals) couples were allocated to, respectively the P&P group and the expectant management group. Web-based tracking of the intervention group showed a high attrition rate (57% of couples) and limited engagement (i.e. median of 16 visits and 33 min total visitation time per couple). Intention-to-treat analyses showed that 19.4% (n = 68/351) of the P&P group and 22.6% (n = 78/345) of the expectant management group achieved a naturally conceived ongoing pregnancy (RR = 0.86; 95% CI = 0.64-1.15, RD = -3.24%; 95% CI -9.28 to 2.81). The time to pregnancy did not differ between the groups (Log rank = 0.23). Live birth occurred in 18.8% (n = 66/351) of the couples of the P&P group and 22.3% (n = 77/345) of the couples of the expectant management group (RR = 0.84; 95% CI = 0.63-1.1). Intercourse frequency decreased equally over time in both groups. Sexual pleasure, orgasm, and satisfaction of women of the P&P group improved while these outcomes remained stable in the expectant management group. Male orgasm, intercourse satisfaction, and overall satisfaction decreased over time with no differences between groups. The intervention did not affect personal and relational well-being. Non-compliance by prematurely starting medically assisted reproduction,

and clinical loss to follow-up were, respectively, 15.1% and 1.4% for the complete study population. Per protocol analysis for the primary outcome did not indicate a difference between the groups. Comparing the most engaged users with the expectant management group added that coital frequency decreased less, and that male sexual desire improved in the intervention group.
LIMITATIONS, REASONS FOR CAUTION: The intended sample size of 1164 was not reached because of a slow recruitment rate. The achieved sample size was, however, large enough to exclude an improvement of more than 8% of the P&P programme on our primary outcome. WIDER IMPLICATIONS OF THE FINDINGS: The P&P programme should not be offered to increase natural pregnancy rates but may be considered to improve sexual health. The attrition from and limited engagement with the P&P programme is in line with research on other eHealth programmes and underlines the importance of a user experience study.
STUDY FUNDING/COMPETING INTEREST(S): Funded by The Netherlands Organisation for Health Research and Development (ZonMw, reference: 843001605) and Flanders Research Foundation. C.B.L. is editor-in-chief of Human Reproduction. H.W.L. received royalties or licences from Prometheus Publishers Springer Media Thieme Verlag. J.B. received support from MercK for attending the ESHRE course 'The ESHRE guideline on ovarian stimulation, do we have agreement?' J.v.D. reports consulting fees and lecture payments from Ferring, not related to the presented work, and support for attending ESHRE from Goodlife and for attending NFI Riga from Merck. A.H. reports consulting fees by Ferring Pharmaceutical company, The Netherlands, paid to institution UMCG, not related to the presented work. H.V. reports consulting fees from Ferring Pharmaceutical company, The Netherlands, and he is a member of the ESHRE guideline development group unexplained infertility and Chair of the Dutch guideline on unexplained infertility (unpaid). M.G. declares unrestricted research and educational grants from Ferring not related to the presented work, paid to their institution VU Medical Centre. The other authors have no conflicts to declare. TRIAL
REGISTRATION NUMBER: NTR5709.
TRIAL REGISTRATION DATE: 4 February 2016.
DATE OF FIRST PATIENT'S ENROLMENT: 27 June 2016.

Gepubliceerd: Hum Reprod. 2024;39(12):2711-21.
Impact factor: 6.1 ; Q1

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4. Outcomes of endometrial cancer prevention strategies in patients with Lynch syndrome: a nationwide cohort study in the Netherlands
Eikenboom EL, van Leeuwen L, Groenendijk F, Woolderink JM, Van Altena AM, Van Leerdam ME, Spaander MCW, van Doorn HC, Wagner A, Collaborative investigators from the Dutch Foundation for Detection of Hereditary Tumors; Koopmans CM.

BACKGROUND: Female Lynch syndrome carriers have an increased risk of developing endometrial cancer. Regardless, research on endometrial carcinoma tumorigenesis is scarce and no uniform, evidence-based gynaecological management guidelines exist. We therefore described gynaecological surveillance and surgery outcomes in a nation-wide Lynch syndrome cohort.
METHODS: For this retrospective cohort study, female Lynch syndrome carriers, prospectively registered in the Dutch Lynch syndrome database (StOET), were included up to February 28th 2022. Carriers were linked to the Dutch national pathology (PALGA) database. The number of carriers with/without gynaecological surveillance, number of index carriers with endometrial carcinoma before Lynch syndrome diagnosis were assessed, as well as uptake of risk-reducing surgery and characteristics of endometrial carcinomas including the requisite for adjuvant therapy according to current guidelines. Overall survival after endometrial carcinoma diagnosis was analyzed using Kaplan Meier time to event analyses, cumulative incidence was calculated after adjusting for competing risks (death and prophylactic hysterectomy).

FINDINGS: In total, 1046 registered female Lynch syndrome carriers were eligible for surveillance, of whom 313 (30.0%) did not have surveillance and 21.4% (n = 224 of 1046) opted for prophylactic hysterectomy. In carriers with surveillance, more cases of endometrial carcinoma and hyperplasia were found than in those without (37 endometrial carcinomas (7.3%) and 28 hyperplasias (5.5%) in 506 carriers with surveillance versus 14 (2.6%) and 4 (0.7%) in 540 carriers without surveillance, respectively); carriers with surveillance were generally younger than those without (median 56 years [IQR 48-65] versus median 65 years [IQR 49-75] at database assembly, respectively; $p < 0.0001$). Endometrial carcinomas were predominantly of endometrioid type and FIGO stage IA, regardless of surveillance. Adjuvant external beam radiotherapy was required in one patient in both groups. Overall survival after endometrial carcinoma diagnosis did not differ between carriers with or without surveillance or carriers with endometrial carcinoma before LS diagnosis ($p = 0.51$). For all endometrial carcinomas together, including index carriers, cumulative incidence was 22.7% at age 70.
INTERPRETATION: In a nation-wide cohort of Lynch syndrome carriers, nearly one-third of eligible carriers did not undergo gynaecological surveillance. Endometrial carcinomas diagnosed during surveillance were slightly more often stage FIGO IA, but this did not seem to substantially decrease the requisite for adjuvant therapy or affect overall survival, questioning effectiveness of current gynaecological management. Prospective research should further assess this, as well as patient preferences.
FUNDING: None.

Gepubliceerd: EClinicalMedicine. 2024;79:103006.
Impact factor: 10.0 ; Q1

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5. Anxiety, depression, and body image among infertile women with and without polycystic ovary syndrome
Jannink T, Bordewijk EM, Aalberts J, Hendriks J, Lehmann V, Hoek A, Goddijn M, van Wely M, ANDES study group; Verberg M.

STUDY QUESTION: In women undergoing fertility treatment, do those with polycystic ovary syndrome (PCOS) have a higher prevalence of symptoms of anxiety and depression and lower body appreciation than women without PCOS?
SUMMARY ANSWER: Having PCOS was not associated with symptoms of anxiety and depression but was associated with somewhat lower body appreciation.
WHAT IS KNOWN ALREADY: PCOS has been associated with a higher chance to develop mental health problems, like anxiety, and body image concerns. The International Guidelines on PCOS recommend that all women with PCOS should routinely be screened for anxiety and depressive disorders. In most studies in this field, the comparison group included healthy women without fertility problems.
STUDY DESIGN, SIZE, DURATION: We conducted a cross-sectional survey study between May 2021 and July 2023, using an online questionnaire. We informed women about this study at fertility clinics in the Netherlands through posters and leaflets and on the websites of the Dutch patient organizations Freya and Stichting PCOS.
PARTICIPANTS/MATERIALS, SETTING, METHODS: This study included women with infertility, with and without PCOS, who were undergoing fertility treatment. Women completed two assessment tools: the Hospital Anxiety and Depression Scale (HADS) and the Body Appreciation Scale-2 (BAS-2). Primary outcomes were clinically relevant symptoms of anxiety (score ≥ 11) and depression (score ≥ 11), and BAS-2 scores. Secondary outcomes were mean anxiety and depression scores and anxiety and depression scores of 8 and higher. Dichotomous outcomes and continuous outcomes were analysed using logistic and linear regression analyses adjusted for age, BMI, and duration of infertility.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 1025 women currently undergoing infertility treatment participated, of whom 502 (49.0%) had PCOS and 523 (51.0%) had other infertility diagnoses. We found self-reported clinically relevant symptoms of anxiety in 33.1% of women with PCOS and in 31.0% of women with other infertility diagnoses (adjusted OR: 0.99, 95% CI 0.74-1.31). Clinically relevant symptoms of depression were reported in 15.5% of women with PCOS versus 14.5% of women with other infertility diagnoses (adjusted OR: 1.04, 95% CI 0.71-1.50). Women with PCOS reported slightly less body appreciation (adjusted mean difference: -1.34, 95% CI -2.32 to -0.36).
LIMITATIONS, REASONS FOR CAUTION: Results are based on self-report and may have been affected by sampling bias.
WIDER IMPLICATIONS OF THE FINDINGS: Although guidelines recommend screening women with PCOS, feelings of anxiety and depression can be present in any woman undergoing fertility treatments. We advise fertility clinics to be aware of women's mental health issues and to offer support accordingly, as a part of routine care.
STUDY FUNDING/COMPETING INTEREST(S): This study did not receive specific funding. All authors report no conflict of interest related to the current research.
TRIAL REGISTRATION NUMBER: This study was pre-registered at OSF: https://osf.io/qbeav.

Gepubliceerd: Hum Reprod. 2024;39(4):784-91.
Impact factor: 6.1 ; Q1

6."Hypertension in Pregnancy Intervention Trial At Term" and "Disproportionate Intrauterine Growth Intervention Trial At Term" Studies
van Pampus MG, van der Post JAM, Verhoeven CJ, Koopmans CM, Langenveld J, Broekhuijsen K, de Sonnaville CMW, van der Tuuk K, Boers K, Groen H, Vijgen S, Bijlenga D, Scherjon S, Mol BW.

In 2003, in the context of a national research funding program in which obstetric research was prioritized, several perinatal centers took the initiative to jointly submit a number of applications to the subsidy programs of Effectiveness Research and Prevention of ZonMw. This has led to the funding of the Obstetric Consortium with several projects, including the "Hypertension in Pregnancy Intervention Trial At Term" and the "Disproportionate Intrauterine Growth Intervention Trial At Term" studies. The studies showed that induction of labor for hypertension and growth restriction at term was the appropriate management. Subsequent implementation improved maternal and perinatal outcomes.

Gepubliceerd: Clin Obstet Gynecol. 2024;67(2):418-25.
Impact factor: 1.4 ; Q3

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7. Unplanned cesarean sections in advanced maternal age: A predictive model
Veenstra J, Cohen Z, Korteweg FJ, van der Ham DP, Kuppens SM, Kroese JA, Hermsen BB, Kamphuis MM, Vanhommerig JW, van Pampus MG.

INTRODUCTION: As maternal age during pregnancy is rising all over the world, there is a growing need for prognostic factors that determine maternal and perinatal outcomes in older women.
MATERIAL AND METHODS: This study is a retrospective cohort study of women aged 40 years or older at the time of delivery in four Santeon hospitals across the Netherlands between January 2016 and December 2019. Outcomes were compared between women of 40-44 years (advanced maternal age) and 45 years and older (very advanced maternal age). Primary outcome was unplanned cesarean section, secondary outcomes included postpartum hemorrhage and neonatal outcomes. Multivariate

regression analysis was performed to analyze predictive factors for unplanned cesarean sections in women who attempted vaginal delivery. Subsequently, a predictive model and risk scores were constructed to predict unplanned cesarean section.
RESULTS: A cohort of 1660 women was analyzed; mean maternal age was 41.4 years, 4.8% of the women were 45 years and older. In both groups, more than half of the women had not delivered vaginally before. Unplanned cesarean sections were performed in 21.1% of the deliveries in advanced maternal age and in 29.1% in very advanced maternal age. Four predictive factors were significantly correlated with unplanned cesarean sections: higher body mass index (BMI), no previous vaginal delivery, spontaneous start of delivery and number of days needed for cervical priming. A predictive model was constructed from these factors with an area under the curve of 0.75 (95% confidence interval 0.72-0.78). A sensitivity analysis in nulliparous women proved that BMI, days of cervical priming, age, and gestational age were risk factors, whereas spontaneous start of delivery and induction were protective factors. There was one occurrence of neonatal death.
CONCLUSIONS: Women of advanced maternal age and those of very advanced maternal age have a higher chance of having an unplanned cesarean section compared to the general obstetric population in the Netherlands. Unplanned cesarean sections can be predicted through use of our predictive model. Risk increases with higher BMI, no previous vaginal delivery, and increasing number of days needed for cervical priming, whereas spontaneous start of labor lowers the risk. In nulliparous women, age and gestational age also increase risk, but induction lowers the risk of having an unplanned cesarean section.

Gepubliceerd: Acta Obstet Gynecol Scand. 2024;103(5):927-37.
Impact factor: 3.1 ; Q1

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8. Immunisatie tegen glycoproteïne IV (CD36) met de vraag naar compatibele trombocytenconcentraten: drie casussen
Vriend LEM, Vicente-Steijn R, van den Berg YW, Akkermans J, Canté CM, Slomp J, Tang MW, Visser O, Gerrits A, Verweij EJT, Zwaginga JJ, de Haas M, Porcelijn L.

Allo-antistoffen tegen glycoproteïne IV (GPIV) zijn zeldzaam, maar kunnen worden gevormd door GPIV-deficiënte personen na een zwangerschap of transfusie. Deze antistoffen kunnen leiden tot ernstige complicaties bij de neonaat/pasgeborene en bij transfusie-afhankelijke GPIV-deficiënte patiënten. Dit artikel beschrijft drie recente casussen waarbij GPIV-antistoffen werden gevonden en de behoefte ontstond voor GPIV-gematchte bloedproducten. Het brengt de uitdagingen aan het licht rondom de transfusieondersteuning van GPIV-deficiënte patiënten en daarmee de noodzaak voor een bestand met GPIV-deficiënte donoren in Nederland.

Gepubliceerd: Ned Tijdschr Hematol. 2024;21:391-6.
IF onbekend

Totale impact factor: 29.5
Gemiddelde impact factor: 3.7

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 0.5
Gemiddelde impact factor: 0.5

Heelkunde

1. ICG-Fluorescence Imaging for Margin Assessment During Minimally Invasive Colorectal Liver Metastasis Resection

Achterberg FB, Bijlstra OD, Slooter MD, Sibinga Mulder BG, Boonstra MC, Bouwense SA, Bosscha K, Coolsen MME, Derksen WJM, Gerhards MF, Gobardhan PD, Hagendoorn J, Lips D, Marsman HA, Zonderhuis BM, Wullaert L, Putter H, Burggraaf J, Mieog JSD, Vahrmeijer AL, Swijnenburg RJ.

IMPORTANCE: Unintended tumor-positive resection margins occur frequently during minimally invasive surgery for colorectal liver metastases and potentially negatively influence oncologic outcomes.
OBJECTIVE: To assess whether indocyanine green (ICG)-fluorescence-guided surgery is associated with achieving a higher radical resection rate in minimally invasive colorectal liver metastasis surgery and to assess the accuracy of ICG fluorescence for predicting the resection margin status.
DESIGN, SETTING, AND PARTICIPANTS: The MIMIC (Minimally Invasive, Indocyanine-Guided Metastasectomy in Patients With Colorectal Liver Metastases) trial was designed as a prospective single-arm multicenter cohort study in 8 Dutch liver surgery centers. Patients were scheduled to undergo minimally invasive (laparoscopic or robot-assisted) resections of colorectal liver metastases between September 1, 2018, and June 30, 2021.
EXPOSURES: All patients received a single intravenous bolus of 10 mg of ICG 24 hours prior to surgery. During surgery, ICG-fluorescence imaging was used as an adjunct to ultrasonography and regular laparoscopy to guide and assess the resection margin in real time. The ICG-fluorescence imaging was performed during and after liver parenchymal transection to enable real-time assessment of the tumor margin. Absence of ICG fluorescence was favorable both during transection and in the tumor bed directly after resection.
MAIN OUTCOMES AND MEASURES: The primary outcome measure was the radical (R0) resection rate, defined by the percentage of colorectal liver metastases resected with at least a 1 mm distance between the tumor and resection plane. Secondary outcomes were the accuracy of ICG fluorescence in detecting margin-positive (R1; <1 mm margin) resections and the change in surgical management.
RESULTS: In total, 225 patients were enrolled, of whom 201 (116 [57.7%] male; median age, 65 [IQR, 57-72] years) with 316 histologically proven colorectal liver metastases were included in the final analysis. The overall R0 resection rate was 92.4%. Re-resection of ICG-fluorescent tissue in the resection cavity was associated with a 5.0% increase in the R0 percentage (from 87.4% to 92.4%; P < .001). The sensitivity and specificity for real-time resection margin assessment were 60% and 90%, respectively (area under the receiver operating characteristic curve, 0.751; 95% CI, 0.668-0.833), with a positive predictive value of 54% and a negative predictive value of 92%. After training and proctoring of the first procedures, participating centers that were new to the technique had a comparable false-positive rate for predicting R1 resections during the first 10 procedures (odds ratio, 1.36; 95% CI, 0.44-4.24). The ICG-fluorescence imaging was associated with changes in intraoperative surgical management in 56 (27.9%) of the patients.
CONCLUSIONS AND RELEVANCE: In this multicenter prospective cohort study, ICG-fluorescence imaging was associated with an increased rate of tumor margin-negative resection and changes in surgical management in more than one-quarter of the patients. The absence of ICG fluorescence during liver parenchymal transection predicted an R0 resection with 92% accuracy. These results suggest that use of ICG fluorescence may provide real-time feedback of the tumor margin and a higher rate of complete oncologic resection.

Gepubliceerd: JAMA Netw Open. 2024;7(4):e246548.
Impact factor: 9.7 ; Q1

2. International Lower Limb Collaborative Paediatric subpopulation analysis (INTELLECT-P) study: multicentre, international, retrospective audit of paediatric open fractures
Allan AY, Berner JE, Chan JK, Gardiner MD, Nanchahal J, Jain A, INTELLECT collaborative; de Groot R.

Gepubliceerd: BJS Open. 2024;8(4).
Impact factor: 4.5 ; Q1

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3. What Is the Patient-reported Outcome and Complication Incidence After Operative Versus Nonoperative Treatment of Minimally Displaced Tibial Plateau Fractures?
Assink N, Vaartjes TP, Kramer C, Bosma E, Nijveldt RJ, Ten Brinke JG, de Groot R, Hoekstra H, FFA IJ.

BACKGROUND: Much controversy remains about whether minimally displaced tibial plateau fractures should be treated operatively or nonoperatively. It is generally accepted that gaps and stepoffs up to 2 mm can be tolerated, but this assumption is based on older studies using plain radiographs instead of CT to assess the degree of initial fracture displacement. Knowledge regarding the relationship between the degree of fracture displacement and expected functional outcome is crucial for patient counseling and shared decision-making, specifically in terms of whether to perform surgery.
QUESTIONS/PURPOSES: (1) Is operative treatment associated with improved patient-reported outcomes compared with nonoperative treatment in minimally displaced tibial plateau fractures (fractures with up to 4 mm of displacement)? (2) What is the difference in the risk of complications after operative versus nonoperative treatment in minimally displaced tibial plateau fractures?
METHODS: A multicenter, cross-sectional study was performed in patients treated for tibial plateau fractures between 2003 and 2019 at six hospitals. Between January 2003 and December 2019, a total of 2241 patients were treated for tibial plateau fractures at six different trauma centers. During that time, the general indication for open reduction and internal fixation (ORIF) was intra-articular displacement of > 2 mm. Patients treated with ORIF and those treated nonoperatively were potentially eligible; 0.2% (4) were excluded because they were treated with amputation because of severe soft tissue damage, whereas 4% (89) were excluded because of coexisting conditions that complicated outcome measurement including Parkinson disease, cerebrovascular accident, or paralysis (conditions causing an inability to walk). A further 2.7% (60) were excluded because their address was unknown, and 1.4% (31) were excluded because they spoke a language other than Dutch. Based on that, 1328 patients were potentially eligible for analysis in the operative group and 729 were potentially eligible in the nonoperative group. At least 1 year after injury, all patients were approached and asked to complete the Knee injury and Osteoarthritis Outcome Scale (KOOS) questionnaire. A total of 813 operatively treated patients (response percentage: 61%) and 345 nonoperatively treated patients (response percentage: 47%) responded to the questionnaire. Patient characteristics including age, gender, BMI, smoking, and diabetes were retrieved from electronic patient records, and imaging data were shared with the initiating center. Displacement (gap and stepoff) was measured for all participating patients, and all patients with minimally displaced fractures (gap or stepoff ≤ 4 mm) were included, leaving 195 and 300 in the operative and nonoperative groups, respectively, for analysis here. Multivariate linear regression was performed to assess the association of treatment choice (nonoperative or operative) with patient-reported outcomes in minimally displaced fractures. In the multivariate analysis, we accounted for nine potential confounders (age, gender, BMI, smoking, diabetes, gap, stepoff, AO/OTA classification, and number of involved segments). In addition, differences in complications after operative and nonoperative treatment were assessed. The minimum clinically important differences for the five subscales of the KOOS are 11 for symptoms, 17 for pain, 18 for activities of daily living, 13 for sports, and 16 for quality of life.
RESULTS: After controlling for potentially confounding variables such as age, gender, BMI, and AO/OTA classification, we found that operative treatment was not associated with an improvement in patient-reported outcomes. Operative treatment resulted in poorer KOOS in terms of pain (-4.7

points; p = 0.03), sports (-7.6 points; p = 0.04), and quality of life (-7.8 points; p = 0.01) compared with nonoperative treatment, but those differences were small enough that they were likely not clinically important. Patients treated operatively had more complications (4% [7 of 195] versus 0% [0 of 300]; p = 0.01) and reoperations (39% [76 of 195] versus 6% [18 of 300]; p < 0.001) than patients treated nonoperatively. After operative treatment, most reoperations (36% [70 of 195]) consisted of elective removal of osteosynthesis material.
CONCLUSION: No differences in patient-reported outcomes were observed at midterm follow-up between patients treated surgically and those treated nonsurgically for tibial plateau fractures with displacement up to 4 mm. Therefore, nonoperative treatment should be the preferred treatment option in minimally displaced fractures. Patients who opt for nonoperative treatment should be told that complications are rare, and only 6% of patients might undergo surgery by midterm follow-up. Patients who opt for surgery of a minimally displaced tibial plateau fracture should be told that complications may occur in up to 4% of patients, and 39% of patients may undergo a secondary intervention (most of which are elective implant removal). LEVEL OF EVIDENCE: Level III, therapeutic study.

Gepubliceerd: Clin Orthop Relat Res. 2024;482(10):1744-52.
Impact factor: 4.4 ; Q1

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4. Development and external evaluation of a self-learning auto-segmentation model for Colorectal Cancer Liver Metastases Assessment (COALA)
Bereska JI, Zeeuw M, Wagenaar L, Jenssen HB, Wesdorp NJ, van der Meulen D, Bereska LF, Gavves E, Janssen BV, Besselink MG, Marquering HA, van Waesberghe JTM, Aghayan DL, Pelanis E, van den Bergh J, Nota IIM, Moos S, Kemmerich G, Syversveen T, Kolrud FK, Huiskens J, Swijnenburg RJ, Punt CJA, Stoker J, Edwin B, Fretland Å A, Kazemier G, Verpalen IM, Pancreatobiliary and Hepatic Artificial Intelligence Research (PHAIR) consortium and Dutch Colorectal Cancer Group Liver Expert Panel; Liem MSL.

OBJECTIVES: Total tumor volume (TTV) is associated with overall and recurrence-free survival in patients with colorectal cancer liver metastases (CRLM). However, the labor-intensive nature of such manual assessments has hampered the clinical adoption of TTV as an imaging biomarker. This study aimed to develop and externally evaluate a CRLM auto-segmentation model on CT scans, to facilitate the clinical adoption of TTV.
METHODS: We developed an auto-segmentation model to segment CRLM using 783 contrast-enhanced portal venous phase CTs (CT-PVP) of 373 patients. We used a self-learning setup whereby we first trained a teacher model on 99 manually segmented CT-PVPs from three radiologists. The teacher model was then used to segment CRLM in the remaining 663 CT-PVPs for training the student model. We used the DICE score and the intraclass correlation coefficient (ICC) to compare the student model's segmentations and the TTV obtained from these segmentations to those obtained from the merged segmentations. We evaluated the student model in an external test set of 50 CT-PVPs from 35 patients from the Oslo University Hospital and an internal test set of 21 CT-PVPs from 10 patients from the Amsterdam University Medical Centers.
RESULTS: The model reached a mean DICE score of 0.85 (IQR: 0.05) and 0.83 (IQR: 0.10) on the internal and external test sets, respectively. The ICC between the segmented volumes from the student model and from the merged segmentations was 0.97 on both test sets.
CONCLUSION: The developed colorectal cancer liver metastases auto-segmentation model achieved a high DICE score and near-perfect agreement for assessing TTV.
CRITICAL RELEVANCE STATEMENT: AI model segments colorectal liver metastases on CT with high performance on two test sets. Accurate segmentation of colorectal liver metastases could facilitate the clinical adoption of total tumor volume as an imaging biomarker for prognosis and treatment response monitoring. KEY POINTS: Developed colorectal liver metastases segmentation model to

facilitate total tumor volume assessment. Model achieved high performance on internal and external test sets. Model can improve prognostic stratification and treatment planning for colorectal liver metastases.

Gepubliceerd: Insights Imaging. 2024;15(1):279.
Impact factor: 4.5 ; Q1

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5. The Diagnostic Value of Biomarkers in Acute Mesenteric Ischaemia Is Insufficiently Substantiated: A Systematic Review
Blauw JTM, Metz FM, Nuzzo A, van Etten-Jamaludin FS, Brusse-Keiser M, Boermeester MA, Peppelenbosch M, Geelkerken RH.

OBJECTIVE: There is an urgent need for accurate biomarkers to support timely diagnosis of acute mesenteric ischaemia (AMI) and thereby improve clinical outcomes. With this systematic review, the aim was to substantiate the potential diagnostic value of biomarkers for arterial occlusive AMI.
DATA SOURCES: The Pubmed, Embase, and the Cochrane Library electronic databases were searched.
REVIEW METHODS: A systematic review of the literature has been conducted to define the potential diagnostic value of biomarkers for arterial occlusive AMI. All studies including ≥ 10 patients describing biomarkers for macrovascular occlusive AMI between 1950 and 17 February 2023 were identified within the Pubmed, Embase, and the Cochrane Library electronic databases. There were no restrictions to any particular study design, but letters and editorials were excluded. The QUADAS-2 tool was used for the critical appraisal of quality. The study protocol was registered on Prospero (CRD42021254970).
RESULTS: Fifty of 4334 studies were eligible for inclusion in this review. Ninety per cent of studies were of low quality. A total of 60 biomarkers were identified, with 24 in two or more studies and 15 in five or more studies. There was variation in reported units, normal range, and cut off values. Meta-analysis was not possible due to study heterogeneity. Biomarkers currently recommended by the European Journal of Vascular and Endovascular Surgery, European Society for Trauma and Emergency Surgery 2016, and World Society of Emergency Surgery 2017 guidelines also had heterogeneous low quality data for use in the diagnosis of AMI.
CONCLUSION: This systematic review demonstrates high heterogeneity and low quality of the available evidence on biomarkers for arterial occlusive AMI. No clinical conclusions can be drawn on a biomarker or combination of biomarkers for patients suspected of arterial occlusive AMI. Restraint is advised when rejecting or determining AMI solely based on biomarkers.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2024;67(4):554-69.
Impact factor: 6.8 ; Q1

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6. The value of splenectomy during left-sided pancreatectomy for pancreatic ductal adenocarcinoma: predefined subanalysis in the DIPLOMA randomized trial
Bruna CL, van Hilst J, Esposito A, Kleive D, Falconi M, Primrose JN, Korrel M, Bianchi D, Zerbi A, Kokkola A, Butturini G, Björnsson B, Morone M, Casadei R, Marudanayagam R, Besselink MG, Abu Hilal M, European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS); Lips DJ.

Gepubliceerd: Br J Surg. 2024;111(9).
Impact factor: 8.7 ; Q1

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7. Unraveling factors associated with textbook outcome after cholecystectomy in patients with uncomplicated cholecystolithiasis: A posthoc analysis of individual data of 1,124 patients
Comes DJ, Thunnissen FM, Latenstein CSS, Stommel MWJ, van Laarhoven C, Drenth JPH, Atsma F, Lantinga MA, de Reuver PR, Dutch Gallbladder Research Group; Steenvoorde P.

BACKGROUND: A textbook outcome for the management of uncomplicated cholecystolithiasis is the targeted clinical scenario and is characterized by no recurrent biliary colic, absence of surgical and biliary complications, and absence or relief of abdominal pain. The aim of this study was to assess the incidence of textbook outcomes after cholecystectomy and identify associated baseline factors.
METHODS: Patients from 2 Dutch multicenter prospective trials between 2014 and 2019 (SECURE and SUCCESS trial) were included. The primary outcome was the proportion of patients with textbook outcomes after cholecystectomy at 6-month follow-up. Regression analysis was used to identify which factors before surgery were associated with textbook outcomes.
RESULTS: A total of 1,124 patients underwent cholecystectomy. A textbook outcome at 6-month follow-up was reached in 67.9% of patients. Persistent abdominal pain was the main reason for the failure to achieve textbook outcome. Patients who did achieve textbook outcomes more often reported severe pain attacks (89.4% vs 81.7%, P < .001) and/or biliary colic (78.6% vs 68.4%, P < .001) at baseline compared with patients without textbook outcomes. The presence of biliary colic at baseline (odds ratio = 1.56, 95% confidence interval: 1.16-2.09, P = .003) and nausea/vomiting at baseline (odds ratio = 1.33, 95% confidence interval: 1.01-1.74, P = .039) were associated with textbook outcome. The use of non-opioid analgesics (odds ratio = 0.76, 95% confidence interval: 0.58-0.99, P = .043) and pain frequency ≥1/month (odds ratio = 0.56, 95% confidence interval: 0.43-0.73, P < .001) were negatively associated with textbook outcome.
CONCLUSION: Textbook outcome is achieved in two-thirds of patients who undergo cholecystectomy for uncomplicated cholecystolithiasis. Intensity and frequency of pain, presence of biliary colic, and nausea/vomiting at baseline are independently associated with achieving textbook outcomes. A more stringent selection of patients may optimize the textbook outcome rate in patients with uncomplicated cholecystolithiasis.

Gepubliceerd: Surgery. 2024;176(2):414-9.
Impact factor: 2.7 ; Q1

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8. Restrictive Strategy vs Usual Care for Cholecystectomy in Patients With Abdominal Pain and Gallstones: 5-Year Follow-Up of the SECURE Randomized Clinical Trial
Comes DJ, Wennmacker SZ, Latenstein CSS, van der Bilt J, Buyne O, Donkervoort SC, Heisterkamp J, In't Hof K, Jansen J, Nieuwenhuijs VB, Steenvoorde P, Stockmann H, Boerma D, Drenth JPH, van Laarhoven C, Boermeester MA, Dijkgraaf MGW, de Reuver PR.

IMPORTANCE: The 1-year results of the SECURE trial, a randomized trial comparing a restrictive strategy vs usual care for select patients with symptomatic cholelithiasis for cholecystectomy, resulted in a significantly lower operation rate after restrictive strategy. However, a restrictive strategy did not result in more pain-free patients at 1 year.
OBJECTIVE: To gauge pain level and determine the proportion of pain-free patients, operation rate, and biliary and surgical complications at the 5-year follow-up.
DESIGN, SETTING, AND PARTICIPANTS: This randomized clinical trial was a multicenter, parallel-arm, noninferiority, prospective study. Between February 2014 and April 2017, patients from 24 hospitals with symptomatic, uncomplicated cholelithiasis were included. Uncomplicated cholelithiasis was defined as gallstone disease without signs of complicated cholelithiasis, ie, biliary pancreatitis, cholangitis, common bile duct stones, or cholecystitis. Follow-up data for this analysis were collected by telephone from July 11, 2019, to September 23, 2023.

INTERVENTIONS: Patients were randomized (1:1) to receive usual care or a restrictive strategy with stepwise selection for cholecystectomy.
MAIN OUTCOMES AND MEASURES: The primary, noninferiority end point was proportion of patients who were pain free as evaluated by Izbicki pain score at the 5-year follow-up. A 5% noninferiority margin was chosen. The secondary end points included cholecystectomy rates, biliary and surgical complications, and patient satisfaction. RESULTS: Among 1067 patients, the median (IQR) age was 49.0 years (38.0-59.0 years); 786 (73.7%) were female, and 281 (26.3%) were male. At the 5-year follow-up, 228 of 363 patients (62.8%) were pain free in the usual care group, compared with 216 of 353 patients (61.2%) in restrictive strategy group (difference, 1.6%; 1-sided 95% lower confidence limit, -7.6%; noninferiority P = .18). After cholecystectomy, 187 of 294 patients (63.6%) in the usual care group and 160 of 254 patients (63.0%) in the restrictive strategy group were pain free, respectively (P = .88). The restrictive care strategy was associated with 387 of 529 cholecystectomies (73.2%) compared with 437 of 536 in the usual care group (81.5%; 8.3% difference; P = .001). No differences between groups were observed in biliary and surgical complications or in patient satisfaction.
CONCLUSIONS AND RELEVANCE: In the long-term, a restrictive strategy results in a significant but small reduction in operation rate compared with usual care and is not associated with increased biliary and surgical complications. However, regardless of the strategy, only two-third of patients were pain free. Further criteria for selecting patients with uncomplicated cholelithiasis for cholecystectomy and rethinking laparoscopic cholecystectomy as treatment is needed to improve patient-reported outcomes.
TRIAL REGISTRATION: CCMO Identifier: NTR4022.

Gepubliceerd: JAMA Surg. 2024;159(11):1235-43.
Impact factor: 14.9 ; Q1

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9. Axillo-Superior Mesenteric Artery-Bifemoral Bypass: An Extraordinary Bypass!
Daans JRE, Metz FM.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2024;68(2):225.
Impact factor: 6.8 ; Q1

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10. Early experience with robotic pancreatoduodenectomy versus open pancreatoduodenectomy: nationwide propensity-score-matched analysis
de Graaf N, Zwart MJW, van Hilst J, van den Broek B, Bonsing BA, Busch OR, Coene PLO, Daams F, van Dieren S, van Eijck CHJ, Festen S, de Hingh I, Lips DJ, Luyer MDP, Mieog JSD, van Santvoort HC, van der Schelling GP, Stommel MWJ, de Wilde RF, Molenaar IQ, Groot Koerkamp B, Besselink MG.

BACKGROUND: Although robotic pancreatoduodenectomy has shown promising outcomes in experienced high-volume centres, it is unclear whether implementation on a nationwide scale is safe and beneficial. The aim of this study was to compare the outcomes of the early experience with robotic pancreatoduodenectomy versus open pancreatoduodenectomy in the Netherlands.
METHODS: This was a nationwide retrospective cohort study of all consecutive patients who underwent robotic pancreatoduodenectomy or open pancreatoduodenectomy who were registered in the mandatory Dutch Pancreatic Cancer Audit (18 centres, 2014-2021), starting from the first robotic pancreatoduodenectomy procedure per centre. The main endpoints were major complications (Clavien-Dindo grade greater than or equal to III) and in-hospital/30-day mortality. Propensity-score matching (1 : 1) was used to minimize selection bias.

RESULTS: Overall, 701 patients who underwent robotic pancreatoduodenectomy and 4447 patients who underwent open pancreatoduodenectomy were included. Among the eight centres that performed robotic pancreatoduodenectomy, the median robotic pancreatoduodenectomy experience was 86 (range 48-149), with a 7.3% conversion rate. After matching (698 robotic pancreatoduodenectomy patients versus 698 open pancreatoduodenectomy control patients), no significant differences were found in major complications (40.3% versus 36.2% respectively; P = 0.186), in-hospital/30-day mortality (4.0% versus 3.1% respectively; P = 0.326), and postoperative pancreatic fistula grade B/C (24.9% versus 23.5% respectively; P = 0.578). Robotic pancreatoduodenectomy was associated with a longer operating time (359 min versus 301 min; P < 0.001), less intraoperative blood loss (200 ml versus 500 ml; P < 0.001), fewer wound infections (7.4% versus 12.2%; P = 0.008), and a shorter hospital stay (11 days versus 12 days; P < 0.001). Centres performing greater than or equal to 20 robotic pancreatoduodenectomies annually had a lower mortality rate (2.9% versus 7.3%; P = 0.009) and a lower conversion rate (6.3% versus 11.2%; P = 0.032).
CONCLUSION: This study indicates that robotic pancreatoduodenectomy was safely implemented nationwide, without significant differences in major morbidity and mortality compared with matched open pancreatoduodenectomy patients. Randomized trials should be carried out to verify these findings and confirm the observed benefits of robotic pancreatoduodenectomy versus open pancreatoduodenectomy.

Gepubliceerd: Br J Surg. 2024;111(2).
Impact factor: 8.7 ; Q1

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11. Trends and overall survival after combined liver resection and thermal ablation of colorectal liver metastases: a nationwide population-based propensity score-matched study
de Graaff MR, Klaase JM, den Dulk M, Coolsen MME, Kuhlmann KFD, Verhoef C, Hartgrink HH, Derksen WJM, van den Boezem P, Rijken AM, Gobardhan P, Liem MSL, Leclercq WKG, Marsman HA, van Duijvendijk P, Bosscha K, Elfrink AKE, Manusama ER, Belt EJT, Doornebosch PG, Oosterling SJ, Ruiter SJS, Grünhagen DJ, Burgmans M, Meijerink M, Kok NFM, Swijnenburg RJ.

BACKGROUND: In colorectal liver metastases (CRLM) patients, combination of liver resection and ablation permit a more parenchymal-sparing approach. This study assessed trends in use of combined resection and ablation, outcomes, and overall survival (OS).
METHODS: This population-based study included all CRLM patients who underwent liver resection between 2014 and 2022. To assess OS, data was linked to two databases containing date of death for patients treated between 2014 and 2018. Hospital variation in the use of combined minor liver resection and ablation versus major liver resection alone in patients with 2-3 CRLM and ≤3 cm was assessed. Propensity score matching (PSM) was applied to evaluate outcomes.
RESULTS: This study included 3593 patients, of whom 1336 (37.2%) underwent combined resection and ablation. Combined resection increased from 31.7% in 2014 to 47.9% in 2022. Significant hospital variation (range 5.9-53.8%) was observed in the use of combined minor liver resection and ablation. PSM resulted in 1005 patients in each group. Major morbidity was not different (11.6% vs. 5%, P = 1.00). Liver failure occurred less often after combined resection and ablation (1.9% vs. 0.6%, P = 0.017). Five-year OS rates were not different (39.3% vs. 33.9%, P = 0.145).
CONCLUSION: Combined resection and ablation should be available and considered as an alternative to resection alone in any patient with multiple metastases.

Gepubliceerd: HPB (Oxford). 2024;26(1):34-43.
Impact factor: 2.4 ; Q1

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12. Hospital variation and outcomes after repeat hepatic resection for colorectal liver metastases: a nationwide cohort study
de Graaff MR, Klaase JM, den Dulk M, Te Riele WW, Hagendoorn J, van Heek NT, Vermaas M, Belt EJT, Bosscha K, Slooter GD, Leclercq WKG, Liem MSL, Mieog JSD, Swijnenburg RJ, van Dam RM, Verhoef C, Kuhlmann K, van Duijvendijk P, Gerhards MF, Gobardhan P, van den Boezem P, Manusama ER, Grünhagen DJ, Kok NFM.

BACKGROUND: Approximately 70% of patients with colorectal liver metastases (CRLM) experiences intrahepatic recurrence after initial liver resection. This study assessed outcomes and hospital variation in repeat liver resections (R-LR).
METHODS: This population-based study included all patients who underwent liver resection for CRLM between 2014 and 2022 in the Netherlands. Overall survival (OS) was collected for patients operated on between 2014 and 2018 by linkage to the insurance database.
RESULTS: Data of 7479 liver resections (1391 (18.6%) repeat and 6088 (81.4%) primary) were analysed. Major morbidity and mortality were not different. Factors associated with major morbidity included ASA 3+, major liver resection, extrahepatic disease, and open surgery. Five-year OS after repeat versus primary liver resection was 42.3% versus 44.8%, P = 0.37. Factors associated with worse OS included largest CRLM >5 cm (aHR 1.58, 95% CI: 1.07-2.34, P = 0.023), >3 CRLM (aHR 1.33, 95% CI: 1.00-1.75, P = 0.046), extrahepatic disease (aHR 1.60, 95% CI: 1.25-2.04, P = 0.001), positive tumour margins (aHR 1.42, 95% CI: 1.09-1.85, P = 0.009). Significant hospital variation in performance of R-LR was observed, median 18.9% (8.2% to 33.3%).
CONCLUSION: Significant hospital variation was observed in performance of R-LR in the Netherlands reflecting different treatment decisions upon recurrence. On a population-based level R-LR leads to satisfactory survival.

Gepubliceerd: HPB (Oxford). 2024;26(6):789-99.
Impact factor: 2.4 ; Q1

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13. Outcomes of liver surgery: A decade of mandatory nationwide auditing in the Netherlands
de Graaff MR, Klaase JM, Dulk MD, Buis CI, Derksen WJM, Hagendoorn J, Leclercq WKG, Liem MSL, Hartgrink HH, Swijnenburg RJ, Vermaas M, Belt EJT, Bosscha K, Verhoef C, Olde Damink S, Kuhlmann K, Marsman HM, Ayez N, van Duijvendijk P, van den Boezem P, Manusama ER, Grünhagen DJ, Kok NFM.

BACKGROUND: In 2013, the nationwide Dutch Hepato Biliary Audit (DHBA) was initiated. The aim of this study was to evaluate changes in indications for and outcomes of liver surgery in the last decade.
METHODS: This nationwide study included all patients who underwent liver surgery for four indications, including colorectal liver metastases (CRLM), hepatocellular carcinoma (HCC), and intrahepatic- and perihilar cholangiocarcinoma (iCCA - pCCA) between 2014 and 2022. Trends in postoperative outcomes were evaluated separately for each indication using multilevel multivariable logistic regression analyses.
RESULTS: This study included 8057 procedures for CRLM, 838 for HCC, 290 for iCCA, and 300 for pCCA. Over time, these patients had higher risk profiles (more ASA-III patients and more comorbidities). Adjusted mortality decreased over time for CRLM, HCC and iCCA, respectively aOR 0.83, 95%CI 0.75-0.92, P < 0.001; aOR 0.86, 95%CI 0.75-0.99, P = 0.045; aOR 0.40, 95%CI 0.20-0.73, P < 0.001. Failure to rescue (FTR) also decreased for these groups, respectively aOR 0.84, 95%CI 0.76-0.93, P = 0.001; aOR 0.81, 95%CI 0.68-0.97, P = 0.024; aOR 0.29, 95%CI 0.08-0.84, P = 0.021). For iCCA severe complications (aOR 0.65 95%CI 0.43-0.99, P = 0.043) also decreased. No significant outcome differences were observed in pCCA. The number of centres performing liver resections decreased

from 26 to 22 between 2014 and 2022, while median annual volumes did not change (40-49, P = 0.66).
CONCLUSION: Over time, postoperative mortality and FTR decreased after liver surgery, despite treating higher-risk patients. The DHBA continues its focus on providing feedback and benchmark results to further enhance outcomes.

Gepubliceerd: Eur J Surg Oncol. 2024;50(6):108264.
Impact factor: 2.9 ; Q1

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14. Two Days Versus Five Days of Postoperative Antibiotics for Complex Appendicitis: Cost Analysis of a Randomized, Noninferiority Trial
de Wijkerslooth EML, Boerma EG, van Rossem CC, Koopmanschap MA, Baeten CIM, Beverdam FH, Bosmans J, Consten ECJ, Dekker JWT, Emous M, van Geloven AAW, Gijsen AF, Heijnen LA, Jairam AP, van der Ploeg APT, Steenvoorde P, Toorenvliet BR, Vermaas M, Wiering B, Wijnhoven BPL, van den Boom AL.

OBJECTIVE: To compare costs for 2 days versus 5 days of postoperative antibiotics within the antibiotics after an aPPendectomy In Complex appendicitis trial.Background:Recent studies suggest that restrictive antibiotic use leads to a significant reduction in hospital stays without compromising patient safety. Its potential effect on societal costs remains underexplored.
METHODS: This was a pragmatic, open-label, multicenter clinical trial powered for noninferiority. Patients with complex appendicitis (age ≥ 8 years) were randomly allocated to 2 days or 5 days of intravenous antibiotics after appendectomy. Patient inclusion lasted from June 2017 to June 2021 in 15 Dutch hospitals. The final follow-up was on September 1, 2021. The primary trial endpoint was a composite endpoint of infectious complications and mortality within 90 days. In the present study, the main outcome measures were overall societal costs (comprising direct health care costs and costs related to productivity loss) and cost-effectiveness. Direct health care costs were recorded based on data in the electronic patient files, complemented by a telephone follow-up at 90 days. In addition, data on loss of productivity were acquired through the validated Productivity Cost Questionnaire at 4 weeks after surgery. Cost estimates were based on prices for the year 2019.
RESULTS: In total, 1005 patients were evaluated in the "intention-to-treat" analysis: 502 patients were allocated to the 2-day group and 503 to the 5-day group. The mean difference in overall societal costs was - €625 (95% CI: -€ 958 to -€ 278) to the advantage of the 2-day group. This difference was largely explained by reduced hospital stay. Productivity losses were similar between the study groups. Restricting postoperative antibiotics to 2 days was cost-effective, with estimated cost savings of €31,117 per additional infectious complication.
CONCLUSIONS: Two days of postoperative antibiotics for complex appendicitis results in a statistically significant and relevant cost reduction, as compared with 5 days. Findings apply to laparoscopic appendectomy in a well-resourced health care setting.

Gepubliceerd: Ann Surg. 2024;279(5):885-90.
Impact factor: 6.4 ; Q1

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15. Intestinal Fatty Acid Binding Protein as a Predictor of Early Mesenteric Injury Preceding Clinical Presentation: A Case Report
Duivenvoorden AAM, Metz FM, Wijenbergh R, Verberght HCR, van Bijnen A, Olde Damink SWM, Geelkerken RH, Lenaerts K, Lubbers T.

INTRODUCTION: Diagnosing non-occlusive mesenteric ischaemia (NOMI) in patients is complicated, due to poor signs and symptoms and non-specific laboratory tests, leading to a high mortality rate. This case study presents the rare case of a patient who developed mesenteric ischaemia after an emergency thoracic endovascular aneurysm repair (TEVAR) for a type B aortic dissection (TBAD) and peri-operative cardiogenic shock. Study outcomes revealed that intestinal fatty acid binding protein (I-FABP) identified early mucosal damage two days before the clinical presentation.
REPORT: A 43 year old male patient was admitted to the emergency department with an acute TBAD and a dissection of the superior mesenteric artery (SMA), for which TEVAR was performed with additional stent placement in the SMA. Peri-operatively, the patient went into cardiogenic shock with a sustained period of hypotension. Post-operatively, the plasma I-FABP levels were measured prospectively, revealing an initial increase on post-operative day five (551.1 pg/mL), which continued beyond day six (610.3 pg/mL). On post-operative day seven, the patient developed a fever and demonstrated signs of peritonitis and bowel perforation. He underwent an emergency laparotomy, followed by an ileocaecal resection (<100 cm) with a transverse ileostomy. Pathological analysis confirmed the diagnosis of mesenteric ischaemia.
DISCUSSION: The diagnosis of NOMI in critically ill patients is often complicated, and the currently available diagnostic markers lack the specificity and sensitivity to detect early intestinal injury. This case report highlights that elevated I-FABP in plasma levels may indicate the presence of early mesenteric injury. Further research needs to be conducted before I-FABP can be applied in daily practice.

Gepubliceerd: EJVES Vasc Forum. 2024;61:136-40.
Impact factor: 1.8 ; Q2

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16. Implementation and outcome of minimally invasive pancreatoduodenectomy in Europe: a registry-based retrospective study - a critical appraisal of the first 3 years of the E-MIPS registry
Emmen A, de Graaf N, Khatkov IE, Busch OR, Dokmak S, Boggi U, Groot Koerkamp B, Ferrari G, Molenaar IQ, Saint-Marc O, Ramera M, Lips DJ, Mieog JSD, Luyer MDP, Keck T, D'Hondt M, Souche FR, Edwin B, Hackert T, Liem MSL, Iben-Khayat A, van Santvoort HC, Mazzola M, de Wilde RF, Kauffmann EF, Aussilhou B, Festen S, Izrailov R, Tyutyunnik P, Besselink MG, Abu Hilal M.

BACKGROUND: International multicenter audit-based studies focusing on the outcome of minimally invasive pancreatoduodenectomy (MIPD) are lacking. The European Registry for Minimally Invasive Pancreatic Surgery (E-MIPS) is the E-AHPBA endorsed registry aimed to monitor and safeguard the introduction of MIPD in Europe.
MATERIALS AND METHODS: A planned analysis of outcomes among consecutive patients after MIPD from 45 centers in 14 European countries in the E-MIPS registry (2019-2021). The main outcomes of interest were major morbidity (Clavien-Dindo grade ≥3) and 30-day/in-hospital mortality.
RESULTS: Overall, 1336 patients after MIPD were included [835 robot-assisted (R-MIPD) and 501 laparoscopic MIPD (L-MIPD)]. Overall, 20 centers performed R-MIPD, 15 centers L-MIPD, and 10 centers both. Between 2019 and 2021, the rate of centers performing L-MIPD decreased from 46.9 to 25%, whereas for R-MIPD this increased from 46.9 to 65.6%. Overall, the rate of major morbidity was 41.2%, 30-day/in-hospital mortality 4.5%, conversion rate 9.7%, postoperative pancreatic fistula grade B/C 22.7%, and postpancreatectomy hemorrhage grade B/C 10.8%. Median length of hospital stay was 12 days (IQR 8-21). A lower rate of major morbidity, postoperative pancreatic fistula grade B/C, postpancreatectomy hemorrhage grade B/C, delayed gastric emptying grade B/C, percutaneous drainage, and readmission was found after L-MIPD. The number of centers meeting the Miami Guidelines volume cut-off of ≥20 MIPDs annually increased from 9 (28.1%) in 2019 to 12 (37.5%) in 2021 (P =0.424). Rates of conversion (7.4 vs. 14.8% P <0.001) and reoperation (8.9 vs. 15.1% P <0.001) were lower in centers, which fulfilled the Miami volume cut-off.

CONCLUSION: During the first 3 years of the pan-European E-MIPS registry, morbidity and mortality rates after MIPD were acceptable. A shift is ongoing from L-MIPD to R-MIPD. Variations in outcomes between the two minimally invasive approaches and the impact of the volume cut-off should be further evaluated over a longer time period.

Gepubliceerd: Int J Surg. 2024;110(4):2226-33.
Impact factor: 10.1 ; Q1

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17. Robot-assisted versus laparoscopic pancreatoduodenectomy: a pan-European multicenter propensity-matched study
Emmen A, Zwart MJW, Khatkov IE, Boggi U, Groot Koerkamp B, Busch OR, Saint-Marc O, Dokmak S, Molenaar IQ, D'Hondt M, Ramera M, Keck T, Ferrari G, Luyer MDP, Moraldi L, Ielpo B, Wittel U, Souche FR, Hackert T, Lips D, Can MF, Bosscha K, Fara R, Festen S, van Dieren S, Coratti A, De Hingh I, Mazzola M, Wellner U, De Meyere C, van Santvoort HC, Aussilhou B, Ibenkhayat A, de Wilde RF, Kauffmann EF, Tyutyunnik P, Besselink MG, Abu Hilal M.

BACKGROUND: The use of robot-assisted and laparoscopic pancreatoduodenectomy is increasing, yet large adjusted analyses that can be generalized internationally are lacking. This study aimed to compare outcomes after robot-assisted pancreatoduodenectomy and laparoscopic pancreatoduodenectomy in a pan-European cohort.
METHODS: An international multicenter retrospective study including patients after robot-assisted pancreatoduodenectomy and laparoscopic pancreatoduodenectomy from 50 centers in 12 European countries (2009-2020). Propensity score matching was performed in a 1:1 ratio. The primary outcome was major morbidity (Clavien-Dindo ≥III).
RESULTS: Among 2,082 patients undergoing minimally invasive pancreatoduodenectomy, 1,006 underwent robot-assisted pancreatoduodenectomy and 1,076 laparoscopic pancreatoduodenectomy. After matching 812 versus 812 patients, the rates of major morbidity (31.9% vs 29.6%; P = .347) and 30-day/in-hospital mortality (4.3% vs 4.6%; P = .904) did not differ significantly between robot-assisted pancreatoduodenectomy and laparoscopic pancreatoduodenectomy, respectively. Robot-assisted pancreatoduodenectomy was associated with a lower conversion rate (6.7% vs 18.0%; P < .001) and higher lymph node retrieval (16 vs 14; P = .003). Laparoscopic pancreatoduodenectomy was associated with shorter operation time (446 minutes versus 400 minutes; P < .001), and lower rates of postoperative pancreatic fistula grade B/C (19.0% vs 11.7%; P < .001), delayed gastric emptying grade B/C (21.4% vs 7.4%; P < .001), and a higher R0-resection rate (73.2% vs 84.4%; P < .001).
CONCLUSION: This European multicenter study found no differences in overall major morbidity and 30-day/in-hospital mortality after robot-assisted pancreatoduodenectomy compared with laparoscopic pancreatoduodenectomy. Further, laparoscopic pancreatoduodenectomy was associated with a lower rate of postoperative pancreatic fistula, delayed gastric emptying, wound infection, shorter length of stay, and a higher R0 resection rate than robot-assisted pancreatoduodenectomy. In contrast, robot-assisted pancreatoduodenectomy was associated with a lower conversion rate and a higher number of retrieved lymph nodes as compared with laparoscopic pancreatoduodenectomy.

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Impact factor: 2.7 ; Q1

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18. Multicentre cohort study evaluating clinical, oncological and functional outcomes following robotic rectal cancer surgery-the EUREKA collaborative: trial protocol
Fleming CA, Duhoky R, Geitenbeek RTJ, Moussion A, Bouazza N, Khan J, Cotte E, Dubois A, Rullier E, Hompes R, Denost Q, Rouanet P, Consten ECJ, EUREKA collaborative; van Duyn EB.

Gepubliceerd: BJS Open. 2024;8(2).
Impact factor: 4.5 ; Q1

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19. Prognostic significance of MRI-detected extramural venous invasion according to grade and response to neo-adjuvant treatment in locally advanced rectal cancer A national cohort study after radiologic training and reassessment
Geffen E, Nederend J, Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; van der Burg S, van Duyn EB.

BACKGROUND: Detection of grade 3-4 extra mural venous invasion (mrEMVI) on magnetic resonance imaging (MRI) is associated with an increased distant metastases (DM)-rate. This study aimed to determine the impact of different grades of mrEMVI and their disappearance after neoadjuvant therapy.
METHODS: A Dutch national retrospective cross-sectional study was conducted, including patients who underwent resection for rectal cancer in 2016 from 60/69 hospitals performing rectal surgery. Patients with a cT3-4 tumour ≤8 cm from the anorectal junction were selected and their MRI-scans were reassessed by trained abdominal radiologists. Positive mrEMVI grades (3 and 4) were analyzed in regard to 4-year local recurrence (LR), DM, disease-free survival (DFS) and overall survival (OS).
RESULTS: The 1213 included patients had a median follow-up of 48 months (IQR 30-54). Positive mrEMVI was present in 324 patients (27%); 161 had grade 3 and 163 had grade 4. A higher mrEMVI stage (grade 4 vs grade 3 vs no mrEMVI) increased LR-risk (21% vs 18% vs 7%, <0.001) and DM-risk (49% vs 30% vs 21%, $p < 0.001$) and decreased DFS (42% vs 55% vs 69%, $p < 0.001$) and OS (62% vs 76% vs 81%, $p < 0.001$), which remained independently associated in multivariable analysis. When mrEMVI had disappeared on restaging MRI, DM-rate was comparable to initial absence of mrEMVI (both 26%), whereas LR-rate remained high (22% vs 9%, $p = 0.006$).
CONCLUSION: The negative oncological impact of mrEMVI on recurrence and survival rates was dependent on grading. Disappearance of mrEMVI on restaging MRI decreased the risk of DM, but not of LR.

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Impact factor: 2.9 ; Q1

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20. Functional outcomes and quality of life following open versus laparoscopic versus robot-assisted versus transanal total mesorectal excision in rectal cancer patients: a systematic review and meta-analysis
Geitenbeek RTJ, Burghgraef TA, Moes CA, Hompes R, Ranchor AV, Consten ECJ, MIRECA study group; van Duyn EB.

BACKGROUND: The standard surgical treatment for rectal cancer is total mesorectal excision (TME), which may negatively affect patients' functional outcomes and quality of life (QoL). However, it is unclear how different TME techniques may impact patients' functional outcomes and QoL. This systematic review and meta-analysis evaluated functional outcomes of urinary, sexual, and fecal

functioning as well as QoL after open, laparoscopic (L-TME), robot-assisted (R-TME), and transanal total mesorectal excision (TaTME).
METHODS: A systematic review and meta-analysis, based on the preferred reporting items for systematic reviews and meta-analysis statement, were conducted (PROSPERO: CRD42021240851). A literature review was performed (sources: PubMed, Medline, Embase, Scopus, Web of Science, and Cochrane Library databases; end-of-search date: September 1, 2023), and a quality assessment was performed using the Methodological index for non-randomized studies. A random-effects model was used to pool the data for the meta-analyses.
RESULTS: Nineteen studies were included, reporting on 2495 patients (88 open, 1171 L-TME, 995 R-TME, and 241 TaTME). Quantitative analyses comparing L-TME vs. R-TME showed no significant differences regarding urinary and sexual functioning, except for urinary function at three months post-surgery, which favoured R-TME (SMD [CI] -0 .15 [- 0.24 to - 0.06], p = 0.02; n = 401). Qualitative analyses identified most studies did not find significant differences in urinary, sexual, and fecal functioning and QoL between different techniques.
CONCLUSIONS: This systematic review and meta-analysis highlight a significant gap in the literature concerning the evaluation of functional outcomes and QoL after TME for rectal cancer treatment. This study emphasizes the need for high-quality, randomized-controlled, and prospective cohort studies evaluating these outcomes. Based on the limited available evidence, this systematic review and meta-analysis suggests no significant differences in patients' urinary, sexual, and fecal functioning and their QoL across various TME techniques.

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Impact factor: 2.7 ; Q1

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21. The use of indocyanine green fluorescence imaging in preventing postoperative bile leakage of the hepaticojejunostomy in robot-assisted pancreatic surgery
Gijsen AF, de Vries RPH, Vaassen HGM, Geelkerken RH, Liem MSL, Lips DJ.

BACKGROUND: Postoperative bile leakage (POBL) due to insufficiency of the hepaticojejunostomy (HJ) after pancreatico-duodenectomy (PD) is associated with high morbidity and mortality. The aim of this cohort study was to determine the clinical relevance of ICG in detecting and preventing POBL of the HJ in robotic minimal invasive pancreatic surgery (R-MIPS).
METHODS: All consecutive robot- and ICG-assisted HJ-anastomoses between 2019 and 2022 were included. Biliary leakage was objectified with near infrared technology. Only clinically relevant POBL were considered in this study.
RESULTS: Sixty patients who underwent a PD between 2019 and 2022 were included. In ten patients, fluorescence imaging revealed an intra-operative hepaticojejunostomy insufficiency (HJI). Five of these patients developed POBL despite revision but preventing POBL in five patients. Detection of HJI with ICG predicted POBL with a sensitivity and specificity of 41.6% and 89.6% respectively. There was a significant higher chance of developing a POBL if the hepatic duct diameter was less than 5 mm (relative risk = 4.68 (p = 0.0345)), or if an intra-operative HJI was detected (relative risk = 3.57 (p = 0.009)).
CONCLUSION: ICG is a simple and useful tool for detecting intra-operative bile leakage. This study shows that bile illumination with ICG in R-MIPS could prevent postoperative bile leakage.

Gepubliceerd: HPB (Oxford). 2024;26(12):1515-20.
Impact factor: 2.4 ; Q1

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22. MRI in addition to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): an international, multicentre, prospective, diagnostic accuracy trial
Görgec B, Hansen IS, Kemmerich G, Syversveen T, Abu Hilal M, Belt EJT, Bosscha K, Burgmans MC, Cappendijk VC, D'Hondt M, Edwin B, van Erkel AR, Gielkens HAJ, Grünhagen DJ, Gobardhan PD, Hartgrink HH, Horsthuis K, Klompenhouwer EG, Kok NFM, Kint PAM, Kuhlmann K, Leclercq WKG, Lips DJ, Lutin B, Maas M, Marsman HA, Meijerink M, Meyer Y, Morone M, Peringa J, Sijberden JP, van Delden OM, van den Bergh JE, Vanhooymissen IJS, Vermaas M, Willemssen F, Dijkgraaf MGW, Bossuyt PM, Swijnenburg RJ, Fretland Å A, Verhoef C, Besselink MG, Stoker J.

BACKGROUND: Guidelines are inconclusive on whether contrast-enhanced MRI using gadoxetic acid and diffusion-weighted imaging should be added routinely to CT in the investigation of patients with colorectal liver metastases who are scheduled for curative liver resection or thermal ablation, or both. Although contrast-enhanced MRI is reportedly superior than contrast-enhanced CT in the detection and characterisation of colorectal liver metastases, its effect on clinical patient management is unknown. We aimed to assess the clinical effect of an additional liver contrast-enhanced MRI on local treatment plan in patients with colorectal liver metastases amenable to local treatment, based on contrast-enhanced CT.
METHODS: We did an international, multicentre, prospective, incremental diagnostic accuracy trial in 14 liver surgery centres in the Netherlands, Belgium, Norway, and Italy. Participants were aged 18 years or older with histological proof of colorectal cancer, a WHO performance status score of 0-4, and primary or recurrent colorectal liver metastases, who were scheduled for local therapy based on contrast-enhanced CT. All patients had contrast-enhanced CT and liver contrast-enhanced MRI including diffusion-weighted imaging and gadoxetic acid as a contrast agent before undergoing local therapy. The primary outcome was change in the local clinical treatment plan (decided by the individual clinics) on the basis of liver contrast-enhanced MRI findings, analysed in the intention-to-image population. The minimal clinically important difference in the proportion of patients who would have change in their local treatment plan due to an additional liver contrast-enhanced MRI was 10%. This study is closed and registered in the Netherlands Trial Register, NL8039.
FINDINGS: Between Dec 17, 2019, and July 31, 2021, 325 patients with colorectal liver metastases were assessed for eligibility. 298 patients were enrolled and included in the intention-to-treat population, including 177 males (59%) and 121 females (41%) with planned local therapy based on contrast-enhanced CT. A change in the local treatment plan based on liver contrast-enhanced MRI findings was observed in 92 (31%; 95% CI 26-36) of 298 patients. Changes were made for 40 patients (13%) requiring more extensive local therapy, 11 patients (4%) requiring less extensive local therapy, and 34 patients (11%) in whom the indication for curative-intent local therapy was revoked, including 26 patients (9%) with too extensive disease and eight patients (3%) with benign lesions on liver contrast-enhanced MRI (confirmed by a median follow-up of 21·0 months [IQR 17·5-24·0]).
INTERPRETATION: Liver contrast-enhanced MRI should be considered in all patients scheduled for local treatment for colorectal liver metastases on the basis of contrast-enhanced CT imaging.
FUNDING: The Dutch Cancer Society and Bayer AG - Pharmaceuticals.

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Impact factor: 35.9 ; Q1

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23. Impact of the new rectal cancer definition on multimodality treatment and interhospital variability: Results from a nationwide cross-sectional study
Hazen SJA, Sluckin TC, Horsthuis K, Lambregts DMJ, Beets-Tan RGH, Hompes R, Buffart TE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; van der Burg S, van Duyn EB.

AIM: This study aimed to determine the consequences of the new definition of rectal cancer for decision-making in multidisciplinary team meetings (MDT). The new definition of rectal cancer, the

lower border of the tumour is located below the sigmoid take-off (STO), was implemented in the Dutch guideline in 2019 after an international Delphi consensus meeting to reduce interhospital variations.
METHOD: All patients with rectal cancer according to the local MDT, who underwent resection in 2016 in the Netherlands were eligible for this nationwide collaborative cross-sectional study. MRI-images were rereviewed, and the tumours were classified as above or on/below the STO.
RESULTS: This study registered 3107 of the eligible 3178 patients (98%), of which 2784 patients had an evaluable MRI. In 314 patients, the tumour was located above the STO (11%), with interhospital variation between 0% and 36%. Based on TN-stage, 175 reclassified patients with colon cancer (6%) would have received different treatment (e.g., omitting neoadjuvant radiotherapy, candidate for adjuvant chemotherapy). Tumour location above the STO was independently associated with lower risk of 4-year locoregional recurrence (HR 0.529; p = 0.030) and higher 4-year overall survival (HR 0.732; p = 0.037) compared to location under the STO.
CONCLUSION: By using the STO, 11% of the prior MDT-based diagnosis of rectal cancer were redefined as sigmoid cancer, with potential implications for multimodality treatment and prognostic value. Given the substantial interhospital variation in proportion of redefined cancers, the use of the STO will contribute to standardisation and comparability of outcomes in both daily practice and trial settings.

Gepubliceerd: Colorectal Dis. 2024;26(6):1131-44.
Impact factor: 2.7 ; Q2

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24. Abandonment of Routine Radiotherapy for Nonlocally Advanced Rectal Cancer and Oncological Outcomes

Hazen SJA, Sluckin TC, Intven MPW, Beets GL, Beets-Tan RGH, Borstlap WAA, Buffart TE, Buijsen J, Burger JWA, van Dieren S, Furnée EJB, Geijsen ED, Hompes R, Horsthuis K, Leijtens JWA, Maas M, Melenhorst J, Nederend J, Peeters K, Rozema T, Tuynman JB, Verhoef C, de Vries M, van Westreenen HL, de Wilt JHW, Zimmerman DDE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; van der Burg S, van Duyn EB.

IMPORTANCE: Neoadjuvant short-course radiotherapy was routinely applied for nonlocally advanced rectal cancer (cT1-3N0-1M0 with >1 mm distance to the mesorectal fascia) in the Netherlands following the Dutch total mesorectal excision trial. This policy has shifted toward selective application after guideline revision in 2014.
OBJECTIVE: To determine the association of decreased use of neoadjuvant radiotherapy with cancer-related outcomes and overall survival at a national level.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter, population-based, nationwide cross-sectional cohort study analyzed Dutch patients with rectal cancer who were treated in 2011 with a 4-year follow-up. A similar study was performed in 2021, analyzing all patients that were surgically treated in 2016. From these cohorts, all patients with cT1-3N0-1M0 rectal cancer and radiologically unthreatened mesorectal fascia were included in the current study. The data of the 2011 cohort were collected between May and October 2015, and the data of the 2016 cohort were collected between October 2020 and November 2021. The data were analyzed between May and October 2022. MAIN **OUTCOMES AND MEASURES**: The main outcomes were 4-year local recurrence and overall survival rates. RESULTS: Among the 2011 and 2016 cohorts, 1199 (mean [SD] age, 68 [11] years; 430 women [36%]) of 2095 patients (57.2%) and 1576 (mean [SD] age, 68 [10] years; 547 women [35%]) of 3057 patients (51.6%) had cT1-3N0-1M0 rectal cancer and were included, with proportions of neoadjuvant radiotherapy of 87% (2011) and 37% (2016). Four-year local recurrence rates were 5.8% and 5.5%, respectively (P = .99). Compared with the 2011 cohort, 4-year overall survival was significantly higher in the 2016 cohort (79.6% vs 86.4%; P < .001), with lower non-cancer-related mortality (13.8% vs 6.3%; P < .001).

CONCLUSIONS AND RELEVANCE: The results of this cross-sectional study suggest that an absolute 50% reduction in radiotherapy use for nonlocally advanced rectal cancer did not compromise cancer-related outcomes at a national level. Optimizing clinical staging and surgery following the Dutch total mesorectal excision trial has potentially enabled safe deintensification of treatment.

Gepubliceerd: JAMA Oncol. 2024;10(2):202-11.
Impact factor: 20.1 ; Q1

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25. Long-term restoration of bowel continuity after rectal cancer resection and the influence of surgical technique: A nationwide cross-sectional study
Hazen SJA, van Geffen EGM, Sluckin TC, Beets GL, Belgers HJ, Borstlap WAA, Consten ECJ, Dekker JT, Hompes R, Tuynman JB, van Westreenen HL, de Wilt JHW, Tanis PJ, Kusters M, Dutch Snapshot Research Group; van der Burg S, van Duyn EB.

AIM: Literature on nationwide long-term permanent stoma rates after rectal cancer resection in the minimally invasive era is scarce. The aim of this population-based study was to provide more insight into the permanent stoma rate with interhospital variability (IHV) depending on surgical technique, with pelvic sepsis, unplanned reinterventions and readmissions as secondary outcomes.
METHOD: Patients who underwent open or minimally invasive resection of rectal cancer (lower border below the sigmoid take-off) in 67 Dutch centres in 2016 were included in this cross-sectional cohort study.
RESULTS: Among 2530 patients, 1470 underwent a restorative resection (58%), 356 a Hartmann's procedure (14%, IHV 0%-42%) and 704 an abdominoperineal resection (28%, IHV 3%-60%). Median follow-up was 51 months. The overall permanent stoma rate at last follow-up was 50% (IHV 13%-79%) and the unintentional permanent stoma rate, permanent stoma after a restorative procedure or an unplanned Hartmann's procedure, was 11% (IHV 0%-29%). A total of 2165 patients (86%) underwent a minimally invasive resection: 1760 conventional (81%), 170 transanal (8%) and 235 robot-assisted (11%). An anastomosis was created in 59%, 80% and 66%, with corresponding unintentional permanent stoma rates of 12%, 24% and 14% (p = 0.001), respectively. When corrected for age, American Society of Anesthesiologists classification, cTNM, distance to the anorectal junction and neoadjuvant (chemo)radiotherapy, the minimally invasive technique was not associated with an unintended permanent stoma (p = 0.071) after a restorative procedure.
CONCLUSION: A remarkable IHV in the permanent stoma rate after rectal cancer resection was found. No beneficial influence of transanal or robot-assisted laparoscopy on the unintentional permanent stoma rate was found, although this might be caused by the surgical learning curve. A reduction in IHV and improving preoperative counselling for decision-making for restorative procedures are required.

Gepubliceerd: Colorectal Dis. 2024;26(6):1153-65.
Impact factor: 2.7 ; Q2

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26. The Association Between Intraoperative Compromised Intestinal Integrity and Postoperative Complications in Cancer Patients
Hendriks S, Huisman MG, Stokmans SC, Plas M, van der Wal-Huisman H, van Munster BC, Absalom AR, Nieuwenhuijs-Moeke GJ, de Bock GH, van Leeuwen BL, de Haan JJ.

BACKGROUND: Because of perioperative splanchnic hypoperfusion, the gut wall becomes more permeable for intraluminal microbes to enter the splanchnic circulation, possibly contributing to development of complications. Hypoperfusion-related injured enterocytes release intestinal fatty acid

binding protein (I-FABP) into plasma, which is used as proxy of intestinal integrity. This study investigates the occurrence of intestinal integrity loss during oncologic surgery, measured by I-FABP change. Secondary the relationship between compromised intestinal integrity, and related variables and complications were studied.
METHODS: Patients undergoing oncologic surgery from prospective cohort studies were included. Urine I-FABP samples were collected preoperatively (T0) and at wound closure (T1), and in a subgroup on Day 1 (D1) and Day 2 (D2) postoperatively. I-FABP dynamics were investigated and logistic regression analyses were performed to study the association between I-FABP levels and patient-related, surgical variables and complications.
RESULTS: A total of 297 patients were included with median age of 70 years. Median I-FABP value increased from 80.0 pg/mL at T0 (interquartile range [IQR] 38.0-142.0) to 115 pg/mL at T1 (IQR 48.0-198.0) ($p < 0.05$). Age (odds ratio [OR] 1.05, 95% confidence interval [CI] 1.02-1.08) and anesthesia time (OR 1.13, 95% CI 1.02-1.25) were related to stronger I-FABP increase. When comparing I-FABP change in patients experiencing any complications versus no complications, relative I-FABP change at T1 was 145% of T0 (IQR 86-260) versus 113% (IQR 44-184) respectively ($p < 0.05$).
CONCLUSIONS: A significant change in I-FABP levels was seen perioperatively indicating compromised intestinal integrity. Age and anesthesia time were related to higher I-FABP increase. In patients experiencing postoperative complications, a higher I-FABP increase was found.

Gepubliceerd: Ann Surg Oncol. 2024;31(4):2699-708.
Impact factor: 3.5 ; Q1

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27. The relation between preoperative radiological sarcopenia and postoperative recovery of physical activity in older surgical cancer patients; an explorative study
Hendriks S, Huisman MG, Weerink L, Jonker LT, van Munster BC, de Haan JJ, de Bock GH, van Leeuwen BL.

To identify older surgical cancer patients at risk of decreased postoperative recovery of physical activity (PA), this study assesses whether preoperative radiological sarcopenia (RS) is associated with a decreased ability to return to baseline PA. RS was defined as decreased psoas muscle mass or -density by gender-specific cut-offs on CT-scans at level of vertebra L3. PA was assessed as steps/day measured with PA tracker and recovery of PA was defined as >90% of preoperative steps/day at 3 months postoperatively. Of 44 included patients aged 65 and over undergoing oncologic surgery, 18 patients (41%) showed RS. Seventeen patients (39%) returned to baseline PA, of which eight patients had RS (47%). RS was not associated with a return to baseline PA (OR: 1.38, 95%CI 0.39-4.92, $p = 0.61$). In this exploratory study, no association was found between preoperative RS and recovery of PA postoperatively.

Gepubliceerd: J Nutr Health Aging. 2024;28(10):100345.
Impact factor: 4.0 ; Q2

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28. A nationwide snapshot study on outcomes one year after surgery for chronic pilonidal sinus disease
Huurman EA, de Raaff CAL, van den Berg R, Baart SJ, Wijnhoven BPL, Schouten R, Furnée EJB, Smeenk RM, Toorenvliet BR, PITS collaborative study group; Steenvoorde P, van der Burg S.

AIM: Managing pilonidal sinus disease (PSD) remains challenging due to high recurrence rates and morbidity associated with treatment. The aim of this study was to evaluate the outcomes one year after surgical treatment for chronic PSD in the Netherlands.

METHOD: Patients with PSD who underwent surgical treatment between March 1, 2020, and March 1, 2021, at 36 participating hospitals were included in a prospective observational cohort study. For the present study, only patients with chronic PSD were included for analysis. One-year after surgical treatment for PSD, all patients received questionnaires on wound healing, quality of life (QoL), and patient reported experience measures (PREMs). Primary outcome was recurrence rate. Secondary outcomes included QoL and PREMs.
RESULTS: Of 681 included patients, 405 patients presented with chronic PSD and underwent surgical treatment. One-year questionnaires were completed by 289 out of 405 patients (71.4%). Patients underwent either excision with secondary wound healing (ESW, n = 73), excision with midline closure (EMC, n = 21), off-midline closure (OMC, n = 17), or a minimally invasive technique (MIT, n = 178). Patient-reported recurrence rates after ESW, EMC, OMC and MIT were 21.5%, 25%, 6.7% and 30.6%, respectively. Pain/discomfort and anxiety/depression were the most frequently reported problems affecting QoL. Patients that underwent OMC were satisfied the most with the care provided.
CONCLUSION: This study demonstrates variation in recurrence rates among surgical procedures for PSD. The highest rates were observed in the MIT and EMC group, while the OMC group exhibited the lowest rate. QoL outcomes differed among the surgical techniques. Patient satisfaction appears highest in the OMC group.

Gepubliceerd: Colorectal Dis. 2024.
Impact factor: 2.7 ; Q2

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29. Acute pilonidal abscess: Prospective nationwide audit in the Netherlands
Huurman EA, den Otter AAS, de Raaff CAL, van den Berg R, Baart SJ, Wijnhoven BPL, Schouten R, Furnée EJB, Smeenk RM, Toorenvliet BR, PITS collaborative study group; Steenvoorde P, van der Burg S.

AIM: The aim of this study was to assess Dutch surgical practice and outcomes for acute pilonidal abscess.
METHOD: Patients with pilonidal sinus disease (PSD) who underwent surgical treatment between 1 March 2020 and 1 March 2021 at 36 participating hospitals were included in a prospective observational cohort study. For the present study, only patients with an acute abscess were included for analysis. Outcomes included symptoms, wound healing, time to resume daily activities and complications. Follow-up was 1 year and included questionnaires on recurrent abscesses, symptomatic chronic PSD, quality of life and patient-reported experience measures.
RESULTS: Of 681 included patients, 208 presented with an acute pilonidal abscess. Incision and drainage (I&D) was performed in 205 of these patients (99%). The wound healing rate after I&D was 42.2% at the outpatient clinic, with a median time to closure of 43 days. The complication rate was 4.4%. One-year questionnaires were completed by 158 out of 205 patients (77.1%). Fifteen patients (7.3%) had a recurrent abscess within 1 year. The symptomatic chronic PSD rate was 8.8%.
CONCLUSION: Of all the patients presenting with PSD in this prospective national study cohort, 30% had a pilonidal abscess. Incision and drainage showed a low complication rate but successful wound healing in less than half of the patients. The study showed that 91.2% of patients did not undergo additional surgical treatment for symptomatic chronic PSD within 1 year of follow-up.

Gepubliceerd: Colorectal Dis. 2024;27(1).
Impact factor: 2.7 ; Q2

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30. Poor Prognostic Factors in Long-Term Survivors of Resected Pancreatic Ductal Adenocarcinoma: An International, Multicenter Cohort Study
Javed AA, Rompen IF, van Goor I, Stoop TF, Andel P, Mahmud O, Fatimi AS, Habib JR, Mughal NA, Schouten T, Lafaro K, Burkhart RA, Burns WR, Santvoort HCV, Dulk MD, Daams F, Mieog JSD, Stommel MWJ, Patijn GA, Hingh I, Festen S, Nijkamp MW, Klaase JM, Lips DJ, Wijsman JH, Harst EV, Manusama E, Eijck C, Koerkamp BG, Kazemier G, Busch OR, Molenaar IQ, Daamen LA, He J, Wolfgang CL, Besselink MG.

OBJECTIVE: To measure the rate of LTS in resected PDAC and determine the association between predictors of OS and LTS.
SUMMARY BACKGROUND DATA: Long-term survival (>5 y, LTS) remains rare in pancreatic ductal adenocarcinoma (PDAC). Multiple predictors of overall survival (OS) are known but their association with LTS remains unclear.
METHODS: An international, multicenter retrospective study was conducted. Included were patients from 2012-2019 with resected PDAC. Excluded were those with metastases at diagnosis or resection, R2 resections, and 90-day mortality. Predictors of OS were identified using multivariable Cox regression and their prevalence in patients with LTS assessed. LTS was calculated by excluding patients with shorter follow-up and predictors of LTS were identified using multivariable logistic regression.
RESULTS: 3,003 patients were included (27.4% received neoadjuvant chemotherapy). Elevated baseline CA19-9, high tumor grade, nodal disease, and perineural and lymphovascular invasion were negative independent predictors of OS, while receipt of adjuvant chemotherapy predicted improved OS (all P<0.05). LTS was observed in 220/2,436 patients (9.0%), of whom 198 (90%) harbored poor prognostic factors: elevated baseline CA19-9 (58.1%), poor tumor differentiation (51.0%), nodal disease (46.8%), and perineural invasion (76.0%). Of those without any of these four features, 50.0% achieved LTS as compared to 21.3%, 13.3%, 5.2%, and 3.5% in those with 1, 2, 3, or 4 features.
CONCLUSIONS: This bi-national cohort demonstrates a true LTS rate of 9.0% in resected PDAC. Clinicians should remain aware that presence of poor prognostic factors does not preclude LTS.

Gepubliceerd: Ann Surg. 2024.
Impact factor: 6.4 ; Q1

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31. Learning curve stratified outcomes after robotic pancreatoduodenectomy: International multicenter experience
Jones LR, Zwart MJW, de Graaf N, Wei K, Qu L, Jiabin J, Ningzhen F, Wang SE, Kim H, Kauffmann EF, de Wilde RF, Molenaar IQ, Chao YJ, Moraldi L, Saint-Marc O, Nickel F, Peng CM, Kang CM, Machado M, Luyer MDP, Lips DJ, Bonsing BA, Hackert T, Shan YS, Groot Koerkamp B, Shyr YM, Shen B, Boggi U, Liu R, Jang JY, Besselink MG, Abu Hilal M.

BACKGROUND: Robotic pancreatoduodenectomy is increasingly being implemented worldwide, with good results reported from individual expert centers. However, it is unclear to what extent outcomes will continue to improve during the learning curve, as large international studies are lacking.
METHODS: An international retrospective multicenter case series, including consecutive patients after robotic pancreatoduodenectomy from 18 centers in 8 countries in Europe, Asia, and South America until December 31, 2019, was conducted. A cumulative sum analysis was performed to determine the inflection points for the feasibility (operative time and blood loss) and proficiency (postoperative pancreatic fistula grade B/C and major morbidity) learning curves. Outcomes were compared in 3 groups on the basis of the learning curve inflection points.
RESULTS: Overall, 2,186 patients after robotic pancreatoduodenectomy were included. The feasibility learning curve was reached after 30-45 robotic pancreatoduodenectomy procedures and the proficiency learning curve after 90 robotic pancreatoduodenectomy procedures. These inflection

points created 3 phases, which were associated with major morbidity (24.7%, 23.4%, and 12.3%, P < .001) but not 30-day mortality (2.1%, 2.0%, and 1.5%, P = .670). Other outcomes mostly continued to improve, including median operative time 432, 390, and 300 minutes (P < .0001), conversion 6.0%, 4.7%, and 2.7% (P = .002), bile leakage 7.2%, 4.1%, and 2.4% (P < .001), postpancreatectomy hemorrhage 6.5%, 6.1%, and 1.8% (n = 21) but not R0 resection (pancreatic ductal adenocarcinoma only) 78.5%, 73.9%, and 82.8% (P = .35), and 90-day mortality rate 3.1%, 3.5%, and 2.1% (P = .191). Centers performing >20 robotic pancreatoduodenectomies annually had lower rates of conversion, reoperation, and shorter median operative time as compared with centers performing 10-20 robotic pancreatoduodenectomies annually.
CONCLUSION: This international multicenter study demonstrates that most outcomes of robotic pancreatoduodenectomy continued to improve during 3 learning curve phases without a negative effect on 90-day mortality. Randomized studies are needed in high-volume centers that have surpassed the first learning curves, to compare these outcomes with the open approach.

Gepubliceerd: Surgery. 2024;176(6):1721-9.
Impact factor: 2.7 ; Q1

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32. Nationwide use and Outcome of Minimally Invasive Distal Pancreatectomy in IDEAL Stage IV following a Training Program and Randomized Trial
Korrel M, van Hilst J, Bosscha K, Busch ORC, Daams F, van Dam R, van Eijck CHJ, Festen S, Groot Koerkamp B, van der Harst E, Lips DJ, Luyer MD, de Meijer VE, Mieog JSD, Molenaar IQ, Patijn GA, van Santvoort HC, van der Schelling GP, Stommel MWJ, Besselink MG.

OBJECTIVE: To assess the nationwide long-term uptake and outcomes of minimally invasive distal pancreatectomy (MIDP) after a nationwide training program and randomized trial.
BACKGROUND: Two randomized trials demonstrated the superiority of MIDP over open distal pancreatectomy (ODP) in terms of functional recovery and hospital stay. Data on implementation of MIDP on a nationwide level are lacking.
METHODS: Nationwide audit-based study including consecutive patients after MIDP and ODP in 16 centers in the Dutch Pancreatic Cancer Audit (2014 to 2021). The cohort was divided into three periods: early implementation, during the LEOPARD randomized trial, and late implementation. Primary endpoints were MIDP implementation rate and textbook outcome.
RESULTS: Overall, 1496 patients were included with 848 MIDP (56.5%) and 648 ODP (43.5%). From the early to the late implementation period, the use of MIDP increased from 48.6% to 63.0% and of robotic MIDP from 5.5% to 29.7% (P <0.001). The overall use of MIDP (45% to 75%) and robotic MIDP (1% to 84%) varied widely between centers (P <0.001). In the late implementation period, 5/16 centers performed >75% of procedures as MIDP. After MIDP, in-hospital mortality and textbook outcome remained stable over time. In the late implementation period, ODP was more often performed in ASA score III-IV (24.9% vs. 35.7%, P =0.001), pancreatic cancer (24.2% vs. 45.9%, P <0.001), vascular involvement (4.6% vs. 21.9%, P <0.001), and multivisceral involvement (10.5% vs. 25.3%, P <0.001). After MIDP, shorter hospital stay (median 7 vs. 8 d, P <0.001) and less blood loss (median 150 vs. 500 mL, P <0.001), but more grade B/C postoperative pancreatic fistula (24.4% vs. 17.2%, P =0.008) occurred as compared to ODP.
CONCLUSION: A sustained nationwide implementation of MIDP after a successful training program and randomized trial was obtained with satisfactory outcomes. Future studies should assess the considerable variation in the use of MIDP between centers and, especially, robotic MIDP.

Gepubliceerd: Ann Surg. 2024;279(2):323-30.
Impact factor: 6.4 ; Q1

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33. [Flucloxacillin-induced hypokalemia]
Lansink DG, Zogaj D, Veldhuis E, Hess D, Wagenaar FBM, Visser FW.

Flucloxacillin-induced hypokalaemia can be progressive and life-threatening, despite of potassium supplementation. In this case description, a high dose of intravenous flucloxacillin was started after a 68-year-old patient presented with an infected knee replacement. After two days, hypokalaemia was noted with an inadequate response to potassium supplementation. It was decided to change antibiotics and increase potassium supplementation, with good results. It is advisable to include monitoring of potassium levels in local treatment protocols when flucloxacillin is prescribed.

Gepubliceerd: Ned Tijdschr Geneeskd. 2024;168.
Impact factor: onbekend

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34. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands: A Stepped-Wedge Randomized Clinical Trial
Mackay TM, Latenstein AEJ, Augustinus S, van der Geest LG, Bogte A, Bonsing BA, Cirkel GA, Hol L, Busch OR, den Dulk M, van Driel L, Festen S, de Groot DA, de Groot JB, Groot Koerkamp B, Haj Mohammad N, Haver JT, van der Harst E, de Hingh IH, Homs MYV, Los M, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, Patijn GA, Quispel R, Römkens TEH, van Santvoort HC, Stommel MWJ, Venneman NG, Verdonk RC, van Vilsteren FGI, de Vos-Geelen J, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG, Dutch Pancreatic Cancer Group; Liem MSL.

IMPORTANCE: Implementation of new cancer treatment strategies as recommended by evidence-based guidelines is often slow and suboptimal. OBJECTIVE: To improve the implementation of guideline-based best practices in the Netherlands in pancreatic cancer care and assess the impact on survival.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter, stepped-wedge cluster randomized trial compared enhanced implementation of best practices with usual care in consecutive patients with all stages of pancreatic cancer. It took place from May 22, 2018 through July 9, 2020. Data were analyzed from April 1, 2022, through February 1, 2023. It included all patients in the Netherlands with pathologically or clinically diagnosed pancreatic ductal adenocarcinoma. This study reports 1-year follow-up (or shorter in case of deceased patients).
INTERVENTION: The 5 best practices included optimal use of perioperative chemotherapy, palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), referral to a dietician, and use of metal stents in patients with biliary obstruction. A 6-week implementation period was completed, in a randomized order, in all 17 Dutch networks for pancreatic cancer care.
MAIN OUTCOMES AND MEASURES: The primary outcome was 1-year survival. Secondary outcomes included adherence to best practices and quality of life (European Organisation for Research and Treatment of Cancer [EORTC] global health score).
RESULTS: Overall, 5887 patients with pancreatic cancer (median age, 72.0 [IQR, 64.0-79.0] years; 50% female) were enrolled, 2641 before and 2939 after implementation of best practices (307 during wash-in period). One-year survival was 24% vs 23% (hazard ratio, 0.98, 95% CI, 0.88-1.08). There was no difference in the use of neoadjuvant chemotherapy (11% vs 11%), adjuvant chemotherapy (48% vs 51%), and referral to a dietician (59% vs 63%), while the use of palliative chemotherapy (24% vs 30%; odds ratio [OR], 1.38; 95% CI, 1.10-1.74), PERT (34% vs 45%; OR, 1.64; 95% CI, 1.28-2.11), and metal biliary stents increased (74% vs 83%; OR, 1.78; 95% CI, 1.13-2.80). The EORTC global health score did not improve (area under the curve, 43.9 vs 42.8; median difference, -1.09, 95% CI, -3.05 to 0.94).
CONCLUSIONS AND RELEVANCE: In this randomized clinical trial, implementation of 5 best practices in pancreatic cancer care did not improve 1-year survival and quality of life. The finding that most

patients received no tumor-directed treatment paired with the poor survival highlights the need for more personalized treatment options.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03513705.

Gepubliceerd: JAMA Surg. 2024;159(4):429-37.
Impact factor: 14.9 ; Q1

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35. Prognostic value of total tumor volume in patients with colorectal liver metastases: A secondary analysis of the randomized CAIRO5 trial with external cohort validation
Michiel Zeeuw J, Wesdorp NJ, Ali M, Bakker AJJ, Voigt KR, Starmans MPA, Roor J, Kemna R, van Waesberghe J, van den Bergh JE, Nota I, Moos SI, van Dieren S, van Amerongen MJ, Bond MJG, Chapelle T, van Dam RM, Engelbrecht MRW, Gerhards MF, van Gulik TM, Hermans JJ, de Jong KP, Klaase JM, Kok NFM, Leclercq WKG, Liem MSL, van Lienden KP, Quintus Molenaar I, Patijn GA, Rijken AM, Ruers TM, de Wilt JHW, Verpalen IM, Stoker J, Grunhagen DJ, Swijnenburg RJ, Punt CJA, Huiskens J, Verhoef C, Kazemier G.

BACKGROUND: This study aimed to assess the prognostic value of total tumor volume (TTV) for early recurrence (within 6 months) and overall survival (OS) in patients with colorectal liver metastases (CRLM), treated with induction systemic therapy followed by complete local treatment.
METHODS: Patients with initially unresectable CRLM from the multicenter randomized phase 3 CAIRO5 trial (NCT02162563) who received induction systemic therapy followed by local treatment were included. Baseline TTV and change in TTV as response to systemic therapy were calculated using the CT scan before and the first after systemic treatment, and were assessed for their added prognostic value. The findings were validated in an external cohort of patients treated at a tertiary center.
RESULTS: In total, 215 CAIRO5 patients were included. Baseline TTV and absolute change in TTV were significantly associated with early recurrence (P = 0.005 and P = 0.040, respectively) and OS in multivariable analyses (P = 0.024 and P = 0.006, respectively), whereas RECIST1.1 was not prognostic for early recurrence (P = 0.88) and OS (P = 0.35). In the validation cohort (n = 85), baseline TTV and absolute change in TTV remained prognostic for early recurrence (P = 0.041 and P = 0.021, respectively) and OS in multivariable analyses (P < 0.0001 and P = 0.012, respectively), and showed added prognostic value over conventional clinicopathological variables (increase C-statistic, 0.06; 95 % CI, 0.02 to 0.14; P = 0.008).
CONCLUSION: Total tumor volume is strongly prognostic for early recurrence and OS in patients who underwent complete local treatment of initially unresectable CRLM, both in the CAIRO5 trial and the validation cohort. In contrast, RECIST1.1 did not show prognostic value for neither early recurrence nor OS.

Gepubliceerd: Eur J Cancer. 2024;207:114185.
Impact factor: 7.1 ; Q1

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36. Trauma-related preventable death; data analysis and panel review at a level 1 trauma centre in Amsterdam, the Netherlands
Mikdad S, Hakkenbrak NAG, Zuidema WP, Reijnders UJL, de Wit RJ, Jansen EH, Schwarte LA, Schouten JW, Bloemers FW, Giannakopoulos GF, Halm JA.

PURPOSE: Trauma-related death is used as a parameter to evaluate the quality of trauma care and identify cases in which mortality could have been prevented under optimal trauma care conditions.

The aim of this study was to identify trauma-related preventable death (TRPD) within our institute by an external expert panel and to evaluate inter-panel reliability.
METHODS: Trauma-related deaths between the 1st of January 2020 and the 1st of February 2022 at the Amsterdam University Medical Centre were identified. The severely injured patients (injury severity score ≥ 16) were enrolled for preventability analysis by an external multidisciplinary panel, consisting of a trauma surgeon, anaesthesiologist, emergency physician, neurosurgeon, and forensic physician. Case descriptions were provided, and panellists were asked to classify deaths as non-preventable, potentially preventable, and preventable. Agreements between the five observers were assessed by Fleiss kappa statistics.
RESULTS: In total 95 trauma-related deaths were identified. Of which 36 fatalities were included for analysis, the mean age was 55.3 years (± 24.5), 69.4% were male and 88.9% suffered blunt trauma. The mean injury severity score was 35.3 (± 15.3). Interobserver agreement within the external panel was moderate for survivability (Fleiss kappa 0.474) but low for categorical preventable death classification (Fleiss kappa 0.298). Most of the disagreements were between non-preventable or potentially preventable with care that could have been improved.
CONCLUSION: Multidisciplinary panel review has a moderate inter-observer agreement regarding survivability and low agreement regarding categorical preventable death classification. A valid definition and classification of TRPD is required to improve inter-observer agreement and quality of trauma care.

Gepubliceerd: Eur J Trauma Emerg Surg. 2024;50(6):3153-60.
Impact factor: 2.2 ; Q2

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37. A European expert consensus surgical technique description for robotic hepatectomy
Pilz da Cunha G, Lips DJ, Ahmad J, Kvarnström N, Aldrighetti L, D'Hondt M, Hagendoorn J, Swijnenburg RJ.

The robotic platform enables surgeons to operate with a similar level of freedom and control as in open surgery, while still providing the patient with the benefits of a minimally invasive approach. More centres continue to adopt robotic liver surgery however standardized training materials and consensus on the surgical technique are currently lacking. The availability of a standardized surgical protocol could benefit the further dissemination of the robotic approach while promoting safe and effective operating techniques. We present a comprehensive surgical technique description for robotic hepatectomy agreed upon by seven expert robotic liver surgeons in Europe. They contributed insights from their extensive experience with the robot to develop this report, highlighting the key steps and important considerations for performing robotic hepatectomy. We describe the surgical technique for four most common hepatectomy types with varying complexity: partial anterolateral resections, partial posterosuperior resections, left hepatectomy and right hepatectomy. This report encompasses recommendations from the experts, covering the preparatory steps such as patient selection and pre-operative imaging, and extending through to care in the postoperative phase. The step-by-step surgical technique description serves as a compendium of best practice methods presently utilized in robotic liver surgery. Although some variations in technique cannot be eliminated from practice, general recommendations in a structured form will help to homogenize the technique, safeguarding surgical quality. This paper aims to inform and advise surgeons in the process of adopting robotic liver surgery and can act as a starting point for further optimization and refinement of the technique.

Gepubliceerd: Hepatobiliary Surg Nutr. 2024;13(6):991-1006.
Impact factor: 7.8 ; Q1

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38. Robotic Versus Laparoscopic Liver Resection: A Nationwide Propensity Score Matched Analysis
Pilz da Cunha G, Sijberden JP, van Dieren S, Gobardhan P, Lips DJ, Terkivatan T, Marsman HA, Patijn GA, Leclercq WKG, Bosscha K, Mieog JSD, van den Boezem PB, Vermaas M, Kok NFM, Belt EJT, de Boer MT, Derksen WJM, Torrenga H, Verheijen PM, Oosterling SJ, Rijken AM, Coolsen MME, Liem MSL, Tran TCK, Gerhards MF, Nieuwenhuijs V, Abu Hilal M, Besselink MG, van Dam RM, Hagendoorn J, Swijnenburg RJ.

OBJECTIVE: To compare nationwide outcomes of robotic liver resection (RLR) with laparoscopic liver resection (LLR).
BACKGROUND: Minimally invasive liver resection is increasingly performed using the robotic approach as this could help overcome inherent technical limitations of laparoscopy. It is unknown if this translates to improved patient outcomes.
METHODS: Data from the mandatory Dutch Hepatobiliary Audit were used to compare perioperative outcomes of RLR and LLR in 20 centers in the Netherlands (2014-2022). Propensity score matching (PSM) was used to mitigate selection bias. Sensitivity analyses assessed the impact of the learning curve (≥50 procedures for LLR and ≥25 procedures for RLR), concurrent noncholecystectomy operations, high-volume centers, and conversion on outcomes.
RESULTS: Overall, 792 RLR and 2738 LLR were included. After PSM (781 RLR vs 781 LLR), RLR was associated with less blood loss (median: 100 mL [interquartile range (IQR): 50-300] vs 200 mL [IQR: 50-500], P = 0.002), less major blood loss (≥500 mL,18.6% vs 25.2%, P = 0.011), less conversions (4.9% vs 12.8%, P < 0.001), and shorter hospital stay (median: 3 days [IQR: 2-5] vs 4 days [IQR: 2-6], P < 0.001), compared with LLR. There were no significant differences in overall and severe morbidity, readmissions, mortality, and R0 resection rate. Sensitivity analyses yielded similar results. When excluding conversions, RLR was only associated with a reduction in reoperations (1.1% vs 2.7%, P = 0.038).
CONCLUSION: In this nationwide analysis, RLR was associated with a reduction in conversion, blood loss and length of hospital stay without compromising patient safety, also when excluding a learning curve effect. The benefits of RLR seem to be mostly related to a reduction in conversions.

Gepubliceerd: Ann Surg Open. 2024;5(4):e527.
IF onbekend

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29. Ten-year mortality after treating obstructive coronary atherosclerosis with contemporary stents in patients with or without concomitant peripheral arterial disease
Pinxterhuis TH, Ploumen EH, van Vliet D, Gert van Houwelingen K, Stoel MG, de Man FH, Hartmann M, Zocca P, Linssen GC, Geelkerken RH, Doggen CJ, von Birgelen C.

BACKGROUND AND AIMS: Previous studies in percutaneous coronary intervention (PCI) patients showed a higher 3-year adverse event risk, including all-cause mortality, in those with concomitant peripheral arterial disease (PADs). Ten-year data of mortality and causes of death are scarce. This analysis assessed PCI patients, treated with contemporary drug-eluting stents, the impact of concomitant PADs on very long-term mortality, and causes of death.
METHODS: We assessed PCI all-comers from our center who participated in the TWENTE and DUTCH PEERS trials (clinicaltrials.gov:NCT01066650, NCT01331707), comparing patients with versus without PADs. Life status was checked in the Dutch Personal Records Database; causes of death were obtained from medical records.
RESULTS: Of 2705 study patients, 668 (24.7%) died during follow-up: 88/212 (41.5%) patients with PADs and 580/2493 (23.1%) without PADs. In PADs patients, the 10-year rate of all-cause mortality was about twice as high as in patients without PADs (41.5% vs.23.1%, HR: 2.05, 95%-CI: 1.64-2.57, p<0.001). For both groups, the rates of patients dying from various causes of death were: cardiac

(14.1% vs.6.8%), vascular (2.8% vs. 1.1%), non-cardiovascular (17.4% vs. 9.8%), and unclear causes (7.1% vs. 5.3%), without a statistically significant between-group difference. When multivariate analysis was adjusted for between-group differences in cardiovascular risk profile, PADs remained predictor of all-cause mortality (adjusted HR: 1.38, 95%-CI: 1.08-1.75, p=0.01).
CONCLUSIONS: The 10-year all-cause mortality rate in PCI patients with concomitant PADs was almost twice as high as in those without PADs. Age and other traditional cardiovascular risk factors were higher in patients with PADs, but after correction for these confounders PADs still accounted for almost 40% increase in mortality.

Gepubliceerd: Atherosclerosis. 2024;392:117488.
Impact factor: 5.7 ; Q1

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40. Invasiveness of previous treatment for peripheral arterial disease and risk of adverse cardiac events after coronary stenting
Pinxterhuis TH, von Birgelen C, Geelkerken RH, Doggen CJM, Menting TP, van Houwelingen KG, Linssen GCM, Ploumen EH.

Patients with peripheral arterial disease (PADs), undergoing percutaneous coronary intervention (PCI), have higher adverse event risks. The effect of invasiveness of PADs treatment on PCI outcome is unknown. This study assessed the impact of the invasiveness of previous PADs treatment (invasive or non-invasive) on event risks after PCI with contemporary drug-eluting stents. This post-hoc analysis pooled 3-year patient-level data of PCI all-comer patients living in the eastern Netherlands, previously treated for PADs. PADs included symptomatic atherosclerotic lesion in the lower or upper extremities; carotid or vertebral arteries; mesenteric arteries or aorta. Invasive PADs treatment comprised endarterectomy, bypass surgery, percutaneous transluminal angioplasty, stenting or amputation; non-invasive treatment consisted of medication and participation in exercise programs. Primary endpoint was (coronary) target vessel failure: composite of cardiac mortality, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. Of 461 PCI patients with PADs, information on PADs treatment was available in 357 (77.4%) patients; 249 (69.7%) were treated invasively and 108 (30.3%) non-invasively. Baseline and PCI procedural characteristics showed no between-group difference. Invasiveness of PADs treatment was not associated with adverse event risks, including target vessel failure (20.5% vs. 16.0%; HR: 1.30, 95%-CI 0.75-2.26, p = 0.35), major adverse cardiac events (23.3% vs. 20.4%; HR: 1.16, 95%-CI 0.71-1.90, p = 0.55), and all-cause mortality (12.1% vs. 8.3%; HR: 1.48, 95%-CI 0.70-3.13, p = 0.30). In PADs patients participating in PCI trials, we found no significant relation between the invasiveness of previous PADs treatment and 3-year outcome after PCI. Consequently, high-risk PCI patients can be identified by consulting medical records, searching for PADs, irrespective of the invasiveness of PADs treatment.

Gepubliceerd: Cardiovasc Interv Ther. 2024;39(2):173-82.
Impact factor: 5.8 ; Q1

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41. Perineural Invasion is an Important Prognostic Factor in Patients With Radically Resected (R0) and Node-negative (pN0) Pancreatic Cancer
Schouten TJ, Kroon VJ, Besselink MG, Bosscha K, Busch OR, Crobach A, van Dam RM, Doukas M, Fariña Sarasquesta A, Festen S, Groot Koerkamp B, van der Harst E, Heij LR, de Hingh I, Kazemier G, Liem MSL, de Meijer VE, Mieog JSD, Patijn GA, Raicu GM, Roos D, Schreinemakers JMJ, Stommel MWJ, Wilmink HJ, Wit F, Brosens LAA, van Santvoort HC, Molenaar IQ, Daamen LA.

OBJECTIVE: To investigate the association between perineural invasion (PNI) and overall survival (OS) in a nationwide cohort of patients with resected pancreatic ductal adenocarcinoma (PDAC), stratified for margin negative (R0) or positive (R1) resection and absence or presence of lymph node metastasis (pN0 or pN1-N2, respectively).
BACKGROUND: Patients with R0 and pN0 resected PDAC have a relatively favorable prognosis. As PNI is associated with worse OS, this might be a useful factor to provide further prognostic information for patients counselling.
METHODS: A nationwide observational cohort study was performed including all patients who underwent PDAC resection in the Netherlands (2014-2019) with complete information on relevant pathological features (PNI, R status, and N status). OS was assessed using Kaplan-Meier curves, and Cox-proportional hazard analyses were performed to calculate hazard ratio's (HR) with corresponding 95% confidence intervals (CI).
RESULTS: In total, 1630 patients were included with a median follow-up of 43 (interquartile range 33-58) months. PNI was independently associated with worse OS in both R0 patients (HR 1.49 [95%CI 1.18-1.88]; P<0.001) and R1 patients (HR 1.39 [95% CI 1.06-1.83]; P=0.02), as well as in pN0 patients (HR 1.75 [95%CI 1.27-2.41]; P<0.001) and pN1-N2 patients (HR 1.35 [95% CI 1.10-1.67]; P<0.01). In 315 patients with R0N0, multivariable analysis showed that PNI was the strongest predictor of OS (HR 2.24 [95% CI 1.52-3.30]; P<0.001).
CONCLUSION: PNI is strongly associated with worse survival in patients with resected PDAC, in particular in patients with relatively favorable pathological features. These findings may aid patient stratification and counselling and help guide treatment strategies.

Gepubliceerd: Ann Surg. 2024.
Impact factor: 6.4 ; Q1

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42. The Value of Biological and Conditional Factors for Staging of Patients with Resectable Pancreatic Cancer Undergoing Upfront Resection: A Nationwide Analysis

Schouten TJ, van Goor I, Dorland GA, Besselink MG, Bonsing BA, Bosscha K, Brosens LAA, Busch OR, Cirkel GA, van Dam RM, Festen S, Groot Koerkamp B, van der Harst E, de Hingh I, Intven MPW, Kazemier G, Liem MSL, van Lienden KP, Los M, de Meijer VE, Patijn GA, Schreinemakers JMJ, Stommel MWJ, van Tienhoven GJ, Verdonk RC, Verkooijen HM, van Santvoort HC, Molenaar IQ, Daamen LA.

BACKGROUND: Novel definitions suggest that resectability status for pancreatic ductal adenocarcinoma (PDAC) should be assessed beyond anatomical criteria, considering both biological and conditional factors. This has, however, yet to be validated on a nationwide scale. This study evaluated the prognostic value of biological and conditional factors for staging of patients with resectable PDAC.
PATIENTS AND METHODS: A nationwide observational cohort study was performed, including all consecutive patients who underwent upfront resection of National Comprehensive Cancer Network resectable PDAC in the Netherlands (2014-2019) with complete information on preoperative carbohydrate antigen (CA) 19-9 and Eastern Cooperative Oncology Group (ECOG) performance status. PDAC was considered biologically unfavorable (R(B+)) if CA19-9 ≥ 500 U/mL and favorable (R(B-)) otherwise. ECOG ≥ 2 was considered conditionally unfavorable (R(C+)) and favorable otherwise (R(C-)). Overall survival (OS) was assessed using Kaplan-Meier and Cox-proportional hazard analysis, presented as hazard ratios (HRs) with 95% confidence interval (CI).
RESULTS: Overall, 688 patients were analyzed with a median overall survival (OS) of 20 months (95% CI 19-23). OS was 14 months (95% CI 10 months-median not reached) in 20 R(B+C+) patients (3%; HR 1.61, 95% CI 0.86-2.70), 13 months (95% CI 11-15) in 156 R(B+C-) patients (23%; HR 1.86, 95% CI 1.50-2.31), and 21 months (95% CI 12-41) in 47 R(B-C+) patients (7%; HR 1.14, 95% CI 0.80-1.62) compared with 24 months (95% CI 22-27) in 465 patients with R(B-C-) PDAC (68%; reference).
CONCLUSIONS: Survival after upfront resection of anatomically resectable PDAC is worse in patients

with CA19-9 ≥ 500 U/mL, while performance status had no impact. This supports consideration of CA19-9 in preoperative staging of resectable PDAC.

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Impact factor: 3.5 ; Q1

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43. Minimum and Optimal CA19-9 Response After Two Months Induction Chemotherapy in Patients With Locally Advanced Pancreatic Cancer: A Nationwide Multicenter Study
Seelen LWF, Doppenberg D, Stoop TF, Nagelhout A, Brada LJH, Bosscha K, Busch OR, Cirkel GA, den Dulk M, Daams F, van Dieren S, van Eijck CHJ, Festen S, Groot Koerkamp B, Haj Mohammad N, de Hingh I, Lips DJ, Los M, de Meijer VE, Patijn GA, Polée MB, Stommel MWJ, Walma MS, de Wilde RF, Wilmink JW, Molenaar IQ, van Santvoort HC, Besselink MG.

OBJECTIVE: This nationwide multicenter study aimed to define clinically relevant thresholds of relative serum CA19-9 response after 2 months of induction chemotherapy in patients with locally advanced pancreatic cancer (LAPC).
BACKGROUND: CA19-9 is seen as leading biomarker for response evaluation in patients with LAPC, but early clinically useful cut-offs are lacking.
METHODS: All consecutive patients with LAPC after 4 cycles (m)FOLFIRINOX or 2 cycles gemcitabine-nab-paclitaxel induction chemotherapy (±radiotherapy) with CA19-9 ≥5 U/mL at baseline were analyzed (2015-2019). The association of CA19-9 response with median OS (mOS) was evaluated for different CA19-9 cut-off points. Minimum and optimal CA19-9 response were established via log-rank test. Predictors for OS were analyzed using COX regression analysis.
RESULTS: Overall, 212 patients were included, of whom 42 (19.8%) underwent resection. Minimum CA19-9 response demonstrating a clinically significant median OS difference (12.7 vs. 19.6 months) was seen at ≥40% CA19-9 decrease. The optimal cutoff for CA19-9 response was ≥60% decrease (21.7 vs. 14.0 mo, P =0.021). Only for patients with elevated CA19-9 levels at baseline (n=184), CA19-9 decrease ≥60% [hazard ratio (HR)=0.59, 95% CI, 0.36-0.98, P =0.042] was independently associated with prolonged OS, as were SBRT (HR=0.42, 95% CI, 0.25-0.70; P =0.001), and resection (HR=0.25, 95% CI, 0.14-0.46, P <0.001), and duration of chemotherapy (HR=0.75, 95% CI, 0.69-0.82, P <0.001).
CONCLUSIONS: CA19-9 decrease of ≥60% following induction chemotherapy as optimal response cut-off in patients with LAPC is an independent predictor for OS when CA19-9 is increased at baseline. Furthermore, ≥40% is the minimum cut-off demonstrating survival benefit. These cut-offs may be used when discussing treatment strategies during early response evaluation.

Gepubliceerd: Ann Surg. 2024;279(5):832-41.
Impact factor: 6.4 ; Q1

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44. Prognostic Implications of Lateral Lymph Nodes in Rectal Cancer: A Population-Based Cross-sectional Study With Standardized Radiological Evaluation After Dedicated Training
Sluckin TC, van Geffen EGM, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; van Duyn EB, van der Burg S.

BACKGROUND: There is an ongoing discussion regarding the prognostic implications of the presence, short-axis diameter, and location of lateral lymph nodes.
OBJECTIVE: To analyze lateral lymph node characteristics, the role of downsizing on restaging MRI, and associated local recurrence rates for patients with cT3-4 rectal cancer after MRI re-review and training.

DESIGN: Retrospective population-based cross-sectional study. SETTINGS: This collaborative project was led by local investigators from surgery and radiology departments in 60 Dutch hospitals.
PATIENTS: A total of 3057 patients underwent rectal cancer surgery in 2016: 1109 had a cT3-4 tumor located ≤8 cm from the anorectal junction, of whom 891 received neoadjuvant therapy. MAIN
OUTCOME MEASURES: Local recurrence and (ipsi) lateral local recurrence rates.
RESULTS: Re-review identified 314 patients (35%) with visible lateral lymph nodes. Of these, 30 patients had either only long-stretched obturator (n = 13) or external iliac (n = 17) nodes, and both did not lead to any lateral local recurrences. The presence of internal iliac/obturator lateral lymph nodes (n = 284) resulted in 4-year local recurrence and lateral local recurrence rates of 16.4% and 8.8%, respectively. Enlarged (≥7 mm) lateral lymph nodes (n = 122) resulted in higher 4-year local recurrence (20.8%, 13.1%, 0%; p <.001) and lateral local recurrence (14.7%, 4.4%, 0%; p < 0.001) rates compared to smaller and no lateral lymph nodes, respectively. Visible lateral lymph nodes (HR 1.8 [1.1-2.8]) and enlarged lateral lymph nodes (HR 1.9 [1.1-3.5]) were independently associated with local recurrence in multivariable analysis. Enlarged lateral lymph nodes with malignant features had higher 4-year lateral local recurrence rates of 17.0%. Downsizing had no impact on lateral local recurrence rates. Enlarged lateral lymph nodes were found to be associated with higher univariate 4-year distant metastasis rates (36.4% vs 24.4%; p = 0.021), but this was not significant in multivariable analyses (HR 1.3 [0.9-1.]) and did not worsen overall survival.
LIMITATIONS: This study was limited by the retrospective design and total number of patients with lateral lymph nodes.
CONCLUSIONS: The risk of lateral local recurrence due to (enlarged) lateral lymph nodes was confirmed, but without the prognostic impact of downsizing after neoadjuvant therapy. These results point toward the incorporation of primary lateral lymph node size into treatment planning.

Gepubliceerd: Dis Colon Rectum. 2024;67(1):42-53.
Impact factor: 3.7 ; Q1

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45. Laparoscopic and robotic total mesorectal excision in overweight and obese patients: multinational cohort study
Smalbroek BP, Geitenbeek RTJ, Dijksman LM, Khan J, Denost Q, Rouanet P, Hompes R, Consten ECJ, Smits AB, MIRECA study group and EUREKA study group; van Duyn EB.

Gepubliceerd: Br J Surg. 2024;111(10).
Impact factor: 8.7 ; Q1

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46. Nationwide Use and Outcome of Surgery for Locally Advanced Pancreatic Cancer Following Induction Chemotherapy
Stoop TF, Seelen LWF, van 't Land FR, Lutchman KRD, van Dieren S, Lips DJ, van der Harst E, Kazemier G, Patijn GA, de Hingh IH, Wijsman JH, Erdmann JI, Festen S, Groot Koerkamp B, Mieog JSD, den Dulk M, Stommel MWJ, Busch OR, de Wilde RF, de Meijer VE, Te Riele W, Molenaar IQ, van Eijck CHJ, van Santvoort HC, Besselink MG.

BACKGROUND: Several international high-volume centers have reported good outcomes after resection of locally advanced pancreatic cancer (LAPC) following chemo(radio)therapy, but it is unclear how this translates to nationwide clinical practice and outcome. This study aims to assess the nationwide use and outcome of resection of LAPC following induction chemo(radio)therapy.
PATIENTS AND METHODS: A multicenter retrospective study including all patients who underwent resection for LAPC following chemo(radio)therapy in all 16 Dutch pancreatic surgery centers (2014-

2020), registered in the mandatory Dutch Pancreatic Cancer Audit. LAPC is defined as arterial involvement > 90° and/or portomesenteric venous > 270° involvement or occlusion.
RESULTS: Overall, 142 patients underwent resection for LAPC, of whom 34.5% met the 2022 National Comprehensive Cancer Network criteria. FOLFIRINOX was the most commonly (93.7%) used chemotherapy [median 5 cycles (IQR 4-8)]. Venous and arterial resections were performed in 51.4% and 14.8% of patients. Most resections (73.9%) were performed in high-volume centers (i.e., ≥ 60 pancreatoduodenectomies/year). Overall median volume of LAPC resections/center was 4 (IQR 1-7). In-hospital/30-day major morbidity was 37.3% and 90-day mortality was 4.2%. Median OS from diagnosis was 26 months (95% CI 23-28) and 5-year OS 18%. Surgery in high-volume centers [HR = 0.542 (95% CI 0.318-0.923)], ypN1-2 [HR = 3.141 (95% CI 1.886-5.234)], and major morbidity [HR = 2.031 (95% CI 1.272-3.244)] were associated with OS.
CONCLUSIONS: Resection of LAPC following chemo(radio)therapy is infrequently performed in the Netherlands, albeit with acceptable morbidity, mortality, and OS. Given these findings, a structured nationwide approach involving international centers of excellence would be needed to improve selection of patients with LAPC for surgical resection following induction therapy.

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Impact factor: 3.5 ; Q1

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47. ASO Author Reflections: Nationwide Experience on Locally Advanced Pancreatic Cancer Surgery After Induction Chemotherapy in the Netherlands: A Stepping Stone for the PREOPANC-4 Trial
Stoop TF, Seelen LWF, van 't Land FR, van Eijck CHJ, van Santvoort HC, Besselink MG, Dutch Pancreatic Cancer Group; Lips DJ.

Gepubliceerd: Ann Surg Oncol. 2024;31(4):2658-9.
IF 3.5 ; Q1

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48. Feasibility, safety and preliminary efficacy of preoperative stereotactic radiotherapy on the future pancreatic neck transection margin to reduce the risk of pancreatic fistula after high-risk pancreatoduodenectomy (FIBROPANC): protocol for a multicentre, single-arm trial
Suurmeijer JA, Wismans LV, Hendriks TE, Bruynzeel AM, Nuyttens JJ, Intven MPW, van Driel L, Groot Koerkamp B, Busch OR, Stoker JJ, Verheij J, Farina A, Doukas M, de Hingh IHJ, Lips DJ, van der Harst E, van Tienhoven G, Besselink MG, van Eijck CHJ.

INTRODUCTION: Postoperative pancreatic fistula (POPF) occurs in 25% of patients undergoing a high-risk pancreatoduodenectomy (PD) and is a driving cause of major morbidity, mortality, prolonged hospital stay and increased costs after PD. There is a need for perioperative methods to decrease these risks. In recent studies, preoperative chemoradiotherapy in patients with pancreatic ductal adenocarcinoma (PDAC) reduced the rate of POPF seemingly due to radiation-induced pancreatic fibrosis. However, patients with a high risk of POPF mostly have a non-pancreatic periampullary tumour and do not receive radiotherapy. Prospective studies using radiotherapy specifically to reduce the risk of POPF have not been performed. We aim to assess the safety, feasibility and preliminary efficacy of preoperative stereotactic radiotherapy on the future pancreatic neck transection margin to reduce the rate of POPF.
METHODS AND ANALYSIS: In this multicentre, single-arm, phase II trial, we aim to assess the feasibility and safety of a single fraction of preoperative stereotactic radiotherapy (12 Gy) to a 4 cm area around the future pancreatic neck transection margin in patients at high risk of developing POPF after PD aimed to reduce the risk of grade B/C POPF. Adult patients scheduled for PD for malignant and premalignant periampullary tumours, excluding PDAC, with a pancreatic duct diameter ≤3 mm

will be included in centres participating in the Dutch Pancreatic Cancer Group. The primary outcome is the safety and feasibility of single-dose preoperative stereotactic radiotherapy before PD. The most relevant secondary outcomes are grade B/C POPF and the difference in the extent of fibrosis between the radiated and non-radiated (uncinate margin) pancreas. Evaluation of endpoints will be performed after inclusion of 33 eligible patients.
ETHICS AND DISSEMINATION: Ethical approval was obtained by the Amsterdam UMC's accredited Medical Research Ethics Committee (METC). All included patients are required to have provided written informed consent. The results of this trial will be used to determine the need for a randomised controlled phase III trial and submitted to a high-impact peer-reviewed medical journal regardless of the study outcome.
TRIAL REGISTRATION NUMBER: NL72913 (Central Committee on Research involving Human Subjects Registry) and NCT05641233 (ClinicalTrials).

Gepubliceerd: BMJ Open. 2024;14(9):e087193.
Impact factor: 2.3 ; Q2

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49. Covered versus bare-metal stenting of the mesenteric arteries in patients with chronic mesenteric ischaemia (CoBaGI): a multicentre, patient-blinded and investigator-blinded, randomised controlled trial
Terlouw LG, van Dijk LJD, van Noord D, Bakker OJ, Bijdevaate DC, Erler NS, Fioole B, Harki J, van den Heuvel DAF, Hinnen JW, Kolkman JJ, Nikkessen S, van Petersen AS, Smits HFM, Verhagen HJM, de Vries AC, de Vries JPM, Vroegindeweij D, Geelkerken RH, Bruno MJ, Moelker A.

BACKGROUND: Mesenteric artery stenting with a bare-metal stent is the current treatment for atherosclerotic chronic mesenteric ischaemia. Long-term patency of bare-metal stents is unsatisfactory due to in-stent intimal hyperplasia. Use of covered stents might improve long-term patency. We aimed to compare the patency of covered stents and bare-metal stents in patients with chronic mesenteric ischaemia.
METHODS: We conducted a multicentre, patient-blinded and investigator-blinded, randomised controlled trial including patients with chronic mesenteric ischaemia undergoing mesenteric artery stenting. Six centres in the Netherlands participated in this study, including two national chronic mesenteric ischaemia expert centres. Patients aged 18 years or older were eligible for inclusion when an endovascular mesenteric artery revascularisation was scheduled and a consensus diagnosis of chronic mesenteric ischaemia was made by a multidisciplinary team of gastroenterologists, interventional radiologists, and vascular surgeons. Exclusion criteria were stenosis length of 25 mm or greater, stenosis caused by median arcuate ligament syndrome or vasculitis, contraindication for CT angiography, or previous target vessel revascularisation. Digital 1:1 block randomisation with block sizes of four or six and stratification by inclusion centre was used to allocate patients to undergo stenting with bare-metal stents or covered stents at the start of the procedure. Patients, physicians performing follow-up, investigators, and radiologists were masked to treatment allocation. Interventionalists performing the procedure were not masked. The primary study outcome was the primary patency of covered stents and bare-metal stents at 24 months of follow-up, evaluated in the modified intention-to-treat population, in which stents with missing data for the outcome were excluded. Loss of primary patency was defined as the performance of a re-intervention to preserve patency, or 75% or greater luminal surface area reduction of the target vessel. CT angiography was performed at 6 months, 12 months, and 24 months post intervention to assess patency. The study is registered with ClinicalTrials.gov (NCT02428582) and is complete.
FINDINGS: Between April 6, 2015, and March 11, 2019, 158 eligible patients underwent mesenteric artery stenting procedures, of whom 94 patients (with 128 stents) provided consent and were included in the study. 47 patients (62 stents) were assigned to the covered stents group (median age 69·0 years [IQR 63·0-76·5], 28 [60%] female) and 47 patients (66 stents) were assigned to the bare-

metal stents group (median age 70·0 years [63·5-76·5], 33 [70%] female). At 24 months, the primary patency of covered stents (42 [81%] of 52 stents) was superior to that of bare-metal stents (26 [49%] of 53; odds ratio [OR] 4·4 [95% CI 1·8-10·5]; p<0·0001). A procedure-related adverse event occurred in 17 (36%) of 47 patients in the covered stents group versus nine (19%) of 47 in the bare-metal stent group (OR 2·4 [95% CI 0·9-6·3]; p=0·065). Most adverse events were related to the access site, including haematoma (five [11%] in the covered stents group vs six [13%] in the bare-metal stents group), pseudoaneurysm (five [11%] vs two [4%]), radial artery thrombosis (one [2%] vs none), and intravascular closure device (none vs one [2%]). Six (13%) patients in the covered stent group versus one (2%) in the bare-metal stent group had procedure-related adverse events not related to the access site, including stent luxation (three [6%] vs none), major bleeding (two (4%) vs none), mesenteric artery perforation (one [2%] vs one [2%]), mesenteric artery dissection (one [2%] vs one [2%]), and death (one [2%] vs none).
INTERPRETATION: The findings of this trial support the use of covered stents for mesenteric artery stenting in patients with chronic mesenteric ischaemia. FUNDING: Atrium Maquet Getinge Group.

Gepubliceerd: Lancet Gastroenterol Hepatol. 2024;9(4):299-309.
Impact factor: 38.6 ; Q1

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50. Prophylactic abdominal drainage after distal pancreatectomy (PANDORINA): an international, multicentre, open-label, randomised controlled, non-inferiority trial
van Bodegraven EA, Balduzzi A, van Ramshorst TME, Malleo G, Vissers FL, van Hilst J, Festen S, Abu Hilal M, Asbun HJ, Michiels N, Koerkamp BG, Busch ORC, Daams F, Luyer MDP, Ramera M, Marchegiani G, Klaase JM, Molenaar IQ, de Pastena M, Lionetto G, Vacca PG, van Santvoort HC, Stommel MWJ, Lips DJ, Coolsen MME, Mieog JSD, Salvia R, van Eijck CHJ, Besselink MG.

BACKGROUND: Prophylactic passive abdominal drainage is standard practice after distal pancreatectomy. This approach aims to mitigate the consequences of postoperative pancreatic fistula (POPF) but its added value, especially in patients at low risk of POPF, is currently being debated. We aimed to assess the non-inferiority of a no-drain policy in patients after distal pancreatectomy.
METHODS: In this international, multicentre, open-label, randomised controlled, non-inferiority trial, we recruited patients aged 18 years or older undergoing open or minimally invasive elective distal pancreatectomy for all indications in 12 centres in the Netherlands and Italy. We excluded patients with an American Society of Anesthesiology (ASA) physical status of 4-5 or WHO performance status of 3-4, added by amendment following the death of a patient with ASA 4 due to a pre-existing cardiac condition. Patients were randomly assigned (1:1) intraoperatively by permuted blocks (size four to eight) to either no drain or prophylactic passive drain placement, stratified by annual centre volume (<40 or ≥40 distal pancreatectomies) and low risk or high risk of grade B or C POPF. High-risk was defined as a pancreatic duct of more than 3 mm in diameter, a pancreatic thickness at the neck of more than 19 mm, or both, based on the Distal Pancreatectomy Fistula Risk Score. Other patients were considered low-risk. The primary outcome was the rate of major morbidity (Clavien-Dindo score ≥III), and the most relevant secondary outcome was grade B or C POPF, grading per the International Study Group for Pancreatic Surgery. Outcomes were assessed up to 90 days postoperatively and analysed in the intention-to-treat population and per-protocol population, which only included patients who received the allocated treatment. A prespecified non-inferiority margin of 8% was compared with the upper limit of the two-sided 95% CI (Wald) of unadjusted risk difference to assess non-inferiority. This trial is closed and registered in the Netherlands Trial Registry, NL9116.
FINDINGS: Between Oct 3, 2020, and April 28, 2023, 376 patients were screened for eligibility and 282 patients were randomly assigned to the no-drain group (n=138; 75 [54%] women and 63 [46%] men) or the drain group (n=144; 73 [51%] women and 71 [49%] men). Seven patients in the no-drain group received a drain intraoperatively; consequently, the per-protocol population included 131 patients in the no-drain group and 144 patients in the drain group. The rate of major morbidity was

non-inferior in the no-drain group compared with the drain group in the intention-to-treat analysis (21 [15%] vs 29 [20%]; risk difference -4·9 percentage points [95% CI -13·8 to 4·0]; p(non-inferiority)=0·0022) and the per-protocol analysis (21 [16%] vs 29 [20%]; risk difference -4·1 percentage points [-13·2 to 5·0]; p(non-inferiority)=0·0045). Grade B or C POPF was observed in 16 (12%) patients in the no-drain group and in 39 (27%) patients in the drain group (risk difference -15·5 percentage points [95% CI -24·5 to -6·5]; p(non-inferiority)<0·0001) in the intention-to-treat analysis. Three patients in the no-drain group died within 90 days; the cause of death in two was not considered related to the trial. The third death was a patient with an ASA score of 4 who died after sepsis and a watershed cerebral infarction at second admission, leading to multiple organ failure. No patients in the drain group died within 90 days.
INTERPRETATION: A no-drain policy is safe in terms of major morbidity and reduced the detection of grade B or C POPF, and should be the new standard approach in eligible patients undergoing distal pancreatectomy.
FUNDING: Ethicon UK (Johnson & Johnson Medical, Edinburgh, UK).

Gepubliceerd: Lancet Gastroenterol Hepatol. 2024;9(5):438-47.
Impact factor: 38.6 ; Q1

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51. Minimally invasive robot-assisted and laparoscopic distal pancreatectomy in a pan-European registry a retrospective cohort study

van Bodegraven EA, van Ramshorst TME, Bratlie SO, Kokkola A, Sparrelid E, Björnsson B, Kleive D, Burgdorf SK, Dokmak S, Groot Koerkamp B, Cabús SS, Molenaar IQ, Boggi U, Busch OR, Petrič M, Roeyen G, Hackert T, Lips DJ, D'Hondt M, Coolsen MME, Ferrari G, Tingstedt B, Serrablo A, Gaujoux S, Ramera M, Khatkov I, Ausania F, Souche R, Festen S, Berrevoet F, Keck T, Sutcliffe RP, Pando E, de Wilde RF, Aussilhou B, Krohn PS, Edwin B, Sandström P, Gilg S, Seppänen H, Vilhav C, Abu Hilal M, Besselink MG.

BACKGROUND: International guidelines recommend monitoring the use and outcome of minimally invasive pancreatic surgery (MIPS). However, data from prospective international audits on minimally invasive distal pancreatectomy (MIDP) are lacking. This study examined the use and outcome of robot-assisted (RDP) and laparoscopic (LDP) distal pancreatectomy in the E-MIPS registry.
PATIENTS AND METHODS: Post-hoc analysis in a prospective audit on MIPS, including consecutive patients undergoing MIDP in 83 centers from 19 European countries (01-01-2019/31-12-2021). Primary outcomes included intraoperative events (grade 1: excessive blood loss, grade 2: conversion/change in operation, grade 3: intraoperative death), major morbidity, and in-hospital/30-day mortality. Multivariable logistic regression analyses identified high-risk groups for intraoperative events. RDP and LDP were compared in the total cohort and high-risk groups.
RESULTS: Overall, 1672 patients undergoing MIDP were included; 606 (36.2%) RDP and 1066 (63.8%) LDP. The annual use of RDP increased from 30.5% to 42.6% (P <0.001). RDP was associated with fewer grade 2 intraoperative events compared with LDP (9.6% vs. 16.8%, P <0.001), with longer operating time (238 vs. 201 min, P <0.001). No significant differences were observed between RDP and LDP regarding major morbidity (23.4% vs. 25.9%, P =0.264) and in-hospital/30-day mortality (0.3% vs. 0.8%, P =0.344). Three high-risk groups were identified; BMI greater than 25 kg/m 2 , previous abdominal surgery, and vascular involvement. In each group, RDP was associated with fewer conversions and longer operative times.
CONCLUSION: This European registry-based study demonstrated favorable outcomes for MIDP, with mortality rates below 1%. LDP remains the predominant approach, whereas the use of RDP is increasing. RDP was associated with fewer conversions and longer operative time, including in high-risk subgroups. Future randomized trials should confirm these findings and assess cost differences.

Gepubliceerd: Int J Surg. 2024;110(6):3554-61.

Impact factor: 10.1 ; Q1

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52. Better stoma care using the Stoma App: does it help? A first randomized double-blind clinical trial on the effect of mobile healthcare on quality of life in stoma patients
van der Storm SL, Consten ECJ, Govaert M, Tuynman JB, Oosterling SJ, Grotenhuis BA, Smits AB, Marsman HA, van Rossem CC, van Duyn EB, de Nes LCF, Verdaasdonk E, de Vries Reilingh TS, Vening W, Bemelman WA, Schijven MP.

BACKGROUND: Receiving a stoma significantly impacts patients' quality of life. Coping with this new situation can be difficult, which may result in a variety of physical and psychosocial problems. It is essential to provide adequate guidance to help patients cope with their stoma, as this positively influences self-efficacy in return. Higher self-efficacy reduces psychosocial problems increasing patient's quality of life. This study investigates whether a new mobile application, the Stoma App, improves quality of life. And if personalized guidance, timed support, and peer contact offered as an in-app surplus makes a difference.
METHODS: A double-blind, randomized controlled trial was conducted between March 2021 and April 2023. Patients aged > 18 years undergoing ileostomy or colostomy surgery, in possession of a compatible smartphone were included. The intervention group received the full version of the app containing personalized and time guidance, peer support, and generic (non-personalized) stoma-related information. The control group received a restricted version with only generic information. Primary outcome was stoma quality of life. Secondary outcomes included psychological adaption, complications, re-admittance, reoperations, and length of hospital stay.
RESULTS: The intervention version of the app was used by 96 patients and the control version by 112 patients. After correction for confounding, the intervention group reported a significant 3.1-point improvement in stoma-related quality of life one month postoperatively (p = 0.038). On secondary outcomes, no significant improvements could be retrieved of the intervention group.
CONCLUSION: The Stoma App improves the quality of life of stoma patients. Peer support and personalized guidance are of significant importance in building self-efficacy. It is to be recommended to implement Stoma app-freely available software qualifying as a medical device-in standard stoma care pathways for the benefits of both patients and healthcare providers.

Gepubliceerd: Surg Endosc. 2024;38(3):1442-53.
Impact factor: 2.7 ; Q1

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53. Metformin boosts antitumor immunity and improves prognosis in upfront resected pancreatic cancer: an observational study
van Eijck CWF, Vadgama D, van Eijck CHJ, Wilmink JW, Dutch Pancreatic Cancer Group: Lips DJ.

BACKGROUND: Beyond demographic and immune factors, metabolic considerations, particularly metformin's recognized impact in oncology, warrant exploration in treating pancreatic cancer. This study aimed to investigate the influence of metformin on patient survival and its potential correlation with distinct immune profiles in pancreatic ductal adenocarcinoma (PDAC) tumors.
METHODS: We included 82 upfront resected and 66 gemcitabine-based neoadjuvant chemoradiotherapy (nCRT)-treated patients from the PREOPANC randomized controlled trial (RCT). Transcriptomic NanoString immunoprofiling was performed for a subset of 96 available resected specimens.
RESULTS: Disparities in survival outcomes and immune profiles were apparent between metformin and non-metformin users in upfront resected patients but lacking in nCRT-treated patients. Compared to non-metformin users, upfront resected metformin users showed a higher median overall survival

(OS) of 29 vs 14 months and a better 5-year OS rate of 19% vs 5%. Furthermore, metformin use was a favorable prognostic factor for OS in the upfront surgery group (HR = 0.56; 95% CI = 0.32 to 0.99). Transcriptomic data revealed that metformin users significantly underexpressed genes related to pro-tumoral immunity, including monocyte to M2 macrophage polarization and activation. Furthermore, the relative abundance of anti-inflammatory CD163+ MRC1+ M2 macrophages in non-metformin users and immune-activating CD1A+ CD1C+ dendritic cells in metformin users was heightened ($P < .001$).
CONCLUSION: This study unveils immune profile changes resulting from metformin use in upfront resected pancreatic cancer patients, possibly contributing to prolonged survival outcomes. Specifically, metformin use may decrease the abundance and activity of pro-tumoral M2 macrophages and increase the recruitment and function of tumor-resolving DCs, favoring antitumor immunity.[PREOPANC trial EudraCT: 2012-003181-40].

Gepubliceerd: J Natl Cancer Inst. 2024;116(8):1374-83.
Impact factor: 7.2 ; Q1

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54. An observational cohort of patients with colorectal peritoneal metastases or pseudomyxoma peritonei treated with CRS-HIPEC: Development and first results of the Dutch CRS-HIPEC quality registry
van Erning FN, van den Heuvel TBM, Sijtsma FPC, Boerma D, Brandt-Kerkhof ARM, Bremers AJ, van Duyn EB, van Grevenstein HMU, Hemmer PHJ, Kok NFM, Madsen E, de Reuver PR, Wiezer RJ, Witkamp AJ, Nienhuijs SW, Poelmann FB, Tuynman JB, Been LB, Rovers KP, de Hingh I.

INTRODUCTION: To improve care for patients with colorectal peritoneal metastases (CRC-PM) or pseudomyxoma peritonei (PMP), the Dutch CRS-HIPEC quality registry was initiated in 2019. The aims are to describe the development and content of this registry and to give insight into the data collected during the first years.
MATERIALS AND METHODS: The registry is an observational cohort in the Netherlands. All patients with CRC-PM or PMP who intend to undergo cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) from 6 hospitals are included. Clinical data and outcomes (including hospital variation) were analyzed.
RESULTS: In 2019-2022, 889 patients were included in the CRS-HIPEC quality registry: 749 (84 %) with CRC-PM and 140 (16 %) with PMP. Peritoneal metastases were diagnosed synchronously in 51 % of CRC-PM patients and in 94 % of PMP patients. In patients undergoing complete CRS, the median peritoneal cancer index was 8 (IQR 4-13) for CRC-PM and 15 (IQR 6-26) for PMP. Complete cytoreduction was achieved in 639 CRC-PM patients (97 %) and 108 PMP patients (82 %). HIPEC was mainly performed with mitomycin C (CRC-PM: 94 %, PMP: 92 %). Major postoperative complications (Clavien-Dindo grade ≥3) occurred in 148 CRC-PM patients (22 %) and 30 PMP patients (23 %) with 90-day mortality rates of 2 %. In CRC-PM, differences between hospitals were observed regarding proportions of diagnostic laparoscopies/laparotomies, (neo)adjuvant treatment, ostomy formations and re-admissions.
CONCLUSION: The CRS-HIPEC quality registry provides insight into the outcomes of CRS-HIPEC and enables clinical auditing and observational cohort studies aiming to improve treatment outcomes for patients with CRC-PM and PMP.

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Impact factor: 2.9 ; Q1

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55. Value of Size and Malignant Features of Lateral Lymph Nodes in Risk Stratification at Lateral Local Recurrence of Rectal Cancer: A National Cohort Study
van Geffen EGM, Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, van Dieren S, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group: van Duyn EB, van der Burg S.

BACKGROUND: Patients with rectal cancer who have enlarged lateral lymph nodes (LLNs) have an increased risk of lateral local recurrence (LLR). However, little is known about prognostic implications of malignant features (internal heterogeneity, irregular margins, loss of fatty hilum, and round shape) on MRI and number of enlarged LLNs, in addition to LLN size.
METHODS: Of the 3,057 patients with rectal cancer included in this national, retrospective, cross-sectional cohort study, 284 with a cT3-4 tumor located ≤8 cm from the anorectal junction who received neoadjuvant treatment and who had visible LLNs on MRI were selected. Imaging was reassessed by trained radiologists. LLNs were categorized based on size. Influence of malignant features and the number of LLNs on LLR was investigated.
RESULTS: Of 284 patients with at least 1 visible LLN, 122 (43%) had an enlarged node (≥7.0 mm) and 157 (55%) had malignant features. Of the 122 patients with enlarged nodes, 25 had multiple (≥2). In patients with a single enlarged node (n=97), a single malignant feature was associated with a 4-year LLR rate of 0% and multiple malignant features was associated with a rate of 17% (P=.060). In the group with multiple malignant features, their disappearance on restaging was associated with an LLR rate of 13% compared with an LLR rate of 20% for persistent malignant features (P=.532). The presence of intermediate-size LLNs (5.0-6.9 mm) with at least 1 malignant feature was associated with a 4-year LLR rate of 8%; the 4-year LLR rate was 13% when the malignant features persisted on restaging MRI (P=.409). Patients with multiple enlarged LLNs had a 4-year LLR rate of 28% compared with 11% for those with a single enlarged LLN (P=.059).
CONCLUSIONS: The presence of multiple enlarged LLNs (≥7.0 mm), as well as multiple malignant features in an enlarged node contribute to the risk of developing an LLR. These radiologic features can be used for clinical decision-making regarding the potential benefit of LLN dissection.

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Impact factor: 16.4 ; Q1

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56. Optimised treatment of patients with enlarged lateral lymph nodes in rectal cancer: protocol of an international, multicentre, prospective registration study after extensive multidisciplinary training (LaNoReC)
van Geffen EGM, Sluckin TC, Hazen SJA, Horsthuis K, Intven M, van Dieren S, Beets G, Lange MM, Taggart MW, Beets-Tan RGH, Marijnen CAM, Konishi T, Tanis PJ, Kusters M, Dutch Snapshot Research Group: van Duyn EB, van der Burg S.

INTRODUCTION: Inadequate treatment of enlarged lateral lymph nodes (LLNs) in rectal cancer patients is associated with an increased lateral local recurrence (LLR) risk, despite neoadjuvant treatment and total mesorectal excision (TME) surgery. There is a promising role for LLN dissection (LLND) to lower this risk, but this challenging procedure requires appropriate training. This study protocol describes a prospective evaluation of oncological outcomes after standardised treatment based on multidisciplinary training, thereby aiming for a 50% reduction in LLR rate.
METHODS AND ANALYSIS: A prospective registration study will be opened in hospitals in which the involved multidisciplinary team members (radiologists, radiation oncologists, surgeons and pathologists) have received dedicated training to enhance knowledge and awareness of LLNs and in which standardised treatment including LLND has been implemented. Patients with rectal cancer and at least one enlarged LLN (short-axis ≥7.0 mm), or intermediate LLN (short-axis 5.0-6.9 mm) with at least one malignant feature on primary MRI, evaluated by a trained radiologist, are eligible. Patients will undergo neoadjuvant treatment by trained radiation oncologists, followed by TME surgery in

combination with a minimally invasive, nerve-sparing LLND performed by trained surgeons. LLND specimens are evaluated by trained pathologists or grossing assistants. The primary outcome is LLR rate 3 years postoperatively. Secondary outcomes are morbidity, disease-free survival, overall survival and quality of life. To demonstrate a significant reduction in LLR rate from 13% (based on historical control data) to 6% after optimised treatment, 200 patients with enlarged LLNs are required.
ETHICS AND DISSEMINATION: The medical ethics board of the Vrije Universiteit Medical Centre (VUMC), the Netherlands, approved the study on 23 November 2022 (reference: 2021.0524). Participating centres must obtain local approval and participants are required to provide written informed consent. Results obtained from this study will be communicated via peer-reviewed medical journals and presentations at conferences.
TRAIL REGISTRATION NUMBER: NCT04486131, 24 July 2020, https://clinicaltrials.gov/ct2/show/NCT04486131.

Gepubliceerd: BMJ Open. 2024;14(10):e083225.
Impact factor: 2.3 ; Q2

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57. Prediction of Isolated Local Recurrence After Resection of Pancreatic Ductal Adenocarcinoma: A Nationwide Study
van Goor I, Andel PCM, Buijs FS, Besselink MG, Bonsing BA, Bosscha K, Busch OR, Cirkel GA, van Dam RM, Festen S, Koerkamp BG, van der Harst E, de Hingh I, Kazemier G, Liem MSL, Meijer G, de Meijer VE, Nieuwenhuijs VB, Roos D, Schreinemakers JMJ, Stommel MWJ, Wit F, Verdonk RC, van Santvoort HC, Molenaar IQ, Intven MPW, Daamen LA.

BACKGROUND: Distinguishing postoperative fibrosis from isolated local recurrence (ILR) after resection of pancreatic ductal adenocarcinoma (PDAC) is challenging. A prognostic model that helps to identify patients at risk of ILR can assist clinicians when evaluating patients' postoperative imaging. This nationwide study aimed to develop a clinically applicable prognostic model for ILR after PDAC resection.
PATIENTS AND METHODS: An observational cohort study was performed, including all patients who underwent PDAC resection in the Netherlands (2014-2019; NCT04605237). On the basis of recurrence location (ILR, systemic, or both), multivariable cause-specific Cox-proportional hazard analysis was conducted to identify predictors for ILR and presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A predictive model was developed using Akaike's Information Criterion, and bootstrapped discrimination and calibration indices were assessed.
RESULTS: Among 1194/1693 patients (71%) with recurrence, 252 patients (21%) developed ILR. Independent predictors for ILR were resectability status (borderline versus resectable, HR 1.42; 95% CI 1.03-1.96; P = 0.03, and locally advanced versus resectable, HR 1.11; 95% CI 0.68-1.82; P = 0.66), tumor location (head versus body/tail, HR 1.50; 95% CI 1.00-2.25; P = 0.05), vascular resection (HR 1.86; 95% CI 1.41-2.45; P < 0.001), perineural invasion (HR 1.47; 95% CI 1.01-2.13; P = 0.02), number of positive lymph nodes (HR 1.04; 95% CI 1.01-1.08; P = 0.02), and resection margin status (R1 < 1 mm versus R0 ≥ 1 mm, HR 1.64; 95% CI 1.25-2.14; P < 0.001). Moderate performance (concordance index 0.66) with adequate calibration (slope 0.99) was achieved.
CONCLUSIONS: This nationwide study identified factors predictive of ILR after PDAC resection. Our prognostic model, available through www.pancreascalculator.com , can be utilized to identify patients with a higher a priori risk of developing ILR, providing important information in patient evaluation and prognostication.

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Impact factor: 3.5 ; Q1

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58. Position- and posture-dependent vascular imaging-a scoping review
van Zandwijk JK, Simmering JA, Schuurmann RCL, Simonis FFJ, Ten Haken B, de Vries JPM, Geelkerken RH.

OBJECTIVES: Position- and posture-dependent deformation of the vascular system is a relatively unexplored field. The goal of this scoping review was to create an overview of existing vascular imaging modalities in different body positions and postures and address the subsequent changes in vascular anatomy.
METHODS: Scopus, Medline, and Cochrane were searched for literature published between January 1, 2000, and June 30, 2022, incorporating the following categories: image modality, anatomy, orientation, and outcomes.
RESULTS: Out of 2446 screened articles, we included 108. The majority of papers used ultrasound (US, n = 74) in different body positions and postures with diameter and cross-sectional area (CSA) as outcome measures. Magnetic resonance imaging (n = 22) and computed tomography (n = 8) were less frequently used but allowed for investigation of other geometrical measures such as vessel curvature and length. The venous system proved more sensitive to postural changes than the arterial system, which was seen as increasing diameters of veins below the level of the heart when going from supine to prone to standing positions, and vice versa.
CONCLUSIONS: The influence of body positions and postures on vasculature was predominantly explored with US for vessel diameter and CSA. Posture-induced deformation and additional geometrical features that may be of interest for the (endovascular) treatment of vascular pathologies have been limitedly reported, such as length and curvature of an atherosclerotic popliteal artery during bending of the knee after stent placement. The most important clinical implications of positional changes are found in diagnosis, surgical planning, and follow-up after stent placement.
CLINICAL RELEVANCE STATEMENT: This scoping review presents the current state and opportunities of position- and posture-dependent imaging of vascular structures using various imaging modalities that are relevant in the fields of clinical diagnosis, surgical planning, and follow-up after stent placement.
KEY POINTS:
• The influence of body positions and postures on the vasculature was predominantly investigated with US for vessel diameter and cross-sectional area.
• Research into geometrical deformation, such as vessel length and curvature adaptation, that may be of interest for the (endovascular) treatment of vascular pathologies is limited in different positions and postures.
• The most important clinical implications of postural changes are found in diagnosis, surgical planning, and follow-up after stent placement.

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Impact factor: 4.7 ; Q1

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59. Association of modified textbook outcome and overall survival after surgery for colorectal liver metastases: A nationwide analysis
Voigt KR, de Graaff MR, Verhoef C, Kazemier G, Swijneburg RJ, Mieog JSD, Derksen WJM, Buis CI, Gobardhan PD, Dulk MD, van Dam RM, Liem MSL, Leclercq WKG, Bosscha K, Belt EJT, Vermaas M, Kok NFM, Patijn GA, Marsman HM, van den Boezem PB, Klaase JM, Grünhagen DJ.

BACKGROUND: Textbook outcome (TO) represents a multidimensional quality measurement, encompassing the desirable short-term outcomes following surgery. This study aimed to investigate whether achieving TO after resection of colorectal liver metastases (CRLM) surgery is related to better overall survival (OS) in a national cohort.

METHOD: Data was retrieved from the Dutch Hepato Biliary Audit. A modified definition of TO (mTO) was used because readmissions were only recorded from 2019. mTO was achieved when no severe postoperative complications, mortality, prolonged length of hospital stay, occurred and when adequate surgical resection margins were obtained. To compare outcomes of patients with and without mTO and reduce baseline differences between both groups propensity score matching (PSM) was used for patients operated on between 2014 and 2018.
RESULTS: Out of 6525 eligible patients, 81 % achieved mTO. For the cohort between 2014 and 2018, those achieving mTO had a 5-year OS of 46.7 % (CI 44.8-48.6) while non-mTO patients had a 5-year OS of 33.7 % (CI 29.8-38.2), p < 0.001. Not achieving mTO was associated with a worse OS (aHR 1.34 (95 % CI 1.17-1.53), p < 0.001. Median follow-up was 76 months., PSM assigned 519 patients to each group. In the PSM cohort patients achieving mTO, 5-year OS was 43.6 % (95 % CI 39.2-48.5) compared to 36.4 % (95 % CI 31.9-41.2) in patients who did not achieve mTO, p = 0.006.
CONCLUSION: Achieving mTO is associated with improved long-term survival. This emphasizes the importance of optimising perioperative care and reducing postoperative complications in surgical treatment of CRLM.

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Impact factor: 2.9 ; Q1

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60. The Difficulty of Detecting Occult Metastases in Patients with Potentially Resectable Pancreatic Cancer: Development and External Validation of a Preoperative Prediction Model
Walma M, Maggino L, Smits FJ, Borggreve AS, Daamen LA, Groot VP, Casciani F, de Meijer VE, Wessels FJ, van der Schelling GP, Nieuwenhuijs VB, Bosscha K, van der Harst E, van Dam R, Liem MS, Festen S, Stommel MWJ, Roos D, Wit F, de Hingh IH, Bonsing BA, Busch OR, Groot Koerkamp B, Kazemier G, Besselink MG, Salvia R, Malleo G, Molenaar IQ, van Santvoort HC.

Occult metastases are detected in 10-15% of patients during exploratory laparotomy for pancreatic cancer. This study developed and externally validated a model to predict occult metastases in patients with potentially resectable pancreatic cancer. Model development was performed within the Dutch Pancreatic Cancer Audit, including all patients operated for pancreatic cancer (January 2013-December 2017). Multivariable logistic regression analysis based on the Akaike Information Criteria was performed with intraoperative pathologically proven metastases as the outcome. The model was externally validated with a cohort from the University Hospital of Verona (January 2013-December 2017). For model development, 2262 patients were included of whom 235 (10%) had occult metastases, located in the liver (n = 143, 61%), peritoneum (n = 73, 31%), or both (n = 19, 8%). The model included age (OR 1.02, 95% CI 1.00-1.03), BMI (OR 0.96, 95% CI 0.93-0.99), preoperative nutritional support (OR 1.73, 95% CI 1.01-2.74), tumor diameter (OR 1.60, 95% CI 1.04-2.45), tumor composition (solid vs. cystic) (OR 2.33, 95% CI 1.20-4.35), and indeterminate lesions on preoperative imaging (OR 4.01, 95% CI 2.16-7.43). External validation showed poor discrimination with a C-statistic of 0.56. Although some predictor variables were significantly associated with occult metastases, the model performed insufficiently at external validation.

Gepubliceerd: J Clin Med. 2024;13(6).
Impact factor: 2.9 ; Q1

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61. The use of outcome data in patient consultations from the healthcare professionals' and patients' perspectives: A mixed methods study
Westerink HJ, Bresser CC, Garvelink MM, van Uden-Kraan CF, Zouitni O, Bart HAJ, van der Wees PJ, van der Nat PB, Santeon Patient Participation Study Group; van Duyn EB.

OBJECTIVES: To gain insight into healthcare professionals' (HCPs') perspectives on the use of outcome data in consultations and to understand which aggregated outcomes patients find important.
METHODS: This study had a mixed-methods design and consisted of two steps:
RESULTS: HCPs indicated that aggregated outcome data are not routinely used in consultations. They pointed out various barriers to using outcome data, e.g., low response rates of PROMs, and suggested actions to address these barriers, including training of HCPs in outcome data usage. Patients rated the majority of aggregated outcomes as important, although preferences differed between the studied health conditions.
CONCLUSION: Both HCPs and patients underscored the importance of discussing outcome data in consultations. Nevertheless, HCPs encountered several barriers to using outcome data. Furthermore, patients with different health conditions have somewhat different information needs.
PRACTICE IMPLICATIONS: The study identified several actionable steps to enhance the collection and application of outcome data in consultations.

Gepubliceerd: Patient Educ Couns. 2024;118:108043.
Impact factor: 3.1 ; Q onbekend

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62. Nutritional support in pancreatic cancer patients and its effect on nutritional status: an observational regional HPB network study investigating current practice
Wijma AG, Hogenbirk RNM, Driessens H, Kluifhooft DA, Jellema-Betten ES, Tjalsma-de Vries M, Liem MSL, Nieuwenhuijs VB, Manusama EM, Hoogwater FJH, Nijkamp MW, Beijer S, Klaase JM.

PURPOSE: Preoperative malnutrition is associated with poor postoperative outcomes in patients with pancreatic cancer. This study evaluated the effectiveness of current practice in nutritional support for patients with pancreatic cancer.
METHODS: Observational multicenter HPB network study conducted at the Isala Clinics Zwolle, Medical Spectrum Twente, Medical Center Leeuwarden, and University Medical Center Groningen between October 2021 and May 2023. Patients with a suspected pancreatic malignancy scheduled for surgery were screened for malnutrition using the Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire and referred to a dedicated dietician for nutritional support comprising pancreatic enzyme replacement therapy, dietary advice, and nutritional supplements to achieve adequate caloric and protein intake. At baseline, 1 day preoperatively, and 3 months postoperatively, the nutritional status and muscle thickness were evaluated.
RESULTS: The study included 30 patients, of whom 12 (40%) classified as malnourished (PG-SGA ≥ 4) at baseline. Compared to well-nourished patients, malnourished patients were younger, were predominantly female, and had a higher body mass index, despite having lost more body weight in the past 6 months. All malnourished patients and 78% of the well-nourished patients received nutritional support. Consequently, a preoperative increase in caloric and protein intake and body weight were observed. Postoperatively, despite a further increase in caloric intake, a considerable decrease in protein intake, body weight, and muscle thickness was observed.
CONCLUSION: Malnutrition is prevalent in patients undergoing pancreatic surgery. Nutritional support by a dedicated dietician is effective in enhancing patients' preoperative nutritional status. However, postoperative monitoring of adequate nutritional intake in patients could be improved.

Gepubliceerd: Support Care Cancer. 2024;32(7):487.
Impact factor: 3.0 ; Q2

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63. Preoperative chemoradiotherapy but not chemotherapy is associated with reduced risk of postoperative pancreatic fistula after pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a nationwide analysis

Wismans LV, Suurmeijer JA, van Dongen JC, Bonsing BA, Van Santvoort HC, Wilmink JW, van Tienhoven G, de Hingh IH, Lips DJ, van der Harst E, de Meijer VE, Patijn GA, Bosscha K, Stommel MW, Festen S, den Dulk M, Nuyttens JJ, Intven MPW, de Vos-Geelen J, Molenaar IQ, Busch OR, Koerkamp BG, Besselink MG, van Eijck CHJ.

BACKGROUND: Postoperative pancreatic fistula remains the leading cause of significant morbidity after pancreatoduodenectomy for pancreatic ductal adenocarcinoma. Preoperative chemoradiotherapy has been described to reduce the risk of postoperative pancreatic fistula, but randomized trials on neoadjuvant treatment in pancreatic ductal adenocarcinoma focus increasingly on preoperative chemotherapy rather than preoperative chemoradiotherapy. This study aimed to investigate the impact of preoperative chemotherapy and preoperative chemoradiotherapy on postoperative pancreatic fistula and other pancreatic-specific surgery related complications on a nationwide level.
METHODS: All patients after pancreatoduodenectomy for pancreatic ductal adenocarcinoma were included in the mandatory nationwide prospective Dutch Pancreatic Cancer Audit (2014-2020). Baseline and treatment characteristics were compared between immediate surgery, preoperative chemotherapy, and preoperative chemoradiotherapy. The relationship between preoperative chemotherapy, chemoradiotherapy, and clinically relevant postoperative pancreatic fistula (International Study Group of Pancreatic Surgery grade B/C) was investigated using multivariable logistic regression analyses.
RESULTS: Overall, 2,019 patients after pancreatoduodenectomy for pancreatic ductal adenocarcinoma were included, of whom 1,678 underwent immediate surgery (83.1%), 192 (9.5%) received preoperative chemotherapy, and 149 (7.4%) received preoperative chemoradiotherapy. Postoperative pancreatic fistula occurred in 8.3% of patients after immediate surgery, 4.2% after preoperative chemotherapy, and 2.0% after preoperative chemoradiotherapy (P = .004). In multivariable analysis, the use of preoperative chemoradiotherapy was associated with reduced risk of postoperative pancreatic fistula (odds ratio, 0.21; 95% confidence interval, 0.03-0.69; P = .033) compared with immediate surgery, whereas preoperative chemotherapy was not (odds ratio, 0.59; 95% confidence interval, 0.25-1.25; P = .199). Intraoperatively hard, or fibrotic pancreatic texture was most frequently observed after preoperative chemoradiotherapy (53% immediate surgery, 62% preoperative chemotherapy, 77% preoperative chemoradiotherapy, P < .001).
CONCLUSION: This nationwide analysis demonstrated that in patients undergoing pancreatoduodenectomy for pancreatic ductal adenocarcinoma, only preoperative chemoradiotherapy, but not preoperative chemotherapy, was associated with a reduced risk of postoperative pancreatic fistula.

Gepubliceerd: Surgery. 2024;175(6):1580-6.
Impact factor: 2.7 ; Q1

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64. Adjuvant Hyperthermic Intraperitoneal Chemotherapy in Patients With Locally Advanced Colon Cancer (COLOPEC): 5-Year Results of a Randomized Multicenter Trial

Zwanenburg ES, El Klaver C, Wisselink DD, Punt CJA, Snaebjornsson P, Crezee J, Aalbers AGJ, Brandt-Kerkhof ARM, Bremers AJA, Burger P, Fabry HFJ, Ferenschild FTJ, Festen S, van Grevenstein WMU, Hemmer PHJ, de Hingh I, Kok NFM, Kusters M, Musters GD, Schoonderwoerd L, Tuynman JB, van de Ven AWH, van Westreenen HL, Wiezer MJ, Zimmerman DDE, van Zweeden A, Dijkgraaf MGW, Tanis PJ, COLOPEC Collaborators Group and COLOOPEC Collaborators Group; van Duyn EB.

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.Whether adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) might prevent peritoneal metastases after curative surgery for high-risk colon cancer is an ongoing debate. This study aimed to determine 5-year oncologic outcomes of the randomized multicenter COLOPEC trial, which included patients with clinical or pathologic T4N0-2M0 or perforated colon cancer and randomly assigned (1:1) to either adjuvant systemic chemotherapy and HIPEC (n = 100) or adjuvant systemic chemotherapy alone (n = 102). HIPEC was performed using a one-time administration of oxaliplatin (460 mg/m(2), 30 minutes, 42°C, concurrent fluorouracil/leucovorin intravenously), either simultaneously (9%) or within 5-8 weeks (91%) after primary tumor resection. Outcomes were analyzed according to the intention-to-treat principle. Long-term data were available of all 202 patients included in the COLOPEC trial, with a median follow-up of 59 months (IQR, 54.5-64.5). No significant difference was found in 5-year overall survival rate between patients assigned to adjuvant HIPEC followed by systemic chemotherapy or only adjuvant systemic chemotherapy (69.6% v 70.9%, log-rank; P = .692). Five-year peritoneal metastases rates were 63.9% and 63.2% (P = .907) and 5-year disease-free survival was 55.7% and 52.3% (log-rank; P = .875), respectively. No differences in quality-of-life outcomes were found. Our findings implicate that adjuvant HIPEC should still be performed in trial setting only.

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Impact factor: 43.4 ; Q1

Totale impact factor: 468.2
Gemiddelde impact factor: 7.3

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 9
Totale impact factor: 37.8
Gemiddelde impact factor: 4.2

Intensive care

1. The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial

Bakker T, Klopotowska JE, Dongelmans DA, Eslami S, Vermeijden WJ, Hendriks S, Ten Cate J, Karakus A, Purmer IM, van Bree SHW, Spronk PE, Hoeksema M, de Jonge E, de Keizer NF, Abu-Hanna A.

BACKGROUND: Drug-drug interactions (DDIs) can harm patients admitted to the intensive care unit (ICU). Yet, clinical decision support systems (CDSSs) aimed at helping physicians prevent DDIs are plagued by low-yield alerts, causing alert fatigue and compromising patient safety. The aim of this multicentre study was to evaluate the effect of tailoring potential DDI alerts to the ICU setting on the frequency of administered high-risk drug combinations.
METHODS: We implemented a cluster randomised stepped-wedge trial in nine ICUs in the Netherlands. Five ICUs already used potential DDI alerts. Patients aged 18 years or older admitted to the ICU with at least two drugs administered were included. Our intervention was an adapted CDSS, only providing alerts for potential DDIs considered as high risk. The intervention was delivered at the ICU level and targeted physicians. We hypothesised that showing only relevant alerts would improve CDSS effectiveness and lead to a decreased number of administered high-risk drug combinations. The order in which the intervention was implemented in the ICUs was randomised by an independent researcher. The primary outcome was the number of administered high-risk drug combinations per 1000 drug administrations per patient and was assessed in all included patients. This trial was registered in the Netherlands Trial Register (identifier NL6762) on Nov 26, 2018, and is now closed.
FINDINGS: In total, 10 423 patients admitted to the ICU between Sept 1, 2018, and Sept 1, 2019, were assessed and 9887 patients were included. The mean number of administered high-risk drug combinations per 1000 drug administrations per patient was 26·2 (SD 53·4) in the intervention group (n=5534), compared with 35·6 (65·0) in the control group (n=4353). Tailoring potential DDI alerts to the ICU led to a 12% decrease (95% CI 5-18%; p=0·0008) in the number of administered high-risk drug combinations per 1000 drug administrations per patient, after adjusting for clustering and prognostic factors.
INTERPRETATION: This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting significantly reduced the number of administered high-risk drug combinations. Our list of high-risk drug combinations can be used in other ICUs, and our strategy of tailoring alerts based on clinical relevance could be applied to other clinical settings.
FUNDING: ZonMw.

Gepubliceerd: Lancet. 2024;403(10425):439-49.
IF 88.5 ; Q1

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2. Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands

Bels JLM, Thiessen S, van Gassel RJJ, Beishuizen A, De Bie Dekker A, Fraipont V, Lamote S, Ledoux D, Scheeren C, De Waele E, van Zanten ARH, Bormans-Russell L, van Bussel BCT, Dictus MMJ, Fivez T, Harks I, van der Horst ICC, Jonckheer J, Marechal H, Massion PB, Meex I, Paulus MC, Rinket M, van Santen S, Tartaglia K, Deane AM, Demuydt F, Puthucheary Z, Vloet LCM, Weijs PJM, van Kuijk SMJ, van de Poll MCG, Mesotten D.

BACKGROUND: Increased protein provision might ameliorate muscle wasting and improve long-term outcomes in critically ill patients. The aim of the PRECISe trial was to assess whether higher enteral

protein provision (ie, 2·0 g/kg per day) would improve health-related quality of life and functional outcomes in critically ill patients who were mechanically ventilated compared with standard enteral protein provision (ie, 1·3 g/kg per day).
METHODS: The PRECISe trial was an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in five Dutch hospitals and five Belgian hospitals. Inclusion criteria were initiation of invasive mechanical ventilation within 24 h of intensive care unit (ICU) admission and an expected duration of invasive ventilation of 3 days or longer. Exclusion criteria were contraindications for enteral nutrition, moribund condition, BMI less than 18 kg/m(2), kidney failure with a no dialysis code, or hepatic encephalopathy. Patients were randomly assigned to one of four randomisation labels, corresponding with two study groups (ie, standard or high protein; two labels per group) in a 1:1:1:1 ratio through an interactive web-response system. Randomisation was done via random permuted-block randomisation in varying block sizes of eight and 12, stratified by centre. Participants, care providers, investigators, outcome assessors, data analysts, and the independent data safety monitoring board were all blinded to group allocation. Patients received isocaloric enteral feeds that contained 1·3 kcal/mL and 0·06 g of protein/mL (ie, standard protein) or 1·3 kcal/mL and 0·10 g of protein/mL (ie, high protein). The study-nutrition intervention was limited to the time period during the patient's ICU stay in which they required enteral feeding, with a maximum of 90 days. The primary outcome was EuroQoL 5-Dimension 5-level (EQ-5D-5L) health utility score at 30 days, 90 days, and 180 days after randomisation, adjusted for baseline EQ-5D-5L health utility score. This trial was registered with ClinicalTrials.gov (NCT04633421) and is closed to new participants.
FINDINGS: Between Nov 19, 2020, and April 14, 2023, 935 patients were randomly assigned. 335 (35·8%) of 935 patients were female and 600 (64·2%) were male. 465 (49·7%) of 935 were assigned to the standard protein group and 470 (50·3%) were assigned to the high protein group. 430 (92·5%) of 465 patients in the standard protein group and 419 (89·1%) of 470 patients in the high protein group were assessed for the primary outcome. The primary outcome, EQ-5D-5L health utility score during 180 days after randomisation (assessed at 30 days, 90 days, and 180 days), was lower in patients allocated to the high protein group than in those allocated to the standard protein group, with a mean difference of -0·05 (95% CI -0·10 to -0·01; p=0·031). Regarding safety outcomes, the probability of mortality during the entire follow-up was 0·38 (SE 0·02) in the standard protein group and 0·42 (0·02) in the high protein group (hazard ratio 1·14, 95% CI 0·92 to 1·40; p=0·22). There was a higher incidence of symptoms of gastrointestinal intolerance in patients in the high protein group (odds ratio 1·76, 95% CI 1·06 to 2·92; p=0·030). Incidence of other adverse events did not differ between groups.
INTERPRETATION: High enteral protein provision compared with standard enteral protein provision resulted in worse health-related quality of life in critically ill patients and did not improve functional outcomes during 180 days after ICU admission.
FUNDING: Netherlands Organisation for Healthcare Research and Development and Belgian Health Care Knowledge Centre.

Gepubliceerd: Lancet. 2024;404(10453):659-69.
IF 88.5 ; Q1

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3. Evaluation of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 Using a Rapid Point of Care Test for Predicting Head Computed Tomography Lesions After Mild Traumatic Brain Injury in a Dutch Multi-Center Cohort
Chayoua W, Visser K, de Koning ME, Beishuizen A, IJmker R, van der Naalt J, Krabbe JG, van der Horn HJ.

Mild traumatic brain injury (mTBI) is a common condition seen in emergency departments worldwide. Blood-based biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are recently U.S. Food and Drug Administration-approved for the prediction of intracranial lesions on head computed tomography (CT) scans in mTBI. We evaluated the diagnostic

performance of GFAP and UCH-L1 in a Dutch cohort using the i-STAT TBI assay. In a multi-center observational study, we enrolled 253 mTBI patients. Head CT scans were scored using the Marshall classification system. Logistic regression models were used to assess the contribution of biomarkers and clinical parameters to diagnostic performance. Detection of UCH-L1 and GFAP resulted in a sensitivity of 97% and specificity of 19% for CT positivity in mTBI patients, along with a negative predictive value of 95% (88-100%) and a positive predictive value of 27% (21-33%). Combining biomarker testing with loss of consciousness and time to sample increased specificity to 46%. Combined testing of UCH-L1 and GFAP testing resulted in possibly more unnecessary CT scans compared with GFAP testing alone, with only limited increase in sensitivity. This study confirmed high sensitivity of GFAP and UCH-L1 for CT abnormalities in mTBI patients using the i-STAT TBI test. The results support the potential use of GFAP and UCH-L1 as tools for determining the indication for CT scanning in mTBI patients, possibly offering a cost- and time-effective approach to management of patients with mTBI. Prospective studies in larger cohorts are warranted to validate our findings.

Gepubliceerd: J Neurotrauma. 2024;41(13-14):e1630-e40.
IF 3.8 ; Q1

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4. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms

Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group; Beishuizen A.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

Gepubliceerd: Heliyon. 2024;10(10):e29591.
IF 3.6 ; Q1

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5. Characteristics of co-infection and secondary infection amongst critically ill COVID-19 patients in the first two waves of the pandemic

De Corte T, Kohler K, Cecconi M, De Waele JJ, Conway Morris A, UNITE-COVID investigators; Beishuizen A, Cornet AD.

Gepubliceerd: Intensive Care Med. 2024;50(6):989-93.
IF 21.2 ; Q1

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6. The association of premorbid conditions with 6-month mortality in acutely admitted ICU patients over 80 years

de Lange DW, Soliman IW, Leaver S, Boumendil A, Haas LEM, Watson X, Boulanger C, Szczeklik W, Artigas A, Morandi A, Andersen F, Jung C, Moreno R, Walther S, Oeyen S, Schefold JC, Cecconi M, Marsh B, Joannidis M, Nalapko Y, Elhadi M, Fjølner J, Guidet B, Flaatten H, VIP2 study group; Cornet AD.

BACKGROUND: Premorbid conditions influence the outcome of acutely ill adult patients aged 80 years and over who are admitted to the ICU. The aim of this study was to determine the influence of such premorbid conditions on 6 month survival.
METHODS: Prospective cohort study in 242 ICUs from 22 countries including patients 80 years or above, admitted over a 6 months period to an ICU between May 2018 and May 2019. Only emergency (acute) ICU admissions in adult patients ≥ 80 years of age were eligible. Patients who were admitted after planned/elective surgery were excluded. We measured the Clinical Frailty Scale (CFS), the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), disability with the Katz activities of daily living (ADL) score, comorbidities and a Polypharmacy Score (CPS).
RESULTS: Overall, the VIP2 study included 3920 patients. During ICU stay 1191 patients died (30.9%), and another 436 patients (11.1%) died after ICU discharge but within the first 30 days of admission, and an additional 895 patients died hereafter but within the first 6 months after admission (22.8%). The 6 months mortality was 64%. The median CFS was 4 (IQR 3-6). Frailty (CFS ≥ 5) was present in 26.6%. Cognitive decline (IQCODE above 3.5) was found in 30.2%. The median IQCODE was 3.19. A Katz ADL of 4 or less was present in 27.7%. Patients who surviving > 6 months were slightly younger (median age survivors 84 with IQR 81-86) than patients dying within the first 6 months (median age 84, IQR 82-87, $p = 0.013$), were less frequently frail (CFS > 5 in 19% versus 34%, $p < 0.01$) and were less dependent based on their Katz activities of daily living measurement (median Katz score 6, IQR 5-6 versus 6 points, IQR 3-6, $p < 0.01$).
CONCLUSIONS: We found that Clinical Frailty Scale, age, and SOFA at admission were independent prognostic factors for 6 month mortality after ICU admission in patients age 80 and above. Adding other geriatric syndromes and scores did not improve the model. This information can be used in shared-decision making.
CLINICALTRIALS: gov: NCT03370692.

Gepubliceerd: Ann Intensive Care. 2024;14(1):46.
IF 5.5 ; Q1

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7. DeltaScan for the Assessment of Acute Encephalopathy and Delirium in ICU and non-ICU Patients, a Prospective Cross-Sectional Multicenter Validation Study

Ditzel FL, Hut SCA, van den Boogaard M, Boonstra M, Leijten FSS, Wils EJ, van Nesselrooij T, Kromkamp M, Rood PJT, Röder C, Bouvy PF, Coesmans M, Osse RJ, Pop-Purceleanu M, van Dellen E, Krulder JWM, Milisen K, Faaij R, Vondeling AM, Kamper AM, van Munster BC, de Jonghe A, Winters MAM, van der Ploeg J, van der Zwaag S, Koek DHL, Drenth-van Maanen CAC, Beishuizen A, van den Bos DM, Cahn W, Schuit E, Slooter AJC.

OBJECTIVES: To measure the diagnostic accuracy of DeltaScan: a portable real-time brain state monitor for identifying delirium, a manifestation of acute encephalopathy (AE) detectable by polymorphic delta activity (PDA) in single-channel electroencephalograms (EEGs). DESIGN:

Prospective cross-sectional study. SETTING: Six Intensive Care Units (ICU's) and 17 non-ICU departments, including a psychiatric department across 10 Dutch hospitals.
PARTICIPANTS: 494 patients, median age 75 (IQR:64-87), 53% male, 46% in ICUs, 29% delirious.
MEASUREMENTS: DeltaScan recorded 4-minute EEGs, using an algorithm to select the first 96 seconds of artifact-free data for PDA detection. This algorithm was trained and calibrated on two independent datasets. METHODS: Initial validation of the algorithm for AE involved comparing its output with an expert EEG panel's visual inspection. The primary objective was to assess DeltaScan's accuracy in identifying delirium against a delirium expert panel's consensus.
RESULTS: DeltaScan had a 99% success rate, rejecting 6 of the 494 EEG's due to artifacts. Performance showed and an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.86 (95% CI: 0.83-0.90) for AE (sensitivity: 0.75, 95%CI=0.68-0.81, specificity: 0.87 95%CI=0.83-0.91. The AUC was 0.71 for delirium (95%CI=0.66-0.75, sensitivity: 0.61 95%CI=0.52-0.69, specificity: 72, 95%CI=0.67-0.77). Our validation aim was an NPV for delirium above 0.80 which proved to be 0.82 (95%CI: 0.77-0.86). Among 84 non-delirious psychiatric patients, DeltaScan differentiated delirium from other disorders with a 94% (95%CI: 87-98%) specificity.
CONCLUSIONS: DeltaScan can diagnose AE at bedside and shows a clear relationship with clinical delirium. Further research is required to explore its role in predicting delirium-related outcomes.

Gepubliceerd: Am J Geriatr Psychiatry. 2024;32(9):1093-104.
IF 3.8 ; Q1

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8. The impact of high versus standard enteral protein provision on functional recovery following intensive care admission: Protocol for a pre-planned secondary Bayesian analysis of the PRECISe trial

Heuts S, de Heer P, Gabrio A, Bels JLM, Lee ZY, Stoppe C, van Kuijk S, Beishuizen A, de Bie-Dekker A, Fraipont V, Lamote S, Ledoux D, Scheeren C, De Waele E, van Zanten A, Mesotten D, van de Poll MCG.

BACKGROUND: The PRECISe trial is a pragmatic, multicenter randomized controlled trial that evaluates the effect of high versus standard enteral protein provision on functional recovery in adult, mechanically ventilated critically ill patients. The current protocol presents the rationale and analysis plan for an evaluation of the primary and secondary outcomes under the Bayesian framework, with an emphasis on clinically important effect sizes.
METHODS: This protocol was drafted in agreement with the ROBUST-statement, and is submitted for publication before database lock and primary data analysis. The primary outcome is health-related quality of life as measured by the EQ-5D-5L health utility score and is longitudinally assessed. Secondary outcomes comprise the 6-min walking test and handgrip strength over the entire follow-up period (longitudinal analyses), and 60-day mortality, duration of mechanical ventilation, and EQ-5D-5L health utility scores at 30, 90 and 180 days (cross-sectional). All analyses will primarily be performed under weakly informative priors. When available, informative priors elicited from contemporary literature will also be incorporated under alternative scenarios. In all other cases, objectively formulated skeptical and enthusiastic priors will be defined to assess the robustness of our results. Relevant identified subgroups were: patients with acute kidney injury, severe multi-organ failure and patients with or without sepsis. Results will be presented as absolute risk differences, mean differences, and odds ratios, with accompanying 95% credible intervals. Posterior probabilities will be estimated for clinically important benefit and harm.
DISCUSSION: The proposed secondary, pre-planned Bayesian analysis of the PRECISe trial will provide additional information on the effects of high protein on functional and clinical outcomes in critically ill patients, such as probabilistic interpretation, probabilities of clinically important effect sizes, and the integration of prior evidence. As such, it will complement the interpretation of the primary outcome as well as several secondary and subgroup analyses.

Gepubliceerd: Clin Nutr ESPEN. 2024;59:162-70.
IF 2.6 ; Q3

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9. Adverse drug events caused by three high-risk drug-drug interactions in patients admitted to intensive care units: A multicentre retrospective observational study
Klopotowska JE, Leopold JH, Bakker T, Yasrebi-de Kom I, Engelaer FM, de Jonge E, Haspels-Hogervorst EK, van den Bergh WM, Renes MH, Jong BT, Kieft H, Wieringa A, Hendriks S, Lau C, van Bree SHW, Lammers HJW, Wierenga PC, Bosman RJ, de Jong VM, Slijkhuis M, Franssen EJF, Vermeijden WJ, Masselink J, Purmer IM, Bosma LE, Hoeksema M, Wesselink E, de Lange DW, de Keizer NF, Dongelmans DA, Abu-Hanna A.

AIMS: Knowledge about adverse drug events caused by drug-drug interactions (DDI-ADEs) is limited. We aimed to provide detailed insights about DDI-ADEs related to three frequent, high-risk potential DDIs (pDDIs) in the critical care setting: pDDIs with international normalized ratio increase (INR(+)) potential, pDDIs with acute kidney injury (AKI) potential, and pDDIs with QTc prolongation potential.
METHODS: We extracted routinely collected retrospective data from electronic health records of intensive care units (ICUs) patients (≥18 years), admitted to ten hospitals in the Netherlands between January 2010 and September 2019. We used computerized triggers (e-triggers) to preselect patients with potential DDI-ADEs. Between September 2020 and October 2021, clinical experts conducted a retrospective manual patient chart review on a subset of preselected patients, and assessed causality, severity, preventability, and contribution to ICU length of stay of DDI-ADEs using internationally prevailing standards.
RESULTS: In total 85 422 patients with ≥1 pDDI were included. Of these patients, 32 820 (38.4%) have been exposed to one of the three pDDIs. In the exposed group, 1141 (3.5%) patients were preselected using e-triggers. Of 237 patients (21%) assessed, 155 (65.4%) experienced an actual DDI-ADE; 52.9% had severity level of serious or higher, 75.5% were preventable, and 19.3% contributed to a longer ICU length of stay. The positive predictive value was the highest for DDI-INR(+) e-trigger (0.76), followed by DDI-AKI e-trigger (0.57).
CONCLUSION: The highly preventable nature and severity of DDI-ADEs, calls for action to optimize ICU patient safety. Use of e-triggers proved to be a promising preselection strategy.

Gepubliceerd: Br J Clin Pharmacol. 2024;90(1):164-75.
IF 3.0 ; Q2

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10. Etomidate versus Ketamine as Prehospital Induction Agent in Patients with Suspected Severe Traumatic Brain Injury
Mansvelder FJ, Bossers SM, Loer SA, Bloemers FW, Van Lieshout EMM, Den Hartog D, Hoogerwerf N, van der Naalt J, Absalom AR, Peerdeman SM, Bulte CSE, Schwarte LA, Schober P, BRAIN-PROTECT collaborators; Beishuizen A.

BACKGROUND: Severe traumatic brain injury is a leading cause of morbidity and mortality among young people around the world. Prehospital care focuses on the prevention and treatment of secondary brain injury and commonly includes tracheal intubation after induction of general anesthesia. The choice of induction agent in this setting is controversial. This study therefore investigated the association between the chosen induction medication etomidate versus S(+)-ketamine and the 30-day mortality in patients with severe traumatic brain injury who received prehospital airway management in the Netherlands.
METHODS: This study is a retrospective analysis of the prospectively collected observational data of the Brain Injury: Prehospital Registry of Outcomes, Treatments and Epidemiology of Cerebral Trauma

(BRAIN-PROTECT) cohort study. Patients with suspected severe traumatic brain injury who were transported to a participating trauma center and who received etomidate or S(+)-ketamine for prehospital induction of anesthesia for advanced airway management were included. Statistical analyses were performed with multivariable logistic regression and inverse probability of treatment weighting analysis.
RESULTS: In total, 1,457 patients were eligible for analysis. No significant association between the administered induction medication and 30-day mortality was observed in unadjusted analyses (32.9% mortality for etomidate versus 33.8% mortality for S(+)-ketamine; P = 0.716; odds ratio, 1.04; 95% CI, 0.83 to 1.32; P = 0.711), as well as after adjustment for potential confounders (odds ratio, 1.08; 95% CI, 0.67 to 1.73; P = 0.765; and risk difference 0.017; 95% CI, -0.051 to 0.084; P = 0.686). Likewise, in planned subgroup analyses for patients with confirmed traumatic brain injury and patients with isolated traumatic brain injury, no significant differences were found. Consistent results were found after multiple imputations of missing data.
CONCLUSIONS: The analysis found no evidence for an association between the use of etomidate or S(+)-ketamine as an anesthetic agent for intubation in patients with traumatic brain injury and mortality after 30 days in the prehospital setting, suggesting that the choice of induction agent may not influence the patient mortality rate in this population.

Gepubliceerd: Anesthesiology. 2024;140(4):742-51.
IF 9.1 ; Q1

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11. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; Beishuizen A.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

Gepubliceerd: Sci Rep. 2024;14(1):16387.
IF 3.9 ; Q1

12. Ghrelin for Neuroprotection in Post-Cardiac Arrest Coma: A Randomized Clinical Trial
Nutma S, Beishuizen A, van den Bergh WM, Foudraine NA, le Feber J, Filius PMG, Cornet AD, van der Palen J, van Putten M, Hofmeijer J.

IMPORTANCE: Out-of-hospital cardiac arrest survival rates have markedly risen in the last decades, but neurological outcome only improved marginally. Despite research on more than 20 neuroprotective strategies involving patients in comas after cardiac arrest, none have demonstrated unequivocal evidence of efficacy; however, treatment with acyl-ghrelin has shown improved functional and histological brain recovery in experimental models of cardiac arrest and was safe in a wide variety of human study populations.
OBJECTIVE: To determine safety and potential efficacy of intravenous acyl-ghrelin to improve neurological outcome in patients in a coma after cardiac arrest.
DESIGN, SETTING, AND PARTICIPANTS: A phase 2, double-blind, placebo-controlled, multicenter, randomized clinical trial, Ghrelin Treatment of Comatose Patients After Cardiac Arrest: A Clinical Trial to Promote Cerebral Recovery (GRECO), was conducted between January 18, 2019, and October 17, 2022. Adult patients 18 years or older who were in a comatose state after cardiac arrest were assessed for eligibility; patients were from 3 intensive care units in the Netherlands. Expected death within 48 hours or unfeasibility of treatment initiation within 12 hours were exclusion criteria.
INTERVENTIONS: Patients were randomized to receive intravenous acyl-ghrelin, 600 µg (intervention group), or placebo (control group) within 12 hours after cardiac arrest, continued for 7 days, twice daily, in addition to standard care.
MAIN OUTCOMES AND MEASURES: Primary outcome was the score on the Cerebral Performance Categories (CPC) scale at 6 months. Safety outcomes included any serious adverse events. Secondary outcomes were mortality and neuron-specific enolase (NSE) levels on days 1 and 3.
RESULTS: A total of 783 adult patients in a coma after cardiac arrest were assessed for eligibility, and 160 patients (median [IQR] age, 68 [57-75] years; 120 male [75%]) were enrolled. A total of 81 patients (51%) were assigned to the intervention group, and 79 (49%) were assigned to the control group. The common odds ratio (OR) for any CPC improvement in the intervention group was 1.78 (95% CI, 0.98-3.22; P = .06). This was consistent over all CPC categories. Mean (SD) NSE levels on day 1 after cardiac arrest were significantly lower in the intervention group (34 [6] µg/L vs 56 [13] µg/L; P = .04) and on day 3 (28 [6] µg/L vs 52 [14] µg/L; P = .08). Serious adverse events were comparable in incidence and type between the groups. Mortality was 37% (30 of 81) in the intervention group vs 51% (40 of 79) in the control group (absolute risk reduction, 14%; 95% CI, -2% to 29%; P = .08).
CONCLUSIONS AND RELEVANCE: In patients in a coma after cardiac arrest, intravenous treatment with acyl-ghrelin was safe and potentially effective to improve neurological outcome. Phase 3 trials are needed for conclusive evidence.
TRIAL REGISTRATION: Clinicaltrialsregister.eu: EUCTR2018-000005-23-NL.

Gepubliceerd: JAMA Neurol. 2024;81(6):603-10.
IF 21.4 ; Q1

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13. Efficacy of Alkaline Phosphatase in Critically Ill Patients with COVID-19: A Multicentre Investigator-Initiated Double-Blind Randomised Placebo-Controlled Trial
Pijpe A, Papendorp SG, van der Heijden JW, Vermin B, Ertugrul I, Ritt MWJ, Stessel B, Callebaut I, Beishuizen A, Vlig M, Jimmink J, Huijgen HJ, van Zuijlen PPM, Middelkoop E, de Jong E.

BACKGROUND: Efforts to identify therapies to treat hospitalised patients with COVID-19 are being continued. Alkaline phosphatase (AP) dephosphorylates pro-inflammatory adenosine triphosphate (ATP) into anti-inflammatory adenosine.
METHODS: In a randomised controlled trial, we investigated the safety and efficacy of AP in patients with SARS-CoV-2 infection admitted to the ICU. AP or a placebo was administered for four days following admission to the ICU. The primary outcome was the duration of mechanical ventilation. Mortality in 28 days, acute kidney injury, need for reintubation, safety, and inflammatory markers relevant to the described high cytokine release associated with SARS-CoV-2 infection were the secondary outcomes.
RESULTS: Between December 2020 and March 2022, 97 patients (of the intended 132) were included, of which 51 were randomised to AP. The trial was terminated prematurely based on meeting the threshold for futility. Compared to the placebo, AP did not affect the duration of mechanical ventilation (9.0 days vs. 9.3 days, p = 1.0). No safety issues were observed. After 28 days, mortality was 9 (18%) in the AP group versus 6 (13%) in the placebo group (p = 0.531). Additionally, no statistically significant differences between the AP and the placebo were observed for the other secondary outcomes.
CONCLUSIONS: Alkaline phosphatase (AP) therapy in COVID-19 ICU patients showed no significant benefits in this trial.

Gepubliceerd: Biomedicines. 2024;12(4).
IF 3.9 ; Q2

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14. Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-injured patients: a secondary analysis of the ENIO study
Robba C, Battaglini D, Abbas A, Sarrió E, Cinotti R, Asehnoune K, Taccone FS, Rocco PR, Schultz MJ, Citerio G, Stevens RD, Badenes R, ENIO collaborators; Cornet AD, Vermeijden WJ.

PURPOSE: The use of arterial partial pressure of carbon dioxide (PaCO(2)) as a target intervention to manage elevated intracranial pressure (ICP) and its effect on clinical outcomes remain unclear. We aimed to describe targets for PaCO(2) in acute brain injured (ABI) patients and assess the occurrence of abnormal PaCO(2) values during the first week in the intensive care unit (ICU). The secondary aim was to assess the association of PaCO(2) with in-hospital mortality.
METHODS: We carried out a secondary analysis of a multicenter prospective observational study involving adult invasively ventilated patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), or ischemic stroke (IS). PaCO(2) was collected on day 1, 3, and 7 from ICU admission. Normocapnia was defined as PaCO(2) > 35 and to 45 mmHg; mild hypocapnia as 32-35 mmHg; severe hypocapnia as 26-31 mmHg, forced hypocapnia as < 26 mmHg, and hypercapnia as > 45 mmHg.
RESULTS: 1476 patients (65.9% male, mean age 52 ± 18 years) were included. On ICU admission, 804 (54.5%) patients were normocapnic (incidence 1.37 episodes per person/day during ICU stay), and 125 (8.5%) and 334 (22.6%) were mild or severe hypocapnic (0.52 and 0.25 episodes/day). Forced hypocapnia and hypercapnia were used in 40 (2.7%) and 173 (11.7%) patients. PaCO(2) had a U-shape relationship with in-hospital mortality with only severe hypocapnia and hypercapnia being associated with increased probability of in-hospital mortality (omnibus p value = 0.0009). Important differences were observed across different subgroups of ABI patients.
CONCLUSIONS: Normocapnia and mild hypocapnia are common in ABI patients and do not affect patients' outcome. Extreme derangements of PaCO(2) values were significantly associated with increased in-hospital mortality.

Gepubliceerd: Intensive Care Med. 2024;50(2):234-46.
IF 21.2 ; Q1

15. Correction: Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-injured patients: a secondary analysis of the ENIO study
Robba C, Battaglini D, Abbas A, Sarrió E, Cinotti R, Asehnoune K, Taccone FS, Rocco PR, Schultz MJ, Citerio G, Stevens RD, Badenes R.

Gepubliceerd: Intensive Care Med. 2024;50(2):317-8.
IF 21.2 ; Q1

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16. Individualized Thresholds of Hypoxemia and Hyperoxemia and their Effect on Outcome in Acute Brain Injured Patients: A Secondary Analysis of the ENIO Study
Robba C, Battaglini D, Cinotti R, Asehnoune K, Stevens R, Taccone FS, Badenes R, Pelosi P, ENIO collaborators; Cornet AD, Vermeijden WJ.

BACKGROUND: In acute brain injury (ABI), the effects of hypoxemia as a potential cause of secondary brain damage and poor outcome are well documented, whereas the impact of hyperoxemia is unclear. The primary aim of this study was to assess the episodes of hypoxemia and hyperoxemia in patients with ABI during the intensive care unit (ICU) stay and to determine their association with in-hospital mortality. The secondary aim was to identify the optimal thresholds of arterial partial pressure of oxygen (PaO(2)) predicting in-hospital mortality.
METHODS: We conducted a secondary analysis of a prospective multicenter observational cohort study. Adult patients with ABI (traumatic brain injury, subarachnoid aneurysmal hemorrhage, intracranial hemorrhage, ischemic stroke) with available data on PaO(2) during the ICU stay were included. Hypoxemia was defined as PaO(2) < 80 mm Hg, normoxemia was defined as PaO(2) between 80 and 120 mm Hg, mild/moderate hyperoxemia was defined as PaO(2) between 121 and 299 mm Hg, and severe hyperoxemia was defined as PaO(2) levels ≥ 300 mm Hg.
RESULTS: A total of 1,407 patients were included in this study. The mean age was 52 (±18) years, and 929 (66%) were male. Over the ICU stay, the fractions of patients in the study cohort who had at least one episode of hypoxemia, mild/moderate hyperoxemia, and severe hyperoxemia were 31.3%, 53.0%, and 1.7%, respectively. PaO(2) values below 92 mm Hg and above 156 mm Hg were associated with an increased probability of in-hospital mortality. Differences were observed among subgroups of patients with ABI, with consistent effects only seen in patients without traumatic brain injury.
CONCLUSIONS: In patients with ABI, hypoxemia and mild/moderate hyperoxemia were relatively frequent. Hypoxemia and hyperoxemia during ICU stay may influence in-hospital mortality. However, the small number of oxygen values collected represents a major limitation of the study.

Gepubliceerd: Neurocrit Care. 2024;40(2):515-28.
IF 3.6 ; Q1

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17. Development and evaluation of regression tree models for predicting in-hospital mortality of a national registry of COVID-19 patients over six pandemic surges
Schut MC, Dongelmans DA, de Lange DW, Brinkman S, de Keizer NF, Abu-Hanna A, Dutch COVID-19 Research Consortium; Silderhuis VM.

BACKGROUND: Objective prognostic information is essential for good clinical decision making. In case of unknown diseases, scarcity of evidence and limited tacit knowledge prevent obtaining this information. Prediction models can be useful, but need to be not only evaluated on how well they

predict, but also how stable these models are under fast changing circumstances with respect to development of the disease and the corresponding clinical response. This study aims to provide interpretable and actionable insights, particularly for clinicians. We developed and evaluated two regression tree predictive models for in-hospital mortality of COVID-19 patient at admission and 24 hours (24 h) after admission, using a national registry. We performed a retrospective analysis of observational routinely collected data.
METHODS: Two regression tree models were developed for admission and 24 h after admission. The complexity of the trees was managed via cross validation to prevent overfitting. The predictive ability of the model was assessed via bootstrapping using the Area under the Receiver-Operating-Characteristic curve, Brier score and calibration curves. The tree models were assessed on the stability of their probabilities and predictive ability, on the selected variables, and compared to a full-fledged logistic regression model that uses variable selection and variable transformations using splines. Participants included COVID-19 patients from all ICUs participating in the Dutch National Intensive Care Evaluation (NICE) registry, who were admitted at the ICU between February 27, 2020, and November 23, 2021. From the NICE registry, we included concerned demographic data, minimum and maximum values of physiological data in the first 24 h of ICU admission and diagnoses (reason for admission as well as comorbidities) for model development. The main outcome measure was in-hospital mortality. We additionally analysed the Length-of-Stay (LoS) per patient subgroup per survival status.
RESULTS: A total of 13,369 confirmed COVID-19 patients from 70 ICUs were included (with mortality rate of 28%). The optimism-corrected AUROC of the admission tree (with seven paths) was 0.72 (95% CI: 0.71-0.74) and of the 24 h tree (with 11 paths) was 0.74 (0.74-0.77). Both regression trees yielded good calibration and variable selection for both trees was stable. Patient subgroups comprising the tree paths had comparable survival probabilities as the full-fledged logistic regression model, survival probabilities were stable over six COVID-19 surges, and subgroups were shown to have added predictive value over the individual patient variables.
CONCLUSIONS: We developed and evaluated regression trees, which operate at par with a carefully crafted logistic regression model. The trees consist of homogenous subgroups of patients that are described by simple interpretable constraints on patient characteristics thereby facilitating shared decision-making.

Gepubliceerd: BMC Med Inform Decis Mak. 2024;24(1):7.
IF 3.8 ; Q2

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18. The Prognostic Value of Troponin-T in Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation: A COACT Substudy
Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van der Pas S, van Royen N.

BACKGROUND: In out-of-hospital cardiac arrest (OHCA) without ST-elevation, predictive markers that can identify those with a high risk of acute coronary syndrome are lacking.
METHODS: In this post hoc analysis of the Coronary Angiography after Cardiac Arrest (COACT) trial, the baseline, median, peak, and time-concentration curves of troponin-T (cTnT) (T-AUC) in OHCA patients without ST-elevation were studied. cTnT values were obtained at predefined time points at 0, 3, 6, 12, 24, 36, 28, and 72 hours after admission. All patients who died within the measurement period were not included. The primary outcome was the association between cTnT and 90-day survival. Secondary outcomes included the association of cTnT and acute thrombotic occlusions, acute unstable lesions, and left ventricular function.

RESULTS: In total, 352 patients were included in the analysis. The mean age was 64 ± 13 years (80.4% men). All cTnT measures were independent prognostic factors for mortality after adjustment for potential confounders age, sex, history of coronary artery disease, witnessed arrest, time to BLS, and time to return of spontaneous circulation (eg, for T-AUC: hazard ratio, 1.44; 95% CI, 1.06-1.94; P = .02; P value for all variables ≤.02). Median cTnT (odds ratio [OR], 1.58; 95% CI, 1.18-2.12; P = .002) and T-AUC (OR, 2.03; 95% CI, 1.25-3.29; P = .004) were independent predictors for acute unstable lesions. Median cTnT (OR, 1.62; 95% CI, 1.17-2.23; P = .003) and T-AUC (OR, 2.16; 95% CI, 1.27-3.68; P = .004) were independent predictors for acute thrombotic occlusions. CTnT values were not associated with the left ventricular function (eg, for T-AUC: OR, 2.01; 95% CI, 0.65-6.19; P = .22; P value for all variables ≥.14).
CONCLUSION: In OHCA patients without ST-segment elevation, cTnT release during the first 72 hours after return of spontaneous circulation was associated with clinical outcomes.

Gepubliceerd: J Soc Cardiovasc Angiogr Interv. 2024;3(2):101191.
IF onbekend

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19. Evaluating the Sum of Eye and Motor Components of the Glasgow Coma Score As a Predictor of Extubation Failure in Patients With Acute Brain Injury
Taran S, Perrot B, Angriman F, Cinotti R, ENIO study group; Cornet AD, Vermeijden WJ.

OBJECTIVES: To evaluate the association between the pre-extubation sum of eye and motor components of the Glasgow Coma Score (GCS-EM) and odds of extubation failure in patients with acute brain injury being liberated from mechanical ventilation.
DESIGN: Secondary analysis of a prospective, multicenter observational study (ClinicalTrials.gov identifier NCT03400904).
SETTING: Sixty-three hospital sites worldwide, with patient recruitment from January 2018 to November 2020. PATIENTS: One thousand one hundred fifty-two critically ill patients with acute brain injury, with a median age of 54 years, of whom 783 (68.0%) were male, 559 (48.5%) had traumatic brain injury, and 905 (78.6%) had a GCS-EM greater than 8 before extubation (scores range from 2 to 10).
INTERVENTIONS: None.
MEASUREMENTS AND MAIN RESULTS: GCS-EM was computed in intubated patients on the day of extubation. The main outcome was extubation failure, defined as unplanned reintubation within 5 days of extubation. Analyses used multilevel logistic regression with adjustment for patient characteristics and a random intercept for hospital site. In the primary analysis, GCS-EM was not associated with extubation failure (odds ratio, 1.07 per additional point; 95% CI, 0.87-1.31). Findings were consistent in sensitivity analyses that: 1) used different adjustment covariates, 2) included a verbal estimate to derive an overall GCS, 3) accounted for missing data, 4) considered a 2-day time interval to define extubation failure, 5) accounted for competing risks, and 6) used a propensity score-based model. There was no association between GCS-EM and extubation outcome in subgroups defined by brain injury diagnosis or age.
CONCLUSIONS: In this large, contemporary, multicenter cohort of patients with acute brain injury, we found no association between the GCS-EM and odds of extubation failure. However, few patients had a pre-extubation GCS-EM less than or equal to 8, and the possibility of a true prognostic association in patients with low scores is not excluded.

Gepubliceerd: Crit Care Med. 2024;52(8):1258-63.
IF 6.0 ; Q1

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20. Characteristics and outcome of COVID-19 patients admitted to the ICU: a nationwide cohort study on the comparison between the consecutive stages of the COVID-19 pandemic in the Netherlands, an update

Termorshuizen F, Dongelmans DA, Brinkman S, Bakhshi-Raiez F, Arbous MS, de Lange DW, van Bussel BCT, de Keizer NF, Dutch COVID-19 Research Consortium; Silderhuis VM.

BACKGROUND: Previously, we reported a decreased mortality rate among patients with COVID-19 who were admitted at the ICU during the final upsurge of the second wave (February-June 2021) in the Netherlands. We examined whether this decrease persisted during the third wave and the phases with decreasing incidence of COVID-19 thereafter and brought up to date the information on patient characteristics.
METHODS: Data from the National Intensive Care Evaluation (NICE)-registry of all COVID-19 patients admitted to an ICU in the Netherlands were used. Patient characteristics and rates of in-hospital mortality (the primary outcome) during the consecutive periods after the first wave (periods 2-9, May 25, 2020-January 31, 2023) were compared with those during the first wave (period 1, February-May 24, 2020).
RESULTS: After adjustment for patient characteristics and ICU occupancy rate, the mortality risk during the initial upsurge of the third wave (period 6, October 5, 2021-January, 31, 2022) was similar to that of the first wave (OR(adj) = 1.01, 95%-CI [0.88-1.16]). The mortality rates thereafter decreased again (e.g., period 9, October 5, 2022-January, 31, 2023: OR(adj) = 0.52, 95%-CI [0.41-0.66]). Among the SARS-CoV-2 positive patients, there was a huge drop in the proportion of patients with COVID-19 as main reason for ICU admission: from 88.2% during the initial upsurge of the third wave to 51.7%, 37.3%, and 41.9% for the periods thereafter. Restricting the analysis to these patients did not modify the results on mortality.
CONCLUSIONS: The results show variation in mortality rates among critically ill COVID-19 patients across the calendar time periods that is not explained by differences in case-mix and ICU occupancy rates or by varying proportions of patients with COVID-19 as main reason for ICU admission. The consistent increase in mortality during the initial, rising phase of each separate wave might be caused by the increased virulence of the contemporary virus strain and lacking immunity to the new strain, besides unmeasured patient-, treatment- and healthcare system characteristics.

Gepubliceerd: Ann Intensive Care. 2024;14(1):11.
IF 5.5 ; Q1

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21. Heterogeneity of treatment effect of vilobelimab in COVID-19: a secondary analysis of a randomised controlled trial

van Amstel RBE, Slim MA, Lim EHT, Rückinger S, Seymour CW, Burnett BP, Bos LDJ, van Vught LA, Riedemann NC, van de Beek D, Vlaar APJ, PANAMO Study Group; Cornet AD.

In a phase 3 trial (PANAMO, NCT04333420), vilobelimab, a complement 5a (C5a) inhibitor, reduced 28-day mortality in mechanically ventilated COVID-19 patients. This post hoc analysis of 368 patients aimed to explore treatment heterogeneity through unsupervised learning. All available clinical variables at baseline were used as input. Treatment heterogeneity was assessed using latent class analysis (LCA), Ward's hierarchical clustering (HC) and the adjudication to previously described clinical sepsis phenotypes. The primary outcome was 28-day mortality. For LCA, a 2-class latent model was deemed most suitable. In the LCA model, 82 (22%) patients were assigned to class 1 and 286 (78%) to class 2. Class 1 was defined by more severely ill patients with significantly higher mortality. In an adjusted logistic regression, no heterogeneity of treatment effect (HTE) between classes was observed (p = 0.998). For HC, no significant classes were found (p = 0.669). Using the previously described clinical sepsis subtypes, 41 patients (11%) were adjudicated subtype alpha (α), 17 (5%) beta (β), 112 (30%) delta (δ) and 198 (54%) gamma (γ). HTE was observed between clinical subtypes

(p = 0.001) with improved 28-day mortality after treatment with vilobelimab for the δ subtype (OR = 0.17, 95% CI 0.07-0.40, p < 0.001). No signal for harm of treatment with vilobelimab was observed in any class or clinical subtype. Overall, treatment effect with vilobelimab was consistent across different classes and subtypes, except for the δ subtype, suggesting potential additional benefit for the most severely ill patients.

Gepubliceerd: Crit Care. 2024;28(1):210.
IF 9.3 ; Q1

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22. Super-relaxed myosins contribute to respiratory muscle hibernation in mechanically ventilated patients
van den Berg M, Shi Z, Claassen WJ, Hooijman P, Lewis CTA, Andersen JL, van der Pijl RJ, Bogaards SJP, Conijn S, Peters EL, Begthel LPL, Uijterwijk B, Lindqvist J, Langlais PR, Girbes ARJ, Stapel S, Granzier H, Campbell KS, Ma W, Irving T, Hwee DT, Hartman JJ, Malik FI, Paul M, Beishuizen A, Ochala J, Heunks L, Ottenheijm CAC.

Patients receiving mechanical ventilation in the intensive care unit (ICU) frequently develop contractile weakness of the diaphragm. Consequently, they may experience difficulty weaning from mechanical ventilation, which increases mortality and poses a high economic burden. Because of a lack of knowledge regarding the molecular changes in the diaphragm, no treatment is currently available to improve diaphragm contractility. We compared diaphragm biopsies from ventilated ICU patients (N = 54) to those of non-ICU patients undergoing thoracic surgery (N = 27). By integrating data from myofiber force measurements, x-ray diffraction experiments, and biochemical assays with clinical data, we found that in myofibers isolated from the diaphragm of ventilated ICU patients, myosin is trapped in an energy-sparing, super-relaxed state, which impairs the binding of myosin to actin during diaphragm contraction. Studies on quadriceps biopsies of ICU patients and on the diaphragm of previously healthy mechanically ventilated rats suggested that the super-relaxed myosins are specific to the diaphragm and not a result of critical illness. Exposing slow- and fast-twitch myofibers isolated from the diaphragm biopsies to small-molecule compounds activating troponin restored contractile force in vitro. These findings support the continued development of drugs that target sarcomere proteins to increase the calcium sensitivity of myofibers for the treatment of ICU-acquired diaphragm weakness.

Gepubliceerd: Sci Transl Med. 2024;16(758):eadg3894.
IF 14.7 ; Q1

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23. Charting a new course in healthcare: early-stage AI algorithm registration to enhance trust and transparency
van Genderen ME, van de Sande D, Hooft L, Reis AA, Cornet AD, Oosterhoff JHF, van der Ster BJP, Huiskens J, Townsend R, van Bommel J, Gommers D, van den Hoven J.

AI holds the potential to transform healthcare, promising improvements in patient care. Yet, realizing this potential is hampered by over-reliance on limited datasets and a lack of transparency in validation processes. To overcome these obstacles, we advocate the creation of a detailed registry for AI algorithms. This registry would document the development, training, and validation of AI models, ensuring scientific integrity and transparency. Additionally, it would serve as a platform for peer review and ethical oversight. By bridging the gap between scientific validation and regulatory approval, such as by the FDA, we aim to enhance the integrity and trustworthiness of AI applications in healthcare.

Gepubliceerd: NPJ Digit Med. 2024;7(1):119.
IF 15.1 ; Q1

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24. Emergency Department Triage, Transfer Times, and Hospital Mortality of Patients Admitted to the ICU: A Retrospective Replication and Continuation Study
van Herwerden MC, Groenland CNL, Termorshuizen F, Rietdijk WJR, Blokzijl F, Cleffken BI, Dormans T, Epker JL, Feyz L, Gritters van den Oever N, van der Heiden P, de Jonge E, Latten GHP, Pruijsten RV, Sir Ö, Spronk PE, Vermeijden WJ, van Vliet P, de Keizer NF, den Uil CA.

OBJECTIVES: This study aimed to provide new insights into the impact of emergency department (ED) to ICU time on hospital mortality, stratifying patients by academic and nonacademic teaching (NACT) hospitals, and considering Acute Physiology and Chronic Health Evaluation (APACHE)-IV probability and ED-triage scores.
DESIGN, SETTING, AND PATIENTS: We conducted a retrospective cohort study (2009-2020) using data from the Dutch National Intensive Care Evaluation registry. Patients directly admitted from the ED to the ICU were included from four academic and eight NACT hospitals. Odds ratios (ORs) for mortality associated with ED-to-ICU time were estimated using multivariable regression, both crude and after adjusting for and stratifying by APACHE-IV probability and ED-triage scores.
INTERVENTIONS: None.
MEASUREMENTS AND MAIN RESULTS: A total of 28,455 patients were included. The median ED-to-ICU time was 1.9 hours (interquartile range, 1.2-3.1 hr). No overall association was observed between ED-to-ICU time and hospital mortality after adjusting for APACHE-IV probability ($p = 0.36$). For patients with an APACHE-IV probability greater than 55.4% (highest quintile) and an ED-to-ICU time greater than 3.4 hours the adjusted OR (ORs adjApache) was 1.24 (95% CI, 1.00-1.54; $p < 0.05$) as compared with the reference category (< 1.1 hr). In the academic hospitals, the ORs adjApache for ED-to-ICU times of 1.6-2.3, 2.3-3.4, and greater than 3.4 hours were 1.21 (1.01-1.46), 1.21 (1.00-1.46), and 1.34 (1.10-1.64), respectively. In NACT hospitals, no association was observed ($p = 0.07$). Subsequently, ORs were adjusted for ED-triage score (ORs adjED). In the academic hospitals the ORs adjED for ED-to-ICU times greater than 3.4 hours was 0.98 (0.81-1.19), no overall association was observed ($p = 0.08$). In NACT hospitals, all time-ascending quintiles had ORs adjED values of less than 1.0 ($p < 0.01$).
CONCLUSIONS: In patients with the highest APACHE-IV probability at academic hospitals, a prolonged ED-to-ICU time was associated with increased hospital mortality. We found no significant or consistent unfavorable association in lower APACHE-IV probability groups and NACT hospitals. The association between longer ED-to-ICU time and higher mortality was not found after adjustment and stratification for ED-triage score.

Gepubliceerd: Crit Care Med. 2024;52(12):1856-65.
IF 6.0 ; Q1

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25. International Survey on Mechanical Ventilation During Extracorporeal Membrane Oxygenation
van Minnen O, Jolink FEJ, van den Bergh WM, Droogh JM, Oude Lansink-Hartgring A, Dutch ECLS Study Group; Cornet AD, Vermeijden WJ, Oude Velthuis B.

The optimal ventilation strategy for patients on extracorporeal membrane oxygenation (ECMO) remains uncertain. This survey reports current mechanical ventilation strategies adopted by ECMO centers worldwide. An international, multicenter, cross-sectional survey was conducted anonymously through an internet-based tool. Participants from North America, Europe, Asia, and Oceania were

recruited from the extracorporeal life support organization (ELSO) directory. Responses were received from 48 adult ECMO centers (response rate 10.6%). Half of these had dedicated ventilation protocols for ECMO support. Pressure-controlled ventilation was the preferred initial ventilation mode for both venovenous ECMO (VV-ECMO) (60%) and venoarterial ECMO (VA-ECMO) (34%). In VV-ECMO, the primary goal was lung rest (93%), with rescue therapies commonly employed, especially neuromuscular blockade (93%) and prone positioning (74%). Spontaneous ventilation was typically introduced after signs of pulmonary recovery, with few centers using it as the initial mode (7%). A quarter of centers stopped sedation within 3 days after ECMO initiation. Ventilation strategies during VA-ECMO focused less on lung-protective goals and transitioned to spontaneous ventilation earlier. Ventilation strategies during ECMO support differ considerably. Controlled ventilation is predominantly used initially to provide lung rest, often facilitated by sedation and neuromuscular blockade. Few centers apply "awake ECMO" early during ECMO support, some utilizing partial neuromuscular blockade.

Gepubliceerd: Asaio j. 2024;70(4):300-4.
IF 2.3 ; Q2

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26. Advanced waveform analysis of diaphragm surface EMG allows for continuous non-invasive assessment of respiratory effort in critically ill patients at different PEEP levels
Warnaar RSP, Cornet AD, Beishuizen A, Moore CM, Donker DW, Oppersma E.

BACKGROUND: Respiratory effort should be closely monitored in mechanically ventilated ICU patients to avoid both overassistance and underassistance. Surface electromyography of the diaphragm (sEMGdi) offers a continuous and non-invasive modality to assess respiratory effort based on neuromuscular coupling (NMCdi). The sEMGdi derived electrical activity of the diaphragm (sEAdi) is prone to distortion by crosstalk from other muscles including the heart, hindering its widespread use in clinical practice. We developed an advanced analysis as well as quality criteria for sEAdi waveforms and investigated the effects of clinically relevant levels of PEEP on non-invasive NMCdi.
METHODS: NMCdi was derived by dividing end-expiratory occlusion pressure (Pocc) by sEAdi, based on three consecutive Pocc manoeuvres at four incremental (+ 2 cmH2O/step) PEEP levels in stable ICU patients on pressure support ventilation. Pocc and sEAdi quality was assessed by applying a novel, automated advanced signal analysis, based on tolerant and strict cut-off criteria, and excluding inadequate waveforms. The coefficient of variations (CoV) of NMCdi after basic manual and automated advanced quality assessment were evaluated, as well as the effect of an incremental PEEP trial on NMCdi.
RESULTS: 593 manoeuvres were obtained from 42 PEEP trials in 17 ICU patients. Waveform exclusion was primarily based on low sEAdi signal-to-noise ratio (N(tolerant) = 155, 37%, N(strict) = 241, 51% waveforms excluded), irregular or abrupt cessation of Pocc (N(tolerant) = 145, 35%, N(strict) = 145, 31%), and high sEAdi area under the baseline (N(tolerant) = 94, 23%, N(strict) = 79, 17%). Strict automated assessment allowed to reduce CoV of NMCdi to 15% from 37% for basic quality assessment. As PEEP was increased, NMCdi decreased significantly by 4.9 percentage point per cmH(2)O.
CONCLUSION: Advanced signal analysis of both Pocc and sEAdi greatly facilitates automated and well-defined identification of high-quality waveforms. In the critically ill, this approach allowed to demonstrate a dynamic NMCdi (Pocc/sEAdi) decrease upon PEEP increments, emphasising that sEAdi-based assessment of respiratory effort should be related to PEEP dependent diaphragm function. This novel, non-invasive methodology forms an important methodological foundation for more robust, continuous, and comprehensive assessment of respiratory effort at the bedside.

Gepubliceerd: Crit Care. 2024;28(1):195.
IF 9.3 ; Q1

27. The INTOXICATE study: methodology and preliminary results of a prospective observational study

Zwaag SM, van den Hengel-Koot IS, Baker S, Druwé P, Elhadi M, Dufol AF, Forsberg S, Halacli B, Jung C, Laubner Sakalauskienė G, Lindqvist E, Moreno R, Rabe C, Reiter N, Rezar R, Țincu R, Topeli A, Wood DM, de Lange DW, Hunault CC, INTOXICATE Study Investigators Group; Cornet AD, Vermeijden WJ.

BACKGROUND: There is currently no practice-based, multicenter database of poisoned patients admitted to intensive care units (ICUs). The INTOXICATE study, endorsed by the ESICM and EAPCCT, aimed to determine the rate of eventful admissions among acutely intoxicated adult ICU patients.
METHODS: Ethical approval was obtained for this multicenter, prospective observational study, and data-sharing agreements were signed with each participating center. An electronic case report form was used to collect data on patient demographics, exposure, clinical characteristics, investigations, treatment, and in-hospital mortality data. The primary outcome, 'eventful admission', was a composite outcome defined as the rate of patients who received any of the following treatments in the first 24 h after the ICU admission: oxygen supplementation with a FiO2 > 40%, mechanical ventilation, vasopressors, renal replacement therapy (RRT), cardiopulmonary resuscitation, antidotes, active cooling, fluid resuscitation (> 1.5 L of intravenous fluid of any kind), sedation, or who died in the hospital.
RESULTS: Seventy-eight ICUs, mainly from Europe, but also from Australia and the Eastern Mediterranean, participated. A total of 2,273 patients were enrolled between November 2020 and June 2023. The median age of the patients was 41 years, 72% were exposed to intoxicating drugs. The observed rate of patients with an eventful ICU admission was 68% (n = 1546/2273 patients). The hospital mortality was 4.5% (n = 103/2273).
CONCLUSIONS: The vast majority of patients survive, and approximately one third of patients do not receive any ICU-specific interventions after admission in an intensive care unit for acute intoxication. High-quality detailed clinical data have been collected from a large cohort of acutely intoxicated ICU patients, providing information on the pattern of severe acute poisoning requiring intensive care admission and the outcomes of these patients.
TRIAL REGISTRATION: OSF registration ID: osf.io/7e5uy.

Gepubliceerd: Crit Care. 2024;28(1):316.
IF 9.3 ; Q1

Totale impact factor: 386.1
Gemiddelde impact factor: 14.3

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 30.7
Gemiddelde impact factor: 15.4

Interne geneeskunde

1. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma
Blank CU, Lucas MW, Scolyer RA, van de Wiel BA, Menzies AM, Lopez-Yurda M, Hoeijmakers LL, Saw RPM, Lijnsvelt JM, Maher NG, Pulleman SM, Gonzalez M, Torres Acosta A, van Houdt WJ, Lo SN, Kuijpers AMJ, Spillane A, Klop WMC, Pennington TE, Zuur CL, Shannon KF, Seinstra BA, Rawson RV, Haanen J, Ch'ng S, Naipal KAT, Stretch J, van Thienen JV, Rtshiladze MA, Wilgenhof S, Kapoor R, Meerveld-Eggink A, Grijpink-Ongering LG, van Akkooi ACJ, Reijers ILM, Gyorki DE, Grünhagen DJ, Speetjens FM, Vliek SB, Placzke J, Spain L, Stassen RC, Amini-Adle M, Lebbé C, Faries MB, Robert C, Ascierto PA, van Rijn R, van den Berkmortel F, Piersma D, van der Westhuizen A, Vreugdenhil G, Aarts MJB, Stevense-den Boer MAM, Atkinson V, Khattak M, Andrews MC, van den Eertwegh AJM, Boers-Sonderen MJ, Hospers GAP, Carlino MS, de Groot JB, Kapiteijn E, Suijkerbuijk KPM, Rutkowski P, Sandhu S, van der Veldt AAM, Long GV.

BACKGROUND: In phase 1-2 trials in patients with resectable, macroscopic stage III melanoma, neoadjuvant immunotherapy was more efficacious than adjuvant immunotherapy.
METHODS: In this phase 3 trial, we randomly assigned patients with resectable, macroscopic stage III melanoma to two cycles of neoadjuvant ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab. Only patients in the neoadjuvant group with a partial response or nonresponse received adjuvant treatment. The primary end point was event-free survival.
RESULTS: A total of 423 patients underwent randomization. At a median follow-up of 9.9 months, the estimated 12-month event-free survival was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) in the neoadjuvant group and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant group. The difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; P<0.001; hazard ratio for progression, recurrence, or death, 0.32; 99.9% CI, 0.15 to 0.66). In the neoadjuvant group, 59.0% of patients had a major pathological response, 8.0% had a partial response, 26.4% had a nonresponse (>50% residual viable tumor), and 2.4% had progression; in 4.2%, surgery had not yet been performed or was omitted. The estimated 12-month recurrence-free survival was 95.1% in patients in the neoadjuvant group who had a major pathological response, 76.1% among those with a partial response, and 57.0% among those with a nonresponse. Adverse events of grade 3 or higher that were related to systemic treatment occurred in 29.7% of patients in the neoadjuvant group and in 14.7% in the adjuvant group.
CONCLUSIONS: Among patients with resectable, macroscopic stage III melanoma, neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy resulted in longer event-free survival than surgery followed by adjuvant nivolumab. (Funded by Bristol Myers Squibb and others; NADINA ClinicalTrials.gov number, NCT04949113.).

Gepubliceerd: N Engl J Med. 2024;391(18):1696-708.
Impact factor: 78.5 ; Q1

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2. Adjuvant treatment with anti-PD-1 in acral melanoma: A nationwide study
Bloem M, van Not OJ, Aarts MJB, van den Berkmortel F, Blank CU, Blokx WAM, Boers-Sonderen MJ, Bonenkamp JJ, de Groot JB, Haanen JB, Hospers GAP, Kapiteijn EW, de Meza MM, Piersma D, van Rijn RS, Stevense-den Boer MAM, van der Veldt AAM, Vreugdenhil G, van den Eertwegh AJM, Suijkerbuijk KPM, Wouters M.

Previous studies demonstrated limited efficacy of immune checkpoint inhibitors in unresectable acral melanoma (AM); it remains unclear how this translates to the adjuvant setting. This study investigates clinical outcomes of acral compared to cutaneous melanoma (CM) patients treated with adjuvant

anti-PD-1 after complete resection. All stages III-IV AM and CM patients receiving adjuvant anti-PD-1 after complete resection between 2018 and 2022 were included from the prospective nationwide Dutch Melanoma Treatment Registry. We analyzed recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). A multivariable Cox regression analysis of RFS was performed to adjust for potential confounders. We included 1958 (86 AM and 1872 CM) patients. At baseline, AM patients more frequently had KIT mutations, higher disease stages, and Eastern Cooperative Oncology Group Performance Status, and fewer BRAF and NRAS mutations. Median RFS was 14.8 months (95% confidence interval [CI]: 11.5-29.3) in AM and 37.4 months (95% CI: 34.6 to not reached) in CM (p = .002). After correcting for potential confounders, AM remained associated with a higher risk of recurrence (HR(adj) 1.53; 95% CI: 1.07-2.17; p = .019). Two-year DMFS tended to be worse for AM than for CM: 64.5% versus 79.7% (p = .050). Two-year OS was significantly lower in AM (71.5% vs. 84.3%; p = .027). The results of this study suggest a poorer outcome of adjuvant-treated AM compared to CM. Studies assessing the added value of adjuvant treatment in AM are needed. Future research should investigate alternative treatment strategies to improve outcomes of high-risk AM.

Gepubliceerd: Int J Cancer. 2024;155(8):1455-65.
Impact factor: 4.7 ; Q1

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3. The effect of dexamethasone on the incidence of delirium in patients hospitalized due COVID-19 infection: a retrospective cohort study
Boersma MN, Kamperman E, van der Palen J.

PURPOSE: Delirium has been suggested to be a complication associated with corticosteroid use. Therefore, the association between dexamethasone use and delirium in COVID-19 patients was studied herein.
METHODS: In this single-center retrospective cohort study, 412 patients who were hospitalized because of COVID-19 between March 2020 and January 2021 were included. Delirium was diagnosed using the Delirium Observation Screening Scale. The association between the daily use of dexamethasone 6 mg and delirium was measured via multivariable logistic regression analysis.
RESULTS: The incidence of delirium was 11.4% in patients treated with dexamethasone (n = 245) and 9.6% in patients not treated with dexamethasone (n = 167) (RR 1.19, CI 0.67-2.13, p = 0.55). After adjusting for age (mean 69 years) and comorbidity score, the odds ratio for developing delirium when using dexamethasone was 1.11 (CI 0.56-2.21, p = 0.76).
CONCLUSION: The use of dexamethasone in hospitalized COVID-19 patients did not affect the incidence of delirium.

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Impact factor: 3.6 ; Q2

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4. Lanreotide versus placebo for tumour reduction in patients with a (68)Ga-DOTATATE PET-positive, clinically non-functioning pituitary macroadenoma (GALANT study): a randomised, multicentre, phase 3 trial with blinded outcome assessment
Boertien TM, Drent ML, Booij J, Majoie C, Stokkel MPM, Hoogmoed J, Pereira AM, Biermasz NR, Simsek S, Groote Veldman R, Weterings AJ, Vink JM, Tanck MWT, Fliers E, Bisschop PH.

BACKGROUND: No established medical treatment options currently exist for patients with non-functioning pituitary macroadenoma (NFPMA). Somatostatin analogues may prevent tumour growth, but randomised controlled trials are lacking. In vivo somatostatin receptor assessment with (68)Ga-

DOTATATE PET could help in selecting patients for treatment. We aimed to determine the effect of the somatostatin analogue lanreotide on tumour size in patients with a (68)Ga-DOTATATE PET-positive NFPMA.
METHODS: The GALANT study was an investigator-initiated, multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial with recruitment at three academic hospitals in the Netherlands. Adult patients with a suprasellar extending NFPMA, either surgery-naïve or postoperative remnant ≥10 mm, were eligible for inclusion. Important exclusion criteria were previous sellar radiotherapy and use of dopamine receptor agonists. Somatostatin receptor expression in the NFPMA was determined through (68)Ga-DOTATATE PET/CT, co-registered with MRI. A predefined sample of 44 patients with PET-positive NFPMA were randomly assigned (1:1) to lanreotide acetate 120 mg or placebo, both administered as deep subcutaneous injections every 28 days for 72 weeks. Primary outcome was the change in cranio-caudal tumour diameter measured on pituitary MRI from baseline to end-of-treatment in the intention-to-treat population. Participants, investigators and outcome assessors were masked to treatment allocation. The trial is registered with the Netherlands Trial Registry, NL5136, and EudraCT, 2015-001234-22.
FINDINGS: Between Nov 3, 2015, and Dec 10, 2019, 49 patients were included in the study. Forty-four patients with a (68)Ga-DOTATATE PET-positive NFPMA were randomly assigned to lanreotide (22 [50%]) or placebo (22 [50%]). Study treatment was completed in 13 (59%) lanreotide and 19 (86%) placebo participants. The mean (SD) change from baseline in cranio-caudal tumour diameter after treatment was +1·2 (2·5) mm with lanreotide and +1·3 (1·5) mm with placebo; adjusted mean difference versus placebo -0·1 mm (95% CI -1·3 to 1·2, p = 0·93). Adverse events occurred in 22 (100%, 147 events) lanreotide and 21 (95%, 94 events) placebo participants. Gastrointestinal complaints were most common, reported by 18 (82%) lanreotide and 8 (36%) placebo participants. There were no treatment-related serious adverse events.
INTERPRETATION: Compared with placebo, lanreotide treatment did not reduce tumour size or growth in patients with (68)Ga-DOTATATE PET-positive NFPMA.
FUNDING: Ipsen Farmaceutica BV.

Gepubliceerd: Lancet Reg Health Eur. 2024;42:100923.
Impact factor: 13.0 ; Q1

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5. Seasonal variation of anti-PD-1 outcome in melanoma-Results from a Dutch patient cohort
Borgers JSW, Burgers FH, Schina A, Van Not OJ, van den Eertwegh AJM, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Boer AMS, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Wouters M, Suijkerbuijk KPM, van Thienen JV, Haanen J.

Despite the improved survival rates of patients with advanced stage melanoma since the introduction of ICIs, many patients do not have (long-term) benefit from these treatments. There is evidence that the exposome, an accumulation of host-extrinsic factors including environmental influences, could impact ICI response. Recently, a survival benefit was observed in patients with BRAF wild-type melanoma living in Denmark who initiated immunotherapy in summer as compared to winter. As the Netherlands lies in close geographical proximity to Denmark and has comparable seasonal differences, a Dutch validation cohort was established using data from our nationwide melanoma registry. In this study, we did not observe a similar seasonal difference in overall survival and are therefore unable to confirm the Danish findings. Validation of either the Dutch or Danish findings in (combined) patient cohorts from other countries would be necessary to determine whether this host-extrinsic factor influences the response to ICI-treatment.

Gepubliceerd: Pigment Cell Melanoma Res. 2024;37(1):15-20.
Impact factor: 2.6 ; Q2

6. Treatment strategies and outcome in relapsed peripheral T-cell lymphoma: results from the Netherlands Cancer Registry
Brink M, Huisman F, Meeuwes FO, van der Poel MWM, Kersten MJ, Wondergem M, Böhmer L, Woei AJF, Visser O, Oostvogels R, Jansen PM, Diepstra A, Snijders TJF, Huls G, Vermaat JSP, Plattel WJ, Nijland M.

Optimal treatment in patients with refractory or relapsed peripheral T-cell lymphomas (R/R T-NHLs) is unknown. In this population-based study, outcomes in R/R peripheral T-cell lymphoma not otherwise specified (PTCL NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase-positive (ALK+) and ALK-negative (ALK-) anaplastic large cell lymphoma (ALCL) were evaluated. Patients with PTCL NOS, AITL, ALK+ ALCL, and ALK- ALCL (≥18 years) diagnosed in 2014 to 2019 were identified using the Netherlands Cancer Registry. End points were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). The 2-year PFS of 821 patients was 57%. Among 311 patients with a relapse, 243 received second-line treatment: 44% received salvage chemotherapy, 20% received brentuximab vedotin (BV), and 36% received other treatment. In third-line treatment, BV was most commonly used (38%). ORR after second-line treatment was 47%. Two-year PFS and OS after relapse were 25% and 34%, respectively. The risk of second relapse was negatively affected by early relapse (<12 months after diagnosis), whereas BV reduced this risk compared with salvage chemotherapy. Reduced risk of relapse was independent of histological subtype. The best outcomes were observed for patients treated with salvage chemotherapy receiving consolidative autologous and allogeneic stem cell transplantation (SCT) (2-year OS 68%), patients treated with BV achieving a second complete remission (2-year OS 74%) and patients with allogeneic SCT (2-year OS 60%). The risk of second relapse was significantly lower for patients with R/R T-NHL treated with BV compared with patients treated with salvage chemotherapy, and this was irrespective of subtype. Therefore, the use of salvage chemotherapy for patients with R/R T-NHL is challenged.

Gepubliceerd: Blood Adv. 2024;8(14):3619-28.
Impact factor: 7.1 ; Q1

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7. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms
Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group; Delsing C, Piersma D.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS:

36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

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Impact factor: 3.6 ; Q1

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8. PrimerX: A Bayesian Multistage Cohort Embedded Randomised Trial to Evaluate the Role of Deferred Local Therapy of the Primary Tumour in Combination with Immune Checkpoint Inhibitor-based First-line Therapy in Metastatic Renal Cell Carcinoma Patients
Figaroa O, Zondervan P, Kessels R, Berkhof J, Aarts M, Hamberg P, Los M, Piersma D, Rikhof B, Suelmann B, Tascilar M, van der Veldt A, Verhagen P, Westgeest H, Yildirim H, Bex A, Bins A.

BACKGROUND: Historically, patients with metastatic renal cell carcinoma (mRCC) have been offered upfront cytoreductive nephrectomy (CN) followed by systemic therapy. Currently, CN is no longer the standard of care (SOC) based on the randomised phase 3 CARMENA study performed in the vascular endothelial growth factor receptor tyrosine kinase inhibitor era. With the advent of immune checkpoint inhibitor (ICI) combination therapy in first line, the role of CN needs to be reassessed. There is indirect evidence from small retrospective series that deferred CN after ICI combination therapy may lead to better outcomes. To reassess the role of CN, we designed PrimerX, a randomised controlled trial following the Trial within Cohorts (TwiCs) study design. The primary objective of this study is to re-evaluate the benefit of deferred local treatment in the current era of immunotherapy.
STUDY DESIGN: This PrimerX study has been designed as a TwiCs study within the Dutch Prospective Renal Cell Carcinoma (PRO-RCC) cohort. The PRO-RCC cohort includes patients with mRCC and nonmetastatic RCC, and has been set up for prospective collection of long-term clinical data and as an infrastructure for initiating TwiCs studies. The PrimerX TwiCs trial follows a Bayesian adaptive multistage design to allow for early discontinuation due to futility or efficacy. PrimerX has appropriate ethics approval and is registered at clinical.trials.gov (NCT05941169).
END POINTS: The primary clinical endpoint is overall survival, defined as the time from randomisation to death from any cause. The secondary endpoint is the objective response rate within the primary tumour prior to local therapy, as assessed by a computed tomography scan.
PATIENTS AND METHODS: A maximum of 700 patients with synchronous mRCC and absence of progression at metastatic sites following at least 6 mo of standard first-line ICI combination therapy will be assigned randomly to receive local treatment of the primary tumour (experimental arm) or SOC (control arm). The experimental intervention consists of (partial) CN, any form of ablative local therapy, or magnetic resonance imaging guided ablative stereotactic radiotherapy, performed within 6 mo and 1.5 yr after the start of systemic treatment.

Gepubliceerd: Eur Urol Open Sci. 2024;70:28-35.
Impact factor: 4.5 ; Q1

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9. Use of a diagnostic Puumala virus real-time RT-PCR in an orthohantavirus endemic region in the Netherlands
Geeraedts F, Wevers M, Bosma F, Boer M, Brinkman JN, Delsing C, GeurtsvanKessel C, Rockx B, van der Zanden A, Laverman GD.

Laboratory diagnosis of orthohantavirus infection is primarily based on serology. However, for a confirmed serological diagnosis, evaluation of a follow-up serum sample is essential, which is time consuming and causes delay. Real-time reverse transcription polymerase chain reaction (RT-PCR) tests, if positive, provide an immediate and definitive diagnosis, and accurately identify the causative agent, where the discriminative nature of serology is suboptimal. We re-evaluated sera from orthohantavirus-suspected clinical cases in the Dutch regions of Twente and Achterhoek from July 2014 to April 2016 for the presence of Puumala orthohantavirus (PUUV), Tula orthohantavirus (TULV), and Seoul orthohantavirus (SEOV) RNA. PUUV RNA was detected in 11% of the total number (n = 85) of sera tested, in 50% of sera positive for anti-PUUV/TULV IgM (n = 16), and in 1.4% of sera negative or indeterminate for anti-PUUV/TULV IgM (n = 69). No evidence was found for the presence of TULV or SEOV viral RNA. Based on these findings, we propose two algorithms to implement real-time RT-PCR testing in routine orthohantavirus diagnostics, which optimally provide clinicians with early confirmed diagnoses and could prevent possible further invasive testing and treatment.
IMPORTANCE: The addition of a real-time reverse transcription polymerase chain reaction test to routine orthohantavirus diagnostics may better aid clinical decision making than the use of standard serology tests alone. Awareness by clinicians and clinical microbiologists of this advantage may ultimately lead to a reduction in over-hospitalization and unnecessary invasive diagnostic procedures.

Gepubliceerd: Microbiol Spectr. 2024;12(7):e0381323.
Impact factor: 3.8 ; Q2

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10. Real-world overall survival after alternative dosing for pembrolizumab in the treatment of non-small cell lung cancer: A nationwide retrospective cohort study with a non-inferiority primary objective

Grit GF, van Geffen E, Malmberg R, van Leeuwen R, Böhringer S, Jm Smit H, Brocken P, Fh Eijsink J, Dronkers E, Gal P, Jaarsma E, Jhm van Drie-Pierik R, Mp Eldering-Heldens A, Machteld Wymenga AN, Gm Mol P, Zwaveling J, Hilarius D.

BACKGROUND: High and increasing expenses on pembrolizumab ask for more cost-effective and sustainable treatment strategies to improve affordability of healthcare. Therefore, a part of the Dutch hospitals implemented an alternative, partially lower, weight-based dosing protocol for pembrolizumab. This provided the unique opportunity to compare the overall survival (OS) of the alternative pembrolizumab dosing protocol to standard dosing using a nationwide registry in non-small cell lung cancer (NSCLC) patients.
METHODS: This is a retrospective cohort study with a non-inferiority primary objective. Forty hospitals in the Dutch Medication Audit and Dutch Lung Cancer Audit treated 1966 patients with NSCLC with first line pembrolizumab (mono- or combination therapy) between Jan 1st 2021, and Mar 31st, 2023. Alternative weight-based pembrolizumab dosing (100/150/200 mg Q3W or 200/300/400 mg Q6W) was administered to 604 patients, and 1362 patients received standard pembrolizumab dosing (200 mg Q3W or 400 mg Q6W). A Cox proportional hazard model with selected covariates was used to compare the OS between alternative and standard dosing protocols. The non-inferiority margin was set at a hazard ratio (HR) of 1.2 for OS. Non-inferiority is established by showing that the upper limit of the 95 % confidence interval (CI) of the HR of OS is smaller or equal to 1.2.
RESULTS: Distribution of age (66.7 years +/-9.4), sex (45 % female) and treatment combinations were similar for both groups, comorbidity score was higher in the standard group. Median daily dose in the alternative dosing group was 22 % lower compared to the standard dosing group, 7.14 mg/day (interquartile range (IQR):5.48-8.04 mg/day) vs. 9.15 mg/day (IQR:8.33-9.52 mg/day), respectively. Alternative dosing was non-inferior to standard dosing regarding overall survival (adjusted HR 0.83, 95 %CI:0.69-1.003).

CONCLUSION: This large, retrospective real-world analysis supports the hypothesis that the alternative, partially lower pembrolizumab dosing protocol in NSCLC maintains treatment effectiveness while reducing treatment costs.

Gepubliceerd: Lung Cancer. 2024;196:107950.
Impact factor: 4.4 ; Q1

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11. Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empa-kidney trial
EMPA-KIDNEY Collaborative Group; van Erp R.

BACKGROUND: Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce progression of chronic kidney disease and the risk of cardiovascular morbidity and mortality in a wide range of patients. However, their effects on kidney disease progression in some patients with chronic kidney disease are unclear because few clinical kidney outcomes occurred among such patients in the completed trials. In particular, some guidelines stratify their level of recommendation about who should be treated with SGLT2 inhibitors based on diabetes status and albuminuria. We aimed to assess the effects of empagliflozin on progression of chronic kidney disease both overall and among specific types of participants in the EMPA-KIDNEY trial.
METHODS: EMPA-KIDNEY, a randomised, controlled, phase 3 trial, was conducted at 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the UK, and the USA), and included individuals aged 18 years or older with an estimated glomerular filtration rate (eGFR) of 20 to less than 45 mL/min per 1·73 m(2), or with an eGFR of 45 to less than 90 mL/min per 1·73 m(2) with a urinary albumin-to-creatinine ratio (uACR) of 200 mg/g or higher. We explored the effects of 10 mg oral empagliflozin once daily versus placebo on the annualised rate of change in estimated glomerular filtration rate (eGFR slope), a tertiary outcome. We studied the acute slope (from randomisation to 2 months) and chronic slope (from 2 months onwards) separately, using shared parameter models to estimate the latter. Analyses were done in all randomly assigned participants by intention to treat. EMPA-KIDNEY is registered at ClinicalTrials.gov, NCT03594110.
FINDINGS: Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and then followed up for a median of 2·0 years (IQR 1·5-2·4). Prespecified subgroups of eGFR included 2282 (34·5%) participants with an eGFR of less than 30 mL/min per 1·73 m(2), 2928 (44·3%) with an eGFR of 30 to less than 45 mL/min per 1·73 m(2), and 1399 (21·2%) with an eGFR 45 mL/min per 1·73 m(2) or higher. Prespecified subgroups of uACR included 1328 (20·1%) with a uACR of less than 30 mg/g, 1864 (28·2%) with a uACR of 30 to 300 mg/g, and 3417 (51·7%) with a uACR of more than 300 mg/g. Overall, allocation to empagliflozin caused an acute 2·12 mL/min per 1·73 m(2) (95% CI 1·83-2·41) reduction in eGFR, equivalent to a 6% (5-6) dip in the first 2 months. After this, it halved the chronic slope from -2·75 to -1·37 mL/min per 1·73 m(2) per year (relative difference 50%, 95% CI 42-58). The absolute and relative benefits of empagliflozin on the magnitude of the chronic slope varied significantly depending on diabetes status and baseline levels of eGFR and uACR. In particular, the absolute difference in chronic slopes was lower in patients with lower baseline uACR, but because this group progressed more slowly than those with higher uACR, this translated to a larger relative difference in chronic slopes in this group (86% [36-136] reduction in the chronic slope among those with baseline uACR <30 mg/g compared with a 29% [19-38] reduction for those with baseline uACR ≥2000 mg/g; p(trend)<0·0001).
INTERPRETATION: Empagliflozin slowed the rate of progression of chronic kidney disease among all types of participant in the EMPA-KIDNEY trial, including those with little albuminuria. Albuminuria alone should not be used to determine whether to treat with an SGLT2 inhibitor.
FUNDING: Boehringer Ingelheim and Eli Lilly.

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Impact factor: 41.8 ; Q1

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12. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial
EMPA-KIDNEY Collaborative Group; van Erp R.

BACKGROUND: The EMPA-KIDNEY trial showed that empagliflozin reduced the risk of the primary composite outcome of kidney disease progression or cardiovascular death in patients with chronic kidney disease mainly through slowing progression. We aimed to assess how effects of empagliflozin might differ by primary kidney disease across its broad population.
METHODS: EMPA-KIDNEY, a randomised, controlled, phase 3 trial, was conducted at 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the UK, and the USA). Patients were eligible if their estimated glomerular filtration rate (eGFR) was 20 to less than 45 mL/min per 1·73 m(2), or 45 to less than 90 mL/min per 1·73 m(2) with a urinary albumin-to-creatinine ratio (uACR) of 200 mg/g or higher at screening. They were randomly assigned (1:1) to 10 mg oral empagliflozin once daily or matching placebo. Effects on kidney disease progression (defined as a sustained ≥40% eGFR decline from randomisation, end-stage kidney disease, a sustained eGFR below 10 mL/min per 1·73 m(2), or death from kidney failure) were assessed using prespecified Cox models, and eGFR slope analyses used shared parameter models. Subgroup comparisons were performed by including relevant interaction terms in models. EMPA-KIDNEY is registered with ClinicalTrials.gov, NCT03594110.
FINDINGS: Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and followed up for a median of 2·0 years (IQR 1·5-2·4). Prespecified subgroupings by primary kidney disease included 2057 (31·1%) participants with diabetic kidney disease, 1669 (25·3%) with glomerular disease, 1445 (21·9%) with hypertensive or renovascular disease, and 1438 (21·8%) with other or unknown causes. Kidney disease progression occurred in 384 (11·6%) of 3304 patients in the empagliflozin group and 504 (15·2%) of 3305 patients in the placebo group (hazard ratio 0·71 [95% CI 0·62-0·81]), with no evidence that the relative effect size varied significantly by primary kidney disease (p(heterogeneity)=0·62). The between-group difference in chronic eGFR slopes (ie, from 2 months to final follow-up) was 1·37 mL/min per 1·73 m(2) per year (95% CI 1·16-1·59), representing a 50% (42-58) reduction in the rate of chronic eGFR decline. This relative effect of empagliflozin on chronic eGFR slope was similar in analyses by different primary kidney diseases, including in explorations by type of glomerular disease and diabetes (p values for heterogeneity all >0·1).
INTERPRETATION: In a broad range of patients with chronic kidney disease at risk of progression, including a wide range of non-diabetic causes of chronic kidney disease, empagliflozin reduced risk of kidney disease progression. Relative effect sizes were broadly similar irrespective of the cause of primary kidney disease, suggesting that SGLT2 inhibitors should be part of a standard of care to minimise risk of kidney failure in chronic kidney disease.
FUNDING: Boehringer Ingelheim, Eli Lilly, and UK Medical Research Council.

Gepubliceerd: Lancet Diabetes Endocrinol. 2024;12(1):51-60.
Impact factor: 41.8 ; Q1

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13. Safe Stop IPI-NIVO trial: early discontinuation of nivolumab upon achieving a complete or partial response in patients with irresectable stage III or metastatic melanoma treated with first-line ipilimumab-nivolumab - study protocol

Janssen JC, van Dijk B, de Joode K, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, van den Eertwegh AJM, de Groot JWB, Jalving M, de Jonge MJA, Joosse A, Kapiteijn E, Kamphuis-Huismans AM, Naipal KAT, Piersma D, Rikhof B, Westgeest HM, Vreugdenhil G, Oomen-de Hoop E, Mulder E, van der Veldt AAM.

BACKGROUND: Patients with irresectable stage III or metastatic melanoma presenting with poor prognostic factors are usually treated with a combination of immune checkpoint inhibitors (ICIs), consisting of ipilimumab and nivolumab. This combination therapy is associated with severe immune related adverse events (irAEs) in about 60% of patients. In current clinical practice, patients are usually treated with ICIs for up to two years or until disease progression or the occurrence of unacceptable AEs. The incidence of irAEs gradually increases with duration of treatment. While durable tumour responses have been observed after early discontinuation of treatment, no consensus has been reached on optimal treatment duration. The objective of the Safe Stop IPI-NIVO trial is to evaluate whether early discontinuation of ICIs is safe in patients with irresectable stage III or metastatic melanoma who are treated with combination therapy.
METHODS: The Safe Stop IPI-NIVO trial is a nationwide, multicentre, prospective, single-arm, interventional study in the Netherlands. A total of 80 patients with irresectable stage III or metastatic melanoma who are treated with combination therapy of ipilimumab-nivolumab and have a complete or partial response (CR/PR) according to RECIST v1.1 will be included to early discontinue maintenance therapy with anti-PD-1. The primary endpoint is the rate of ongoing response at 12 months after start of ICI. Secondary endpoints include ongoing response at 24 months, disease control at different time points, melanoma specific and overall survival, the incidence of irAEs and health-related quality of life.
DISCUSSION: From a medical, healthcare and economic perspective, overtreatment should be prevented and shorter treatment duration of ICIs is preferred. If early discontinuation of ICIs is safe for patients who are treated with the combination of ipilimumab-nivolumab, the treatment duration of nivolumab could be shortened in patients with a favourable tumour response.
TRIAL REGISTRATION: ClinicalTrials.gov ID NCT05652673, registration date: 08-12-2022.

Gepubliceerd: BMC Cancer. 2024;24(1):632.
Impact factor: 3.4 ; Q2

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14. Regional disparities in the use of intensive chemotherapy for AML in the Netherlands: does it influence survival?

Kaplan ZLR, van Leeuwen N, van Klaveren D, Visser O, Posthuma EFM, van Lammeren-Venema D, Snijders TJF, van Elssen C, van Rhenen A, von dem Borne PA, Blijlevens NMA, Cornelissen JJ, Raaijmakers M, van de Loosdrecht AA, Huls G, Lemmens V, Lingsma HF, Dinmohamed AG.

OBJECTIVE: Acute myeloid leukaemia (AML) prognosis is enhanced with intensive remission induction chemotherapy (ICT) in eligible patients. However, ICT eligibility perceptions may differ among healthcare professionals. This nationwide, population-based study aimed to explore regional variation in ICT application and its relation with overall survival (OS).
METHODS AND ANALYSIS: We compared nine Dutch regional networks using data from the Netherlands Cancer Registry. Regional variance was assessed for the entire population and age subgroups (ie, ≤60 years and >60 years) using multivariable mixed effects logistic and Cox proportional hazard regression analyses, expressed via median OR (MOR) and median HR (MHR).
RESULTS: Including all adult AML patients from 2014 to 2018 (N=4060 patients; 58% males; median age, 70 years), 1761 (43%) received ICT. ICT application varied from 36% to 57% (MOR 1.36 (95% CI

1.11 to 1.58)) across regions, with minor variations for patients aged ≤60 years (MOR 1.16 (95% CI 1.00 to 1.40)) and more extensive differences for those aged >60 years (MOR 1.43 (95% CI 1.16 to 1.63)). Median OS spanned 4.9-8.4 months across regions (MHR 1.11 (95% CI 1.00 to 1.15)), with pronounced differences in older patients (MHR 1.12 (95% CI 1.08 to 1.20)) but negligible differences in the younger group (MHR 1.02 (95% CI 1.00 to 1.14)). Survival differences for the total population and the older patients decreased to respectively, MHR 1.09 (95% CI 1.00 to 1.13) and 1.10 (95% CI 1.04 to 1.18), after additional adjustment for the probability of receiving ICT within a region, indicating approximately 10% unexplained differences.
CONCLUSION: Regional disparities in ICT application and survival exist, especially in older AML patients. However, ICT application differences partially explain survival disparities, indicating the need for more standardised ICT eligibility criteria and a better understanding of underlying causes of outcome disparities.

Gepubliceerd: BMJ Oncol. 2024;3(1):e000264.
IF onbekend

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15. Risk factors for graft-versus-host-disease after donor lymphocyte infusion following T-cell depleted allogeneic stem cell transplantation
Koster EAS, von dem Borne PA, van Balen P, Marijt EWA, Tjon JML, Snijders TJF, van Lammeren D, Veelken H, Falkenburg JHF, Halkes CJM, de Wreede LC.

INTRODUCTION: Unmodified donor lymphocyte infusions (DLI) after allogeneic stem cell transplantation (alloSCT) can boost the beneficial Graft-versus-Leukemia (GvL) effect but may also induce severe Graft-versus-Host-Disease (GvHD). To improve the balance between GvL and GvHD, it is crucial to identify factors that influence the alloreactivity of DLI.
METHODS: We investigated the effects of the presence of patient-derived antigen-presenting cells at time of DLI as estimated by the bone marrow (BM) chimerism status, lymphopenia as measured by the absolute lymphocyte count (ALC) at time of DLI, and the presence of a viral infection (de novo or reactivation) close to DLI on the risk of GvHD after DLI. The cohort consisted of patients with acute leukemia or myelodysplastic syndrome who prophylactically or pre-emptively received DLI as standard care after alemtuzumab-based alloSCT. In patients at high risk for relapse, DLI was administered at 3 months after alloSCT (n=88) with a dose of 0.3x10(6) or 0.15x10(6) T cells/kg in case of a related or unrelated donor, respectively. All other patients (n=76) received 3x10(6) or 1.5x10(6) T cells/kg, respectively, at 6 months after alloSCT.
RESULTS: For both DLIs, patients with reduced-intensity conditioning and an unrelated donor had the highest risk of GvHD. For DLI given at three months, viral infection within 1 week before and 2 weeks after DLI was an additional significant risk factor (hazard ratio (HR) 3.66 compared to no viral infection) for GvHD. At six months after alloSCT, viral infections were rare and not associated with GvHD. In contrast, mixed BM chimerism (HR 3.63 for ≥5% mixed chimerism compared to full donor) was an important risk factor for GvHD after DLI given at six months after alloSCT. ALC of <1000x10(6)/l showed a trend for association with GvHD after this DLI (HR 2.05 compared to ≥1000x106/l, 95% confidence interval 0.94-4.45). Furthermore, the data suggested that the presence of a viral infection close to the DLI at three months or ≥5% mixed chimerism at time of the DLI at six months correlated with the severity of GvHD, thereby increasing their negative impact on the current GvHD-relapse-free survival.
CONCLUSION: These data demonstrate that the risk factors for GvHD after DLI depend on the setting of the DLI.

Gepubliceerd: Front Immunol. 2024;15:1335341.
Impact factor: 5.9 ; Q1

16. Assessing the clinical benefit of systemic anti-cancer treatments in the Netherlands: The impact of different thresholds for effectiveness
Leeneman B, Xander NSH, Fiets WE, de Jong WK, Uyl NEM, Wymenga ANM, Reyners AKL, Uyl-de Groot CA.

BACKGROUND: In the Netherlands, the clinical benefit of systemic anti-cancer treatments (SACTs) is assessed by the Committee for the Evaluation of Oncological Agents (cieBOM). For non-curative SACTs, the assessment is based on the hazard ratio (HR) for progression-free survival and/or overall survival (OS), and the difference in median survival. We evaluated the impact of different thresholds for effectiveness by reassessing the clinical benefit of SACTs.
METHODS: We reassessed SACTs that were initially assessed by cieBOM between 2015 and 2017. Four scenarios were formulated: replacing an "OR" approach (initial assessment) by an "AND" approach (used in all scenarios), changing the HR threshold from < 0.70 (initial assessment) to < 0.60, changing the threshold for the difference in median survival from > 12 weeks (initial assessment) to > 16 weeks, and including thresholds for OS rates. The outcomes of these scenarios were compared to the outcomes of the initial assessment.
RESULTS: Reassessments were conducted for 41 treatments. Replacing the "OR" approach by an "AND" approach substantially decreased the number of positive assessments (from 33 to 22), predominantly affecting immunotherapies. This number further decreased (to 21 and 19, respectively) in case more restrictive thresholds for the HR and difference in median survival were used. Including thresholds for OS rates slightly mitigated the impact of applying an "AND" approach.
CONCLUSIONS: The scenario-specific thresholds had a substantial impact; the number of negative assessments more than doubled. Since this was not limited to treatments with marginal survival benefits, understanding the potential challenges that may arise from applying more restrictive thresholds is essential.

Gepubliceerd: Eur J Cancer. 2024;202:114002.
Impact factor: 7.1 ; Q1

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17. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands: A Stepped-Wedge Randomized Clinical Trial
Mackay TM, Latenstein AEJ, Augustinus S, van der Geest LG, Bogte A, Bonsing BA, Cirkel GA, Hol L, Busch OR, den Dulk M, van Driel L, Festen S, de Groot DA, de Groot JB, Groot Koerkamp B, Haj Mohammad N, Haver JT, van der Harst E, de Hingh IH, Homs MYV, Los M, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, Patijn GA, Quispel R, Römkens TEH, van Santvoort HC, Stommel MWJ, Venneman NG, Verdonk RC, van Vilsteren FGI, de Vos-Geelen J, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG.

IMPORTANCE: Implementation of new cancer treatment strategies as recommended by evidence-based guidelines is often slow and suboptimal. OBJECTIVE: To improve the implementation of guideline-based best practices in the Netherlands in pancreatic cancer care and assess the impact on survival.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter, stepped-wedge cluster randomized trial compared enhanced implementation of best practices with usual care in consecutive patients with all stages of pancreatic cancer. It took place from May 22, 2018 through July 9, 2020. Data were analyzed from April 1, 2022, through February 1, 2023. It included all patients in the Netherlands with pathologically or clinically diagnosed pancreatic ductal adenocarcinoma. This study reports 1-year follow-up (or shorter in case of deceased patients).

INTERVENTION: The 5 best practices included optimal use of perioperative chemotherapy, palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), referral to a dietician, and use of metal stents in patients with biliary obstruction. A 6-week implementation period was completed, in a randomized order, in all 17 Dutch networks for pancreatic cancer care.
MAIN OUTCOMES AND MEASURES: The primary outcome was 1-year survival. Secondary outcomes included adherence to best practices and quality of life (European Organisation for Research and Treatment of Cancer [EORTC] global health score).
RESULTS: Overall, 5887 patients with pancreatic cancer (median age, 72.0 [IQR, 64.0-79.0] years; 50% female) were enrolled, 2641 before and 2939 after implementation of best practices (307 during wash-in period). One-year survival was 24% vs 23% (hazard ratio, 0.98, 95% CI, 0.88-1.08). There was no difference in the use of neoadjuvant chemotherapy (11% vs 11%), adjuvant chemotherapy (48% vs 51%), and referral to a dietician (59% vs 63%), while the use of palliative chemotherapy (24% vs 30%; odds ratio [OR], 1.38; 95% CI, 1.10-1.74), PERT (34% vs 45%; OR, 1.64; 95% CI, 1.28-2.11), and metal biliary stents increased (74% vs 83%; OR, 1.78; 95% CI, 1.13-2.80). The EORTC global health score did not improve (area under the curve, 43.9 vs 42.8; median difference, -1.09, 95% CI, -3.05 to 0.94).
CONCLUSIONS AND RELEVANCE: In this randomized clinical trial, implementation of 5 best practices in pancreatic cancer care did not improve 1-year survival and quality of life. The finding that most patients received no tumor-directed treatment paired with the poor survival highlights the need for more personalized treatment options.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03513705.

Gepubliceerd: JAMA Surg. 2024;159(4):429-37.
Impact factor: 14.9 ; Q1

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18. Frailty, Multimorbidity, and Polypharmacy: Exploratory Analyses of the Effects of Empagliflozin from the EMPA-KIDNEY Trial

Mayne KJ, Sardell RJ, Staplin N, Judge PK, Zhu D, Sammons E, Cherney DZI, Cheung AK, Maggioni AP, Nangaku M, Rossello X, Tuttle KR, Ihara K, Iwata T, Wanner C, Emberson J, Preiss D, Landray MJ, Baigent C, Haynes R, Herrington WG, EMPA-KIDNEY Collaborative Group; van Erp R.

BACKGROUND: Sodium-glucose cotransporter-2 inhibitors are recommended treatment for adults with CKD, but uncertainty exists regarding their use in patients with frailty and/or multimorbidity, among whom polypharmacy is common. We derived a multivariable logistic regression model to predict hospitalization (reflecting frailty) and assessed empagliflozin's risk–benefit profile in a post hoc analysis of the double-blind, placebo-controlled EMPA-KIDNEY trial.
METHODS: The EMPA-KIDNEY trial randomized 6609 patients with CKD (eGFR ≥20 to <45 ml/min per 1.73 m2, or ≥45 to <90 ml/min per 1.73 m2 with urinary albumin-to-creatinine ratio ≥200 mg/g) to receive either empagliflozin 10 mg daily or matching placebo and followed them for 2 years (median). Additional characteristics analyzed in subgroups were multimorbidity, polypharmacy, and health-related quality of life at baseline. Cox regression analyses were performed with subgroups defined by approximate thirds of each variable.
RESULTS: The strongest predictors of hospitalization were N-terminal prohormone of brain natriuretic peptide, poor mobility, and diabetes and then eGFR and other comorbidities. Empagliflozin was generally well tolerated independent of predicted risk of hospitalization. In relative terms, allocation to empagliflozin reduced the risk of the primary outcome of kidney disease progression or cardiovascular death by 28% (hazard ratio, 0.72; 95% confidence interval, 0.64 to 0.82) and all-cause hospitalization by 14% (hazard ratio, 0.86; 95% confidence interval, 0.78 to 0.95), with broadly consistent effects across subgroups of predicted risk of hospitalization, multimorbidity, polypharmacy, or health-related quality of life. In absolute terms, the estimated benefits of empagliflozin were greater in those at highest predicted risk of hospitalization (reflecting frailty) and outweighed potential serious harms.

CONCLUSIONS: These findings support the use of sodium-glucose cotransporter-2 inhibitors in CKD, irrespective of frailty, multimorbidity, or polypharmacy.

Gepubliceerd: Clin J Am Soc Nephrol. 2024;19(9):1119-29.
Impact factor: 7.1 ; Q1

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19. Outcome of combined modality treatment in first-line for stage I(E) peripheral T-cell lymphoma; a nationwide population-based cohort study from the Netherlands
Meeuwes FO, Brink M, Plattel W, Van der Poel MWM, Kersten MJ, Wondergem M, Böhmer L, Woei AJF, Visser O, Oostvogels R, Jansen PM, Neelis KJ, Crijns APG, Daniëls LA, Snijders TJF, Vermaat JSP, Huls GA, Nijland M.

Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of mature T-cell neoplasms with an unfavorable prognosis; presentation with stage I(E) disease is uncommon. In clinical practice, an abbreviated chemotherapy treatment regimen combined with radiotherapy (combined modality treatment [CMT]) is commonly used, although evidence from clinical trials is lacking. The aim of this nationwide population-based cohort study is to describe first-line treatment and outcome of patients with stage I(E) PTCL. All newly diagnosed patients ≥18 years with stage I(E) anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma NOS (PTCL not otherise specified [NOS]) in 1989-2020 were identified in the Netherlands Cancer Registry. Patients were categorized according to treatment regimen, i.e., chemotherapy (CT), radiotherapy (RT), CMT, other therapy and no treatment. The primary endpoint was overall survival (OS). Patients with stage I(E) ALCL, AITL and PTCL NOS (n=576) were most commonly treated with CMT (28%) or CT (29%), 2% underwent SCT. RT only was given in 18%, and 8% received other therapy and 16% no treatment. Overall, the 5-year OS was 59%. According to subtype, 5-year OS was superior for ALCL as compared to PTCL NOS and AITL (68% vs. 55% and 52%, respectively; P=0.03). For patients treated with CMT, 5-year OS was significantly higher (72%) as compared to patients treated with either CT or RT alone (55% and 55%, respectively; P<0.01). In multivariable analysis, age per year increment (hazard ratio [HR] =1.06, 95% confidence interval [CI]: 1.05-1.07), male sex (HR=1.53, 95% CI: 1.23-1.90), and CT, or no treatment (HR=1.64, 95% CI: 1.21-2.21, and HR=1.55, 95% CI: 1.10-2.17, respectively) were associated with a higher risk of mortality. For stage I(E) ALCL, AITL and PTCL NOS, 5-year OS is 59%, comparing favorably to historical outcome in advanced-stage disease. Superior outcome estimates were observed in patients treated with CMT.

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Impact factor: 7.9 ; Q1

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20. Enteropathy-associated T-cell lymphoma: A population-based cohort study on incidence, treatment, and outcome in the Netherlands
Meeuwes FO, Brink M, Plattel WJ, Vermaat JSP, Kersten MJ, Wondergem M, Visser O, van der Poel MWM, Oostvogels R, Woei AJF, Böhmer L, Snijders TJF, Huls GA, Nijland M.

INTRODUCTION: Enteropathy-associated T-cell lymphoma (EATL) is a peripheral T-cell lymphoma (PTCL) with a poor prognosis. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without etoposide consolidated by autologous stem cell transplantation (ASCT) are recommended for fit PTCL patients. The role of etoposide and ASCT in EATL is unclear.
METHODS: This study reports the incidence, treatment, and outcome of EATL patients using the Netherlands Cancer Registry, with nationwide coverage of >95%.

RESULTS: All patients diagnosed in 1989-2021 (n = 351, 77% treated) were identified (median age 67 years, 56% male, 50% limited stage). Time period analysis assessed trends in primary therapy and overall survival (OS). Treatment included chemotherapy (CT) (34%), surgery (18%), surgery and CT (19%) or CT followed by ASCT (7%). The 5-year OS for treated patients with limited versus advanced stage was 19% and 9% respectively. The 2-year OS improved over time (21%-33%, p = 0.06). Surgery only (hazard ratio [HR] 2.16; 95% confidence interval [CI] 1.55-3.01, p < 0.01) and advanced-stage disease (HR 1.67; 95% CI 1.25-2.23, p = 0.01) were predictors of poor prognosis. ASCT (HR 0.31; 95% CI 0.18-0.56) was associated with improved OS.
CONCLUSION: There was no statistical difference in OS between patients treated with or without etoposide. Current first-line treatment is ineffective.

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Impact factor: 1.2 ; Q4

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21. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; Delsing C, Piersma D.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

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Impact factor: 3.9 ; Q1

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22. Vascular fingerprint tool to identify patients with testicular cancer treated with cisplatin-based chemotherapy at high risk of early cardiovascular events
Meuleman AT, Volders ELD, Lubberts S, Kerst JM, Wymenga ANM, Aarts MJB, Goncalves MB, Lefrandt JD, Steursma G, Meijer J, Nuver J, Gietema JA.

BACKGROUND: Patients with testicular cancer treated with chemotherapy have an increased risk of developing early cardiovascular events. Identification of patients with testicular cancer at a high risk of these events enables the development of preventative strategies. This study validates the vascular fingerprint tool to identify these patients.
PATIENTS AND METHODS: We carried out a multicenter prospective study in patients with metastatic testicular cancer [International Germ Cell Cancer Collaborative Group (IGCCCG) good or intermediate risk; retroperitoneal mass <5 cm]. In eligible patients, the vascular fingerprint was assessed before the start of cisplatin-based chemotherapy, which consists of five risk factors, namely, smoking, overweight (body mass index >25 kg/m(2)), hypertension (blood pressure >140/90 mmHg), dyslipidemia (fasting cholesterol >5.1 mmol/l or low-density lipoprotein-cholesterol >2.5 mmol/l), and diabetes mellitus (fasting glucose ≥7.0 mmol/l). The presence of three or more risk factors was defined as high-risk vascular fingerprints. A log-rank test was carried out with a cardiovascular event within 1 year after the start of chemotherapy as the primary endpoint.
RESULTS: A total of 196 patients with metastatic testicular cancer were included; 15 patients (8%) developed a cardiovascular event: 4 (2%) arterial events and 11 (6%) venous thrombotic events. Overall, 189 vascular fingerprint scores were available. Patients with a high-risk vascular fingerprint (62/189) had a higher risk of developing a cardiovascular event (hazard ratio 3.27, 95% confidence interval 1.16-9.18; log-rank: P = 0.017). Histological diagnosis, prognosis group, cumulative chemotherapy dose, and retroperitoneal mass size did not differ between patients with or without a cardiovascular event. All patients with an arterial event had a high-risk vascular fingerprint compared with 5/11 patients with a venous event. Overweight was more prevalent in patients with cardiovascular events (87% versus 59%; P = 0.037).
CONCLUSIONS: The vascular fingerprint is a validated tool to identify patients with testicular cancer at a high risk of developing early cardiovascular events. This tool can be used to develop preventative strategies with anticoagulant treatment.

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Impact factor: 8.3 ; Q1

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23. Real-world effectiveness and tolerability of switching to doravirine-based antiretroviral therapy in people with HIV: a nationwide, matched, prospective cohort study
Oomen PGA, Wit F, Brinkman K, Vrouenraets SME, Mudrikova T, van Welzen BJ, van der Valk M, ATHENA National Observational Cohort Study; Kootstra GJ, Delsing CE.

BACKGROUND: Currently, real-world data on doravirine are scarce. In a national prospective cohort, we assessed the effectiveness and tolerability of switching to doravirine-based antiretroviral therapy (ART) in people with HIV.
METHODS: We did a nationwide, matched, prospective cohort study of people with HIV without previous virological failure and stable for at least 12 months on non-doravirine-containing triple or dual ART switching to doravirine before Sept 1, 2020 (exposed group). Participants in the exposed group were matched 1:2 to individuals continuing stable non-doravirine-containing ART, on age, sex, HIV acquisition category, time since ART initiation, calendar time, pre-ART CD4-count, pre-ART plasma viral load (PVL) and anchor drug class before switching. The primary outcome was protocol-defined virological failure (PDVF; PVL of ≥200 copies per mL) in the intention-to-treat (ITT) population at week 104, with participants modifying their regimen or becoming lost to follow-up considered as PDVF (non-inferiority margin +5%). In contrast, in the on-treatment population, those who modified their regimen or became lost to follow-up were censored from that moment onwards. Tolerability was a secondary outcome.
FINDINGS: In total, 590 participants in the exposed group and 1180 participants in the unexposed group (of whom 55·3% used integrase strand transfer inhibitor-based regimens) were included. In the ITT analysis, PDVF occurred in 135 (22·9%) exposed participants and in 295 (25·0%) unexposed

participants (risk difference -2·12%, upper limit of the one-sided 95% CI +1·40%). In the on-treatment analysis, 10 (2·2%) of 455 non-censored exposed participants and 26 (2·9%) of 885 non-censored unexposed participants had PDVF (risk difference -0·70%, upper limit of the one-sided 95% CI +0·73%). All exposed participants with a PVL of 200 copies or more per mL resuppressed without regimen modification: no confirmed virological failure (two consecutive PVLs of ≥200 copies per mL) was observed. 104 (17·6%) exposed participants and 211 (17·9%) unexposed participants modified their regimen. 73 (12.4%) exposed participants discontinued doravirine due to adverse events: abnormal dreams (1·7%) and insomnia (1·5%) were most common.
INTERPRETATION: Switching to doravirine in well suppressed people with HIV without previous virological failure was non-inferior compared with continuing non-doravirine-containing regimens after 2 years in a real-world setting.
FUNDING: None.

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Impact factor: 13.0 ; Q1

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24. Adjuvant immunotherapy in older patients with stage III and resected stage IV melanoma: Toxicity and recurrence-free survival outcomes from the Dutch melanoma treatment registry
Özkan A, Kapiteijn E, van den Bos F, Aarts MJB, van den Berkmortel F, Blank CU, Bloem M, Blokx WAM, Boers-Sonderen MJ, Bonenkamp JJ, van den Eertwegh AJM, de Groot JWB, Haanen JB, Holtslag CE, Hospers GAP, Piersma D, van Rijn RS, Stevense-den Boer AM, Suijkerbuijk KPM, van der Veldt AAM, Vreugdenhil G, Wouters M, Portielje JEA, de Glas NA.

BACKGROUND: Adjuvant anti-PD-1 therapy improves relapse free survival in stage III melanoma, but also leads to immune-related adverse events (irAEs). Older patients are of particular interest due to comorbidities and frailty, which may impact their ability to tolerate irAEs and benefit from anti-PD-1 therapy. This study aimed to explore associations between clinical parameters and the occurrence of grade ≥ 3 irAEs and recurrence-free survival (RFS) in older patients with radically resected stage III/IV cutaneous melanoma treated with adjuvant anti-PD-1 therapy.
METHODS: Patients aged ≥ 65 with resected stage III/IV cutaneous melanoma treated with adjuvant anti-PD-1 therapy between 2018 and 2022 were selected using real-world data from the nationwide Dutch Melanoma Treatment Registry (DMTR). A univariate and multivariable logistic regression was used to compare determinants of grade ≥ 3 irAEs, and univariate and multivariable Cox-proportional hazard models were fitted to identify factors influencing RFS.
RESULTS: The study included 885 patients, with 280 aged 75 and older. The incidence of grade ≥ 3 irAEs was 15.5 % in the 65-74 age group and 13.9 % in the ≥ 75 age group. No significant correlation was found between age and grade ≥ 3 irAEs. However, an increasing number of comorbidities was associated with a higher risk of grade ≥ 3 irAEs (multivariable analyses: OR 1.83, 95 % C.I. 0.99-3.40). The 1-year RFS rate of 80.0 % of this study was comparable to those reported in previous registration trials and real-world data. Having ≥ 3 comorbidities was significantly associated with a decrease in RFS (HR: 1.68, 95 % C.I. 1.15-2.44).
CONCLUSION: Older patients had similar benefit of adjuvant immunotherapy compared to older subgroups in previous trials. However, patients with multiple comorbidities were at increased risk of grade ≥ 3 irAEs and had a lower RFS. This should be considered when deciding upon adjuvant treatment.

Gepubliceerd: Eur J Cancer. 2024;212:115056.
Impact factor: 7.1 ; Q1

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25. Results from the UNITED study: a multicenter study validating the prognostic effect of the tumor-stroma ratio in colon cancer
Polack M, Smit MA, van Pelt GW, Roodvoets AGH, Meershoek-Klein Kranenbarg E, Putter H, Gelderblom H, Crobach A, Terpstra V, Petrushevska G, Gašljević G, Kjær-Frifeldt S, de Cuba EMV, Bulkmans NWJ, Vink GR, Al Dieri R, Tollenaar R, van Krieken J, Mesker WE, UNITED Collaboration; Mekenkamp L.

BACKGROUND: The TNM (tumor-node-metastasis) Evaluation Committee of Union for International Cancer Control (UICC) and College of American Pathologists (CAP) recommended to prospectively validate the cost-effective and robust tumor-stroma ratio (TSR) as an independent prognostic parameter, since high intratumor stromal percentages have previously predicted poor patient-related outcomes.
PATIENTS AND METHODS: The 'Uniform Noting for International application of Tumor-stroma ratio as Easy Diagnostic tool' (UNITED) study enrolled patients in 27 participating centers in 12 countries worldwide. The TSR, categorized as stroma-high (>50%) or stroma-low (≤50%), was scored through standardized microscopic assessment by certified pathologists, and effect on disease-free survival (DFS) was evaluated with 3-year median follow-up. Secondary endpoints were benefit assessment of adjuvant chemotherapy (ACT) and overall survival (OS).
RESULTS: A total of 1537 patients were included, with 1388 eligible stage II/III patients curatively operated between 2015 and 2021. DFS was significantly shorter in stroma-high (n = 428) than in stroma-low patients (n = 960) (3-year rates 70% versus 83%; P < 0.001). In multivariate analysis, TSR remained an independent prognosticator for DFS (P < 0.001, hazard ratio 1.49, 95% confidence interval 1.17-1.90). As secondary outcome, DFS was also worse in stage II and III stroma-high patients despite adjuvant treatment (3-year rates stage II 73% versus 92% and stage III 66% versus 80%; P = 0.008 and P = 0.011, respectively). In stage II patients not receiving ACT (n = 322), the TSR outperformed the American Society of Clinical Oncology (ASCO) criteria in identifying patients at risk of events (event rate 21% versus 9%), with a higher discriminatory 3-year DFS rate (stroma-high 80% versus ASCO high risk 91%). A trend toward worse 5-year OS in stroma-high was noticeable (74% versus 83% stroma-low; P = 0.102).
CONCLUSION: The multicenter UNITED study unequivocally validates the TSR as an independent prognosticator, confirming worse outcomes in stroma-high patients. The TSR improved current selection criteria for patients at risk of events, and stroma-high patients potentially experienced chemotherapy resistance. TSR implementation in pathology diagnostics and international guidelines is highly recommended as aid in personalized treatment.

Gepubliceerd: ESMO Open. 2024;9(4):102988.
Impact factor: 8.3 ; Q1

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26. Adverse Events in Anti-PD-1-Treated Adjuvant and First-Line Advanced Melanoma Patients
Rauwerdink DJW, Not OV, de Meza M, Doorn RV, Hage JV, Eertwegh A, Haanen JB, Aarts MJB, Berkmortel F, Blank CU, Boers-Sonderen MJ, Groot JWB, Hospers GAP, Piersma D, van Rijn RS, Stevense-den Boer AM, Veldt A, Vreugdenhil G, Wouters M, Suijkerbuijk KPM, Kapiteijn E.

INTRODUCTION: The difference in incidence and severity of anti-PD-1 therapy-related adverse events (irAEs) between adjuvant and advanced treated melanoma patients remains unclear, as no head-to-head studies have compared these groups.
METHODS: This multi-center cohort study analyzed melanoma patients treated with anti-PD-1 in adjuvant or advanced settings between 2015 and 2021. Comorbidities and ECOG performance status were assessed before treatment, and grade III-IV irAEs were monitored during treatment. Univariate and multivariate regression analyses were conducted to identify factors associated with irAE development.

RESULTS: A total of 1465 advanced melanoma patients and 908 resected melanoma patients received anti-PD-1 therapy. Adjuvant-treated patients were younger, with a median age of 63 years compared to 69 years in the advanced group ($p < 0.01$), and had a better ECOG performance status ($p < 0.01$). Comorbidities were seen more frequently in advanced melanoma patients than in those receiving adjuvant treatment, 76% versus 68% ($p < 0.01$). Grade III-IV irAEs occurred in 214 (15%) advanced treated patients and in 119 (13%) adjuvant-treated patients. Multivariate analysis showed an increased risk of severe irAE development with the presence of any comorbidity (adjusted OR 1.22, 95% CI 1.02-1.44) and ECOG status greater than 1 (adjusted OR 2.00, 95% CI 1.20-3.32). Adjuvant therapy was not associated with an increased risk of irAE development compared to advanced treatment (adjusted OR 0.95, 95% CI 0.74-1.21) after correcting for comorbidities and ECOG performance score. Anti-PD-1 therapy was halted due to toxicity (any grade irAE) more often in the adjuvant setting than in the advanced setting, 20% versus 15% ($p < 0.01$).
CONCLUSIONS: Higher ECOG performance status and presence of any comorbidity were independently associated with an increased risk of Grade III-IV irAE in adjuvant and advanced treated melanoma patients. Patients treated in the adjuvant setting did not have an increased risk of developing severe irAEs compared to advanced melanoma patients. These findings are of clinical significance in consulting patients for adjuvant anti-PD-1 treatment.

Gepubliceerd: Cancers (Basel). 2024;16(15).
Impact factor: 4.4 ; Q2

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27. Determinants of Physical Activity among Patients with Colorectal Cancer: From Diagnosis to 5 Years after Diagnosis

Smit KC, Derksen JWG, Stellato RK, AS VANL, Wesselink E, Belt EJT, Balen MC, Coene P, Dekker JWT, JW DEG, Haringhuizen AW, HK VANH, TT VANH, Helgason HH, Hendriks MP, IHJT DEH, Hoekstra R, Houtsma D, Janssen JJB, Kok N, Konsten JLM, Los M, Meijerink MR, Mekenkamp LJM, Peeters K, Polée MB, Rietbroek RC, Schiphorst AHW, Schrauwen RWM, Schreinemakers J, Sie MPS, Simkens L, Sonneveld EJA, Terheggen F, Iersel LV, Vles WJ, Wasowicz-Kemps DK, JHW DEW, Kok DE, Winkels RM, Kampman E, FJB VAND, Koopman M, May AM.

INTRODUCTION: Physical activity (PA) is associated with higher quality of life and probably better prognosis among colorectal cancer (CRC) patients. This study focuses on determinants of PA among CRC patients from diagnosis until 5 yr postdiagnosis.
METHODS: Sociodemographic and disease-related factors of participants of two large CRC cohort studies were combined. Moderate-to-vigorous PA during sport and leisure time (MVPA-SL) was measured at diagnosis (T0) and 6, 12, 24, and 60 months (T6 to T60) postdiagnosis, using the SQUASH questionnaire. Mixed-effects models were performed to identify sociodemographic and disease-related determinants of MVPA-SL, separately for stage I-III colon (CC), stage I-III rectal cancer (RC), and stage IV CRC (T0 and T6 only). Associations were defined as consistently present when significant at ≥4 timepoints for the stage I-III subsets. MVPA-SL levels were compared with an age- and sex-matched sample of the general Dutch population.
RESULTS: In total, 2905 CC, 1459 RC and 436 stage IV CRC patients were included. Patients with higher fatigue scores, and women compared with men had consistently lower MVPA-SL levels over time, regardless of tumor type and stage. At T6, having a stoma was significantly associated with lower MVPA-SL among stage I-III RC patients. Systemic therapy and radiotherapy were not significantly associated with MVPA-SL changes at T6. Compared with the general population, MVPA-SL levels of CRC patients were lower at all timepoints, most notably at T6.
CONCLUSIONS: Female sex and higher fatigue scores were consistent determinants of lower MVPA-SL levels among all CRC patients, and MVPA-SL levels were lowest at 6 months postdiagnosis. Our results can inform the design of intervention studies aimed at improving PA, and guide healthcare professionals in optimizing individualized support.

Gepubliceerd: Med Sci Sports Exerc. 2024;56(4):623-34.
Impact factor: 3.9 ; Q1

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28. Nationwide Use and Outcome of Surgery for Locally Advanced Pancreatic Cancer Following Induction Chemotherapy
Stoop TF, Seelen LWF, van 't Land FR, Lutchman KRD, van Dieren S, Lips DJ, van der Harst E, Kazemier G, Patijn GA, de Hingh IH, Wijsman JH, Erdmann JI, Festen S, Groot Koerkamp B, Mieog JSD, den Dulk M, Stommel MWJ, Busch OR, de Wilde RF, de Meijer VE, Te Riele W, Molenaar IQ, van Eijck CHJ, van Santvoort HC, Besselink MG, Dutch Pancreatic Cancer Group; Mekenkamp LJ.

BACKGROUND: Several international high-volume centers have reported good outcomes after resection of locally advanced pancreatic cancer (LAPC) following chemo(radio)therapy, but it is unclear how this translates to nationwide clinical practice and outcome. This study aims to assess the nationwide use and outcome of resection of LAPC following induction chemo(radio)therapy.
PATIENTS AND METHODS: A multicenter retrospective study including all patients who underwent resection for LAPC following chemo(radio)therapy in all 16 Dutch pancreatic surgery centers (2014-2020), registered in the mandatory Dutch Pancreatic Cancer Audit. LAPC is defined as arterial involvement > 90° and/or portomesenteric venous > 270° involvement or occlusion.
RESULTS: Overall, 142 patients underwent resection for LAPC, of whom 34.5% met the 2022 National Comprehensive Cancer Network criteria. FOLFIRINOX was the most commonly (93.7%) used chemotherapy [median 5 cycles (IQR 4-8)]. Venous and arterial resections were performed in 51.4% and 14.8% of patients. Most resections (73.9%) were performed in high-volume centers (i.e., ≥ 60 pancreatoduodenectomies/year). Overall median volume of LAPC resections/center was 4 (IQR 1-7). In-hospital/30-day major morbidity was 37.3% and 90-day mortality was 4.2%. Median OS from diagnosis was 26 months (95% CI 23-28) and 5-year OS 18%. Surgery in high-volume centers [HR = 0.542 (95% CI 0.318-0.923)], ypN1-2 [HR = 3.141 (95% CI 1.886-5.234)], and major morbidity [HR = 2.031 (95% CI 1.272-3.244)] were associated with OS.
CONCLUSIONS: Resection of LAPC following chemo(radio)therapy is infrequently performed in the Netherlands, albeit with acceptable morbidity, mortality, and OS. Given these findings, a structured nationwide approach involving international centers of excellence would be needed to improve selection of patients with LAPC for surgical resection following induction therapy.

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Impact factor: 3.5 ; Q1

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29. ASO Author Reflections: Nationwide Experience on Locally Advanced Pancreatic Cancer Surgery After Induction Chemotherapy in the Netherlands: A Stepping Stone for the PREOPANC-4 Trial
Stoop TF, Seelen LWF, van 't Land FR, van Eijck CHJ, van Santvoort HC, Besselink MG, Dutch Pancreatic Cancer Group: Mekenkamp LJ.

Gepubliceerd: Ann Surg Oncol. 2024;31(4):2658-9.
Impact factor: 3.5 ; Q1

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30. Deep learning on CT scans to predict checkpoint inhibitor treatment outcomes in advanced melanoma
Ter Maat LS, De Mooij RAJ, Van Duin IAJ, Verhoeff JJC, Elias SG, Leiner T, van Amsterdam WAC, Troenokarso MF, Arntz E, Van den Berkmortel F, Boers-Sonderen MJ, Boomsma MF, Van den Eertwegh FJM, de Groot JW, Hospers GAP, Piersma D, Vreugdenhil A, Westgeest HM, Kapiteijn E, De Wit AA, Blokx WAM, Van Diest PJ, De Jong PA, Pluim JPW, Suijkerbuijk KPM, Veta M.

Immune checkpoint inhibitor (ICI) treatment has proven successful for advanced melanoma, but is associated with potentially severe toxicity and high costs. Accurate biomarkers for response are lacking. The present work is the first to investigate the value of deep learning on CT imaging of metastatic lesions for predicting ICI treatment outcomes in advanced melanoma. Adult patients that were treated with ICI for advanced melanoma were retrospectively identified from ten participating centers. A deep learning model (DLM) was trained on volumes of lesions on baseline CT to predict clinical benefit. The DLM was compared to and combined with a model of known clinical predictors (presence of liver and brain metastasis, level of lactate dehydrogenase, performance status and number of affected organs). A total of 730 eligible patients with 2722 lesions were included. The DLM reached an area under the receiver operating characteristic (AUROC) of 0.607 [95%CI 0.565-0.648]. In comparison, a model of clinical predictors reached an AUROC of 0.635 [95%CI 0.59 -0.678]. The combination model reached an AUROC of 0.635 [95% CI 0.595-0.676]. Differences in AUROC were not statistically significant. The output of the DLM was significantly correlated with four of the five input variables of the clinical model. The DLM reached a statistically significant discriminative value, but was unable to improve over known clinical predictors. The present work shows that the assessment over known clinical predictors is an essential step for imaging-based prediction and brings important nuance to the almost exclusively positive findings in this field.

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Impact factor: 3.9 ; Q1

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31. Trends in Mortality in People With HIV From 1999 through 2020: A Multicohort Collaboration
Tusch E, Ryom L, Pelchen-Matthews A, Mocroft A, Elbirt D, Oprea C, Günthard HF, Staehelin C, Zangerle R, Suarez I, Vehreschild JJ, Wit F, Menozzi M, d'Arminio Monforte A, Spagnuolo V, Pradier C, Carlander C, Suanzes P, Wasmuth JC, Carr A, Petoumenos K, Borgans F, Bonnet F, De Wit S, El-Sadr W, Neesgaard B, Jaschinski N, Greenberg L, Hosein SR, Gallant J, Vannappagari V, Young L, Sabin C, Lundgren J, Peters L, Reekie J, D:A:D cohort study and RESPOND cohort study; Kootstra GJ, Delsing CE.

BACKGROUND: Mortality among people with human immunodeficiency virus (HIV) declined with the introduction of combination antiretroviral therapy. We investigated trends in mortality in people with HIV from 1999 through 2020.
METHODS: Data were collected from the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort between January 1999 through January 2015 and the International Cohort Consortium of Infectious Disease (RESPOND) from October 2017 through December 2020. Age-standardized all-cause and cause-specific mortality rates, classified using Coding Causes of Death in HIV, were calculated. Poisson models were used to assess mortality over time.
RESULTS: Among 55 716 participants followed for median 6 years (interquartile range, 3-11), 5263 died (mortality rate [MR], 13.7/1000 person-years of follow-up [PYFU]; 95% confidence interval [CI], 13.4-14.1). Changing mortality was observed: AIDS mortality was most common between 1999-2009 (n = 952; MR, 4.2/1000 PYFU; 95% CI, 4.0-4.5) and non-AIDS-defining malignancy (NADM) between 2010-2020 (n = 444; MR, 2.8/1000 PYFU; 95% CI, 2.5-3.1). In multivariable analysis, all-cause mortality declined (adjusted mortality rate ratio [aMRR], 0.97 per year; 95% CI, .96-.98), mostly 1999-2010 (aMRR, 0.96 per year; 95% CI, .95-.97) but was stable 2011-2020 (aMRR, 1.00 per year; 95% CI, .96-1.05). Mortality due to all known causes except NADM also declined.

CONCLUSIONS: Mortality among people with HIV in the D:A:D and/or RESPOND cohorts declined between 1999-2009 and was stable over the period 2010-2020. This decline in mortality was not fully explained by improvements in immunologic-virologic status or other risk factors.

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Impact factor: 7.3 ; Q1

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32. Bihormonal fully closed-loop system for the treatment of type 1 diabetes: a real-world multicentre, prospective, single-arm trial in the Netherlands
van Bon AC, Blauw H, Jansen TJP, Laverman GD, Urgert T, Geessink-Mennink J, Mulder AH, Out M, Groote Veldman R, Onvlee AJ, Schouwenberg B, Vermeulen MAR, Diekman MJM, Gerding MN, van Wijk JPH, Klaassen M, Witkop M, DeVries JH.

BACKGROUND: Management of insulin administration for intake of carbohydrates and physical activity can be burdensome for people with type 1 diabetes on hybrid closed-loop systems. Bihormonal fully closed-loop (FCL) systems could help reduce this burden. In this trial, we assessed the long-term performance and safety of a bihormonal FCL system.
METHODS: The FCL system (Inreda AP; Inreda Diabetic, Goor, Netherlands) that uses two hormones (insulin and glucagon) was assessed in a 1 year, multicentre, prospective, single-arm intervention trial in adults with type 1 diabetes. Participants were recruited in eight outpatient clinics in the Netherlands. We included adults with type 1 diabetes aged 18-75 years who had been using flash glucose monitoring or continuous glucose monitors for at least 3 months. Study visits were integrated into standard care, usually every three months, to evaluate glycaemic control, adverse events, and person-reported outcomes. The primary endpoint was time in range (TIR; glucose concentration 3·9-10·0 mmol/L) after 1 year. The study is registered in the Dutch Trial Register, NL9578.
FINDINGS: Between June 1, 2021, and March 2, 2022, we screened 90 individuals and enrolled 82 participants; 78 were included in the analyses. 79 started the intervention and 71 were included in the 12 month analysis. Mean age was 47.7 (SD 12·4) years and 38 (49%) were female participants. The mean preintervention TIR of participants was 55·5% (SD 17·2). After 1 year of FCL treatment, mean TIR was 80·3% (SD 5·4) and median time below range was 1·36% (IQR 0·80-2·11). Questionnaire scores improved on Problem Areas in Diabetes (PAID) from 30·0 (IQR 18·8-41·3) preintervention to 10·0 (IQR 3·8-21·3; p<0·0001) at 12 months and on World Health Organization-Five Well-Being Index (WHO-5) from 60·0 (IQR 44·0-72·0) preintervention to 76·0 (IQR 60·0-80·0; p<0·0001) at 12 months. Five serious adverse events were reported (one cerebellar stroke, two severe hypoglycaemic, and two hyperglycaemic events).
INTERPRETATION: Real-world data obtained in this trial demonstrate that use of the bihormonal FCL system was associated with good glycaemic control in patients who completed 1 year of treatment, and could help relieve these individuals with type 1 diabetes from making treatment decisions and the burden of carbohydrate counting. FUNDING: Inreda Diabetic.

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Impact factor: 24.1 ; Q1

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33. Determinants of lenalidomide response with or without erythropoiesis-stimulating agents in myelodysplastic syndromes: the HOVON89 trial
van de Loosdrecht AA, Cremers EMP, Alhan C, Duetz C, In 't Hout FEM, Visser-Wisselaar HA, Chitu DA, Verbrugge A, Cunha SM, Ossenkoppele GJ, Janssen J, Klein SK, Vellenga E, Huls GA, Muus P, Langemeijer SMC, de Greef GE, Te Boekhorst PAW, Raaijmakers MHG, van Marwijk Kooy M, Legdeur MC, Wegman JJ, Deenik W, de Weerdt O, van Maanen-Lamme TM, Jobse P, van Kampen RJW, Beeker A, Wijermans PW, Biemond BJ, Tanis BC, van Esser JWJ, Schaar CG, Noordzij-Nooteboom HS, Jacobs EMG, de Graaf AO, Jongen-Lavrencic M, Stevens-Kroef M, Westers TM, Jansen JH.

A randomized phase-II study was performed in low/int-1 risk MDS (IPSS) to study efficacy and safety of lenalidomide without (arm A) or with (arm B) ESA/G-CSF. In arm B, patients without erythroid response (HI-E) after 4 cycles received ESA; G-CSF was added if no HI-E was obtained by cycle 9. HI-E served as primary endpoint. Flow cytometry and next-generation sequencing were performed to identify predictors of response. The final evaluation comprised 184 patients; 84% non-del(5q), 16% isolated del(5q); median follow-up: 70.7 months. In arm A and B, 39 and 41% of patients achieved HI-E; median time-to-HI-E: 3.2 months for both arms, median duration of-HI-E: 9.8 months. HI-E was significantly lower in non-del(5q) vs. del(5q): 32% vs. 80%. The same accounted for transfusion independency-at-week 24 (16% vs. 67%), but similar in both arms. Apart from presence of del(5q), high percentages of bone marrow lymphocytes and progenitor B-cells, a low number of mutations, absence of ring sideroblasts, and SF3B1 mutations predicted HI-E. In conclusion, lenalidomide induced HI-E in patients with non-del(5q) and del(5q) MDS without additional effect of ESA/G-CSF. The identified predictors of response may guide application of lenalidomide in lower-risk MDS in the era of precision medicine. (EudraCT 2008-002195-10).

Gepubliceerd: Leukemia. 2024;38(4):840-50.
Impact factor: 13.4 ; Q1

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34. Baseline tumor-infiltrating lymphocyte patterns and response to immune checkpoint inhibition in metastatic cutaneous melanoma
van Duin IAJ, Schuiveling M, Ter Maat LS, van Amsterdam WAC, van den Berkmortel F, Boers-Sonderen M, de Groot JWB, Hospers GAP, Kapiteijn E, Labots M, Piersma D, Schrader AMR, Vreugdenhil G, Westgeest H, Veta M, Blokx WAM, van Diest PJ, Suijkerbuijk KPM.

INTRODUCTION: The presence of tumor-infiltrating lymphocytes (TILs) in melanoma has been linked to survival. Their predictive capability for immune checkpoint inhibition (ICI) response remains uncertain. Therefore, we investigated the association between treatment response and TILs in the largest cohort to date and analyzed if this association was independent of known clinical predictors.
METHODS: In this multicenter cohort study, patients who received first-line anti-PD1 ± anti-CTLA4 for advanced melanoma were identified. TILs were scored on hematoxylin and eosin (H&E) slides of primary melanoma and pre-treatment metastases using the validated TILs-WG, Clark and MIA score. The primary outcome was objective response rate (ORR), with progression free survival and overall survival being secondary outcomes. Univariable and multivariable logistic regression and Cox proportional hazard were performed, adjusting for known clinical predictors.
RESULTS: Metastatic melanoma specimens were available for 650 patients and primary specimens for 565 patients. No association was found in primary melanoma specimens. In metastatic specimens, a 10-point increase in the TILs-WG score was associated with a higher probability of response (aOR 1.17, 95 % CI 1.07-1.28), increased PFS (HR 0.93, 95 % CI 0.87-0.996), and OS (HR 0.94, 95 % CI 0.89-0.99). When categorized, patients in the highest tertile TILs-WG score (15-100 %) compared to the lowest tertile (0 %) had a longer median PFS (13.1 vs. 7.3 months, p = 0.04) and OS (49.4 vs. 19.5 months, p = 0.003). Similar results were noted using the MIA and Clark scores.

CONCLUSION: In advanced melanoma patients, TIL patterns on H&E slides of pre-treatment metastases, regardless of measurement method, are independently associated with ICI response. TILs are easily scored on readily available H&Es, facilitating the use of this biomarker in clinical practice.

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Impact factor: 7.1 ; Q1

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35. Tumor-infiltrating lymphocytes and immune-related adverse events in advanced melanoma
van Duin IAJ, Schuiveling M, Ter Maat LS, Veta M, van Eijs MJM, Verheijden RJ, van den Berkmortel F, Boers-Sonderen MJ, Hospers GAP, Labots M, de Groot JWB, Kapiteijn E, Piersma D, Vreugdenhil G, Westgeest H, Schrader AMR, van Diest PJ, Blokx WAM, Suijkerbuijk KPM.

BACKGROUND: The predictive value of tumor-infiltrating lymphocytes (TILs) in immune-related adverse event (irAE) development remains unknown, although an association between tumor immunogenicity and irAEs has been suggested. We investigated the association between TIL abundance in pretreatment primary and metastasis specimens and the subsequent development of severe irAEs.
PATIENTS AND METHODS: We retrospectively identified patients with advanced cutaneous melanoma who received first-line anti-programmed cell death protein 1 (PD-1) with or without anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA-4) from 10 hospitals in the Netherlands. TILs were scored on representative hematoxylin and eosin (H&E) stains of the primary melanoma and pretreatment melanoma metastasis as 'absent', 'nonbrisk', or 'brisk'. A univariable logistic regression analysis was carried out to assess the association between the TIL scores and the development of severe irAEs. Fine and Gray subdistribution hazard models were used to estimate the cumulative incidence of severe irAEs.
RESULTS: Of the 1346 eligible patients, 536 patients had primary melanoma specimens available, and 613 patients had metastasis specimens available. Severe irAEs occurred in 15% of anti-PD-1-treated patients and 49% of anti-PD-1 + anti-CTLA-4-treated patients. The presence of TILs was not associated with the occurrence of grade ≥3 irAEs in primary melanoma specimens (P = 0.70) nor pretreatment metastasis specimens (P = 0.91). In the univariable analysis, patients with brisk TILs did not have a higher chance of developing severe irAEs compared with patients with absent TILs, for both primary specimen (odds ratio 1.15, 95% confidence interval 0.60-2.18) and metastasis specimen (odds ratio 0.77, 95% confidence interval 0.37-1.59). There was also no significant difference in the lifetime risk or timing of the development of severe irAEs in patients with TILs present compared with patients with TILs absent.
CONCLUSION: There was no association between the TIL scores on H&E-stained slides from the primary melanoma or pretreatment metastasis and the development of grade 3 or higher irAEs. Additionally, no correlation was found between the presence of TILs and the timing of irAEs.

Gepubliceerd: Immunooncol Technol. 2024;24:100714.
IF onbekend

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36. A prediction model for response to immune checkpoint inhibition in advanced melanoma
van Duin IAJ, Verheijden RJ, van Diest PJ, Blokx WAM, El-Sharouni MA, Verhoeff JJC, Leiner T, van den Eertwegh AJM, de Groot JWB, van Not OJ, Aarts MJB, van den Berkmortel F, Blank CU, Haanen J, Hospers GAP, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil G, Wouters M, Stevense-den Boer MAM, Boers-Sonderen MJ, Kapiteijn E, Suijkerbuijk KPM, Elias SG.

Predicting who will benefit from treatment with immune checkpoint inhibition (ICI) in patients with advanced melanoma is challenging. We developed a multivariable prediction model for response to ICI, using routinely available clinical data including primary melanoma characteristics. We used a population-based cohort of 3525 patients with advanced cutaneous melanoma treated with anti-PD-1-based therapy. Our prediction model for predicting response within 6 months after ICI initiation was internally validated with bootstrap resampling. Performance evaluation included calibration, discrimination and internal-external cross-validation. Included patients received anti-PD-1 monotherapy (n = 2366) or ipilimumab plus nivolumab (n = 1159) in any treatment line. The model included serum lactate dehydrogenase, World Health Organization performance score, type and line of ICI, disease stage and time to first distant recurrence-all at start of ICI-, and location and type of primary melanoma, the presence of satellites and/or in-transit metastases at primary diagnosis and sex. The over-optimism adjusted area under the receiver operating characteristic was 0.66 (95% CI: 0.64-0.66). The range of predicted response probabilities was 7%-81%. Based on these probabilities, patients were categorized into quartiles. Compared to the lowest response quartile, patients in the highest quartile had a significantly longer median progression-free survival (20.0 vs 2.8 months; P < .001) and median overall survival (62.0 vs 8.0 months; P < .001). Our prediction model, based on routinely available clinical variables and primary melanoma characteristics, predicts response to ICI in patients with advanced melanoma and discriminates well between treated patients with a very good and very poor prognosis.

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Impact factor: 4.7 ; Q1

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37. Metformin boosts antitumor immunity and improves prognosis in upfront resected pancreatic cancer: an observational study

van Eijck CWF, Vadgama D, van Eijck CHJ, Wilmink JW, Dutch Pancreatic Cancer Group; Mekenkamp L.

BACKGROUND: Beyond demographic and immune factors, metabolic considerations, particularly metformin's recognized impact in oncology, warrant exploration in treating pancreatic cancer. This study aimed to investigate the influence of metformin on patient survival and its potential correlation with distinct immune profiles in pancreatic ductal adenocarcinoma (PDAC) tumors.
METHODS: We included 82 upfront resected and 66 gemcitabine-based neoadjuvant chemoradiotherapy (nCRT)-treated patients from the PREOPANC randomized controlled trial (RCT). Transcriptomic NanoString immunoprofiling was performed for a subset of 96 available resected specimens.
RESULTS: Disparities in survival outcomes and immune profiles were apparent between metformin and non-metformin users in upfront resected patients but lacking in nCRT-treated patients. Compared to non-metformin users, upfront resected metformin users showed a higher median overall survival (OS) of 29 vs 14 months and a better 5-year OS rate of 19% vs 5%. Furthermore, metformin use was a favorable prognostic factor for OS in the upfront surgery group (HR = 0.56; 95% CI = 0.32 to 0.99). Transcriptomic data revealed that metformin users significantly underexpressed genes related to pro-tumoral immunity, including monocyte to M2 macrophage polarization and activation. Furthermore, the relative abundance of anti-inflammatory CD163+ MRC1+ M2 macrophages in non-metformin users and immune-activating CD1A+ CD1C+ dendritic cells in metformin users was heightened (P < .001).
CONCLUSION: This study unveils immune profile changes resulting from metformin use in upfront resected pancreatic cancer patients, possibly contributing to prolonged survival outcomes. Specifically, metformin use may decrease the abundance and activity of pro-tumoral M2 macrophages and increase the recruitment and function of tumor-resolving DCs, favoring antitumor immunity. [PREOPANC trial EudraCT: 2012-003181-40].

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Impact factor: 7.2 ; Q1

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38. Feasibility study of the Digital Patient Benefit Assessment Scale (P-BAS): A Digital Tool to Assess Individual Patient Goals
van Erp RAL, de Rooij SE, Wymenga ANM, Zeegers A, van der Palen J.

The study objective was to assess the feasibility of the Patient Benefit Assessment Scale (P-BAS), a digital tool designed to enable older outpatients (≥70 years) to elucidate at home their individual goals regarding their current medical issue. Several digital tools are developed to assist older people in identifying their goals, thereby facilitating the process of shared decision making. However, studies on the feasibility of these digital tools, especially in older patients, are limited. Data were collected from 36 older patients. The study comprised three stages. In stage I and II, cognitive interviews were conducted to strengthen the feasibility of the P-BAS. In stage III, 80% of the patients completed the P-BAS independently at home. The cognitive interviews provided insight into patients' interpretation and individual understanding of the digital visual P-BAS and associated opportunities for improvement, which were subsequently implemented. One conclusion is that the digital visual P-BAS might be of added value for patients and contributes to the process of shared decision making, assuring that the goals of the patient will be into account in treatment options. Findings are useful for researchers interested in technological tools that contribute to shared decision making.

Gepubliceerd: Gerontol Geriatr Med. 2024;10:23337214241230159.
Impact factor: 1.8 ; Q4

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39. Lethal Capecitabine Toxicity in Patients With Complete Dihydropyrimidine Dehydrogenase Deficiency Due to Ultra-Rare DPYD Variants
van Kuilenburg ABP, Pleunis-van Empel MCH, Brouwer RB, Sijben AEJ, Knapen DG, Oude Munnink TH, van Zanden JJ, Janssens-Puister J, Dobritzsch D, Meinsma R, Meijer-Jansen J, van Dooren SJM, Vijzelaar R, Pop A, Salomons GS, Maring JG, Niezen-Koning KE.

A DPD deficiency should be considered in case of severe toxicity even in the absence of common risk variants in DPYD.

Gepubliceerd: JCO Precis Oncol. 2024;8:e2300599.
Impact factor: 5.8 ; Q1

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40. Improving sustainability of a patient decision aid for systemic treatment of metastatic colorectal cancer: A qualitative study
van Nassau S, Voogdt-Pruis HR, de Jong VMW, Otten HM, Valkenburg-van Iersel LB, Swarte BJ, Buffart TE, Pruijt HJ, Mekenkamp LJ, Koopman M, May AM.

OBJECTIVE: To improve sustainability of a patient decision aid for systemic treatment of metastatic colorectal cancer, we evaluated real-world experiences and identified ways to optimize decision aid content and future implementation.
METHODS: Semi-structured interviews with patients and medical oncologists addressed two main subjects: user experience and decision aid content. Content analysis was applied. Fifteen experts discussed the results and devised improvements based on experience and literature review.

RESULTS: Thirteen users were interviewed. They confirmed the relevance of the decision aid for shared decision making. Areas for improvement of content concerned; 1) outdated and missing information, 2) an imbalance in presentation of treatment benefits and harms, and 3) medical oncologists' expressed preference for a more center-specific or patient individualized decision aid, presenting a selection of the guideline recommended treatment options. Key points for improvement of implementation were better alignment within the care pathway, and clear instruction to users.
CONCLUSION: We identified relevant opportunities for improvement of an existing decision aid and developed an updated version and accompanying implementation strategy accordingly.
INNOVATION: This paper outlines an approach for continued decision aid and implementation strategy development which will add to sustainability. Implementation success of the improved decision aid is currently being studied in a multi-center mixed-methods implementation study.

Gepubliceerd: PEC Innov. 2024;4:100300.
IF onbekend

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41. Improving survival in advanced melanoma patients: a trend analysis from 2013 to 2021
van Not OJ, van den Eertwegh AJM, Haanen JB, Blank CU, Aarts MJB, van Breeschoten J, van den Berkmortel F, de Groot JB, Hospers GAP, Ismail RK, Kapiteijn E, Bloem M, De Meza MM, Piersma D, van Rijn RS, Stevense-den Boer MAM, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Blokx WAM, Wouters M, Suijkerbuijk KPM.

BACKGROUND: The prognosis of advanced melanoma patients has significantly improved over the years. We aimed to evaluate the survival per year of diagnosis.
METHODS: All systemically treated patients diagnosed with advanced melanoma from 2013 to 2021 were included from the Dutch Melanoma Treatment Registry. Baseline characteristics and overall survival (OS) were compared between the different years of diagnosis. A multivariable Cox proportional hazards model was used to estimate the association between year of diagnosis and OS.
FINDINGS: For this cohort study, we included 6260 systemically treated advanced melanoma patients. At baseline, there was an increase over the years in age, the percentage of patients with an ECOG PS ≥ 2, with brain metastases, and a synchronous diagnosis of primary and unresectable melanoma. Median OS increased from 11.2 months (95% CI 10.0-12.4) for patients diagnosed in 2013 to 32.0 months (95% CI 26.6-36.7) for patients diagnosed in 2019. Median OS was remarkably lower for patients diagnosed in 2020 (26.6 months; 95% CI 23.9-35.1) and 2021 (24.0 months; 95% CI 20.4-NR). Patients diagnosed in 2020 and 2021 had a higher hazard of death compared to patients diagnosed in 2019, although this was not significant. The multivariable Cox regression showed a lower hazard of death for the years of diagnosis after 2013. In contrast, patients diagnosed in 2020 and 2021 had a higher hazard of death compared to patients diagnosed in 2019.
INTERPRETATION: After a continuous survival improvement for advanced melanoma patients between 2013 and 2019, outcomes of patients diagnosed in 2020 and 2021 seem poorer. This trend of decreased survival remained after correcting for known prognostic factors and previous neoadjuvant or adjuvant treatment, suggesting that it is explained by unmeasured factors, which-considering the timing-could be COVID-19-related. FUNDING: For the Dutch Melanoma Treatment Registry (DMTR), the Dutch Institute for Clinical Auditing foundation received a start-up grant from governmental organization The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). The DMTR is structurally funded by Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, and Roche Pharma. Roche Pharma stopped funding in 2019, and Pierre Fabre started funding the DMTR in 2019. For this work, no funding was granted.

Gepubliceerd: EClinicalMedicine. 2024;69:102485.
Impact factor: 10.0 ; Q1

42. BRAF/MEK inhibitor rechallenge in advanced melanoma patients
Van Not OJ, van den Eertwegh AJM, Haanen JB, van Rijn RS, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, de Groot J, Hospers GAP, Kapiteijn E, Bloem M, Piersma D, Stevense-den Boer M, Verheijden RJ, van der Veldt AAM, Wouters M, Blokx WAM, Suijkerbuijk KPM.

BACKGROUND: Effectivity of BRAF(/MEK) inhibitor rechallenge has been described in prior studies. However, structured data are largely lacking.
METHODS: Data from all advanced melanoma patients treated with BRAFi(/MEKi) rechallenge were retrieved from the Dutch Melanoma Treatment Registry. The authors analyzed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) for both first treatment and rechallenge. They performed a multivariable logistic regression and a multivariable Cox proportional hazards model to assess factors associated with response and survival.
RESULTS: The authors included 468 patients in the largest cohort to date who underwent at least two treatment episodes of BRAFi(/MEKi). Following rechallenge, ORR was 43%, median PFS was 4.6 months (95% confidence interval [CI], 4.1-5.2), and median OS was 8.2 months (95% CI, 7.2-9.4). Median PFS after rechallenge for patients who discontinued first BRAFi(/MEKi) treatment due to progression was 3.1 months (95% CI, 2.7-4.0) versus 5.2 months (95% CI, 4.5-5.9) for patients who discontinued treatment for other reasons. Discontinuing first treatment due to progression and lactate dehydrogenase (LDH) levels greater than two times the upper limit of normal were associated with lower odds of response and worse PFS and OS. Symptomatic brain metastases were associated with worse survival, whereas a longer treatment interval between first treatment and rechallenge was associated with better survival. Responding to the first BRAFi(/MEKi) treatment was not associated with response or survival.
CONCLUSIONS: This study confirms that patients benefit from rechallenge. Elevated LDH levels, symptomatic brain metastases, and discontinuing first BRAFi(/MEKi) treatment due to progression are associated with less benefit from rechallenge. A prolonged treatment interval is associated with more benefit from rechallenge.

Gepubliceerd: Cancer. 2024;130(9):1673-83.
Impact factor: 5.1 ; Q1

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43. Long-Term Survival in Patients With Advanced Melanoma
van Not OJ, van den Eertwegh AJM, Jalving H, Bloem M, Haanen JB, van Rijn RS, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, de Groot JWBJ, Hospers GAP, Kapiteijn E, Leeneman B, Piersma D, Stevense-den Boer M, van der Veldt AAM, Vreugdenhil GG, Wouters M, Blokx WAM, Suijkerbuijk KPM.

IMPORTANCE: Long-term survival data from clinical trials show that survival curves of patients with advanced melanoma treated with immune checkpoint inhibitors (ICIs) gradually reach a plateau, suggesting that patients have a chance of achieving long-term survival.
OBJECTIVE: To investigate long-term survival in patients with advanced melanoma treated with ICIs outside clinical trials.
DESIGN, SETTING, AND PARTICIPANTS: Cohort study using prospectively collected data from the nationwide Dutch Melanoma Treatment Registry, including patients in the Netherlands with advanced melanoma treated with first-line ICIs from 2012 to 2019. Data were analyzed from January to September 2023.
EXPOSURES: Patients were treated with first-line ipilimumab-nivolumab, antibodies that target programmed cell death (anti-PD-1), or ipilimumab.

MAIN OUTCOMES AND MEASURES: Progression-free survival (PFS) and melanoma-specific survival were analyzed, and a Cox proportional hazards model was used to investigate factors associated with PFS after reaching partial response (PR) or complete response (CR). RESULTS: A total of 2490 patients treated with first-line ICIs were included (median [IQR] age, 65.0 [55.3-73.0] years; 1561 male patients [62.7%]). Most patients had an Eastern Cooperative Oncology Group Performance Status of 1 or lower (2202 patients [88.5%]) and normal lactate dehydrogenase levels (1715 patients [68.9%]). PFS for all patients was 23.4% (95% CI, 21.7%-25.2%) after 3 years and 19.7% (95% CI, 18.0%-21.4%) after 5 years. Overall survival for all patients was 44.0% (95% CI, 42.1%-46.1%) after 3 years and 35.9% (95% CI, 33.9%-38.0%) after 5 years. Patients with metastases in 3 or more organ sites had a significantly higher hazard of progression after reaching PR or CR (adjusted hazard ratio, 1.37; 95% CI, 1.11-1.69).
CONCLUSIONS AND RELEVANCE: This cohort study of patients with advanced melanoma treated with ICIs in clinical practice showed that their survival reached a plateau, comparable with patients participating in clinical trials. These findings can be used in daily clinical practice to guide long-term surveillance strategies and inform both physicians and patients regarding long-term treatment outcomes.

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Impact factor: 9.7 ; Q1

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44. Health-related quality of life and symptom burden in patients on haemodialysis
van Oevelen M, Bonenkamp AA, van Eck van der Sluijs A, Bos WJW, Douma CE, van Buren M, Meuleman Y, Dekker FW, van Jaarsveld BC, Abrahams AC, DOMESTICO study group; Wijering RMJ.

BACKGROUND: Patients on haemodialysis (HD) generally experience poor health-related quality of life (HRQoL) and a broad range of physical and mental symptoms, but it is unknown whether this differs between younger and older patients. We aimed to describe the trajectories of HRQoL and symptom burden of patients <70 and ≥70 years old and to assess the impact of symptom burden on HRQoL.
METHODS: In incident Dutch HD patients, HRQoL and symptoms were measured with the 12-item Short Form Health Survey and Dialysis Symptom Index. We used linear mixed models for examining the trajectories of HRQoL and symptom burden during the first year of dialysis and linear regression for the impact of symptom burden on HRQoL.
RESULTS: In 774 patients, the trajectories of physical HRQoL, mental HRQoL and symptom burden were stable during the first year of dialysis. Compared with patients <70 years of age, patients ≥70 years reported similar physical HRQoL {mean difference -0.61 [95% confidence interval (CI) -1.86-0.63]}, better mental HRQoL [1.77 (95% CI 0.54-3.01)] and lower symptom burden [-2.38 (95% CI -5.08-0.32)]. With increasing symptom burden, physical HRQoL declined more in older than in younger patients (β = -0.287 versus -0.189, respectively; P-value for interaction = .007). For mental HRQoL, this decrease was similar in both age groups (β = -0.295 versus -0.288, P = .847).
CONCLUSION: Older HD patients generally experience a better mental HRQoL and a (non-statistically significant) lower symptom burden compared with younger patients. Their physical HRQoL declines more rapidly with increasing symptom burden.

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Impact factor: 5.6 ; Q1

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45. Dolutegravir/Lamivudine Is Noninferior to Continuing Dolutegravir- and Non-Dolutegravir-Based Triple-Drug Antiretroviral Therapy in Virologically Suppressed People With Human Immunodeficiency Virus: DUALING Prospective Nationwide Matched Cohort Study
Vasylyev M, Wit F, Jordans CCE, Soetekouw R, van Lelyveld SFL, Kootstra GJ, Delsing CE, Ammerlaan HSM, van Kasteren MEE, Brouwer AE, Leyten EMS, Claassen MAA, Hassing RJ, den Hollander JG, van den Berge M, Roukens AHE, Bierman WFW, Groeneveld PHP, Lowe SH, van Welzen BJ, Richel O, Nellen JF, van den Berk GEL, van der Valk M, Rijnders BJA, Rokx C.

BACKGROUND: Confirming the efficacy of dolutegravir/lamivudine in clinical practice solidifies recommendations on its use.
METHODS: Prospective cohort study (DUALING) in 24 human immunodeficiency virus (HIV) treatment centers in the Netherlands. HIV RNA-suppressed cases were on triple-drug antiretroviral regimens without prior virological failure or resistance and started dolutegravir/lamivudine. Cases were 1:2 matched to controls on triple-drug antiretroviral regimens by the use of dolutegravir-based regimens, age, sex, transmission route, CD4(+) T-cell nadir, and HIV RNA zenith. The primary endpoint was the treatment failure rate in cases versus controls at 1 year by intention-to-treat and on-treatment analyses with 5% noninferiority margin.
RESULTS: The 2040 participants were 680 cases and 1380 controls. Treatment failure in the 390 dolutegravir-based cases versus controls occurred in 8.72% and 12.50% (difference: -3.78% [95% confidence interval {CI}, -7.49% to .08%]) by intention-to-treat and 1.39% and 0.80% (difference: 0.59% [95% CI, -.80% to 1.98%]) by on-treatment analyses. The treatment failure risk in 290 non-dolutegravir-based cases was also noninferior to controls. Antiretroviral regimen modifications unrelated to virological failure explained the higher treatment failure rate by intention-to-treat. A shorter time on triple-drug antiretroviral therapy and being of non-Western origin was associated with treatment failure. Treatment failure, defined as 2 consecutive HIV RNA >50 copies/mL, occurred in 4 cases and 5 controls but without genotypic resistance detected. Viral blips occured comparable in cases and controls but cases gained more weight, especially when tenofovir-based regimens were discontinued.
CONCLUSIONS: In routine care, dolutegravir/lamivudine was noninferior to continuing triple-drug antiretroviral regimens after 1 year, supporting the use of dolutegravir/lamivudine in clinical practice.
CLINICAL TRIALS REGISTRATION: NCT04707326.

Gepubliceerd: Open Forum Infect Dis. 2024;11(4):ofae160.
Impact factor: 3.8 ; Q1

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46. Corticosteroids and other immunosuppressants for immune-related adverse events and checkpoint inhibitor effectiveness in melanoma
Verheijden RJ, Burgers FH, Janssen JC, Putker AE, Veenstra S, Hospers GAP, Aarts MJB, Hehenkamp KW, Doornebosch VLE, Verhaert M, van den Berkmortel F, Chatzidionysiou K, Llobell A, Barros M, Maria ATJ, Takeji A, García Morillo JS, Lidar M, van Eijs MJM, Blank CU, Aspeslagh S, Piersma D, Kapiteijn E, Labots M, Boers-Sonderen MJ, van der Veldt AAM, Haanen J, May AM, Suijkerbuijk KPM.

BACKGROUND: Recent studies indicate an association between immunosuppression for immune-related adverse events (irAEs) and impaired survival in patients who received immune checkpoint inhibitors. Whether this is related to corticosteroids or second-line immunosuppressants is unknown. In the largest cohort thus far, we assessed the association of immunosuppressant type and dose with survival in melanoma patients with irAEs.
METHODS: Patients with advanced melanoma who received immunosuppressants for irAEs induced by first-line anti-PD-1 ± anti-CTLA-4 were included from 18 hospitals worldwide. Associations of cumulative and peak dose corticosteroids and use of second-line immunosuppression with survival

from start of immunosuppression were assessed using multivariable Cox proportional hazard regression.
RESULTS: Among 606 patients, 404 had anti-PD-1 + anti-CTLA-4-related irAEs and 202 had anti-PD-1-related irAEs. 425 patients (70 %) received corticosteroids only; 181 patients (30 %) additionally received second-line immunosuppressants. Median PFS and OS from starting immunosuppression were 4.5 (95 %CI 3.4-8.1) and 31 (95 %CI 15-not reached) months in patients who received second-line immunosuppressants, and 11 (95 %CI 9.4-14) and 55 (95 %CI 41-not reached) months in patients who did not. High corticosteroid peak dose was associated with worse PFS and OS (HR(adj) 1.14; 95 %CI 1.01-1.29; HR(adj) 1.29; 95 %CI 1.12-1.49 for 80vs40mg), while cumulative dose was not. Second-line immunosuppression was associated with worse PFS (HR(adj) 1.32; 95 %CI 1.02-1.72) and OS (HR(adj) 1.34; 95 %CI 0.99-1.82) compared with corticosteroids alone.
CONCLUSIONS: High corticosteroid peak dose and second-line immunosuppressants to treat irAEs are both associated with impaired survival. While immunosuppression is indispensable for treatment of severe irAEs, clinicians should weigh possible detrimental effects on survival against potential disadvantages of undertreatment.

Gepubliceerd: Eur J Cancer. 2024;207:114172.
Impact factor: 7.1 ; Q1

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47. The degree of HLA matching determines the incidence of cytokine release syndrome and associated nonrelapse mortality in matched related and unrelated allogeneic stem cell transplantation with post-transplant cyclophosphamide
von dem Borne PA, Kemps-Mols BM, de Wreede LC, van Beek AA, Snijders TJF, van Lammeren D, Tijmensen J, Sijs-Szabó A, Oudshoorn MA, Halkes CJM, van Balen P, Marijt WAE, Tjon JML, Vermaat JSP, Veelken H.

Cytokine release syndrome (CRS) occurs frequently after haplo-identical allogeneic stem cell transplantation (alloSCT) with post-transplant cyclophosphamide (PTCy), increasing nonrelapse mortality (NRM) and decreasing survival. Data on CRS in HLA-matched alloSCT are limited and effects of specific HLA-mismatches on CRS development unknown. We hypothesized that in HLA-matched alloSCT increasing degrees of HLA-mismatching influence CRS incidence, NRM and survival. Retrospective analysis of 126 HLA-matched PTCy-alloSCT patients showed that higher degrees of HLA-mismatching significantly increased CRS incidence (26%, 75% and 90% CRS with 12/12, 10/10 and 9/10 matched donors, respectively). Maximum temperature during CRS increased with higher HLA-mismatch. Specific associations between HLA-mismatches and CRS could be determined. Grade 2 CRS and CRS-induced grade 3 fever were associated with significantly increased NRM ($p < 0.001$ and $p = 0.003$, respectively) and inferior survival ($p < 0.001$ and $p = 0.005$, respectively). NRM was mainly caused by disease conditions that may be considered CRS-induced inflammatory responses (encephalopathy, cryptogenic organizing pneumonia and multi-organ failure).

Gepubliceerd: Leuk Lymphoma. 2024;65(9):1270-80.
Impact factor: 2.2 ; Q3

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48. Using non-randomized trials to assess the clinical benefit of systemic anti-cancer treatments: Viable or not?
Xander NSH, Leeneman B, Dingemans AC, Fiets WE, de Jong WK, Uyl NEM, Wymenga ANM, Reyners AKL, Uyl-de Groot CA.

BACKGROUND: The Dutch Committee for the Evaluation of Oncological Agents (cieBOM) assesses the clinical benefit of systemic anti-cancer treatments (SACTs). For SACTs tested in non-randomized trials (NRTs), cieBOM primarily utilizes response-related thresholds as assessment criteria. As sufficiency of NRT-based evidence for benefit assessments is questionable, this study investigated whether and how NRTs can be used to assess the clinical benefit of new SACTs initially appraised by cieBOM based on randomized controlled trials (RCTs).
METHODS: Using the RCTs underpinning cieBOM recommendations issued between 2015 and 2017, we searched for matching NRTs and applied the NRT-related assessment criteria by cieBOM to them. We then compared the assessment outcomes to the respective RCT-based cieBOM recommendations. Further, we investigated how the assessments would change when applying different response-related thresholds and adding a progression-free survival (PFS) threshold.
RESULTS: For 13 of the 37 eligible recommendations, a matching NRT was found. Two treatments were assessed positively and six negatively; five treatments were non-assessable. Two positive recommendations matched a positive NRT-based assessment; one matching negative assessment was found, and one treatment could not be assessed based on either trial results. Adding a > 6 months PFS threshold decreased the number of non-assessable NRTs (five to two).
CONCLUSIONS: Limited publications and inconsistent data reporting hampered the viability of NRTs for clinical benefit assessments of SACTs beyond the scope of rare indications. Further, response-related assessment criteria alone might not fully grasp the clinical benefit of novel SACTs. NRT-based assessments should be considered with caution due to uncertainty of the trial results.

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Impact factor: 7.1 ; Q1

Totale impact factor: 438.7
Gemiddelde impact factor: 9.1

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 11.2
Gemiddelde impact factor: 3.7

Kindergeneeskunde

1. Heterozygous BTNL8 variants in individuals with multisystem inflammatory syndrome in children (MIS-C)
Bellos E, Santillo D, Vantourout P, Jackson HR, Duret A, Hearn H, Seeleuthner Y, Talouarn E, Hodeib S, Patel H, Powell O, Yeoh S, Mustafa S, Habgood-Coote D, Nichols S, Estramiana Elorrieta L, D'Souza G, Wright VJ, Estrada-Rivadeneyra D, Tremoulet AH, Dummer KB, Netea SA, Condino-Neto A, Lau YL, Núñez Cuadros E, Toubiana J, Holanda Pena M, Rieux-Laucat F, Luyt CE, Haerynck F, Mège JL, Chakravorty S, Haddad E, Morin MP, Metin Akcan Ö, Keles S, Emiroglu M, Alkan G, Tüter Öz SK, Elmas Bozdemir S, Morelle G, Volokha A, Kendir-Demirkol Y, Sözeri B, Coskuner T, Yahsi A, Gulhan B, Kanik-Yuksek S, Bayhan GI, Ozkaya-Parlakay A, Yesilbas O, Hatipoglu N, Ozcelik T, Belot A, Chopin E, Barlogis V, Sevketoglu E, Menentoglu E, Gayretli Aydin ZG, Bloomfield M, AlKhater SA, Cyrus C, Stepanovskiy Y, Bondarenko A, Öz FN, Polat M, Fremuth J, Lebl J, Geraldo A, Jouanguy E, Carter MJ, Wellman P, Peters M, Pérez de Diego R, Edwards LA, Chiu C, Noursadeghi M, Bolze A, Shimizu C, Kaforou M, Hamilton MS, Herberg JA, Schmitt EG, Rodriguez-Palmero A, Pujol A, Kim J, Cobat A, Abel L, Zhang SY, Casanova JL, Kuijpers TW, Burns JC, Levin M, Hayday AC, Sancho-Shimizu V, Collaborators; Thio BJ.

Multisystem inflammatory syndrome in children (MIS-C) is a rare condition following SARS-CoV-2 infection associated with intestinal manifestations. Genetic predisposition, including inborn errors of the OAS-RNAseL pathway, has been reported. We sequenced 154 MIS-C patients and utilized a novel statistical framework of gene burden analysis, "burdenMC," which identified an enrichment for rare predicted-deleterious variants in BTNL8 (OR = 4.2, 95% CI: 3.5-5.3, P < 10-6). BTNL8 encodes an intestinal epithelial regulator of Vγ4+γδ T cells implicated in regulating gut homeostasis. Enrichment was exclusive to MIS-C, being absent in patients with COVID-19 or bacterial disease. Using an available functional test for BTNL8, rare variants from a larger cohort of MIS-C patients (n = 835) were tested which identified eight variants in 18 patients (2.2%) with impaired engagement of Vγ4+γδ T cells. Most of these variants were in the B30.2 domain of BTNL8 implicated in sensing epithelial cell status. These findings were associated with altered intestinal permeability, suggesting a possible link between disrupted gut homeostasis and MIS-C-associated enteropathy triggered by SARS-CoV-2.

Gepubliceerd: J Exp Med. 2024;221(12).
Impact factor: 10.6 ; Q1

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2. Cerebrospinal fluid inflammatory markers to differentiate between neonatal bacterial meningitis and sepsis: A prospective study of diagnostic accuracy
Groeneveld NS, Olie SE, Visser DH, Snoek L, van de Beek D, Brouwer MC, Bijlsma MW, NOGBS study group; Kaspers AG.

OBJECTIVES: We evaluated the diagnostic accuracy of cerebrospinal fluid (CSF) inflammatory markers for diagnosing bacterial meningitis in neonates with sepsis and/or meningitis.
METHODS: Cases were identified from a prospective multicenter study including patients aged 0-3 months with Group B Streptococcal (GBS) or Escherichia coli culture positive sepsis/meningitis. CSF CXCL10, MDC, IL-6, IL-8, IL-10, TNF- α, MIF, IL-1RA, CXCL13, IL-1β, CRP and procalcitonin concentrations were measured with Luminex technology.
RESULTS: In 61/373 patients (17%) residual CSF from the lumbar puncture was available, of whom 16 (26%) had definitive meningitis, 15 (25%) probable meningitis and 30 (49%) had sepsis. All biomarkers were detectable in CSF and showed significantly higher concentrations in definitive meningitis versus sepsis patients and six biomarkers in probable meningitis versus sepsis patients. Discrimination between definitive meningitis and sepsis was excellent for IL-1RA (area under the receiver operating characteristic curve [AUC] 0.93), TNF-α (AUC 0.92), CXCL10 (AUC 0.90), IL-1β (AUC 0.92), IL-6 (AUC

0.94), IL-10 (AUC 0.93) and a combination of IL-1RA, TNF-α, CXCL-10 and CSF leukocyte count (AUC 0.95). CSF leukocyte count remained the predictor with the highest diagnostic accuracy (AUC 0.96).
CONCLUSION: CSF inflammatory markers can be used to differentiate between neonatal sepsis and meningitis.

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Impact factor: 4.3 ; Q1

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3. Improved Clinical Outcomes With Early Anti-Tumour Necrosis Factor Alpha Therapy in Children With Newly Diagnosed Crohn's Disease: Real-world Data from the International Prospective PIBD-SETQuality Inception Cohort Study
Klomberg RCW, van der Wal HC, Aardoom MA, Kemos P, Rizopoulos D, Ruemmele FM, Charrout M, Escher HC, Croft NM, de Ridder L, PIBD-SETQuality collaborative group; Hummel TZ.

BACKGROUND AND AIMS: Treatment guidelines for paediatric Crohn's disease [CD] suggest early use of anti-tumour necrosis factor alpha [anti-TNFα] in high-risk individuals. The aim is to evaluate the effect of early anti-TNF in a real-world cohort.
METHODS: Children with newly diagnosed CD were prospectively recruited at 28 participating sites of the international observational PIBD-SETQuality study. Outcomes were compared at 3 months, 1 and 2 years between patients receiving early anti-TNF [<90 days after diagnosis] and those not receiving early anti-TNF. Outcomes included sustained steroid-free remission [SSFR] without treatment intensification [specified as SSFR*] and sustained steroid-free mild/inactive disease without treatment intensification [specified as SSFMI*]. Penalised logistic regression model-based standardisation was applied to estimate the relative risks [RR] of early therapy on outcomes. RRs were estimated for high-risk and low-risk patients, based on presence of predictors of poor outcome [POPOs] and disease activity at diagnosis.
RESULTS: In total, 331 children (median age 13.9 years [IQR 12.2-15.3]) were enrolled, with 135 [41%] receiving early anti-TNF. At 1 year, patients on early anti-TNF had higher rates of SSFR* [30% vs 14%, p <0.001] and SSFMI* [69% vs 33%, p <0.001], with RRs of 2.95 [95% CI 1.63-5.36] and 4.67 [95% CI 2.46-8.87], respectively. At 1 year, the RRs for SSFMI* were higher, and statistically significant in high-risk patients, i.e. those with moderate/severe disease compared with mild/inactive disease at diagnosis (5.50 [95% CI 2.51-12.05] vs 2.91 [95% CI 0.92-9.11]), and those with any POPO compared with no POPO (5.05 [95% CI 2.45-10.43] vs 3.41 [95% CI 0.54-21.7]).
CONCLUSION: In this cohort of children with newly-diagnosed CD, early anti-TNF demonstrated superior effectiveness in high-risk patients.

Gepubliceerd: J Crohns Colitis. 2024;18(5):738-50.
Impact factor: 8.7 ; Q1

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4. Host gene expression signatures to identify infection type and organ dysfunction in children evaluated for sepsis: a multicentre cohort study
Schlapbach LJ, Ganesamoorthy D, Wilson C, Raman S, George S, Snelling PJ, Phillips N, Irwin A, Sharp N, Le Marsney R, Chavan A, Hempenstall A, Bialasiewicz S, MacDonald AD, Grimwood K, Kling JC, McPherson SJ, Blumenthal A, Kaforou M, Levin M, Herberg JA, Gibbons KS, Coin LJM, EUCLIDS consortium and RAPIDS Study Group; Thio BJ.

BACKGROUND: Sepsis is defined as dysregulated host response to infection that leads to life-threatening organ dysfunction. Biomarkers characterising the dysregulated host response in sepsis

are lacking. We aimed to develop host gene expression signatures to predict organ dysfunction in children with bacterial or viral infection.
METHODS: This cohort study was done in emergency departments and intensive care units of four hospitals in Queensland, Australia, and recruited children aged 1 month to 17 years who, upon admission, underwent a diagnostic test, including blood cultures, for suspected sepsis. Whole-blood RNA sequencing of blood was performed with Illumina NovaSeq (San Diego, CA, USA). Samples with completed phenotyping, monitoring, and RNA extraction by March 31, 2020, were included in the discovery cohort; samples collected or completed thereafter and by Oct 27, 2021, constituted the Rapid Paediatric Infection Diagnosis in Sepsis (RAPIDS) internal validation cohort. An external validation cohort was assembled from RNA sequencing gene expression count data from the observational European Childhood Life-threatening Infectious Disease Study (EUCLIDS), which recruited children with severe infection in nine European countries between 2012 and 2016. Feature selection approaches were applied to derive novel gene signatures for disease class (bacterial vs viral infection) and disease severity (presence vs absence of organ dysfunction 24 h post-sampling). The primary endpoint was the presence of organ dysfunction 24 h after blood sampling in the presence of confirmed bacterial versus viral infection. Gene signature performance is reported as area under the receiver operating characteristic curves (AUCs) and 95% CI.
FINDINGS: Between Sept 25, 2017, and Oct 27, 2021, 907 patients were enrolled. Blood samples from 595 patients were included in the discovery cohort, and samples from 312 children were included in the RAPIDS validation cohort. We derived a ten-gene disease class signature that achieved an AUC of 94·1% (95% CI 90·6-97·7) in distinguishing bacterial from viral infections in the RAPIDS validation cohort. A ten-gene disease severity signature achieved an AUC of 82·2% (95% CI 76·3-88·1) in predicting organ dysfunction within 24 h of sampling in the RAPIDS validation cohort. Used in tandem, the disease class and disease severity signatures predicted organ dysfunction within 24 h of sampling with an AUC of 90·5% (95% CI 83·3-97·6) for patients with predicted bacterial infection and 94·7% (87·8-100·0) for patients with predicted viral infection. In the external EUCLIDS validation dataset (n=362), the disease class and disease severity predicted organ dysfunction at time of sampling with an AUC of 70·1% (95% CI 44·1-96·2) for patients with predicted bacterial infection and 69·6% (53·1-86·0) for patients with predicted viral infection.
INTERPRETATION: In children evaluated for sepsis, novel host transcriptomic signatures specific for bacterial and viral infection can identify dysregulated host response leading to organ dysfunction.
FUNDING: Australian Government Medical Research Future Fund Genomic Health Futures Mission, Children's Hospital Foundation Queensland, Brisbane Diamantina Health Partners, Emergency Medicine Foundation, Gold Coast Hospital Foundation, Far North Queensland Foundation, Townsville Hospital and Health Services SERTA Grant, and Australian Infectious Diseases Research Centre.

Gepubliceerd: Lancet Child Adolesc Health. 2024;8(5):325-38.
Impact factor: 15.5 ; Q1

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5. Randomised clinical trial: First-line infliximab biosimilar is cost-effective compared to conventional treatment in paediatric Crohn's disease

Vuijk SA, Jongsma MME, Hoeven BM, Cozijnsen MA, van Pieterson M, de Meij TGJ, Norbruis OF, Groeneweg M, Wolters VM, van Wering H, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg S, Rizopoulos D, Poley MJ, Escher JC, de Ridder L.

BACKGROUND: Data on cost-effectiveness of first-line infliximab in paediatric patients with Crohn's disease are limited. Since biologics are increasingly prescribed and accompanied by high costs, this knowledge gap needs to be addressed. AIM: To investigate the cost-effectiveness of first-line infliximab compared to conventional treatment in children with moderate-to-severe Crohn's disease.
METHODS: We included patients from the Top-down Infliximab Study in Kids with Crohn's disease randomised controlled trial. Children with newly diagnosed moderate-to-severe Crohn's disease were

treated with azathioprine maintenance and either five induction infliximab (biosimilar) infusions or conventional induction treatment (exclusive enteral nutrition or corticosteroids). Direct healthcare consumption and costs were obtained per patient until week 104. This included data on outpatient hospital visits, hospital admissions, drug costs, endoscopies and surgeries. The primary health outcome was the odds ratio of being in clinical remission (weighted paediatric Crohn's disease activity index<12.5) during 104 weeks.
RESULTS: We included 89 patients (44 in the first-line infliximab group and 45 in the conventional treatment group). Mean direct healthcare costs per patient were €36,784 for first-line infliximab treatment and €36,874 for conventional treatment over 2 years (p = 0.981). The odds ratio of first-line infliximab versus conventional treatment to be in clinical remission over 104 weeks was 1.56 (95%CI 1.03-2.35, p = 0.036).
CONCLUSIONS: First-line infliximab treatment resulted in higher odds of being in clinical remission without being more expensive, making it the dominant strategy over conventional treatment in the first 2 years after diagnosis in children with moderate-to-severe Crohn's disease.
TRIAL REGISTRATION NUMBER: NCT02517684.

Gepubliceerd: Aliment Pharmacol Ther. 2024;59(12):1510-20.
Impact factor: 6.7 ; Q1

Totale impact factor: 45.8
Gemiddelde impact factor: 9.2

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Klinische chemie

1. High first trimester ferritin levels differ according to parity and are independently related to preterm birth: A prospective cohort study
Broekhuis A, Koenen SV, Broeren MAC, Krabbe JG, Pop VJM.

INTRODUCTION: A considerable amount of neonatal morbidity and mortality worldwide is caused by preterm birth. To date, the underlying etiology of preterm birth has not been fully clarified. Previous studies demonstrate that inflammation is one of the pathological factors that might cause preterm birth, and that there is a difference between primiparous and multiparous women in immune response to pregnancy. The objective of this prospective cohort study was to investigate the role of two inflammatory markers, ferritin and C-reactive protein (CRP) and preterm birth, in first trimester women, stratified for parity. In addition, a possible association between high ferritin and CRP, and a possible association between high ferritin and CRP and preterm birth were assessed.
MATERIAL AND METHODS: A total of 2044 healthy, low-risk pregnant women from primary obstetric care in the Netherlands participated in this study. Their ferritin and CRP levels were evaluated at 12 weeks' gestation. Levels above the parity specific 95th percentile were defined as high. The main outcome of this study was to assess the presence of a possible association between parity specific high ferritin and CRP, and preterm birth. The secondary outcomes were the ferritin and CRP levels of women, stratified for parity, and the possible association between high ferritin and CRP levels. Logistic regression analysis was performed with preterm birth as a dependent variable and parity specific high ferritin and CRP as an independent variable, adjusting for age and history of preterm birth.
RESULTS: Ferritin levels decreased with increasing parity. Ferritin and CRP levels at 12 weeks' gestation were significantly higher in women with preterm birth. In primiparous women, high ferritin levels (OR: 2.5, CI: 1.14-5.38) and high CRP levels (OR: 5.0, CI: 2.61-9.94) were independently associated with preterm birth. In multiparous women, high ferritin levels (OR: 6.0, CI: 2.28-16.67) were independently associated with preterm birth while high CRP levels were not.
CONCLUSIONS: First trimester parity specific ferritin and CRP levels could play a part in predictive models for preterm birth, and further research for their additive role in preterm birth is needed.

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Impact factor: 3.1 ; Q1

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2. Evaluation of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 Using a Rapid Point of Care Test for Predicting Head Computed Tomography Lesions After Mild Traumatic Brain Injury in a Dutch Multi-Center Cohort
Chayoua W, Visser K, de Koning ME, Beishuizen A, Ijmker R, van der Naalt J, Krabbe JG, van der Horn HJ.

Mild traumatic brain injury (mTBI) is a common condition seen in emergency departments worldwide. Blood-based biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are recently U.S. Food and Drug Administration-approved for the prediction of intracranial lesions on head computed tomography (CT) scans in mTBI. We evaluated the diagnostic performance of GFAP and UCH-L1 in a Dutch cohort using the i-STAT TBI assay. In a multi-center observational study, we enrolled 253 mTBI patients. Head CT scans were scored using the Marshall classification system. Logistic regression models were used to assess the contribution of biomarkers and clinical parameters to diagnostic performance. Detection of UCH-L1 and GFAP resulted in a sensitivity of 97% and specificity of 19% for CT positivity in mTBI patients, along with a negative predictive value of 95% (88-100%) and a positive predictive value of 27% (21-33%). Combining

biomarker testing with loss of consciousness and time to sample increased specificity to 46%. Combined testing of UCH-L1 and GFAP testing resulted in possibly more unnecessary CT scans compared with GFAP testing alone, with only limited increase in sensitivity. This study confirmed high sensitivity of GFAP and UCH-L1 for CT abnormalities in mTBI patients using the i-STAT TBI test. The results support the potential use of GFAP and UCH-L1 as tools for determining the indication for CT scanning in mTBI patients, possibly offering a cost- and time-effective approach to management of patients with mTBI. Prospective studies in larger cohorts are warranted to validate our findings.

Gepubliceerd: J Neurotrauma. 2024;41(13-14):e1630-e40.
Impact factor: 3.8 ; Q1

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3. The dark side of apnea: altered 24-hour melatonin secretion in obstructive sleep apnea (OSAS) is disease severity dependent
Karel P, Schilperoord M, Reichman LJA, Krabbe JG.

PURPOSE: Melatonin aids in the synchronization of the circadian rhythm to the external environment. Few studies have tried to elucidate the relationship between melatonin and obstructive sleep apnea syndrome (OSAS). These often include few patients, do not differentiate between OSAS severity and/or do not analyse a 24-h melatonin profile. This study set out to investigate disease severity dependent differences in 24-h salivary melatonin secretion of OSAS patients compared to a reference population in a retrospective design.
METHODS: 24-h salivary melatonin profiles of 169 OSAS patients were analysed (55 light, 66 moderate, 48 severe) as well as 91 reference patients. Several aspects of the melatonin curve were analysed and stratified according to OSAS severity. Parameters included: dim light melatonin onset (DLMO), time of returning below DLMO (DLMOoff), peak melatonin concentration and time, and total melatonin exposure.
RESULTS: Significant effects were corrected for confounding by age and sex using linear regression. Our analysis shows that, compared to reference and in a disease dependent manner, OSAS patients have a significantly lower 24-h melatonin curve, lower melatonin peak concentration, lower total melatonin exposure and a smaller proportion of patients reach DLMO. The differences in peak melatonin production and total melatonin exposure were resistant to confounding by age and/or sex.
CONCLUSION: This study describes clear OSAS severity dependent abnormalities in melatonin production in OSAS patients, independent of sex and/or age. Future research should indicate whether oral melatonin supplementation has beneficial effects in OSAS patients with attenuated endogenous melatonin production.

Gepubliceerd: Sleep Breath. 2024;28(4):1751-9.
Impact factor: 2.0 ; Q3

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4. Predicting hemoglobinopathies using ChatGPT
Kurstjens S, Schipper A, Krabbe J, Kusters R.

Gepubliceerd: Clin Chem Lab Med. 2024;62(3):e59-e61.
Impact factor: 3.7 ; Q1

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5. Inconsistency in ferritin reference intervals across laboratories: a major concern for clinical decision making
Kurstjens S, van Dam AD, Oortwijn E, den Elzen WPJ, Candido F, Kusters R, Schipper A, Kortmann YFC, Herings RMC, Kok M, Krabbe J, de Boer BA, de Jong AM, Frasa MAM.

OBJECTIVES: Iron deficiency anemia is a significant global health concern, diagnosed by measuring hemoglobin concentrations in combination with plasma ferritin concentration. This study investigated the variability in ferritin reference intervals among laboratories in the Netherlands and examined how this affects the identification of iron-related disorders.
METHODS: Ferritin reference intervals from 52 Dutch ISO15189-certified medical laboratories were collected. Ferritin, hemoglobin and mean corpuscular volume data of non-anemic apparently healthy primary care patients, measured by four laboratory platforms (Beckman, Abbott, Siemens, and Roche), were collected (n=397,548). Median ferritin levels were determined per platform, stratified by sex and age. The proportion of ferritin measurements outside of the reference interval was calculated using the reference intervals from the 52 laboratories (using a total of n=1,093,442 ferritin measurements). Lastly, ferritin data from 3,699 patients as captured in general practitioner (GP) data from the PHARMO Data Network were used to assess the variation of abnormal ferritin measurements per GP.
RESULTS: Median plasma ferritin concentrations were approximately four times higher in men and twice as high in postmenopausal women compared to premenopausal women. Moreover, there are substantial differences in the median plasma ferritin concentration between the four platforms. However, even among laboratories using the same platform, ferritin reference intervals differ widely. This leads to significant differences in the percentages of measurements classified as abnormal, with the percentage of ferritin measurements below the reference limit in premenopausal women ranging from 11 to 53 %, in postmenopausal women from 3 to 37 %, and in men from 2 to 19 %. The percentage of ferritin measurements above the reference limit in premenopausal women ranged from 0.2 to 11 %, in postmenopausal women from 3 to 36 % and in men from 7 to 32 %.
CONCLUSIONS: The lack of harmonization in ferritin measurement and the disagreement in plasma ferritin reference intervals significantly impact the interpretation of the iron status of patients and thereby the number of iron disorder diagnoses made. Standardization or harmonization of the ferritin assays and establishing uniform reference intervals and medical decision limits are essential to reduce the substantial variability in clinical interpretations of ferritin results.

Gepubliceerd: Clin Chem Lab Med. 2024;63(3):600-10.
Impact factor: 3.7 ; Q1

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6. Hypothyroxinaemia during gestation is associated with low ferritin and increased levels of inflammatory markers
Pop VJM, Krabbe JG, Broeren M, Wiersinga W, Rayman MP.

OBJECTIVE: Pregnancy is a state of physiological inflammation facilitating implantation. Early isolated hypothyroxinaemia (IH) and increased inflammation (including obesity) have been associated with severe obstetric complications. The current study evaluated the association between IH, low ferritin and inflammation parameters (interleukin 6 (IL-6), C-reactive protein (CRP), human chorionic gonadotrophin (hCG) and obesity. Moreover, the course of these parameters throughout pregnancy was evaluated in relation to IH.
METHODS: In the cross-sectional study (A) at 12 weeks, 2759 women participated and 2433 participated in the longitudinal study (B) with assessments at 12, 20 and 28 weeks gestation. At the first trimester, 122 (4.4%) IH women (free thyroxine (FT4) <5th percentile, normal TSH levels) were compared with 2114 (76.6%) reference women (FT4 between tenth and 90th percentiles, normal thyrotrophin (TSH) levels), in study B these figures were 99 (4.1%) and 1847 (75.9%), respectively.

RESULTS: Cross-sectionally, compared to reference women, IH was independently associated with low ferritin (<5th percentile, OR: 2.6, 95% CI: 1.4-4.9), high CRP (>95th percentile: OR: 1.9, 95% CI: 1.04-3.7), low hCG (<median, OR: 2.1, 95% CI: 1.40-3.16), obesity (BMI > 30, OR: 1.7, 95% CI: 1.12.9) and higher age (OR: 1.1, 95% CI: 1.04-1.15). Longitudinally, compared to reference women, women with IH at 12 weeks gestation showed persistently and significantly lower ferritin and hCG levels, and persistently higher CRP and IL-6 levels throughout gestation.
CONCLUSION: Gestational IH could be viewed as a condition of increased inflammation, as reported in non-thyroidal illness syndrome. Less favourable inflammation parameters and low iron status during early gestation in IH women seem to persist throughout gestation.

Gepubliceerd: Eur Thyroid J. 2024;13(2).
Impact factor: 4.3 ; Q2

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7. Machine Learning-Based Prediction of Hemoglobinopathies Using Complete Blood Count Data
Schipper A, Rutten M, van Gammeren A, Harteveld CL, Urrechaga E, Weerkamp F, den Besten G, Krabbe J, Slomp J, Schoonen L, Broeren M, van Wijnen M, Huijskens M, Koopmann T, van Ginneken B, Kusters R, Kurstjens S.

BACKGROUND: Hemoglobinopathies, the most common inherited blood disorder, are frequently underdiagnosed. Early identification of carriers is important for genetic counseling of couples at risk. The aim of this study was to develop and validate a novel machine learning model on a multicenter data set, covering a wide spectrum of hemoglobinopathies based on routine complete blood count (CBC) testing.
METHODS: Hemoglobinopathy test results from 10 322 adults were extracted retrospectively from 8 Dutch laboratories. eXtreme Gradient Boosting (XGB) and logistic regression models were developed to differentiate negative from positive hemoglobinopathy cases, using 7 routine CBC parameters. External validation was conducted on a data set from an independent Dutch laboratory, with an additional external validation on a Spanish data set (n = 2629) specifically for differentiating thalassemia from iron deficiency anemia (IDA).
RESULTS: The XGB and logistic regression models achieved an area under the receiver operating characteristic (AUROC) of 0.88 and 0.84, respectively, in distinguishing negative from positive hemoglobinopathy cases in the independent external validation set. Subclass analysis showed that the XGB model reached an AUROC of 0.97 for β-thalassemia, 0.98 for α0-thalassemia, 0.95 for homozygous α+-thalassemia, 0.78 for heterozygous α+-thalassemia, and 0.94 for the structural hemoglobin variants Hemoglobin C, Hemoglobin D, Hemoglobin E. Both models attained AUROCs of 0.95 in differentiating IDA from thalassemia.
CONCLUSIONS: Both the XGB and logistic regression model demonstrate high accuracy in predicting a broad range of hemoglobinopathies and are effective in differentiating hemoglobinopathies from IDA. Integration of these models into the laboratory information system facilitates automated hemoglobinopathy detection using routine CBC parameters.

Gepubliceerd: Clin Chem. 2024;70(8):1064-75.
Impact factor: 6.3 ; Q1

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8. Analytical interference of intravascular contrast agents with clinical laboratory tests: a joint guideline by the ESUR Contrast Media Safety Committee and the Preanalytical Phase Working Group of the EFLM Science Committee
van der Molen AJ, Krabbe JG, Dekkers IA, Geenen RWF, Bellin MF, Bertolotto M, Brismar TB, Cadamuro J, Correas JM, Heinz-Peer G, Langlois MR, Mahnken AH, Ozben T, Quattrocchi CC, Radbruch A, Reimer P, Roditi G, Romanini L, Sebastià C, Simundic AM, Stacul F, Clement O.

The Contrast Media Safety Committee of the European Society of Urogenital Radiology has, together with the Preanalytical Phase Working Group of the EFLM Science Committee, reviewed the literature and updated its recommendations to increase awareness and provide insight into these interferences.
CLINICAL RELEVANCE STATEMENT: Contrast Media may interfere with clinical laboratory tests. Awareness of potential interference may prevent unwanted misdiagnosis.
KEY POINTS:
• Contrast Media may interfere with clinical laboratory tests; therefore awareness of potential interference may prevent unwanted misdiagnosis.
• Clinical Laboratory tests should be performed prior to radiological imaging with contrast media or alternatively, blood or urine collection should be delayed, depending on kidney function.

Gepubliceerd: Eur Radiol. 2024;34(7):4821-7.
Impact factor: 4.7 ; Q1

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9. Immunisatie tegen glycoproteïne IV (CD36) met de vraag naar compatibele trombocytenconcentraten: drie casussen
Vriend LEM, Vicente-Steijn R, van den Berg YW, Akkermans J, Canté CM, Slomp J, Tang MW, Visser O, Gerrits A, Verweij EJT, Zwaginga JJ, de Haas M, Porcelijn L.

Allo-antistoffen tegen glycoproteïne IV (GPIV) zijn zeldzaam, maar kunnen worden gevormd door GPIV-deficiënte personen na een zwangerschap of transfusie. Deze antistoffen kunnen leiden tot ernstige complicaties bij de neonaat/pasgeborene en bij transfusie-afhankelijke GPIV-deficiënte patiënten. Dit artikel beschrijft drie recente casussen waarbij GPIV-antistoffen werden gevonden en de behoefte ontstond voor GPIV-gematchte bloedproducten. Het brengt de uitdagingen aan het licht rondom de transfusieondersteuning van GPIV-deficiënte patiënten en daarmee de noodzaak voor een bestand met GPIV-deficiënte donoren in Nederland.

Gepubliceerd: Ned Tijdschr Hematol. 2024;21:391-6.
Impact factor: onbekend

Totale impact factor: 31.6
Gemiddelde impact factor: 3.5

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 14.8
Gemiddelde impact factor: 3.7

Klinische farmacie

1. The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial
Bakker T, Klopotowska JE, Dongelmans DA, Eslami S, Vermeijden WJ, Hendriks S, Ten Cate J, Karakus A, Purmer IM, van Bree SHW, Spronk PE, Hoeksema M, de Jonge E, de Keizer NF, Abu-Hanna A, SIMPLIFY study group; Movig K.

BACKGROUND: Drug-drug interactions (DDIs) can harm patients admitted to the intensive care unit (ICU). Yet, clinical decision support systems (CDSSs) aimed at helping physicians prevent DDIs are plagued by low-yield alerts, causing alert fatigue and compromising patient safety. The aim of this multicentre study was to evaluate the effect of tailoring potential DDI alerts to the ICU setting on the frequency of administered high-risk drug combinations.
METHODS: We implemented a cluster randomised stepped-wedge trial in nine ICUs in the Netherlands. Five ICUs already used potential DDI alerts. Patients aged 18 years or older admitted to the ICU with at least two drugs administered were included. Our intervention was an adapted CDSS, only providing alerts for potential DDIs considered as high risk. The intervention was delivered at the ICU level and targeted physicians. We hypothesised that showing only relevant alerts would improve CDSS effectiveness and lead to a decreased number of administered high-risk drug combinations. The order in which the intervention was implemented in the ICUs was randomised by an independent researcher. The primary outcome was the number of administered high-risk drug combinations per 1000 drug administrations per patient and was assessed in all included patients. This trial was registered in the Netherlands Trial Register (identifier NL6762) on Nov 26, 2018, and is now closed.
FINDINGS: In total, 10 423 patients admitted to the ICU between Sept 1, 2018, and Sept 1, 2019, were assessed and 9887 patients were included. The mean number of administered high-risk drug combinations per 1000 drug administrations per patient was 26·2 (SD 53·4) in the intervention group (n=5534), compared with 35·6 (65·0) in the control group (n=4353). Tailoring potential DDI alerts to the ICU led to a 12% decrease (95% CI 5-18%; p=0·0008) in the number of administered high-risk drug combinations per 1000 drug administrations per patient, after adjusting for clustering and prognostic factors.
INTERPRETATION: This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting significantly reduced the number of administered high-risk drug combinations. Our list of high-risk drug combinations can be used in other ICUs, and our strategy of tailoring alerts based on clinical relevance could be applied to other clinical settings.
FUNDING: ZonMw.

Gepubliceerd: Lancet. 2024;403(10425):439-49.
Impact factor: 88.5 ; Q1

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2. Effectiveness of intra-articular analgesia in reducing postoperative pain after minimally invasive sacroiliac joint fusion: a double-blind randomized controlled trial
Hermans SMM, Nellensteijn JM, Knoef R, van Santbrink H, Droeghaag R, Most J, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

During the first postoperative days following minimally invasive sacroiliac joint fusion (MISJF), patients often report serious pain, which contributes to high utilization of painkillers and prevention of early mobilization. This prospective, double-blind randomized controlled trial investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% versus placebo (NaCl 0.9%) in 42 patients in reducing postoperative pain after MISJF. The primary outcome was difference in pain

between bupivacaine and placebo groups, assessed as fixed factor in a linear mixed model. Secondary outcomes were opioid consumption, patient satisfaction, adverse events, and length of hospital stay. We found that SIJ infiltration with bupivacaine did not affect postoperative pain scores in comparison with placebo, neither as group-effect (p = 0.68), nor dependent on time (group*time: p = 0.87). None of the secondary outcome parameters were affected in the postoperative period in comparison with placebo, including opioid consumption (p = 0.81). To conclude, intra-articular infiltration of the SIJ with bupivacaine at the end of MISJF surgery is not effective in reducing postoperative pain. Hence, we do not recommend routine use of intraoperative SIJ infiltration with analgesia in MISJF.

Gepubliceerd: Sci Rep. 2024;14(1):22647.
Impact factor: 3.9 ; Q1

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3. Structured medication reviews in Parkinson's disease: pharmacists' views, experiences and needs - a qualitative study
Oonk NGM, Dorresteijn LDA, Te Braake E, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Bode C.

BACKGROUND: Executing structured medication reviews (SMRs) in primary care to optimize drug treatment is considered standard care of community pharmacists in the Netherlands. Patients with Parkinson's disease (PD) often face complex drug regimens for their symptomatic treatment and might, therefore, benefit from an SMR. However, previously, no effect of an SMR on quality of life in PD was found. In trying to improve the case management of PD, it is interesting to understand if and to what extent SMRs in PD patients are of added value in the pharmacist's opinion and what are assumed facilitating and hindering factors.
OBJECTIVES: To analyse the process of executing SMRs in PD patients from a community pharmacist's point of view.
DESIGN: A cross-sectional, qualitative study was performed, consisting of face-to-face semi-structured in-depth interviews.
METHODS: The interviews were conducted with community pharmacists who executed at least one SMR in PD, till data saturation was reached. Interviews were transcribed verbatim, coded and analysed thematically using an iterative approach. RESULTS: Thirteen pharmacists were interviewed. SMRs in PD were considered of added value, especially regarding patient contact and bonding, individualized care and its possible effect in the future, although PD treatment is found already well monitored in secondary care. Major constraints were time, logistics and collaboration with medical specialists.
CONCLUSION: Although community pharmacist-led SMRs are time-consuming and sometimes logistically challenging, they are of added value in primary care in general, and also in PD, of which treatment occurs mainly in secondary care. It emphasizes the pharmacist's role in PD treatment and might tackle future drug-related issues. Improvements concern multidisciplinary collaboration for optimized SMR execution and results.

Gepubliceerd: Ther Adv Drug Saf. 2024;15:20420986241237071.
Impact factor: 3.4 ; Q2

Totale impact factor: 95.8
Gemiddelde impact factor: 31.9

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

KNO

1. A multicenter study comparing the bacterial reduction on flexible endoscopes without a working channel between UV-C light disinfection versus standard endoscope Washer Disinfection: a randomized controlled trial
Halmans Y, Wellenstein DJ, Romijn M, van Bemmel AJM, van den Berge H, Scheeren RA, Kalpoe JS, Klont R, van Zeijl JH, Sikkema H, Euser SM, Hopman J, Takes RP, van den Broek GB.

BACKGROUND: To prevent cross-contamination between patients, adequate reprocessing is necessary when using flexible endoscopes (FEs) without a working channel. The current reprocessing process using an Endoscope Washer Disinfector (EWD) is time-consuming. Ultraviolet light group C (UV-C) exposition is an alternative and fast disinfection method and has previously been shown to adequately reduce Colony Forming Units (CFUs) on FEs without a working channel. The objective of this study was to examine whether UV-C light is as effective in reducing CFUs on contaminated FEs without a working channel compared to the EWD.
METHODS: FEs without a working channel were collected in three different Otorhinolaryngology Departments in the Netherlands. After pharyngolaryngoscopy, a manual pre-cleaning with tap water was performed and a culture was collected by rolling the distal 8-10 cm of the FE over an agar plate. Next, the FE was randomly assigned to be disinfected with UV-C light (D60) or the EWD (gold standard). After disinfection, another culture was taken. The primary outcome was microbiological contamination, defined by Colony Forming Units (CFU).
RESULTS: 600 FEs without a working channel were randomized. After clinical use and manual pre-cleaning, 239/300 (79.7%) FEs in the UV-C group and 262/300 (87.3%) FEs in the EWD group were contaminated (i.e., > 0 CFU). FEs without culture confirmed contamination were excluded from further analysis. After UV-C light disinfection, 195/239 (81.6%) FEs showed 0 CFUs, compared to 187/262 (71.4%) FEs disinfected with the EWD ($p < 0.01$). A multivariate logistics regression analysis showed an increased odds of 0 CFUs when using UV-C light (OR 1.83, 95% CI 1.19-2.79; $p < 0.01$), conditional on participating hospitals and types of FE.
CONCLUSIONS: UV-C light disinfection of FEs without a working channel appears more effective in reducing CFUs compared to the EWD and might be a good alternative disinfection method.
TRIAL REGISTRATION: Not applicable.

Gepubliceerd: Antimicrob Resist Infect Control. 2024;13(1):128.
Impact factor: 4.4 ; Q1

Totale impact factor: 4,4
Gemiddelde impact factor: 4,4

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Longgeneeskunde

1. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms
Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group: van Veen I.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

Gepubliceerd: Heliyon. 2024;10(10):e29591.
Impact factor: 3.6 ; Q1

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2. D-dimer cut-off value for pulmonary embolism diagnosis in COVID-19
Engels SYH, Oudkerk M, Heuvelmans MA.

Gepubliceerd: J Thorac Dis. 2024;16(4):2707-8.
Impact factor: 1.9 ; Q3

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3. Basic Bronchoscopy Competence Achieved by a Nationwide One-day Simulation-based Training
Gerretsen ECF, Groenier M, Annema JT, van der Heijden E, van Mook W, Aldenkamp AF, Citgez E, Crombag L, Hagmolen Of Ten Have W, Hiddinga BI, Hoppe BPC, Ninaber MK, van de Pol MA, Robberts B, Rutten M, Sprooten R, Wagenaar M, Smeenk F.

BACKGROUND: In 2020, a mandatory, nationwide 1-day bronchoscopy simulation-based training (SBT) course was implemented for novice pulmonology residents in the Netherlands. This pretest-posttest study was the first to evaluate the effectiveness of such a nationwide course in improving residents' simulated basic bronchoscopy skills.
METHODS: After passing a theoretical test, residents followed a 1-day SBT course, available in 7 centers, where they practiced their bronchoscopy skills step-by-step on a virtual reality simulator under pulmonologist supervision. Residents practiced scope handling efficiency (task 1) and navigational skills combined with lung anatomy knowledge (task 2). Task 1 outcome measures were navigational skill simulator metrics: percentage of time at mid-lumen, percentage of time with scope-wall contact, procedure time (PT), number of wall contacts and number of wall contacts per minute

of PT. Task 2 outcome measures were PT, observational assessment scores of a validated tool with a 5-point scale (1 representing the worst and 5 the best competence) and blinded dexterity assessments.
RESULTS: The study included 100 residents. All outcome measures of task 1 improved significantly (P<0.001), except for the number of wall contacts per minute of PT (4.3 [IQR 3.0 to 6.2] pre vs. 3.5 [IQR 2.6 to 5.3] post, P=0.07). For task 2, PT was reduced by 54% (10.3±2.7 minutes pre vs. 4.7±0.9 minutes post, P<0.001) with an improvement in overall-competence scores (2.0 [IQR 1.0 to 2.0] pre vs. 4.0 [IQR 4.0 to 5.0] post, P<0.001) and all dexterity parameters (P<0.001).
CONCLUSION: Nationwide implementation of a SBT course led to rapid improvement of residents' basic bronchoscopy skills while halving PT.

Gepubliceerd: J Bronchology Interv Pulmonol. 2024;32(1).
Impact factor: 3.2 ; Q2

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4. Potential for personalised and biomarker-guided COPD self-treatment approaches
Lenferink A, Citgez E, van der Valk P, van der Palen J, Effing TW, Brusse-Keizer MGJ.

Gepubliceerd: Lancet Respir Med. 2024;12(8):e48-e9.
IF 32.8 ; Q1

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5. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; van Veen I.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

Gepubliceerd: Sci Rep. 2024;14(1):16387.
Impact factor: 3.9 ; Q1

6. ERS/ATS Global Lung Function Initiative normal values and classifying severity based on z-scores instead of per cent predicted
Ong-Salvador R, Laveneziana P, de Jongh F.

Among the most discussed issues in the field of pulmonary function testing are reference equations and standardised methods of interpreting pulmonary function test (PFT) results. The Global Lung Function Initiative (GLI) task force gathered information from multiple countries with diverse ethnicities to create a multi-ethnic reference formula suitable for a broad age range. Their first output was the GLI-2012 spirometry reference equations. Together with the GLI-2012 reference equations, the GLI document recommended the use of z-scores to standardise the interpretation of PFT results. Z-scores were introduced as an alternative to per cent predicted and fixed thresholds in interpreting PFTs. After more than a decade, there is still debate on which method of interpretation is better.

Gepubliceerd: Breathe (Sheff). 2024;20(3):230227.
Impact factor: 3.4 ; Q2

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7. Diaphragmatic electromyography in infants: an overview of possible clinical applications
Scholten AWJ, van Leuteren RW, de Waal CG, Kraaijenga JV, de Jongh FH, van Kaam AH, Hutten GJ.

Preterm infants often experience breathing instability and a hampered lung function. Therefore, these infants receive cardiorespiratory monitoring and respiratory support. However, the current respiratory monitoring technique may be unreliable for especially obstructive apnea detection and classification and it does not provide insight in breathing effort. The latter makes the selection of the adequate mode and level of respiratory support difficult. Electromyography of the diaphragm (dEMG) has the potential of monitoring heart rate (HR) and respiratory rate (RR), and it provides additional information on breathing effort. This review summarizes the available evidence on the clinical potential of dEMG to provide cardiorespiratory monitoring, to synchronize patient-ventilator interaction, and to optimize the mode and level of respiratory support in the individual newborn infant. We also try to identify gaps in knowledge and future developments needed to ensure widespread implementation in clinical practice. IMPACT: Preterm infants require cardiorespiratory monitoring and respiratory support due to breathing instability and a hampered lung function. The current respiratory monitoring technique may provide unreliable measurements and does not provide insight in breathing effort, which makes the selection of the optimal respiratory support settings difficult. Measuring diaphragm activity could improve cardiorespiratory monitoring by providing insight in breathing effort and could potentially have an important role in individualizing respiratory support in newborn infants.

Gepubliceerd: Pediatr Res. 2024;95(1):52-8.
Impact factor: 3.1 ; Q1

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8. Lack of Evidence Regarding Markers Identifying Acute Heart Failure in Patients with COPD: An AI-Supported Systematic Review
van Dijk SHB, Brusse-Keizer MGJ, Bucsán CC, Ploumen EH, van Beurden WJC, van der Palen J, Doggen CJM, Lenferink A.

BACKGROUND: Due to shared symptoms, acute heart failure (AHF) is difficult to differentiate from an acute exacerbation of COPD (AECOPD). This systematic review aimed to identify markers that can diagnose AHF underlying acute dyspnea in patients with COPD presenting at the hospital.
METHODS: All types of observational studies and clinical trials that investigated any marker's ability to diagnose AHF in acutely dyspneic COPD patients were considered eligible for inclusion. An AI tool (ASReview) supported the title and abstract screening of the articles obtained from PubMed, Scopus, Web of Science, the Cochrane Library, Embase, and CINAHL until April 2023. Full text screening was independently performed by two reviewers. Twenty percent of the data extraction was checked by a second reviewer and the risk of bias was assessed in duplicate using the QUADAS-2 tool. Markers' discriminative abilities were evaluated in terms of sensitivity, specificity, positive and negative predictive values, and the area under the curve when available.
RESULTS: The search identified 10,366 articles. After deduplication, title and abstract screening was performed on 5,386 articles, leaving 153 relevant, of which 82 could be screened full text. Ten distinct studies (reported in 16 articles) were included, of which 9 had a high risk of bias. Overall, these studies evaluated 12 distinct laboratory and 7 non-laboratory markers. BNP, NT-proBNP, MR-proANP, and inspiratory inferior vena cava diameter showed the highest diagnostic discrimination.
CONCLUSION: There is not much evidence for the use of markers to diagnose AHF in acutely dyspneic COPD patients in the hospital setting. BNPs seem most promising, but should be interpreted alongside imaging and clinical signs, as this may lead to improved diagnostic accuracy. Future validation studies are urgently needed before any AHF marker can be incorporated into treatment decision-making algorithms for patients with COPD.
PROTOCOL REGISTRATION: CRD42022283952.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2024;19:531-41.
Impact factor: 3.1 ; Q2

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9. Living happily ever after? The hidden health risks of Disney princesses
van Dijk SHB, Bui M, Eijkelboom AH.

Gepubliceerd: Bmj. 2024;387:q2497.
Impact factor: 42.7 ; Q1

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10. Exploring the feasibility, acceptability, usability and safety of a digitally supported self-management intervention for uncontrolled asthma: A pre-post pilot study in secondary care
Zijp A, Versluis A, Joosse L, Kind T, Rouveroy van Nieuwaal TM, Wassink-Bergman C, van Veen IH, Weersink EJ, Chavannes NH, Aardoom JJ.

INTRODUCTION: Asthma control is often suboptimal, which is associated with incorrect medication use and poor asthma management by patients. Astmakompas, a digital self-management intervention, comprises a mobile app for patients, a web portal for healthcare professionals (HCP), and a wireless spirometer. Together, these components are intended to facilitate symptom monitoring, patient-HCP communication and assist in asthma-related self-management.
OBJECTIVE: The pilot study primarily aims to assess the feasibility, acceptability, usability and safety of Astmakompas from patient and HCP perspectives, and secondarily to explore potential effects on asthma control, medication use, Quality of Life, self-efficacy and (in)direct costs.
METHODS: A mixed-method, multi-center, pre-post study design was conducted in two Dutch hospitals, involving patients with uncontrolled asthma and four HCPs. Primary outcomes were assessed post-intervention using questionnaires and in-depth interviews. Secondary outcomes were

assessed at baseline and post-intervention using questionnaires, and post-intervention using in-depth interviews.
RESULTS: In general, the data show that Astmakompas was considered feasible, acceptable, usable and safe by both patients (n = 14) and HCPs (n = 4). Furthermore, qualitative data of 11 patients and all HCPs showed the importance of guidance from HCPs and tailoring of Astmakompas to care needs. Astmakompas helped patients recognise symptoms and provided valuable insights into asthma control while being easy to use. Asthma control improved from baseline (M = 2.1, SD = 1.3) to post-intervention (M = 1.3, SD = 1.0, t(13) = 2.61; p = .02).
CONCLUSION: Astmakompas shows promise for further implementation and research. Future randomized studies with longer evaluation periods are crucial to assess the tool's impact on asthma outcomes and workload. It is important that HCPs guide and tailor interventions to meet the patient's individual needs and circumstances.

Gepubliceerd: Digit Health. 2024;10:20552076241292391.
Impact factor: 3.3 ; Q1

Totale impact factor: 101.0
Gemiddelde impact factor: 10.1

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 5
Totale impact factor: 83.9
Gemiddelde impact factor: 16.8

MDL

1. Long-term treatment outcomes of mindfulness-based cognitive therapy for fatigue in patients with inflammatory bowel disease: Results of a randomized controlled trial
Bredero QM, Fleer J, Smink A, Kuiken G, Potjewijd J, Laroy M, Visschedijk MC, Russel M, van der Lugt M, Meijssen MAC, van der Wouden EJ, Dijkstra G, Schroevers MJ.

OBJECTIVES: Fatigue is prevalent in patients with inflammatory bowel disease (IBD) in remission. Previously, we showed that fatigued IBD patients experienced a significant decrease in fatigue after receiving mindfulness-based cognitive therapy (MBCT). The current study examined to what extent these short-term beneficial effects of MBCT on fatigue were maintained over nine months follow-up, and whether patient characteristics were associated with clinically relevant improvement in fatigue.
METHODS: A randomized controlled trial, including an MBCT and waiting-list control condition, was performed in fatigued IBD patients in remission. For this study, we analysed long-term outcomes of 108 patients who received MBCT (either directly or after three months waiting). The primary outcome was fatigue, assessed with the Checklist Individual Strenght-20. Secondary outcomes included fatigue interference, depression, anxiety, and quality of life.
RESULTS: The reduced level of fatigue post-treatment did not change significantly during follow-up ($F(2,76) = 1.68$, $p = 0.19$). In total, 29% of patients reported clinically relevant improvement from pre-treatment to nine months follow-up. We found few significant differences in baseline characteristics between those reporting clinically relevant improvement and those not, except that patients who improved were significantly more often unemployed ($\chi(2)(1, n = 73) = 4.40$, $p = 0.04$). Secondary outcomes, which did not change significantly during MBCT, also remained stable during follow-up.
CONCLUSION: Findings suggest that reductions in IBD-related fatigue after receiving MBCT are sustained over nine months follow-up, with around one-third of patients reporting clinically relevant improvement from pre-treatment to follow-up. Employment status might be related to improvements in fatigue. Future research is needed to confirm these long-term outcomes.
PREREGISTRATION: ClinicalTrials.gov ID: NCT03162575.

Gepubliceerd: J Psychosom Res. 2024;187:111949.
Impact factor: 2.4 ; Q2

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2. Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis
Colapietro F, Maisonneuve P, Lytvyak E, Beuers U, Verdonk RC, van der Meer AJ, van Hoek B, Kuiken SD, Brouwer JT, Muratori P, Aghemo A, Carella F, van den Berg AP, Zachou K, Dalekos GN, Di Zeo-Sánchez DE, Robles M, Andrade RJ, Montano-Loza AJ, van den Brand FF, Slooter CD, Macedo G, Liberal R, de Boer YS, Lleo A, Dutch AIH Study Group and International Autoimmune Hepatitis Group; Guichelaar M.

BACKGROUND AND AIMS: Autoimmune hepatitis (AIH) is a rare chronic liver disease of unknown aetiology; the risk of hepatocellular carcinoma (HCC) remains unclear and risk factors are not well-defined. We aimed to investigate the risk of HCC across a multicentre AIH cohort and to identify predictive factors.
METHODS: We performed a retrospective, observational, multicentric study of patients included in the International Autoimmune Hepatitis Group Retrospective Registry. The assessed clinical outcomes were HCC development, liver transplantation, and death. Fine and Gray regression analysis stratified by centre was applied to determine the effects of individual covariates; the cumulative incidence of HCC was estimated using the competing risk method with death as a competing risk.
RESULTS: A total of 1,428 patients diagnosed with AIH from 1980 to 2020 from 22 eligible centres across Europe and Canada were included, with a median follow-up of 11.1 years (interquartile range

5.2-15.9). Two hundred and ninety-three (20.5%) patients had cirrhosis at diagnosis. During follow-up, 24 patients developed HCC (1.7%), an incidence rate of 1.44 cases/1,000 patient-years; the cumulative incidence of HCC increased over time (0.6% at 5 years, 0.9% at 10 years, 2.7% at 20 years, and 6.6% at 30 years of follow-up). Patients who developed cirrhosis during follow-up had a significantly higher incidence of HCC. The cumulative incidence of HCC was 2.6%, 4.6%, 5.6% and 6.6% at 5, 10, 15, and 20 years after the development of cirrhosis, respectively. Obesity (hazard ratio [HR] 2.94, p = 0.04), cirrhosis (HR 3.17, p = 0.01), and AIH/PSC variant syndrome (HR 5.18, p = 0.007) at baseline were independent risk factors for HCC development.
CONCLUSIONS: HCC incidence in AIH is low even after cirrhosis development and is associated with risk factors including obesity, cirrhosis, and AIH/PSC variant syndrome.
IMPACT AND IMPLICATIONS: The risk of developing hepatocellular carcinoma (HCC) in individuals with autoimmune hepatitis (AIH) seems to be lower than for other aetiologies of chronic liver disease. Yet, solid data for this specific patient group remain elusive, given that most of the existing evidence comes from small, single-centre studies. In our study, we found that HCC incidence in patients with AIH is low even after the onset of cirrhosis. Additionally, factors such as advanced age, obesity, cirrhosis, alcohol consumption, and the presence of the AIH/PSC variant syndrome at the time of AIH diagnosis are linked to a higher risk of HCC. Based on these findings, there seems to be merit in adopting a specialized HCC monitoring programme for patients with AIH based on their individual risk factors.

Gepubliceerd: J Hepatol. 2024;80(1):53-61.
Impact factor: 33.0 ; Q1

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3. Treatment of non-constipated irritable bowel syndrome with the histamine 1 receptor antagonist ebastine: a randomised, double-blind, placebo-controlled trial
Decraecker L, De Looze D, Hirsch DP, De Schepper H, Arts J, Caenepeel P, Bredenoord AJ, Kolkman J, Bellens K, Van Beek K, Pia F, Peetermans W, Vanuytsel T, Denadai-Souza A, Belmans A, Boeckxstaens G.

OBJECTIVE: We evaluated the histamine 1 receptor antagonist ebastine as a potential treatment for patients with non-constipated irritable bowel syndrome (IBS) in a randomised, placebo-controlled phase 2 study.
METHODS: Non-constipated patients with IBS fulfilling the Rome III criteria were randomly assigned to 20 mg ebastine or placebo for 12 weeks. Subjects scored global relief of symptoms (GRS) and abdominal pain intensity (API). A subject was considered a weekly responder for GRS if total or obvious relief was reported and a responder for API if the weekly average pain score was reduced by at least 30% vs baseline. The primary endpoints were the proportion of subjects who were weekly responders for at least 6 out of the 12 treatment weeks for both GRS and API ('GRS+API', composite endpoint) and for GRS and API separately.
RESULTS: 202 participants (32±11 years, 68% female) were randomly allocated to receive ebastine (n=101) or placebo (n=101). Treatment with ebastine resulted in significantly more responders (12%, 12/92) for GRS+API compared with placebo (4%, 4/87, p=0.047) while the proportion of responders for GRS and API separately was higher for ebastine compared with placebo, although not statistically significant (placebo vs ebastine, GRS: 7% (6/87) vs 15% (14/91), p=0.072; API: 25% (20/85) vs 37% (34/92), p=0.081).
CONCLUSIONS: Our study shows that ebastine is superior to placebo and should be further evaluated as novel treatment for patients with non-constipated IBS.
TRIAL REGISTRATION NUMBER: The study protocol was approved by the local ethics committee of each study site (EudraCT number: 2013-001199-39; ClinicalTrials.gov identifier: NCT01908465).

Gepubliceerd: Gut. 2024;73(3):459-69.

Impact factor: 25.8 ; Q1

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4. Standard of Care Versus Octreotide in Angiodysplasia-Related Bleeding (the OCEAN Study): A Multicenter Randomized Controlled Trial

Goltstein L, Grooteman KV, Bernts LHP, Scheffer RCH, Laheij RJF, Gilissen LPL, Schrauwen RWM, Talstra NC, Zuur AT, Braat H, Hadithi M, Brouwer JT, Nagengast WB, Oort FA, Tenthof van Noorden J, Kievit W, van Geenen EJM, Drenth JPH.

BACKGROUND & AIMS: Gastrointestinal angiodysplasias are vascular anomalies that may result in transfusion-dependent anemia despite endoscopic therapy. An individual patient data meta-analysis of cohort studies suggests that octreotide decreases rebleeding rates, but component studies possessed a high risk of bias. We investigated the efficacy of octreotide in reducing the transfusion requirements of patients with angiodysplasia-related anemia in a clinical trial setting.
METHODS: The study was designed as a multicenter, open-label, randomized controlled trial. Patients with angiodysplasia bleeding were required to have had at least 4 red blood cell (RBC) units or parental iron infusions, or both, in the year preceding randomization. Patients were allocated (1:1) to 40-mg octreotide long-acting release intramuscular every 28 days or standard of care, including endoscopic therapy. The treatment duration was 1 year. The primary outcome was the mean difference in the number of transfusion units (RBC + parental iron) between the octreotide and standard of care groups. Patients who received at least 1 octreotide injection or followed standard of care for at least 1 month were included in the intention-to-treat analyses. Analyses of covariance were used to adjust for baseline transfusion requirements and incomplete follow-up.
RESULTS: We enrolled 62 patients (mean age, 72 years; 32 men) from 17 Dutch hospitals in the octreotide (n = 31) and standard of care (n = 31) groups. Patients required a mean number of 20.3 (standard deviation, 15.6) transfusion units and 2.4 (standard deviation, 2.0) endoscopic procedures in the year before enrollment. The total number of transfusions was lower with octreotide (11.0; 95% confidence interval [CI], 5.5-16.5) compared with standard of care (21.2; 95% CI, 15.7-26.7). Octreotide reduced the mean number of transfusion units by 10.2 (95% CI, 2.4-18.1; P = .012). Octreotide reduced the annual volume of endoscopic procedures by 0.9 (95% CI, 0.3-1.5).
CONCLUSIONS: Octreotide effectively reduces transfusion requirements and the need for endoscopic therapy in patients with angiodysplasia-related anemia.
CLINICALTRIALS: gov, NCT02384122.

Gepubliceerd: Gastroenterology. 2024;166(4):690-703.
Impact factor: 25.1 ; Q1

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5. Long-term follow-up study of necrotising pancreatitis: interventions, complications and quality of life

Hollemans RA, Timmerhuis HC, Besselink MG, Bouwense SAW, Bruno M, van Duijvendijk P, van Geenen EJ, Hadithi M, Hofker S, Van-Hooft JE, Kager LM, Manusama ER, Poley JW, Quispel R, Römkens T, van der Schelling GP, Schwartz MP, Spanier BWM, Stommel M, Tan A, Venneman NG, Vleggaar F, van Wanrooij RLJ, Bollen TL, Voermans RP, Verdonk RC, van Santvoort HC.

OBJECTIVE: To describe the long-term consequences of necrotising pancreatitis, including complications, the need for interventions and the quality of life.
DESIGN: Long-term follow-up of a prospective multicentre cohort of 373 necrotising pancreatitis patients (2005-2008) was performed. Patients were prospectively evaluated and received questionnaires. Readmissions (ie, for recurrent or chronic pancreatitis), interventions, pancreatic insufficiency and quality of life were compared between initial treatment groups: conservative,

endoscopic/percutaneous drainage alone and necrosectomy. Associations of patient and disease characteristics during index admission with outcomes during follow-up were assessed.
RESULTS: During a median follow-up of 13.5 years (range 12-15.5 years), 97/373 patients (26%) were readmitted for recurrent pancreatitis. Endoscopic or percutaneous drainage was performed in 47/373 patients (13%), of whom 21/47 patients (45%) were initially treated conservatively. Pancreatic necrosectomy or pancreatic surgery was performed in 31/373 patients (8%), without differences between treatment groups. Endocrine insufficiency (126/373 patients; 34%) and exocrine insufficiency (90/373 patients; 38%), developed less often following conservative treatment ($p<0.001$ and $p=0.016$, respectively). Quality of life scores did not differ between groups. Pancreatic gland necrosis >50% during initial admission was associated with percutaneous/endoscopic drainage (OR 4.3 (95% CI 1.5 to 12.2)), pancreatic surgery (OR 3.2 (95% CI 1.1 to 9.5) and development of endocrine insufficiency (OR13.1 (95% CI 5.3 to 32.0) and exocrine insufficiency (OR6.1 (95% CI 2.4 to 15.5) during follow-up.
CONCLUSION: Acute necrotising pancreatitis carries a substantial disease burden during long-term follow-up in terms of recurrent disease, the necessity for interventions and development of pancreatic insufficiency, even when treated conservatively during the index admission. Extensive (>50%) pancreatic parenchymal necrosis seems to be an important predictor of interventions and complications during follow-up.

Gepubliceerd: Gut. 2024;73(5):787-96.
Impact factor: 25.8 ; Q1

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6. Mucosal host-microbe interactions associate with clinical phenotypes in inflammatory bowel disease
Hu S, Bourgonje AR, Gacesa R, Jansen BH, Björk JR, Bangma A, Hidding IJ, van Dullemen HM, Visschedijk MC, Faber KN, Dijkstra G, Harmsen HJM, Festen EAM, Vich Vila A, Spekhorst LM, Weersma RK.

Disrupted host-microbe interactions at the mucosal level are key to the pathophysiology of IBD. This study aimed to comprehensively examine crosstalk between mucosal gene expression and microbiota in patients with IBD. To study tissue-specific interactions, we perform transcriptomic (RNA-seq) and microbial (16S-rRNA-seq) profiling of 697 intestinal biopsies (645 derived from 335 patients with IBD and 52 from 16 non-IBD controls). Mucosal gene expression patterns in IBD are mainly determined by tissue location and inflammation, whereas the mucosal microbiota composition shows a high degree of individual specificity. Analysis of transcript-bacteria interactions identifies six distinct groups of inflammation-related pathways that are associated with intestinal microbiota (adjusted $P < 0.05$). An increased abundance of Bifidobacterium is associated with higher expression of genes involved in fatty acid metabolism, while Bacteroides correlates with increased metallothionein signaling. In patients with fibrostenosis, a transcriptional network dominated by immunoregulatory genes is associated with Lachnoclostridium bacteria in non-stenotic tissue (adjusted $P < 0.05$), while being absent in CD without fibrostenosis. In patients using TNF-α-antagonists, a transcriptional network dominated by fatty acid metabolism genes is linked to Ruminococcaceae (adjusted $P < 0.05$). Mucosal microbiota composition correlates with enrichment of intestinal epithelial cells, macrophages, and NK-cells. Overall, these data demonstrate the presence of context-specific mucosal host-microbe interactions in IBD, revealing significantly altered inflammation-associated gene-taxa modules, particularly in patients with fibrostenotic CD and patients using TNF-α-antagonists. This study provides compelling insights into host-microbe interactions that may guide microbiota-directed precision medicine and fuels the rationale for microbiota-targeted therapeutics as a strategy to alter disease course in IBD.

Gepubliceerd: Nat Commun. 2024;15(1):1470.

Impact factor: 15.7 ; Q1

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7. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands: A Stepped-Wedge Randomized Clinical Trial

Mackay TM, Latenstein AEJ, Augustinus S, van der Geest LG, Bogte A, Bonsing BA, Cirkel GA, Hol L, Busch OR, den Dulk M, van Driel L, Festen S, de Groot DA, de Groot JB, Groot Koerkamp B, Haj Mohammad N, Haver JT, van der Harst E, de Hingh IH, Homs MYV, Los M, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, Patijn GA, Quispel R, Römkens TEH, van Santvoort HC, Stommel MWJ, Venneman NG, Verdonk RC, van Vilsteren FGI, de Vos-Geelen J, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG.

IMPORTANCE: Implementation of new cancer treatment strategies as recommended by evidence-based guidelines is often slow and suboptimal.
OBJECTIVE: To improve the implementation of guideline-based best practices in the Netherlands in pancreatic cancer care and assess the impact on survival.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter, stepped-wedge cluster randomized trial compared enhanced implementation of best practices with usual care in consecutive patients with all stages of pancreatic cancer. It took place from May 22, 2018 through July 9, 2020. Data were analyzed from April 1, 2022, through February 1, 2023. It included all patients in the Netherlands with pathologically or clinically diagnosed pancreatic ductal adenocarcinoma. This study reports 1-year follow-up (or shorter in case of deceased patients).
INTERVENTION: The 5 best practices included optimal use of perioperative chemotherapy, palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), referral to a dietician, and use of metal stents in patients with biliary obstruction. A 6-week implementation period was completed, in a randomized order, in all 17 Dutch networks for pancreatic cancer care.
MAIN OUTCOMES AND MEASURES: The primary outcome was 1-year survival. Secondary outcomes included adherence to best practices and quality of life (European Organisation for Research and Treatment of Cancer [EORTC] global health score).
RESULTS: Overall, 5887 patients with pancreatic cancer (median age, 72.0 [IQR, 64.0-79.0] years; 50% female) were enrolled, 2641 before and 2939 after implementation of best practices (307 during wash-in period). One-year survival was 24% vs 23% (hazard ratio, 0.98, 95% CI, 0.88-1.08). There was no difference in the use of neoadjuvant chemotherapy (11% vs 11%), adjuvant chemotherapy (48% vs 51%), and referral to a dietician (59% vs 63%), while the use of palliative chemotherapy (24% vs 30%; odds ratio [OR], 1.38; 95% CI, 1.10-1.74), PERT (34% vs 45%; OR, 1.64; 95% CI, 1.28-2.11), and metal biliary stents increased (74% vs 83%; OR, 1.78; 95% CI, 1.13-2.80). The EORTC global health score did not improve (area under the curve, 43.9 vs 42.8; median difference, -1.09, 95% CI, -3.05 to 0.94).
CONCLUSIONS AND RELEVANCE: In this randomized clinical trial, implementation of 5 best practices in pancreatic cancer care did not improve 1-year survival and quality of life. The finding that most patients received no tumor-directed treatment paired with the poor survival highlights the need for more personalized treatment options.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03513705.

Gepubliceerd: JAMA Surg. 2024;159(4):429-37.
Impact factor: 14.9 ; Q1

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8. Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study): a multicentre cluster randomised trial
Meulen LWT, Bogie RMM, Siersema PD, Winkens B, Vlug MS, Wolfhagen FHJ, Baven-Pronk M, van der Voorn M, Schwartz MP, Vogelaar L, de Vos Tot Nederveen Cappel WH, Seerden TCJ, Hazen WL, Schrauwen RWM, Alvarez Herrero L, Schreuder RM, van Nunen AB, Stoop E, de Bruin GJ, Bos P, Marsman WA, Kuiper E, de Bièvre M, Alderlieste YA, Roomer R, Groen J, Bargeman M, van Leerdam ME, Roberts-Bos L, Boersma F, Thurnau K, de Vries RS, Ramaker JM, Vleggaar FP, de Ridder RJ, Pellisé M, Bourke MJ, Masclee AAM, Moons LMG.

OBJECTIVE: Endoscopic mucosal resection (EMR) is the preferred treatment for non-invasive large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs) but is associated with an early recurrence rate of up to 30%. We evaluated whether standardised EMR training could reduce recurrence rates in Dutch community hospitals.
DESIGN: In this multicentre cluster randomised trial, 59 endoscopists from 30 hospitals were randomly assigned to the intervention group (e-learning and 2-day training including hands-on session) or control group. From April 2019 to August 2021, all consecutive EMR-treated LNPCPs were included. Primary endpoint was recurrence rate after 6 months.
RESULTS: A total of 1412 LNPCPs were included; 699 in the intervention group and 713 in the control group (median size 30 mm vs 30 mm, 45% vs 52% size, morphology, site and access (SMSA) score IV, 64% vs 64% proximal location). Recurrence rates were lower in the intervention group compared with controls (13% vs 25%, OR 0.43; 95% CI 0.23 to 0.78; p=0.005) with similar complication rates (8% vs 9%, OR 0.93; 95% CI 0.64 to 1.36; p=0.720). Recurrences were more often unifocal in the intervention group (92% vs 76%; p=0.006). In sensitivity analysis, the benefit of the intervention on recurrence rate was only observed in the 20-40 mm LNPCPs (5% vs 20% in 20-29 mm, p=0.001; 10% vs 21% in 30-39 mm, p=0.013) but less evident in ≥40 mm LNPCPs (24% vs 31%; p=0.151). In a post hoc analysis, the training effect was maintained in the study group, while in the control group the recurrence rate remained high.
CONCLUSION: A compact standardised EMR training for LNPCPs significantly reduced recurrences in community hospitals. This strongly argues for a national dedicated training programme for endoscopists performing EMR of ≥20 mm LNPCPs. Interestingly, in sensitivity analysis, this benefit was limited for LNPCPs ≥40 mm.
TRIAL REGISTRATION NUMBER: NTR7477.

Gepubliceerd: Gut. 2024;73(5):741-50.
Impact factor: 25.8 ; Q1

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9. Effect of optical diagnosis training on recognition and treatment of submucosal invasive colorectal cancer in community hospitals: a prospective multicenter intervention study
Meulen LWT, Haasnoot KJC, Vlug MS, Wolfhagen FHJ, Baven-Pronk M, van der Voorn M, Schwartz MP, Vogelaar L, de Vos Tot Nederveen Cappel WH, Seerden TCJ, Hazen WL, Schrauwen RWM, Alvarez-Herrero L, Schreuder RM, van Nunen AB, Stoop E, de Bruin GJ, Bos P, Marsman WA, Kuiper E, de Bièvre M, Alderlieste YA, Roomer R, Groen J, Bigirwamungu-Bargeman M, Siersema PD, Elias SG, Masclee AAM, Moons LMG.

BACKGROUND: Recognition of submucosal invasive colorectal cancer (T1 CRC) is difficult, with sensitivities of 35%-60% in Western countries. We evaluated the real-life effects of training in the OPTICAL model, a recently developed structured and validated prediction model, in Dutch community hospitals.
METHODS: In this prospective multicenter study (OPTICAL II), 383 endoscopists from 40 hospitals were invited to follow an e-learning program on the OPTICAL model, to increase sensitivity in detecting T1 CRC in nonpedunculated polyps. Real-life recognition of T1 CRC was then evaluated in 25

hospitals. Endoscopic and pathologic reports of T1 CRCs detected during the next year were collected retrospectively, with endoscopists unaware of this evaluation. Sensitivity for T1 CRC recognition, R0 resection rate, and treatment modality were compared for trained vs. untrained endoscopists.
RESULTS: 1 year after e-learning, 528 nonpedunculated T1 CRCs were recorded for endoscopies performed by 251 endoscopists (118 [47 %] trained). Median T1 CRC size was 20 mm. Lesions were mainly located in the distal colorectum (66 %). Trained endoscopists recognized T1 CRCs more frequently than untrained endoscopists (sensitivity 74 % vs. 62 %; mixed model analysis odds ratio [OR] 2.90, 95 %CI 1.54-5.45). R0 resection rate was higher for T1 CRCs detected by trained endoscopists (69 % vs. 56 %; OR 1.73, 95 %CI 1.03-2.91).
CONCLUSION: Training in optical recognition of T1 CRCs in community hospitals was associated with increased recognition of T1 CRCs, leading to higher en bloc and R0 resection rates. This may be an important step toward more organ-preserving strategies.

Gepubliceerd: Endoscopy. 2024;56(10):770-9.
Impact factor: 12.8 ; Q1

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10. Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: First report of the IAIHG retrospective registry
Slooter CD, van den Brand FF, Lleo A, Colapietro F, Lenzi M, Muratori P, Kerkar N, Dalekos GN, Zachou K, Lucena MI, Robles-Díaz M, Di Zeo-Sánchez DE, Andrade RJ, Montano-Loza AJ, Lytvyak E, Lissenberg-Witte BI, Maisonneuve P, Bouma G, Macedo G, Liberal R, de Boer YS, Dutch AIH Study Group and International Autoimmune Hepatitis Group; Guichelaar M.

BACKGROUND AND AIMS: The International Autoimmune Hepatitis Group retrospective registry (IAIHG-RR) is a web-based platform with subjects enrolled with a clinical diagnosis of autoimmune hepatitis (AIH). As prognostic factor studies with enough power are scarce, this study aimed to ascertain data quality and identify prognostic factors in the IAIHG-RR cohort.
METHODS: This retrospective, observational, multicenter study included all patients with a clinical diagnosis of AIH from the IAIHG-RR. The quality assessment consisted of external validation of completeness and consistency for 29 predefined variables. Cox regression was used to identify risk factors for liver-related death and liver transplantation (LT).
RESULTS: This analysis included 2559 patients across 7 countries. In 1700 patients, follow-up was available, with a completeness of individual data of 90% (range: 30-100). During a median follow-up period of 10 (range: 0-49) years, there were 229 deaths, of which 116 were liver-related, and 143 patients underwent LT. Non-White ethnicity (HR 4.1 95% CI: 2.3-7.1), cirrhosis (HR 3.5 95% CI: 2.3-5.5), variant syndrome with primary sclerosing cholangitis (PSC) (HR 3.1 95% CI: 1.6-6.2), and lack of complete biochemical response within 6 months (HR 5.7 95% CI: 3.4-9.6) were independent prognostic factors.
CONCLUSIONS: The IAIHG-RR represents the world's largest AIH cohort with moderate-to-good data quality and a relevant number of liver-related events. The registry is a suitable platform for patient selection in future studies. Lack of complete biochemical response to treatment, non-White ethnicity, cirrhosis, and PSC-AIH were associated with liver-related death and LT.

Gepubliceerd: Hepatology. 2024;79(3):538-50.
Impact factor: 15.8 ; Q1

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11. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis

Snijders R, Stoelinga AEC, Gevers TJG, Pape S, Biewenga M, Tushuizen ME, Verdonk RC, de Jonge HJM, Vrolijk JM, Bakker SF, Vanwolleghem T, de Boer YS, Baven Pronk M, Beuers U, van der Meer AJ, Gerven N, Sijtsma MGM, van Eijck BC, van IMC, van Herwaarden M, van den Brand FF, Korkmaz KS, van den Berg AP, Guichelaar MMJ, Levens AD, van Hoek B, Drenth JPH.

BACKGROUND & AIMS: Patients with autoimmune hepatitis (AIH) almost invariably require lifelong immunosuppressive treatment. There is genuine concern about the efficacy and tolerability of the current standard combination therapy of prednisolone and azathioprine. Mycophenolate mofetil (MMF) has emerged as an alternative option. The aim of this study was to compare MMF to azathioprine as induction therapy for AIH.
METHODS: In this 24-week, prospective, randomised, open-label, multicentre superiority trial, 70 patients with treatment-naive AIH received either MMF or azathioprine, both in combination with prednisolone. The primary endpoint was biochemical remission defined as normalisation of serum levels of alanine aminotransferase and IgG after 24 weeks of treatment. Secondary endpoints included safety and tolerability.
RESULTS: Seventy patients (mean 57.9 years [SD 14.0]; 72.9% female) were randomly assigned to the MMF plus prednisolone (n = 39) or azathioprine plus prednisolone (n = 31) group. The primary endpoint was met in 56.4% and 29.0% of patients assigned to the MMF group and the azathioprine group, respectively (difference, 27.4 percentage points; 95% CI 4.0 to 46.7; p = 0.022). The MMF group exhibited higher complete biochemical response rates at 6 months (72.2% vs. 32.3%; p = 0.004). No serious adverse events occurred in patients who received MMF (0%) but serious adverse events were reported in four patients who received azathioprine (12.9%) (p = 0.034). Two patients in the MMF group (5.1%) and eight patients in the azathioprine group (25.8%) discontinued treatment owing to adverse events or serious adverse events (p = 0.018).
CONCLUSIONS: In patients with treatment-naive AIH, MMF with prednisolone led to a significantly higher rate of biochemical remission at 24 weeks compared to azathioprine combined with prednisolone. Azathioprine use was associated with more (serious) adverse events leading to cessation of treatment, suggesting superior tolerability of MMF.
IMPACT AND IMPLICATIONS: This randomised-controlled trial directly compares azathioprine and mycophenolate mofetil, both in combination with prednisolone, for the induction of biochemical remission in treatment-naive patients with autoimmune hepatitis. Achieving complete remission is desirable to prevent disease progression. Patients assigned to the mycophenolate mofetil group reached biochemical remission more often and experienced fewer adverse events. The findings in this trial may contribute to the re-evaluation of international guidelines for the standard of care in treatment-naive patients with autoimmune hepatitis.
TRIAL REGISTRATION NUMBER: #NCT02900443.

Gepubliceerd: J Hepatol. 2024;80(4):576-85.
Impact factor: 33.0 ; Q1

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12. Diagnostic criteria and long-term outcomes in AIH-PBC variant syndrome under combination therapy

Stoelinga AEC, Biewenga M, Drenth JPH, Verhelst X, van der Meer AJP, de Boer YS, Bouma G, de Vries ES, Verdonk RC, van der Berg AP, Brouwer JT, Vanwolleghem T, Lammers W, Beuers U, Sarasqueta AF, Verheij J, Roskams T, Crobach S, Tushuizen ME, van Hoek B, Dutch Autoimmune Hepatitis Study Group; Guichelaar M.

BACKGROUND & AIMS: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) can co-exist in AIH-PBC, requiring combined treatment with immunosuppression and ursodeoxycholic acid

(UDCA). The Paris criteria are commonly used to identify these patients; however, the optimal diagnostic criteria are unknown. We aimed to evaluate the use and clinical relevance of both Paris and Zhang criteria.
METHODS: Eighty-three patients with a clinical suspicion of AIH-PBC who were treated with combination therapy were included. Histology was re-evaluated. Characteristics and long-term outcomes were retrospectively compared to patients with AIH and PBC.
RESULTS: Seventeen (24%) patients treated with combination therapy fulfilled the Paris criteria. Fifty-two patients (70%) fulfilled the Zhang criteria. Patients who met Paris and Zhang criteria more often had inflammation and fibrosis on histology compared to patients only meeting the Zhang criteria. Ten-year liver transplant (LT)-free survival was 87.3% (95% CI 78.9-95.7%) in patients with AIH-PBC. This did not differ in patients in or outside the Paris or Zhang criteria ($p = 0.46$ and $p = 0.40$, respectively) or from AIH ($p = 0.086$). LT-free survival was significantly lower in patients with PBC and severe hepatic inflammation - not receiving immunosuppression - compared to those with AIH-PBC (65%; 95% CI 52.2-77.8% vs. 87%; 95% CI 83.2-90.8%; hazard ratio 0.52; $p = 0.043$).
CONCLUSIONS: In this study, patients with AIH-PBC outside Paris or Zhang criteria were frequently labeled as having AIH-PBC and were successfully treated with combination therapy with similar outcomes. LT-free survival was worse in patients with PBC and hepatic inflammation than in those treated as having AIH-PBC. More patients may benefit from combination therapy.
IMPACT AND IMPLICATIONS: This study demonstrated that patients with AIH-PBC variant syndrome treated with combined therapy consisting of immunosuppressants and ursodeoxycholic acid often do not fulfill the Paris criteria. They do however have comparable response to therapy and long-term outcomes as patients who do fulfill the diagnostic criteria. Additionally, patients with PBC and additional signs of hepatic inflammation have poorer long-term outcomes compared to patients treated as having AIH-PBC. These results implicate that a larger group of patients with features of both AIH and PBC may benefit from combined treatment. With our results, we call for improved consensus among experts in the field on the diagnosis and management of AIH-PBC variant syndrome.

Gepubliceerd: JHEP Rep. 2024;6(7):101088.
Impact factor: 7.5 ; Q1

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13. Tacrolimus versus mycophenolate for AutoImmune hepatitis patients with incompLete response On first-line therapy (TAILOR study): a study protocol for a phase III, open-label, multicentre, randomised controlled trial

Stoelinga AEC, Tushuizen ME, van den Hout WB, Girondo M, de Vries ES, Levens AD, Moes DAR, Gevers TJG, van der Meer S, Brouwer HT, de Jonge HJM, de Boer YS, Beuers UHW, van der Meer AJ, van den Berg AP, Guichelaar MMJ, Drenth JPH, van Hoek B.

BACKGROUND: Autoimmune hepatitis (AIH) is a rare, chronic inflammatory disease of the liver. The treatment goal is reaching complete biochemical response (CR), defined as the normalisation of aspartate and alanine aminotransferases and immunoglobulin gamma. Ongoing AIH activity can lead to fibrosis and (decompensated) cirrhosis. Incomplete biochemical response is the most important risk factor for liver transplantation or liver-related mortality. First-line treatment consists of a combination of azathioprine and prednisolone. If CR is not reached, tacrolimus (TAC) or mycophenolate mofetil (MMF) can be used as second-line therapy. Both products are registered for the prevention of graft rejection in solid organ transplant recipients. The aim of this study is to compare the effectiveness and safety of TAC and MMF as second-line treatment for AIH.
METHODS: The TAILOR study is a phase IIIB, multicentre, open-label, parallel-group, randomised (1:1) controlled trial performed in large teaching and university hospitals in the Netherlands. We will enrol 86 patients with AIH who have not reached CR after at least 6 months of treatment with first-line therapy. Patients are randomised to TAC (0.07 mg/kg/day initially and adjusted by trough levels) or

MMF (max 2000 mg/day), stratified by the presence of cirrhosis at inclusion. The primary endpoint is the difference in the proportion of patients reaching CR after 12 months. Secondary endpoints include the difference in the proportion of patients reaching CR after 6 months, adverse effects, difference in fibrogenesis, quality of life and cost-effectiveness.
DISCUSSION: This is the first randomised controlled trial comparing two second-line therapies for AIH. Currently, second-line treatment is based on retrospective cohort studies. The rarity of AIH is the main issue in clinical research for alternative treatment options. The results of this trial can be implemented in existing international clinical guidelines.
TRIAL REGISTRATION: ClinicalTrials.gov NCT05221411 . Retrospectively registered on 3 February 2022; EudraCT number 2021-003420-33. Prospectively registered on 16 June 2021.

Gepubliceerd: Trials. 2024;25(1):61.
Impact factor: 2.0 ; Q3

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14. Covered versus bare-metal stenting of the mesenteric arteries in patients with chronic mesenteric ischaemia (CoBaGI): a multicentre, patient-blinded and investigator-blinded, randomised controlled trial

Terlouw LG, van Dijk LJD, van Noord D, Bakker OJ, Bijdevaate DC, Erler NS, Fioole B, Harki J, van den Heuvel DAF, Hinnen JW, Kolkman JJ, Nikkessen S, van Petersen AS, Smits HFM, Verhagen HJM, de Vries AC, de Vries JPM, Vroegindeweij D, Geelkerken RH, Bruno MJ, Moelker A.

BACKGROUND: Mesenteric artery stenting with a bare-metal stent is the current treatment for atherosclerotic chronic mesenteric ischaemia. Long-term patency of bare-metal stents is unsatisfactory due to in-stent intimal hyperplasia. Use of covered stents might improve long-term patency. We aimed to compare the patency of covered stents and bare-metal stents in patients with chronic mesenteric ischaemia.
METHODS: We conducted a multicentre, patient-blinded and investigator-blinded, randomised controlled trial including patients with chronic mesenteric ischaemia undergoing mesenteric artery stenting. Six centres in the Netherlands participated in this study, including two national chronic mesenteric ischaemia expert centres. Patients aged 18 years or older were eligible for inclusion when an endovascular mesenteric artery revascularisation was scheduled and a consensus diagnosis of chronic mesenteric ischaemia was made by a multidisciplinary team of gastroenterologists, interventional radiologists, and vascular surgeons. Exclusion criteria were stenosis length of 25 mm or greater, stenosis caused by median arcuate ligament syndrome or vasculitis, contraindication for CT angiography, or previous target vessel revascularisation. Digital 1:1 block randomisation with block sizes of four or six and stratification by inclusion centre was used to allocate patients to undergo stenting with bare-metal stents or covered stents at the start of the procedure. Patients, physicians performing follow-up, investigators, and radiologists were masked to treatment allocation. Interventionalists performing the procedure were not masked. The primary study outcome was the primary patency of covered stents and bare-metal stents at 24 months of follow-up, evaluated in the modified intention-to-treat population, in which stents with missing data for the outcome were excluded. Loss of primary patency was defined as the performance of a re-intervention to preserve patency, or 75% or greater luminal surface area reduction of the target vessel. CT angiography was performed at 6 months, 12 months, and 24 months post intervention to assess patency. The study is registered with ClinicalTrials.gov (NCT02428582) and is complete.
FINDINGS: Between April 6, 2015, and March 11, 2019, 158 eligible patients underwent mesenteric artery stenting procedures, of whom 94 patients (with 128 stents) provided consent and were included in the study. 47 patients (62 stents) were assigned to the covered stents group (median age 69·0 years [IQR 63·0-76·5], 28 [60%] female) and 47 patients (66 stents) were assigned to the bare-metal stents group (median age 70·0 years [63·5-76·5], 33 [70%] female). At 24 months, the primary patency of covered stents (42 [81%] of 52 stents) was superior to that of bare-metal stents (26 [49%]

of 53; odds ratio [OR] 4·4 [95% CI 1·8-10·5]; p<0·0001). A procedure-related adverse event occurred in 17 (36%) of 47 patients in the covered stents group versus nine (19%) of 47 in the bare-metal stent group (OR 2·4 [95% CI 0·9-6·3]; p=0·065). Most adverse events were related to the access site, including haematoma (five [11%] in the covered stents group vs six [13%] in the bare-metal stents group), pseudoaneurysm (five [11%] vs two [4%]), radial artery thrombosis (one [2%] vs none), and intravascular closure device (none vs one [2%]). Six (13%) patients in the covered stent group versus one (2%) in the bare-metal stent group had procedure-related adverse events not related to the access site, including stent luxation (three [6%] vs none), major bleeding (two (4%) vs none), mesenteric artery perforation (one [2%] vs one [2%]), mesenteric artery dissection (one [2%] vs one [2%]), and death (one [2%] vs none).
INTERPRETATION: The findings of this trial support the use of covered stents for mesenteric artery stenting in patients with chronic mesenteric ischaemia. FUNDING: Atrium Maquet Getinge Group.

Gepubliceerd: Lancet Gastroenterol Hepatol. 2024;9(4):299-309.
Impact factor: 38.6 ; Q1

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15. Corrigendum to 'A mixed-methods study to define Textbook Outcome for the treatment of patients with uncomplicated symptomatic gallstone disease with hospital variation analyses in Dutch trial data' [Volume 25, Issue 9, September 2023, Pages 1000-1010]
Thunnissen FM, Comes DJ, Latenstein CSS, Stommel MWJ, van Laarhoven C, Drenth JPH, Lantinga MA, Atsma F, de Reuver PR, Invited International Collaborators; Venneman NG.

Gepubliceerd: HPB (Oxford). 2024;26(2):321.
Impact factor: 2.4 ; Q1

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16. Intraluminal oxygen can keep small bowel mucosa intact in a segmental ischemia model
Trentadue G, Mensink PBF, Kruse C, Reszel B, Kats-Ugurlu G, Blokzijl T, Haveman JW, Faber KN, Dijkstra G, Hölscher UM, Kolkman JJ, Knichwitz G.

Intestinal preservation for transplantation is accompanied by hypoperfusion with long periods of ischemia with total blood cessation and absolute withdrawal of oxygen leading to structural damage. The application of intraluminal oxygen has been successfully tested in small-animal series during storage and transport of the organ but have been so far clinically unrelatable. In this study, we tested whether a simple and clinically approachable method of intraluminal oxygen application could prevent ischemic damage in a large animal model, during warm ischemia time. We utilised a local no-flow ischemia model of the small intestine in pigs. A low-flow and high-pressure intraluminal oxygen deliverance system was applied in 6 pigs and 6 pigs served as a control group. Mucosal histopathology, hypoxia and barrier markers were evaluated after two hours of no-flow conditions, in both treatment and sham groups, and in healthy tissue. Macro- and microscopically, the luminal oxygen delivered treatment group showed preserved small bowel's appearance, viability, and mucosal integrity. A gradual deterioration of histopathology and barrier markers and increase in hypoxia-inducible factor 1-α expression towards the sites most distant from the oxygen application was observed. Intraluminal low-flow, high oxygen delivery can preserve the intestinal mucosa during total ischemia of the small intestine. This finding can be incorporated in methods to overcome small bowel ischemia and improve intestinal preservation for transplantation.

Gepubliceerd: Sci Rep. 2024;14(1):13732.
Impact factor: 3.9 ; Q1

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17. A Prediction Model for Successful Increase of Adalimumab Dose Intervals in Patients with Crohn's Disease: Secondary Analysis of the Pragmatic Open-Label Randomised Controlled Non-inferiority LADI Trial

van Linschoten RCA, Jansen FM, Pauwels RWM, Smits LJT, Atsma F, Kievit W, de Jong DJ, de Vries AC, Boekema PJ, West RL, Bodelier AGL, Gisbertz IAM, Wolfhagen FHJ, Römkens TEH, Lutgens M, van Bodegraven AA, Oldenburg B, Pierik MJ, Russel M, de Boer NK, Mallant-Hent RC, Ter Borg PCJ, van der Meulen-de Jong AE, Jansen JM, Jansen SV, Tan A, van der Woude CJ, Hoentjen F.

BACKGROUND: In the pragmatic open-label randomised controlled non-inferiority LADI trial we showed that increasing adalimumab (ADA) dose intervals was non-inferior to conventional dosing for persistent flares in patients with Crohn's disease (CD) in clinical and biochemical remission.
AIMS: To develop a prediction model to identify patients who can successfully increase their ADA dose interval based on secondary analysis of trial data.
METHODS: Patients in the intervention group of the LADI trial increased ADA intervals to 3 and then to 4 weeks. The dose interval increase was defined as successful when patients had no persistent flare (> 8 weeks), no intervention-related severe adverse events, no rescue medication use during the study, and were on an increased dose interval while in clinical and biochemical remission at week 48. Prediction models were based on logistic regression with relaxed LASSO. Models were internally validated using bootstrap optimism correction.
RESULTS: We included 109 patients, of which 60.6% successfully increased their dose interval. Patients that were active smokers (odds ratio [OR] 0.90), had previous CD-related intra-abdominal surgeries (OR 0.85), proximal small bowel disease (OR 0.92), an increased Harvey-Bradshaw Index (OR 0.99) or increased faecal calprotectin (OR 0.997) were less likely to successfully increase their dose interval. The model had fair discriminative ability (AUC = 0.63) and net benefit analysis showed that the model could be used to select patients who could increase their dose interval.
CONCLUSION: The final prediction model seems promising to select patients who could successfully increase their ADA dose interval. The model should be validated externally before it may be applied in clinical practice.
CLINICAL TRIAL REGISTRATION NUMBER: ClinicalTrials.gov, number NCT03172377.

Gepubliceerd: Dig Dis Sci. 2024;69(6):2165-74.
Impact factor: 2.5 ; Q2

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18. Long-Term Outcome of Immediate Versus Postponed Intervention in Patients With Infected Necrotizing Pancreatitis (POINTER): Multicenter Randomized Trial

Van Veldhuisen CL, Sissingh NJ, Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bouwense SAW, Bruno MJ, Cappendijk VC, van Duijvendijk P, van Eijck CHJ, Fockens P, van Goor H, Hadithi M, Haveman JW, Jacobs M, Jansen JM, Kop MPM, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Dijkgraaf MGW, Stommel MWJ, Straathof JWA, Venneman NG, Voermans RP, van Hooft JE, van Santvoort HC, Besselink MG.

OBJECTIVE: To compare the long-term outcomes of immediate drainage versus the postponed-drainage approach in patients with infected necrotizing pancreatitis.
BACKGROUND: In the randomized POINTER trial, patients assigned to the postponed-drainage approach using antibiotic treatment required fewer interventions, as compared with immediate drainage, and over a third were treated without any intervention.
METHODS: Clinical data of those patients alive after the initial 6-month follow-up were re-evaluated. The primary outcome was a composite of death and major complications.

RESULTS: Out of 104 patients, 88 were re-evaluated with a median follow-up of 51 months. After the initial 6-month follow-up, the primary outcome occurred in 7 of 47 patients (15%) in the immediate-drainage group and 7 of 41 patients (17%) in the postponed-drainage group (RR 0.87, 95% CI 0.33-2.28; P =0.78). Additional drainage procedures were performed in 7 patients (15%) versus 3 patients (7%) (RR 2.03; 95% CI 0.56-7.37; P =0.34). The median number of additional interventions was 0 (IQR 0-0) in both groups (P =0.028). In the total follow-up, the median number of interventions was higher in the immediate-drainage group than in the postponed-drainage group (4 vs. 1, P =0.001). Eventually, 14 of 15 patients (93%) in the postponed-drainage group who were successfully treated in the initial 6-month follow-up with antibiotics and without any intervention remained without intervention. At the end of follow-up, pancreatic function and quality of life were similar.
CONCLUSIONS: Also, during long-term follow-up, a postponed-drainage approach using antibiotics in patients with infected necrotizing pancreatitis results in fewer interventions as compared with immediate drainage and should therefore be the preferred approach.
TRIAL REGISTRATION: ISRCTN33682933.

Gepubliceerd: Ann Surg. 2024;279(4):671-8.
Impact factor: 6.4 ; Q1

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19. Randomised clinical trial: First-line infliximab biosimilar is cost-effective compared to conventional treatment in paediatric Crohn's disease
Vuijk SA, Jongsma MME, Hoeven BM, Cozijnsen MA, van Pieterson M, de Meij TGJ, Norbruis OF, Groeneweg M, Wolters VM, van Wering H, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg S, Rizopoulos D, Poley MJ, Escher JC, de Ridder L.

BACKGROUND: Data on cost-effectiveness of first-line infliximab in paediatric patients with Crohn's disease are limited. Since biologics are increasingly prescribed and accompanied by high costs, this knowledge gap needs to be addressed.
AIM: To investigate the cost-effectiveness of first-line infliximab compared to conventional treatment in children with moderate-to-severe Crohn's disease.
METHODS: We included patients from the Top-down Infliximab Study in Kids with Crohn's disease randomised controlled trial. Children with newly diagnosed moderate-to-severe Crohn's disease were treated with azathioprine maintenance and either five induction infliximab (biosimilar) infusions or conventional induction treatment (exclusive enteral nutrition or corticosteroids). Direct healthcare consumption and costs were obtained per patient until week 104. This included data on outpatient hospital visits, hospital admissions, drug costs, endoscopies and surgeries. The primary health outcome was the odds ratio of being in clinical remission (weighted paediatric Crohn's disease activity index<12.5) during 104 weeks.
RESULTS: We included 89 patients (44 in the first-line infliximab group and 45 in the conventional treatment group). Mean direct healthcare costs per patient were €36,784 for first-line infliximab treatment and €36,874 for conventional treatment over 2 years (p = 0.981). The odds ratio of first-line infliximab versus conventional treatment to be in clinical remission over 104 weeks was 1.56 (95%CI 1.03-2.35, p = 0.036).
CONCLUSIONS: First-line infliximab treatment resulted in higher odds of being in clinical remission without being more expensive, making it the dominant strategy over conventional treatment in the first 2 years after diagnosis in children with moderate-to-severe Crohn's disease.
TRIAL REGISTRATION NUMBER: NCT02517684.

Gepubliceerd: Aliment Pharmacol Ther. 2024;59(12):1510-20.
Impact factor: 6.7 ; Q1

Totale impact factor: 300.1
Gemiddelde impact factor: 15.8

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.9
Gemiddelde impact factor: 3.9

Medical School Twente

1. The effect of dexamethasone on the incidence of delirium in patients hospitalized due COVID-19 infection: a retrospective cohort study
Boersma MN, Kamperman E, van der Palen J.

PURPOSE: Delirium has been suggested to be a complication associated with corticosteroid use. Therefore, the association between dexamethasone use and delirium in COVID-19 patients was studied herein.
METHODS: In this single-center retrospective cohort study, 412 patients who were hospitalized because of COVID-19 between March 2020 and January 2021 were included. Delirium was diagnosed using the Delirium Observation Screening Scale. The association between the daily use of dexamethasone 6 mg and delirium was measured via multivariable logistic regression analysis.
RESULTS: The incidence of delirium was 11.4% in patients treated with dexamethasone (n = 245) and 9.6% in patients not treated with dexamethasone (n = 167) (RR 1.19, CI 0.67-2.13, p = 0.55). After adjusting for age (mean 69 years) and comorbidity score, the odds ratio for developing delirium when using dexamethasone was 1.11 (CI 0.56-2.21, p = 0.76).
CONCLUSION: The use of dexamethasone in hospitalized COVID-19 patients did not affect the incidence of delirium.

Gepubliceerd: Eur Geriatr Med. 2024;15(4):971-5.
Impact factor: 3.6 ; Q2

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2. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms
Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group; Brusse-Keizer M, Haalboom M, van der Palen J.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

Gepubliceerd: Heliyon. 2024;10(10):e29591.
Impact factor: 3.6 ; Q1

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3. Adherence to single inhaler triple therapy and digital inhalers in Chronic Obstructive Pulmonary Disease: a literature review and protocol for a randomized controlled trial (TRICOLON study)
Cuperus LJA, van der Palen J, Aldenkamp A, van Huisstede A, Bischoff E, van Boven JFM, Brijker F, Dik S, van Excel J, Goosens M, van Hal PTW, Kuijvenhoven JC, Kunz LIZ, Vasbinder EC, Kerstjens HAM, In 't Veen J.

BACKGROUND: Medication non-adherence is a significant problem in patients with Chronic Obstructive Pulmonary Disease (COPD). Efforts to address this issue are receiving increased attention. Simplifying treatment by prescribing single-inhaler triple therapy (SITT) as an alternative to multi-inhaler triple therapy (MITT) or with smart inhalers are often considered potential solutions. However, the actual impact of these innovations on adherence and clinical outcomes is unclear.
METHODS: To address this knowledge gap we first conducted a literature review focusing on two research questions: 1) the difference in adherence between SITT and MITT users in COPD, and 2) the effect of smart inhalers on adherence in COPD. Separate searches were conducted in PubMed and two authors independently assessed the articles. In addition, we present a protocol for a study to acquire knowledge for the gaps identified.
RESULTS: To address the first research question, 8 trials were selected for further review. All trials were observational, i.e. randomized controlled trials were lacking. Seven of these trials showed higher adherence and/or persistence in patients on SITT compared with patients on MITT. In addition, four studies showed a positive effect of SITT on various clinical outcomes. For the second research question, 11 trials were selected for review. While most of the studies showed a positive effect of smart inhalers on adherence, there was considerable variation in the results regarding their effect on other clinical outcomes. The TRICOLON (TRIple therapy COnvenience by the use of one or multipLe Inhalers and digital support in ChrONic Obstructive Pulmonary Disease) trial aims to improve understanding regarding the effectiveness of SITT and smart inhalers in enhancing adherence. This open-label, randomized, multi-center study will enroll COPD patients requiring triple therapy at ten participating hospitals. In total, 300 patients will be randomized into three groups: 1) MITT; 2) SITT; 3) SITT with digital support through a smart inhaler and an e-health platform. The follow-up period will be one year, during which three methods of measuring adherence will be used: smart inhaler data, self-reported data using the Test of Adherence to Inhalers (TAI) questionnaire, and drug analysis in scalp hair samples. Finally, differences in clinical outcomes between the study groups will be compared.
DISCUSSION: Our review suggests promising results concerning the effect of SITT, as opposed to MITT, and smart inhalers on adherence. However, the quality of evidence is limited due to the absence of randomized controlled trials and/or the short duration of follow-up in many studies. Moreover, its impact on clinical outcomes shows considerable variation. The TRICOLON trial aims to provide solid data on these frequently mentioned solutions to non-adherence in COPD. Collecting data in a well-designed randomized controlled trial is challenging, but the design of this trial addresses both the usefulness of SITT and smart inhalers while ensuring minimal interference in participants' daily lives.
TRIAL REGISTRATION: NCT05495698 (Clinicaltrials.gov), registered at 08-08-2022. Protocol version: version 5, date 27-02-2023.

Gepubliceerd: BMC Pulm Med. 2024;24(1):317.
Impact factor: 2.8 ; Q2

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4. The effect of enhanced recovery after surgery (ERAS) in renal surgery
Elferink SEM, Bretveld R, Kwast ABG, Asselman M, Essink JGJ, Potters JW, van der Palen J.

OBJECTIVE: To study the effect of ERAS on a textbook outcome (TO) after elective renal surgery.
PATIENTS AND METHODS: Retrospective study of all patients who underwent a robot-assisted laparoscopic partial or radical nephrectomy or robot-assisted laparoscopic radical nephroureterectomy in Medisch Spectrum Twente (MST), Enschede, the Netherlands. In total, 277 patients were included. 66 patients from 2018 to 2021 (pre-ERAS group) and 211 patients from 2021 to 2023 (ERAS group). TO is a maximum of two nights in the hospital after surgery, no severe complications during or after surgery ≥ grade IIIb, no blood transfusions, no intensive care, no readmissions, and no mortality within 30 days after surgery. Comparisons were made between the pre-ERAS and ERAS groups using unpaired t-test, Mann-Whitney U test, the chi-squared test or Fisher's exact test. Multivariate logistic regression was used to adjust for possible confounding.
RESULTS: TO was significantly (p = 0.005) better in the ERAS group (TO = 76.8%) compared to the pre-ERAS group (TO = 59.1%). Compared to a pre-ERAS patient, the adjusted odds ratio for achieving a TO as an ERAS patient is 2.1 (95% CI 1.15-3.78).
CONCLUSIONS: The implementation of ERAS showed a positive effect on the TO of elective renal surgery patients.

Gepubliceerd: World J Urol. 2024;42(1):490.
Impact factor: 2.9 ; Q2

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5. Contrasting results in sacroiliac joint fusion studies: the role of bilateral complaints
Kampkuiper N, Schröder F, Brusse-Keizer M, Nellensteijn J.

Gepubliceerd: EClinicalMedicine. 2024;79:102978.
Impact factor: 10.0 ; Q1

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6. Effect of Physical Exercise on MRI-Assessed Brain Perfusion in Chemotherapy-Treated Breast Cancer Patients: A Randomized Controlled Trial
Koevoets EW, Petr J, Monninkhof EM, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, van der Palen J, Mutsaerts H, de Ruiter MB, May AM, Schagen SB.

BACKGROUND: Exercise is a promising intervention to alleviate cognitive problems in breast cancer patients, but studies on mechanisms underlying these effects are lacking.
PURPOSE: Investigating whether an exercise intervention can affect cerebral blood flow (CBF) in cognitively impaired breast cancer patients and to determine if CBF changes relate to memory function.
STUDY TYPE: Prospective.
POPULATION: A total of 181 chemotherapy-treated stage I-III breast cancer patients with cognitive problems and relatively low physical activity levels (≤150 minutes moderate to vigorous physical activity per week), divided into an exercise (N = 91) or control group (N = 90).
FIELD STRENGTH/SEQUENCE: Two-dimensional echo planar pseudo-continuous arterial spin labeling CBF sequence at 3 T.
ASSESSMENT: The 6-month long intervention consisted of (supervised) aerobic and strength training, 4 × 1 hour/week. Measurements at baseline (2-4 years post-diagnosis) and after 6 months included gray matter CBF in the whole brain, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. Physical fitness and memory function were also assessed. Subgroup analyses were performed in patients with high fatigue levels at baseline.
STATISTICAL TESTS: Multiple regression analyses with a two-sided alpha of 0.05 for all analyses.
RESULTS: There was a significant improvement in physical fitness (VO(2peak) in mL/minute/kg) in the intervention group (N = 53) compared to controls (N = 51, β = 1.47 mL/minute/kg, 95% CI: 0.44-2.50).

However, no intervention effects on CBF were found (eg, whole brain: P = 0.565). Highly fatigued patients showed larger but insignificant treatment effects on CBF (eg, whole brain: P = 0.098). Additionally, irrespective of group, a change in physical fitness was positively associated with changes in CBF (eg, whole brain: β = 0.75, 95% CI: 0.07-1.43). There was no significant relation between CBF changes and changes in memory performance.
DATA CONCLUSION: The exercise intervention did not affect CBF of cognitively affected breast cancer patients. A change in physical fitness was associated with changes in CBF, but changes in CBF were not associated with memory functioning.
LEVEL OF EVIDENCE: 1
TECHNICAL EFFICACY STAGE: 5.

Gepubliceerd: J Magn Reson Imaging. 2024;59(5):1667-80.
Impact factor: 3.5 ; Q1

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7. Verpleegkundigen en het leefstijlgesprek: beïnvloedende factoren en methoden
Kroeze W, van Hogen-Koster S.

Er is steeds meer aandacht voor leefstijl in de zorg en er is een toename van beschikbare effectieve methodieken voor gedragsverandering. Desondanks is de implementatie van leefstijlinterventies complex en ingewikkeld, waardoor leefstijl nog geen integraal onderdeel van de reguliere zorg is. Verpleegkundigen hebben een belangrijke rol bij het bevorderen van een gezonde leefstijl. Verpleegkundigen ervaren echter barrières om leefstijl te integreren in de dagelijkse zorg. Tijd, onvoldoende kennis en middelen en weerstand bij de patiënt spelen hierin een centrale rol. Dit artikel laat een aantal eenvoudig toe te passen methodieken voor gedragsverandering zien, waarmee verpleegkundigen en mogelijk ook andere zorgprofessionals aan de slag kunnen gaan. Van belang is om aan te sluiten bij de wensen en behoeften van de patiënt, zoals vanuit de benadering van Positieve Gezondheid, om de eigen regie en intrinsieke motivatie te vergroten. Op deze manier hopen we een bijdrage te leveren aan het versterken van de implementatie van leefstijl in de zorg, aansluitend bij de Coalitie Leefstijl in de Zorg.

Gepubliceerd: Ned Tijdschr Geneeskd. 2024;2(3):120-6.
IF onbekend

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8. A Critical Appraisal of the Whack-a-Mole and Swivel Chair Signs in the Diagnosis of Functional Movement Disorders
Lagrand TJ, Brusse-Keizer M, Charmley A, Edwards MJ, Tijssen MAJ, Lehn AC.

BACKGROUND: The demonstration of positive signs during neurological examination is a cornerstone of the diagnosis of functional movement disorders, however, the available data supporting the diagnostic value of some of these signs is limited.
OBJECTIVES: To determine the diagnostic value (sensitivity and specificity) of the "whack-a-mole" (WAM) and "swivel chair" (SC) tests in patients with functional movement disorders (FMD).
METHODS: We enrolled patients with functional and organic movements in the WAM test if they exhibited tremor, dystonia, myoclonus, chorea, or tics. For the SC test, patients with a gait disorder as their primary impairment were recruited. Two blinded movement disorder specialists rated the presence of these signs in edited videos.
RESULTS: Inclusion criteria were met by 42 patients with FMD and 65 patients with organic movement disorders. Both tests demonstrated high specificity (means, 78% and 96%), but their sensitivity was low (means, 52% and 37%). Interobserver agreement for the WAM sign was 0.77 in

the FMD group, against 0.28 in patients with organic movement disorders, whereas Movement Disorders Clinical Practice for Review Only for the SC sign was 0.69 in both groups. CONCLUSIONS: The present study indicates that physicians must be cautious in the application and interpretation of these clinical signs in the diagnosis of functional movement disorders, and they should be carefully considered and used as necessary.

Gepubliceerd: Mov Disord Clin Pract. 2024;11(1):63-8.
Impact factor: 2.7 ; Q2

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9. Potential for personalised and biomarker-guided COPD self-treatment approaches
Lenferink A, Citgez E, van der Valk P, van der Palen J, Effing TW, Brusse-Keizer MGJ.

Gepubliceerd: Lancet Respir Med. 2024;12(8):e48-e9.
Impact factor: 32.8 ; Q1

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10. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; Brusse-Keizer M, Haalboom M, van der Palen J.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

Gepubliceerd: Sci Rep. 2024;14(1):16387.
Impact factor: 3.9 ; Q1

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11. Ghrelin for Neuroprotection in Post-Cardiac Arrest Coma: A Randomized Clinical Trial
Nutma S, Beishuizen A, van den Bergh WM, Foudraine NA, le Feber J, Filius PMG, Cornet AD, van der Palen J, van Putten M, Hofmeijer J.

IMPORTANCE: Out-of-hospital cardiac arrest survival rates have markedly risen in the last decades, but neurological outcome only improved marginally. Despite research on more than 20 neuroprotective strategies involving patients in comas after cardiac arrest, none have demonstrated unequivocal evidence of efficacy; however, treatment with acyl-ghrelin has shown improved functional and histological brain recovery in experimental models of cardiac arrest and was safe in a wide variety of human study populations.
OBJECTIVE: To determine safety and potential efficacy of intravenous acyl-ghrelin to improve neurological outcome in patients in a coma after cardiac arrest.
DESIGN, SETTING, AND PARTICIPANTS: A phase 2, double-blind, placebo-controlled, multicenter, randomized clinical trial, Ghrelin Treatment of Comatose Patients After Cardiac Arrest: A Clinical Trial to Promote Cerebral Recovery (GRECO), was conducted between January 18, 2019, and October 17, 2022. Adult patients 18 years or older who were in a comatose state after cardiac arrest were assessed for eligibility; patients were from 3 intensive care units in the Netherlands. Expected death within 48 hours or unfeasibility of treatment initiation within 12 hours were exclusion criteria.
INTERVENTIONS: Patients were randomized to receive intravenous acyl-ghrelin, 600 µg (intervention group), or placebo (control group) within 12 hours after cardiac arrest, continued for 7 days, twice daily, in addition to standard care.
MAIN OUTCOMES AND MEASURES: Primary outcome was the score on the Cerebral Performance Categories (CPC) scale at 6 months. Safety outcomes included any serious adverse events. Secondary outcomes were mortality and neuron-specific enolase (NSE) levels on days 1 and 3. RESULTS: A total of 783 adult patients in a coma after cardiac arrest were assessed for eligibility, and 160 patients (median [IQR] age, 68 [57-75] years; 120 male [75%]) were enrolled. A total of 81 patients (51%) were assigned to the intervention group, and 79 (49%) were assigned to the control group. The common odds ratio (OR) for any CPC improvement in the intervention group was 1.78 (95% CI, 0.98-3.22; P = .06). This was consistent over all CPC categories. Mean (SD) NSE levels on day 1 after cardiac arrest were significantly lower in the intervention group (34 [6] µg/L vs 56 [13] µg/L; P = .04) and on day 3 (28 [6] µg/L vs 52 [14] µg/L; P = .08). Serious adverse events were comparable in incidence and type between the groups. Mortality was 37% (30 of 81) in the intervention group vs 51% (40 of 79) in the control group (absolute risk reduction, 14%; 95% CI, -2% to 29%; P = .08).
CONCLUSIONS AND RELEVANCE: In patients in a coma after cardiac arrest, intravenous treatment with acyl-ghrelin was safe and potentially effective to improve neurological outcome. Phase 3 trials are needed for conclusive evidence.
TRIAL REGISTRATION: Clinicaltrialsregister.eu: EUCTR2018-000005-23-NL.

Gepubliceerd: JAMA Neurol. 2024;81(6):603-10.
Impact factor: 21.4 ; Q1

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12. Structured medication reviews in Parkinson's disease: pharmacists' views, experiences and needs - a qualitative study
Oonk NGM, Dorresteijn LDA, Te Braake E, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Bode C.

BACKGROUND: Executing structured medication reviews (SMRs) in primary care to optimize drug treatment is considered standard care of community pharmacists in the Netherlands. Patients with Parkinson's disease (PD) often face complex drug regimens for their symptomatic treatment and might, therefore, benefit from an SMR. However, previously, no effect of an SMR on quality of life in PD was found. In trying to improve the case management of PD, it is interesting to understand if and

to what extent SMRs in PD patients are of added value in the pharmacist's opinion and what are assumed facilitating and hindering factors.
OBJECTIVES: To analyse the process of executing SMRs in PD patients from a community pharmacist's point of view.
DESIGN: A cross-sectional, qualitative study was performed, consisting of face-to-face semi-structured in-depth interviews.
METHODS: The interviews were conducted with community pharmacists who executed at least one SMR in PD, till data saturation was reached. Interviews were transcribed verbatim, coded and analysed thematically using an iterative approach.
RESULTS: Thirteen pharmacists were interviewed. SMRs in PD were considered of added value, especially regarding patient contact and bonding, individualized care and its possible effect in the future, although PD treatment is found already well monitored in secondary care. Major constraints were time, logistics and collaboration with medical specialists.
CONCLUSION: Although community pharmacist-led SMRs are time-consuming and sometimes logistically challenging, they are of added value in primary care in general, and also in PD, of which treatment occurs mainly in secondary care. It emphasizes the pharmacist's role in PD treatment and might tackle future drug-related issues. Improvements concern multidisciplinary collaboration for optimized SMR execution and results.

Gepubliceerd: Ther Adv Drug Saf. 2024;15:20420986241237071.
Impact factor: 3.4 ; Q2

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13. Transforming Healthcare: Integrating Positive Health Principles for Enhanced Wellbeing and Lifestyle Change
van Hogen-Koster S.

AIM: To provide insight into the importance of nursing and para medical competencies to act from Positive Health in order to contribute to greater health well-being and a healthier lifestyle for patients
DESIGN: This position paper will describe the aim the first results and the coming focus of the professorship of Positive Health Lifestyle and leadership
METHODS: We used several methods like depth interviews and focus groups with about 30 patients most cardiology and rheumatology and about 30 professionals most nurses and para medics incardiology and rheumatology and a cardiologicpatient journey to determine what is necessary for nurses and para medics to act from Positive Health. All studies were approved by the Institutional Review Board and the attributes benefits and uses of the studies were explained to all participants and informed consent was obtained
RESULTS: There is still too little attention for lifestyle and hardly for sustainable behavioural change Communication and leadership competencies and multidisciplinary collaboration are essential in this
CONCLUSION: Applying Positive Health requires a transformation of the healthcare system and the healthcare professionals themselves. More knowledge is needed about the competencies of nurses and para medics to act from Positive Health Implications for the Profession and or Patient Care. A toolbox of tools will be created based on practice-oriented research with ways to increase the competencies of healthcare professionals and to act more from Positive Health. By encouraging healthcare professionals to think and act differently based on Positive Health we hope to promote patients self-management and intrinsic motivation and thus contribute to a healthier lifestyle
IMPACT: An unhealthy lifestyle can lead to various diseases. A positive lifestyle change can lead to the prevention reduction or even disappearance of the disease. It is important that nurses and para medics pay attention to lifestyle from a broad view of health such as Positive Health. In the professorship we develop tools to increase the competencies of nurses and paramedics to act more from Positive Health and integrate lifestyle into daily care and treatment. And so towards greater health well-being and a healthier lifestyle.

Gepubliceerd: Global Journal of Medical Research. 2024;24(k2):1-6.
IF onbekend

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14. Affect and post-COVID-19 symptoms in daily life: An exploratory experience sampling study
Schaap G, Wensink M, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

Insight into the daily life experiences of patients with post-COVID-19 syndrome is lacking. The current study explored temporal fluctuations of and associations between positive and negative affect and symptoms throughout the day in previously hospitalised post-COVID-19 patients using an experience sampling methodology. Ten participants (age: median = 60, interquartile range = 9 years; 50% women; 80% ≥1 comorbidity; 8-12 months since hospital discharge) filled out brief online questionnaires, six times a day for 14 consecutive days. Positive and negative affect, and self-reported symptoms (physical and mental fatigue, cognitive functioning, dyspnoea, and pain) were assessed in real-time. Primarily, graphs were analysed to assess the individual longitudinal courses of and (concurrent and time-lagged) associations between affect and symptoms. Secondly, correlations or multilevel linear regression models were used to support these interpretations. Visual assessment showed limited temporal fluctuation in affect and symptoms. All symptoms appeared to associate positively with each other (correlations between .26 and .85). Positive affect was associated with lower symptoms severity (β's between -.28 and -.67), and negative affect with higher symptoms severity (β's between .24 and .66). Time-lagged analyses showed that-adjusted for residual symptom severity of prior measurements-both types of affect predicted symptom severity two hours later (β's between -.09 and -.31 for positive affect; between .09 and .28 for negative affect). These findings suggest that positive and negative affect may play important roles in post-COVID-19 symptom experience and temporal fluctuation.

Gepubliceerd: PLoS One. 2024;19(10):e0295217.
Impact factor: 2.6 ; Q2

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15. Does adherence to exacerbation action plans matter? Insights from two COPD self-management studies
Schrijver J, Effing T, van Helden J, van der Palen J, van der Valk P, Brusse-Keizer M, Lenferink A.

INTRODUCTION: Patients' adherence is essential for COPD self-management, as beneficial effects can only be expected in adherent patients. We explored associations between patients' adherence to COPD exacerbation action plans and health outcomes.
MATERIALS AND METHODS: Pooled COPD self-treatment intervention group data from two RCTs were analysed, only including patients who had ≥1 COPD exacerbation or started ≥1 course of oral corticosteroids over one-year follow-up. Optimal adherence was defined as 'self-treatment initiated ≤1 day before or after exacerbation start', suboptimal adherence as 'self-treatment initiated 2 days before or after exacerbation start or no self-treatment initiated for a short (1-3 days) exacerbation', and significant delay or no treatment as 'self-treatment initiated >2 days after exacerbation start or no self-treatment initiated for a longer (>3 days) exacerbation'. Regression models were built for several health outcomes, with the number of COPD exacerbation days/patient/year being the primary outcome.
RESULTS: Patients with significant delay or no treatment (n = 46) had more exacerbation days/patient/year (33.3 (95 % CI 10.9; 55.6)) than optimal adherent patients (n = 38) (23.7 (95 % CI 1.7; 45.7)). The duration per COPD exacerbation was longer for patients with significant delay or no

treatment (15.5 days) compared to optimal adherent patients (7.8 days). No differences in health outcomes were observed between optimal and suboptimal adherent patients.
CONCLUSIONS: Being adherent to action plans is associated with better health outcomes than significant delayed treatment or no treatment at all. Interestingly, suboptimal adherence demonstrated health benefits comparable to optimal adherence. COPD self-management interventions should prioritise strategies to optimise patients' adherence to action plans.

Gepubliceerd: Heliyon. 2024;10(20):e39070.
Impact factor: 3.6 ; Q1

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16. An alternative treatment for degenerative triangular fibrocartilage complex injuries with distal radioulnar joint instability: first experience with 48 patients
Shaer SA, van der Palen J, Teunissen J, Fink A, van der Heijden B, Zöphel O.

Treatment of ulnar impaction syndrome combined with distal radioulnar joint instability due to irreparable degenerative triangular fibrocartilage complex injuries can be complex. We describe the outcomes of a novel technique for restoring distal radioulnar stability due to ulnar impaction syndrome using a distally based extensor carpi ulnaris tendon strip combined with ulnar shortening osteotomy in 48 patients. Patients were assessed using standardized outcome measurements. The patient-rated wrist/hand evaluation total score improved from 66 (SD 15) at intake to 40 (SD 25) at 3 months, and 28 (SD 23) at 12 months postoperatively ($p < 0.001$). Wrist extension and flexion improved significantly at 12 months from 53° (SD 11) to 65° (SD 8) ($p < 0.001$) and from 45° (SD 10) to 56° (SD 12) ($p = 0.01$), respectively. Adding a distally based longitudinal extensor carpi ulnaris strip to ulnar shortening osteotomy for restoring distal radioulnar joint stability seems to be an effective treatment in patients with irreparable degenerative triangular fibrocartilage complex injuries due to ulnar impaction syndrome. Level of evidence: IV.

Gepubliceerd: J Hand Surg Eur Vol. 2024;49(2):240-9.
Impact factor: 1.7 ; Q2

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17. Comparing the Effectiveness of the Blended Delivery Mode With the Face-to-Face Delivery Mode of Smoking Cessation Treatment: Noninferiority Randomized Controlled Trial
Siemer L, Pieterse ME, Ben Allouch S, Postel MG, Brusse-Keizer MGJ.

BACKGROUND: Tobacco consumption is a leading cause of death and disease, killing >8 million people each year. Smoking cessation significantly reduces the risk of developing smoking-related diseases. Although combined treatment for addiction is promising, evidence of its effectiveness is still emerging. Currently, there is no published research comparing the effectiveness of blended smoking cessation treatments (BSCTs) with face-to-face (F2F) treatments, where web-based components replace 50% of the F2F components in blended treatment.
OBJECTIVE: The primary objective of this 2-arm noninferiority randomized controlled trial was to determine whether a BSCT is noninferior to an F2F treatment with identical ingredients in achieving abstinence rates.
METHODS: This study included 344 individuals who smoke (at least 1 cigarette per day) attending an outpatient smoking cessation clinic in the Netherlands. The participants received either a blended 50% F2F and 50% web-based BSCT or only F2F treatment with similar content and intensity. The primary outcome measure was cotinine-validated abstinence rates from all smoking products at 3 and 15 months after treatment initiation. Additional measures included carbon monoxide-validated

point prevalence abstinence; self-reported point prevalence abstinence; and self-reported continuous abstinence rates at 3, 6, 9, and 15 months after treatment initiation.
RESULTS: None of the 13 outcomes showed statistically confirmed noninferiority of the BSCT, whereas 4 outcomes showed significantly (P<.001) inferior abstinence rates of the BSCT: cotinine-validated point prevalence abstinence rate at 3 months (difference 12.7, 95% CI 6.2-19.4), self-reported point prevalence abstinence rate at 6 months (difference 19.3, 95% CI 11.5-27.0) and at 15 months (difference 11.7, 95% CI 5.8-17.9), and self-reported continuous abstinence rate at 6 months (difference 13.8, 95% CI 6.8-20.8). The remaining 9 outcomes, including the cotinine-validated point prevalence abstinence rate at 15 months, were inconclusive.
CONCLUSIONS: In this high-intensity outpatient smoking cessation trial, the blended mode was predominantly less effective than the traditional F2F mode. The results contradict the widely assumed potential benefits of blended treatment and suggest that further research is needed to identify the critical factors in the design of blended interventions.
TRIAL REGISTRATION: Netherlands Trial Register 27150; https://onderzoekmetmensen.nl/nl/trial/27150.
INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): RR2-doi.org/10.1186/s12889-016-3851-x.

Gepubliceerd: J Med Internet Res. 2024;26:e47040.
Impact factor: 6.0 ; Q1

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18. A randomized crossover study assessing critical errors, preferences, and ease of use of two multidose powder inhalers
Tinke P, van Beurden W, Goosens M, van der Palen J.

BACKGROUND: The effectiveness of inhaled medications in asthma and COPD is significantly impacted by inhalation errors. Feedback mechanisms, built into the design of the inhaler might reduce the number of critical errors. This study compares critical errors, preferences, and ease of use of two dry powder inhalers, the Nexthaler, and the Turbuhaler.
RESEARCH DESIGN AND METHODS: In this multi-center, prospective, randomized, open-label, cross-over study, the proportions of asthma and COPD patients making critical errors were compared between the Nexthaler and Turbuhaler after 4 weeks of clinical use, after having been trained for the correct use of both inhalers.
RESULTS: Ninety and 49 patients with asthma and COPD, respectively, were assessed. No significant difference was found in the number of critical errors between the two inhalers (3 with Nexthaler and 5 with Turbuhaler). However, more patients preferred the Nexthaler (57.6%) over the Turbuhaler (34.5%) (p = 0.006), while 7.9% stated no preference.
CONCLUSIONS: The study found no significant differences in critical error rate between the Nexthaler and Turbuhaler but the Nexthaler was preferred over the Turbuhaler. This study highlights the importance of dedicating sufficient time to instructing patients on the correct inhalation technique, which can lead to long-term retention of the inhalation technique.
We compared two inhalers on critical use errors, 4 weeks after a thorough instruction, and asked for a preference for either inhaler. No difference in error rate was observed, but the Nexthaler was preferred over the Turbuhaler.

Gepubliceerd: Expert Opin Drug Deliv. 2024;21(12):1889-96.
Impact factor: 5.4 ; Q1

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19. Instability Severity Index Score predicts recurrent shoulder instability after arthroscopic Bankart repair
van Blommestein MYH, Govaert LHM, van der Palen J, Verra WC, Koorevaar RCT, Schröder FF, Veen EJD.

PURPOSE: The Instability Severity Index (ISI) Score was developed to preoperatively assess the risk of recurrent shoulder instability after an arthroscopic Bankart repair. This study aims to validate the use of ISI Score for predicting the risk of recurrence after an arthroscopic Bankart repair in a heterogeneous population and proposes an appropriate cut-off point for treating patients with an arthroscopic Bankart repair or otherwise.
METHODS: This study analysed 99 shoulders after a traumatic dislocation that underwent arthroscopic Bankart repair with at least 3 years follow-up. Patients were divided into subcategories based on their respective ISI Score. Recurrence includes either a postoperative dislocation or perceived instability.
RESULTS: The overall recurrence rate was found to be 26.3%. A significant correlation was identified between ISI Score and the recurrence rate (odds ratio [OR]: 1.545, 95% confidence interval [CI]: 1.231-1.939, $p < 0.001$). Furthermore, ISI Score 4-6 (OR: 4.498, 95% CI: 1.866-10.842, $p < 0.001$) and ISI Score > 6 (OR: 7.076, 95% CI: 2.393-20.924, $p < 0.001$) both had a significantly higher risk of recurrence compared to ISI Score 0-3. In ISI Score subcategories 0-3, 4-6 and >6, the recurrence rate was, respectively, 15.4%, 40.7% and 71.4%.
CONCLUSION: ISI Score has predictive value in determining the recurrence risk of shoulder instability following an arthroscopic Bankart repair in a heterogeneous population. Based on the findings of this study, we recommend using arthroscopic Bankart repair in patients with ISI Score 0-3. Clinical and shared decision-making are essential in the group with ISI Score 4-6, since the recurrence rate is significantly higher than in patients with ISI Score 0-3. Arthroscopic Bankart repair is not suitable for patients with ISI Score > 6.
LEVEL OF EVIDENCE: Level III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2024;32(8):2152-60.
Impact factor: 5.0 ; Q1

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20. Routine transthoracic echocardiography in ischaemic stroke or transient ischaemic attack of undetermined cause: a prospective multicentre study
van der Maten G, Meijs MFL, Timmer JR, Brouwers P, von Birgelen C, Coutinho JM, Bouma BJ, Kerkhoff H, Helming AM, van Tuijl JH, van der Meer NA, Saxena R, Ebink C, van der Palen J, den Hertog HM.

BACKGROUND: Guidelines recommend routine transthoracic echocardiography (TTE) after ischaemic stroke or transient ischaemic attack of undetermined cause; yet, only limited scientific evidence exists. Therefore, we aimed to determine in these patients the prevalence of TTE-detected major cardiac sources of embolism (CSE), which are abnormalities leading to therapeutic changes.
METHODS: Six Dutch hospitals conducted a prospective observational study that enrolled patients with ischaemic stroke or transient ischaemic attack of undetermined cause. Patients underwent TTE after comprehensive diagnostic evaluation on stroke units, including blood chemistry, 12-lead electrocardiogram (ECG), ≥ 24 h continuous ECG monitoring, brain imaging and cervical artery imaging. Primary outcome measure was the proportion of patients with TTE-detected major CSE.
RESULTS: From March 2018 to October 2020, 1084 patients, aged 66.6 ± 12.5 years, were enrolled; 456 (42.1%) patients were female and 869 (80.2%) had ischaemic stroke. TTE detected major CSE in only 11 (1.0%) patients. Ten (90.9%) of these patients also had major ECG abnormalities (previous infarction, major repolarisation abnormalities, or previously unknown left bundle branch block) that would have warranted TTE assessment regardless of stroke evaluation. Such ECG abnormalities were

present in 11.1% of the total study population. A single patient (0.1%) showed a major CSE despite having no ECG abnormality.
CONCLUSIONS: This multicentre cross-sectional study in patients who-after workup on contemporary stroke units-were diagnosed with ischaemic stroke or transient ischaemic attack of undetermined cause found TTE-detected major CSE in only 1% of all patients. Most of these patients also had major ECG abnormalities. These findings question the value of routine TTE assessment in this clinical setting.

Gepubliceerd: Neth Heart J. 2024;32(2):91-8.
Impact factor: 2.0 ; Q3

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21. Lack of Evidence Regarding Markers Identifying Acute Heart Failure in Patients with COPD: An AI-Supported Systematic Review
van Dijk SHB, Brusse-Keizer MGJ, Bucsán CC, Ploumen EH, van Beurden WJC, van der Palen J, Doggen CJM, Lenferink A.

BACKGROUND: Due to shared symptoms, acute heart failure (AHF) is difficult to differentiate from an acute exacerbation of COPD (AECOPD). This systematic review aimed to identify markers that can diagnose AHF underlying acute dyspnea in patients with COPD presenting at the hospital.
METHODS: All types of observational studies and clinical trials that investigated any marker's ability to diagnose AHF in acutely dyspneic COPD patients were considered eligible for inclusion. An AI tool (ASReview) supported the title and abstract screening of the articles obtained from PubMed, Scopus, Web of Science, the Cochrane Library, Embase, and CINAHL until April 2023. Full text screening was independently performed by two reviewers. Twenty percent of the data extraction was checked by a second reviewer and the risk of bias was assessed in duplicate using the QUADAS-2 tool. Markers' discriminative abilities were evaluated in terms of sensitivity, specificity, positive and negative predictive values, and the area under the curve when available.
RESULTS: The search identified 10,366 articles. After deduplication, title and abstract screening was performed on 5,386 articles, leaving 153 relevant, of which 82 could be screened full text. Ten distinct studies (reported in 16 articles) were included, of which 9 had a high risk of bias. Overall, these studies evaluated 12 distinct laboratory and 7 non-laboratory markers. BNP, NT-proBNP, MR-proANP, and inspiratory inferior vena cava diameter showed the highest diagnostic discrimination.
CONCLUSION: There is not much evidence for the use of markers to diagnose AHF in acutely dyspneic COPD patients in the hospital setting. BNPs seem most promising, but should be interpreted alongside imaging and clinical signs, as this may lead to improved diagnostic accuracy. Future validation studies are urgently needed before any AHF marker can be incorporated into treatment decision-making algorithms for patients with COPD.
PROTOCOL REGISTRATION: CRD42022283952.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2024;19:531-41.
Impact factor 3.1 ; Q2

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22. Feasibility study of the Digital Patient Benefit Assessment Scale (P-BAS): A Digital Tool to Assess Individual Patient Goals
van Erp RAL, de Rooij SE, Wymenga ANM, Zeegers A, van der Palen J.

The study objective was to assess the feasibility of the Patient Benefit Assessment Scale (P-BAS), a digital tool designed to enable older outpatients (≥70 years) to elucidate at home their individual goals regarding their current medical issue. Several digital tools are developed to assist older people

in identifying their goals, thereby facilitating the process of shared decision making. However, studies on the feasibility of these digital tools, especially in older patients, are limited. Data were collected from 36 older patients. The study comprised three stages. In stage I and II, cognitive interviews were conducted to strengthen the feasibility of the P-BAS. In stage III, 80% of the patients completed the P-BAS independently at home. The cognitive interviews provided insight into patients' interpretation and individual understanding of the digital visual P-BAS and associated opportunities for improvement, which were subsequently implemented. One conclusion is that the digital visual P-BAS might be of added value for patients and contributes to the process of shared decision making, assuring that the goals of the patient will be into account in treatment options. Findings are useful for researchers interested in technological tools that contribute to shared decision making.

Gepubliceerd: Gerontol Geriatr Med. 2024;10:23337214241230159.
Impact factor: 1.8 ; Q4

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23. Rapid Review on the Concept of Positive Health and Its Implementation in Practice
van Vliet M, de Kleijn M, van den Brekel-Dijkstra K, Huijts T, van Hogen-Koster S, Jung HP, Huber M.

Positive health (PH) has been described as a promising transformative innovation to address the challenges of promoting well-being and reducing the burden of disease. For this study, we conducted a scientific literature review of the current state of knowledge about PH as introduced by Huber and colleagues, following the Cochrane Rapid Review recommendations. Three databases were searched (PubMed, Google Scholar, and CINAHL). Data were extracted and synthesised using a narrative approach. A total of 55 articles were included. The initial evaluation revealed promising results at both the individual and collective levels. However, several articles gave reason for further refinement of the conceptualisation of PH and of ways to measure the effects of PH interventions in greater detail. Professionals also expressed a desire for a more informed application and elaboration of the PH method, in various settings and populations, to increase its effectiveness in practice. The results from the rapid review highlight the transformative potential of PH in shifting from a disease-oriented to a health-oriented paradigm of healthcare. This underlines the need for continued research regarding further development of the concept and its practical method, along with the necessity for methodological innovation.

Gepubliceerd: Healthcare (Basel). 2024;12(6).
Impact factor: 2.7 ; Q2

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24. 'Effects of a home-based bimodal lifestyle intervention in frail patients with end-stage liver disease awaiting orthotopic liver transplantation': study protocol of a non-randomised clinical trial
Wijma AG, Bongers BC, Annema C, Dekker R, Blokzijl H, van der Palen JAM, De Meijer VE, Cuperus FJ, Klaase JM.

INTRODUCTION: Patients with end-stage liver disease awaiting orthotopic liver transplantation (OLT) are generally classified as frail due to disease-related malnutrition and a progressive decline in musculoskeletal and aerobic fitness, which is associated with poor pre-OLT, peri-OLT and post-OLT outcomes. However, frailty in these patients may be reversable with adequate exercise and nutritional interventions.
METHODS AND ANALYSIS: Non-randomised clinical trial evaluating the effect of a home-based bimodal lifestyle programme in unfit patients with a preoperative oxygen uptake (VO(2)) at the ventilatory anaerobic threshold ≤13 mL/kg/min and/or VO(2) at peak exercise ≤18 mL/kg/min listed for OLT at the University Medical Center Groningen (UMCG). The programme is patient tailored and

comprises high-intensity interval and endurance training, and functional exercises three times per week, combined with nutritional support. Patients will go through two training periods, each lasting 6 weeks.The primary outcome of this study is the impact of the programme on patients' aerobic fitness after the first study period. Secondary outcomes include aerobic capacity after the second study period, changes in sarcopenia, anthropometry, functional mobility, perceived quality of life and fatigue, incidence of hepatic encephalopathy and microbiome composition. Moreover, number and reasons of intercurrent hospitalisations during the study and postoperative outcomes up to 12 months post OLT will be recorded. Finally, feasibility of the programme will be assessed by monitoring the participation rate and reasons for non-participation, number and severity of adverse events, and dropout rate and reasons for dropout.
ETHICS AND DISSEMINATION: This study was approved by the Medical Research Ethics Committee of the UMCG (registration number NL83612.042.23, August 2023) and is registered in the Clinicaltrials.gov register (NCT05853484). Good Clinical Practice guidelines and the principles of the Declaration of Helsinki will be applied. Results of this study will be submitted for presentation at (inter)national congresses and publication in peer-reviewed journals.
TRIAL REGISTRATION NUMBER: NCT05853484.

Gepubliceerd: BMJ Open. 2024;14(1):e080430.
Impact factor: 2.3 ; Q2

Totale impact factor: 126.8
Gemiddelde impact factor: 5.3

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 11
Totale impact factor: 59.9
Gemiddelde impact factor: 5.4

Microbiologie

1. Influenza Infection and Acute Myocardial Infarction

de Boer AR, Riezebos-Brilman A, van Hout D, van Mourik MSM, Rümke LW, de Hoog MLA, Vaartjes I, Bruijning-Verhagen P.

BACKGROUND: Acute respiratory infections can trigger acute myocardial infarction. We aimed to quantify the association between laboratory-confirmed influenza infection and acute myocardial infarction, particularly in patients with and without known coronary artery disease.
METHODS: This observational, registry-based, self-controlled case series study evaluated the association between laboratory-confirmed influenza infection and occurrence of acute myocardial infarction. Laboratory records on respiratory virus polymerase chain reaction (PCR) testing from 16 laboratories across the Netherlands were linked to national mortality, hospitalization, medication, and administrative registries. Influenza infection was defined as a positive PCR test result. Acute myocardial infarction was defined as a registered diagnostic code for either acute myocardial infarction hospitalization or death. Using a self-controlled case series method, we then compared the incidence of acute myocardial infarction during the risk period (days 1 to 7 after influenza infection) versus the control period (1 year before and 51 weeks after the risk period).
RESULTS: Between 2008 and 2019, we identified 158,777 PCR tests for influenza in the study population; 26,221 were positive for influenza, constituting 23,405 unique influenza illness episodes. A total of 406 episodes were identified with acute myocardial infarction occurring within 1 year before and 1 year after confirmed influenza infection and were included in analysis. Twenty-five cases of acute myocardial infarction occurred during the risk period versus 394 during the control period. The adjusted relative incidence of acute myocardial infarction during the risk period compared with the control period was 6.16 (95% confidence interval [CI], 4.11 to 9.24). The relative incidence of acute myocardial infarction in individuals without prior hospitalization for coronary artery disease was 16.60 (95% CI, 10.45 to 26.37) compared with 1.43 (95% CI, 0.53 to 3.84) for those with prior admission for coronary artery disease.
CONCLUSIONS: Influenza infection was associated with an increased risk of acute myocardial infarction, especially in individuals without a prior hospitalization for coronary artery disease. (Funded by the Dutch Research Council [NWO].).

Gepubliceerd: NEJM Evid. 2024;3(7):EVIDoa2300361.
Impact factor: onbekend

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2. Use of a diagnostic Puumala virus real-time RT-PCR in an orthohantavirus endemic region in the Netherlands

Geeraedts F, Wevers M, Bosma F, Boer M, Brinkman JN, Delsing C, GeurtsvanKessel C, Rockx B, van der Zanden A, Laverman GD.

Laboratory diagnosis of orthohantavirus infection is primarily based on serology. However, for a confirmed serological diagnosis, evaluation of a follow-up serum sample is essential, which is time consuming and causes delay. Real-time reverse transcription polymerase chain reaction (RT-PCR) tests, if positive, provide an immediate and definitive diagnosis, and accurately identify the causative agent, where the discriminative nature of serology is suboptimal. We re-evaluated sera from orthohantavirus-suspected clinical cases in the Dutch regions of Twente and Achterhoek from July 2014 to April 2016 for the presence of Puumala orthohantavirus (PUUV), Tula orthohantavirus (TULV), and Seoul orthohantavirus (SEOV) RNA. PUUV RNA was detected in 11% of the total number (n = 85) of sera tested, in 50% of sera positive for anti-PUUV/TULV IgM (n = 16), and in 1.4% of sera negative or indeterminate for anti-PUUV/TULV IgM (n = 69). No evidence was found for the presence of TULV or SEOV viral RNA. Based on these findings, we propose two algorithms to implement real-time RT-

PCR testing in routine orthohantavirus diagnostics, which optimally provide clinicians with early confirmed diagnoses and could prevent possible further invasive testing and treatment.
IMPORTANCE: The addition of a real-time reverse transcription polymerase chain reaction test to routine orthohantavirus diagnostics may better aid clinical decision making than the use of standard serology tests alone. Awareness by clinicians and clinical microbiologists of this advantage may ultimately lead to a reduction in over-hospitalization and unnecessary invasive diagnostic procedures.

Gepubliceerd: Microbiol Spectr. 2024;12(7):e0381323.
Impact factor: 3.8 ; Q2

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3. Epidemiological and Clinical Insights into the Enterovirus D68 Upsurge in Europe 2021-2022 and Emergence of Novel B3-Derived Lineages, ENPEN Multicentre Study
Simoes MP, Hodcroft EB, Simmonds P, Albert J, Alidjinou EK, Ambert-Balay K, Andrés C, Antón A, Auvray C, Bailly JL, Baldanti F, Bastings C, Beard S, Berengua C, Berginc N, Bloemen M, Blomqvist S, Bosma F, Böttcher S, Bubba L, Buderus S, Cabrerizo M, Calvo C, Celma C, Ceriotti F, Clark G, Costa I, Coste-Burel M, Couderé K, Cremer J, Del Cuerpo Casas M, Daehne T, de Beer J, de Ceano-Vivas M, De Gascun C, de Rougemont A, Dean J, Dembinski JL, Diedrich S, Diez-Domingo J, Dillner L, Dorenberg DH, Ducancelle A, Dudman S, Dyrdak R, Eis-Huebinger AM, Falces-Romero I, Farkas A, Feeney S, Fernandez-Garcia MD, Flipse J, Franck KT, Galli C, Garrigue I, Geeraedts F, Georgieva I, Giardina F, Guiomar R, Hauzenberger E, Heikens E, Henquell C, Hober D, Hönemann M, Howson-Wells H, Hruškar Ž, Ikonen N, Imbert B, Jansz AR, Jeannoël M, Jiřincová H, Josset L, Keeren K, Kramer-Lindhout N, Krokstad S, Lazrek M, Le Guillou-Guillemette H, Lefeuvre C, Lind A, Lunar MM, Maier M, Marque-Juillet S, McClure CP, McKenna J, Meijer A, Menasalvas Ruiz A, Mengual-Chuliá B, Midgley S, Mirand A, Molenkamp R, Montes M, Moreno-Docón A, Morley U, Murk JL, Navascués-Ortega A, Nijhuis R, Nikolaeva-Glomb L, Nordbø SA, Numanovic S, Oggioni M, Oñate Vergara E, Pacaud J, Pacreau ML, Panning M, Pariani E, Pekova L, Pellegrinelli L, Petrovec M, Pietsch C, Pilorge L, Piñeiro L, Piralla A, Poljak M, Prochazka B, Rabella N, Rahamat-Langendoen JC, Rainetova P, Reynders M, Riezebos-Brilman A, Roorda L, Savolainen-Kopra C, Schuffenecker I, Smeets LC, Stoyanova A, Stefic K, Swanink C, Tabain I, Tjhie J, Thouault L, Tumiotto C, Uceda Renteria S, Uršič T, Vallet S, Van Ranst M, Van Wunnik P, Verweij JJ, Vila J, Wintermans B, Wollants E, Wolthers KC, Xavier López-Labrador F, Fischer TK, Harvala H, Benschop KSM.

Enterovirus D68 (EV-D68) infections are associated with severe respiratory disease and acute flaccid myelitis (AFM). The European Non-Polio Enterovirus Network (ENPEN) aimed to investigate the epidemiological and genetic characteristics of EV-D68 infections and its clinical impact during the fall-winter season of 2021-2022. From 19 European countries, 58 institutes reported 10 481 (6.8%) EV-positive samples of which 1004 (9.6%) were identified as EV-D68 (including 852 respiratory samples). Clinical data were reported for 969 cases; 78.9% of infections were reported in children (0-5 years); and 37.9% of cases were hospitalized. Acute respiratory distress was commonly noted (93.1%) followed by fever (49.4%). Neurological problems were observed in 6.4% of cases including 6 diagnosed with AFM. Phylodynamic/Nextstrain and phylogenetic analyses based on 694 sequences showed the emergence of 2 novel B3-derived lineages, with no regional clustering. In conclusion, we describe a large-scale European EV-D68 upsurge with severe clinical impact and the emergence of B3-derived lineages.

Gepubliceerd: J Infect Dis. 2024;230(4):e917-e28.
Impact factor: 4.5 ; Q1

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4. The power of interactive maps for communicating spatio-temporal data to health professionals
Tjaden N, Geeraedts F, Kioko CK, Riezebos-Brilman A, Al Naiemi N, Blanford J, Beerlage-de Jong N.

While more and more health-related data is being produced and published every day, few of it is being prepared in a way that would be beneficial for daily use outside the scientific realm. Interactive visualizations that can slice and condense enormous amounts of multi-dimensional data into easy-to-digest portions are a promising tool that has been under-utilized for health-related topics. Here we present two case studies for how interactive maps can be utilized to make raw health data accessible to different target audiences: i) the European Notifiable Diseases Interactive Geovisualization (ENDIG) which aims to communicate the implementation status of disease surveillance systems across the European Union to public health experts and decision makers, and ii) the Zoonotic Infection Risk in Twente-Achterhoek Map (ZIRTA map), which aims to communicate information about zoonotic diseases and their regional occurrence to general practitioners and other healthcare providers tasked with diagnosing infectious diseases on a daily basis. With these two examples, we demonstrate that relatively straight-forward interactive visualization approaches that are already widely used elsewhere can be of benefit for the realm of public health.

Gepubliceerd: Geospat Health. 2024;19(2).
Impact factor: 0.9 ; Q4

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5. Trends in Mortality in People With HIV From 1999 through 2020: A Multicohort Collaboration
Tusch E, Ryom L, Pelchen-Matthews A, Mocroft A, Elbirt D, Oprea C, Günthard HF, Staehelin C, Zangerle R, Suarez I, Vehreschild JJ, Wit F, Menozzi M, d'Arminio Monforte A, Spagnuolo V, Pradier C, Carlander C, Suanzes P, Wasmuth JC, Carr A, Petoumenos K, Borgans F, Bonnet F, De Wit S, El-Sadr W, Neesgaard B, Jaschinski N, Greenberg L, Hosein SR, Gallant J, Vannappagari V, Young L, Sabin C, Lundgren J, Peters L, Reekie J, D:A:D cohort study and RESPOND cohort study; Riezebos-Brilman A.

BACKGROUND: Mortality among people with human immunodeficiency virus (HIV) declined with the introduction of combination antiretroviral therapy. We investigated trends in mortality in people with HIV from 1999 through 2020.
METHODS: Data were collected from the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort between January 1999 through January 2015 and the International Cohort Consortium of Infectious Disease (RESPOND) from October 2017 through December 2020. Age-standardized all-cause and cause-specific mortality rates, classified using Coding Causes of Death in HIV, were calculated. Poisson models were used to assess mortality over time.
RESULTS: Among 55 716 participants followed for median 6 years (interquartile range, 3-11), 5263 died (mortality rate [MR], 13.7/1000 person-years of follow-up [PYFU]; 95% confidence interval [CI], 13.4-14.1). Changing mortality was observed: AIDS mortality was most common between 1999-2009 (n = 952; MR, 4.2/1000 PYFU; 95% CI, 4.0-4.5) and non-AIDS-defining malignancy (NADM) between 2010-2020 (n = 444; MR, 2.8/1000 PYFU; 95% CI, 2.5-3.1). In multivariable analysis, all-cause mortality declined (adjusted mortality rate ratio [aMRR], 0.97 per year; 95% CI, .96-.98), mostly 1999-2010 (aMRR, 0.96 per year; 95% CI, .95-.97) but was stable 2011-2020 (aMRR, 1.00 per year; 95% CI, .96-1.05). Mortality due to all known causes except NADM also declined.
CONCLUSIONS: Mortality among people with HIV in the D:A:D and/or RESPOND cohorts declined between 1999-2009 and was stable over the period 2010-2020. This decline in mortality was not fully explained by improvements in immunologic-virologic status or other risk factors.

Gepubliceerd: Clin Infect Dis. 2024;79(5):1242-57.
Impact factor: 7.3 ; Q1

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6. How to verify and validate a clinical microbiology test before it can be used in routine diagnostics: a practical guide
Yusuf E, Schijffelen MJ, Leeflang M.

BACKGROUND: Before a new test can be routinely used in your laboratory, its reliability must be established in the laboratory where it will be used. International standards demand validation and verification procedures for new tests. The International Organization for Standardization (ISO) 15189 was recently updated, and the European Commission's In Vitro Diagnostic Regulation (IVDR) came into effect. These events will likely increase the need for validation and verification procedures.
OBJECTIVES: This paper aims to provide practical guidance in validating or verifying microbiology tests, including antimicrobial susceptibility tests in a clinical microbiology laboratory.
SOURCES: It summarizes and interprets certain parts of standards such as ISO 15189:2022, and regulations, such as IVDR 2017/746 regarding validation or verification of a new test in a routine clinical microbiology laboratory.
CONTENT: The reasons for choosing a new test and the outline of the validation and verification plan are discussed. Furthermore, the following topics are touched upon: the choice of reference standard, number of samples, testing procedures, how to solve the discrepancies between results from new test and reference standard, and acceptance criteria. Arguments for selecting certain parameters (such as reference standard and sample size) and examples are given.
IMPLICATIONS: With the expected increase in validation and verification procedures because of the implementation of IVDR, this paper may aid in planning and executing these procedures.

Gepubliceerd: Clin Microbiol Infect. 2024;30(10):1261-9.
Impact factor: 8.5 ; Q1

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7. Reactivation of Multidrug-Resistant HSV-1 in a Post-Allogenic Hematopoietic Stem Cell Transplant Patient: Dynamic Detection of the Rare A605V Mutation by Next-Generation Sequencing
Zheng S, Rümke LLW, Tello Rubio B, Rogers MRC, van Sluis GL, Kuball JHE, Riezebos-Brilman A, Lebbink RJ, Verduyn Lunel FM.

We present an immunocompromised patient with a multiresistant herpes simplex virus-1 reactivation with a rare mutation (A605V) in the viral DNA polymerase gene. Next-generation sequencing suggests the presence of multiple drug-resistant strains before treatment and altered ratios during treatment, affecting the clinical response to aciclovir and foscarnet.

Gepubliceerd: Open Forum Infect Dis. 2024;11(5):ofae250.
Impact factor: 3.8 ; Q1

Totale impact factor: 28.8
Gemiddelde impact factor: 4.1

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 8.5
Gemiddelde impact factor: 4.3

MKA chirurgie

1. Correction: Effect of emphysema on AI software and human reader performance in lung nodule detection from low-dose chest CT
Sourlos N, Pelgrim G, Wisselink HJ, Yang X, de Jonge G, Rook M, Prokop M, Sidorenkov G, van Tuinen M, Vliegenthart R, van Ooijen PMA.

Gepubliceerd: Eur Radiol Exp. 2024;8(1):94.
IF 3.6 ; Q1

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2. Detecting Mandible Fractures in CBCT Scans Using a 3-Stage Neural Network
van Nistelrooij N, Schitter S, van Lierop P, Ghoul KE, König D, Hanisch M, Tel A, Xi T, Thiem DGE, Smeets R, Dubois L, Flügge T, van Ginneken B, Bergé S, Vinayahalingam S.

After nasal bone fractures, fractures of the mandible are the most frequently encountered injuries of the facial skeleton. Accurate identification of fracture locations is critical for effectively managing these injuries. To address this need, JawFracNet, an innovative artificial intelligence method, has been developed to enable automated detection of mandibular fractures in cone-beam computed tomography (CBCT) scans. JawFracNet employs a 3-stage neural network model that processes 3-dimensional patches from a CBCT scan. Stage 1 predicts a segmentation mask of the mandible in a patch, which is subsequently used in stage 2 to predict a segmentation of the fractures and in stage 3 to classify whether the patch contains any fracture. The final output of JawFracNet is the fracture segmentation of the entire scan, obtained by aggregating and unifying voxel-level and patch-level predictions. A total of 164 CBCT scans without mandibular fractures and 171 CBCT scans with mandibular fractures were included in this study. Evaluation of JawFracNet demonstrated a precision of 0.978 and a sensitivity of 0.956 in detecting mandibular fractures. The current study proposes the first benchmark for mandibular fracture detection in CBCT scans. Straightforward replication is promoted by publicly sharing the code and providing access to JawFracNet on grand-challenge.org.

Gepubliceerd: J Dent Res. 2024;103(13):1384-91.
IF 5.9 ; Q1

Totale impact factor: 9.5
Gemiddelde impact factor: 4.8

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.6
Gemiddelde impact factor: 3.6

Neurocentrum

1. Neurophysiological signatures of mild traumatic brain injury in the acute and subacute phase
Barone V, de Koning ME, van der Horn HJ, van der Naalt J, Eertman-Meyer CJ, van Putten M.

BACKGROUND: Mild traumatic brain injury (mTBI) affects 48 million people annually, with up to 30% experiencing long-term complaints such as fatigue, blurred vision, and poor concentration. Assessing neurophysiological features related to visual attention and outcome measures aids in understanding clinical symptoms and prognostication.
METHODS: We recorded EEG and eye movements in mTBI patients during a computerized task performed in the acute (< 24 h, TBI-A) and subacute phase (4-6 weeks thereafter). We estimated the posterior dominant rhythm, reaction times (RTs), fixation duration, and event-related potentials (ERPs). Clinical outcome measures were assessed using the Head Injury Symptom Checklist (HISC) and the Extended Glasgow Outcome Scale (GOSE) at 6 months post-injury. Similar analyses were performed in an age-matched control group (measured once). Linear mixed effect modeling was used to examine group differences and temporal changes within the mTBI group.
RESULTS: Twenty-nine patients were included in the acute phase, 30 in the subacute phase, and 19 controls. RTs and fixation duration were longer in mTBI patients compared to controls ($p < 0.05$), but not between TBI-A and TBI-S ($p < 0.05$). The frequency of the posterior dominant rhythm was significantly slower in TBI-A (0.6 Hz, $p < 0.05$) than TBI-S. ERP mean amplitude was significantly lower in mTBI patients than in controls. Neurophysiological features did not significantly relate to clinical outcome measures.
CONCLUSION: mTBI patients demonstrate impaired processing speed and stimulus evaluation compared to controls, persisting up to 6 weeks after injury. Neurophysiological features in mTBI can assist in determining the extent and temporal progression of recovery.

Gepubliceerd: Neurol Sci. 2024;45(7):3313-23.
Impact factor: 2.4 ; Q3

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2. Reply to Neurophysiological signatures of visual attention during absence seizures
Barone V, Piastra MC, van Dijk JP, Visser GH, Debeij-van Hall M, van Putten M.

Gepubliceerd: Clin Neurophysiol. 2024;162:276.
Impact factor: 3.6 ; Q1

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3. The VEBAS score: a practical scoring system for intracranial dural arteriovenous fistula obliteration
Becerril-Gaitan A, Ding D, Ironside N, Buell TJ, Kansagra AP, Lanzino G, Brinjikji W, Kim L, Levitt MR, Abecassis IJ, Bulters D, Durnford A, Fox WC, Blackburn S, Chen PR, Polifka AJ, Laurent D, Gross B, Hayakawa M, Derdeyn C, Amin-Hanjani S, Alaraj A, van Dijk JMC, Potgieser ARE, Starke RM, Peterson EC, Satomi J, Tada Y, Abla AA, Winkler EA, Du R, Lai PMR, Zipfel GJ, Chen CJ, Sheehan JP.

BACKGROUND: Tools predicting intracranial dural arteriovenous fistulas (dAVFs) treatment outcomes remain scarce. This study aimed to use a multicenter database comprising more than 1000 dAVFs to develop a practical scoring system that predicts treatment outcomes.
METHODS: Patients with angiographically confirmed dAVFs who underwent treatment within the Consortium for Dural Arteriovenous Fistula Outcomes Research-participating institutions were retrospectively reviewed. A subset comprising 80% of patients was randomly selected as training dataset, and the remaining 20% was used for validation. Univariable predictors of complete dAVF

obliteration were entered into a stepwise multivariable regression model. The components of the proposed score (VEBAS) were weighted based on their ORs. Model performance was assessed using receiver operating curves (ROC) and areas under the ROC.
RESULTS: A total of 880 dAVF patients were included. Venous stenosis (presence vs absence), elderly age (<75 vs ≥75 years), Borden classification (I vs II-III), arterial feeders (single vs multiple), and past cranial surgery (presence vs absence) were independent predictors of obliteration and used to derive the VEBAS score. A significant increase in the likelihood of complete obliteration (OR=1.37 (1.27-1.48)) with each additional point in the overall patient score (range 0-12) was demonstrated. Within the validation dataset, the predicted probability of complete dAVF obliteration increased from 0% with a 0-3 score to 72-89% for patients scoring ≥8.
CONCLUSION: The VEBAS score is a practical grading system that can guide patient counseling when considering dAVF intervention by predicting the likelihood of treatment success, with higher scores portending a greater likelihood of complete obliteration.

Gepubliceerd: J Neurointerv Surg. 2024;16(3):272-9.
Impact factor: 4.4 ; Q1

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4. Brain health: A concern for anaesthesiologists and intensivists
Bonhomme V, Putensen C, Böttiger BW, Stevens MF, Marczin N, Arnal D, Brotfain E, Raz A, Defresne A, Bogossian E, Sviri S, Cardone P, Mair A, Robba C, Dilmen OK, Ly J, Crisan MI, De Graaff JC, Najafi N, Vutskits L, Absalom A, Abramovich I, Souberbielle Q, Momeni M, Campbell D, Evered L, Vacas S, Saxena S, Bruder N, Oksuz DA, Lobo FA, van Putten M, Sahinovic M, Hawryluk GWJ, Kustura A, Yürek F, Baron Shahaf D, Shahaf G, Radke F, Khalifa C.

Damage to the brain can have disastrous and long-lasting consequences. The European Society of Anaesthesiology and Intensive Care (ESAIC) is aware of the importance of taking good care of the brain, both of patients and of anaesthesia and intensive care unit (ICU) caregivers, and has organised a complete learning track on brain health to bring this concern to the attention of practitioners. This learning track included an online Focus Meeting on Brain Health (November 25, 2023). We here provide readers with a digest of the information that was delivered during that meeting in an opinion paper driven by the authors' own reading of the literature. It is divided according to the meeting's sessions, including how to improve the health of an injured brain, how to keep a young or old brain healthy, how to keep a healthy adult brain unimpaired, how monitoring can impact brain health in the operating room and in the intensive care unit, and how to keep the anaesthesia and ICU caregivers' brain healthy. Each part is a brief and focused summary. The main delivered messages are that the management of injured brain patients involves an adequate choice of sedation, adequate brain monitoring, and focused attention to specific points depending on the underlying pathology; that several measures can be undertaken to protect the brain of the very young needing anaesthesia; that it is possible to detect older patients at risk of postoperative neurocognitive disorders, and that dedicated perioperative management by a multidisciplinary expert team may improve their outcomes; that apparently healthy adult brains may suffer during anaesthesia; that the electroencephalogram may track peri-operative brain dysfunction, and that female patients should be given special care in this respect; that multimodal brain monitoring helps to detect pathological processes and to maintain brain homeostasis; and that burnout in anaesthesiologists can be effectively fought using personal, organisational, managerial and legal approaches.

Gepubliceerd: Eur J Anaesthesiol Intensive Care. 2024;3(6):e0063.
Impact factor: 6.8 ; Q1

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5. Management of an acute intracranial emergency in pregnancy
Brokkelkamp P, Baalman JH, Driesse MJ, Kho KH.

We report a case of a mid-20s primigravida at 37 weeks' gestation who presented with severe headache and acute neurological deterioration. The CT brain scan showed hydrocephalus caused by a colloid cyst in the third ventricle. The patient underwent emergency placement of an external ventricular drain for decompression of acute hydrocephalus. Four hours later, labour commenced spontaneously, and in view of her neurological status, a decision was taken to perform a caesarean section under general anaesthetics. Four days postpartum, the patient underwent an endoscopic removal of the cyst. Intracranial emergencies during pregnancy are rare and challenging to manage. The mortality rate can be significant. Diagnostic and surgical intervention should not be delayed because of pregnancy. An individualised treatment approach is required with multidisciplinary input. The collaborative efforts of our multidisciplinary team resulted in prompt diagnosis and surgical treatment in this case that resulted in both a healthy mother and child.

Gepubliceerd: BMJ Case Rep. 2024;17(3).
Impact factor: 0.5 ; Q3

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6. Survival, neurocognitive function, and health-related quality of life outcomes after rituximab-methotrexate, BCNU, teniposide, and prednisolone for primary CNS lymphoma: Final results of the HOVON 105/ALLG NHL 24 study
Bromberg JEC, Issa S, van der Holt B, van der Meulen M, Dirven L, Minnema MC, Seute T, Durian M, Cull G, van der Poel MWM, Stevens WBC, Zijlstra JM, Brandsma D, Nijland M, Mason KD, Beeker A, Abrahamse-Testroote MCJ, van den Bent MJ, de Jong D, Doorduijn JK.

BACKGROUND: Studies on the efficacy of rituximab in primary CNS lymphoma (PCNSL) reported conflicting results. Our international randomized phase 3 study showed that the addition of rituximab to high-dose methotrexate, BCNU, teniposide, and prednisolone (MBVP) in PCNSL was not efficacious in the short term. Here we present long-term results after a median follow-up of 82.3 months.
METHODS: One hundred and ninety-nine eligible newly diagnosed, nonimmunocompromised patients with PCNSL aged 18-70 years with WHO performance status 0-3 was randomized between treatment with MBVP chemotherapy with or without rituximab, followed by high-dose cytarabine consolidation in responding patients, and reduced-dose WBRT in patients aged ≤ 60 years. Event-free survival was the primary endpoint. Overall survival rate, neurocognitive functioning (NCF), and health-related quality of life (HRQoL) were additionally assessed, with the IPCG test battery, EORTC QLQ-C30 and QLQ-BN20 questionnaires, respectively.
RESULTS: For event-free survival, the hazard ratio was 0.85, 95% CI 0.61-1.18, P = .33. Overall survival rate at 5 years for MBVP and R-MBVP was 49% (39-59) and 53% (43-63) respectively. In total, 64 patients died in the MBVP arm and 55 in the R-MBVP arm, of which 69% were due to PCNSL. At the group level, all domains of NCF and HRQoL improved to a clinically relevant extent after treatment initiation, and remained stable thereafter up to 60 months of follow-up, except for motor speed which deteriorated between 24 and 60 months. Although fatigue improved initially, high levels persisted in the long term.
CONCLUSIONS: Long-term follow-up confirms the lack of added value of rituximab in addition to MBVP and HD-cytarabine for PCNSL.

Gepubliceerd: Neuro Oncol. 2024;26(4):724-34.
Impact factor: 13.4 ; Q1

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7. Evaluation of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 Using a Rapid Point of Care Test for Predicting Head Computed Tomography Lesions After Mild Traumatic Brain Injury in a Dutch Multi-Center Cohort
Chayoua W, Visser K, de Koning ME, Beishuizen A, Ijmker R, van der Naalt J, Krabbe JG, van der Horn HJ.

Mild traumatic brain injury (mTBI) is a common condition seen in emergency departments worldwide. Blood-based biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are recently U.S. Food and Drug Administration-approved for the prediction of intracranial lesions on head computed tomography (CT) scans in mTBI. We evaluated the diagnostic performance of GFAP and UCH-L1 in a Dutch cohort using the i-STAT TBI assay. In a multi-center observational study, we enrolled 253 mTBI patients. Head CT scans were scored using the Marshall classification system. Logistic regression models were used to assess the contribution of biomarkers and clinical parameters to diagnostic performance. Detection of UCH-L1 and GFAP resulted in a sensitivity of 97% and specificity of 19% for CT positivity in mTBI patients, along with a negative predictive value of 95% (88-100%) and a positive predictive value of 27% (21-33%). Combining biomarker testing with loss of consciousness and time to sample increased specificity to 46%. Combined testing of UCH-L1 and GFAP testing resulted in possibly more unnecessary CT scans compared with GFAP testing alone, with only limited increase in sensitivity. This study confirmed high sensitivity of GFAP and UCH-L1 for CT abnormalities in mTBI patients using the i-STAT TBI test. The results support the potential use of GFAP and UCH-L1 as tools for determining the indication for CT scanning in mTBI patients, possibly offering a cost- and time-effective approach to management of patients with mTBI. Prospective studies in larger cohorts are warranted to validate our findings.

Gepubliceerd: J Neurotrauma. 2024;41(13-14):e1630-e40.
Impact factor: 3.8 ; Q1

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8. Good Health-Related Quality of Life in Older Patients One Year after mTBI despite Incomplete Recovery: An Indication of the Disability Paradox?
Coffeng SM, Abdulle AE, van der Horn HJ, de Koning ME, Ter Maaten JC, Spikman JM, van der Naalt J.

BACKGROUND: Older adults (OAs) with mild traumatic brain injury (OA-mTBI) are a growing population, but studies on long-term outcomes and quality of life are scarce. Our aim was to determine the health-related quality of life (HRQoL) in OA-mTBI one year after injury and to assess the early predictors of HRQoL.
METHODS: Data from a prospective follow-up study of 164 older (≥60 years) and 289 younger mTBI patients (<60 years) admitted to the emergency department were analyzed. Post-traumatic complaints, emotional distress and coping were evaluated 2 weeks post-injury using standardized questionnaires. At 12 months post-injury, HRQoL and functional recovery were determined with the abbreviated version of the World Health Organization Quality of Life scale and Glasgow Outcome Scale Extended (GOSE), respectively.
RESULTS: One year post-injury, 80% (n = 131) of the OA-mTBI rated their HRQoL as "good" or "very good", which was comparable to younger patients (79% (n = 226), p = 0.72). Incomplete recovery (GOSE <8) was present in 43% (n = 69) of OA-mTBI, with 67% (n = 46) reporting good HRQoL. Two weeks post-injury, fewer OA-mTBI had (≥2) post-traumatic complaints compared to younger patients (68% vs. 80%, p = 0.01). In the multivariable analyses, only depression-related symptoms (OR = 1.20 for each symptom, 95% CI = 1.01-1.34, p < 0.01) were predictors of poor HRQoL in OA-mTBI.
CONCLUSIONS: Similar to younger patients, most OA-mTBI rated their HRQoL as good at one year after injury, although a considerable proportion showed incomplete recovery according to the GOSE, suggesting a disability paradox. Depression-related symptoms emerged as a significant predictor for poor HRQoL and can be identified as an early target for treatment after mTBI.

Gepubliceerd: J Clin Med. 2024;13(9).
Impact factor: 2.9 ; Q1

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9. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage
Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Członkowska A, Lindgren AG, Molina CA, Bereczki D, Toni D, Seiffge DJ, Tanne D, Sandset EC, Tsivgoulis G, Christensen H, Beyer-Westendorf J, Coutinho JM, Crowther M, Verhamme P, Amarenco P, Roine RO, Mikulik R, Lemmens R, Veltkamp R, Middeldorp S, Robinson TG, Milling TJ, Jr., Tedim-Cruz V, Lang W, Himmelmann A, Ladenvall P, Knutsson M, Ekholm E, Law A, Taylor A, Karyakina T, Xu L, Tsiplova K, Poli S, Kallmünzer B, Gumbinger C, Shoamanesh A, ANNEXA-I Investigators; van der Meulen M, van Putten MJAM.

BACKGROUND: Patients with acute intracerebral hemorrhage who are receiving factor Xa inhibitors have a risk of hematoma expansion. The effect of andexanet alfa, an agent that reverses the effects of factor Xa inhibitors, on hematoma volume expansion has not been well studied.
METHODS: We randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15 hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.
RESULTS: A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P = 0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti-factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P = 0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.
CONCLUSIONS: Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.).

Gepubliceerd: N Engl J Med. 2024;390(19):1745-55.
Impact factor: 78.5 ; Q1

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10. Life expectancy and causes of death in patients with Myotonic Dystrophy Type 2
Damen MJ, Muilwijk OG, Olde Dubbelink TB, van Engelen BG, Voermans NC, Tieleman AA.

BACKGROUND: Myotonic Dystrophy type 2 (DM2) is a dominantly inherited multisystem disease caused by a CCTG repeat expansion in intron 1 of the CNBP gene. Although in the last two decades over 1500 patients with DM2 have been diagnosed worldwide, our clinical impression of a reduced life expectancy in DM2 has not been investigated previously.

OBJECTIVE: The aim of this observational study was to determine the life expectancy and the causes of death in patients with genetically confirmed DM2.
METHODS: We identified the data of all deceased patients with DM2 in the Dutch neuromuscular database between 2000 and 2023. Ages and causes of death and the patients' clinical features during lifetime were determined. Age of death in DM2 was compared to the general population by using life tables with prognostic cohort life expectancy (CLE) and period life expectancy (PLE) data of the Dutch electronic database of statistics (CBS StatLine).
RESULTS: Twenty-six deceased patients were identified in the Dutch DM2 cohort (n = 125). Median age of death in DM2 (70.9 years) was significantly lower compared to sex- and age-matched CLE (78.1 years) and PLE (82.1 years) in the Netherlands. Main causes of death were cardiac diseases (31%) and pneumonia (27%). Seven patients (27%) had a malignancy at the time of death.
CONCLUSION: These results provide new insights into the phenotype of DM2. Life expectancy in patients with DM2 is reduced, possibly attributable to multiple causes including increased risk of cardiac disease, pneumonia, and malignancies. The occurrence of a significantly reduced life expectancy has implications for clinical practice and may form a basis for advanced care planning, including end-of-life care, to optimize quality of life for patients with DM2 and their family. Research in larger cohorts should be done to confirm these findings and to ascertain more about the natural course in DM2.

Gepubliceerd: J Neuromuscul Dis. 2024;11(6):1221-8.
Impact factor: 3.4 ; Q2

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11. Primary central nervous system lymphoma
de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC, van der Meulen M.

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL) manifesting in the brain, spinal cord, cerebrospinal fluid and/or eyes, in the absence of systemic manifestations. With an increasing incidence and a 30% 5-year overall survival if promptly treated, timely diagnosis and subsequent treatment is paramount. The typical MRI appearance for PCNSL is a solitary or multiple T2-hypointense, homogeneous gadolinium-enhancing lesion with restricted diffusion. Dexamethasone treatment might compromise and delay the diagnosis. Hallmark of treatment is induction with intravenous high-dose methotrexate consisting polychemotherapy followed by consolidation treatment. Consolidation treatment consists of either whole brain radiotherapy (WBRT) or autologous stem cell transplantation (ASCT). Given the (cognitive) side effects of WBRT, ASCT is increasingly being used as the first choice of treatment.

Gepubliceerd: J Neurol. 2024;271(5):2906-13.
Impact factor: 4.6 ; Q1

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12. Breaking the burst: Unveiling mechanisms behind fragmented network bursts in patient-derived neurons
Doorn N, Voogd E, Levers MR, van Putten M, Frega M.

Fragmented network bursts (NBs) are observed as a phenotypic driver in many patient-derived neuronal networks on multi-electrode arrays (MEAs), but the pathophysiological mechanisms underlying this phenomenon are unknown. Here, we used our previously developed biophysically detailed in silico model to investigate these mechanisms. Fragmentation of NBs in our model simulations occurred only when the level of short-term synaptic depression (STD) was enhanced, suggesting that STD is a key player. Experimental validation with Dynasore, an STD enhancer, induced

fragmented NBs in healthy neuronal networks in vitro. Additionally, we showed that strong asynchronous neurotransmitter release, NMDA currents, or short-term facilitation (STF) can support the emergence of multiple fragments in NBs by producing excitation that persists after high-frequency firing stops. Our results provide important insights into disease mechanisms and potential pharmaceutical targets for neurological disorders modeled using human induced pluripotent stem cell (hiPSC)-derived neurons.

Gepubliceerd: Stem Cell Reports. 2024;19(11):1583-97.
Impact factor: 5.1 ; Q1

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13. Resting state EEG relates to short- and long-term cognitive functioning after cardiac arrest
Glimmerveen AB, Verhulst M, de Kruijf NLM, van Gils P, Delnoij T, Bonnes J, van Heugten CM, Van Putten M, Hofmeijer J.

BACKGROUND: Approximately half of cardiac arrest survivors have persistent cognitive impairment. Guidelines recommend early screening to identify patients at risk for cognitive impairment, but there is no consensus on the best screening method. We aimed to identify quantitative EEG measures relating with short- and long-term cognitive function after cardiac arrest for potential to cognitive outcome prediction.
METHODS: We analyzed data from a prospective longitudinal multicenter cohort study designed to develop a prediction model for cognitive outcome after cardiac arrest. For the current analysis, we used twenty-minute EEG registrations from 80 patients around one week after cardiac arrest. We calculated power spectral density, normalized alpha-to-theta ratio (nATR), peak frequency, and center of gravity (CoG) of this peak frequency. We related these with global cognitive functioning (scores on the Montreal Cognitive Assessment (MoCA)) at one week, three and twelve months follow-up with multivariate mixed effect models, and with performance on standard neuropsychological examination at twelve months using Pearson correlation coefficients.
RESULTS: Each individual EEG parameter related to MoCA at one week (β(nATR) = 7.36; P < 0.01; β(peak) frequency = 1.73, P < 0.01; β(CoG) = -9.88, P < 0.01). The nATR also related with the MoCA at three months ((β(nATR) = 2.49; P 0.01). No EEG metrics significantly related to the MoCA score at twelve months. nATR and peak frequency related with memory performance at twelve months. Results were consistent in sensitivity analyses.
CONCLUSION: Early resting-state EEG parameters relate with short-term global cognitive functioning and with memory function at one year after cardiac arrest. Additional predictive values in multimodal prediction models need further study.

Gepubliceerd: Resuscitation. 2024;201:110253.
Impact factor: 4.6 ; Q1

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14. Chronic Traumatic Encephalopathy in Soccer Players: Review of 14 Cases
Hageman G, Hageman I, Nihom J.

OBJECTIVE: Exposure to repetitive sports-related concussions or (sub)concussive head trauma may lead to chronic traumatic encephalopathy (CTE). Which impact (heading or concussion) poses the greatest risk of CTE development in soccer players?
DESIGN: Narrative review.
SETTING: Teaching hospital and University of Applied sciences.
PATIENTS: A literature search (PubMed) was conducted for neuropathologic studies in the period 2005-December 2022, investigating soccer players with dementia and a CTE diagnosis, limited to

English language publications. 210 papers were selected for final inclusion, of which 7 papers described 14 soccer players.
ASSESSMENT: Magnetic resonance imaging studies in soccer players show that lifetime estimates of heading numbers are inversely correlated with cortical thickness, grey matter volume, and density of the anterior temporal cortex. Using diffusion tensor imaging-magnetic resonance imaging, higher frequency of headings-particularly with rotational accelerations-are associated with impaired white matter integrity. Serum neurofilament light protein is elevated after heading.
MAIN OUTCOME MEASURES: Chronic traumatic encephalopathy pathology, history of concussion, heading frequency.
RESULTS: In 10 of 14 soccer players, CTE was the primary diagnosis. In 4 cases, other dementia types formed the primary diagnosis and CTE pathology was a concomitant finding. Remarkably, 6 of the 14 cases had no history of concussion, suggesting that frequent heading may be a risk for CTE in patients without symptomatic concussion. Rule changes in heading duels, management of concussion during the game, and limiting the number of high force headers during training are discussed.
CONCLUSIONS: Data suggest that heading frequency and concussions are associated with higher risk of developing CTE in (retired) soccer players. However based on this review of only 14 players, questions persist as to whether or not heading is a risk factor for CTE or long-term cognitive decline.

Gepubliceerd: Clin J Sport Med. 2024;34(1):69-80.
Impact factor: 1.8 ; Q2

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15. The role of carbon monoxide in aerotoxic syndrome
Hageman G, van Broekhuizen P, Nihom J.

Chronic low-level exposure to toxic compounds in airplane cabin air may result in Aerotoxic Syndrome (AS). Aetiologic agents are organophosphates and numerous volatile organic hydrocarbons originating from leaks of engine oil and hydraulic fluids. Despite a documented history spanning decades, the role of carbon monoxide remains controversial. What evidence exists that carbon monoxide (CO), present in the cocktail of toxic compounds in bleed air, contributes to the AS? We selected 22 publications encompassing 888 flights with 18 different aircraft types. In one study of 100 flights, fume events were confirmed in 38. Four studies were initialized after air quality incidents. The cabin CO concentrations could be categorized in three levels, 1) low (<5 ppm), without health implications, 2) moderate (5-10 ppm) with probably health implications in case of chronic exposure, and 3) high > 10 ppm, with health effects in case of acute and chronic exposure. These levels were recorded in 12, 6 and 4 studies respectively. In the six studies in category 2, max CO concentrations ranged from 5.8-9.4 ppm. The four studies with CO > 10 ppm comprised 376 of the 888 flights (42%) with six aircraft types. Toxic CO levels ranging between 13-60 ppm were identified in at least 129 of 888 (14.5%) flights. In one study with high CO levels four flight attendants were diagnosed with CO poisoning with elevated HbCO levels. Max CO levels in aviation are either the same or higher than current occupational exposure limits (OEL) for ground-based workplace exposures or levels for urban street transport environments. Specific aspects of aviation should be taken into consideration: the effect of low(er) air pressure at high altitudes increasing the toxicity of CO, and the binding of CO to CYP enzymes, leading to impaired organophosphate detoxification. We conclude that CO must be considered an important factor in the lubrication derived cocktail of airborne toxic compounds causing AS. In line with the WHO advice, a reduction of the OEL to 5 ppm over 8 hr time weighted average (TWA) for aircrew is strongly recommended. And we advocate continuous monitoring during all phases of flight and installation of CO detectors in the air supply ducts to the aircraft cabin.

Gepubliceerd: Neurotoxicology. 2024;100:107-16.
Impact factor: 3.9 ; Q1

16. The role of nanoparticles in bleed air in the etiology of Aerotoxic Syndrome: A review of cabin air-quality studies of 2003-2023
Hageman G, van Broekhuizen P, Nihom J.

Aerotoxic Syndrome may develop as a result of chronic, low-level exposure to organophosphates (OPs) and volatile organic compounds in the airplane cabin air, caused by engine oil leaking past wet seals. Additionally, acute high-level exposures, so-called "fume events," may occur. However, air quality monitoring studies concluded that levels of inhaled chemicals might be too low to cause adverse effects. The presence of aerosols of nanoparticles (NPs) in bleed air has often been described. The specific hypothesis is a relation between NPs acting as a vector for toxic compounds in the etiology of the Aerotoxic Syndrome. These NPs function as carriers for toxic engine oil compounds leaking into the cabin air. Inhaled by aircrew NPs carrying soluble and insoluble components deposit in the alveolar region, where they are absorbed into the bloodstream. Subsequently, they may cross the blood-brain barrier and release their toxic compounds in the central nervous system. Olfactory absorption is another route for NPs with access to the brain. To study the hypothesis, all published in-flight measurement studies (2003-2023) of airborne volatile (and low-volatile) organic pollutants in cabin air were reviewed, including NPs (10-100 nm). Twelve studies providing data for a total of 387 flights in 16 different large-passenger jet aircraft types were selected. Maximum particle number concentrations (PNC) varied from 10(4) to 2.8 × 10(6) #/cm(3) and maximum mass concentrations from 9 to 29 µg/m(3). NP-peaks occurred after full-power take-off, in tailwind condition, after auxiliary power unit (APU) bleed air introduction, and after air conditioning pack failure. Chemical characterization of the NPs showed aliphatic hydrocarbons, black carbon, and metallic core particles. An aerosol mass-spectrometry pattern was consistent with aircraft engine oil. It is concluded that chronic exposure of aircrew to NP-aerosols, carrying oil derivatives, maybe a significant feature in the etiology of Aerotoxic Syndrome. Mobile NP measuring equipment should be made available in the cockpit for long-term monitoring of bleed air. Consequently, risk assessment of bleed air should include monitoring and analysis of NPs, studied in a prospective cohort design.

Gepubliceerd: J Occup Environ Hyg. 2024;21(6):423-38.
Impact factor: 1.5 ; Q3

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17. Diagnostics and treatment delay in primary central nervous system lymphoma: What the neurosurgeon should know
Hasner MC, van Opijnen MP, van der Meulen M, Verdijk RM, Maas SLN, Te Boome LCJ, Broekman MLD.

PURPOSE: The gold standard for diagnostics in primary central nervous system lymphoma (PCNSL) is histopathological diagnosis after stereotactic biopsy. Yet, PCNSL has a multidisciplinary diagnostic work up, which associated with diagnostic delay and could result in treatment delay. This article offers recommendations to neurosurgeons involved in clinical decision-making regarding (novel) diagnostics and care for patients with PCNSL with the aim to improve uniformity and timeliness of the diagnostic process for patients with PCNSL.
METHODS: We present a mini review to discuss the role of stereotactic biopsy in the context of novel developments in diagnostics for PCNSL, as well as the role for cytoreductive surgery.
RESULTS: Cerebrospinal fluid-based diagnostics are supplementary and cannot replace stereotactic biopsy-based diagnostics.

CONCLUSION: Histopathological diagnosis after stereotactic biopsy of the brain remains the gold standard for diagnosis. Additional diagnostics should not be a cause of diagnostic delay. There is currently no sufficient evidence supporting cytoreductive surgery in PCNSL, with recent studies showing contradictive data and suboptimal study designs.

Gepubliceerd: Acta Neurochir (Wien). 2024;166(1):261.
Impact factor: 1.9 ; Q2

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18. Therapeutic patterns and migraine disease burden in switchers of CGRP-targeted monoclonal antibodies - insights from the German NeuroTransData registry
Hong JB, Israel-Willner H, Peikert A, Schanbacher P, Tozzi V, Köchling M, Reuter U, Raffaelli B.

BACKGROUND: Monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway have shown good efficacy in migraine prophylaxis. However, a subset of patients does not respond to the first mAb treatment and switches among the available mAbs. The goal of this study is to characterize the switching pattern of migraine patients treated with anti-CGRP(-receptor, -R) mAbs, and to describe the headache burden of those who did not switch, switched once, and switched twice.
METHODS: This study used real world data from the NeuroTransData Cohort, a registry of migraine patients treated at outpatient neurology clinics across Germany. Patients who had received at least one anti-CGRP(-R) mAb were included. Headache diaries were collected at baseline and during treatment, along with quality of life measures every three months. Results were summarized for the subgroups of patients who did not switch and those with one and two switches.
RESULTS: Of the 655 eligible patients, 479 did not switch, 135 switched once, 35 twice, and 6 three or more times. The ≥ 50% response rates for monthly migraine days were 64.7%, 50.7%, and 25.0% for the no switch, one switch, and two switches groups in their last treatment cycles, respectively. Quality of life measures improved for the no switch and one switch groups, but not for the two switches group.
CONCLUSION: Patients who switched among anti-CGRP(-R) mAbs during the course of their treatment still benefited overall but to a lesser extent than those who did not switch. Treatment response in patients who switched twice was markedly lower compared to the no switch and one switch subgroup.

Gepubliceerd: J Headache Pain. 2024;25(1):90.
Impact factor: 7.9 ; Q1

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19. Trigger factors in patients with a patent foramen ovale-associated stroke: A case-crossover study
Immens MH, Ekker MS, Verburgt E, Verhoeven JI, Schellekens MM, Hilkens NA, Boot EM, Van Alebeek ME, Brouwers PJ, Arntz RM, Van Dijk GW, Gons RA, Van Uden IW, den Heijer T, de Kort PL, de Laat KF, Van Norden AG, Vermeer SE, Van Zagten MS, Van Oostenbrugge RJ, Wermer MJ, Nederkoorn PJ, Kerkhoff H, Rooyer FA, Van Rooij FG, Van den Wijngaard IR, Klijn CJ, Tuladhar AM, Ten Cate TJ, de Leeuw FE.

BACKGROUND: Patent foramen ovale (PFO) is a congenital anatomical variant which is associated with strokes in young adults. Contrary to vascular risk factors and atherosclerosis, a PFO is present from birth. However, it is completely unknown how an anatomical structure that is already present at birth in a large proportion of the population can convert into a PFO that causes stroke in a few.

Recent studies reported a significant association between certain trigger factors and ischemic stroke in young adults. This study aims to investigate these triggers in PFO-associated stroke.
METHODS: The ODYSSEY study, a multicenter prospective cohort study between 2013 and 2021, included patients aged 18-49 years experiencing their first-ever ischemic event. Participants completed a questionnaire about exposure to potential trigger factors. A case-crossover design was used to assess the relative risks (RR) with 95% confidence intervals (95% CI). The primary outcome was the RR of potential trigger factors for PFO-associated stroke.
RESULTS: Overall, 1043 patients completed the questionnaire and had an ischemic stroke, of which 124 patients had a PFO-associated stroke (median age 42.1 years, 45.2% men). For patients with PFO-associated stroke, the RR was 26.0 (95% CI 8.0-128.2) for fever, 24.2 (95% CI 8.5-68.7) for flu-like disease, and 3.31 (95% CI 2.2-5.1) for vigorous exercise.
CONCLUSION: In conclusion, flu-like disease, fever, and vigorous exercise may convert an asymptomatic PFO into a stroke-causing PFO in young adults.
DATA ACCESS STATEMENT: The raw and anonymized data used in this study can be made available to other researchers on request. Written proposals can be addressed to the corresponding author and will be assessed by the ODYSSEY investigators for appropriateness of use, and a data sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

Gepubliceerd: Int J Stroke. 2024;19(7):809-16.
Impact factor: 8.7 ; Q1

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20. Evolution of glucose levels in patients with anterior circulation acute ischemic stroke treated with endovascular therapy using continuous glucose monitoring
Kersten C, Zandbergen AAM, Fokkert MJ, Slingerland RJ, Knottnerus ILH, van der Molen M, Wijlens MLB, Hofmeijer J, den Hertog HM.

INTRODUCTION: Hyperglycemia is common in acute ischemic stroke, and associated with larger infarct volume and unfavorable functional outcome. To identify a subgroup that may benefit from glucose lowering in future studies, we assessed the evolution of glucose levels in the first 24 hrs after admission using continuous glucose monitoring in patients with anterior circulation large vessel occlusion ischemic stroke who underwent endovascular therapy (EVT).
METHODS: In a prospective two center cohort study, consecutive patients with anterior circulation ischemic stroke, who were eligible for EVT within 24 hrs of symptom onset, were enrolled. Glucose monitoring was performed using a Freestyle Libre Flash 2 device during 24 hrs. We analysed median glucose on admission, time ratio of glucose > 7.8 mmol/L (7.8 time-ratio) and coefficient of variation (% CV), including relations with predefined patient characteristics and outcomes.
RESULTS: One hundred and two patients were included in the analyses, with a median stroke-onset-to-measurement-time of 4 hrs. Median glucose on admission was 7.0 mmol/L (IQR 6.0-8.4 mmol/L). Overall, 7.8 time-ratio and % CV were 13% and 4% respectively. In patients who were normoglycemic or hyperglycemic on admission, the glucose variability was small with % CV of 6% and 4% respectively. Hyperglycemia on admission, high HbA1C, successful recanalization, older age, and high NIHSS scores were associated with higher 7.8 time-ratio.
CONCLUSION: Glucose monitoring and studies on effectiveness of glucose lowering may be especially useful in EVT patients with hyperglycemia on admission, high HbA1C, successful recanalization, older age and high initial NIHSS scores.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2024;33(12):108103.
Impact factor: 1.8 ; Q3

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21. Reactie op het artikel 'Behandeling van neuropathische pijn bij patiënten met dunnevezelneuropathie'
Kho KH, Flipse DHK, Monteira de Oliveira NP, Huygen FJPM, Theys T.

Gepubliceerd: Tijdschr Neurol Neurochir. 2024;125(3):112.
IF onbekend

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22. Intravenous Thrombolysis Before Endovascular Treatment in Posterior Circulation Occlusions: A MR CLEAN Registry Study
Knapen R, Pirson FAV, Langezaal LCM, Brouwer J, Majoie C, Emmer BJ, Vos JA, van Doormaal PJ, Yoo AJ, Bruggeman AAE, Lycklama À Nijeholt GJ, van der Leij C, van Oostenbrugge RJ, van Zwam WH, Schonewille WJ, MR CLEAN Registry Investigators; Brouwers PJAM.

BACKGROUND: The effectiveness of intravenous thrombolysis (IVT) before endovascular treatment (EVT) has been investigated in randomized trials and meta-analyses. These studies mainly concerned anterior circulation occlusions. We aimed to investigate clinical, technical, and safety outcomes of IVT before EVT in posterior circulation occlusions in a nationwide registry.
METHODS: Patients were included from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), a nationwide, prospective, multicenter registry of patients with acute ischemic stroke due to a large intracranial vessel occlusion receiving EVT between 2014 and 2019. All patients with a posterior circulation occlusion were included. Primary outcome was a shift toward better functional outcome on the modified Rankin Scale at 90 days. Secondary outcomes were favorable functional outcome (modified Rankin Scale scores, 0-3), occurrence of symptomatic intracranial hemorrhages, successful reperfusion (extended Thrombolysis in Cerebral Ischemia ≥2B), first-attempt successful reperfusion, and mortality at 90 days. Regression analyses with adjustments based on univariable analyses and literature were applied.
RESULTS: A total of 248 patients were included, who received either IVT (n=125) or no IVT (n=123) before EVT. Results show no differences in a shift on the modified Rankin Scale (adjusted common odds ratio, 1.04 [95% CI, 0.61-1.76]). Although symptomatic intracranial hemorrhages occurred more often in the IVT group (4.8% versus 2.4%), regression analysis did not show a significant difference (adjusted odds ratio, 1.65 [95% CI, 0.33-8.35]). Successful reperfusion, favorable functional outcome, first-attempt successful reperfusion, and mortality did not differ between patients treated with and without IVT.
CONCLUSIONS: We found no significant differences in clinical, technical, and safety outcomes between patients with a large vessel occlusion in the posterior circulation treated with or without IVT before EVT. Our results are in line with the literature on the anterior circulation.

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Impact factor: 8.9 ; Q1

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23. Validity of the modified Rankin Scale in patients with aneurysmal subarachnoid hemorrhage: a randomized study
Nobels-Janssen E, Postma EN, Abma IL, van Dijk JMC, de Ridder IR, Schenck H, Moojen WA, den Hertog MH, Nanda D, Potgieser ARE, Coert BA, Verhagen WIM, Bartels R, van der Wees PJ, Verbaan D, Boogaarts HD.

PURPOSE: The modified Rankin Scale (mRS), a clinician-reported outcome measure of global disability, has never been validated in patients with aneurysmal subarachnoid hemorrhage (aSAH). The aims of this study are to assess: (1) convergent validity of the mRS; (2) responsiveness of the mRS; and (3) the distribution of mRS scores across patient-reported outcome measures (PROMs).
METHODS: This is a prospective randomized multicenter study. The mRS was scored by a physician for all patients, and subsequently by structured interview for half of the patients and by self-assessment for the other half. All patients completed EuroQoL 5D-5L, RAND-36, Stroke Specific Quality of Life scale (SS-QoL) and Global Perceived Effect (GPE) questionnaires. Convergent validity and responsiveness were assessed by testing hypotheses.
RESULTS: In total, 149 patients with aSAH were included for analysis. The correlation of the mRS with EQ-5D-5L was r = - 0.546, while with RAND-36 physical and mental component scores the correlation was r = - 0.439and r = - 0.574 respectively, and with SS-QoL it was r = - 0.671. Three out of four hypotheses for convergent validity were met. The mRS assessed through structured interviews was more highly correlated with the mental component score than with the physical component score of RAND-36. Improvement in terms of GPE was indicated by 83% of patients; the mean change score of these patients on the mRS was - 0.08 (SD 0.915). None of the hypotheses for responsiveness were met.
CONCLUSION: The results show that the mRS generally correlates with other instruments, as expected, but it lacks responsiveness. A structured interview of the mRS is best for detecting disabling neuropsychological complaints.
REGISTRATION: URL: https://trialsearch.who.int ; Unique identifier: NL7859, Date of first administration: 08-07-2019.

Gepubliceerd: BMC Neurol. 2024;24(1):23.
Impact factor: 2.2 ; Q3

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24. Ghrelin for Neuroprotection in Post-Cardiac Arrest Coma: A Randomized Clinical Trial
Nutma S, Beishuizen A, van den Bergh WM, Foudraine NA, le Feber J, Filius PMG, Cornet AD, van der Palen J, van Putten M, Hofmeijer J.

IMPORTANCE: Out-of-hospital cardiac arrest survival rates have markedly risen in the last decades, but neurological outcome only improved marginally. Despite research on more than 20 neuroprotective strategies involving patients in comas after cardiac arrest, none have demonstrated unequivocal evidence of efficacy; however, treatment with acyl-ghrelin has shown improved functional and histological brain recovery in experimental models of cardiac arrest and was safe in a wide variety of human study populations.
OBJECTIVE: To determine safety and potential efficacy of intravenous acyl-ghrelin to improve neurological outcome in patients in a coma after cardiac arrest.
DESIGN, SETTING, AND PARTICIPANTS: A phase 2, double-blind, placebo-controlled, multicenter, randomized clinical trial, Ghrelin Treatment of Comatose Patients After Cardiac Arrest: A Clinical Trial to Promote Cerebral Recovery (GRECO), was conducted between January 18, 2019, and October 17, 2022. Adult patients 18 years or older who were in a comatose state after cardiac arrest were assessed for eligibility; patients were from 3 intensive care units in the Netherlands. Expected death within 48 hours or unfeasibility of treatment initiation within 12 hours were exclusion criteria.
INTERVENTIONS: Patients were randomized to receive intravenous acyl-ghrelin, 600 µg (intervention group), or placebo (control group) within 12 hours after cardiac arrest, continued for 7 days, twice daily, in addition to standard care.
MAIN OUTCOMES AND MEASURES: Primary outcome was the score on the Cerebral Performance Categories (CPC) scale at 6 months. Safety outcomes included any serious adverse events. Secondary outcomes were mortality and neuron-specific enolase (NSE) levels on days 1 and 3.

RESULTS: A total of 783 adult patients in a coma after cardiac arrest were assessed for eligibility, and 160 patients (median [IQR] age, 68 [57-75] years; 120 male [75%]) were enrolled. A total of 81 patients (51%) were assigned to the intervention group, and 79 (49%) were assigned to the control group. The common odds ratio (OR) for any CPC improvement in the intervention group was 1.78 (95% CI, 0.98-3.22; P = .06). This was consistent over all CPC categories. Mean (SD) NSE levels on day 1 after cardiac arrest were significantly lower in the intervention group (34 [6] µg/L vs 56 [13] µg/L; P = .04) and on day 3 (28 [6] µg/L vs 52 [14] µg/L; P = .08). Serious adverse events were comparable in incidence and type between the groups. Mortality was 37% (30 of 81) in the intervention group vs 51% (40 of 79) in the control group (absolute risk reduction, 14%; 95% CI, -2% to 29%; P = .08).
CONCLUSIONS AND RELEVANCE: In patients in a coma after cardiac arrest, intravenous treatment with acyl-ghrelin was safe and potentially effective to improve neurological outcome. Phase 3 trials are needed for conclusive evidence.
TRIAL REGISTRATION: Clinicaltrialsregister.eu: EUCTR2018-000005-23-NL.

Gepubliceerd: JAMA Neurol. 2024;81(6):603-10.
Impact factor: 21.4 ; Q1

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25. Long term functioning with poor neurologic outcome after cardiac arrest
Nutma S, Roesink O, van Heugten CM, Hofmeijer J.

AIM: Around six percent of comatose patients after cardiac arrest have a Cerebral Performance Categories score of three (CPC3) at six months after the arrest, classified as severe neurological disability. There is limited knowledge regarding the likelihood of further recovery in the cognitive, emotional, and quality of life domains. We aimed to estimate the probability of recovery towards independency.
METHODS: From a prospective Registry on comatose cardiac arrest patients admitted between 2013 and 2017 in two Dutch hospitals, we included patients with a CPC3 at six months after cardiac arrest. We followed patients up to November 2023. The primary outcome measure was the CPC score at time of follow up. Secondary outcomes were scores on questionnaires on cognition, mood, and quality of life according to the minimal dataset of acquired brain injury.
RESULTS: In our cohort of 667 patients, 29 (4.3%) had a CPC3 score at six months (median age 68 years, 83% male). At a median time of eight years after cardiac arrest, sixteen patients had died. Twelve of thirteen alive patients still had a CPC3 score (92%) and one a CPC2 (8%). Seven patients agreed with further interviewing, one showed independency in activities of daily living (14%). Six patients (86%) reported limitations due to physical and one (14%) due to emotional problems. All had severe cognitive impairment. Six (86%) missed cognitive rehabilitation.
CONCLUSION: Our study shows that while the probability of recovery towards independence for patients with severe neurological disability at six months after cardiac arrest is limited, most long-term survivors are satisfied with their quality of life.

Gepubliceerd: Resuscitation. 2024;203:110375.
Impact factor: 4.6 ; Q1

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26. Structured medication reviews in Parkinson's disease: pharmacists' views, experiences and needs - a qualitative study
Oonk NGM, Dorresteijn LDA, Te Braake E, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Bode C.

BACKGROUND: Executing structured medication reviews (SMRs) in primary care to optimize drug treatment is considered standard care of community pharmacists in the Netherlands. Patients with Parkinson's disease (PD) often face complex drug regimens for their symptomatic treatment and might, therefore, benefit from an SMR. However, previously, no effect of an SMR on quality of life in PD was found. In trying to improve the case management of PD, it is interesting to understand if and to what extent SMRs in PD patients are of added value in the pharmacist's opinion and what are assumed facilitating and hindering factors.
OBJECTIVES: To analyse the process of executing SMRs in PD patients from a community pharmacist's point of view.
DESIGN: A cross-sectional, qualitative study was performed, consisting of face-to-face semi-structured in-depth interviews.
METHODS: The interviews were conducted with community pharmacists who executed at least one SMR in PD, till data saturation was reached. Interviews were transcribed verbatim, coded and analysed thematically using an iterative approach.
RESULTS: Thirteen pharmacists were interviewed. SMRs in PD were considered of added value, especially regarding patient contact and bonding, individualized care and its possible effect in the future, although PD treatment is found already well monitored in secondary care. Major constraints were time, logistics and collaboration with medical specialists.
CONCLUSION: Although community pharmacist-led SMRs are time-consuming and sometimes logistically challenging, they are of added value in primary care in general, and also in PD, of which treatment occurs mainly in secondary care. It emphasizes the pharmacist's role in PD treatment and might tackle future drug-related issues. Improvements concern multidisciplinary collaboration for optimized SMR execution and results.

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Impact factor: 3.4 ; Q2

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27. Hyponatremia is associated with unfavorable outcomes after reperfusion treatment in acute ischemic stroke

Pelouto A, Reimer J, Hoorn EJ, Zandbergen AAM, den Hertog HM.

BACKGROUND AND PURPOSE: In patients with acute ischemic stroke, hyponatremia (plasma sodium < 136 mmol/L) is common and associated with unfavorable outcomes. However, data are limited for patients who underwent intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT). Therefore, our aim was to assess the impact of hyponatremia on postreperfusion outcomes.
METHODS: We analyzed data of consecutive patients who presented with acute ischemic stroke and were treated with IVT and/or EVT at Isala Hospital, the Netherlands, in 2019 and 2020. The primary outcome measure was the adjusted common odds ratio (acOR) for a worse modified Rankin Scale (mRS) score at 3-month follow-up. Secondary outcomes included symptomatic intracranial hemorrhage, in-hospital mortality, infarct core, and penumbra volumes.
RESULTS: Of the 680 patients (median age = 73 years, 49% female, median National Institutes of Health Stroke Scale = 5), 430 patients (63%) were treated with IVT, 120 patients (18%) with EVT, and 130 patients (19%) with both. Ninety-two patients (14%) were hyponatremic on admission. Hyponatremia was associated with a worse mRS score at 3 months (acOR = 1.76, 95% confidence interval [CI] = 1.12-2.76) and in-hospital mortality (aOR = 2.39, 95% CI = 1.23-4.67), but not with symptomatic intracranial hemorrhage (OR = 1.17, 95% CI = 0.39-3.47). Hyponatremia was also associated with a larger core (17.2 mL, 95% CI = 2.9-31.5) and core to penumbra ratio (55.0%, 95% CI = 7.1-102.9).
CONCLUSIONS: Admission hyponatremia in patients with acute ischemic stroke treated with IVT and/or EVT was independently associated with unfavorable postreperfusion outcomes, a larger

infarct core, and a larger core to penumbra ratio. Future studies should address whether correction of hyponatremia improves the prognosis.

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Impact factor: 3.9 ; Q1

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28. Changes in postictal cerebral perfusion are related to the duration of electroconvulsive therapy-induced seizures
Pottkämper JCM, Verdijk J, Aalbregt E, Stuiver S, van de Mortel L, Norris DG, van Putten M, Hofmeijer J, van Wingen GA, van Waarde JA.

OBJECTIVE: Postictal symptoms may result from cerebral hypoperfusion, which is possibly a consequence of seizure-induced vasoconstriction. Longer seizures have previously been shown to cause more severe postictal hypoperfusion in rats and epilepsy patients. We studied cerebral perfusion after generalized seizures elicited by electroconvulsive therapy (ECT) and its relation to seizure duration.
METHODS: Patients with a major depressive episode who underwent ECT were included. During treatment, 21-channel continuous electroencephalogram (EEG) was recorded. Arterial spin labeling magnetic resonance imaging scans were acquired before the ECT course (baseline) and approximately 1 h after an ECT-induced seizure (postictal) to quantify global and regional gray matter cerebral blood flow (CBF). Seizure duration was assessed from the period of epileptiform discharges on the EEG. Healthy controls were scanned twice to assess test-retest variability. We performed hypothesis-driven Bayesian analyses to study the relation between global and regional perfusion changes and seizure duration.
RESULTS: Twenty-four patients and 27 healthy controls were included. Changes in postictal global and regional CBF were correlated with seizure duration. In patients with longer seizure durations, global decrease in CBF reached values up to 28 mL/100 g/min. Regional reductions in CBF were most prominent in the inferior frontal gyrus, cingulate gyrus, and insula (up to 35 mL/100 g/min). In patients with shorter seizures, global and regional perfusion increased (up to 20 mL/100 g/min). These perfusion changes were larger than changes observed in healthy controls, with a maximum median global CBF increase of 12 mL/100 g/min and a maximum median global CBF decrease of 20 mL/100 g/min.
SIGNIFICANCE: Seizure duration is a key factor determining postictal perfusion changes. In future studies, seizure duration needs to be considered as a confounding factor due to its opposite effect on postictal perfusion.

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Impact factor: 6.6 ; Q1

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29. Exploring postictal recovery with acetaminophen or nimodipine: A randomized-controlled crossover trial
Pottkämper JCM, Verdijk J, Stuiver S, Aalbregt E, Ten Doesschate F, Verwijk E, Schmettow M, van Wingen GA, van Putten M, Hofmeijer J, van Waarde JA.

OBJECTIVE: The postictal state is underrecognized in epilepsy. Animal models show improvement of postictal symptoms and cerebral perfusion with acetaminophen or nimodipine. We studied the effects of acetaminophen or nimodipine on postictal electroencephalographic (EEG) recovery, clinical reorientation, and hypoperfusion in patients with ECT-induced seizures.

METHODS: In this prospective clinical trial with three-condition randomized crossover design, study interventions were administered orally 2 h before ECT sessions (1000 mg acetaminophen, 60 mg nimodipine, or a placebo condition). Primary outcome measure was the speed of postictal EEG recovery. Secondary outcomes were the extent of postictal EEG recovery, clinical reorientation time, and postictal cerebral blood flow as assessed by perfusion-weighted MRI. Bayesian generalized mixed-effects models were applied for analyses.
RESULTS: We included 300 seizures, postictal EEGs, and reorientation time values, and 76 MRI perfusion measures from 33 patients (median age 53 years, 19 female). Pretreatment with acetaminophen or nimodipine was not associated with change in speed of EEG recovery compared to placebo (1.13 [95%CI 0.92, 1.40] and 1.07 [95%CI 0.87, 1.31], respectively), nor with the secondary outcomes. No patient reached full EEG recovery at 1 h post-seizure, despite clinical recovery in 89%. Longer seizures were associated with slower EEG recovery and lower postictal perfusion. Nimodipine altered regional perfusion in the posterior cortex.
INTERPRETATION: Pretreatment with acetaminophen or nimodipine did not alleviate symptoms and signs of the postictal state. Systematic study of the postictal state after ECT-induced seizures is feasible.

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Impact factor: 3.9 ; Q1

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30. Microsurgical Treatment of Intracranial Dural Arteriovenous Fistulas: A Collaborative Investigation From the Multicenter Consortium for Dural Arteriovenous Fistula Outcomes Research
Raygor KP, Abdelsalam A, Tonetti DA, Raper DMS, Guniganti R, Durnford AJ, Giordan E, Brinjikji W, Chen CJ, Abecassis IJ, Levitt MR, Polifka AJ, Derdeyn CP, Samaniego EA, Kwasnicki A, Alaraj A, Potgieser ARE, Chen S, Tada Y, Kansagra AP, Satomi J, Eatz T, Peterson EC, Starke RM, van Dijk JMC, Amin-Hanjani S, Hayakawa M, Gross BA, Fox WC, Kim L, Sheehan J, Lanzino G, Du R, Lai PMR, Bulters DO, Zipfel GJ, Abla AA.

BACKGROUND AND OBJECTIVES: First-line therapy for most intracranial dural arteriovenous fistulas (dAVFs) is endovascular embolization, but some require microsurgical ligation due to limited endovascular accessibility, anticipated lower cure rates, or unacceptable risk profiles. We investigated the most common surgically treated dAVF locations and the approaches and outcomes of each.
METHODS: The Consortium for Dural Arteriovenous Fistula Outcomes Research database was retrospectively reviewed. Patients who underwent dAVF microsurgical ligation were included. Patient demographics, angiographic information, surgical details, and postoperative outcomes were collected. The 5 most common surgically treated dAVF locations were analyzed about used surgical approaches and postoperative outcomes. Univariate analyses were performed with statistical significance set at a threshold of $P < .05$.
RESULTS: In total, 248 patients in the Consortium for Dural Arteriovenous Fistula Outcomes Research database met inclusion criteria. The 5 most common surgically treated dAVF locations were tentorial, anterior cranial fossa (ACF), transverse-sigmoid sinus (TSS), convexity/superior sagittal sinus (SSS), and torcular. Most tentorial dAVFs were approached using a suboccipital, lateral supracerebellar infratentorial approach (39.3%); extended retrosigmoid approach (ERS) (25%); or posterior subtemporal approach (19.6%). All ACF dAVFs used a subfrontal approach; 5.3% also included an anterior interhemispheric approach. Most TSS dAVFs were ligated via ERS (31.3%) or subtemporal (31.3%) approaches. All convexity/SSS dAVFs used an interhemispheric approach. All torcular dAVFs used the suboccipital, lateral supracerebellar infratentorial approach, with 10.5% undergoing simultaneous ERS craniotomy. Angiographic occlusion rates after microsurgery were 85.5%, 100%, 75.8%, 79.2%, and 73.7% for tentorial, ACF, TSS, convexity/SSS, and torcular dAVFs, respectively ($P = .02$); the permanent neurological complication rates were 1.8%, 2.6%, 9.1%, 0%, and 0% ($P = .31$).

There were no statistically significant differences in development of complications (P = .08) or Modified Rankin Scale at the last follow-up (P = .11) by fistula location.
CONCLUSION: Although endovascular embolization is the first-line treatment for most intracranial dAVFs, surgical ligation is an important alternative. ACF and tentorial fistulas particularly demonstrate high rates of postoperative obliteration.

Gepubliceerd: Neurosurgery. 2024.
Impact factor: 3.9 ; Q1

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31. Cognitive impairment in young adults following cerebellar stroke: Prevalence and longitudinal course
Reumers SFI, Schellekens MMI, Lugtmeijer S, Maas R, Verhoeven JI, Boot EM, Ekker MS, Tuladhar AM, van de Warrenburg BPC, Schutter D, Kessels RPC, de Leeuw FE, ODYSSEY study group; Arntz RM, Brouwers PJAM.

INTRODUCTION: Cognitive impairment is a well-known result of a stroke, but for cerebellar stroke in young patients detailed knowledge on the nature and extent of cognitive deficits is limited. This study examined the prevalence and course of cognitive impairment in a large cohort of patients with cerebellar stroke.
METHODS: Sixty young (18-49 years) cerebellar stroke patients completed extensive neuropsychological assessments in the subacute (<9 months post-stroke) and/or chronic phase (≥9 months post-stroke). Performance and course were assessed using standardized scores and Reliable Change Index analyses. Associations between cognitive deficits and lesion locations were explored using subtraction analyses, and associations with subjective cognitive complaints and fatigue were examined.
RESULTS: Sixty patients (52% male) were included with a mean age at event of 43.1 years. Cognitive impairment was observed in 60.3% of patients in the subacute phase and 51.2% during the chronic phase. Deficits were most frequent for visuo-spatial skills and executive functioning (42.5-54.6%). Both improvement and decline were observed over time, in 17.9% and 41.0% of participants, respectively. Cognitive deficits seem to be associated with lesions in certain cerebellar regions, however, no distinct correlation was found for a specific subregion. Subjective cognitive complaints were present in the majority of participants (61-80.5%) and positively correlated with fatigue in both phases ($\rho = -.661$ and $\rho = -.757$, $p < .001$, respectively).
DISCUSSION: Cognitive impairment in cerebellar stroke patients is common, with deficits most pronounced for visuo-spatial skills and executive functioning, as in line with the Cerebellar Cognitive Affective Syndrome. The course of cognitive performance was heterogenous, with cognitive decline despite the fact that no recurrent strokes occurred. No clear association between lesion location and cognitive deficits was observed. Subjective cognitive complaints and fatigue were prevalent and positively correlated. Clinicians could use this information to actively screen for and better inform patients about possible cognitive sequalae.

Gepubliceerd: Cortex. 2024;178:104-15.
Impact factor: 3.3 ; Q1

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32. Feasibility and repeatability of ultrasound-guided surface electroenterography to measure colonic slow wave motility in healthy adults
Rolleman NH, Visser IM, Klein WM, Van Putten M, De Blaauw I, Botden S.

Surface electroenterography is a potential non-invasive alternative to current diagnostics of colonic motility disorders. However, electrode positioning in electroenterography is often based on general anatomy and may lack generalizability. Furthermore, the repeatability of electroenterography measurements is unknown. This study aimed to evaluate ultrasound-guided electrode positioning for electroenterography measurements and to determine the repeatability of those measurements. In ten healthy adults, two electroenterography procedures were performed, consisting of fasting, ultrasound-guided electrode localization and two 20-minute electroenterography recordings separated by a meal. The dominant frequency, the mean power density (magnitude of colonic motility) and the power percent difference (relative pre- to postprandial increase in magnitude) were determined. Repeatability was determined by Lin's concordance correlation coefficient. The results demonstrated that the dominant frequency did not differ between pre- and postprandial recordings and was 3 cpm, characteristic of colonic motility. The mean power density increased between the pre- and postprandial measurements, with an average difference of over 200%. The repeatability of both the dominant frequency and power density was poor to moderate, whereas the correlation coefficient of the power percent difference was poor. Concluding, ultrasound-guided surface electroenterography seems able to measure the gastrocolic reflex, but the dissatisfactory repeatability necessitates optimization of the measurement protocol.

Gepubliceerd: BMC Gastroenterol. 2024;24(1):114.
Impact factor: 2.6 ; Q2

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33. Identification of At-Risk Patients That Need More Intensive Treatment Following mTBI: Post-Hoc Insights From the UPFRONT-Study
Scheenen ME, van der Horn HJ, de Koning ME, van der Naalt J, Spikman JM.

OBJECTIVE: To investigate which factors within an at-risk group make patients less likely to benefit from preventive treatment following mild traumatic brain injury (mTBI).
SETTING: Inclusion in 3 level I trauma centers in the Netherlands. Data collection through surveys as outpatients.
PARTICIPANTS: mTBI patients (18-66 years), reporting 3 or more complaints 2 weeks postinjury (at-risk status). Eighty-four patients included and randomized (39 patients cognitive behavioral therapy, 45 patients telephonic counseling). Eighty patients filled out the questionnaires 12 months postinjury. Post hoc analysis investigating 80 patients as 1 at-risk group receiving psychological treatment.
DESIGN: Post hoc study of a randomized controlled trial (RCT). Binomial logistic regression performed determining which variables 2 weeks postinjury contributed strongly to unsuccessful return to work/study (RTW) and unfavorable outcome at 12 months.
MAIN MEASURES: RTW and functional outcome as measured with the Glasgow Outcome Scale-Extended (GOSE) at 12 months postinjury.
RESULTS: Out of 80 patients, 43 (53.8%) showed a favorable functional outcome at 12 months, and 56 (70%) patients had a full RTW. Patients with unfavorable outcome had a higher age and higher reports of anxiety, depression at 2 weeks and 12 months postinjury. Patients with an unsuccessful RTW had a higher age and higher reports of depression, and posttraumatic stress disorder at 2 weeks and 12 months postinjury. A logistic regression model for functional outcome (GOSE) was statistically significant (χ^2 7 = 40.30, P < .0001). Of 6 predictor variables, 3 were significant: anxiety, depression, and treatment condition. For RTW, logistic regression was also statistically significant (χ^2 7 = 19.15, P = .008), with only 1 out of 6 predictor variables (ie, age) being significant.
CONCLUSION: Main findings comprise differences in demographic and psychological measures between patients with favorable and unfavorable outcomes and patients with RTW versus no RTW. Prediction models of outcome and RTW showed several psychological measures at 2 weeks greatly determining patients' likelihood benefitting from the preventive treatment. Results suggest that from the beginning there are some patients for whom a short preventive treatment is not sufficient.

Selection and treatment of at-risk patients might be better based on psychological symptoms instead of posttraumatic complaints.

Gepubliceerd: J Head Trauma Rehabil. 2024;39(5):E372-e80.
Impact factor: 3.3 ; Q1

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34. Cognitive trajectory in the first year after first-ever ischaemic stroke in young adults: the ODYSSEY study
Schellekens MMI, Springer RCS, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, van Tuijl JH, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, Van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Kort PLM, De Leeuw FE, Kessels RPC, Tuladhar AM.

BACKGROUND: Limited data exists on cognitive recovery in young stroke patients. We aimed to investigate the longitudinal course of cognitive performance during the first year after stroke at young age and identify predictors for cognitive recovery.
METHODS: We conducted a multicentre prospective cohort study between 2013 and 2021, enrolling patients aged 18-49 years with first-ever ischaemic stroke. Cognitive assessments were performed within 6 months and after 1 year following the index event, covering seven cognitive domains. Composite Z-scores using normative data determined cognitive impairment (Z-score<-1.5). A Reliable Change Index (RCI) assessed cognitive recovery (RCI>1.96) or decline (RCI<-1.96).
RESULTS: 393 patients (median age 44.3 years, IQR 38.4-47.2) completed cognitive assessments with a median time interval of 403 days (IQR 364-474) between assessments. Based on RCI, a similar proportion of patients showed improvement and decline in each cognitive domain, while the majority exhibited no cognitive change. Among cognitively impaired patients at baseline, improvements were observed in processing speed (23.1%), visuoconstruction (40.1%) and executive functioning (20.0%). Younger age was associated with better cognitive recovery in visuoconstruction, and larger lesion volume was related to cognitive recovery in processing speed. No other predictors for cognitive recovery were identified.
CONCLUSIONS: Cognitive impairment remains prevalent in young stroke even 1 year after the event. Most patients showed no cognitive change, however, recovery may have occurred in the early weeks after stroke, which was not assessed in our study. Among initially cognitively impaired patients, cognitive recovery is observed in processing speed, visuoconstruction and executive functioning. It is still not possible to predict cognitive recovery in individual patients.

Gepubliceerd: J Neurol Neurosurg Psychiatry. 2024;95(6):571-9.
Impact factor: 7.8 ; Q1

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35. Cortical excitation/inhibition ratios in patients with major depression treated with electroconvulsive therapy: an EEG analysis
Stuiver S, Pottkämper JCM, Verdijk J, Ten Doesschate F, Aalbregt E, van Putten M, Hofmeijer J, van Waarde JA.

Electroconvulsive therapy (ECT) is an effective treatment for major depression, but its working mechanisms are poorly understood. Modulation of excitation/inhibition (E/I) ratios may be a driving factor. Here, we estimate cortical E/I ratios in depressed patients and study whether these ratios change over the course of ECT in relation to clinical effectiveness. Five-minute resting-state electroencephalography (EEG) recordings of 28 depressed patients were recorded before and after their ECT course. Using a novel method based on critical dynamics, functional E/I (fE/I) ratios in the

frequency range of 0.5-30 Hz were estimated in frequency bins of 1 Hz for the whole brain and for pre-defined brain regions. Change in Hamilton Depression Rating Scale (HDRS) score was used to estimate clinical effectiveness. To account for test-retest variability, repeated EEG recordings from an independent sample of 31 healthy controls (HC) were included. At baseline, no differences in whole brain and regional fE/I ratios were found between patients and HC. At group level, whole brain and regional fE/I ratios did not change over the ECT course. However, in responders, frontal fE/I ratios in the frequencies 12-28 Hz increased significantly (p(FDR) < 0.05 [FDR = false discovery rate]) over the ECT course. In non-responders and HC, no changes occurred over time. In this sample, frontal fE/I ratios increased over the ECT course in relation to treatment response. Modulation of frontal fE/I ratios may be an important mechanism of action of ECT.

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Impact factor: 3.7 ; Q1

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36. Restoration of postictal cortical activity after electroconvulsive therapy relates to recovery of orientation in person, place, and time
Stuiver S, Pottkämper JCM, Verdijk J, Ten Doesschate F, van Putten M, Hofmeijer J, van Waarde JA.

BACKGROUND: Most patients show temporary impairments in clinical orientation after electroconvulsive therapy (ECT)-induced seizures. It is unclear how postictal reorientation relates to electroencephalography (EEG) restoration. This relationship may provide additional measures to quantify postictal recovery and shed light on neurophysiological aspects of reorientation after ECT.
METHODS: We analyzed prospectively collected clinical and continuous ictal and postictal EEG data from ECT patients. Postictal EEG restoration up to 1 h was estimated by the evolution of the normalized alpha-delta ratio (ADR). Times to reorientation in the cognitive domains of person, place, and time were assessed postictally. In each cognitive domain, a linear mixed model was fitted to investigate the relationships between time to reorientation and postictal EEG restoration.
RESULTS: In total, 272 pairs of ictal-postictal EEG and reorientation times of 32 patients were included. In all domains, longer time to reorientation was associated with slower postictal EEG recovery. Longer seizure duration and postictal administration of midazolam were related to longer time to reorientation in all domains. At 1-hour post-seizure, most patients were clinically reoriented, while their EEG had only partly restored.
CONCLUSIONS: We show a relationship between postictal EEG restoration and clinical reorientation after ECT-induced seizures. EEG was more sensitive than reorientation time in all domains to detect postictal recovery beyond 1-hour post-seizure. Our findings indicate that clinical reorientation probably depends on gradual cortical synaptic recovery, with longer seizure duration leading to longer postsynaptic suppression after ECT seizures.

Gepubliceerd: Eur Psychiatry. 2024;67(1):e16.
Impact factor: 6.7 ; Q1

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37. The role of imaging in focal neuropathies
Telleman JA, Sneag DB, Visser LH.

Electrodiagnostic testing (EDX) has been the diagnostic tool of choice in peripheral nerve disease for many years, but in recent years, peripheral nerve imaging has been used ever more frequently in daily clinical practice. Nerve ultrasound and magnetic resonance (MR) neurography are able to visualize nerve structures reliably. These techniques can aid in localizing nerve pathology and can reveal significant anatomical abnormalities underlying nerve pathology that may have been

otherwise undetected by EDX. As such, nerve ultrasound and MR neurography can significantly improve diagnostic accuracy and can have a significant effect on treatment strategy. In this chapter, the basic principles and recent developments of these techniques will be discussed, as well as their potential application in several types of peripheral nerve disease, such as carpal tunnel syndrome (CTS), ulnar neuropathy at the elbow (UNE), radial neuropathy, brachial and lumbosacral plexopathy, neuralgic amyotrophy (NA), fibular, tibial, sciatic, femoral neuropathy, meralgia paresthetica, peripheral nerve trauma, tumors, and inflammatory neuropathies.

Gepubliceerd: Handb Clin Neurol. 2024;201:19-42.
IF onbekend

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38. Ultra-Early and Short-Term Tranexamic Acid Treatment in Patients With Good- and Poor-Grade Aneurysmal Subarachnoid Hemorrhage
Tjerkstra MA, Post R, Germans MR, Vergouwen MDI, Jellema K, Koot RW, Kruyt ND, Wolfs JFC, De Beer FC, Kieft HH, Nanda D, Van Der Pol B, Roks G, De Beer F, Reichman LJA, Brouwers P, Kwa VIH, Van Der Ree TC, Bienfait HP, Boogaarts HD, Klijn CJ, Visser V, van den Berg R, Coert BA, Horn J, Majoie C, Rinkel GJE, Roos Y, Vandertop WP, Verbaan D.

BACKGROUND AND OBJECTIVES: The results of the ULTRA trial showed that ultra-early and short-term treatment with tranexamic acid (TXA) does not improve clinical outcome after aneurysmal subarachnoid hemorrhage (aSAH). Possibly, the lack of a beneficial effect in all patients with aSAH is masked by antagonistic effects of TXA in certain subgroups. In this post hoc subgroup analysis, we investigated the effect of TXA on clinical outcome in patients with good-grade and poor-grade aSAH.
METHODS: The ULTRA trial was a multicenter, prospective, randomized, controlled, open-label trial with blinded outcome assessment. Participants received ultra-early and short-term TXA in addition to usual care or usual care only. This post hoc subgroup analysis included only ULTRA participants with confirmed aSAH and available World Federation of Neurosurgical Societies (WFNS) grade on admission. Patients were categorized into those with good-grade (WFNS 1-3) and poor-grade (WFNS 4-5) aSAH. The primary outcome was clinical outcome assessed by the modified Rankin scale (mRS). Odds ratios (ORs) and adjusted ORs (aORs) with 95% CIs were calculated using ordinal regression analyses. Analyses were performed using the as-treated principle. In all patients with aSAH, no significant effect modification of TXA on clinical outcome was observed for admission WFNS grade ($p = 0.10$).
RESULTS: Of the 812 ULTRA participants, 473 patients had (58%; N = 232 TXA, N = 241 usual care) good-grade and 339 (42%; N = 162 TXA, N = 176 usual care) patients had poor-grade aSAH. In patients with good-grade aSAH, the TXA group had worse clinical outcomes (OR: 0.67, 95% CI 0.48-0.94, aOR 0.68, 95% CI 0.48-0.94) compared with the usual care group. In patients with poor-grade aSAH, clinical outcomes were comparable between treatment groups (OR: 1.04, 95% CI 0.70-1.55, aOR 1.05, 95% CI 0.70-1.56).
DISCUSSION: This post hoc subgroup analysis provides another important argument against the use of TXA treatment in patients with aSAH, by showing worse clinical outcomes in patients with good-grade aSAH treated with TXA and no clinical benefit of TXA in patients with poor-grade aSAH, compared with patients treated with usual care.
TRIAL REGISTRATION INFORMATION: ClinicalTrials.gov (NCT02684812; submission date February 18, 2016, first patient enrollment on July 24, 2013). CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that tranexamic acid, given for <24 hours within the first 24 hours, does not improve the 6-month outcome in good-grade or poor initial-grade aneurysmal SAH.

Gepubliceerd: Neurology. 2024;102(12):e209169.
Impact factor: 9.0 ; Q1

39. Routine transthoracic echocardiography in ischaemic stroke or transient ischaemic attack of undetermined cause: a prospective multicentre study
van der Maten G, Meijs MFL, Timmer JR, Brouwers P, von Birgelen C, Coutinho JM, Bouma BJ, Kerkhoff H, Helming AM, van Tuijl JH, van der Meer NA, Saxena R, Ebink C, van der Palen J, den Hertog HM.

BACKGROUND: Guidelines recommend routine transthoracic echocardiography (TTE) after ischaemic stroke or transient ischaemic attack of undetermined cause; yet, only limited scientific evidence exists. Therefore, we aimed to determine in these patients the prevalence of TTE-detected major cardiac sources of embolism (CSE), which are abnormalities leading to therapeutic changes.
METHODS: Six Dutch hospitals conducted a prospective observational study that enrolled patients with ischaemic stroke or transient ischaemic attack of undetermined cause. Patients underwent TTE after comprehensive diagnostic evaluation on stroke units, including blood chemistry, 12-lead electrocardiogram (ECG), ≥ 24 h continuous ECG monitoring, brain imaging and cervical artery imaging. Primary outcome measure was the proportion of patients with TTE-detected major CSE.
RESULTS: From March 2018 to October 2020, 1084 patients, aged 66.6 ± 12.5 years, were enrolled; 456 (42.1%) patients were female and 869 (80.2%) had ischaemic stroke. TTE detected major CSE in only 11 (1.0%) patients. Ten (90.9%) of these patients also had major ECG abnormalities (previous infarction, major repolarisation abnormalities, or previously unknown left bundle branch block) that would have warranted TTE assessment regardless of stroke evaluation. Such ECG abnormalities were present in 11.1% of the total study population. A single patient (0.1%) showed a major CSE despite having no ECG abnormality.
CONCLUSIONS: This multicentre cross-sectional study in patients who-after workup on contemporary stroke units-were diagnosed with ischaemic stroke or transient ischaemic attack of undetermined cause found TTE-detected major CSE in only 1% of all patients. Most of these patients also had major ECG abnormalities. These findings question the value of routine TTE assessment in this clinical setting.

Gepubliceerd: Neth Heart J. 2024;32(2):91-8.
Impact factor: 2.0 ; Q3

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40. The Value of Etoposide for Recurrent Glioma
van der Meulen M, Chahal M, Mason WP.

BACKGROUND: For multiply recurrent glioma, options are few and choices are very limited. Etoposide in combination with carboplatin and/or bevacizumab has been evaluated in recurrent glioma with modest efficacy. This retrospective study describes the efficacy of etoposide monotherapy in adults with multiply recurrent diffuse glioma.
METHODS: In this single center retrospective series, all adult patients with radiographically proven multiply recurrent diffuse glioma (WHO grade 2-4) treated with etoposide between 2016 and 2020 were evaluated. Progression-free survival (PFS) and overall survival (OS) after initiating etoposide were calculated for the total group and for different histologic tumor types. In addition, treatment-related toxicity was recorded.
RESULTS: Totally, 48 patients with a median age 43 years-old (range 24-78) were included. Etoposide was given as 3rd line of treatment in 18 patients (37.5%) and as 4th or 5th line of treatment in 30 patients (62.5%). The majority were diagnosed with a glioblastoma, WHO grade 4 (27, 56.3%). The median PFS was 8.6 weeks (95% confidence interval [CI]: 8.3-8.9). The median OS of the total population was 4.0 months (95% CI: 2.4-5.6). Patients with an oligodendroglioma had the best OS

(median 13 months), compared to astrocytoma and glioblastoma, but the difference was not statistically significant (p = 0.15). Etoposide was stopped due to progression in the majority of the patients (81.3%). Only 1 patient had a grade 3 toxicity.
CONCLUSION: Etoposide is a well-tolerated chemotherapy in heavily pretreated patients with multiply recurrent glioma and could be considered when other options are not available. OS was 4 months after initiating etoposide.

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Impact factor: 2.2 ; Q3

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41. Differences in methylation profiles between long-term survivors and short-term survivors of IDH-wild-type glioblastoma
van der Meulen M, Ramos RC, Voisin MR, Patil V, Wei Q, Singh O, Climans SA, Kalidindi N, Or R, Aldape K, Diamandis P, Munoz DG, Zadeh G, Mason WP.

BACKGROUND: Patients with glioblastoma (GBM) have a median overall survival (OS) of approximately 16 months. However, approximately 5% of patients survive >5 years. This study examines the differences in methylation profiles between long-term survivors (>5 years, LTS) and short-term survivors (<1 year, STS) with isocitrate dehydrogenase (IDH)-wild-type GBMs.
METHODS: In a multicenter retrospective analysis, we identified 25 LTS with a histologically confirmed GBM. They were age- and sex-matched to an STS. The methylation profiles of all 50 samples were analyzed with EPIC 850k, classified according to the DKFZ methylation classifier, and the methylation profiles of LTS versus STS were compared.
RESULTS: After methylation profiling, 16/25 LTS and 23/25 STS were confirmed to be IDH-wild-type GBMs, all with +7/-10 signature. LTS had significantly increased O6-methylguanine methyltransferase (MGMT) promoter methylation and higher prevalence of FGFR3-TACC3 fusion (P = .03). STS were more likely to exhibit CDKN2A/B loss (P = .01) and higher frequency of NF1 (P = .02) mutation. There were no significant CpGs identified between LTS versus STS at an adjusted P-value of .05. Unadjusted analyses identified key pathways involved in both LTS and STS. The most common pathways were the Hippo signaling pathway and the Wnt pathway in LTS, and GPCR ligand binding and cell-cell signaling in STS.
CONCLUSIONS: A small group of patients with IDH-wild-type GBM survive more than 5 years. While there are few differences in the global methylation profiles of LTS compared to STS, our study highlights potential pathways involved in GBMs with a good or poor prognosis.

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Impact factor: 4.1 ; Q1

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42. Education and training in neurology: developments and future challenges
van der Meulen M, Wijnenga MMJ.

BACKGROUND AND PURPOSE: Training and education is essential for best practice medicine and is especially important in a rapidly evolving field such as neurology. Due to improved imaging techniques and laboratory testing, there is a better understanding of the pathophysiology of diseases. As a result more treatments have become available. The most important developments in neurology over the last two decades and their effect on training and education are described. In addition, how future training should be aware of the challenges ahead of us is described.
METHODS: This is a narrative review describing developments and challenges based on personal experience and the literature.

RESULTS: Due to major developments in radiological and immunological testing, major changes have been seen in different subspecialties of neurology, including but not limited to, the treatment of ischaemic stroke, the development of new entities in the field of demyelinating diseases and auto-immune encephalitis, and diffuse glioma. These developments challenge the education and training in neurology with, ahead of us, technological developments, an aging population, and potentially more superspecialization.
CONCLUSION: Although there are differences in the training curricula between European countries, the developments and future challenges within the field of neurology are very similar. In the development of future curricula it is important to face these developments and challenges and to adapt to them.

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Impact factor: 3.9 ; Q1

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43. Clinical consequence of vessel perforations during endovascular treatment of acute ischemic stroke

van der Sluijs PM, Su R, Cornelissen SAP, van Es A, Lycklama ANG, Roozenbeek B, van Doormaal PJ, Hofmeijer J, van der Lugt A, van Walsum T, MR CLEAN Registry Investigators; Brouwers PJAM.

PURPOSE: Endovascular treatment (EVT) of acute ischemic stroke can be complicated by vessel perforation. We studied the incidence and determinants of vessel perforations. In addition, we studied the association of vessel perforations with functional outcome, and the association between location of perforation on digital subtraction angiography (DSA) and functional outcome, using a large EVT registry.
METHODS: We included all patients in the MR CLEAN Registry who underwent EVT. We used DSA to determine whether EVT was complicated by a vessel perforation. We analyzed the association with baseline clinical and interventional parameters using logistic regression models. Functional outcome was measured using the modified Rankin Scale at 90 days. The association between vessel perforation and angiographic imaging features and functional outcome was studied using ordinal logistic regression models adjusted for prognostic parameters. These associations were expressed as adjusted common odds ratios (acOR).
RESULTS: Vessel perforation occurred in 74 (2.6%) of 2794 patients who underwent EVT. Female sex (aOR 2.0 (95% CI 1.2-3.2)) and distal occlusion locations (aOR 2.2 (95% CI 1.3-3.5)) were associated with increased risk of vessel perforation. Functional outcome was worse in patients with vessel perforation (acOR 0.38 (95% CI 0.23-0.63)) compared to patients without a vessel perforation. No significant association was found between location of perforation and functional outcome.
CONCLUSION: The incidence of vessel perforation during EVT in this cohort was low, but has severe clinical consequences. Female patients and patients treated at distal occlusion locations are at higher risk.

Gepubliceerd: Neuroradiology. 2024;66(2):237-47.
Impact factor: 2.6 ; Q2

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44. Lethal Capecitabine Toxicity in Patients With Complete Dihydropyrimidine Dehydrogenase Deficiency Due to Ultra-Rare DPYD Variants

van Kuilenburg ABP, Pleunis-van Empel MCH, Brouwer RB, Sijben AEJ, Knapen DG, Oude Munnink TH, van Zanden JJ, Janssens-Puister J, Dobritzsch D, Meinsma R, Meijer-Jansen J, van Dooren SJM, Vijzelaar R, Pop A, Salomons GS, Maring JG, Niezen-Koning KE.

A DPD deficiency should be considered in case of severe toxicity even in the absence of common risk variants in DPYD.

Gepubliceerd: JCO Precis Oncol. 2024;8:e2300599.
Impact factor: 5.8 ; Q1

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45. A New Case Series Suggests That SCA48 (ATX/STUB1) Is Primarily a Monogenic Disorder
van Prooije TH, Pennings M, Dorresteijn L, Gardeitchik T, Odekerken VJJ, Oosterloo M, Pedersen A, Verschuuren-Bemelmans CC, Vrancken A, Kamsteeg EJ, van de Warrenburg BPC.

BACKGROUND: Monoallelic, pathogenic STUB1 variants cause autosomal dominant cerebellar ataxia (ATX-STUB1/SCA48). Recently, a genetic interaction between STUB1 variants and intermediate or high-normal CAG/CAA repeats in TBP was suggested, indicating digenic inheritance or a disease-modifying role for TBP expansions.
OBJECTIVE: To determine the presence and impact of intermediate or high-normal TBP expansions in ataxic patients with heterozygous STUB1 variants.
METHODS: We describe 21 patients with ataxia carrying a heterozygous STUB1 variant and determined TBP repeat length.
RESULTS: A total of 15 of 21 patients (71%) carried a normal TBP (<40) allele, 4 (19%) carried an intermediate TBP (41-42) allele, and two carried a high-normal TBP (40) allele (9.5%). Five of six carriers (83%) of both STUB1 variants and TBP (40-42) alleles showed marked cognitive impairment.
CONCLUSIONS: SCA48 is predominantly a monogenic disorder, because most patients carried an isolated, heterozygous STUB1 variant and presented with the typical combined phenotype of ataxia and cognitive dysfunction. Still, co-occurrence of TBP (41-42) or high-normal TBP(40) alleles was relatively frequent and associated with marked cognitive defects (28.5%), suggesting a modifying effect on clinical expression in some cases.

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Impact factor: 7.6 ; Q1

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46. Quantitative Characterization of Rhythmic and Periodic EEG Patterns in Patients in a Coma After Cardiac Arrest and Association With Outcome
van Putten M, Ruijter BJ, Horn J, van Rootselaar AF, Tromp SC, van Kranen-Mastenbroek V, Gaspard N, Hofmeijer J.

OBJECTIVES: Rhythmic and periodic patterns (RPPs) on EEG in patients in a coma after cardiac arrest are associated with a poor neurologic outcome. We characterize RPPs using qEEG in relation to outcomes.
METHODS: Post hoc analysis was conducted on 172 patients in a coma after cardiac arrest from the TELSTAR trial, all with RPPs. Quantitative EEG included corrected background continuity index (BCI*), relative discharge power (RDP), discharge frequency, and shape similarity. Neurologic outcomes at 3 months after arrest were categorized as poor (CPC = 3-5) or good (CPC = 1-2).
RESULTS: A total of 16 patients (9.3%) had a good outcome. Patients with good outcomes showed later RPP onset (28.5 vs 20.1 hours after arrest, $p < 0.05$) and higher background continuity at RPP onset (BCI(*) = 0.83 vs BCI(*) = 0.59, $p < 0.05$). BCI* <0.45 at RPP onset, maximum BCI* <0.76, RDP >0.47, or shape similarity >0.75 were consistently associated with poor outcomes, identifying 36%, 22%, 40%, or 24% of patients with poor outcomes, respectively. In patients meeting both BCI* >0.44 at RPP onset and BCI* >0.75 within 72 hours, the probability of good outcomes doubled to 18%.
DISCUSSION: Sufficient EEG background continuity before and during RPPs is crucial for meaningful

recovery. Background continuity, discharge power, and shape similarity can help select patients with relevant chances of recovery and may guide treatment.
TRIAL REGISTRATION INFORMATION: February 4, 2014, ClinicalTrial.gov, NCT02056236.

Gepubliceerd: Neurology. 2024;103(3):e209608.
Impact factor: 9.0 ; Q1

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47. Costs and health effects of CT perfusion-based selection for endovascular thrombectomy within 6 hours of stroke onset: a model-based health economic evaluation
van Voorst H, Hoving JW, Koopman MS, Daems JD, Peerlings D, Buskens E, Lingsma H, Marquering HA, de Jong H, Berkhemer OA, van Zwam WH, van Walderveen MAA, van den Wijngaard IR, Dippel DWJ, Yoo AJ, Campbell B, Kunz WG, Majoie CB, Emmer BJ, CLEOPATRA and MR CLEAN Registry and CONTRAST Consortium Investigators; Brouwers PJAM.

BACKGROUND: Although CT perfusion (CTP) is often incorporated in acute stroke workflows, it remains largely unclear what the associated costs and health implications are in the long run of CTP-based patient selection for endovascular treatment (EVT) in patients presenting within 6 hours after symptom onset with a large vessel occlusion.
METHODS: Patients with a large vessel occlusion were included from a Dutch nationwide cohort (n=703) if CTP imaging was performed before EVT within 6 hours after stroke onset. Simulated cost and health effects during 5 and 10 years follow-up were compared between CTP based patient selection for EVT and providing EVT to all patients. Outcome measures were the net monetary benefit at a willingness-to-pay of €80 000 per quality-adjusted life year, incremental cost-effectiveness ratio), difference in costs from a healthcare payer perspective (ΔCosts) and quality-adjusted life years (ΔQALY) per 1000 patients for 1000 model iterations as outcomes.
RESULTS: Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds resulted in losses of health (median ΔQALYs for ICV≥110 mL: -3.3 (IQR: -5.9 to -1.1), for MMR≤1.4: 0.0 (IQR: -1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of -€348 966 (IQR: -€712 406 to -€51 158) and for MMR≤1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including patients aged ≥80 years
CONCLUSION: In EVT-eligible patients presenting within 6 hours after symptom onset, excluding patients based on CTP parameters was not cost-effective and could potentially harm patients.

Gepubliceerd: J Neurol Neurosurg Psychiatry. 2024;95(6):515-27.
Impact factor: 7.8 ; Q1

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48. Short-Term and Long-Term Risk of Recurrent Vascular Event by Cause After Ischemic Stroke in Young Adults
Verburgt E, Hilkens NA, Ekker MS, Schellekens MMI, Boot EM, Immens MHM, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, van Tuijl JH, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Kerkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Ten Cate TJF, Tuladhar AM, de Leeuw FE, Verhoeven JI.

IMPORTANCE: Cause of ischemic stroke in young people is highly variable; however, the risk of recurrence is often presented with all subtypes of stroke grouped together in classification systems such as the Trial of ORG (danaparoid sodium [Orgaran]) 10172 in Acute Stroke Treatment (TOAST)

criteria, which limits the ability to individually inform young patients with stroke about their risk of recurrence.
OBJECTIVE: To determine the short-term and long-term risk of recurrent vascular events after ischemic stroke at a young age by stroke cause and to identify factors associated with recurrence.
DESIGN, SETTING, AND PARTICIPANTS: This cohort study used data from the Observational Dutch Young Symptomatic Stroke Study, a prospective, multicenter, hospital-based cohort study, conducted at 17 hospitals in the Netherlands between 2013 and 2021. Eligible participants included 30-day survivors of an initial, neuroimaging-proven ischemic stroke (aged 18-49 years). Data analysis was conducted from June to July 2023.
EXPOSURE: Diagnosis of a first-ever, ischemic stroke via neuroimaging.
MAIN OUTCOME AND MEASURES: The primary outcome was short-term (within 6 months) and long-term (within 5 years) recurrence risk of any vascular event, defined as fatal or nonfatal recurrent ischemic stroke, transient ischemic attack, myocardial infarction, and revascularization procedure. Predefined characteristics were chosen to identify factors associated with risk of recurrence (cause of stroke, age, sex, stroke severity, and cardiovascular health factors).
RESULTS: A total of 1216 patients (median [IQR] age, 44.2 [38.4-47.7] years; 632 male [52.0%]; 584 female [48.0%]) were included, with a median (IQR) follow-up of 4.3 (2.6-6.0) years. The 6-month risk of any recurrent ischemic event was 6.7% (95% CI, 5.3%-8.1%), and the 5-year risk was 12.2% (95% CI, 10.2%-14.2%)The short-term risk was highest for patients with cervical artery dissections (13.2%; 95% CI, 7.6%-18.7%). Other factors associated with a recurrent short-term event were atherothrombotic stroke, rare causes of stroke, and hypertension. The long-term cumulative risk was highest for patients with atherothrombotic stroke (22.7%; 95% CI, 10.6%-34.7%) and lowest for patients with cryptogenic stroke (5.8%; 95% CI, 3.0%-8.5%). Cardioembolic stroke was associated with a recurrent long-term event, as were diabetes and alcohol abuse.
CONCLUSIONS AND RELEVANCE: The findings of this cohort study of 1216 patients with an ischemic stroke at a young age suggest that the risk of recurrent vascular events was high and varied by cause of stroke both for short-term and long-term follow-up, including causes that remained concealed when combined into 1 category in the routinely used TOAST criteria. This knowledge will allow for more personalized counseling of young patients with stroke.

Gepubliceerd: JAMA Netw Open. 2024;7(2):e240054.
Impact factor: 9.7 ; Q1

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49. Exploring the kynurenine pathway in mild traumatic brain injury: A longitudinal study
Visser K, Ciubotariu D, de Koning ME, Jacobs B, van Faassen M, van der Ley C, Mayer AR, Meier TB, Bourgonje AR, Kema IP, van Goor H, van der Naalt J, van der Horn HJ.

A potential source of novel biomarkers for mTBI is the kynurenine pathway (KP), a metabolic pathway of tryptophan (Trp), that is up-regulated by neuroinflammation and stress. Considering that metabolites of the KP (kynurenines) are implicated in various neuropsychiatric diseases, exploration of this pathway could potentially bridge the gap between physiological and psychological factors in the recovery process after mTBI. This study, therefore, set out to characterize the KP after mTBI and to examine associations with long-term outcome. Patients were prospectively recruited at the emergency department (ED), and blood samples were obtained in the acute phase (<24 h; N = 256) and at 1-month follow-up (N = 146). A comparison group of healthy controls (HC; N = 32) was studied at both timepoints. Trp, kynurenines, and interleukin (IL)-6 and IL-10 were quantified in plasma. Clinical outcome was measured at six months post-injury. Trp, xanthurenic acid (XA), and picolinic acid (PA) were significantly reduced in patients with mTBI relative to HC, corrected for age and sex. For Trp (d = -0.57 vs. d = -0.29) and XA (d = -0.98 vs. d = -0.32), larger effects sizes were observed during the acute phase compared to one-month follow-up, while for PA (d = -0.49 vs. d = -0.52) effect sizes remained consistent. Findings for other kynurenines (e.g., kynurenine, kynurenic acid, and

quinolinic acid) were non-significant after correction for multiple testing. Within the mTBI group, lower acute Trp levels were significantly related to incomplete functional recovery and higher depression scores at 6 months post-injury. No significant relationships were found for Trp, XA, and PA with IL-6 or IL-10 concentrations. In conclusion, our findings indicate that perturbations of the plasma KP in the hyperacute phase of mTBI and 1 month later are limited to the precursor Trp, and glutamate system modulating kynurenines XA and PA. Correlations between acute reductions of Trp and unfavorable outcomes may suggest a potential substrate for pharmacological intervention.

Gepubliceerd: J Neurochem. 2024;168(9):2710-21.
Impact factor: 4.0 ; Q2

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50. An exploratory study on the association between blood-based biomarkers and subacute neurometabolic changes following mild traumatic brain injury
Visser K, de Koning ME, Ciubotariu D, Kok MGJ, Sibeijn-Kuiper AJ, Bourgonje AR, van Goor H, van der Naalt J, van der Horn HJ.

BACKGROUND AND OBJECTIVES: Blood-based biomarkers and advanced neuroimaging modalities such as magnetic resonance spectroscopy (MRS) or diffusion tensor imaging (DTI) have enhanced our understanding of the pathophysiology of mild traumatic brain injury (mTBI). However, there is limited published data on how blood biomarkers relate to neuroimaging biomarkers post-mTBI.
METHODS: To investigate this, 30 patients with mTBI and 21 healthy controls were enrolled. Data was collected at two timepoints postinjury: acute, < 24 h, (blood) and subacute, four-to-six weeks, (blood and imaging). Interleukin (IL) 6 and 10 (inflammation), free thiols (systemic oxidative stress) and neurofilament light (NF-L) (axonal injury) were quantified in plasma. The neurometabolites total N-acetyl aspartate (tNAA) (neuronal energetics), Myo-Inositol (Ins) and total Choline (tCh) (inflammation) and, Glutathione (GSH, oxidative stress) were quantified using MRS.
RESULTS: Concentrations of IL-6 and IL-10 were significantly elevated in the acute phase post-mTBI, while NF-L was elevated only in the subacute phase. Total NAA was lowered in patients with mTBI, although this difference was only nominally significant (uncorrected $P < 0.05$). Within the patient group, acute IL-6 and subacute tNAA levels were negatively associated ($r = -0.46$, uncorrected-$P = 0.01$), albeit not at a threshold corrected for multiple testing (corrected-$P = 0.17$). When age was added as a covariate a significant increase in correlation magnitude was observed ($\rho = -0.54$, corrected-$P = 0.03$).
CONCLUSION: This study demonstrates potential associations between the intensity of the inflammatory response in the acute phase post-mTBI and neurometabolic perturbations in the subacute phase. Future studies should assess the longitudinal dynamics of blood-based and imaging biomarkers after injury.

Gepubliceerd: J Neurol. 2024;271(4):1985-98.
Impact factor: 4.6 ; Q1

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51. Dural arteriovenous fistulas are not observed to convert to a higher grade after partial embolization
Walker E, Srienc A, Lew D, Guniganti R, Lanzino G, Brinjikji W, Hayakawa M, Samaniego EA, Derdeyn CP, Du R, Lai R, Sheehan JP, Starke RM, Abla A, Abdelsalam A, Gross B, Albuquerque F, Lawton MT, Kim LJ, Levitt M, Amin-Hanjani S, Alaraj A, Winkler E, Fox WC, Polifka A, Hall S, Bulters D, Durnford A, Satomi J, Tada Y, van Dijk JMC, Potgieser ARE, Chen CJ, Becerril-Gaitan A, Osbun JW, Zipfel GJ.

OBJECTIVE: Borden-Shucart type I dural arteriovenous fistulas (dAVFs) lack cortical venous drainage and occasionally necessitate intervention depending on patient symptoms. Conversion is the rare transformation of a low-grade dAVF to a higher grade. Factors associated with increased risk of dAVF conversion to a higher grade are poorly understood. The authors hypothesized that partial treatment of type I dAVFs is an independent risk factor for conversion.
METHODS: The multicenter Consortium for Dural Arteriovenous Fistula Outcomes Research database was used to perform a retrospective analysis of all patients with type I dAVFs.
RESULTS: Three hundred fifty-eight (33.2%) of 1077 patients had type I dAVFs. Of those 358 patients, 206 received endovascular treatment and 131 were not treated. Two (2.2%) of 91 patients receiving partial endovascular treatment for a low-grade dAVF experienced conversion to a higher grade, 2 (1.5%) of 131 who were not treated experienced conversion, and none (0%) of 115 patients who received complete endovascular treatment experienced dAVF conversion. The majority of converted dAVFs localized to the transverse-sigmoid sinus and all received embolization as part of their treatment. **CONCLUSIONS**: Partial treatment of type I dAVFs does not appear to be significantly associated with conversion to a higher grade.

Gepubliceerd: Neurosurg Focus. 2024;56(3):E8.
Impact factor: 3.0 ; Q1

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52. Safety and efficacy of active blood-pressure reduction to the recommended thresholds for intravenous thrombolysis in patients with acute ischaemic stroke in the Netherlands (TRUTH): a prospective, observational, cluster-based, parallel-group study
Zonneveld TP, Vermeer SE, van Zwet EW, Groot AED, Algra A, Aerden LAM, Alblas KCL, de Beer F, Brouwers P, de Gans K, van Gemert HMA, van Ginneken B, Grooters GS, Halkes PHA, van der Heijden-Montfroy T, Jellema K, de Jong SW, Lövenich-Ciccarello H, van der Meulen WDM, Peters EW, van der Ree TC, Remmers MJM, Richard E, Rovers JMP, Saxena R, van Schaik SM, Schonewille WJ, Schreuder T, de Schryver E, Schuiling WJ, Spaander FH, van Tuijl JH, Visser MC, Zinkstok SM, Zock E, Dippel DWJ, Kappelle LJ, van Oostenbrugge RJ, Roos Y, Vermeij FH, Wermer MJH, van der Worp HB, Nederkoorn PJ, Kruyt ND.

BACKGROUND: Intravenous thrombolysis is contraindicated in patients with ischaemic stroke with blood pressure higher than 185/110 mm Hg. Prevailing guidelines recommend to actively lower blood pressure with intravenous antihypertensive agents to allow for thrombolysis; however, there is no robust evidence for this strategy. Because rapid declines in blood pressure can also adversely affect clinical outcomes, several Dutch stroke centres use a conservative strategy that does not involve the reduction of blood pressure. We aimed to compare the clinical outcomes of both strategies.
METHODS: Thrombolysis and Uncontrolled Hypertension (TRUTH) was a prospective, observational, cluster-based, parallel-group study conducted across 37 stroke centres in the Netherlands. Participating centres had to strictly adhere to an active blood-pressure-lowering strategy or to a non-lowering strategy. Eligible participants were adults (≥18 years) with ischaemic stroke who had blood pressure higher than 185/110 mm Hg but were otherwise eligible for intravenous thrombolysis. The primary outcome was functional status at 90 days, measured using the modified Rankin Scale and assessed through telephone interviews by trained research nurses. Secondary outcomes were symptomatic intracranial haemorrhage, the proportion of patients treated with intravenous thrombolysis, and door-to-needle time. All ordinal logistic regression analyses were adjusted for age, sex, stroke severity, endovascular thrombectomy, and baseline imbalances as fixed-effect variables and centre as a random-effect variable to account for the clustered design. Analyses were done according to the intention-to-treat principle, whereby all patients were analysed according to the treatment strategy of the participating centre at which they were treated.
FINDINGS: Recruitment began on Jan 1, 2015, and was prematurely halted because of a declining inclusion rate and insufficient funding on Jan 5, 2022. Between these dates, we recruited 853 patients

from 27 centres that followed an active blood-pressure-lowering strategy and 199 patients from ten centres that followed a non-lowering strategy. Baseline characteristics of participants from the two groups were similar. The 90-day mRS score was missing for 15 patients. The adjusted odds ratio (aOR) for a shift towards a worse 90-day functional outcome was 1·27 (95% CI 0·96-1·68) for active blood-pressure reduction compared with no active blood-pressure reduction. 798 (94%) of 853 patients in the active blood-pressure-lowering group were treated with intravenous thrombolysis, with a median door-to-needle time of 35 min (IQR 25-52), compared with 104 (52%) of 199 patients treated in the non-lowering group with a median time of 47 min (29-78). 42 (5%) of 852 patients in the active blood-pressure-lowering group had a symptomatic intracranial haemorrhage compared with six (3%) of 199 of those in the non-lowering group (aOR 1·28 [95% CI 0·62-2·62]).
INTERPRETATION: Insufficient evidence was available to establish a difference between an active blood-pressure-lowering strategy-in which antihypertensive agents were administered to reduce blood pressure below 185/110 mm Hg-and a non-lowering strategy for the functional outcomes of patients with ischaemic stroke, despite higher intravenous thrombolysis rates and shorter door-to-needle times among those in the active blood-pressure-lowering group. Randomised controlled trials are needed to inform the use of an active blood-pressure-lowering strategy. FUNDING: Fonds NutsOhra.

Gepubliceerd: Lancet Neurol. 2024;23(8):807-15.
Impact factor: 45.5 ; Q1

Totale impact factor: 368.5
Gemiddelde impact factor: 7.1

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 17
Totale impact factor: 48.4
Gemiddelde impact factor: 2.8

Oogheelkunde

1. Genome-wide association analyses identify distinct genetic architectures for age-related macular degeneration across ancestries
Gorman BR, Voloudakis G, Igo RP, Jr., Kinzy T, Halladay CW, Bigdeli TB, Zeng B, Venkatesh S, Cooke Bailey JN, Crawford DC, Markianos K, Dong F, Schreiner PA, Zhang W, Hadi T, Anger MD, Stockwell A, Melles RB, Yin J, Choquet H, Kaye R, Patasova K, Patel PJ, Yaspan BL, Jorgenson E, Hysi PG, Lotery AJ, Gaziano JM, Tsao PS, Fliesler SJ, Sullivan JM, Greenberg PB, Wu WC, Assimes TL, Pyarajan S, Roussos P, Peachey NS, Iyengar SK, Collaborators; Saksens NTM.

To effectively reduce vision loss due to age-related macular generation (AMD) on a global scale, knowledge of its genetic architecture in diverse populations is necessary. A critical element, AMD risk profiles in African and Hispanic/Latino ancestries, remains largely unknown. We combined data in the Million Veteran Program with five other cohorts to conduct the first multi-ancestry genome-wide association study of AMD and discovered 63 loci (30 novel). We observe marked cross-ancestry heterogeneity at major risk loci, especially in African-ancestry populations which demonstrate a primary signal in a major histocompatibility complex class II haplotype and reduced risk at the established CFH and ARMS2/HTRA1 loci. Dissecting local ancestry in admixed individuals, we find significantly smaller marginal effect sizes for CFH risk alleles in African ancestry haplotypes. Broadening efforts to include ancestrally distinct populations helped uncover genes and pathways that boost risk in an ancestry-dependent manner and are potential targets for corrective therapies.

Gepubliceerd: Nat Genet. 2024;56(12):2659-71.
Impact factor: 29.0 ; Q1

Totale impact factor: 29.0
Gemiddelde impact factor: 29.0

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Orthopedie

1. The effectiveness of a protocol without routine radiographs for follow-up of adolescent idiopathic scoliosis patients (CURVE): a study protocol
Baetsen JTF, Hooff ML, Bisseling P, Van Dongen JM, Van de Fliert DG, Hoebink E, Kempen DHR, Rutges J, Schlösser TPC, Van West HM, Van der Wees PJ, Willems PC, De Kleuver M, Dutch AIS consortium; den Hartog YM.

BACKGROUND AND PURPOSE: Current follow-up protocols for adolescent idiopathic scoliosis (AIS) are based on consensus and consist of regular full-spine radiographs to monitor curve progression and surgical complications. Consensus exists to avoid inappropriate use of radiographs in children. It is unknown whether a standard radiologic follow-up (S-FU) approach is necessary or if a patient-empowered follow-up (PE-FU) approach can reduce the number of radiographs without treatment consequences.
METHODS AND ANALYSES: A nationwide multicenter pragmatic randomized preference trial was designed for 3 follow-up subgroups (pre-treatment, post-brace, post-surgery) to compare PE-FU and S-FU. 812 patients with AIS (age 10-18 years) will be included in the randomized trial or preference cohorts. Primary outcome is the proportion of radiographs with a treatment consequence for each subgroup. Secondary outcomes consist of the proportion of patients with delayed initiation of treatment due to non-routine radiographic follow-up, radiation exposure, societal costs, positive predictive value, and interrelation of clinical assessment, quality of life, and parameters for initiation of treatment during follow-up. Outcomes will be analyzed using linear mixed-effects models, adjusted for relevant baseline covariates, and are based on intention-to-treat principle. Study summary: (i) a national, multicenter pragmatic randomized trial addressing the optimal frequency of radiographic follow-up in patients with AIS; (ii) first study that includes patient-empowered follow-up; (iii) an inclusive study with 3 follow-up subgroups and few exclusion criteria representative for clinical reality; (iv) preference cohorts alongside to amplify generalizability; (v) first study conducting an economic evaluation comparing both follow-up approaches.

Gepubliceerd: Acta Orthop. 2024;95:298-306.
Impact factor: 2.4 ; Q2

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2. Three cases of posttraumatic wrist problems solved with 3D-printed patient-specific guides
Haandrikman S, Schröder FF, de Graaff F, Olde Heuvel J, Vochteloo AJH.

Symptomatic malunion of the wrist is one of the most common posttraumatic wrist problems. This study demonstrates three patients with complex malunions of the wrist who benefited from a corrective osteotomy using preplanned 3D-printed patient-specific guides, by experiencing improvement in their wrist function, grip strength and a reduction in pain.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2024;11(1):2311730.
Impact factor: 0.6 ; Q4

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3. Effectiveness of intra-articular analgesia in reducing postoperative pain after minimally invasive sacroiliac joint fusion: a double-blind randomized controlled trial
Hermans SMM, Nellensteijn JM, Knoef R, van Santbrink H, Droeghaag R, Most J, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

During the first postoperative days following minimally invasive sacroiliac joint fusion (MISJF), patients often report serious pain, which contributes to high utilization of painkillers and prevention of early mobilization. This prospective, double-blind randomized controlled trial investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% versus placebo (NaCl 0.9%) in 42 patients in reducing postoperative pain after MISJF. The primary outcome was difference in pain between bupivacaine and placebo groups, assessed as fixed factor in a linear mixed model. Secondary outcomes were opioid consumption, patient satisfaction, adverse events, and length of hospital stay. We found that SIJ infiltration with bupivacaine did not affect postoperative pain scores in comparison with placebo, neither as group-effect ($p = 0.68$), nor dependent on time (group*time: $p = 0.87$). None of the secondary outcome parameters were affected in the postoperative period in comparison with placebo, including opioid consumption ($p = 0.81$). To conclude, intra-articular infiltration of the SIJ with bupivacaine at the end of MISJF surgery is not effective in reducing postoperative pain. Hence, we do not recommend routine use of intraoperative SIJ infiltration with analgesia in MISJF.

Gepubliceerd: Sci Rep. 2024;14(1):22647.
Impact factor: 3.9 ; Q1

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4. Contrasting results in sacroiliac joint fusion studies: the role of bilateral complaints
Kampkuiper N, Schröder F, Brusse-Keizer M, Nellensteijn J.

Gepubliceerd: EClinicalMedicine. 2024;79:102978.
Impact factor: 10.0 ; Q1

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5. Sacroiliac joint fusion guided by intraoperatively superimposed virtual surgical planning using simulated fluoroscopic images
Lankheet S, Kampkuiper N, Nellensteijn J, Hekman E, Tuijthof G, Schröder F, Koenrades M.

INTRODUCTION: Sacroiliac joint fusion (SIJF) is a minimally invasive treatment for sacroiliac (SI) dysfunction. It involves placing implants through the SI joint under fluoroscopic guidance, requiring precise implant positioning to avoid nerve injury. Preoperative virtual surgical planning (VSP) aids in optimal positioning, but replicating it accurately in the operating room is challenging.
RESEARCH QUESTION: This study aims to assess the feasibility of superimposing VSP onto intraoperative fluoroscopic images to aid in optimal implant placement.
MATERIAL AND METHODS: A method for intraoperative guidance using 3D/2D registration was developed and tested during SIJF as an available and potentially efficient alternative for costly and more invasive navigation systems. Preoperatively, a VSP is performed and simulated fluoroscopic images are generated from a preoperative CT scan. During surgery, the simulated image that visually best matches the intraoperative fluoroscopic image is selected. Subsequently, the VSP is superimposed onto the intraoperative fluoroscopic image using a developed script-based workflow. The surgeon then places the implants accordingly. Postoperative implant placement accuracy was evaluated.
RESULTS: Five interventions were performed on five patients, resulting in a total of 15 placed implants. Minor complications without clinical consequences occurred in one case, primarily attributable to the patient's anatomy and pathological manifestations. Mean deviations at implant apex and 3D angle were 4.7 ± 1.6 mm and 3.5 ± 1.3°, respectively.
DISCUSSION AND CONCLUSIONS: The developed intraoperative workflow was feasible and resulted in implants placed with low deviations from the VSP. Further research is needed to automate and validate this method in a larger cohort.

Gepubliceerd: Brain Spine. 2024;4:102905.
Impact factor: 2.5 ; Q2

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6. A novel patient specific guide design to correct a complex multiplanar foot deformity.
Lankheet S, Schröder F, Kappert K, Ten Cate W, Hekman E, Asseln M, Koenrades M, Zeegers AVCM.

Surgical intervention is often indicated for complex multiplanar foot deformities (CMFDs). Addressing the 3D nature of these deformities proves challenging for achieving optimal foot alignment and reoperations are often necessary. Virtual surgical planning (VSP) can aid in the understanding of the multiplanar deformity and determine the osteotomies needed for correction. This study introduces a patient-specific guide (PSG) applied to a CMFD patient undergoing midfoot closing wedge osteotomy. The PSG design allowed for accurate reconstruction of the angular deformity, while allowing for intra-operative translational adjustments. Further improvement of the PSG design was proposed to ensure an even better fit in future applications.

Gepubliceerd: Proceedings of The 24th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery. 2024;7:107-11.
Impact factor: onbekend

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7. The effect of rectus femoris transfer on kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait
Tenniglo MJB, Buurke JH, Zeegers A, Fleuren JFM, Rietman JS, Prinsen EC.

BACKGROUND: Stiff knee gait is characterized by a reduced peak knee flexion during swing. Overactivity of the rectus femoris is often cited as a main cause for stiff knee gait. Little is known about the effect of an isolated rectus femoris transfer treatment on kinematic and functional outcomes in a group of stroke survivors.
OBJECTIVE: To perform an experimental study to evaluate the effect of an isolated rectus femoris transfer on knee and hip kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait.
METHOD: In this experimental study, 10 stroke survivors were included. During the surgical procedure, the distal rectus femoris tendon of the affected side was transferred to the medial knee flexors to improve knee flexion during swing. Knee and hip kinematics and a variety of functional outcomes were measured within 3 weeks before surgery and between 6 and 7 months after the surgery.
RESULTS: We found a statistically significant improvements in peak knee flexion during swing and knee range of motion of 10.6° (sd 4.7, p=0.000) and 10.5° (sd 6.2, p=0.001) post-surgery, respectively. Hip kinematics showed no significant differences. In addition, we found statistically significant improvements on the 6-minute walk test (42.5, sd 36.7, p=0.008), 10-meter walk test (1.26, sd 1.4, p=0.030), Timed up-and-go test (1.34, sd 1.18, p=0.009), L-test (2.97 sd 2.85, p=0.014) and on a subjective BORG scoring of foot clearance (1.8, sd 0.6, p=0.006). No significant differences were found on other measured functional outcomes.
CONCLUSIONS: Rectus femoris transfer is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics and a selection of functional outcomes. There are no detrimental side effects on hip kinematics.

Gepubliceerd: Gait Posture. 2024;114:101-7.
Impact factor: 2.4 ; Q3

8. Instability Severity Index Score predicts recurrent shoulder instability after arthroscopic Bankart repair
van Blommestein MYH, Govaert LHM, van der Palen J, Verra WC, Koorevaar RCT, Schröder FF, Veen EJD.

PURPOSE: The Instability Severity Index (ISI) Score was developed to preoperatively assess the risk of recurrent shoulder instability after an arthroscopic Bankart repair. This study aims to validate the use of ISI Score for predicting the risk of recurrence after an arthroscopic Bankart repair in a heterogeneous population and proposes an appropriate cut-off point for treating patients with an arthroscopic Bankart repair or otherwise.
METHODS: This study analysed 99 shoulders after a traumatic dislocation that underwent arthroscopic Bankart repair with at least 3 years follow-up. Patients were divided into subcategories based on their respective ISI Score. Recurrence includes either a postoperative dislocation or perceived instability.
RESULTS: The overall recurrence rate was found to be 26.3%. A significant correlation was identified between ISI Score and the recurrence rate (odds ratio [OR]: 1.545, 95% confidence interval [CI]: 1.231-1.939, $p < 0.001$). Furthermore, ISI Score 4-6 (OR: 4.498, 95% CI: 1.866-10.842, $p < 0.001$) and ISI Score > 6 (OR: 7.076, 95% CI: 2.393-20.924, $p < 0.001$) both had a significantly higher risk of recurrence compared to ISI Score 0-3. In ISI Score subcategories 0-3, 4-6 and >6, the recurrence rate was, respectively, 15.4%, 40.7% and 71.4%.
CONCLUSION: ISI Score has predictive value in determining the recurrence risk of shoulder instability following an arthroscopic Bankart repair in a heterogeneous population. Based on the findings of this study, we recommend using arthroscopic Bankart repair in patients with ISI Score 0-3. Clinical and shared decision-making are essential in the group with ISI Score 4-6, since the recurrence rate is significantly higher than in patients with ISI Score 0-3. Arthroscopic Bankart repair is not suitable for patients with ISI Score > 6.
LEVEL OF EVIDENCE: Level III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2024;32(8):2152-60.
Impact factor: 5.0 ; Q1

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9. Exploratory study of the lateral body sway predictability as frame of reference for gait rehabilitation following a total knee arthroplasty
van de Ven WAF, Bosga J, Hullegie W, Verra WC, Meulenbroek RGJ.

AIMS: The aim of the present study was to investigate whether the predictability of fronto-parallel trunk rotations (lateral body sway) could serve as a frame of reference to monitor recovery after total knee arthroplasty (TKA).
METHODS: Before surgery, 11 TKA patients were asked to perform a treadmill walking task at three different speeds. In addition, their gait abilities were scored on three standard clinical walking tests. The treadmill walking task was repeated at three different timepoints following surgery, i.e., at 3, 6 and 12 months post-TKA. The movements of the trunk were digitized with an inertial sensor to capture the amplitude and the sample entropy (SEn) of the lateral body sway that were evaluated in separate ANOVAs.
RESULTS: Before surgery the TKA group showed larger body sway ($P = 0.025$) with smaller SEn values ($P = 0.038$), which both restored to levels of healthy adults in the 12 months following surgery. Systematic correlations between the SEn values and the clinical test scores were found.
CONCLUSIONS: The current findings show that movement behavior of the trunk in the fronto-parallel

plane was affected by knee osteoarthritis and suggest that the predictability of the lateral body sway may serve as an index of recovery after TKA.

Gepubliceerd: Knee. 2024;49:192-200.
Impact factor: 2.0 ; Q2

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10. Feasibility study of the Digital Patient Benefit Assessment Scale (P-BAS): A Digital Tool to Assess Individual Patient Goals
van Erp RAL, de Rooij SE, Wymenga ANM, Zeegers A, van der Palen J.

The study objective was to assess the feasibility of the Patient Benefit Assessment Scale (P-BAS), a digital tool designed to enable older outpatients (≥70 years) to elucidate at home their individual goals regarding their current medical issue. Several digital tools are developed to assist older people in identifying their goals, thereby facilitating the process of shared decision making. However, studies on the feasibility of these digital tools, especially in older patients, are limited. Data were collected from 36 older patients. The study comprised three stages. In stage I and II, cognitive interviews were conducted to strengthen the feasibility of the P-BAS. In stage III, 80% of the patients completed the P-BAS independently at home. The cognitive interviews provided insight into patients' interpretation and individual understanding of the digital visual P-BAS and associated opportunities for improvement, which were subsequently implemented. One conclusion is that the digital visual P-BAS might be of added value for patients and contributes to the process of shared decision making, assuring that the goals of the patient will be into account in treatment options. Findings are useful for researchers interested in technological tools that contribute to shared decision making.

Gepubliceerd: Gerontol Geriatr Med. 2024;10:23337214241230159.
Impact factor: 1.8 ; Q4

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11. Development of a virtual surgical plan for reverse shoulder arthroplasty as a treatment for complex proximal humerus fracture in an elderly patient
van Luit RJ, Rijntjes J, Hekman E, Govaert L, Hollman F, Schröder FF, Veen EJD.

Gepubliceerd: JSES Rev Rep Tech. 2024;5(1):92-6.
Impact factor: onbekend

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12. Erratum to: Compensatory Movement Patterns Are Based on Abnormal Activity of the Biceps Brachii and Posterior Deltoid Muscles in Patients with Symptomatic Rotator Cuff Tears
Veen EJD, Koorevaar CT, Verdonschot KHM, Sluijter TE, de Groot TM, van der Hoeven JH, Diercks RL, Stevens M.

Gepubliceerd: Clin Orthop Relat Res. 2024;482(6):1098.
Impact factor: 4.4 ; Q1

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13. Shared decision-making for non-operative management versus operative management of hip fractures in selected frail older adults with a limited life expectancy: a protocol for a nationwide implementation study
Zeelenberg ML, Oosterwijk PC, Willems HC, Gosens T, Den Hartog D, Joosse P, Loggers SAI, Nijdam TM, Pel-Littel RE, Polinder S, Schuijt HJ, Wijnen HH, Van der Velde D, Van Lieshout EMM, Verhofstad MHJ, NOM-Implementation study group; Zeegers AVCM.

BACKGROUND AND PURPOSE: Recent research has highlighted non-operative management (NOM) as a viable alternative for frail older adults with hip fractures in the final phase of life. This study aims to guide Dutch physicians and hospitals nationwide in a standardised implementation of shared decision-making regarding surgery or NOM in selected frail older adults with a hip fracture.
METHODS AND ANALYSIS: The patient population for implementation includes frail older adults aged ≥70 years with an acute proximal femoral fracture, nursing home care or a similar level of care elsewhere and at least one additional criterion (ie, malnutrition, severe mobility impairment or ASA≥4). The 2-year implementation study will be conducted in four phases. In phases 1 and 2, barriers and facilitators for implementation will be identified and an implementation protocol, educational materials and patient information will be developed. Phase 3 will involve an implementation pilot in 14 hospitals across the Netherlands. The protocol and educational material will be improved based on healthcare provider and patient experiences gathered through interviews. Phase 4 will focus on upscaling to nationwide implementation and the effect of the implementation on NOM rate will be measured using data from the Dutch Hip Fracture Audit.
ETHICS AND DISSEMINATION: The study was exempted by the local Medical Research Ethics Committee (MEC-2023-0270, 10 May 2023) and Medical Ethics Committee United (W23.083, 26 April 2023). The study's results will be submitted to an open access international peer-reviewed journal. Its protocols, tools and results will be presented at several national and international academic conferences of relevant orthogeriatric (scientific) associations.
TRIAL REGISTRATION NUMBER: NCT06079905 .

Gepubliceerd: BMJ Open. 2024;14(4):e083429.
Impact factor: 2.3 ; Q2

Totale impact factor: 37.3
Gemiddelde impact factor: 2.9

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 26.4
Gemiddelde impact factor: 3.3

Pathologie

1. Primary central nervous system lymphoma
de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC, van der Meulen M.

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL) manifesting in the brain, spinal cord, cerebrospinal fluid and/or eyes, in the absence of systemic manifestations. With an increasing incidence and a 30% 5-year overall survival if promptly treated, timely diagnosis and subsequent treatment is paramount. The typical MRI appearance for PCNSL is a solitary or multiple T2-hypointense, homogeneous gadolinium-enhancing lesion with restricted diffusion. Dexamethasone treatment might compromise and delay the diagnosis. Hallmark of treatment is induction with intravenous high-dose methotrexate consisting polychemotherapy followed by consolidation treatment. Consolidation treatment consists of either whole brain radiotherapy (WBRT) or autologous stem cell transplantation (ASCT). Given the (cognitive) side effects of WBRT, ASCT is increasingly being used as the first choice of treatment.

Gepubliceerd: J Neurol. 2024;271(5):2906-13.
Impact factor: 4.6 ; Q1

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2. Artificial Intelligence-based Segmentation of Residual Pancreatic Cancer in Resection Specimens Following Neoadjuvant Treatment (ISGPP-2): International Improvement and Validation Study
Janssen BV, Oteman B, Ali M, Valkema PA, Adsay V, Basturk O, Chatterjee D, Chou A, Crobach S, Doukas M, Drillenburg P, Esposito I, Gill AJ, Hong SM, Jansen C, Kliffen M, Mittal A, Samra J, van Velthuysen MF, Yavas A, Kazemier G, Verheij J, Steyerberg E, Besselink MG, Wang H, Verbeke C, Fariña A, de Boer OJ.

Neoadjuvant therapy (NAT) has become routine in patients with borderline resectable pancreatic cancer. Pathologists examine pancreatic cancer resection specimens to evaluate the effect of NAT. However, an automated scoring system to objectively quantify residual pancreatic cancer (RPC) is currently lacking. Herein, we developed and validated the first automated segmentation model using artificial intelligence techniques to objectively quantify RPC. Digitized histopathological tissue slides were included from resected pancreatic cancer specimens from 14 centers in 7 countries in Europe, North America, Australia, and Asia. Four different scanner types were used: Philips (56%), Hamamatsu (27%), 3DHistech (10%), and Leica (7%). Regions of interest were annotated and classified as cancer, non-neoplastic pancreatic ducts, and others. A U-Net model was trained to detect RPC. Validation consisted of by-scanner internal-external cross-validation. Overall, 528 unique hematoxylin and eosin (H & E) slides from 528 patients were included. In the individual Philips, Hamamatsu, 3DHistech, and Leica scanner cross-validations, mean F1 scores of 0.81 (95% CI, 0.77-0.84), 0.80 (0.78-0.83), 0.76 (0.65-0.78), and 0.71 (0.65-0.78) were achieved, respectively. In the meta-analysis of the cross-validations, the mean F1 score was 0.78 (0.71-0.84). A final model was trained on the entire data set. This ISGPP model is the first segmentation model using artificial intelligence techniques to objectively quantify RPC following NAT. The internally-externally cross-validated model in this study demonstrated robust performance in detecting RPC in specimens. The ISGPP model, now made publically available, enables automated RPC segmentation and forms the basis for objective NAT response evaluation in pancreatic cancer.

Gepubliceerd: Am J Surg Pathol. 2024;48(9):1108-16.
Impact factor: 4.2 ; Q1

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3. Next generation sequencing of high-grade adult-type diffuse glioma in the Netherlands: interlaboratory variation in the primary diagnostic and recurrent setting
van Opijnen MP, Broekman MLD, Cuppen E, Dubbink HJ, Ter Elst A, van Eijk R, Mühlebner A, Jansen C, van der Geize R, Speel EM, Groenen P, de Vos FYF, Wesseling P, de Leng WWJ, Maas SLN.

PURPOSE: Next generation sequencing (NGS) is an important tool used in clinical practice to obtain the required molecular information for accurate diagnostics of high-grade adult-type diffuse glioma (HGG). Since individual centers use either in-house produced or standardized panels, interlaboratory variation could play a role in the practice of HGG diagnosis and treatment. This study aimed to investigate the current practice in NGS application for both primary and recurrent HGG.
METHODS: This nationwide Dutch survey used the expertise of (neuro)pathologists and clinical scientists in molecular pathology (CSMPs) by sending online questionnaires on clinical and technical aspects. Primary outcome was an overview of panel composition in the different centers for diagnostic practice of HGG. Secondary outcomes included practice for recurrent HGG and future perspectives.
RESULTS: Out of twelve neuro-oncology centers, the survey was filled out by eleven (neuro)pathologists and seven CSMPs. The composition of the diagnostic NGS panels differed in each center with numbers of genes ranging from 12 to 523. Differences are more pronounced when tests are performed to find therapeutic targets in the case of recurrent disease: about half of the centers test for gene fusions (60%) and tumor mutational burden (40%).
CONCLUSION: Current notable interlaboratory variations as illustrated in this study should be reduced in order to refine diagnostics and improve precision oncology. In-house developed tests, standardized panels and routine application of broad gene panels all have their own advantages and disadvantages. Future research would be of interest to study the clinical impact of variation in diagnostic approaches.

Gepubliceerd: J Neurooncol. 2024;166(3):485-92.
Impact factor: 3.1 ; Q2

Totale impact factor: 11.9
Gemiddelde impact factor: 4.0

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Plastische chirurgie

1. International Lower Limb Collaborative Paediatric subpopulation analysis (INTELLECT-P) study: multicentre, international, retrospective audit of paediatric open fractures
Allan AY, Berner JE, Chan JK, Gardiner MD, Nanchahal J, Jain A, INTELLECT Collaborative; Rakhorst HA.

Gepubliceerd: BJS Open. 2024;8(4).
Impact factor: 4.5 ; Q1

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2. Reconstruction of an Early-Stage Scapholunate Advanced Collapse Wrist with the 3-Ligament Tenodesis Procedure: A Controversial Reappraisal
Dullemans KN, van der Oest MJW, Hakkesteegt SN, Vermeulen GM, Zuidam JM, Duraku LS, Feitz R, Hand-Wrist Study Group; Blomme RAM.

BACKGROUND: The authors hypothesized that the 3-ligament tenodesis (3-LT) procedure is still sufficient-even in scapholunate advanced collapse (SLAC) cases-to reduce pain and improve wrist function. The authors compared patient-reported outcomes of scapholunate interosseus ligament (SLIL) injury patients with SLAC, to SLIL injury patients treated with 3-LT, and then to patients who underwent proximal row carpectomy (PRC), as a control group.
METHODS: The authors included all patients with a traumatic SLIL injury and associated SLAC components treated with 3-LT and completed patient-rated wrist evaluation (PRWE) questionnaires preoperatively and at 12-month follow-up. First, the authors compared matched patients with SLIL injury and SLIL injury with SLAC, stage 1 to 3, who received 3-LT. Second, the authors compared patients who received 3-LT with patients who underwent PRC, while having SLAC stage 2 or 3.
RESULTS: The authors compared 51 patients with SLAC to 95 patients with SLIL injury who had a 3-LT procedure, and 10 3-LT patients were compared with 18 patients undergoing PRC, given SLAC stage 2 or 3. In both analyses, the PRWE scores had significantly improved in all groups; however, no significant differences in PRWE were found between 3-LT in SLIL injury and SLIL injury with SLAC (6.9 points; 95% CI, -14.92 to 1.22; P = 0.096) and between 3-LT and PRC, given SLAC stage 2 or 3, 15.1 points (not enough power).
CONCLUSIONS: There is no difference in PRWE between matched SLIL injury patients with or without degenerative changes treated with a 3-LT. Therefore, the 3-LT procedure seems to be a viable treatment option for patients with early-stage SLAC wrist.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Gepubliceerd: Plast Reconstr Surg. 2024;154(5):1015-24.
Impact factor: 3.4 ; Q1

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3. Three-Phase Video-Assisted Multidisciplinary Team Debriefing in High-Fidelity Blast Simulation through the Advocacy and Inquiry Method
Gasteratos K, Daniels B, Gebhart SJ, Patterson N, Tarrant MJ, Goverman J, Rakhorst H, van der Hulst R.

BACKGROUND: Video-assisted debriefing (VAD) combined with the advocacy and inquiry (A&I) technique is a tool that allows video playback of selected segments of a simulation, thereby helping the debriefers structure the session. However, no consensus exists on how to optimally perform a team debriefing. The authors demonstrate and describe the methodology of A&I debriefing in an instructional simulated blast scenario and assess the impact of VAD on residents' technical and nontechnical skills.

METHODS: After institutional review board approval, the authors performed a study with 50 residents who were randomly assigned to 2 groups. Group 1 (control, or no VAD; n = 25) consisted of residents who received oral debriefing by 1 independent faculty member without the recorded video of the simulation. Group 2 (intervention, or VAD; n = 25) consisted of residents who received VAD from the second independent faculty member. These residents repeated the same simulation scenario 1 week after their debrief. Every resident was assessed on the primary and secondary survey, as well as the nontechnical skills, based on the integrated skills score.
RESULTS: The VAD group presented significantly higher values for the integrated skills score (P < 0.001) compared with the no-VAD group.
CONCLUSIONS: This demonstration of 3-phase VAD emphasizes important aspects of coherent simulation-based training: psychologic safety, A&I, reflection, cognitive frames, prebrief, main debrief, summary, and translation of new discoveries to real-life patient care. The unique audiovisual aspect of the VAD enhanced residents' performance in simulation.

Gepubliceerd: Plast Reconstr Surg. 2024;154(2):453-63.
Impact factor: 3.4 ; Q1

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4. Instructional Video of a Standardized Interprofessional Postsimulation Facilitator-guided Debriefing of a Fatality in Plastic Surgery
Gasteratos K, Michalopoulos J, Nona M, Morsi-Yeroyiannis A, Goverman J, Rakhorst H, van der Hulst R.

BACKGROUND: Postsimulation facilitator-guided debriefing (PSFGD) is the process of intentional discussion of thoughts, actions, and events that took place during simulation amongst the facilitator(s) and trainees. Despite the significance of delivering high-quality debriefings, there is a lack of evidence-based guidelines. Our study aimed to provide an instructional video demonstration of a PSFGD of a fatality.
METHODS: Fifty surgical interns participated in a burn simulation scenario in two groups. Group 1 (control, or "no exposure," n = 25) consisted of residents who received oral postsimulation debriefing from an independent faculty member who had no exposure to our instructional video on how to debrief effectively. Group 2 (intervention, or "exposure," n = 25) consisted of interns who were debriefed by the second faculty member who did watch our instructional video before the simulation and learned about "advocacy and inquiry" techniques. The outcome measures were the Debriefing Assessment for Simulation in Healthcare score and the postdebrief multiple-choice question (MCQ) quiz scores to assess debriefers' performance and interns' knowledge consolidation, respectively.
RESULTS: The "exposure" group presented statistically significantly higher values for the Debriefing Assessment for Simulation in Healthcare score (P < 0.001) and MCQ score (P < 0.001) compared with the "no exposure" group.
CONCLUSIONS: Debriefers who followed the methodology as demonstrated in our instructional video were considered more competent, and the residents achieved higher MCQ scores. The quality of the debriefing ensures improved critical thinking and problem-solving skills. Safer practice and better patient outcomes are achieved by developing debriefing programs for educators.

Gepubliceerd: Plast Reconstr Surg Glob Open. 2024;12(2):e5583.
Impact factor: 1.8 ; Q2

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5. Correction: ESPRAS Survey: National and European Societies for Plastic Surgeons
Giunta RE, Schaefer DJ, Demirdöver C, Di Benedetto G, Elander A, Zic R, Georgescu A, Henley M, Spendel S, Saboye J, Schultz I, Kneafsey B, Psaras G, Verstreken F, Stark B, Santanelli di Pompeo F, Kaartinen I, Ylä-Kotola T, Ahm Sørensen J, Gilis J, Rakhorst H, Aquilina D, Fradinho N, Foroglou P, Nunez-Villaveiran MT, Jeffers L, Karabeg R, Yankov D, Nürnberger T, Kuhlmann C.

Gepubliceerd: Handchir Mikrochir Plast Chir. 2024;56(2):e2.
Impact factor: 0.6 ; Q4

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6. ESPRAS Survey: National and European Societies for Plastic Surgeons
Giunta RE, Schaefer DJ, Demirdöver C, Di Benedetto G, Elander A, Zic R, Georgescu A, Henley M, Spendel S, Saboye J, Schultz I, Kneafsey B, Psaras G, Verstreken F, Stark B, Santanelli di Pompeo F, Kaartinen I, Ylä-Kotola T, Ahm Sørensen J, Gilis J, Rakhorst H, Aquilina D, Fradinho N, Foroglou P, Nunez-Villaveiran MT, Jeffers L, Karabeg R, Yankov D, Nürnberger T, Kuhlmann C.

BACKGROUND: The European Society of Plastic, Reconstructive and Aesthetic Surgery (ESPRAS) comprises 40 national societies across Europe. In addition to ESPRAS, there are 8 different European Plastic Surgery societies representing Plastic Surgeons in Europe. The 4(th) European Leadership Forum (ELF) of ESPRAS, held under the motto "Stronger together in Europe" in Munich in 2023, aimed to collect and disseminate information regarding the national member societies of ESPRAS and European societies for Plastic Surgeons. The purpose was to identify synergies and redundancies and promote improved cooperation and exchange to enhance coordinated decision-making at the European level.
MATERIAL AND METHODS: An online survey was conducted regarding the organisational structures, objectives and challenges of national and European societies for Plastic Surgeons in Europe. This survey was distributed to official representatives (Presidents, Vice Presidents and General Secretaries) and delegates of national and European societies at the ELF meeting. Missing information was completed using data obtained from the official websites of the respective European societies. Preliminary results were discussed during the 4(th) ELF meeting in Munich in March 2023.
RESULTS: The ESPRAS survey included 22 national and 9 European Plastic Surgery societies representing more than 7000 Plastic Surgeons in Europe. Most national societies consist of less than 500 full members (median 182 members (interquartile range (IQR) 54-400); n=22). European societies, which covered the full spectrum or subspecialities, differed in membership types and congress cycles, with some requiring applications by individuals and others including national societies. The main purposes of the societies include research, representation against other disciplines, specialisation and education as well as more individual goals like patient care and policy regulation.
CONCLUSION: This ESPRAS survey offers key insights into the structures, requirements and challenges of national and European societies for Plastic Surgeons, highlighting the relevance of ongoing close exchange between the societies to foster professional advancement and reduce redundancies. Future efforts of the ELF will continue to further explore strategies for enhancing collaboration and harmonisation within the European Plastic Surgery landscape.

Gepubliceerd: Handchir Mikrochir Plast Chir. 2024;56(2):156-65.
Impact factor: 0.6 ; Q4

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7. Comparing Patient-Reported Outcomes on Three-Ligament Tenodesis Between Partial and Complete Scapholunate Ligament Injuries: A Cohort Study
Hakkesteegt SN, van der Oest MJW, Dullemans KN, Duraku LS, Hundepool CA, Selles RW, Feitz R, Zuidam JM, Hand-Wrist Study Group; Blomme RAM.

PURPOSE: Multiple studies report outcomes after 3-ligament tenodesis (3-LT) in treating traumatic scapholunate interosseous ligament injury (SLIL). However, investigators do not differentiate between patients with partial or complete SLIL injury. The relation between the extent of SLIL disruption and surgical outcomes and if this should be considered when treating a patient with SLIL injury remains unknown. We aimed to evaluate differences in patient-rated wrist evaluation (PRWE) scores, satisfaction and return to work between patients with partial or complete chronic traumatic SLIL injury treated with 3 ligament tenodesis at 12 months after surgery.
METHODS: All patients with chronic SLIL injury (partial and complete) who were treated with 3-LT at our clinic and received the same postoperative management between December 2011 and December 2019 were studied. Only patients who had completed the PRWE and return to work questionnaires preoperatively and 12 months after surgery were included. Patients were allocated to the partial (classified as Geissler 2 or 3) or complete SLIL injury group (classified as Geissler 4) by retrospectively assessing wrist arthroscopy reports.
RESULTS: Thirty-nine patients with partial and 90 with complete SLIL injuries were included. At 1-year follow-up, PRWE scores had significantly improved in both groups. When adjusting for clinical baseline characteristics, there was no statistically significant difference between patients with partial or complete SLIL injury. Patients with complete SLIL injury had a 70% higher return to work within the first 12 months after 3-LT; however, satisfaction with the treatment result was similar for both study groups 1 year after surgery.
CONCLUSIONS: Patients with complete and partial traumatic SLIL injury report better PRWE total scores at 12 months after 3-LT, but there was no statistically significant difference between the groups in PRWE scores or satisfaction with the treatment result.
TYPE OF STUDY/LEVEL OF EVIDENCE: Therapeutic IV.

Gepubliceerd: J Hand Surg Am. 2024;49(7):712.e1-.e9.
Impact factor: 2.1 ; Q2

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8. From Data to Decisions: How Artificial Intelligence Is Revolutionizing Clinical Prediction Models in Plastic Surgery
Kooi K, Talavera E, Freundt L, Oflazoglu K, Ritt M, Eberlin KR, Selles RW, Clemens MW, Rakhorst HA.

The impact of clinical prediction models within artificial intelligence (AI) and machine learning is significant. With its ability to analyze vast amounts of data and identify complex patterns, machine learning has the potential to improve and implement evidence-based plastic, reconstructive, and hand surgery. In addition, it is capable of predicting the diagnosis, prognosis, and outcomes of individual patients. This modeling aids daily clinical decision-making, most commonly at the moment, as decision support. The purpose of this article is to provide a practice guideline to plastic surgeons implementing AI in clinical decision-making or setting up AI research to develop clinical prediction models using the 7-step approach and the ABCD validation steps of Steyerberg and Vergouwe. The authors also describe 2 important protocols that are in the development stage for AI research: (1) the transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis checklist, and (2) the Prediction Model Risk of Bias Assessment Tool checklist to access potential biases.

Gepubliceerd: Plast Reconstr Surg. 2024;154(6):1341-52.
Impact factor: 3.4 ; Q1

9. Patient-reported esthetic outcomes following lower extremity free flap reconstruction: A cross-sectional multicenter study
Krijgh DD, List EB, Beljaars B, Qiu Shao SS, de Jong T, Rakhorst HA, Verheul EM, Maarse W, Coert JH.

INTRODUCTION: The goal of lower-extremity reconstructions is primarily to salvage the leg; however, esthetic outcomes are also important. This study aimed to assess the impact of a lower extremity free tissue transfer regarding social functioning, patient-reported esthetic outcomes, and possible differences between fasciocutaneous vs. muscle flaps.
MATERIAL AND METHODS: For this cross-sectional multicenter study, patients operated between 2003 and 2021, with a minimum follow-up of 12 months, were identified. Outcomes were obtained from 89 patients. Patient-reported outcomes were assessed using a questionnaire containing 5-point Likert scale questions grouped in three groups: aspect of the reconstructed leg, the aspect of the donor site, and the negative impact on social functioning. Physical functioning and mental health were assessed with the Short-Form-36.
RESULTS: The overall score for negative impact on social functioning was 22.2. This was 46.7 for the esthetic satisfaction of the reconstructed leg and 57.1 for the donor site. No significant differences were seen between patients who underwent a reconstruction with a fasciocutaneous flap compared to a muscle flap. Secondary surgical procedures for improving the esthetic aspect were performed in 12% of the patients in the fasciocutaneous group and 0% in the muscle group.
CONCLUSION: Our results show that the most optimal esthetic outcome is not defined by the type of flap. We found a strong correlation between physical functioning and the negative impact on social functioning that a reconstructed lower extremity may have. The result of this study can be taken into consideration during the shared decision-making process of choosing the most optimal reconstruction.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2024;93:1-8.
Impact factor: 2.4 ; Q2

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10. Adverse Events Associated with Hyaluronic Acid Filler Injection for Non-surgical Facial Aesthetics: A Systematic Review of High Level of Evidence Studies
Kyriazidis I, Spyropoulou GA, Zambacos G, Tagka A, Rakhorst HA, Gasteratos K, Berner JE, Mandrekas A.

BACKGROUND: Hyaluronic acid (HA) dermal fillers are widely used in aesthetic medicine. While generally safe, potential complications can arise.
OBJECTIVE: This systematic review aims to identify and classify potential complications linked to the use of HA dermal fillers, as informed by high-quality, low-risk-of-bias studies.
METHODS: This review follows the Cochrane review standards for clinical systematic reviews. This systematic review analyzed 48 high level of evidence studies on the use of hyaluronic acid (HA) dermal fillers in non-surgical facial aesthetics and the adverse events that occurred.The inclusion criteria were randomized control studies on HA dermal fillers and their complications. Excluded were case reports, case series, observational studies, and other non-randomized research due to their inability to provide generalized conclusions and their inherent publication bias.
RESULTS: Adverse events were classified into three categories: expected reactions, product or technique-related adverse events, and severe adverse events. Most adverse events were short-lived injection site reactions, which resolved spontaneously. Specific HA fillers and injection techniques influenced the occurrence of adverse events, which generally resolved within weeks without

treatment. Severe adverse events were rare, persisting for months and requiring active medical intervention.
DISCUSSION: This classification system can enhance understanding, prevention, and treatment of HA filler complications, and support patient education. The common complications were injection site reactions, with persistent symptoms treated with topical steroids, NSAIDs, or hyaluronidase. Severe complications included severe edema, angioedema and others, often necessitating specific treatments.
CONCLUSION: HA dermal fillers are generally safe and effective, with most adverse events being transient and mild to moderate in severity. Severe adverse events, although rare, do occur and are generally non-treatment related. Informed consent, patient education, and professional training are crucial for safe and successful outcomes. Level of Evidence II This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266 .

Gepubliceerd: Aesthetic Plast Surg. 2024;48(4):719-41.
Impact factor: 2.8 ; Q1

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11. Patient-Reported and Clinical Outcomes After Tendon Autograft Reconstruction of the Thumb Ulnar Collateral Ligament
Legerstee IWF, van der Oest MJW, Souer JS, Hundepool CA, Duraku LS, Selles RW, Zuidam JM, Hand-Wrist Study Group; Blomme RAM.

PURPOSE: This study aimed to report clinical and patient-reported outcomes collected in a registry after thumb ulnar collateral ligament (UCL) reconstruction with a free tendon autograft. Furthermore, the patient-reported outcomes of patients with persistent instability after reconstruction and patients with concomitant metacarpophalangeal joint arthritis diagnosed during surgery were analyzed.
METHODS: Patients undergoing reconstruction with a tendon autograft between December 2011 and February 2021 were included. Michigan Hand Outcomes Questionnaire (MHQ) scores at baseline were compared with those at 3 and 12 months after surgery. Stability was tested at 3 months after surgery. Tip and key pinch strength and metacarpophalangeal joint range of motion were measured at baseline and 12 months after surgery.
RESULTS: We included 31 patients with thumb UCL insufficiency or failed UCL surgery who underwent reconstruction. The MHQ total score improved significantly from 62 at baseline to 75 at 3 months and continued to increase to 84 at 12 months after surgery. The MHQ function and pain scores improved significantly from intake to 3 and 12 months after surgery. Twenty-six of 31 patients (84%) regained postoperative metacarpophalangeal stability. Key pinch strength improved significantly 12 months after surgery from 5.2 kg at baseline to 6.4 kg at 12 months. The MHQ total, pain, and function scores of patients with persistent instability remained similar from baseline to 12 months after surgery. In four patients with metacarpophalangeal arthritis, the MHQ total and pain score improved significantly from baseline to 3 and 12 months after surgery.
CONCLUSIONS: Patient-reported outcomes, including pain and function, improved after thumb UCL reconstruction with a tendon autograft. Although the sample size of patients with thumb metacarpophalangeal arthritis diagnosed during surgery was small, they reached adequate patient-reported outcomes at 12 months after surgery.
TYPE OF STUDY/LEVEL OF EVIDENCE: Therapeutic IV.

Gepubliceerd: J Hand Surg Am. 2024.
Impact factor: 2.1 ; Q2

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12. Health symptoms and cosmetic silicone breast implants: A retrospective cohort study
Lieffering AS, Ramerman L, Hommes JE, Rakhorst HA, Mureau MAM, van der Hulst R, Verheij RA.

BACKGROUND: There has been a growing concern about a possible causal relationship between silicone breast implants (SBIs) and health symptoms, referred to as breast implant illness. This study assessed the association between SBIs for cosmetic augmentation and health symptoms.
METHODS: This retrospective cohort study used the data from the Dutch Breast Implant Registry and Nivel Primary Care Database. A total of 688 women with cosmetic SBIs were age-matched with 1301 women without SBIs. The occurrence of 13 health symptoms presented in general practice was assessed 1 year before implantation until 3 years after implantation. Comparisons were made regarding the number of symptoms and general practice consultations, before and after implantation and between the two groups.
RESULTS: Women with SBIs were more likely to experience three or more distinct health symptoms and a combination of multiple symptoms with multiple consultations during follow-up than women without SBIs (adjusted OR 1.44, 95% CI 1.06 to 1.96; adjusted OR 1.44, 95% CI 1.04 to 2.00, respectively). Women with SBIs also had more than twice the likelihood of manifesting these outcomes in the second year after implantation compared to the first year before implantation (OR 2.13, 95% CI 1.27 to 3.57; OR 2.13, 95% CI 1.22 to 3.72, respectively).
CONCLUSIONS: Women with cosmetic SBIs had increased odds of developing health symptoms after implantation compared to those before implantation and to women without SBIs. These results suggest an association between health symptoms and cosmetic SBIs that needs further research to explore whether there is causality or residual confounding.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2024;99:506-14.
Impact factor: 2.4 ; Q2

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13. Medical Specialist Care Utilization Prior to the Explantation of Cosmetic Silicone Breast Implants: A Nationwide Retrospective Data Linkage Study
Lieffering AS, Ramerman L, Verheij RA, Rakhorst HA, Mureau MAM, van der Hulst R, Hommes JE.

BACKGROUND: Explantation is the proposed treatment for breast implant illness (BII). Little is known about which medical specialists are visited and what diagnoses are made before explantation is provided as the treatment.
OBJECTIVES: This study investigated medical specialist care utilization in women with cosmetic breast implants who underwent explantation compared to women who chose breast implant replacement surgery and to women without breast implants.
METHODS: Retrospective cohort study using data linkage with the Dutch Breast Implant Registry and the Dutch health insurance claims database. Visits to medical specialists were examined over the 3 years before explantation. A total of 832 explantation patients were matched and compared to 1463 breast implant replacement patients and 1664 women without breast implants.
RESULTS: Explantation patients were more likely to have visited > 5 different medical specialties compared to both replacement patients (12.3% vs. 5.7%; $p < 0.001$) and women without breast implants (12.3% vs. 3.7%; $p < 0.001$). Among explantation patients, women who underwent explantation because of BII were more likely to have visited > 5 different medical specialties compared to women who underwent explantation because of other reasons (25.0% vs. 11.0%; $p < 0.001$).
CONCLUSIONS: Women who underwent explantation of breast implants had higher utilization of medical specialist care in the years before explantation compared to women who underwent breast implant replacement surgery and women without breast implants. Medical specialist care use was especially high among women for whom BII was the registered reason for explantation. These

findings suggest further research is needed into the link between BII and the use of medical specialist care.
LEVEL OF EVIDENCE III: This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266 .

Gepubliceerd: Aesthetic Plast Surg. 2024;48(21):4404-13.
Impact factor: 2.8 ; Q1

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14. Free Fasciocutaneous versus Muscle Flaps in Lower Extremity Reconstruction: Implications for Functionality and Quality of Life
List EB, Hahn BA, Qiu SS, de Jong T, Rakhorst HA, Verheul EM, Maarse W, Coert JH, Krijgh DD.

BACKGROUND: Free tissue transplantations are commonly used to treat complex lower extremity defects caused by trauma, vascular disease, or malignancy, particularly when vital structures are exposed. This study aimed to expand the knowledge on patient-reported outcomes by comparing fasciocutaneous and muscle flaps, with the goal of facilitating patient counseling. Additionally, patient-level risk factors associated with decreased functioning and health-related quality of life were identified.
METHODS: This retrospective, cross-sectional, multicenter study included patients who underwent microsurgical lower extremity reconstruction using free fasciocutaneous or muscle flaps between 2003 and 2021, with a minimum follow-up of 12 months. Data were collected from medical records, pain scores, Short-Form 36 (SF-36), and Lower Extremity Functional Scale (LEFS). Mean scores were compared between flap types and predictors of LEFS, SF-36 mental component summary (MCS), and SF-36 physical component summary (PCS) scores were determined using a backward stepwise regression model.
RESULTS: Of the 206 patients eligible, 100 (49%) were included in the retrospective part. A total of 89 (43%) responded to the questionnaires, with 62 treated using a fasciocutaneous flap and 27 with a muscle flap. No significant differences in total LEFS, SF-36 PCS, or MCS scores were found between the two flap type. Pain was a significant predictor of decreased functional outcomes for both flap types and was also linked to poorer mental health in patients treated with fasciocutaneous flaps. Other predictors of low patient-reported outcome scores included obesity, diabetes, poorer mental health, and a follow-up of less than 2 years.
CONCLUSION: Patients treated with fasciocutaneous and muscle flaps experience comparable levels of functionality and quality of life after surgery. Flap selection should be based on defect characteristics, along with the surgeon's individual skills and preferences. A comprehensive approach that considers physical comorbidities, pain, and mental health is essential, as these factors significantly impact patient functionality and quality of life.

Gepubliceerd: J Reconstr Microsurg. 2024.
Impact factor: 2.3 ; Q2

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15. Data quality assessment of the Dutch Breast Implant Registry by automated data verification using medical billing data
Melse PE, Vrolijk JJ, Becherer BE, Stangenberger VA, Winkelmolen C, Hommes JE, Rakhorst HA, Mureau MAM.

BACKGROUND: The Dutch Breast Implant Registry (DBIR) provides real-time population-based data to monitor and improve the quality and safety of breast implants and to trace patients in the event of an

(inter)national recall. To serve these main goals, the capture rate and percentage of implants that are actually registered should be known and data should be complete. This study aimed to describe an automated verification process for capture rates and data completeness using medical billing data as the external source.
METHODS: DBIR-data on reconstructive permanent breast implants and tissue expanders (TEs) from 2019 were compared to medical billing data. At the hospital level, the capture rate of DBIR and accuracy of the selected data points were assessed.
RESULTS: In total, 2389 implants (1420 patients) were included from 12 participating hospitals (11% of all healthcare institutions registering in DBIR). DBIR had capture rates of 99% to 114% for inserted permanent implants and TEs and 49% for explanted permanent implants and TEs. Among the 9015 data points analyzed in DBIR, 8861 (98%) matched the medical billing data. Mastopexy had the highest matching percentage (100%) and capsulectomy the lowest (86%).
CONCLUSION: This study showed varying capture rates in DBIR depending on the intervention group, indicating that registration of DBIR-data and medical billing codes could be further optimized. Data accuracy was high as only 2% of data points did not correspond to medical billing data. For future data verification, other external data sources could be explored, including sources that enable verification of cosmetic implants.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2024;99:96-102.
Impact factor: 2.4 ; Q2

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16. The economic impact of open lower limb fractures in the Netherlands: a cost-of-illness study
Noorlander-Borgdorff MP, Kievit W, Giannakópoulos GF, Botman M, Tromp TN, Oflazoglu K, Rakhorst HA, de Jong T.

PURPOSE: To estimate the one-year sum of direct costs related to open lower limb fracture treatment in an academic setting in the Netherlands. The secondary objective was to estimate the impact of deep infection and nonunion on one-year total direct costs.
METHODS: A multi-center, retrospective cost analysis of open lower limb fractures treated in an academic setting in the Netherlands, between 1 January 2017 and 31 December 2018, was conducted. The costing methodology was based on patient level aggregation using a bottom-up approach. A multiple linear regression model was used to predict the total costs based on Fracture-related-infections, multitrauma, intensive care unit (ICU) admission, Gustilo-Anderson grade and nonunion.
RESULTS: Overall, 70 fractures were included for analysis, the majority Gustilo-Anderson grade III fractures (57%). Median (IQR) one-year hospital costs were €31,258 (20,812-58,217). Costs were primarily attributed to the length of hospital stay (58%) and surgical procedures (30%). The median length of stay was 16 days, with an increase to 50 days in Fracture-related infections. Subsequent costs (46,075 [25,891-74,938] vs. 15,244 [8970-30,173]; $p = 0.002$), and total hospital costs (90,862 [52,868-125,004] vs. 29,297 [21,784-40,677]; $p < 0.001$) were significantly higher for infected cases. It was found that Fracture-related infection, multitrauma, and Gustilo-Anderson grade IIIA-C fractures were significant predictors of increased costs.
CONCLUSION: In treatment of open lower limb fractures, deep infection, higher Gustilo-Anderson classification, and multitrauma significantly increase direct hospital costs. Considering the impact of infection on morbidity and total healthcare costs, future research should focus on preventing Fracture-related infections.

Gepubliceerd: Eur J Trauma Emerg Surg. 2024;50(5):2605-13.
Impact factor: 2.2 ; Q2

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17. Driving Factors of Recommending a Hand Surgery Clinic After Surgery
Porsius JT, Ter Stege MHP, Selles RW, Slijper HP, Hand-Wrist Study Group; Blomme RAM.

PURPOSE: Since a patient's recommendation of a clinic to others is an important indicator of patient experience, more insight is needed into the underlying factors that motivate such recommendations. This retrospective cohort study assessed the relative contribution of the following: (1) patient-related characteristics, (2) treatment outcome, (3) satisfaction with treatment outcome, and (4) patients' experience with the process of care to patients' recommendation of a specific clinic after elective surgery.
METHODS: Patients of specialized outpatient hand surgery clinics (N = 6,895) reported the likelihood of recommending the clinic to friends or family 3-5 months after surgery by filling in the Net Promoter Score. Potential predictors of the Net Promoter Score were preoperative patient characteristics, patient-reported treatment outcomes, satisfaction with treatment outcome, and experience with several health care delivery domains. Linear regression analyses were used to examine the contribution of the predictors.
RESULTS: Mean age of the patients was 53 (SD, 14) years, 62.5% were women, and 62.5% were employed. Preoperative patient characteristics explained 1% of the variance in clinic recommendations. An additional 6% was explained by the treatment outcome, 21.6% by satisfaction with treatment outcome, and 33.8% by patients' experience with care delivery (total explained variance was 62.3%). The strongest independent predictors of clinic recommendations were positive experiences with the quality of the facilities and the communication skills of the physician.
CONCLUSIONS: Patient recommendations are more strongly driven by patients' experience with care delivery than by treatment outcome and patient characteristics. CLINICAL RELEVANCE: In elective surgery, improving patient experiences is pivotal in boosting patient recommendation of the clinic.

Gepubliceerd: J Hand Surg Am. 2024;49(2):114-23.
Impact factor: 2.1 ; Q2

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18. Forearm rotation improves after corrective osteotomy in patients with symptomatic distal radius malunion
van Es EM, Dijkhof M, Souer JS, van Ewijk FJ, Hoogendam L, Slijper HP, Selles RW, Colaris JW, Hand-Wrist Study Group; Blomme RAM.

OBJECTIVES: Distal radius malunion can result in pain and functional complaints. One of the functional problems that can affect daily life is impaired forearm rotation. The primary aim of this study was to investigate the effect of corrective osteotomy for distal radius malunion on forearm rotation at 12 months after surgery. We secondarily studied the effect on grip strength, radiological measurements, and patient-reported outcome measurements (PROMs).
PATIENTS AND METHODS: This cohort study analysed prospectively collected data of adult patients with symptomatic distal radius malunion. All patients underwent corrective osteotomy for malunion and were followed for 1 year. We measured forearm rotation (pronation and supination) and grip strength and analysed radiographs. PROMs consisted of the Patient-Rated Hand/Wrist Evaluation (PRWHE) questionnaire, Visual Analogue Scale for pain, and satisfaction with hand function.
RESULTS: Preoperative total forearm rotation was 112° (SD: 34°), of which supination of 49° (SD: 25°) was more impaired than pronation of 63° (SD: 17°). Twelve months after surgery, an unpaired Student's t-test showed a significant improvement of total forearm rotation to 142° (SD: 17°) ($p < 0.05$). Pronation improved to 72° (SD: 10°), and supination to 69° (SD: 13°) ($p < 0.05$). Grip strength, PROMs, as well as inclination and volar tilt on radiographs improved significantly during the first year after surgery ($p < 0.05$).

CONCLUSION: In patients with reduced forearm rotation due to distal radius malunion, corrective osteotomy is an effective treatment that significantly improves forearm rotation. In addition, this intervention improves grip strength, the PRWHE-score, pain, and satisfaction with hand function.

Gepubliceerd: Heliyon. 2024;10(9):e29570.
Impact factor: 3.6 ; Q1

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19. High-impact complications after breast cancer surgery in the Dutch national quality registry: evaluating case-mix adjustment for hospital comparisons
Verheul EM, van Klaveren D, Lingsma HF, Vos E, Hoornweg MJ, Siesling S, Koppert LB, NBCA consortium; Rakhorst HA.

BACKGROUND: Comparison of quality indicators can improve quality of care. However, case-mix adjustment is deemed essential. The aim of this study was to develop and validate case-mix adjustment models and to evaluate the effect of case-mix adjustment for the quality indicators related to complications after breast cancer surgery.
METHODS: Multivariable logistic regression with backward selection ($P < 0.1$) was used to develop case-mix models in patients undergoing breast cancer surgery (all types, breast-conserving surgery, mastectomy with or without immediate reconstruction) in the Netherlands (NABON Breast Cancer Audit). High-impact complications were defined as Clavien Dindo grade ≥3. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), corrected for optimism with bootstrap validation. Observed-to-expected plots were used to visualize the difference between unadjusted and case-mix adjusted hospital performance (hospital shifts).
RESULTS: In total 32 084 patients from 72 hospitals treated in 2021-2022 were included. A between-hospital variation in complication rates was observed for all surgeries (interquartile range 2.4-6.0%), breast-conserving surgery (interquartile range 1.4-3.4%), and mastectomy with (interquartile range 9.4-9.1%) and without reconstruction (interquartile range 3.3-9.7%). Of the considered variables, body mass index, smoking, multifocality and neoadjuvant therapy were weakly associated with complications. However, surgery type was strongly related to complications (AUC 0.70), resulting in noticeable hospital shifts in the quality indicator scores comprising all surgeries. After stratification for surgery type, no evident hospital shifts were observed after case-mix correction.
CONCLUSION: For valid comparison of complication rates after breast cancer surgery between hospitals, stratification by surgery type is crucial. Subsequently, the evaluated patient and tumour characteristics have a negligible effect on the hospital variation.

Gepubliceerd: BJS Open. 2024;9(1).
Impact factor: 4.5 ; Q1

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20. Risk Factors for Unplanned Reoperation during the Expansion Phase in Two-Stage Breast Reconstruction in the Dutch Breast Implant Registry
Vrolijk JJ, Bargon CA, Becherer BE, Wilschut JA, van Bommel ACM, Hommes JE, Keuter XHA, Young-Afat DA, Verkooijen HM, van der Hulst R, Mureau MAM, Rakhorst HA.

BACKGROUND: The majority of postmastectomy breast reconstructions (PMBRs) are currently performed in two stages using a tissue expander (TE). However, complications during the expansion phase occur regularly, leading to unplanned reoperations and/or reconstruction failure. This study aimed to identify risk factors for unplanned reoperation after TE placement, assessed the time until unplanned and planned reoperation, and investigated indications for unplanned reoperation.
METHODS: Patient- and surgery-related characteristics of patients who underwent two-stage PMBR

between 2017 and 2021 were collected from the Dutch Breast Implant Registry (DBIR). Unplanned reoperation was defined as TE explantation followed by either no replacement or replacement with the same or a different TE. Covariate-adjusted characteristics associated with unplanned reoperation were determined using backward stepwise selection and multivariable logistic regression analyses.
RESULTS: In total, 2529 patients (mean age, 50.2 years) were included. Unplanned reoperation occurred in 19.4% of all registered TEs (n = 3190). Independent factors associated with unplanned reoperation were body mass index (BMI) greater than or equal to 25 kg/m 2 (adjusted OR [aOR], 1.63, 99% CI, 1.20 to 2.57 for BMI of 25 to 29.9 kg/m 2 ; aOR, 2.57, 99% CI, 1.74 to 3.78 for BMI ≥30 kg/m 2), low institutional volume (aOR, 1.51; 99% CI, 1.06 to 2.18), no drains (aOR, 2.06; 99% CI, 1.15 to 3.60), subcutaneous TE placement (aOR, 5.71; 99% CI, 3.59 to 9.10), and partial pectoralis major muscle coverage (aOR, 1.35; 99% CI, 1.02 to 1.79). Age younger than 40 years (aOR, 0.49; 99% CI, 0.32 to 0.74) and delayed PMBR (aOR, 0.35; 99% CI, 0.19 to 0.60) reduced the risk of unplanned reoperation. Median time until reoperation was 97 days for unplanned and 213 days for planned reoperation. Deep wound infections were most often registered as indication for unplanned reoperation (34.4%).
CONCLUSION: This study identified several risk factors for unplanned reoperation that may be used to reduce complications in expander-based PMBR.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Gepubliceerd: Plast Reconstr Surg. 2024;154(1):33e-43e.
Impact factor: 3.4 ; Q1

Totale impact factor: 52.8
Gemiddelde impact factor: 2.6

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: 3.4
Gemiddelde impact factor: 3.4

Raad van Bestuur

1. Developing Game-Based Design for eHealth in Practice: 4-Phase Game Design Process
de Vette F, Ruiz-Rodriguez A, Tabak M, Oude Nijeweme-d'Hollosy W, Hermens H, Vollenbroek-Hutten M.

BACKGROUND: Games are increasingly used in eHealth as a strategy for user engagement. There is an enormous diversity of end users and objectives targeted by eHealth. Hence, identifying game content that drives and sustains engagement is challenging. More openness in the game design process and motivational strategies could aid researchers and designers of future game-based apps.
OBJECTIVE: This study aims to provide insights into our approach to develop game-based eHealth in practice with a case study (Personalised ICT Supported Services for Independent Living and Active Ageing [PERSSILAA]). PERSSILAA is a self-management platform that aims to counter frailty by offering training modules to older adults in the domains of healthy nutrition and physical and cognitive training to maintain a healthy lifestyle. We elaborate on the entire game design process and show the motivational strategies applied.
METHODS: We introduce four game design phases in the process toward game-based eHealth: (1) end-user research, (2) conceptualization, (3) creative design, and (4) refinement (ie, prototyping and evaluations).
RESULTS: First, 168 participants participated in end-user research, resulting in an overview of their preferences for game content and a set of game design recommendations. We found that conventional games popular among older adults do not necessarily translate well into engaging concepts for eHealth. Recommendations include focusing game concepts on thinking, problem-solving, variation, discovery, and achievement and using high-quality aesthetics. Second, stakeholder sessions with development partners resulted in strategies for long-term engagement using indicators of user performance on the platform's training modules. These performance indicators, for example, completed training sessions or exercises, form the basis for game progression. Third, results from prior phases were used in creative design to create the game "Stranded!" The user plays a person who is shipwrecked who must gather parts for a life raft by completing in-game objectives. Finally, iterative prototyping resulted in the final prototype of the game-based app. A total of 35 older adults participated using simulated training modules. End users scored appreciation (74/100), ease of use (73/100), expected effectivity and motivation (62/100), fun and pleasantness of using the app (75/100), and intended future use (66/100), which implies that the app is ready for use by a larger population.
CONCLUSIONS: The study resulted in a game-based app for which the entire game design process within eHealth was transparently documented and where engagement strategies were based on extensive user research. Our user evaluations indicate that the strategies for long-term engagement led to game content that was perceived as engaging by older adults. As a next step, research is needed on the user experience and actual engagement with the game to support the self-management of older adults, followed by clinical studies on its added value.

Gepubliceerd: JMIR Form Res. 2024;8:e13723.
Impact factor: 2.1 ; Q3

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2. Consequences of Data Loss on Clinical Decision-Making in Continuous Glucose Monitoring: Retrospective Cohort Study
den Braber N, Braem CIR, Vollenbroek-Hutten MMR, Hermens HJ, Urgert T, Yavuz US, Veltink PH, Laverman GD.

BACKGROUND: The impact of missing data on individual continuous glucose monitoring (CGM) data is unknown but can influence clinical decision-making for patients.
OBJECTIVE: We aimed to investigate the consequences of data loss on glucose metrics in individual patient recordings from continuous glucose monitors and assess its implications on clinical decision-making.
METHODS: The CGM data were collected from patients with type 1 and 2 diabetes using the FreeStyle Libre sensor (Abbott Diabetes Care). We selected 7-28 days of 24 hours of continuous data without any missing values from each individual patient. To mimic real-world data loss, missing data ranging from 5% to 50% were introduced into the data set. From this modified data set, clinical metrics including time below range (TBR), TBR level 2 (TBR2), and other common glucose metrics were calculated in the data sets with and that without data loss. Recordings in which glucose metrics deviated relevantly due to data loss, as determined by clinical experts, were defined as expert panel boundary error (ε(EPB)). These errors were expressed as a percentage of the total number of recordings. The errors for the recordings with glucose management indicator <53 mmol/mol were investigated.
RESULTS: A total of 84 patients contributed to 798 recordings over 28 days. With 5%-50% data loss for 7-28 days recordings, the ε(EPB) varied from 0 out of 798 (0.0%) to 147 out of 736 (20.0%) for TBR and 0 out of 612 (0.0%) to 22 out of 408 (5.4%) recordings for TBR2. In the case of 14-day recordings, TBR and TBR2 episodes completely disappeared due to 30% data loss in 2 out of 786 (0.3%) and 32 out of 522 (6.1%) of the cases, respectively. However, the initial values of the disappeared TBR and TBR2 were relatively small (<0.1%). In the recordings with glucose management indicator <53 mmol/mol the ε(EPB) was 9.6% for 14 days with 30% data loss.
CONCLUSIONS: With a maximum of 30% data loss in 14-day CGM recordings, there is minimal impact of missing data on the clinical interpretation of various glucose metrics.
TRIAL REGISTRATION: ClinicalTrials.gov NCT05584293; https://clinicaltrials.gov/study/NCT05584293.

Gepubliceerd: Interact J Med Res. 2024;13:e50849.
Impact factor: 2.2 ; Q3

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3. Analysing physical activity measures and clustering in patients with type 2 diabetes in secondary care: insights from the DIAbetes and LifEstyle Cohort Twente (DIALECT)-an observational cohort study

den Braber N, Vollenbroek-Hutten MM, Kappert KDR, Laverman GD.

OBJECTIVES: To analyse variance in accelerometer-based physical activity (PA) measures in patients with type 2 diabetes, identify the most distinctive PA measures and classify patients into different PA clusters based on these measures.
DESIGN: DIAbetes and LifEstyle Cohort Twente (DIALECT), an observational cohort study. SETTING: Secondary care in the Netherlands.
PARTICIPANT: 253 patients, with three excluded due to insufficient data. The cohort was predominantly male (66%) with an average age of 64.7 years.
PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcomes of DIALECT were all-cause mortality, microvascular and macrovascular diseases. The secondary outcomes are blood pressure levels, kidney function indicators and albuminuria levels
RESULTS: Principal component analysis (PCA) was applied to 53 accelerometer-derived PA measures. Principal components were identified using a scree plot, key measures determining the principal components were derived and k-mean cluster analysis was applied to the components. The main PA measures were steps/day, active time, zero steps, total sedentary behaviour (SB) bout duration and total moderate to vigorous physical activity (MVPA) bout duration. Based on three PCA components, three clusters were identified. The inactive cluster had a higher BMI, diabetes duration, age and SB bout duration, and lower steps/day and MVPA bout duration compared with the other clusters

(p<0.05). The active cluster still scores low on MVPA bout duration (18 min/week) and high on SB bout duration (5.0 hours/day).
CONCLUSIONS: PA behaviour in patients can be categorised into three distinct clusters. The identified PA measures and behaviour clusters offer promising opportunities for tailored lifestyle treatment. However, further studies are needed to determine which PA measures are clinically most relevant, validate the usefulness of this classification and evaluate whether tailoring lifestyle advice according to these clusters adds clinical value.
TRIAL REGISTRATION NUMBER: NTR5855.

Gepubliceerd: BMJ Open. 2024;14(12):e082059.
Impact factor: 2.3 ; Q2

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4. The Contribution of Postprandial Glucose Levels to Hyperglycemia in Type 2 Diabetes Calculated from Continuous Glucose Monitoring Data: Real World Evidence from the DIALECT-2 Cohort
den Braber N, Vollenbroek-Hutten MMR, Teunissen SEM, Oosterwijk MM, Kappert KDR, Laverman GD.

BACKGROUND/OBJECTIVES: Traditional glycemic monitoring in type 2 diabetes is limited, whereas continuous glucose monitoring (CGM) offers better insights into glucose fluctuations. This study aimed to determine the correlations and relative contributions of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels to hyperglycemia.
METHODS: We utilized CGM and recorded carbohydrate intake data from lifestyle diaries of 59 patients enrolled in the Diabetes and Lifestyle Cohort Twente (DIALECT-2). Correlations between FPG and the glucose management indicator (GMI), FPG and Time Above Range (TAR), PPG and GMI, and PPG and TAR were conducted. Daily and mealtime relative contributions of PPG and FPG to glycated hemoglobin (HbA(1c)) and GMI were determined, considering two ranges: on target (<7.0%, 53 mmol/mol) and not on target (≥7.0%, 53 mmol/mol). Correlations between mealtime PPG and carbohydrate consumption were examined.
RESULTS: FPG and PPG correlated with GMI (r = 0.82 and 0.41, respectively, p < 0.05). The relative contribution of PPG in patients with HbA(1c), GMI, and TAR values not on target was lower than in patients with HbA(1c), GMI, and TAR values on target. When analyzing different mealtimes, patients with target GMI values had a higher PPG (73 ± 21%) than FPG after breakfast (27 ± 21%, p < 0.001). Individuals with elevated GMI levels had lower PPG after lunch (30 ± 20%), dinner (36 ± 23%), and snacks (34 ± 23%) than FPG. PPG after breakfast positively correlated (r = 0.41, p < 0.01) with breakfast carbohydrate intake.
CONCLUSIONS: Both PPG and FPG contribute to hyperglycemia, with PPG playing a larger role in patients with better glycemic control, especially after breakfast. Targeting PPG may be crucial for optimizing glucose management.

Gepubliceerd: Nutrients. 2024;16(20).
Impact factor: 5.0 ; Q1

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5. Rehabilitation of Frail Older Adults after Hip Fracture Surgery: Predictors for the Length of Geriatric Rehabilitation Stay at a Skilled Nursing Home
Krakers SM, Woudsma S, van Dartel D, Vermeer M, Vollenbroek-Hutten MMR, Hegeman JH, On Behalf Of The Up Amp Go After AHFG.

BACKGROUND: Approximately 50% of older patients hospitalized for hip fractures are admitted to a geriatric rehabilitation department at a skilled nursing home. Given the wide variation in

rehabilitation stay lengths, predicting the length of stay upon hospital discharge would help manage patients' recovery expectations and create appropriate therapy schedules. Existing literature on length of stay predictors included both acute hospital and in-hospital rehabilitation phases or involved small sample sizes. The present study aims to identify predictors for the length of geriatric rehabilitation stay in skilled nursing homes for older patients after hip fracture surgery upon hospital discharge.
METHODS: This retrospective cohort study was conducted from 1 October 2017 to 1 July 2023, including 561 patients. Potential predictors of the length of geriatric rehabilitation stay were first tested univariately, with variables showing $p < 0.15$ entered into a multivariate forward linear regression model.
RESULTS: This model identified the following independent predictors of a longer length of geriatric rehabilitation stay: Functional Ambulation Categories (FACs) 0 (B = 29.9, 95% CI 24.1-35.7), 1 (B = 18.0, 95% CI 11.8-24.2), 2 (B = 12.0, 95% CI 7.1-17.0), or 3 (B = 3.6, 95% CI -1.2-9.4) at hospital discharge vs. FAC 4, living independently with home care services (B = 5.9, 95% CI 2.5-9.3) or in a residential home prior to the hip fracture (B = 0.2, 95% CI -7.4-7.8) vs. living independently without home care services, non- or partial weight-bearing mobilization vs. full weight-bearing mobilization (B = 15.4, 95% CI 8.5-22.2), internal fixation vs. hemiarthroplasty (B = 4.7, 95% CI 1.4-7.9), in-hospital delirium (B = 7.0, 95% CI 2.2-11.7), and in-hospital heart failure (B = 7.9, 95% CI 0.5-15.3). The explained variance was 32.0%.
CONCLUSIONS: This study identified FAC at hospital discharge, premorbid living situation, postoperative weight-bearing protocol, surgery type, in-hospital delirium, and in-hospital heart failure as independent predictors of the length of geriatric rehabilitation stay. Future investigations are needed to identify additional predictors, such as cognitive functioning, to better predict the length of geriatric rehabilitation stay upon hospital discharge.

Gepubliceerd: J Clin Med. 2024;13(15).
Impact factor: 2.9 ; Q1

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6. Physical Activity Levels of Community-Dwelling Older Adults During Daily Life Activities: A Descriptive Study
van Dartel D, Wang Y, Hegeman JH, Vollenbroek-Hutten MMR.

BACKGROUND/OBJECTIVES: Measuring the physical functioning of older hip fracture patients using wearables is desirable, with physical activity monitoring offering a promising approach. However, it is first important to assess physical activity in healthy older adults. This study quantifies physical functioning with physical activity parameters and assesses those parameters in community-dwelling older adults. The results are compared with the results from one case participant 2 months post-hip fracture surgery.
METHODS: Twenty-four community-dwelling older adults (aged ≥ 80) participated. The acts of moving around the house, toileting, getting in/out of bed, and preparing meals was quantified by total time, time spent sitting, standing, and walking, number of transfers, and intensity of physical activity. MOX and APDM sensors measured the intensity of physical activity, with the tasks performed in a living lab while video-recorded. The case participant's total time and intensity of physical activity were measured for walking to a door and getting in/out of bed.
RESULTS: Preparing meals showed the longest total time and time spent standing/walking, while moving around the house and getting in/out of bed had the highest intensity of physical activity. Only getting in/out of bed required sitting. The physical activity parameters varied among participants, with very active participants completing tasks faster. The case participant had longer total times and lower intensities of physical activity two months post-surgery compared to before the fracture.
CONCLUSIONS: This study provides initial insights into the physical activity levels of community-

dwelling older adults. It represents the beginning of more efficient and continuous monitoring of physical functioning.

Gepubliceerd: Healthcare (Basel). 2024;12(24).
Impact factor: 2.7 ; Q2

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7. Face and content validity of a holistic assessment questionnaire to assess cancer-related fatigue after breast cancer
Wijlens KAE, Witteveen A, Beenhakker L, Siemerink EJM, Achterkamp R, Siesling S, Vollenbroek-Hutten MMR, Bode C.

BACKGROUND AND OBJECTIVE: Cancer-related fatigue (CRF) affects the quality of life after breast cancer. In a previous study, we developed a 72-item questionnaire that assesses CRF from a holistic point of view; named the Holistic Assessment of CRF (HA-CRF) questionnaire. The current study assessed the face and content validity of the HA-CRF questionnaire.
METHODS: Using a mixed-method approach, ten breast cancer survivors (BCS) did a cognitive walkthrough of the HA-CRF via an app followed by a semi-structured interview about relevancy and essentiality (qualitative). In addition, ten health care professionals (HCPs) assessed the relevancy, clarity, and essentiality of each item via a questionnaire (quantitative).
RESULTS: BCS indicated minor textual improvement for four items and six items were not completely clear. The app was considered easy to use and the HC-CRF was on average completed in 18 minutes. The HA-CRF questionnaire provided openness about fatigue and gave the feeling of being heard. The items were helpful and induced self-awareness. HCPs indicated 71% of items being very clear or minor revisions proposed by the minority, with 64% of items being essential and 92% considered relevant.
CONCLUSIONS: The HA-CRF showed good face and excellent content validity. Further research is needed to assess its ability to monitor in daily life.

Gepubliceerd: Fatigue. 2024;12(4):293-307.
Impact factor: 2.2 ; Q3

Totale impact factor: 19.4
Gemiddelde impact factor: 2.8

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 12.1
Gemiddelde impact factor: 3.0

Radiologie

1. Sex differences in outcomes after endovascular treatment in posterior circulation stroke: results from the MR CLEAN Registry
Ali M, Dekker L, Ali M, Van Zwet EW, Hofmeijer J, Nederkoorn PJ, Majoie CB, van Es AC, Uyttenboogaart M, van der Meij A, van Walderveen MAA, Visser MC, Dippel DW, Schonewille WJ, van den Wijngaard IR, Kruyt ND, Wermer MJH, MR CLEAN Registry Investigators; Bulut T, Gerrits D.

BACKGROUND: Women with anterior circulation large vessel occlusion (LVO) have been reported to have worse outcomes after endovascular treatment (EVT) than men. Whether these disparities also exist in LVO of the posterior circulation is yet uncertain. We assessed sex differences in clinical, technical, and safety outcomes of EVT in posterior circulation LVO.
METHODS: We used data of patients with posterior circulation LVO included in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry (2014-2018). Primary outcome was the modified Rankin Scale (mRS) score at 90 days assessed with multivariable ordinal regression analysis. Secondary outcomes included favorable functional outcome (mRS ≤3), functional independence (mRS ≤2), death within 90 days, National Institutes of Health Stroke Scale (NIHSS) score 24-48 hours postintervention, complications, successful reperfusion (extended Thrombolysis in Cerebral Ischemia 2B-3), and procedure duration analyzed with multivariable logistic and linear regression analyses.
RESULTS: We included 264 patients (42% women). Compared with men, women were older (median age 68 vs 63 years), more often had prestroke disability (mRS ≥1: 37% vs 30%), and received intravenous thrombolytics less often (45% vs 56%). Clinical outcomes were similar between sexes (adjusted (common) OR (aOR) 0.82, 95% CI 0.51 to 1.34; favorable functional outcome 50% vs 43%, aOR 1.31, 95% CI 0.77 to 2.25; death 32% vs 29%, aOR 0.98, 95% CI 0.52 to 1.84). In addition, NIHSS score after 24-48 hours (median 7 vs 9), successful reperfusion (77% vs 73%), and complications did not differ between men and women.
CONCLUSIONS: Outcomes in women treated with EVT for posterior circulation LVO were similar compared with men despite less favorable baseline characteristics in women. Therefore men and women may benefit equally from EVT.

Gepubliceerd: J Neurointerv Surg. 2024;17(e1):e74-e82.
Impact factor: 4.4 ; Q1

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2. Who is at risk of lung nodules on low-dose CT in a Western country? A population-based approach
Cai J, Vonder M, Du Y, Pelgrim GJ, Rook M, Kramer G, Groen HJM, Vliegenthart R, de Bock GH.

BACKGROUND: This population-based study aimed to identify the risk factors for lung nodules in a Western European general population.
METHODS: We quantified the presence or absence of lung nodules among 12 055 participants of the Dutch population-based ImaLife (Imaging in Lifelines) study (age ≥45 years) who underwent low-dose chest computed tomography. Outcomes included the presence of 1) at least one solid lung nodule (volume ≥30 mm(3)) and 2) a clinically relevant lung nodule (volume ≥100 mm(3)). Fully adjusted multivariable logistic regression models were applied overall and stratified by smoking status to identify independent risk factors for the presence of nodules.
RESULTS: Among the 12 055 participants (44.1% male; median age 60 years; 39.9% never-smokers; 98.7% White), we found lung nodules in 41.8% (5045 out of 12 055) and clinically relevant nodules in 11.4% (1377 out of 12 055); the corresponding figures among never-smokers were 38.8% and 9.5%, respectively. Factors independently associated with increased odds of having any lung nodule

included male sex, older age, low educational level, former smoking, asbestos exposure and COPD. Among never-smokers, a family history of lung cancer increased the odds of both lung nodules and clinically relevant nodules. Among former and current smokers, low educational level was positively associated with lung nodules, whereas being overweight was negatively associated. Among current smokers, asbestos exposure and low physical activity were associated with clinically relevant nodules. **CONCLUSIONS**: The study provides a large-scale evaluation of lung nodules and associated risk factors in a Western European general population: lung nodules and clinically relevant nodules were prevalent, and never-smokers with a family history of lung cancer were a non-negligible group.

Gepubliceerd: Eur Respir J. 2024;63(6).
Impact factor: 21.0 ; Q1

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3. Distribution of Solid Lung Nodules Presence and Size by Age and Sex in a Northern European Nonsmoking Population
Cai J, Vonder M, Pelgrim GJ, Rook M, Kramer G, Groen HJM, de Bock GH, Vliegenthart R.

BACKGROUND: Most of the data regarding prevalence and size distribution of solid lung nodules originates from lung cancer screening studies that target high-risk populations or from Asian general cohorts. In recent years, the identification of lung nodules in non-high-risk populations, scanned for clinical indications, has increased. However, little is known about the presence of solid lung nodules in the Northern European nonsmoking population. Purpose To study the prevalence and size distribution of solid lung nodules by age and sex in a nonsmoking population.
MATERIALS AND METHODS: Participants included nonsmokers (never or former smokers) from the population-based Imaging in Lifelines study conducted in the Northern Netherlands. Participants (age ≥ 45 years) with completed lung function tests underwent chest low-dose CT scans. Seven trained readers registered the presence and size of solid lung nodules measuring 30 mm(3) or greater using semiautomated software. The prevalence and size of lung nodules (≥30 mm(3)), clinically relevant lung nodules (≥100 mm(3)), and actionable nodules (≥300 mm(3)) are presented by 5-year categories and by sex.
RESULTS: A total of 10 431 participants (median age, 60.4 years [IQR, 53.8-70.8 years]; 56.6% [n = 5908] female participants; 46.1% [n = 4812] never smokers and 53.9% [n = 5619] former smokers) were included. Of these, 42.0% (n = 4377) had at least one lung nodule (male participants, 47.5% [2149 of 4523]; female participants, 37.7% [2228 of 5908]). The prevalence of lung nodules increased from age 45-49.9 years (male participants, 39.4% [219 of 556]; female participants, 27.7% [236 of 851]) to age 80 years or older (male participants, 60.7% [246 of 405]; female participants, 50.9% [163 of 320]). Clinically relevant lung nodules were present in 11.1% (1155 of 10 431) of participants, with prevalence increasing with age (male participants, 8.5%-24.4%; female participants, 3.7%-15.6%), whereas actionable nodules were present in 1.1%-6.4% of male participants and 0.6%-4.9% of female participants.
CONCLUSION: Lung nodules were present in a substantial proportion of all age groups in the Northern European nonsmoking population, with slightly higher prevalence for male participants than female participants. © RSNA, 2024 Supplemental material is available for this article.

Gepubliceerd: Radiology. 2024;312(2):e231436.
Impact factor: 15.2 ; Q1

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4. The Additional Value of Somatostatin Receptor Positron Emission Computed Tomography ([(68)Ga]Ga-DOTATOC PET/CT) Compared with Magnetic Resonance Imaging of the Head and Neck Region in Paraganglioma Patients: A Pilot Study
de Bresser CJM, Petri BJ, Braat A, de Keizer B, van Treijen MJC, Dankbaar JW, Pameijer FA, Kok MGJ, de Ridder M, van Nesselrooij BPM, de Bree R, de Borst GJ, Rijken JA.

The Dutch guideline for patients suspected of head and neck paragangliomas (HNPGLs) recommends magnetic resonance imaging (MRI) and/or computed tomography (CT) of the head and neck area. Additionally, it suggests considering additional nuclear imaging. The aim of this study was to evaluate the outcomes of [(68)Ga]Ga-DOTATOC PET/CT compared to MRI in patients with suspected HNPGLs and carriers of genetic variations.
METHODS: In this single-center pilot study, retrospective data were obtained from consecutive patients between 2016 and 2023. Both MRI and [(68)Ga]Ga-DOTATOC PET/CT were performed within 12 months. The primary outcome was the location of HNPGLs.
RESULTS: A total of 25 consecutive patients were included, and 7 patients (28.0%, p = 0.5) showed differences between the imaging modalities, of whom 5 patients had unexpected localizations with additional uptake by somatostatin receptors (SSTR) on the [(68)Ga]Ga-DOTATOC PET/CT.
CONCLUSIONS: The authors recommend performing baseline imaging with [(68)Ga]Ga-DOTATOC PET/CT (if available) in variant carriers and using MRI/CT for follow-up according to the regional protocol, thereby shifting the gold standard for baseline imaging from MRI/CT to [(68)Ga]Ga-DOTATOC PET/CT.

Gepubliceerd: Cancers (Basel). 2024;16(5).
Impact factor: 4.4 ; Q2

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5. Primary central nervous system lymphoma
de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC, van der Meulen M.

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL) manifesting in the brain, spinal cord, cerebrospinal fluid and/or eyes, in the absence of systemic manifestations. With an increasing incidence and a 30% 5-year overall survival if promptly treated, timely diagnosis and subsequent treatment is paramount. The typical MRI appearance for PCNSL is a solitary or multiple T2-hypointense, homogeneous gadolinium-enhancing lesion with restricted diffusion. Dexamethasone treatment might compromise and delay the diagnosis. Hallmark of treatment is induction with intravenous high-dose methotrexate consisting polychemotherapy followed by consolidation treatment. Consolidation treatment consists of either whole brain radiotherapy (WBRT) or autologous stem cell transplantation (ASCT). Given the (cognitive) side effects of WBRT, ASCT is increasingly being used as the first choice of treatment.

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Impact factor: 4.6 ; Q1

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6. MRI in addition to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): an international, multicentre, prospective, diagnostic accuracy trial
Görgec B, Hansen IS, Kemmerich G, Syversveen T, Abu Hilal M, Belt EJT, Bosscha K, Burgmans MC, Cappendijk VC, D'Hondt M, Edwin B, van Erkel AR, Gielkens HAJ, Grünhagen DJ, Gobardhan PD, Hartgrink HH, Horsthuis K, Klompenhouwer EG, Kok NFM, Kint PAM, Kuhlmann K, Leclercq WKG, Lips DJ, Lutin B, Maas M, Marsman HA, Meijerink M, Meyer Y, Morone M, Peringa J, Sijberden JP, van Delden OM, van den Bergh JE, Vanhooymissen IJS, Vermaas M, Willemssen F, Dijkgraaf MGW, Bossuyt PM, Swijnenburg RJ, Fretland Å A, Verhoef C, Besselink MG, Stoker J.

BACKGROUND: Guidelines are inconclusive on whether contrast-enhanced MRI using gadoxetic acid and diffusion-weighted imaging should be added routinely to CT in the investigation of patients with colorectal liver metastases who are scheduled for curative liver resection or thermal ablation, or both. Although contrast-enhanced MRI is reportedly superior than contrast-enhanced CT in the detection and characterisation of colorectal liver metastases, its effect on clinical patient management is unknown. We aimed to assess the clinical effect of an additional liver contrast-enhanced MRI on local treatment plan in patients with colorectal liver metastases amenable to local treatment, based on contrast-enhanced CT.
METHODS: We did an international, multicentre, prospective, incremental diagnostic accuracy trial in 14 liver surgery centres in the Netherlands, Belgium, Norway, and Italy. Participants were aged 18 years or older with histological proof of colorectal cancer, a WHO performance status score of 0-4, and primary or recurrent colorectal liver metastases, who were scheduled for local therapy based on contrast-enhanced CT. All patients had contrast-enhanced CT and liver contrast-enhanced MRI including diffusion-weighted imaging and gadoxetic acid as a contrast agent before undergoing local therapy. The primary outcome was change in the local clinical treatment plan (decided by the individual clinics) on the basis of liver contrast-enhanced MRI findings, analysed in the intention-to-image population. The minimal clinically important difference in the proportion of patients who would have change in their local treatment plan due to an additional liver contrast-enhanced MRI was 10%. This study is closed and registered in the Netherlands Trial Register, NL8039.
FINDINGS: Between Dec 17, 2019, and July 31, 2021, 325 patients with colorectal liver metastases were assessed for eligibility. 298 patients were enrolled and included in the intention-to-treat population, including 177 males (59%) and 121 females (41%) with planned local therapy based on contrast-enhanced CT. A change in the local treatment plan based on liver contrast-enhanced MRI findings was observed in 92 (31%; 95% CI 26-36) of 298 patients. Changes were made for 40 patients (13%) requiring more extensive local therapy, 11 patients (4%) requiring less extensive local therapy, and 34 patients (11%) in whom the indication for curative-intent local therapy was revoked, including 26 patients (9%) with too extensive disease and eight patients (3%) with benign lesions on liver contrast-enhanced MRI (confirmed by a median follow-up of 21·0 months [IQR 17·5-24·0]).
INTERPRETATION: Liver contrast-enhanced MRI should be considered in all patients scheduled for local treatment for colorectal liver metastases on the basis of contrast-enhanced CT imaging.
FUNDING: The Dutch Cancer Society and Bayer AG - Pharmaceuticals.

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Impact factor: 35.9 ; Q1

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7. Cerebrovascular reactivity to hypercapnia in patients with migraine: A dual-echo arterial spin labeling MRI study
Hoogeveen ES, Pelzer N, Ghariq E, van Osch MJP, Dahan A, Terwindt GM, Kruit MC.

OBJECTIVE: This study aimed to compare cerebrovascular reactivity between patients with migraine and controls using state-of-the-art magnetic resonance imaging (MRI) techniques.

BACKGROUND: Migraine is associated with an increased risk of cerebrovascular disease, but the underlying mechanisms are still not fully understood. Impaired cerebrovascular reactivity has been proposed as a link. Previous studies have evaluated cerebrovascular reactivity with different methodologies and results are conflicting.
METHODS: In this single-center, observational, case-control study, we included 31 interictal patients with migraine without aura (aged 19-66 years, 17 females) and 31 controls (aged 22-64 years, 18 females) with no history of vascular disease. Global and regional cerebrovascular reactivities were assessed with a dual-echo arterial spin labeling (ASL) 3.0 T MRI scan of the brain which measured the change in cerebral blood flow (CBF) and BOLD (blood oxygen level dependent) signal to inhalation of 5% carbon dioxide.
RESULTS: When comparing patients with migraine to controls, cerebrovascular reactivity values were similar between the groups, including mean gray matter CBF-based cerebrovascular reactivity (3.2 ± 0.9 vs 3.4 ± 1% ΔCBF/mmHg CO(2) ; p = 0.527), mean gray matter BOLD-based cerebrovascular reactivity (0.18 ± 0.04 vs 0.18 ± 0.04% ΔBOLD/mmHg CO(2) ; p = 0.587), and mean white matter BOLD-based cerebrovascular reactivity (0.08 ± 0.03 vs 0.08 ± 0.02% ΔBOLD/mmHg CO(2) ; p = 0.621).There was no association of cerebrovascular reactivity with monthly migraine days or migraine disease duration (all analyses p > 0.05).
CONCLUSION: Cerebrovascular reactivity to carbon dioxide seems to be preserved in patients with migraine without aura.

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Impact factor: 4.0 ; Q1

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8. Collateral-based selection for endovascular treatment of acute ischaemic stroke in the late window (MR CLEAN-LATE): 2-year follow-up of a phase 3, multicentre, open-label, randomised controlled trial in the Netherlands

Huijberts I, Pinckaers FME, Olthuis SGH, van Kuijk SMJ, Postma AA, Boogaarts HD, Roos Y, Majoie C, van der Lugt A, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ, MR CLEAN Registry Investigators; Bulut T, Gerrits D.

BACKGROUND: The MR CLEAN-LATE trial provided evidence for the safety and efficacy of endovascular treatment for acute ischaemic stroke within the late window (after 6-24 h) in patients who were preselected based on the presence of collateral flow on CT angiography. We aimed to evaluate clinical outcomes 2 years after randomisation.
METHODS: MR CLEAN-LATE was a phase 3, multicentre, open-label, blinded-endpoint, randomised controlled trial conducted at 18 stroke intervention centres in the Netherlands. If endovascular treatment could be initiated within 6-24 h of symptom onset or last seen well, patients (aged 18 years or older) with an acute ischaemic stroke due to a large vessel occlusion in the anterior circulation and at least some collateral flow in the affected middle cerebral artery territory on CT angiography were randomly assigned (1:1) to either endovascular treatment with best medical treatment (endovascular treatment group) or best medical treatment alone (control group). Web-based randomisation, stratified by centre, was performed with the use of permuted blocks (block size eight to 20). The researchers who collected clinical outcomes and analysed the results were masked to treatment allocation; treating physicians, local investigators, and patients were aware of the received treatment. The primary outcome of MR CLEAN-LATE was the modified Rankin Scale (mRS) score at 90 days after randomisation. For this 2-year prespecified analysis, the primary outcome was mRS score at 2 years (minus 3 months to plus 6 months). Primary and safety analyses were performed based on the modified intention-to-treat principle, and included patients who provided (deferred) consent or died before consent could be obtained. Missing data were handled with multiple imputation by chained equations. The trial is completed and is registered at ISRCTN, ISRCTN19922220.

FINDINGS: Between Feb 2, 2018, and Jan 27, 2022, 535 patients were randomly assigned in the MR CLEAN-LATE trial, of whom 502 (94%) gave deferred consent and comprised the modified intention-to-treat population (255 in the endovascular treatment group and 247 in the control group). 261 (52%) patients were female and 241 (48%) were male. Data for mRS score at 2 years were available for 226 (89%) patients in the endovascular treatment group and for 202 (82%) patients in the control group. The median mRS score at 2 years was 4 (IQR 2-6) in the endovascular treatment group and 6 (2-6) in the control group. The endovascular treatment group demonstrated a shift towards better functional outcomes on the mRS (adjusted common odds ratio 1·41 [95% CI 1·00-1·99]; p=0·049). All-cause mortality at 2 years was 34% (87 of 255) in the endovascular treatment group and 41% (101 of 247) in the control group (adjusted hazard ratio 0·81 [95% CI 0·60-1·08]; p=0·15). Major vascular events (ie, transient ischaemic attack, ischaemic stroke, haemorrhagic stroke, and cardiac events) were reported between 90 days and 2 years in 23 patients in the endovascular treatment group and 13 patients in the control group.
INTERPRETATION: Our results show that the effectiveness of late-window (after 6-24 h) endovascular treatment in improving clinical outcomes is sustained for up to 2 years in a population preselected based on the presence of collateral flow on CT angiography. This finding might be important for prompting further evaluations of cost-effectiveness, health-care policy development, and clinical decision making.
FUNDING: The Dutch Organization for Health Research and Health Innovation (ZonMW), Collaboration for New Treatments of Acute Stroke Consortium, Dutch Heart Foundation, Stryker, Medtronic, Cerenovus, Health Holland Top Sector Life Sciences & Health, and the Netherlands Brain Foundation.

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Impact factor: 45.5 ; Q1

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9. Clinical consequence of vessel perforations during endovascular treatment of acute ischemic stroke

van der Sluijs PM, Su R, Cornelissen SAP, van Es A, Lycklama ANG, Roozenbeek B, van Doormaal PJ, Hofmeijer J, van der Lugt A, van Walsum T, MR CLEAN Registry Investigators; Bulut T, Gerrits D.

PURPOSE: Endovascular treatment (EVT) of acute ischemic stroke can be complicated by vessel perforation. We studied the incidence and determinants of vessel perforations. In addition, we studied the association of vessel perforations with functional outcome, and the association between location of perforation on digital subtraction angiography (DSA) and functional outcome, using a large EVT registry.
METHODS: We included all patients in the MR CLEAN Registry who underwent EVT. We used DSA to determine whether EVT was complicated by a vessel perforation. We analyzed the association with baseline clinical and interventional parameters using logistic regression models. Functional outcome was measured using the modified Rankin Scale at 90 days. The association between vessel perforation and angiographic imaging features and functional outcome was studied using ordinal logistic regression models adjusted for prognostic parameters. These associations were expressed as adjusted common odds ratios (acOR).
RESULTS: Vessel perforation occurred in 74 (2.6%) of 2794 patients who underwent EVT. Female sex (aOR 2.0 (95% CI 1.2-3.2)) and distal occlusion locations (aOR 2.2 (95% CI 1.3-3.5)) were associated with increased risk of vessel perforation. Functional outcome was worse in patients with vessel perforation (acOR 0.38 (95% CI 0.23-0.63)) compared to patients without a vessel perforation. No significant association was found between location of perforation and functional outcome.
CONCLUSION: The incidence of vessel perforation during EVT in this cohort was low, but has severe clinical consequences. Female patients and patients treated at distal occlusion locations are at higher risk.

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Impact factor: 2.6 ; Q2

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10. Optimised treatment of patients with enlarged lateral lymph nodes in rectal cancer: protocol of an international, multicentre, prospective registration study after extensive multidisciplinary training (LaNoReC)
van Geffen EGM, Sluckin TC, Hazen SJA, Horsthuis K, Intven M, van Dieren S, Beets G, Lange MM, Taggart MW, Beets-Tan RGH, Marijnen CAM, Konishi T, Tanis PJ, Kusters M, LaNoRec study group; Gielkens HAJ.

INTRODUCTION: Inadequate treatment of enlarged lateral lymph nodes (LLNs) in rectal cancer patients is associated with an increased lateral local recurrence (LLR) risk, despite neoadjuvant treatment and total mesorectal excision (TME) surgery. There is a promising role for LLN dissection (LLND) to lower this risk, but this challenging procedure requires appropriate training. This study protocol describes a prospective evaluation of oncological outcomes after standardised treatment based on multidisciplinary training, thereby aiming for a 50% reduction in LLR rate.
METHODS AND ANALYSIS: A prospective registration study will be opened in hospitals in which the involved multidisciplinary team members (radiologists, radiation oncologists, surgeons and pathologists) have received dedicated training to enhance knowledge and awareness of LLNs and in which standardised treatment including LLND has been implemented. Patients with rectal cancer and at least one enlarged LLN (short-axis ≥7.0 mm), or intermediate LLN (short-axis 5.0-6.9 mm) with at least one malignant feature on primary MRI, evaluated by a trained radiologist, are eligible. Patients will undergo neoadjuvant treatment by trained radiation oncologists, followed by TME surgery in combination with a minimally invasive, nerve-sparing LLND performed by trained surgeons. LLND specimens are evaluated by trained pathologists or grossing assistants. The primary outcome is LLR rate 3 years postoperatively. Secondary outcomes are morbidity, disease-free survival, overall survival and quality of life. To demonstrate a significant reduction in LLR rate from 13% (based on historical control data) to 6% after optimised treatment, 200 patients with enlarged LLNs are required.
ETHICS AND DISSEMINATION: The medical ethics board of the Vrije Universiteit Medical Centre (VUMC), the Netherlands, approved the study on 23 November 2022 (reference: 2021.0524). Participating centres must obtain local approval and participants are required to provide written informed consent. Results obtained from this study will be communicated via peer-reviewed medical journals and presentations at conferences.
TRAIL REGISTRATION NUMBER: NCT04486131, 24 July 2020, https://clinicaltrials.gov/ct2/show/NCT04486131.

Gepubliceerd: BMJ Open. 2024;14(10):e083225.
Impact factor: 2.3 ; Q2

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11. Costs and health effects of CT perfusion-based selection for endovascular thrombectomy within 6 hours of stroke onset: a model-based health economic evaluation
van Voorst H, Hoving JW, Koopman MS, Daems JD, Peerlings D, Buskens E, Lingsma H, Marquering HA, de Jong H, Berkhemer OA, van Zwam WH, van Walderveen MAA, van den Wijngaard IR, Dippel DWJ, Yoo AJ, Campbell B, Kunz WG, Majoie CB, Emmer BJ, CLEOPATRA and MR CLEAN Registry and CONTRAST Consortium Investigators; Bulut T, Gerrits D.

BACKGROUND: Although CT perfusion (CTP) is often incorporated in acute stroke workflows, it remains largely unclear what the associated costs and health implications are in the long run of CTP-

based patient selection for endovascular treatment (EVT) in patients presenting within 6 hours after symptom onset with a large vessel occlusion.
METHODS: Patients with a large vessel occlusion were included from a Dutch nationwide cohort (n=703) if CTP imaging was performed before EVT within 6 hours after stroke onset. Simulated cost and health effects during 5 and 10 years follow-up were compared between CTP based patient selection for EVT and providing EVT to all patients. Outcome measures were the net monetary benefit at a willingness-to-pay of €80 000 per quality-adjusted life year, incremental cost-effectiveness ratio), difference in costs from a healthcare payer perspective (ΔCosts) and quality-adjusted life years (ΔQALY) per 1000 patients for 1000 model iterations as outcomes.
RESULTS: Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds resulted in losses of health (median ΔQALYs for ICV≥110 mL: -3.3 (IQR: -5.9 to -1.1), for MMR≤1.4: 0.0 (IQR: -1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of -€348 966 (IQR: -€712 406 to -€51 158) and for MMR≤1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including patients aged ≥80 years
CONCLUSION: In EVT-eligible patients presenting within 6 hours after symptom onset, excluding patients based on CTP parameters was not cost-effective and could potentially harm patients.

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Impact factor: 7.8 ; Q1

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12. Deep learning-based white matter lesion volume on CT is associated with outcome after acute ischemic stroke
van Voorst H, Pitkänen J, van Poppel L, de Vries L, Mojtahedi M, Martou L, Emmer BJ, Roos Y, van Oostenbrugge R, Postma AA, Marquering HA, Majoie C, Curtze S, Melkas S, Bentley P, Caan MWA, MR CLEAN No-IV and CONTRAST consortium collaborators; Bulut T, Gerrits D.

BACKGROUND: Intravenous thrombolysis (IVT) before endovascular treatment (EVT) for acute ischemic stroke might induce intracerebral hemorrhages which could negatively affect patient outcomes. Measuring white matter lesions size using deep learning (DL-WML) might help safely guide IVT administration. We aimed to develop, validate, and evaluate a DL-WML volume on CT compared to the Fazekas scale (WML-Faz) as a risk factor and IVT effect modifier in patients receiving EVT directly after IVT.
METHODS: We developed a deep-learning model for WML segmentation on CT and validated with internal and external test sets. In a post hoc analysis of the MR CLEAN No-IV trial, we associated DL-WML volume and WML-Faz with symptomatic-intracerebral hemorrhage (sICH) and 90-day functional outcome according to the modified Rankin Scale (mRS). We used multiplicative interaction terms between WML measures and IVT administration to evaluate IVT treatment effect modification. Regression models were used to report unadjusted and adjusted common odds ratios (cOR/acOR).
RESULTS: In total, 516 patients from the MR CLEAN No-IV trial (male/female, 291/225; age median, 71 [IQR, 62-79]) were analyzed. Both DL-WML volume and WML-Faz are associated with sICH (DL-WML volume acOR, 1.78 [95%CI, 1.17; 2.70]; WML-Faz acOR, 1.53 95%CI [1.02; 2.31]) and mRS (DL-WML volume acOR, 0.70 [95%CI, 0.55; 0.87], WML-Faz acOR, 0.73 [95%CI 0.60; 0.88]). Only in the unadjusted IVT effect modification analysis WML-Faz was associated with more sICH if IVT was given (p = 0.046). Neither WML measure was associated with worse mRS if IVT was given.
CONCLUSION: DL-WML volume and WML-Faz had a similar relationship with functional outcome and sICH. Although more sICH might occur in patients with more severe WML-Faz receiving IVT, no worse functional outcome was observed.
CLINICAL RELEVANCE STATEMENT: White matter lesion severity on baseline CT in acute ischemic stroke patients has a similar predictive value if measured with deep learning or the Fazekas scale.

Safe administration of intravenous thrombolysis using white matter lesion severity should be further studied.
KEY POINTS: White matter damage is a predisposing risk factor for intracranial hemorrhage in patients with acute ischemic stroke but remains difficult to measure on CT. White matter lesion volume on CT measured with deep learning had a similar association with symptomatic intracerebral hemorrhages and worse functional outcome as the Fazekas scale. A patient-level meta-analysis is required to study the benefit of white matter lesion severity-based selection for intravenous thrombolysis before endovascular treatment.

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Impact factor: 4.7 ; Q1

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13. An exploratory study on the association between blood-based biomarkers and subacute neurometabolic changes following mild traumatic brain injury
Visser K, de Koning ME, Ciubotariu D, Kok MGJ, Sibeijn-Kuiper AJ, Bourgonje AR, van Goor H, van der Naalt J, van der Horn HJ.

BACKGROUND AND OBJECTIVES: Blood-based biomarkers and advanced neuroimaging modalities such as magnetic resonance spectroscopy (MRS) or diffusion tensor imaging (DTI) have enhanced our understanding of the pathophysiology of mild traumatic brain injury (mTBI). However, there is limited published data on how blood biomarkers relate to neuroimaging biomarkers post-mTBI.
METHODS: To investigate this, 30 patients with mTBI and 21 healthy controls were enrolled. Data was collected at two timepoints postinjury: acute, < 24 h, (blood) and subacute, four-to-six weeks, (blood and imaging). Interleukin (IL) 6 and 10 (inflammation), free thiols (systemic oxidative stress) and neurofilament light (NF-L) (axonal injury) were quantified in plasma. The neurometabolites total N-acetyl aspartate (tNAA) (neuronal energetics), Myo-Inositol (Ins) and total Choline (tCh) (inflammation) and, Glutathione (GSH, oxidative stress) were quantified using MRS.
RESULTS: Concentrations of IL-6 and IL-10 were significantly elevated in the acute phase post-mTBI, while NF-L was elevated only in the subacute phase. Total NAA was lowered in patients with mTBI, although this difference was only nominally significant (uncorrected $P < 0.05$). Within the patient group, acute IL-6 and subacute tNAA levels were negatively associated ($r = -0.46$, uncorrected-$P = 0.01$), albeit not at a threshold corrected for multiple testing (corrected-$P = 0.17$). When age was added as a covariate a significant increase in correlation magnitude was observed ($\rho = -0.54$, corrected-$P = 0.03$).
CONCLUSION: This study demonstrates potential associations between the intensity of the inflammatory response in the acute phase post-mTBI and neurometabolic perturbations in the subacute phase. Future studies should assess the longitudinal dynamics of blood-based and imaging biomarkers after injury.

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Impact factor: 4.6 ; Q1

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14. Image quality of DWI at breast MRI depends on the amount of fibroglandular tissue: implications for unenhanced screening
Wielema M, Sijens PE, Pijnappel RM, De Bock GH, Zorgdrager M, Kok MGJ, Rainer E, Varga R, Clauser P, Oudkerk M, Dorrius MD, Baltzer PAT.

OBJECTIVES: To compare image quality of diffusion-weighted imaging (DWI) and contrast-enhanced breast MRI (DCE-T1) stratified by the amount of fibroglandular tissue (FGT) as a measure of breast density.
METHODS: Retrospective, multi-reader, bicentric visual grading analysis study on breast density (A-D) and overall image and fat suppression quality of DWI and DCE-T1, scored on a standard 5-point Likert scale. Cross tabulations and visual grading characteristic (VGC) curves were calculated for fatty breasts (A/B) versus dense breasts (C/D).
RESULTS: Image quality of DWI was higher in the case of increased breast density, with good scores (score 3-5) in 85.9% (D) and 88.4% (C), compared to 61.6% (B) and 53.5% (A). Overall image quality of DWI was in favor of dense breasts (C/D), with an area under the VGC curve of 0.659 ($p < 0.001$). Quality of DWI and DCE-T1 fat suppression increased with higher breast density, with good scores (score 3-5) for 86.9% and 45.7% of density D, and 90.2% and 42.9% of density C cases, compared to 76.0% and 33.6% for density B and 54.7% and 29.6% for density A (DWI and DCE-T1 respectively).
CONCLUSIONS: Dense breasts show excellent fat suppression and substantially higher image quality in DWI images compared with non-dense breasts. These results support the setup of studies exploring DWI-based MR imaging without IV contrast for additional screening of women with dense breasts.
CLINICAL RELEVANCE STATEMENT: Our findings demonstrate that image quality of DWI is robust in women with an increased amount of fibroglandular tissue, technically supporting the feasibility of exploring applications such as screening of women with mammographically dense breasts.
KEY POINTS:
• Image and fat suppression quality of diffusion-weighted imaging are dependent on the amount of fibroglandular tissue (FGT) which is closely connected to breast density.
• Fat suppression quality in diffusion-weighted imaging of the breast is best in women with a high amount of fibroglandular tissue.
• High image quality of diffusion-weighted imaging in women with a high amount of FGT in MRI supports that the technical feasibility of DWI can be explored in the additional screening of women with mammographically dense breasts.

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Impact factor: 4.7 ; Q1

Totale impact factor: 161.7
Gemiddelde impact factor: 11.6

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 4.6
Gemiddelde impact factor: 4.6

Radiotherapie

1. Prognostic significance of MRI-detected extramural venous invasion according to grade and response to neo-adjuvant treatment in locally advanced rectal cancer A national cohort study after radiologic training and reassessment
Geffen E, Nederend J, Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

BACKGROUND: Detection of grade 3-4 extra mural venous invasion (mrEMVI) on magnetic resonance imaging (MRI) is associated with an increased distant metastases (DM)-rate. This study aimed to determine the impact of different grades of mrEMVI and their disappearance after neoadjuvant therapy.
METHODS: A Dutch national retrospective cross-sectional study was conducted, including patients who underwent resection for rectal cancer in 2016 from 60/69 hospitals performing rectal surgery. Patients with a cT3-4 tumour ≤8 cm from the anorectal junction were selected and their MRI-scans were reassessed by trained abdominal radiologists. Positive mrEMVI grades (3 and 4) were analyzed in regard to 4-year local recurrence (LR), DM, disease-free survival (DFS) and overall survival (OS).
RESULTS: The 1213 included patients had a median follow-up of 48 months (IQR 30-54). Positive mrEMVI was present in 324 patients (27%); 161 had grade 3 and 163 had grade 4. A higher mrEMVI stage (grade 4 vs grade 3 vs no mrEMVI) increased LR-risk (21% vs 18% vs 7%, <0.001) and DM-risk (49% vs 30% vs 21%, $p < 0.001$) and decreased DFS (42% vs 55% vs 69%, $p < 0.001$) and OS (62% vs 76% vs 81%, $p < 0.001$), which remained independently associated in multivariable analysis. When mrEMVI had disappeared on restaging MRI, DM-rate was comparable to initial absence of mrEMVI (both 26%), whereas LR-rate remained high (22% vs 9%, $p = 0.006$).
CONCLUSION: The negative oncological impact of mrEMVI on recurrence and survival rates was dependent on grading. Disappearance of mrEMVI on restaging MRI decreased the risk of DM, but not of LR.

Gepubliceerd: Eur J Surg Oncol. 2024;50(6):108307.
Impact factor: 2.9 ; Q1

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2. Treatment-specific risk of subsequent malignant neoplasms in five-year survivors of diffuse large B-cell lymphoma
Geurts YM, Neppelenbroek SIM, Aleman BMP, Janus CPM, Krol ADG, van Spronsen DJ, Plattel WJ, Roesink JM, Verschueren KMS, Zijlstra JM, Koene HR, Nijziel MR, Schimmel EC, de Jongh E, Ong F, Te Boome LCJ, van Rijn RS, Böhmer LH, Ta BDP, Visser HPJ, Posthuma EFM, Bilgin YM, Muller K, van Kampen D, So-Osman C, Vermaat JSP, de Weijer RJ, Kersten MJ, van Leeuwen FE, Schaapveld M.

BACKGROUND: The introduction of rituximab significantly improved the prognosis of diffuse large B-cell lymphoma (DLBCL), emphasizing the importance of evaluating the long-term consequences of exposure to radiotherapy, alkylating agents and anthracycline-containing (immuno)chemotherapy among DLBCL survivors.
METHODS: Long-term risk of subsequent malignant neoplasms (SMNs) was examined in a multicenter cohort comprising 2373 5-year DLBCL survivors treated at ages 15-61 years in 1989-2012. Observed SMN numbers were compared with expected cancer incidence to estimate standardized incidence ratios (SIRs) and absolute excess risks (AERs/10 000 person-years). Treatment-specific risks were assessed using multivariable Cox regression.
RESULTS: After a median follow-up of 13.8 years, 321 survivors developed one or more SMNs (SIR 1.5, 95% CI 1.3-1.8, AER 51.8). SIRs remained increased for at least 20 years after first-line treatment (SIR ≥20-year follow-up 1.5, 95% CI 1.0-2.2, AER 81.8) and were highest among patients ≤40 years at first

DLBCL treatment (SIR 2.7, 95% CI 2.0-3.5). Lung (SIR 2.0, 95% CI 1.5-2.7, AER 13.4) and gastrointestinal cancers (SIR 1.5, 95% CI 1.2-2.0, AER 11.8) accounted for the largest excess risks. Treatment with >4500 mg/m(2) cyclophosphamide/>300 mg/m(2) doxorubicin versus ≤2250 mg/m(2)/≤150 mg/m(2), respectively, was associated with increased solid SMN risk (hazard ratio 1.5, 95% CI 1.0-2.2). Survivors who received rituximab had a lower risk of subdiaphragmatic solid SMNs (hazard ratio 0.5, 95% CI 0.3-1.0) compared with survivors who did not receive rituximab.
CONCLUSION: Five-year DLBCL survivors have an increased risk of SMNs. Risks were higher for survivors ≤40 years at first treatment and survivors treated with >4500 mg/m(2) cyclophosphamide/>300 mg/m(2) doxorubicin, and may be lower for survivors treated in the rituximab era, emphasizing the need for studies with longer follow-up for rituximab-treated patients.

Gepubliceerd: ESMO Open. 2024;9(2):102248.
Impact factor: 8.3 ; Q1

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3. Validation of quantitative magnetic resonance imaging techniques in head and neck healthy structures involved in the salivary and swallowing function: Accuracy and repeatability
Guerreiro F, van Houdt PJ, Navest RJM, Hoekstra N, de Jong M, Heijnen BJ, Zijlema SE, Verbist B, van der Heide UA, Astreinidou E.

BACKGROUND AND PURPOSE: Radiation-induced damage to the organs at risk (OARs) in head-and-neck cancer (HNC) patient can result in long-term complications. Quantitative magnetic resonance imaging (qMRI) techniques such as diffusion-weighted imaging (DWI), DIXON for fat fraction (FF) estimation and T(2) mapping could potentially provide a spatial assessment of such damage. The goal of this study is to validate these qMRI techniques in terms of accuracy in phantoms and repeatability in-vivo across a broad selection of healthy OARs in the HN region.
MATERIALS AND METHODS: Scanning was performed at a 3 T diagnostic MRI scanner, including the calculation of apparent diffusion coefficient (ADC) from DWI, FF and T(2) maps. Phantoms were scanned to estimate the qMRI techniques bias using Bland-Altman statistics. Twenty-six healthy subjects were scanned twice in a test-retest study to determine repeatability. Repeatability coefficients (RC) were calculated for the parotid, submandibular, sublingual and tubarial salivary glands, oral cavity, pharyngeal constrictor muscle and brainstem. Additionally, a linear mixed-effect model analysis was used to evaluate the effect of subject-specific characteristics on the qMRI values.
RESULTS: Bias was 0.009x10(-3) mm(2)/s for ADC, -0.7 % for FF and -7.9 ms for T(2). RCs ranged 0.11-0.25x10(-3) mm(2)/s for ADC, 1.2-6.3 % for FF and 2.5-6.3 ms for T(2). A significant positive linear relationship between age and the FF and T(2) for some of the OARs was found.
CONCLUSION: These qMRI techniques are feasible, accurate and repeatable, which is promising for treatment response monitoring and/or differentiating between healthy and unhealthy tissues due to radiation-induced damage in HNC patients.

Gepubliceerd: Phys Imaging Radiat Oncol. 2024;31:100608.
Impact factor: 3.3 ; Q2

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4. Impact of the new rectal cancer definition on multimodality treatment and interhospital variability: Results from a nationwide cross-sectional study
Hazen SJA, Sluckin TC, Horsthuis K, Lambregts DMJ, Beets-Tan RGH, Hompes R, Buffart TE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

AIM: This study aimed to determine the consequences of the new definition of rectal cancer for decision-making in multidisciplinary team meetings (MDT). The new definition of rectal cancer, the

lower border of the tumour is located below the sigmoid take-off (STO), was implemented in the Dutch guideline in 2019 after an international Delphi consensus meeting to reduce interhospital variations.
METHOD: All patients with rectal cancer according to the local MDT, who underwent resection in 2016 in the Netherlands were eligible for this nationwide collaborative cross-sectional study. MRI-images were rereviewed, and the tumours were classified as above or on/below the STO.
RESULTS: This study registered 3107 of the eligible 3178 patients (98%), of which 2784 patients had an evaluable MRI. In 314 patients, the tumour was located above the STO (11%), with interhospital variation between 0% and 36%. Based on TN-stage, 175 reclassified patients with colon cancer (6%) would have received different treatment (e.g., omitting neoadjuvant radiotherapy, candidate for adjuvant chemotherapy). Tumour location above the STO was independently associated with lower risk of 4-year locoregional recurrence (HR 0.529; p = 0.030) and higher 4-year overall survival (HR 0.732; p = 0.037) compared to location under the STO.
CONCLUSION: By using the STO, 11% of the prior MDT-based diagnosis of rectal cancer were redefined as sigmoid cancer, with potential implications for multimodality treatment and prognostic value. Given the substantial interhospital variation in proportion of redefined cancers, the use of the STO will contribute to standardisation and comparability of outcomes in both daily practice and trial settings.

Gepubliceerd: Colorectal Dis. 2024;26(6):1131-44.
Impact factor: 2.7 ; Q2

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5. Abandonment of Routine Radiotherapy for Nonlocally Advanced Rectal Cancer and Oncological Outcomes

Hazen SJA, Sluckin TC, Intven MPW, Beets GL, Beets-Tan RGH, Borstlap WAA, Buffart TE, Buijsen J, Burger JWA, van Dieren S, Furnée EJB, Geijsen ED, Hompes R, Horsthuis K, Leijtens JWA, Maas M, Melenhorst J, Nederend J, Peeters K, Rozema T, Tuynman JB, Verhoef C, de Vries M, van Westreenen HL, de Wilt JHW, Zimmerman DDE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

IMPORTANCE: Neoadjuvant short-course radiotherapy was routinely applied for nonlocally advanced rectal cancer (cT1-3N0-1M0 with >1 mm distance to the mesorectal fascia) in the Netherlands following the Dutch total mesorectal excision trial. This policy has shifted toward selective application after guideline revision in 2014.
OBJECTIVE: To determine the association of decreased use of neoadjuvant radiotherapy with cancer-related outcomes and overall survival at a national level.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter, population-based, nationwide cross-sectional cohort study analyzed Dutch patients with rectal cancer who were treated in 2011 with a 4-year follow-up. A similar study was performed in 2021, analyzing all patients that were surgically treated in 2016. From these cohorts, all patients with cT1-3N0-1M0 rectal cancer and radiologically unthreatened mesorectal fascia were included in the current study. The data of the 2011 cohort were collected between May and October 2015, and the data of the 2016 cohort were collected between October 2020 and November 2021. The data were analyzed between May and October 2022.
MAIN OUTCOMES AND MEASURES: The main outcomes were 4-year local recurrence and overall survival rates. RESULTS: Among the 2011 and 2016 cohorts, 1199 (mean [SD] age, 68 [11] years; 430 women [36%]) of 2095 patients (57.2%) and 1576 (mean [SD] age, 68 [10] years; 547 women [35%]) of 3057 patients (51.6%) had cT1-3N0-1M0 rectal cancer and were included, with proportions of neoadjuvant radiotherapy of 87% (2011) and 37% (2016). Four-year local recurrence rates were 5.8% and 5.5%, respectively (P = .99). Compared with the 2011 cohort, 4-year overall survival was significantly higher in the 2016 cohort (79.6% vs 86.4%; P < .001), with lower non-cancer-related mortality (13.8% vs 6.3%; P < .001).

CONCLUSIONS AND RELEVANCE: The results of this cross-sectional study suggest that an absolute 50% reduction in radiotherapy use for nonlocally advanced rectal cancer did not compromise cancer-related outcomes at a national level. Optimizing clinical staging and surgery following the Dutch total mesorectal excision trial has potentially enabled safe deintensification of treatment.

Gepubliceerd: JAMA Oncol. 2024;10(2):202-11.
Impact factor: 20.1 ; Q1

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6. Long-term restoration of bowel continuity after rectal cancer resection and the influence of surgical technique: A nationwide cross-sectional study
Hazen SJA, van Geffen EGM, Sluckin TC, Beets GL, Belgers HJ, Borstlap WAA, Consten ECJ, Dekker JT, Hompes R, Tuynman JB, van Westreenen HL, de Wilt JHW, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

AIM: Literature on nationwide long-term permanent stoma rates after rectal cancer resection in the minimally invasive era is scarce. The aim of this population-based study was to provide more insight into the permanent stoma rate with interhospital variability (IHV) depending on surgical technique, with pelvic sepsis, unplanned reinterventions and readmissions as secondary outcomes.
METHOD: Patients who underwent open or minimally invasive resection of rectal cancer (lower border below the sigmoid take-off) in 67 Dutch centres in 2016 were included in this cross-sectional cohort study.
RESULTS: Among 2530 patients, 1470 underwent a restorative resection (58%), 356 a Hartmann's procedure (14%, IHV 0%-42%) and 704 an abdominoperineal resection (28%, IHV 3%-60%). Median follow-up was 51 months. The overall permanent stoma rate at last follow-up was 50% (IHV 13%-79%) and the unintentional permanent stoma rate, permanent stoma after a restorative procedure or an unplanned Hartmann's procedure, was 11% (IHV 0%-29%). A total of 2165 patients (86%) underwent a minimally invasive resection: 1760 conventional (81%), 170 transanal (8%) and 235 robot-assisted (11%). An anastomosis was created in 59%, 80% and 66%, with corresponding unintentional permanent stoma rates of 12%, 24% and 14% (p = 0.001), respectively. When corrected for age, American Society of Anesthesiologists classification, cTNM, distance to the anorectal junction and neoadjuvant (chemo)radiotherapy, the minimally invasive technique was not associated with an unintended permanent stoma (p = 0.071) after a restorative procedure.
CONCLUSION: A remarkable IHV in the permanent stoma rate after rectal cancer resection was found. No beneficial influence of transanal or robot-assisted laparoscopy on the unintentional permanent stoma rate was found, although this might be caused by the surgical learning curve. A reduction in IHV and improving preoperative counselling for decision-making for restorative procedures are required.

Gepubliceerd: Colorectal Dis. 2024;26(6):1153-65.
Impact factor: 2.7 ; Q2

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7. The EORTC 22922/10925 trial investigating regional nodal irradiation in stage I-III breast cancer: Outcomes according to locoregional and systemic therapies
Kaidar-Person O, Boersma LJ, De Brouwer P, Weltens C, Kirkove C, Peignaux-Casasnovas K, Budach V, van der Leij F, Peters M, Weidner N, Rivera S, van Tienhoven G, Fourquet A, Noel G, Valli M, Guckenberger M, Koiter E, Racadot S, Abdah-Bortnyak R, Bartelink H, Struikmans H, Fortpied C, Poortmans PM.

The EORTC 22922/10925 trial aimed to investigate the impact on overall survival (OS) of elective internal mammary and medial supraclavicular (IM-MS) radiation therapy (RT) in breast cancer stage I-III. Surgery for the primary tumour and axillary lymph nodes, chest wall RT, boost RT after whole breast RT in breast conserving therapy (BCT), RT to operated axilla, and systemic therapy were per physician's preference. The aim of the current analysis is to assess breast cancer outcomes according to different locoregional and systemic therapy used in the trial.
MATERIAL/METHODS: Data with a median follow-up of 15.7 years were extracted from the trial's case report forms. Kaplan-Meier curves of disease-free and OS and cumulative incidence curves of breast cancer events were produced. An exploratory analysis of the effect of the type of locoregional and systemic therapy on breast cancer outcomes was conducted using the Cox model or the Fine & Gray model accounting for competing risks, both models being adjusted for baseline patient and disease characteristics and treatment. The significance level was set at 5 %, 2-sided.
RESULTS: Of the 4,004 patients included, 625 (16%) did not receive any postoperative systemic therapy, 1,185 (30%) received endocrine therapy only, 994 (25%) chemotherapy only, and 1,200 (30%) both chemotherapy and endocrine therapy, without differences between the randomisation arms. Administration and type of therapy was associated with age, menopausal status, clinical T- and N-stage and ER status ($p < 0.0001$). Local control was better with mastectomy (with/without postmastectomy RT) as compared to BCT, but mastectomy was associated with more distant metastasis (DM) as first event. Similarly, DM as first event occurred more in the BCT group that received a boost as compared to no boost and in those who received RT to the lower axillary level. IM-MS RT reduced significantly regional recurrences and improved disease-free survival in a sensitivity stratified analysis. OS was worse with mastectomy as compared to BCT and with irradiation of the axilla but better with sentinel node dissection and adjuvant combined chemo and hormonal therapy.
CONCLUSION: Different components of therapy influenced the site of first event. IM-MS RT improved outcomes in different breast cancer outcomes were most probably related that the group were balanced due to the trial arms and stratification methods.

Gepubliceerd: Radiother Oncol. 2024;201:110563.
Impact factor: 5.3 ; Q1

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8. Molecular and Clinicopathologic Characterization of Mismatch Repair-Deficient Endometrial Carcinoma Not Related to MLH1 Promoter Hypermethylation
Kaya M, Post CCB, Tops CM, Nielsen M, Crosbie EJ, Leary A, Mileshkin LR, Han K, Bessette P, de Boer SM, Jürgenliemk-Schulz IM, Lutgens L, Jobsen JJ, Haverkort MAD, Nout RA, Kroep J, Creutzberg CL, Smit V, Horeweg N, van Wezel T, Bosse T.

Universal tumor screening in endometrial carcinoma (EC) is increasingly adopted to identify individuals at risk of Lynch syndrome (LS). These cases involve mismatch repair-deficient (MMRd) EC without MLH1 promoter hypermethylation (PHM). LS is confirmed through the identification of germline MMR pathogenic variants (PV). In cases where these are not detected, emerging evidence highlights the significance of double-somatic MMR gene alterations as a sporadic cause of MMRd, alongside POLE/POLD1 exonuclease domain (EDM) PV leading to secondary MMR PV. Our understanding of the incidence of different MMRd EC origins not related to MLH1-PHM, their associations with clinicopathologic characteristics, and the prognostic implications remains limited. In a combined analysis of the PORTEC-1, -2, and -3 trials (n = 1254), 84 MMRd EC not related to MLH1-PHM were identified that successfully underwent paired tumor-normal tissue next-generation sequencing of the MMR and POLE/POLD1 genes. Among these, 37% were LS associated (LS-MMRd EC), 38% were due to double-somatic hits (DS-MMRd EC), and 25% remained unexplained. LS-MMRd EC exhibited higher rates of MSH6 (52% vs 19%) or PMS2 loss (29% vs 3%) than DS-MMRd EC, and exclusively showed MMR-deficient gland foci. DS-MMRd EC had higher rates of combined

MSH2/MSH6 loss (47% vs 16%), loss of >2 MMR proteins (16% vs 3%), and somatic POLE-EDM PV (25% vs 3%) than LS-MMRd EC. Clinicopathologic characteristics, including age at tumor onset and prognosis, did not differ among the various groups. Our study validates the use of paired tumor-normal next-generation sequencing to identify definitive sporadic causes in MMRd EC unrelated to MLH1-PHM. MMR immunohistochemistry and POLE-EDM mutation status can aid in the differentiation between LS-MMRd EC and DS-MMRd EC. These findings emphasize the need for integrating tumor sequencing into LS diagnostics, along with clear interpretation guidelines, to improve clinical management. Although not impacting prognosis, confirmation of DS-MMRd EC may release patients and relatives from burdensome LS surveillance.

Gepubliceerd: Mod Pathol. 2024;37(3):100423.
Impact factor: 5.5 ; Q1

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9. Effect of Physical Exercise on MRI-Assessed Brain Perfusion in Chemotherapy-Treated Breast Cancer Patients: A Randomized Controlled Trial
Koevoets EW, Petr J, Monninkhof EM, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, van der Palen J, Mutsaerts H, de Ruiter MB, May AM, Schagen SB.

BACKGROUND: Exercise is a promising intervention to alleviate cognitive problems in breast cancer patients, but studies on mechanisms underlying these effects are lacking.
PURPOSE: Investigating whether an exercise intervention can affect cerebral blood flow (CBF) in cognitively impaired breast cancer patients and to determine if CBF changes relate to memory function.
STUDY TYPE: Prospective.
POPULATION: A total of 181 chemotherapy-treated stage I-III breast cancer patients with cognitive problems and relatively low physical activity levels (≤150 minutes moderate to vigorous physical activity per week), divided into an exercise (N = 91) or control group (N = 90). FIELD
STRENGTH/SEQUENCE: Two-dimensional echo planar pseudo-continuous arterial spin labeling CBF sequence at 3 T.
ASSESSMENT: The 6-month long intervention consisted of (supervised) aerobic and strength training, 4 × 1 hour/week. Measurements at baseline (2-4 years post-diagnosis) and after 6 months included gray matter CBF in the whole brain, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. Physical fitness and memory function were also assessed. Subgroup analyses were performed in patients with high fatigue levels at baseline.
STATISTICAL TESTS: Multiple regression analyses with a two-sided alpha of 0.05 for all analyses.
RESULTS: There was a significant improvement in physical fitness (VO(2peak) in mL/minute/kg) in the intervention group (N = 53) compared to controls (N = 51, β = 1.47 mL/minute/kg, 95% CI: 0.44-2.50). However, no intervention effects on CBF were found (eg, whole brain: P = 0.565). Highly fatigued patients showed larger but insignificant treatment effects on CBF (eg, whole brain: P = 0.098). Additionally, irrespective of group, a change in physical fitness was positively associated with changes in CBF (eg, whole brain: β = 0.75, 95% CI: 0.07-1.43). There was no significant relation between CBF changes and changes in memory performance.
DATA CONCLUSION: The exercise intervention did not affect CBF of cognitively affected breast cancer patients. A change in physical fitness was associated with changes in CBF, but changes in CBF were not associated with memory functioning.
LEVEL OF EVIDENCE: 1 TECHNICAL EFFICACY STAGE: 5.

Gepubliceerd: J Magn Reson Imaging. 2024;59(5):1667-80.
Impact factor: 3.5 ; Q1

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10. Large-scale dose evaluation of deep learning organ contours in head-and-neck radiotherapy by leveraging existing plans
Mody P, Huiskes M, Chaves-de-Plaza NF, Onderwater A, Lamsma R, Hildebrandt K, Hoekstra N, Astreinidou E, Staring M, Dankers F.

BACKGROUND AND PURPOSE: Retrospective dose evaluation for organ-at-risk auto-contours has previously used small cohorts due to additional manual effort required for treatment planning on auto-contours. We aimed to do this at large scale, by a) proposing and assessing an automated plan optimization workflow that used existing clinical plan parameters and b) using it for head-and-neck auto-contour dose evaluation.
MATERIALS AND METHODS: Our automated workflow emulated our clinic's treatment planning protocol and reused existing clinical plan optimization parameters. This workflow recreated the original clinical plan (POG) with manual contours (PMC) and evaluated the dose effect (POG - PMC) on 70 photon and 30 proton plans of head-and-neck patients. As a use-case, the same workflow (and parameters) created a plan using auto-contours (PAC) of eight head-and-neck organs-at-risk from a commercial tool and evaluated their dose effect (PMC - PAC).
RESULTS: For plan recreation (POG - PMC), our workflow had a median impact of 1.0% and 1.5% across dose metrics of auto-contours, for photon and proton respectively. Computer time of automated planning was 25% (photon) and 42% (proton) of manual planning time. For auto-contour evaluation (PMC - PAC), we noticed an impact of 2.0% and 2.6% for photon and proton radiotherapy. All evaluations had a median ΔNTCP (Normal Tissue Complication Probability) less than 0.3%.
CONCLUSIONS: The plan replication capability of our automated program provides a blueprint for other clinics to perform auto-contour dose evaluation with large patient cohorts. Finally, despite geometric differences, auto-contours had a minimal median dose impact, hence inspiring confidence in their utility and facilitating their clinical adoption.

Gepubliceerd: Phys Imaging Radiat Oncol. 2024;30:100572.
Impact factor: 3.3 ; Q2

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11. Doxorubicin Exposure and Breast Cancer Risk in Survivors of Adolescent and Adult Hodgkin Lymphoma
Neppelenbroek SIM, Geurts YM, Aleman BMP, Lugtenburg PJ, Rademakers SE, de Weijer RJ, Schippers MGA, Ta BDP, Plattel WJ, Zijlstra JM, van der Maazen RWM, Nijziel MR, Ong F, Schimmel EC, Posthuma EFM, Kersten MJ, Böhmer LH, Muller K, Koene HR, Te Boome LCJ, Bilgin YM, de Jongh E, Janus CPM, van Leeuwen FE, Schaapveld M.

PURPOSE: Female Hodgkin lymphoma (HL) survivors treated with chest radiotherapy (RT) at a young age have a strongly increased risk of breast cancer (BC). Studies in childhood cancer survivors have shown that doxorubicin exposure may also increase BC risk. Although doxorubicin is the cornerstone of HL chemotherapy, the association between doxorubicin and BC risk has not been examined in HL survivors treated at adult ages.
METHODS: We assessed BC risk in a cohort of 1,964 female 5-year HL survivors, treated at age 15-50 years in 20 Dutch hospitals between 1975 and 2008. We calculated standardized incidence ratios, absolute excess risks, and cumulative incidences. Doxorubicin exposure was analyzed using multivariable Cox regression analyses.
RESULTS: After a median follow-up of 21.6 years (IQR, 15.8-27.1 years), 252 women had developed invasive BC or ductal carcinoma in situ. The 30-year cumulative incidence was 20.8% (95% CI, 18.2 to 23.4). Survivors treated with a cumulative doxorubicin dose of >200 mg/m(2) had a 1.5-fold increased BC risk (95% CI, 1.08 to 2.1), compared with survivors not treated with doxorubicin. BC risk increased 1.18-fold (95% CI, 1.05 to 1.32) per additional 100 mg/m(2) doxorubicin (P(trend) = .004). The risk

increase associated with doxorubicin (yes v no) was not modified by age at first treatment (hazard ratio [HR](age <21 years), 1.5 [95% CI, 0.9 to 2.6]; HR(age ≥21 years), 1.3 [95% CI, 0.9 to 1.9) or chest RT (HR(without mantle/axillary field RT), 1.9 [95% CI, 1.06 to 3.3]; HR(with mantle/axillary field RT), 1.2 [95% CI, 0.8 to 1.8]).
CONCLUSION: This study shows that treatment with doxorubicin is associated with increased BC risk in both adolescent and adult HL survivors. Our results have implications for BC surveillance guidelines for HL survivors and treatment strategies for patients with newly diagnosed HL.

Gepubliceerd: J Clin Oncol. 2024;42(16):1903-13.
Impact factor: 43.4 ; Q1

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12. Prognostic Implications of Lateral Lymph Nodes in Rectal Cancer: A Population-Based Cross-sectional Study With Standardized Radiological Evaluation After Dedicated Training
Sluckin TC, van Geffen EGM, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

BACKGROUND: There is an ongoing discussion regarding the prognostic implications of the presence, short-axis diameter, and location of lateral lymph nodes.
OBJECTIVE: To analyze lateral lymph node characteristics, the role of downsizing on restaging MRI, and associated local recurrence rates for patients with cT3-4 rectal cancer after MRI re-review and training.
DESIGN: Retrospective population-based cross-sectional study.
SETTINGS: This collaborative project was led by local investigators from surgery and radiology departments in 60 Dutch hospitals.
PATIENTS: A total of 3057 patients underwent rectal cancer surgery in 2016: 1109 had a cT3-4 tumor located ≤8 cm from the anorectal junction, of whom 891 received neoadjuvant therapy.
MAIN OUTCOME MEASURES: Local recurrence and (ipsi) lateral local recurrence rates.
RESULTS: Re-review identified 314 patients (35%) with visible lateral lymph nodes. Of these, 30 patients had either only long-stretched obturator (n = 13) or external iliac (n = 17) nodes, and both did not lead to any lateral local recurrences. The presence of internal iliac/obturator lateral lymph nodes (n = 284) resulted in 4-year local recurrence and lateral local recurrence rates of 16.4% and 8.8%, respectively. Enlarged (≥7 mm) lateral lymph nodes (n = 122) resulted in higher 4-year local recurrence (20.8%, 13.1%, 0%; p <.001) and lateral local recurrence (14.7%, 4.4%, 0%; p < 0.001) rates compared to smaller and no lateral lymph nodes, respectively. Visible lateral lymph nodes (HR 1.8 [1.1-2.8]) and enlarged lateral lymph nodes (HR 1.9 [1.1-3.5]) were independently associated with local recurrence in multivariable analysis. Enlarged lateral lymph nodes with malignant features had higher 4-year lateral local recurrence rates of 17.0%. Downsizing had no impact on lateral local recurrence rates. Enlarged lateral lymph nodes were found to be associated with higher univariate 4-year distant metastasis rates (36.4% vs 24.4%; p = 0.021), but this was not significant in multivariable analyses (HR 1.3 [0.9-1.]) and did not worsen overall survival.
LIMITATIONS: This study was limited by the retrospective design and total number of patients with lateral lymph nodes.
CONCLUSIONS: The risk of lateral local recurrence due to (enlarged) lateral lymph nodes was confirmed, but without the prognostic impact of downsizing after neoadjuvant therapy. These results point toward the incorporation of primary lateral lymph node size into treatment planning.

Gepubliceerd: Dis Colon Rectum. 2024;67(1):42-53.
Impact factor: 3.7 ; Q1

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13. Value of Size and Malignant Features of Lateral Lymph Nodes in Risk Stratification at Lateral Local Recurrence of Rectal Cancer: A National Cohort Study
van Geffen EGM, Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, van Dieren S, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Hendriksen EM.

BACKGROUND: Patients with rectal cancer who have enlarged lateral lymph nodes (LLNs) have an increased risk of lateral local recurrence (LLR). However, little is known about prognostic implications of malignant features (internal heterogeneity, irregular margins, loss of fatty hilum, and round shape) on MRI and number of enlarged LLNs, in addition to LLN size.
METHODS: Of the 3,057 patients with rectal cancer included in this national, retrospective, cross-sectional cohort study, 284 with a cT3-4 tumor located ≤8 cm from the anorectal junction who received neoadjuvant treatment and who had visible LLNs on MRI were selected. Imaging was reassessed by trained radiologists. LLNs were categorized based on size. Influence of malignant features and the number of LLNs on LLR was investigated.
RESULTS: Of 284 patients with at least 1 visible LLN, 122 (43%) had an enlarged node (≥7.0 mm) and 157 (55%) had malignant features. Of the 122 patients with enlarged nodes, 25 had multiple (≥2). In patients with a single enlarged node (n=97), a single malignant feature was associated with a 4-year LLR rate of 0% and multiple malignant features was associated with a rate of 17% (P=.060). In the group with multiple malignant features, their disappearance on restaging was associated with an LLR rate of 13% compared with an LLR rate of 20% for persistent malignant features (P=.532). The presence of intermediate-size LLNs (5.0-6.9 mm) with at least 1 malignant feature was associated with a 4-year LLR rate of 8%; the 4-year LLR rate was 13% when the malignant features persisted on restaging MRI (P=.409). Patients with multiple enlarged LLNs had a 4-year LLR rate of 28% compared with 11% for those with a single enlarged LLN (P=.059).
CONCLUSIONS: The presence of multiple enlarged LLNs (≥7.0 mm), as well as multiple malignant features in an enlarged node contribute to the risk of developing an LLR. These radiologic features can be used for clinical decision-making regarding the potential benefit of LLN dissection.

Gepubliceerd: J Natl Compr Canc Netw. 2024;22(1):17-25.
Impact factor: 16.4 ; Q1

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14. Optimised treatment of patients with enlarged lateral lymph nodes in rectal cancer: protocol of an international, multicentre, prospective registration study after extensive multidisciplinary training (LaNoReC)
van Geffen EGM, Sluckin TC, Hazen SJA, Horsthuis K, Intven M, van Dieren S, Beets G, Lange MM, Taggart MW, Beets-Tan RGH, Marijnen CAM, Konishi T, Tanis PJ, Kusters M, LaNoReC study group; Hendriksen EM.

INTRODUCTION: Inadequate treatment of enlarged lateral lymph nodes (LLNs) in rectal cancer patients is associated with an increased lateral local recurrence (LLR) risk, despite neoadjuvant treatment and total mesorectal excision (TME) surgery. There is a promising role for LLN dissection (LLND) to lower this risk, but this challenging procedure requires appropriate training. This study protocol describes a prospective evaluation of oncological outcomes after standardised treatment based on multidisciplinary training, thereby aiming for a 50% reduction in LLR rate.
METHODS AND ANALYSIS: A prospective registration study will be opened in hospitals in which the involved multidisciplinary team members (radiologists, radiation oncologists, surgeons and pathologists) have received dedicated training to enhance knowledge and awareness of LLNs and in which standardised treatment including LLND has been implemented. Patients with rectal cancer and at least one enlarged LLN (short-axis ≥7.0 mm), or intermediate LLN (short-axis 5.0-6.9 mm) with at least one malignant feature on primary MRI, evaluated by a trained radiologist, are eligible. Patients will undergo neoadjuvant treatment by trained radiation oncologists, followed by TME surgery in

combination with a minimally invasive, nerve-sparing LLND performed by trained surgeons. LLND specimens are evaluated by trained pathologists or grossing assistants. The primary outcome is LLR rate 3 years postoperatively. Secondary outcomes are morbidity, disease-free survival, overall survival and quality of life. To demonstrate a significant reduction in LLR rate from 13% (based on historical control data) to 6% after optimised treatment, 200 patients with enlarged LLNs are required.
ETHICS AND DISSEMINATION: The medical ethics board of the Vrije Universiteit Medical Centre (VUMC), the Netherlands, approved the study on 23 November 2022 (reference: 2021.0524). Participating centres must obtain local approval and participants are required to provide written informed consent. Results obtained from this study will be communicated via peer-reviewed medical journals and presentations at conferences.
TRAIL REGISTRATION NUMBER: NCT04486131, 24 July 2020, https://clinicaltrials.gov/ct2/show/NCT04486131.

Gepubliceerd: BMJ Open. 2024;14(10):e083225.
Impact factor: 2.3 ; Q2

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15. Author Correction: Prediction of recurrence risk in endometrial cancer with multimodal deep learning
Volinsky-Fremond S, Horeweg N, Andani S, Barkey Wolf J, Lafarge MW, de Kroon CD, Ørtoft G, Høgdall E, Dijkstra J, Jobsen JJ, Lutgens L, Powell ME, Mileshkin LR, Mackay H, Leary A, Katsaros D, Nijman HW, de Boer SM, Nout RA, de Bruyn M, Church D, Smit V, Creutzberg CL, Koelzer VH, Bosse T.

Gepubliceerd: Nat Med. 2024;30(7):2092.
Impact factor: 50.0 ; Q1

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16. Prediction of recurrence risk in endometrial cancer with multimodal deep learning
Volinsky-Fremond S, Horeweg N, Andani S, Barkey Wolf J, Lafarge MW, de Kroon CD, Ørtoft G, Høgdall E, Dijkstra J, Jobsen JJ, Lutgens L, Powell ME, Mileshkin LR, Mackay H, Leary A, Katsaros D, Nijman HW, de Boer SM, Nout RA, de Bruyn M, Church D, Smit V, Creutzberg CL, Koelzer VH, Bosse T.

Predicting distant recurrence of endometrial cancer (EC) is crucial for personalized adjuvant treatment. The current gold standard of combined pathological and molecular profiling is costly, hampering implementation. Here we developed HECTOR (histopathology-based endometrial cancer tailored outcome risk), a multimodal deep learning prognostic model using hematoxylin and eosin-stained, whole-slide images and tumor stage as input, on 2,072 patients from eight EC cohorts including the PORTEC-1/-2/-3 randomized trials. HECTOR demonstrated C-indices in internal (n = 353) and two external (n = 160 and n = 151) test sets of 0.789, 0.828 and 0.815, respectively, outperforming the current gold standard, and identified patients with markedly different outcomes (10-year distant recurrence-free probabilities of 97.0%, 77.7% and 58.1% for HECTOR low-, intermediate- and high-risk groups, respectively, by Kaplan-Meier analysis). HECTOR also predicted adjuvant chemotherapy benefit better than current methods. Morphological and genomic feature extraction identified correlates of HECTOR risk groups, some with therapeutic potential. HECTOR improves on the current gold standard and may help delivery of personalized treatment in EC.

Gepubliceerd: Nat Med. 2024;30(7):1962-73.
Impact factor: 50.0 ; Q1

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17. Prognostic impact and causality of age on oncological outcomes in women with endometrial cancer: a multimethod analysis of the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials
Wakkerman FC, Wu J, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens L, Haverkort MAD, de Jong MA, Mens JWM, Wortman BG, Nout RA, Léon-Castillo A, Powell ME, Mileshkin LR, Katsaros D, Alfieri J, Leary A, Singh N, de Boer SM, Nijman HW, Smit V, Bosse T, Koelzer VH, Creutzberg CL, Horeweg N.

BACKGROUND: Numerous studies have shown that older women with endometrial cancer have a higher risk of recurrence and cancer-related death. However, it remains unclear whether older age is a causal prognostic factor, or whether other risk factors become increasingly common with age. We aimed to address this question with a unique multimethod study design using state-of-the-art statistical and causal inference techniques on datasets of three large, randomised trials.
METHODS: In this multimethod analysis, data from 1801 women participating in the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials were used for statistical analyses and causal inference. The cohort included 714 patients with intermediate-risk endometrial cancer, 427 patients with high-intermediate risk endometrial cancer, and 660 patients with high-risk endometrial cancer. Associations of age with clinicopathological and molecular features were analysed using non-parametric tests. Multivariable competing risk analyses were performed to determine the independent prognostic value of age. To analyse age as a causal prognostic variable, a deep learning causal inference model called AutoCI was used.
FINDINGS: Median follow-up as estimated using the reversed Kaplan-Meier method was 12·3 years (95% CI 11·9-12·6) for PORTEC-1, 10·5 years (10·2-10·7) for PORTEC-2, and 6·1 years (5·9-6·3) for PORTEC-3. Both overall recurrence and endometrial cancer-specific death significantly increased with age. Moreover, older women had a higher frequency of deep myometrial invasion, serous tumour histology, and p53-abnormal tumours. Age was an independent risk factor for both overall recurrence (hazard ratio [HR] 1·02 per year, 95% CI 1·01-1·04; p=0·0012) and endometrial cancer-specific death (HR 1·03 per year, 1·01-1·05; p=0·0012) and was identified as a significant causal variable.
INTERPRETATION: This study showed that advanced age was associated with more aggressive tumour features in women with endometrial cancer, and was independently and causally related to worse oncological outcomes. Therefore, our findings suggest that older women with endometrial cancer should not be excluded from diagnostic assessments, molecular testing, and adjuvant therapy based on their age alone.
FUNDING: None.

Gepubliceerd: Lancet Oncol. 2024;25(6):779-89.
Impact factor: 35.9 ; Q1

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18. Safety and Efficiency Analysis of Operational Decision-Making During Cone Beam Computed Tomography-Based Online Adaptive Radiation Therapy
Wong LM, Byrne M, van Dieren E, Zwart L, Ray X, Harms J, Aland T, Stanley D, Pawlicki T.

PURPOSE: Cone beam computed tomography (CBCT)-based online adaptive radiation therapy (ART) is especially beneficial for patients with large interfractional anatomic changes. However, treatment planning and review decisions need to be made at the treatment console in real-time and may be delegated to clinical staff whose conventional scope of practice does not include making such decisions. Therefore, implementation can create new safety risks and inefficiencies. The objective of this work is to systematically analyze the safety and efficiency implications of human decision-making during the treatment session for CBCT-based online ART.
METHODS AND MATERIALS: The analysis was performed by applying the Systems-Theoretical Process Analysis technique and its extension for human decision-making. Four centers of different CBCT-based online ART practice models comprised the analysis team.

RESULTS: The general radiation therapy control structure was refined to model the interactions between routine treatment delivery staff and in-person or remote support staff. The treatment delivery staff perform 6 key control actions. Eighteen undesirable states of those control actions were identified as affecting safety and/or efficiency. In turn, 97 hazardous clinical scenarios were identified, with the control action "prepare and position patient" having the least number of scenarios and "delineate/edit influencer and target structures" having the most. Five of these are specific to either in-person or remote support during the treatment session, and 12 arise from staff support in general. **CONCLUSIONS**: An optimally safe and efficient online ART program should require little to no support staff at the treatment console to reduce staff coordination. Uptraining of the staff already at the treatment console is needed to achieve this goal. Beyond the essential knowledge and skills such as contour editing and the selection of an optimal plan, uptraining should also target the specific cognitive biases identified in this work and the cognitive strategies to overcome these biases. Additionally, technological and organizational changes are necessary.

Gepubliceerd: Int J Radiat Oncol Biol Phys. 2024;119(4):1307-16.
Impact factor: 6.5 ; Q1

Totale impact factor: 265.4
Gemiddelde impact factor: 14.7

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Reumatologie

1. What benefit-risk trade-offs are acceptable to rheumatoid arthritis patients during treatment selection? Evidence from a multicountry choice experiment
Alten R, Nieto-Gonzalez JC, Jacques P, Montecucco C, Moots R, Radner H, Vonkeman HE, Heidenreich S, Whichello C, Krucien N, Van Beneden K.

OBJECTIVE: Understanding preferences of patients with rheumatoid arthritis (RA) can facilitate tailored patient-centric care. This study elicited trade-offs that patients with RA were willing to make during treatment selection.
METHODS: Patients with RA completed an online discrete choice experiment, consisting of a series of choices between hypothetical treatments. Treatment attributes were selected based on literature review and qualitative patient interviews. Eligible patients were ≥18 years old, diagnosed with RA, receiving systemic disease-modifying antirheumatic drug therapy, and residents of Europe or USA. Male patients were oversampled for subgroup analyses. Data were analysed using a correlated mixed logit model.
RESULTS: Of 2090 participants, 42% were female; mean age was 45.2 years (range 18-83). Estimated effects were significant for all attributes ($p<0.001$) but varied between patients. Average relative attribute importance scores revealed different priorities ($p<0.001$) between males and females. While reducing pain and negative effect on semen parameters was most important to males, females were most concerned by risk of blood clots and serious infections. No single attribute explained treatment preferences by more than 30%. Preferences were also affected by patients' age: patients aged 18-44 years placed less importance on frequency and mode of treatment administration ($p<0.05$) than older age groups. Patients were willing to accept higher risk of serious infections and blood clots in exchange for improvements in pain, daily activities or administration convenience. However, acceptable trade-offs varied between patients ($p<0.05$).
CONCLUSION: Treatment preferences of patients with RA were individual-specific, but driven by benefits and risks, with no single attribute dominating the decision-making.

Gepubliceerd: RMD Open. 2024;10(1).
Impact factor: 4.8 ; Q1

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2. Induction of Cure in Early Arthritis (I CEA): study protocol for an investigator-initiated randomized single-blind clinical trial with open-label extension to compare three treatment strategies in patients with newly diagnosed undifferentiated arthritis
Bergstra SA, van Ouwerkerk L, Nevins IS, van der Pol JA, Helmich GS, Hest I, van Veen A, Bos R, Goekoop-Ruiterman YPM, Vonkeman HE, Bijsterbosch J, de Jong PHP, Güler-Yüksel M, Böhringer S, Huizinga TWJ, van Gaalen FA.

BACKGROUND: Undifferentiated arthritis (UA) is a term used to describe patients with inflammatory arthritis that has not differentiated into a specific rheumatic disease. UA may be a pre-stage of rheumatoid arthritis (RA) or another inflammatory disease or remain undifferentiated, but a substantial proportion of patients may also achieve spontaneous remission. As UA may be an early presentation of RA, rheumatologists often start methotrexate (or another csDMARD) as early as possible. There are however very little data on the potential benefits of early DMARD treatment, and longitudinal data suggests that long-term outcomes such as physical functioning hardly improved in these patients in the past decades. In the I CEA trial, we investigate if it is beneficial to start early treatment with MTX or baricitinib, a more rapidly acting drug with a broader mechanism of action, compared to waiting for spontaneous remission with symptomatic therapy in patients with UA.
METHODS: The I CEA is a multicenter single-blind (independent assessor) randomized clinical trial

with a 3-month interventional and 9-month observational follow-up period. The study includes patients with early (< 1 year symptom duration) DMARD-naïve undifferentiated arthritis. Patients with an increased risk of AEs with baricitinib treatment are excluded. Participants are randomized 1:1:1 to (1) symptom relief with NSAIDs and a single injection of glucocorticoids and (waiting for spontaneous remission); (2) methotrexate and a single injection of glucocorticoids, and NSAIDs are optional; and (3) baricitinib and a single injection of glucocorticoids and NSAIDs are optional. During the observational follow-up period, patients are treated in shared decision with their rheumatologist. The primary outcome will be the change in DAS at 3 months. Secondary outcomes include radiographic progression, physical functioning, patient-reported outcomes, cost utilities, safety, progression to classifiable RA, and disease activity over time.
DISCUSSION: The 12-month I CEA trial studies early treatment of patients with UA with methotrexate, baricitinib, or NSAIDs. The study initially had a more complex design. Emerging safety warnings about baricitinib necessitated adjustment of the trial protocol including more extensive exclusion criteria. The number of included patients was lower than initially planned, supported by an updated sample size calculation.
TRIAL REGISTRATION: Dutch trial register NL73202.058.20, EudraCT 2019-004359-35, registered 10-06-2020. Protocol version 1Q, 06-05-2024.

Gepubliceerd: Trials. 2024;25(1):758.
Impact factor: 2.0 ; Q3

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3. Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms
Citarella BW, Kartsonaki C, Ibáñez-Prada ED, Gonçalves BP, Baruch J, Escher M, Pritchard MG, Wei J, Philippy F, Dagens A, Hall M, Lee J, Kutsogiannis DJ, Wils EJ, Fernandes MA, Tirupakuzhi Vijayaraghavan BK, Panda PK, Martin-Loeches I, Ohshimo S, Fatoni AZ, Horby P, Dunning J, Rello J, Merson L, Rojek A, Vaillant M, Olliaro P, Reyes LF, ISARIC Clinical Characterisation Group; Vonkeman H.

BACKGROUND: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.
METHODS: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
RESULTS: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83-0.93]).
CONCLUSION: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

Gepubliceerd: Heliyon. 2024;10(10):e29591.
Impact factor: 3.6 ; Q1

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4. 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases
Dures E, Farisoğulları B, Santos EJF, Molto A, Feldthusen C, Harris C, Elling-Audersch C, Connolly D, Elefante E, Estévez-López F, Bini I, Primdahl J, Hoeper K, Urban M, van de Laar M, Redondo M, Böhm P, Amarnani R, Hayward R, Geenen R, Rednic S, Pettersson S, Thomsen T, Uhlig T, Ritschl V, Machado PM.

OBJECTIVES: Fatigue is prevalent in people with inflammatory rheumatic and musculoskeletal diseases (I-RMDs) and recognised as one of the most challenging symptoms to manage. The existence of multiple factors associated with driving and maintaining fatigue, and the evidence about what improves fatigue has led to a multifaceted approach to its management. However, there are no recommendations for fatigue management in people with I-RMDs. This lack of guidance is challenging for those living with fatigue and health professionals delivering clinical care. Therefore, our aim was to develop EULAR recommendations for the management of fatigue in people with I-RMDs.
METHODS: A multidisciplinary taskforce comprising 26 members from 14 European countries was convened, and two systematic reviews were conducted. The taskforce developed the recommendations based on the systematic review of evidence supplemented with taskforce members' experience of fatigue in I-RMDs.
RESULTS: Four overarching principles (OAPs) and four recommendations were developed. OAPs include health professionals' awareness that fatigue encompasses multiple biological, psychological and social factors which should inform clinical care. Fatigue should be monitored and assessed, and people with I-RMDs should be offered management options. Recommendations include offering tailored physical activity and/or tailored psychoeducational interventions and/or, if clinically indicated, immunomodulatory treatment initiation or change. Patient-centred fatigue management should consider the individual's needs and preferences, their clinical disease activity, comorbidities and other psychosocial and contextual factors through shared decision-making.
CONCLUSIONS: These 2023 EULAR recommendations provide consensus and up-to-date guidance on fatigue management in people with I-RMDs.

Gepubliceerd: Ann Rheum Dis. 2024;83(10):1260-7.
Impact factor: 20.6 ; Q1

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5. Patient-initiated follow-up supported by asynchronous telemedicine versus usual care in spondyloarthritis (TeleSpA-study): a randomised controlled trial of clinical and cost-effectiveness
Hermans K, Webers C, Boonen A, Vonkeman HE, van Tubergen A.

BACKGROUND: With rising health-care expenditures and workforce shortages, sustainable alternatives to traditional outpatient follow-up strategies are required to optimise care efficiency. We aimed to investigate the cost-effectiveness and clinical effectiveness of patient-initiated follow-up (PIFU) supported by asynchronous telemedicine for patients with spondyloarthritis compared with usual care in daily practice.
METHODS: TeleSpA was a multicentre, pragmatic, open-label, randomised controlled trial. Patients with spondyloarthritis and stable disease were randomly assigned (1:1) to either the PIFU and asynchronous telemedicine group or usual care group. All patients received a scheduled outpatient visit at baseline and after 1 year. Patients were monitored remotely at 6 months (PIFU and asynchronous telemedicine) or at the discretion of the treating rheumatologist (usual care). The primary outcome was the number of rheumatology visits within a 1-year period. A trial-based 1-year health-economic evaluation from a Dutch health-care perspective (only including health-care costs) and societal perspective (also including travel costs and work productivity losses), per the Dutch guidelines was used to estimate cost-effectiveness. The safety analysis was done in the intention-to-

treat population and was based on spontaneous reports of adverse events and serious adverse events or as observed by the research team. The primary analysis was in the intention-to-treat population. Individuals with relevant lived experience were involved in the study design. This trial was registered with the Dutch National Trial Register (NL71041.068.19) and ClinicalTrials.gov (NCT04673825) and is completed.
FINDINGS: Between Dec 2, 2020, and June 20, 2022, 200 patients were randomly assigned to PIFU and asynchronous telemedicine (n=100) or usual care (n=100). 79 (40%) of 200 participants were women, 121 (60%) were men, and the mean age was 55·0 years (SD 11·9). After 1 year, the mean number of rheumatology visits was 1·9 (SD 1·5) for the PIFU and asynchronous telemedicine group and 2·6 (1·3) in the usual care group (mean difference -0·7 [95% CI -1·0 to -0·3]; 25·4% reduction; p<0·0001). PIFU and asynchronous telemedicine was cost-effective from a health-care perspective, saving health-care costs (-€180 [95% CI -921 to 560]) without a loss in quality-adjusted life-years (0·004 [95 % CI -0·022 to 0·030]). Seven non-trial-related adverse events occurred in the PIFU and asynchronous telemedicine group and eight in usual care group (including one death).
INTERPRETATION: PIFU and asynchronous telemedicine resulted in significant and clinically meaningful reductions in rheumatology visits. This was not at the expense of health outcomes and saved health-care costs.
FUNDING: Dutch Arthritis Society.

Gepubliceerd: Lancet Rheumatol. 2024;6(12):e848-e59.
Impact factor: 16.4 ; Q1

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6. Increased vascular inflammation on PET/CT in psoriatic arthritis patients in comparison with controls
Kleinrensink NJ, Spierings J, Vonkeman HE, Seddiqi N, Herman A, Suijkerbuijk KPM, Heijstek MW, Jansen MP, de Jong PA, Foppen W.

BACKGROUND: Patients with psoriatic arthritis (PsA) have an increased risk of cardiovascular disease, possibly due to a chronic inflammatory state.
OBJECTIVES: The main objective of this study was to investigate the difference in vascular inflammation, measured with 18-fluorodeoxyglucose positron emission tomography/CT (PET/CT), in PsA patients and controls. We conducted a secondary analysis to assess the association between clinical parameters of disease activity with vascular inflammation in PsA.
METHODS: We included a total of 75 PsA patients with active peripheral arthritis (defined as ≥2 tender and swollen joints) from an ongoing clinical trial (EudraCT 2017-003900-28) and a retrospective group of 40 controls diagnosed with melanoma, without distant metastases and not receiving immunotherapy. The main outcome measure was aortic vascular inflammation which was measured on PET/CT scans using target-to-background ratios. Clinical disease activity in PsA was assessed with joint counts, body surface area and the Disease Activity index for PsA. Laboratory assessments included C reactive protein and erythrocyte sedimentation rate. RESULTS: Vascular inflammation was increased in patients with PsA in comparison with controls (mean target-to-background ratio for entire aorta, respectively, 1.63±0.17 vs 1.49±0.16; p=<0.001). This association remained significant after correction for gender, age, body mass index, mean arterial pressure and aortic calcification (p=0.002). Vascular inflammation was not associated with disease-related parameters.
CONCLUSIONS: Aortic vascular inflammation was significantly increased in patients with active PsA compared with controls. This evidence supports the theory that inflammation in PsA is not limited to the skin and joints but also involves the vascular system.

Gepubliceerd: RMD Open. 2024;10(1).
Impact factor: 4.8 ; Q1

7. Quantification of longitudinal patient-reported burden of adverse drug reactions attributed to the use of TNF-α inhibitors in inflammatory rheumatic diseases: an observational prospective cohort study
König BH, Gosselt HR, van Lint JA, Kosse LJ, van den Bemt BJF, Ten Klooster PM, Vonkeman HE, Jessurun NT.

BACKGROUND: There is a lack of knowledge on patient perspectives on adverse drug reactions (ADRs) attributed to the use of biologics. The aim of this study is to quantify the burden over time of ADRs attributed to TNF-α inhibitors in patients with inflammatory rheumatic diseases (IRDs) and investigate whether the burden over time differs between different types of ADRs.
RESEARCH DESIGN AND METHODS: Data were used from the Dutch Biologic Monitor (DBM), an observational prospective cohort study for patient-reported ADRs attributed to biologics. Patients with an IRD using a TNF-α inhibitor reporting an ADR, lasting for three consecutive questionnaires, were included. Questionnaires were sent every 2 months and the burden was scored on a 5-point Likert-type scale. Burden scores were analyzed using linear mixed models.
RESULTS: Data from 166 unique patients reporting 274 ADRs were included. The burden score decreased every month by 0.29 points (95% CI -0.34 - -0.24) on average on a 5-point Likert-type scale. The burden score for infections and infestations decreased significantly faster than the burden score for injection site reactions.
CONCLUSIONS: Patient-reported burden of ADRs attributed to the use of a TNF-α inhibitor in patients with IRDs decreased significantly over time, especially for infections and infestations.

Gepubliceerd: Expert Opin Drug Saf. 2024:1-6.
Impact factor: 3.1 ; Q2

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8. At-admission prediction of mortality and pulmonary embolism in an international cohort of hospitalised patients with COVID-19 using statistical and machine learning methods
Mesinovic M, Wong XC, Rajahram GS, Citarella BW, Peariasamy KM, van Someren Greve F, Olliaro P, Merson L, Clifton L, Kartsonaki C, ISARIC Characterisation Group; Vonkeman H.

By September 2022, more than 600 million cases of SARS-CoV-2 infection have been reported globally, resulting in over 6.5 million deaths. COVID-19 mortality risk estimators are often, however, developed with small unrepresentative samples and with methodological limitations. It is highly important to develop predictive tools for pulmonary embolism (PE) in COVID-19 patients as one of the most severe preventable complications of COVID-19. Early recognition can help provide life-saving targeted anti-coagulation therapy right at admission. Using a dataset of more than 800,000 COVID-19 patients from an international cohort, we propose a cost-sensitive gradient-boosted machine learning model that predicts occurrence of PE and death at admission. Logistic regression, Cox proportional hazards models, and Shapley values were used to identify key predictors for PE and death. Our prediction model had a test AUROC of 75.9% and 74.2%, and sensitivities of 67.5% and 72.7% for PE and all-cause mortality respectively on a highly diverse and held-out test set. The PE prediction model was also evaluated on patients in UK and Spain separately with test results of 74.5% AUROC, 63.5% sensitivity and 78.9% AUROC, 95.7% sensitivity. Age, sex, region of admission, comorbidities (chronic cardiac and pulmonary disease, dementia, diabetes, hypertension, cancer, obesity, smoking), and symptoms (any, confusion, chest pain, fatigue, headache, fever, muscle or joint pain, shortness of breath) were the most important clinical predictors at admission. Age, overall presence of symptoms, shortness of breath, and hypertension were found to be key predictors for PE using our extreme gradient boosted model. This analysis based on the, until now, largest global dataset for this set of

problems can inform hospital prioritisation policy and guide long term clinical research and decision-making for COVID-19 patients globally. Our machine learning model developed from an international cohort can serve to better regulate hospital risk prioritisation of at-risk patients.

Gepubliceerd: Sci Rep. 2024;14(1):16387.
Impact factor: 3.9 ; Q1

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9. The burden of adverse drug reactions reported by patients in the Dutch ADR monitor: a proof of concept
Quik JM, Gosselt HR, van Lint JA, Kosse LJ, Ten Klooster PM, Vonkeman HE, van den Bemt BJF, Jessurun NT.

BACKGROUND: We aimed to describe the burden of adverse drug reactions (ADRs) reported by patients participating in the Dutch ADR Monitor using a multifactorial burden measurement instrument.
METHODS: The Dutch ADR Monitor is a cohort event monitoring system that collects information on ADR experiences, including burden. This study includes the initial data (November 2022 until May 2023). Patients were asked if experienced ADRs impacted 7 domains of burden: appearance, medical treatment, daily life, fatigue, physical consequences, mental consequences and the course of ADRs. Burden was scored from 0 to 10 on impacted domains. The distributions of these burden scores were demonstrated in Likert plots. The burden between persistent and recurrent ADRs was compared.
RESULTS: 92 patients reported 199 ADRs. Impact on the domains fatigue and daily life were experienced most frequently, except for skin and subcutaneous tissue ADRs, where impact on appearance and mental consequences were experienced most frequently. Fatigue was considered the most burdensome domain. No difference in burden was found between persistent (median = 7, IQR = 4) and recurrent ADRs (median = 6, IQR = 4, p = 0.59).
CONCLUSIONS: This is the first study investigating burden of ADRs on 7 domains in patients with chronic diseases. Impact on the domain fatigue was considered most burdensome.
Patients with skin and subcutaneous ADRs experienced impact on appearance and mental consequences most often, but found impact on fatigue most burdensome.For most reported ADRs, patients scored the highest burden on the domain fatigue and thus found impact on this domain to be the most burdensome.Patients with skin and subcutaneous ADRs experienced impact on appearance and mental consequences most often, but found impact on fatigue most burdensome.
eng.

Gepubliceerd: Expert Opin Drug Saf. 2024.
Impact factor: 3.1 ; Q2

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10. Affect and post-COVID-19 symptoms in daily life: An exploratory experience sampling study
Schaap G, Wensink M, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

Insight into the daily life experiences of patients with post-COVID-19 syndrome is lacking. The current study explored temporal fluctuations of and associations between positive and negative affect and symptoms throughout the day in previously hospitalised post-COVID-19 patients using an experience sampling methodology. Ten participants (age: median = 60, interquartile range = 9 years; 50% women; 80% ≥1 comorbidity; 8-12 months since hospital discharge) filled out brief online questionnaires, six times a day for 14 consecutive days. Positive and negative affect, and self-reported symptoms (physical and mental fatigue, cognitive functioning, dyspnoea, and pain) were assessed in real-time. Primarily, graphs were analysed to assess the individual longitudinal courses of and

(concurrent and time-lagged) associations between affect and symptoms. Secondly, correlations or multilevel linear regression models were used to support these interpretations. Visual assessment showed limited temporal fluctuation in affect and symptoms. All symptoms appeared to associate positively with each other (correlations between .26 and .85). Positive affect was associated with lower symptoms severity (β's between -.28 and -.67), and negative affect with higher symptoms severity (β's between .24 and .66). Time-lagged analyses showed that-adjusted for residual symptom severity of prior measurements-both types of affect predicted symptom severity two hours later (β's between -.09 and -.31 for positive affect; between .09 and .28 for negative affect). These findings suggest that positive and negative affect may play important roles in post-COVID-19 symptom experience and temporal fluctuation.

Gepubliceerd: PLoS One. 2024;19(10):e0295217.
Impact factor: 2.6 ; Q2

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11. Limited content overlap between commonly used self-report instruments for central (pain) sensitization in rheumatology
Ten Klooster PM, Simoes JP, Vonkeman HE.

OBJECTIVES: Central pain mechanisms may be prominent in a considerable subset of rheumatology patients with persistent pain. Several self-report instruments have been used in previous research to infer the presence and severity of central sensitization (CS) that stem from different definitions or approaches of CS. The current study aimed to evaluate and quantify the overlap of actual symptoms measured among self-report measures of CS in rheumatology.
METHODS: We used Fried's (2017) comprehensive systematic approach to analyse the content of five commonly used or typical self-report measures (Generalized Pain Questionnaire, Pain Sensitivity Questionnaire, Central Sensitization Inventory, Central Aspects of Pain in the Knee scale and the painDETECT) used in rheumatology research and to visualize and quantify the overlap in symptoms measured.
RESULTS: The five instruments together measured 39 different symptoms, most of which could be grouped into nociplastic pain manifestations (7 symptoms), neuropathic pain qualities (5 symptoms), and psychosomatic symptoms and emotional distress (25 symptoms). Most symptoms (74.4%) were unique to a single instrument. Thermal allodynia was the most frequently measured symptom across the different instruments, assessed in four of the measures. Average content overlap was very low and ranged from no overlap at all to moderate overlap (Jaccard index = 0.43) between pairs of instruments.
CONCLUSION: There is high heterogeneity and limited overlap in the content of self-report measures used to infer central pain sensitization. This may lead to results that are specific to the particular instrument and may limit the generalizability and comparability of study findings in rheumatology research.

Gepubliceerd: Rheumatol Adv Pract. 2024;8(3):rkae108.
Impact factor: 2.1 ; Q3

Totale impact factor: 67.0
Gemiddelde impact factor: 6.1

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.1
Gemiddelde impact factor: 2.1

Spoedeisende hulp

1. Evaluation of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 Using a Rapid Point of Care Test for Predicting Head Computed Tomography Lesions After Mild Traumatic Brain Injury in a Dutch Multi-Center Cohort
Chayoua W, Visser K, de Koning ME, Beishuizen A, Ijmker R, van der Naalt J, Krabbe JG, van der Horn HJ.

Mild traumatic brain injury (mTBI) is a common condition seen in emergency departments worldwide. Blood-based biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are recently U.S. Food and Drug Administration-approved for the prediction of intracranial lesions on head computed tomography (CT) scans in mTBI. We evaluated the diagnostic performance of GFAP and UCH-L1 in a Dutch cohort using the i-STAT TBI assay. In a multi-center observational study, we enrolled 253 mTBI patients. Head CT scans were scored using the Marshall classification system. Logistic regression models were used to assess the contribution of biomarkers and clinical parameters to diagnostic performance. Detection of UCH-L1 and GFAP resulted in a sensitivity of 97% and specificity of 19% for CT positivity in mTBI patients, along with a negative predictive value of 95% (88-100%) and a positive predictive value of 27% (21-33%). Combining biomarker testing with loss of consciousness and time to sample increased specificity to 46%. Combined testing of UCH-L1 and GFAP testing resulted in possibly more unnecessary CT scans compared with GFAP testing alone, with only limited increase in sensitivity. This study confirmed high sensitivity of GFAP and UCH-L1 for CT abnormalities in mTBI patients using the i-STAT TBI test. The results support the potential use of GFAP and UCH-L1 as tools for determining the indication for CT scanning in mTBI patients, possibly offering a cost- and time-effective approach to management of patients with mTBI. Prospective studies in larger cohorts are warranted to validate our findings.

Gepubliceerd: J Neurotrauma. 2024;41(13-14):e1630-e40.
Impact factor: 3.8 ; Q1

Totale impact factor: 3.8
Gemiddelde impact factor: 3.8

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Technische geneeskunde

1. The optimal treatment for patients with stage I non-small cell lung cancer: minimally invasive lobectomy versus stereotactic ablative radiotherapy - a nationwide cohort study
de Ruiter JC, van der Noort V, van Diessen JNA, Smit EF, Damhuis RAM, Hartemink KJ, ESLUNG group; Halfwerk FR.

OBJECTIVES: The aim of the Early-Stage LUNG cancer (ESLUNG) study was to compare outcomes after minimally invasive lobectomy (MIL) and stereotactic ablative radiotherapy (SABR) in patients with stage I non-small cell lung cancer (NSCLC).
MATERIALS AND METHODS: In this retrospective cohort study, patients with clinical stage I NSCLC (according to TNM7), treated in 2014-2016 with MIL or SABR, were included. 5-year overall survival (OS) and recurrence-free survival (RFS) were calculated and compared between patients treated with MIL and a propensity score (PS)-weighted SABR population with characteristics comparable to those of the MIL group.
RESULTS: 1211 MIL and 972 SABR patients were included. Nodal upstaging occurred in 13.0 % of operated patients. 30-day mortality was 1.0 % after MIL and 0.2 % after SABR. After SABR, the 5-year regional recurrence rate (18.1 versus 14.2 %; HR 0.74, 95 % CI 0.58-0.94) and distant metastasis rate (26.2 versus 20.2 %; HR 0.72, 95 % CI 0.59-0.88) were significantly higher than after MIL, with similar local recurrence rate (13.1 versus 12.1 %; HR 0.90, 95 % CI 0.68-1.19). Unadjusted 5-year OS and RFS were 70.2 versus 40.3 % and 58.0 versus 25.1 % after MIL and SABR, respectively. PS-weighted, multivariable analyses showed no significant difference in OS (HR 0.89, 95 % CI 0.65-1.20) and better RFS after MIL (HR 0.70, 95 % CI 0.49-0.99).
CONCLUSION: OS was not significantly different between stage I NSCLC patients treated with MIL and the PS-weighted population of patients treated with SABR. For operable patients with stage I NSCLC, SABR could therefore be an alternative treatment option with comparable OS outcome. However, RFS was better after MIL due to fewer regional recurrences and distant metastases. Future studies should focus on optimization of patient selection for MIL or SABR to further reduce postoperative mortality and morbidity after MIL and nodal failures after SABR.

Gepubliceerd: Lung Cancer. 2024;191:107792.
Impact factor: 4.4 ; Q1

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2. The use of indocyanine green fluorescence imaging in preventing postoperative bile leakage of the hepaticojejunostomy in robot-assisted pancreatic surgery
Gijsen AF, de Vries RPH, Vaassen HGM, Geelkerken RH, Liem MSL, Lips DJ.

BACKGROUND: Postoperative bile leakage (POBL) due to insufficiency of the hepaticojejunostomy (HJ) after pancreatico-duodenectomy (PD) is associated with high morbidity and mortality. The aim of this cohort study was to determine the clinical relevance of ICG in detecting and preventing POBL of the HJ in robotic minimal invasive pancreatic surgery (R-MIPS).
METHODS: All consecutive robot- and ICG-assisted HJ-anastomoses between 2019 and 2022 were included. Biliary leakage was objectified with near infrared technology. Only clinically relevant POBL were considered in this study. RESULTS: Sixty patients who underwent a PD between 2019 and 2022 were included. In ten patients, fluorescence imaging revealed an intra-operative hepaticojejunostomy insufficiency (HJI). Five of these patients developed POBL despite revision but preventing POBL in five patients. Detection of HJI with ICG predicted POBL with a sensitivity and specificity of 41.6% and 89.6% respectively. There was a significant higher chance of developing a POBL if the hepatic duct diameter was less than 5 mm (relative risk = 4.68 (p = 0.0345)), or if an intra-operative HJI was detected (relative risk = 3.57 (p = 0.009)). CONCLUSION: ICG is a simple and useful tool for detecting

intra-operative bile leakage. This study shows that bile illumination with ICG in R-MIPS could prevent postoperative bile leakage.

Gepubliceerd: HPB (Oxford). 2024;26(12):1515-20.
Impact factor: 2.4 ; Q1

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3. Three cases of posttraumatic wrist problems solved with 3D-printed patient-specific guides
Haandrikman S, Schröder FF, de Graaff F, Olde Heuvel J, Vochteloo AJH.

Symptomatic malunion of the wrist is one of the most common posttraumatic wrist problems. This study demonstrates three patients with complex malunions of the wrist who benefited from a corrective osteotomy using preplanned 3D-printed patient-specific guides, by experiencing improvement in their wrist function, grip strength and a reduction in pain.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2024;11(1):2311730.
Impact factor: 0.6 ; Q4

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4. Contrasting results in sacroiliac joint fusion studies: the role of bilateral complaints
Kampkuiper N, Schröder F, Brusse-Keizer M, Nellensteijn J.

Gepubliceerd: EClinicalMedicine. 2024;79:102978.
Impact factor: 10.0 ; Q1

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5. Sacroiliac joint fusion guided by intraoperatively superimposed virtual surgical planning using simulated fluoroscopic images
Lankheet S, Kampkuiper N, Nellensteijn J, Hekman E, Tuijthof G, Schröder F, Koenrades M.

INTRODUCTION: Sacroiliac joint fusion (SIJF) is a minimally invasive treatment for sacroiliac (SI) dysfunction. It involves placing implants through the SI joint under fluoroscopic guidance, requiring precise implant positioning to avoid nerve injury. Preoperative virtual surgical planning (VSP) aids in optimal positioning, but replicating it accurately in the operating room is challenging.
RESEARCH QUESTION: This study aims to assess the feasibility of superimposing VSP onto intraoperative fluoroscopic images to aid in optimal implant placement.
MATERIAL AND METHODS: A method for intraoperative guidance using 3D/2D registration was developed and tested during SIJF as an available and potentially efficient alternative for costly and more invasive navigation systems. Preoperatively, a VSP is performed and simulated fluoroscopic images are generated from a preoperative CT scan. During surgery, the simulated image that visually best matches the intraoperative fluoroscopic image is selected. Subsequently, the VSP is superimposed onto the intraoperative fluoroscopic image using a developed script-based workflow. The surgeon then places the implants accordingly. Postoperative implant placement accuracy was evaluated.
RESULTS: Five interventions were performed on five patients, resulting in a total of 15 placed implants. Minor complications without clinical consequences occurred in one case, primarily attributable to the patient's anatomy and pathological manifestations. Mean deviations at implant apex and 3D angle were 4.7 ± 1.6 mm and 3.5 ± 1.3°, respectively.

DISCUSSION AND CONCLUSIONS: The developed intraoperative workflow was feasible and resulted in implants placed with low deviations from the VSP. Further research is needed to automate and validate this method in a larger cohort.

Gepubliceerd: Brain Spine. 2024;4:102905.
Impact factor: 2.5 ; Q2

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6. A novel patient specific guide design to correct a complex multiplanar foot deformity.
Lankheet S, Schröder F, Kappert K, Ten Cate W, Hekman E, Asseln M, Koenrades M, Zeegers AVCM.

Surgical intervention is often indicated for complex multiplanar foot deformities (CMFDs). Addressing the 3D nature of these deformities proves challenging for achieving optimal foot alignment and reoperations are often necessary. Virtual surgical planning (VSP) can aid in the understanding of the multiplanar deformity and determine the osteotomies needed for correction. This study introduces a patient-specific guide (PSG) applied to a CMFD patient undergoing midfoot closing wedge osteotomy. The PSG design allowed for accurate reconstruction of the angular deformity, while allowing for intra-operative translational adjustments. Further improvement of the PSG design was proposed to ensure an even better fit in future applications.

Gepubliceerd: Proceedings of The 24th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery. 2024;7:107-11.
Impact factor: onbekend

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7. Ex vivo validation of magnetically actuated intravascular untethered robots in a clinical setting
Ligtenberg LW, Rabou NCA, Goulas C, Duinmeijer WC, Halfwerk FR, Arens J, Lomme R, Magdanz V, Klingner A, Klein Rot EAM, Nijland CHE, Wasserberg D, Liefers HR, Jonkheijm P, Susarrey-Arce A, Warlé M, Khalil ISM.

Intravascular surgical instruments require precise navigation within narrow vessels, necessitating maximum flexibility, minimal diameter, and high degrees of freedom. Existing tools often lack control during insertion due to undesirable bending, limiting vessel accessibility and risking tissue damage. Next-generation instruments aim to develop hemocompatible untethered devices controlled by external magnetic forces. Achieving this goal remains complex due to testing and implementation challenges in clinical environments. Here we assess the operational effectiveness of hemocompatible untethered magnetic robots using an ex vivo porcine aorta model. The results demonstrate a linear decrease in the swimming speed of untethered magnetic robots as arterial blood flow increases, with the capability to navigate against a maximum arterial flow rate of 67 mL/min. The untethered magnetic robots effectively demonstrate locomotion in a difficult-to-access target site, navigating through the abdominal aorta and reaching the distal end of the renal artery.

Gepubliceerd: Commun Eng. 2024;3(1):68.
Impact factor: onbekend

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8. Influence of utilizing hemodialysis membranes outside-in on solute clearance and filtration efficiency – One step towards a novel combined lung and kidney support device
Martins Costa A, Halfwerk FR, Thiel J-N, Wiegmann B, Neidlin M, Arens J.

Many membrane oxygenator patients suffer from renal disfunction. For these patients, a novel device integrating artificial lung and kidney support is being developed. Although outside-in blood flow is standard for membrane oxygenators, this is not typical for hemodialysis systems. The effect of outside-in blood flow on the efficiency of hemodialysis fibers for continuous hemodialysis and hemofiltration is yet unclear. This study evaluates the efficiency of commercial hemodialyzer membranes utilized outside-in compared to traditional inside-out mode regarding clearance of urea and creatinine, and ultrafiltration coefficient during in-vitro tests with porcine blood. Our results showed that dialyzers (1.2 m2, asymmetric hollow fibers) utilized outside-in had similar clearances of urea and creatinine compared to dialyzers used in the traditional mode ($p > 0.7$). However, outside-in dialyzers had an ultrafiltration coefficient four times lower than dialyzers applied in a conventional way, but adequate fluid removal could be achieved by controlling pressures in the system. This in-vitro study indicates that outside-in fibers could be sufficiently effective to maintain typical continuous renal replacement therapy doses. We regard this as one step towards a novel device with a mixed membrane fiber bundle utilizing blood flow outside both hemodialysis fibers and gas exchange fibers to provide simultaneous lung and kidney support.

Gepubliceerd: Journal of Membrane Science. 2024;698:122575.
Impact factor: 9.0 ; Q1

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9. Three-Dimensional Heart Modeling of Hypertrophic Obstructive Cardiomyopathy for In Situ Patient-Specific Simulation to Optimize Septal Myectomy

Smits KC, Speekenbrink RGH, Hekman EEG, Koenrades MA, Heeringa TJP, Arens J, Halfwerk FR.

OBJECTIVE: Hypertrophic obstructive cardiomyopathy (HOCM) develops in at least 1 out of 715 young adults. Patients who are refractory to medical therapy qualify for septal myectomy. Due to anatomy, serious complications such as ventricular septal defect and heart block may occur. Establishing cardiovascular magnetic resonance (CMR)-based 3-dimensional (3D) models as part of preoperative planning and training has the potential to decrease procedure-related complications and improve results.
METHODS: CMR images were used to segment cardiac structures. Left ventricular wall thickness was calculated and projected on top of the in silico model. A 3D model was printed with a red layer indicating a wall thickness exceeding 15 mm and used for preoperative resection planning and patient counseling. To provide preoperative patient-specific in situ simulation, the planned resection volume was replaced with silicone in a second model. For perioperative quality control, resected silicone was compared with resected myocardial tissue. The impact of the models was evaluated descriptively through consultation of both the cardiothoracic surgeon and patients and through patient outcomes.
RESULTS: Three-dimensional in silico and 3D-printed heart models of 5 patients were established preoperatively. Since the introduction of the models in October 2020, the surgeon feels better prepared, more confident, and less difficulty with making decisions. In addition, patients feel better informed preoperatively.
CONCLUSIONS: Using 3D heart models optimized preoperative planning and training, intraoperative quality control, and patient consultation. Reduction of procedure-related complications and clinical outcome should be studied in larger cohorts.

Gepubliceerd: Innovations (Phila). 2024;19(5):532-40.
Impact factor: 1.6 ; Q2

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10. Instability Severity Index Score predicts recurrent shoulder instability after arthroscopic Bankart repair
van Blommestein MYH, Govaert LHM, van der Palen J, Verra WC, Koorevaar RCT, Schröder FF, Veen EJD.

PURPOSE: The Instability Severity Index (ISI) Score was developed to preoperatively assess the risk of recurrent shoulder instability after an arthroscopic Bankart repair. This study aims to validate the use of ISI Score for predicting the risk of recurrence after an arthroscopic Bankart repair in a heterogeneous population and proposes an appropriate cut-off point for treating patients with an arthroscopic Bankart repair or otherwise.
METHODS: This study analysed 99 shoulders after a traumatic dislocation that underwent arthroscopic Bankart repair with at least 3 years follow-up. Patients were divided into subcategories based on their respective ISI Score. Recurrence includes either a postoperative dislocation or perceived instability.
RESULTS: The overall recurrence rate was found to be 26.3%. A significant correlation was identified between ISI Score and the recurrence rate (odds ratio [OR]: 1.545, 95% confidence interval [CI]: 1.231-1.939, $p < 0.001$). Furthermore, ISI Score 4-6 (OR: 4.498, 95% CI: 1.866-10.842, $p < 0.001$) and ISI Score > 6 (OR: 7.076, 95% CI: 2.393-20.924, $p < 0.001$) both had a significantly higher risk of recurrence compared to ISI Score 0-3. In ISI Score subcategories 0-3, 4-6 and >6, the recurrence rate was, respectively, 15.4%, 40.7% and 71.4%.
CONCLUSION: ISI Score has predictive value in determining the recurrence risk of shoulder instability following an arthroscopic Bankart repair in a heterogeneous population. Based on the findings of this study, we recommend using arthroscopic Bankart repair in patients with ISI Score 0-3. Clinical and shared decision-making are essential in the group with ISI Score 4-6, since the recurrence rate is significantly higher than in patients with ISI Score 0-3. Arthroscopic Bankart repair is not suitable for patients with ISI Score > 6.
LEVEL OF EVIDENCE: Level III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2024;32(8):2152-60.
Impact factor: 5.0 ; Q1

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11. ECMOve: A Mobilization Device for Extracorporeal Membrane Oxygenation Patients
van Galen DJM, Meinders Q, Halfwerk FR, Arens J.

Extracorporeal membrane oxygenation (ECMO) is a temporary lifesaving treatment for critically ill patients with severe respiratory or cardiac failure. Studies demonstrated the feasibility of in-hospital mobilizing during and after ECMO treatment preventing neuromuscular weakness and impaired physical functioning. Despite more compact mobile ECMO devices, implementation of ambulatory ECMO remains labor-intensive, complex, and challenging. It requires a large multidisciplinary team to carry equipment, monitor and physically support the patient, and to provide a back-up wheelchair in case of fatigue. Moreover, there is no adequate solution to ensure the stability of the patient's cannula and circuit management during ambulation. We developed a system contributing to improvement and innovation of current ambulatory ECMO patient programs. Our modular cart-in-cart system carries necessary ECMO equipment, features an extendable walking frame, and contains a folding seat for patient transport. An adjustable shoulder brace with lockable tubing-connectors enables safe fixation of the blood tubing. ECMOve provides safety, support, and accessibility while performing ambulatory ECMO for both patient and caregiver. Prototype evaluation in a simulated intensive care unit showed feasibility of our design, but needs to be evaluated in clinical care.

Gepubliceerd: Asaio j. 2024;70(5):377-86.
Impact factor: 2.3 ; Q2

12. Development of a virtual surgical plan for reverse shoulder arthroplasty as a treatment for complex proximal humerus fracture in an elderly patient
van Luit RJ, Rijntjes J, Hekman E, Govaert L, Hollman F, Schröder FF, Veen EJD.

Gepubliceerd: JSES Rev Rep Tech. 2024;5(1):92-6.
Impact factor: onbekend

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13. Safety and Efficiency Analysis of Operational Decision-Making During Cone Beam Computed Tomography-Based Online Adaptive Radiation Therapy
Wong LM, Byrne M, van Dieren E, Zwart L, Ray X, Harms J, Aland T, Stanley D, Pawlicki T.

PURPOSE: Cone beam computed tomography (CBCT)-based online adaptive radiation therapy (ART) is especially beneficial for patients with large interfractional anatomic changes. However, treatment planning and review decisions need to be made at the treatment console in real-time and may be delegated to clinical staff whose conventional scope of practice does not include making such decisions. Therefore, implementation can create new safety risks and inefficiencies. The objective of this work is to systematically analyze the safety and efficiency implications of human decision-making during the treatment session for CBCT-based online ART.
METHODS AND MATERIALS: The analysis was performed by applying the Systems-Theoretical Process Analysis technique and its extension for human decision-making. Four centers of different CBCT-based online ART practice models comprised the analysis team.
RESULTS: The general radiation therapy control structure was refined to model the interactions between routine treatment delivery staff and in-person or remote support staff. The treatment delivery staff perform 6 key control actions. Eighteen undesirable states of those control actions were identified as affecting safety and/or efficiency. In turn, 97 hazardous clinical scenarios were identified, with the control action "prepare and position patient" having the least number of scenarios and "delineate/edit influencer and target structures" having the most. Five of these are specific to either in-person or remote support during the treatment session, and 12 arise from staff support in general.
CONCLUSIONS: An optimally safe and efficient online ART program should require little to no support staff at the treatment console to reduce staff coordination. Uptraining of the staff already at the treatment console is needed to achieve this goal. Beyond the essential knowledge and skills such as contour editing and the selection of an optimal plan, uptraining should also target the specific cognitive biases identified in this work and the cognitive strategies to overcome these biases. Additionally, technological and organizational changes are necessary.

Gepubliceerd: Int J Radiat Oncol Biol Phys. 2024;119(4):1307-16.
Impact factor: 6.5 ; Q1

Totale impact factor: 44.3
Gemiddelde impact factor: 3.4

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 23.7
Gemiddelde impact factor: 4.0

Thoraxcentrum Twente

1. Serial cardiac biomarkers, pulmonary artery pressures and traditional parameters of fluid status in relation to prognosis in patients with chronic heart failure: Design and rationale of the BioMEMS study

Allach Y, Barry-Loncq de Jong M, Clephas PRD, van Gent MWF, Brunner-La Rocca HP, Szymanski MK, van Halm VP, Handoko ML, Kok WEM, Asselbergs FW, van Kimmenade RRJ, Manintveld OC, van Mieghem N, Beeres S, Rienstra M, Post MC, van Heerebeek L, Borleffs CJW, Tukkie R, Mosterd A, Linssen GCM, Spee RF, Emans ME, Smilde TDJ, van Ramshorst J, Kirchhof C, Feenema-Aardema MW, da Fonseca CA, van den Heuvel M, Hazeleger R, van Eck JWM, Boersma E, Kardys I, de Boer RA, Brugts JJ.

AIMS: Heart failure (HF), a global pandemic affecting millions of individuals, calls for adequate predictive guidance for improved therapy. Congestion, a key factor in HF-related hospitalizations, further underscores the need for timely interventions. Proactive monitoring of intracardiac pressures, guided by pulmonary artery (PA) pressure, offers opportunities for efficient early-stage intervention, since haemodynamic congestion precedes clinical symptoms.
METHODS: The BioMEMS study, a substudy of the MONITOR-HF trial, proposes a multifaceted approach integrating blood biobank data with traditional and novel HF parameters. Two additional blood samples from 340 active participants in the MONITOR-HF trial were collected at baseline, 3-, 6-, and 12-month visits and stored for the BioMEMS biobank. The main aims are to identify the relationship between temporal biomarker patterns and PA pressures derived from the CardioMEMS-HF system, and to identify the biomarker profile(s) associated with the risk of HF events and cardiovascular death.
CONCLUSION: Since the prognostic value of single baseline measurements of biomarkers like N-terminal pro-B-type natriuretic peptide is limited, with the BioMEMS study we advocate a dynamic, serial approach to better capture HF progression. We will substantiate this by relating repeated biomarker measurements to PA pressures. This design rationale presents a comprehensive review on cardiac biomarkers in HF, and aims to contribute valuable insights into personalized HF therapy and patient risk assessment, advancing our ability to address the evolving nature of HF effectively.

Gepubliceerd: Eur J Heart Fail. 2024;26(8):1736-44.
Impact factor: 10.8 ; Q1

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2. Impact of intravascular ultrasound for coronary bifurcations treated with last generations stents: insights from the BIFURCAT-ULTRA registry

Bruno F, Choi KH, De Filippo O, Kim HK, Doronzo M, Cho YK, Pinxterhuis TH, Kang J, Mattesini A, Song YB, Piccolo R, Koo BK, Wańha W, Lee J, Cortese B, Gwon HC, Perl L, Kim HS, Tuttolomondo D, Iannaccone M, Chun WJ, Capodanno D, Leone A, Giachet AT, Hur SH, Stefanini G, Han SH, Escaned J, Carmeci A, Campo G, Patti G, von Birgelen C, de Ferrari GM, Nam CW, D'Ascenzo F.

BACKGROUND: Bifurcation lesions are associated with higher rates of major adverse cardiovascular events (MACE). AIM: To investigate the impact of imaging-guided PCI in a real-world population with coronary bifurcation lesions.
METHODS: From the ULTRA-BIFURCAT registry, we compared IVUS vs. angiographic guidance in a cohort of 3486 propensity matched patients. MACE a composite of all-cause death, myocardial infarction (MI), target-lesion revascularization (TLR) and stent-thrombosis was the primary endpoint. Subgroup analyses were performed for unprotected left main (ULM) and non-ULM disease.
RESULTS: PSM generated 1743 pairs. MACE occurred in 154 (9%) patients in the IVUS guided group and in 199 (11%) patients in the angio-guided group (p = 0.09). IVUS guidance was associated with

lower MACE in the ULM population [HR 0.62, 95% CI 0.46-0.83], but had no impact in the non-ULM population [HR 1.12, 95% CI 0.83-1.51], p for interaction = 0.006. IVUS was associated with reduction in all-MI [HR 0.32, 95% CI 0.16-0.64] in the ULM population and with lower ST in the non-ULM population [HR 0.24, 95% CI 0.08-0.71]. Provisional stenting was associated with lower MACE in the ULM population [HR 0.67, 95% CI 0.45-0.98], whereas kissing balloon [HR 0.75, 95% CI 0.56-0.99] and ultra-thin stents [HR 0.44, 95% CI 0.29-0.67] were protective factors in the non-ULM population.
CONCLUSIONS: In a real-world scenario, IVUS guidance during DES implantation is associated with a lower rate of MACE in patients with ULM coronary bifurcation lesions. In non-ULM bifurcations, no difference was observed on MACE, while IVUS guidance was associated with a lower rate of ST.

Gepubliceerd: Eur Heart J Qual Care Clin Outcomes. 2024.
Impact factor: 4.6 ; Q1

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3. Guideline implementation, drug sequencing, and quality of care in heart failure: design and rationale of TITRATE-HF
Clephas PRD, Malgie J, Schaap J, Koudstaal S, Emans M, Linssen GCM, de Boer GA, van Heerebeek L, Borleffs CJW, Manintveld OC, van Empel V, van Wijk S, van den Heuvel M, da Fonseca C, Damman K, van Ramshorst J, van Kimmenade R, van de Ven ART, Tio RA, van Veghel D, Asselbergs FW, de Boer RA, van der Meer P, Greene SJ, Brunner-La Rocca HP, Brugts JJ.

AIMS: Current heart failure (HF) guidelines recommend to prescribe four drug classes in patients with HF with reduced ejection fraction (HFrEF). A clear challenge exists to adequately implement guideline-directed medical therapy (GDMT) regarding the sequencing of drugs and timely reaching target dose. It is largely unknown how the paradigm shift from a serial and sequential approach for drug therapy to early parallel application of the four drug classes will be executed in daily clinical practice, as well as the reason clinicians may not adhere to new guidelines. We present the design and rationale for the real-world TITRATE-HF study, which aims to assess sequencing strategies for GDMT initiation, dose titration patterns (order and speed), intolerance for GDMT, barriers for implementation, and long-term outcomes in patients with de novo, chronic, and worsening HF.
METHODS AND RESULTS: A total of 4000 patients with HFrEF, HF with mildly reduced ejection fraction, and HF with improved ejection fraction will be enrolled in >40 Dutch centres with a follow-up of at least 3 years. Data collection will include demographics, physical examination and vital parameters, electrocardiogram, laboratory measurements, echocardiogram, medication, and quality of life. Detailed information on titration steps will be collected for the four GDMT drug classes. Information will include date, primary reason for change, and potential intolerances. The primary clinical endpoints are HF-related hospitalizations, HF-related urgent visits with a need for intravenous diuretics, all-cause mortality, and cardiovascular mortality.
CONCLUSIONS: TITRATE-HF is a real-world multicentre longitudinal registry that will provide unique information on contemporary GDMT implementation, sequencing strategies (order and speed), and prognosis in de novo, worsening, and chronic HF patients.

Gepubliceerd: ESC Heart Fail. 2024;11(1):550-9.
Impact factor: 3.7 ; Q1

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4. Pulmonary artery pressure monitoring in chronic heart failure: effects across clinically relevant subgroups in the MONITOR-HF trial
Clephas PRD, Zwartkruis VW, Malgie J, van Gent MWF, Brunner-La Rocca HP, Szymanski MK, van Halm VP, Handoko ML, Kok WEM, Asselbergs FW, van Kimmenade RRJ, Manintveld OC, van Mieghem N, Beeres S, Post MC, Borleffs CJW, Tukkie R, Mosterd A, Linssen GCM, Spee RF, Emans ME, Smilde TDJ, van Ramshorst J, Kirchhof C, Feenema-Aardema MW, da Fonseca CA, van den Heuvel M, Hazeleger R, van Eck M, van Heerebeek L, Boersma E, Rienstra M, de Boer RA, Brugts JJ.

BACKGROUND AND AIMS: In patients with chronic heart failure (HF), the MONITOR-HF trial demonstrated the efficacy of pulmonary artery (PA)-guided HF therapy over standard of care in improving quality of life and reducing HF hospitalizations and mean PA pressure. This study aimed to evaluate the consistency of these benefits in relation to clinically relevant subgroups.
METHODS: The effect of PA-guided HF therapy was evaluated in the MONITOR-HF trial among predefined subgroups based on age, sex, atrial fibrillation, diabetes mellitus, left ventricular ejection fraction, HF aetiology, cardiac resynchronization therapy, and implantable cardioverter defibrillator. Outcome measures were based upon significance in the main trial and included quality of life-, clinical-, and PA pressure endpoints, and were assessed for each subgroup. Differential effects in relation to the subgroups were assessed with interaction terms. Both unadjusted and multiple testing adjusted interaction terms were presented.
RESULTS: The effects of PA monitoring on quality of life, clinical events, and PA pressure were consistent in the predefined subgroups, without any clinically relevant heterogeneity within or across all endpoint categories (all adjusted interaction P-values were non-significant). In the unadjusted analysis of the primary endpoint quality-of-life change, weak trends towards a less pronounced effect in older patients (Pinteraction = .03; adjusted Pinteraction = .33) and diabetics (Pinteraction = .01; adjusted Pinteraction = .06) were observed. However, these interaction effects did not persist after adjusting for multiple testing.
CONCLUSIONS: This subgroup analysis confirmed the consistent benefits of PA-guided HF therapy observed in the MONITOR-HF trial across clinically relevant subgroups, highlighting its efficacy in improving quality of life, clinical, and PA pressure endpoints in chronic HF patients.

Gepubliceerd: Eur Heart J. 2024;45(32):2954-64.
Impact factor: 35.6 ; Q1

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5. Drug-coated balloons as a first choice for patients with de novo lesions: pros and cons
Colombo A, Leone PP, Ploumen EH, von Birgelen C.

Gepubliceerd: EuroIntervention. 2024;20(2):e120-e2.
Impact factor: 9.5 ; Q1

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6. First-time surgical aortic valve replacement: nationwide trends and outcomes from The Netherlands Heart Registration
Daeter EJ, de Beaufort HWL, Roefs MM, van Boven WJP, van Veghel D, van der Kaaij NP.

OBJECTIVES: The aim of this study was to describe trends and outcomes for patients undergoing surgical aortic valve replacement (SAVR) in the Netherlands.
METHODS: The Netherlands Heart Registration database was used to report the number and outcomes of isolated, primary SAVR procedures performed from 2007 to 2018 in adult patients.
RESULTS: A total of 17 142 procedures were included, of which 77.9% were performed using a biological prosthesis and 21.0% with a mechanical prosthesis. Median logistic EuroSCORE I decreased

from 4.6 [interquartile range (IQR) 2.4-7.7] to 4.0 (IQR 2.6-6.0). The 120-day mortality decreased from 3.3% in 2007 to 0.7% in 2018. The median duration of follow-up was 76 months (IQR 53-111). Ten-year survival, when adjusted for age, EuroSCORE I and body surface area, was 72.4%, and adjusted 10-year freedom from reinvervention was 98.1%. Additional analysis for patients under the age of 60 showed no difference between patients treated with a biological or mechanical prosthesis in adjusted 10-year survival, 89.7% vs 91.9±%, respectively (P = 0.25), but a significant difference in adjusted 10-year freedom from reintervention, 90.0±% vs 95.9%, respectively (P < 0.01).
CONCLUSIONS: Between 2007 and 2018, age and risk profile of patients undergoing SAVR decreased, especially for patients treated with a biological prosthesis. The 120-day mortality decreased over time. Patients undergoing SAVR nowadays have a risk of 120-day mortality of <1% and 10-year freedom from valve-related reintervention of >95%.

Gepubliceerd: Eur J Cardiothorac Surg. 2024;65(5).
Impact factor: 3.0 ; Q2

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7. Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study
Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, Borbély A, Erdal F, Benkouar R, Cobo-Marcos M, Barge-Caballero G, George V, Zara C, Ross NT, Barker D, Lekhakul A, Frea S, Ghazi AM, Knappe D, Doghmi N, Klincheva M, Fialho I, Bovolo V, Findeisen H, Alhaddad IA, Galluzzo A, de la Espriella R, Tabbalat R, Miró Ò, Singh JS, Nijst P, Dupont M, Martens P, Mullens W.

BACKGROUND: The use of urinary sodium to guide diuretics in acute heart failure is recommended by experts and the most recent European Society of Cardiology guidelines. However, there are limited data to support this recommendation. The ENACT-HF study (Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure) investigated the feasibility and efficacy of a standardized natriuresis-guided diuretic protocol in patients with acute heart failure and signs of volume overload.
METHODS: ENACT-HF was an international, multicenter, open-label, pragmatic, 2-phase study, comparing the current standard of care of each center with a standardized diuretic protocol, including urinary sodium to guide therapy. The primary end point was natriuresis after 1 day. Secondary end points included cumulative natriuresis and diuresis after 2 days of treatment, length of stay, and in-hospital mortality. All end points were adjusted for baseline differences between both treatment arms.
RESULTS: Four hundred one patients from 29 centers in 18 countries worldwide were included in the study. The natriuresis after 1 day was significantly higher in the protocol arm compared with the standard of care arm (282 versus 174 mmol; adjusted mean ratio, 1.64; P<0.001). After 2 days, the natriuresis remained higher in the protocol arm (538 versus 365 mmol; adjusted mean ratio, 1.52; P<0.001), with a significantly higher diuresis (5776 versus 4381 mL; adjusted mean ratio, 1.33; P<0.001). The protocol arm had a shorter length of stay (5.8 versus 7.0 days; adjusted mean ratio, 0.87; P=0.036). In-hospital mortality was low and did not significantly differ between the 2 arms (1.4% versus 2.0%; P=0.852).
CONCLUSIONS: A standardized natriuresis-guided diuretic protocol to guide decongestion in acute heart failure was feasible, safe, and resulted in higher natriuresis and diuresis, as well as a shorter length of stay.

Gepubliceerd: Circ Heart Fail. 2024;17(1):e011105.
Impact factor: 8.4 ; Q1

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8. Treatment of in-stent restenosis with ultrathin-strut versus thin-strut drug-eluting stents or drug-eluting balloons: a multicentre registry

De Filippo O, Wańha W, Sanavia T, Januszek R, Giacobbe F, Campo G, Pinxterhuis TH, Capodanno D, Tomasiewicz B, Iannaccone M, Leone A, Wolny R, Bruno F, Patti G, Musumeci G, Liccardo G, Verardi R, Roubin SR, Tarantini G, Kuźma Ł, Perl L, Gagnor A, Reczuch K, Conrotto F, Tuttolomondo D, Ploumen EH, Niezgoda P, Caglioni S, Omedè P, Greco A, Kubica J, Gil RJ, Piccolo R, Kornowski R, Bil J, Morena A, Zocca P, Pennone M, Gąsior M, Jaguszewski M, von Birgelen C, Fariselli P, De Ferrari GM, Wojakowski W, D'Ascenzo F.

BACKGROUND: Limited data exist on ultrathin-strut drug-eluting stent (ultrathin DES) performance in DES in-stent restenosis (ISR). AIMS: We aimed to assess the efficacy and safety of ultrathin DES compared to thin-strut DES and drug-eluting balloons (DEB) for DES-ISR.
METHODS: Patients from the DEB Dragon (ClinicalTrials.gov: NCT04415216) and ULTRA registries (ClinicalTrials.gov: NCT05205148) were divided into ultrathin DES, thin-strut DES, or DEB groups for DES-ISR treatment. Both propensity score matching (PSM) and inverse probability weighting (IPW) were considered to adjust the distribution of patients in each class. Cox regression was applied to the following main endpoints: device-oriented composite endpoints (DOCE; including cardiac death, target lesion revascularisation [TLR] and target vessel myocardial infarction), TLR and target vessel revascularisation (TVR).
RESULTS: A total of 269, 541, and 557 patients received an ultrathin DES, thin-strut DES, and DEB, respectively. After 3 years of follow-up, in the IPW-adjusted overall cohort, ultrathin DES were associated with a significantly reduced risk of DOCE compared to DEBs (hazard ratio [HR] 0.353, 95% confidence interval [CI]: 0.194-0.642; p<0.001), as well as thin-strut DES (HR 0.645, 95% CI: 0.457-0.911; p=0.013). Compared to DEBs, ultrathin DES also reduced the risks of both TLR (HR 0.184, 95% CI: 0.081-0.417; p<0.001) and TVR (HR 0.188, 95% CI: 0.093-0.379; p<0.001), while thin-strut DES did not (TLR: HR 0.686, 95% CI: 0.407-1.157; p=0.157; TVR: HR 0.706, 95% CI: 0.453-1.101; p=0.124). For diffuse ISR patients, ultrathin DES reduced the risk of DOCE (HR 0.364, 95% CI: 0.188-0.705; p=0.003), as did thin-strut DES (HR 0.602, 95% CI: 0.367-0.987; p=0.044), while a reduction of TLR (HR 0.220, 95% CI: 0.091-0.531; p<0.001) and TVR (HR 0.241, 95% CI: 0.113-0.513; p<0.001) was achieved only by ultrathin DES.
CONCLUSIONS: Ultrathin DES were associated with reduced DOCE, TLR and TVR risks in diffuse ISR compared to DEBs.

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Impact factor: 9.5 ; Q1

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9. Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study

Ekanem E, Neuzil P, Reichlin T, Kautzner J, van der Voort P, Jais P, Chierchia GB, Bulava A, Blaauw Y, Skala T, Fiala M, Duytschaever M, Szeplaki G, Schmidt B, Massoullie G, Neven K, Thomas O, Vijgen J, Gandjbakhch E, Scherr D, Johannessen A, Keane D, Boveda S, Maury P, García-Bolao I, Anic A, Hansen PS, Raczka F, Lepillier A, Guyomar Y, Gupta D, Van Opstal J, Defaye P, Sticherling C, Sommer P, Kucera P, Osca J, Tabrizi F, Roux A, Gramlich M, Bianchi S, Adragão P, Solimene F, Tondo C, Russo AD, Schreieck J, Luik A, Rana O, Frommeyer G, Anselme F, Kreis I, Rosso R, Metzner A, Geller L, Baldinger SH, Ferrero A, Willems S, Goette A, Mellor G, Mathew S, Szumowski L, Tilz R, Iacopino S, Jacobsen PK, George A, Osmancik P, Spitzer S, Balasubramaniam R, Parwani AS, Deneke T, Glowniak A, Rossillo A, Pürerfellner H, Duncker D, Reil P, Arentz T, Steven D, Olalla JJ, de Jong J, Wakili R, Abbey S, Timo G, Asso A, Wong T, Pierre B, Ewertsen NC, Bergau L, Lozano-Granero C, Rivero M, Breitenstein A, Inkovaara J, Fareh S, Latcu DG, Linz D, Müller P, Ramos-Maqueda J, Beiert T, Themistoclakis S, Meininghaus DG, Stix G, Tzeis S, Baran J, Almroth H, Munoz DR, de Sousa J, Efremidis M, Balsam P, Petru J, Küffer T, Peichl P, Dekker L, Della Rocca DG, Moravec O, Funasako M, Knecht S, Jauvert G,

Chun J, Eschalier R, Füting A, Zhao A, Koopman P, Laredo M, Manninger M, Hansen J, O'Hare D, Rollin A, Jurisic Z, Fink T, Chaumont C, Rillig A, Gunawerdene M, Martin C, Kirstein B, Nentwich K, Lehrmann H, Sultan A, Bohnen J, Turagam MK, Reddy VY.

Pulsed field ablation (PFA) is an emerging technology for the treatment of atrial fibrillation (AF), for which pre-clinical and early-stage clinical data are suggestive of some degree of preferentiality to myocardial tissue ablation without damage to adjacent structures. Here in the MANIFEST-17K study we assessed the safety of PFA by studying the post-approval use of this treatment modality. Of the 116 centers performing post-approval PFA with a pentaspline catheter, data were received from 106 centers (91.4% participation) regarding 17,642 patients undergoing PFA (mean age 64, 34.7% female, 57.8% paroxysmal AF and 35.2% persistent AF). No esophageal complications, pulmonary vein stenosis or persistent phrenic palsy was reported (transient palsy was reported in 0.06% of patients; 11 of 17,642). Major complications, reported for ~1% of patients (173 of 17,642), were pericardial tamponade (0.36%; 63 of 17,642) and vascular events (0.30%; 53 of 17,642). Stroke was rare (0.12%; 22 of 17,642) and death was even rarer (0.03%; 5 of 17,642). Unexpected complications of PFA were coronary arterial spasm in 0.14% of patients (25 of 17,642) and hemolysis-related acute renal failure necessitating hemodialysis in 0.03% of patients (5 of 17,642). Taken together, these data indicate that PFA demonstrates a favorable safety profile by avoiding much of the collateral damage seen with conventional thermal ablation. PFA has the potential to be transformative for the management of patients with AF.

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Impact factor: 50.0 ; Q1

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10. Apolipoprotein A1 Infusions and Cardiovascular Outcomes after Acute Myocardial Infarction
Gibson CM, Duffy D, Korjian S, Bahit MC, Chi G, Alexander JH, Lincoff AM, Heise M, Tricoci P, Deckelbaum LI, Mears SJ, Nicolau JC, Lopes RD, Merkely B, Lewis BS, Cornel JH, Trebacz J, Parkhomenko A, Libby P, Sacks FM, Povsic TJ, Bonaca M, Goodman SG, Bhatt DL, Tendera M, Steg PG, Ridker PM, Aylward P, Kastelein JJP, Bode C, Mahaffey KW, Nicholls SJ, Pocock SJ, Mehran R, Harrington RA, AEGIS-II Committees and Investigators; von Birgelen C.

BACKGROUND: Cardiovascular events frequently recur after acute myocardial infarction, and low cholesterol efflux - a process mediated by apolipoprotein A1, which is the main protein in high-density lipoprotein - has been associated with an increased risk of cardiovascular events. CSL112 is human apolipoprotein A1 derived from plasma that increases cholesterol efflux capacity. Whether infusions of CSL112 can reduce the risk of recurrent cardiovascular events after acute myocardial infarction is unclear.
METHODS: We conducted an international, double-blind, placebo-controlled trial involving patients with acute myocardial infarction, multivessel coronary artery disease, and additional cardiovascular risk factors. Patients were randomly assigned to receive either four weekly infusions of 6 g of CSL112 or matching placebo, with the first infusion administered within 5 days after the first medical contact for the acute myocardial infarction. The primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes from randomization through 90 days of follow-up.
RESULTS: A total of 18,219 patients were included in the trial (9112 in the CSL112 group and 9107 in the placebo group). There was no significant difference between the groups in the risk of a primary end-point event at 90 days of follow-up (439 patients [4.8%] in the CSL112 group vs. 472 patients [5.2%] in the placebo group; hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.05; P = 0.24), at 180 days of follow-up (622 patients [6.9%] vs. 683 patients [7.6%]; hazard ratio, 0.91; 95% CI, 0.81 to 1.01), or at 365 days of follow-up (885 patients [9.8%] vs. 944 patients [10.5%]; hazard ratio, 0.93; 95% CI, 0.85 to 1.02). The percentage of patients with adverse events was similar in the two groups; a higher number of hypersensitivity events was reported in the CSL112 group.

CONCLUSIONS: Among patients with acute myocardial infarction, multivessel coronary artery disease, and additional cardiovascular risk factors, four weekly infusions of CSL112 did not result in a lower risk of myocardial infarction, stroke, or death from cardiovascular causes than placebo through 90 days. (Funded by CSL Behring; AEGIS-II ClinicalTrials.gov number, NCT03473223.).

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Impact factor: 78.5 ; Q1

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11. External validation of EuroSCORE I and II in patients with infective endocarditis: results from a nationwide prospective registry
Heinen FJ, Peijster AJL, Fu EL, Kamp O, Chamuleau SAJ, Post MC, van der Stoel MD, Keyhan-Falsafi MA, van Nieuwkoop C, Klautz RJM, Tanis W, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration; Speekenbrink RGH.

OBJECTIVES: The primary objective was to externally validate EuroSCORE I and II in surgically treated endocarditis patients. The secondary objective was to assess the predictive performance of both models across sex, redo surgery, age, and urgency.
METHODS: Data were retrieved from the Netherlands Heart Registration. All patients with infective endocarditis who underwent cardiac surgery between 2013 and 2021 were included. Predictive performance was assessed by discrimination (area under the curve), calibration (calibration-in-the-large and calibration plots), and a decision curve analysis.
RESULTS: Two thousand five hundred and sixty-nine cases were included. Overall postoperative 30-day mortality was 10.2%. The area under the curve was 0.73 for EuroSCORE I and 0.72 for EuroSCORE II. Both models overpredict postoperative 30-day mortality, with observed-to-expected ratios of 0.37 and 0.69. EuroSCORE I overpredicts mortality across the full range, whereas EuroSCORE II overpredicts mortality only above a 20% predicted probability. We observed no significant differences in predictive performance across sex, redo surgery, or age. Discriminative capacity of EuroSCORE II was poor in emergency surgeries.
CONCLUSIONS: Both EuroSCORE models demonstrate acceptable discriminative capacity in IE patients. EuroSCORE I consistently overestimates mortality and should not be utilized in endocarditis patients. EuroSCORE II can be used in IE patients up to a predicted probability of approximately 20%, regardless of sex, redo surgery, or age. Beyond this point, the predicted mortality risk should be halved to approach the true mortality risk. EuroSCORE II should not be used for risk prediction in emergency endocarditis surgeries and patients should not be withheld from indicated surgical treatment solely based on high EuroSCOREs.

Gepubliceerd: Eur J Cardiothorac Surg. 2024;66(6).
Impact factor: 3.0 ; Q2

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12. Automated echocardiography view classification and quality assessment with recognition of unknown views
Jansen GE, de Vos BD, Molenaar MA, Schuuring MJ, Bouma BJ, Išgum I.

PURPOSE: Interpreting echocardiographic exams requires substantial manual interaction as videos lack scan-plane information and have inconsistent image quality, ranging from clinically relevant to unrecognizable. Thus, a manual prerequisite step for analysis is to select the appropriate views that showcase both the target anatomy and optimal image quality. To automate this selection process, we present a method for automatic classification of routine views, recognition of unknown views, and quality assessment of detected views.

APPROACH: We train a neural network for view classification and employ the logit activations from the neural network for unknown view recognition. Subsequently, we train a linear regression algorithm that uses feature embeddings from the neural network to predict view quality scores. We evaluate the method on a clinical test set of 2466 echocardiography videos with expert-annotated view labels and a subset of 438 videos with expert-rated view quality scores. A second observer annotated a subset of 894 videos, including all quality-rated videos.
RESULTS: The proposed method achieved an accuracy of 84.9% ± 0.67 for the joint objective of routine view classification and unknown view recognition, whereas a second observer reached an accuracy of 87.6%. For view quality assessment, the method achieved a Spearman's rank correlation coefficient of 0.71, whereas a second observer reached a correlation coefficient of 0.62.
CONCLUSION: The proposed method approaches expert-level performance, enabling fully automatic selection of the most appropriate views for manual or automatic downstream analysis.

Gepubliceerd: J Med Imaging (Bellingham). 2024;11(5):054002.
Impact factor: 1.7 ; Q3

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13. Quality of Life in Subcutaneous or Transvenous Implantable Cardioverter-Defibrillator Patients: A Secondary Analysis of the PRAETORIAN Trial
Knops RE, de Veld JA, Ghani A, Boersma LVA, Kuschyk J, El Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kääb S, Mittal S, Pepplinkhuizen S, Quast ABE, Smeding L, van der Stuijt W, de Weger A, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Jansen WPJ, Whinnett ZI, Nordbeck P, Knaut M, Philbert BT, van Opstal JM, Chicos AB, Allaart CP, Borger van der Burg AE, Dizon JM, Miller MA, Nemirovksy D, Surber R, Upadhyay GA, Tijssen JGP, Wilde AAM, Olde Nordkamp LRA.

BACKGROUND: The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed to overcome the risk of lead-related complications associated with the transvenous implantable cardioverter-defibrillator (TV-ICD). In contrast to the TV-ICD, the S-ICD is a completely extrathoracic device. Subsequently, complications differ between these 2 implantable cardioverter-defibrillators, which might impact patient perceptions of the therapies. This prespecified secondary analysis of the PRAETORIAN trial evaluates differences in quality of life.
METHODS: The PRAETORIAN trial (A Prospective, Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy) randomized patients with an implantable cardioverter-defibrillator indication, without the need for pacing to S-ICD or TV-ICD therapy. Two questionnaires were collected at baseline, discharge, 12 months, and 30 months. The Duke Activity Status Index measures cardiac-specific physical functioning, and the 36-Item Short Form Health Survey measures physical and mental well-being, with the subscales bodily pain and mental health being of interest in this analysis. Mann-Whitney U tests were used to compare study arms, and a mixed model was used to describe the questionnaire outcomes over time.
RESULTS: Patients were randomized to S-ICD (n=426) and TV-ICD (n=423). In the S-ICD group, 20% were women versus 19% in the TV-ICD group. The median age was 63 (interquartile range, 54-69) years in the S-ICD group versus 64 (interquartile range, 56-69) years in the TV-ICD group. There were no significant differences in the Duke Activity Status Index and 36-Item Short Form Health Survey subscales for bodily pain and mental health between the groups at any time point. Patients with a shock in the last 90 days had significantly lower scores for social functioning (P=0.008) and role limitations due to emotional problems (P=0.001) than patients without a shock, but this effect did not differ between treatment arms.
CONCLUSIONS: In a large randomized cohort of patients with an S-ICD or TV-ICD, no difference in overall quality of life was observed. However, implantable cardioverter-defibrillator shocks resulted in a reduction in quality of life, regardless of the device type or appropriateness.
REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01296022.

Gepubliceerd: Circ Cardiovasc Qual Outcomes. 2024;17(11):e010822.
Impact factor: 6.7 ; Q1

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14. Impact of the number of modifiable risk factors on clinical outcomes after percutaneous coronary intervention: An analysis from the e-Ultimaster registry
Kobo O, Levi Y, Abu-Fanne R, Von Birgelen C, Guédès A, Aminian A, Laanmets P, Dewilde W, Witkowski A, Monsegu J, Romo Iniguez A, Halabi M, Mamas MA, Roguin A.

AIMS: A substantial proportion of the patients undergoing percutaneous coronary intervention (PCI) have none of the of standard modifiable cardiovascular risk factors (SMuRFs): hypertension, diabetes, hypercholesterolaemia and smoking. The aim of this analysis was to compare clinical outcomes after PCI according to the number of SMuRFs.
METHODS: Patients with an indication for a PCI were stratified based upon the number of SMuRFs: 0, 1, 2 or 3-4. The primary outcome was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction or clinically driven target lesion revascularization at 1-year. Inverse weighted propensity score (IWPS) adjustment was performed to adjust for differences in baseline characteristics.
RESULTS: The prevalence of SMuRFs was: 0 SMuRF 16.4 %; 1 SMuRF 27.8 %; 2 SMuRFs 34.7 % and 3-4 SMuRFs 21.1 %. Patients without SMuRFs were younger, more likely to be male and had less complex coronary artery disease. The incidence of TLF increased with the number of SMuRFs: 2.65 %, 2.75 %, 3.23 %, and 4.24 %, P(trend) < 0.001. The relative risk (RR) for a TLF was 60 % higher (95 % confidence interval 1.32-1.93, p < 0.01) for patients with 3-4 SMuRFs compared to patients without SMuRFs. The trend remained (P(trend) < 0.01) after IWPS with TLF rates of 2.88 %, 2.64 %, 2.88 % and 3.65 %. The RR for a TLF was 27 % higher (95 % CI 1.05-1.53, p < 0.01).
CONCLUSION: The incidence of clinical events at 1-year increased with the number of SMuRFs. While patients without SMuRFs have a relatively favourable risk profile, more research is needed to optimize therapeutic management in the majority of patients.

Gepubliceerd: Int J Cardiol Heart Vasc. 2024;51:101370.
Impact factor: 2.5 ; Q2

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15. Value of Extended Arrhythmia Screening in Adult Congenital Heart Disease Patients
Koole MA, de Jong S, Mulder BJ, Bouma BJ, Schuuring MJ.

The European Society of Cardiology guidelines for the management of adult congenital heart disease patients recommend screening for arrhythmias and bradycardias in symptomatic patients, often being done by means of an ambulatory 24-48-hour Holter or implantable loop recorder (ILR). However, nowadays non-invasive instruments, such as patches, smartwatches and smartphones based on single-lead ECGs that perform extended monitoring, are also available. The aim of this narrative review was to assess whether these instruments, when they detect arrhythmias and bradycardias in patients with adult congenital heart disease, will lead to meaningful changes in clinical care. Clinically meaningful changes include adjustment of medication, cardioversion, electrophysiology study, ablation or implantation of a cardiovascular implantable electronic device. The following monitoring instruments are discussed: cumulative Holter, 2-week continuous monitor, smartwatchand smartphone-based single-lead ECG, and ILR. The diagnostic yield of extended rhythm monitoring is high, and varies between 18% (smartphone-based single-lead ECG) and 41% with ILR. In conclusion, contemporary arrhythmia screening includes various new non-invasive technologies that

are promising new tools as an alternative to Holter monitoring or ILR. However, the optimal mode of detection is still unclear due to the lack of head-to-head comparisons.

Gepubliceerd: Arrhythm Electrophysiol Rev. 2024;13:e07.
Impact factor: 3.3 ; Q2

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16. Abbreviated or Standard Dual Antiplatelet Therapy by Sex in Patients at High Bleeding Risk: A Prespecified Secondary Analysis of a Randomized Clinical Trial
Landi A, Alasnag M, Heg D, Frigoli E, Malik FTN, Gomez-Blazquez I, Pourbaix S, Chieffo A, Spaulding C, Sainz F, Routledge H, Andò G, Testa L, Sciahbasi A, Contractor H, Jepson N, Mieres J, Imran SS, Noor H, Smits PC, Valgimigli M, MASTER DAPT Investigators; von Birgelen C.

IMPORTANCE: Abbreviated dual antiplatelet therapy (DAPT) reduces bleeding with no increase in ischemic events in patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI).
OBJECTIVES: To evaluate the association of sex with the comparative effectiveness of abbreviated vs standard DAPT in patients with HBR.
DESIGN, SETTING, AND PATIENTS: This prespecified subgroup comparative effectiveness analysis followed the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs Standard DAPT Regimen (MASTER DAPT) trial, a multicenter, randomized, open-label clinical trial conducted at 140 sites in 30 countries and performed from February 28, 2017, to December 5, 2019. A total of 4579 patients with HBR were randomized at 1 month after PCI to abbreviated or standard DAPT. Data were analyzed from July 1 to October 31, 2022.
INTERVENTIONS: Abbreviated (immediate DAPT discontinuation, followed by single APT for ≥6 months) or standard (DAPT for ≥2 additional months, followed by single APT for 11 months) treatment groups.
MAIN OUTCOMES AND MEASURES: One-year net adverse clinical events (NACEs) (a composite of death due to any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (MACCEs) (a composite of death due to any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding (MCB).
RESULTS: Of the 4579 patients included in the analysis, 1408 (30.7%) were women and 3171 (69.3%) were men (mean [SD] age, 76.0 [8.7] years). Ischemic and bleeding events were similar between sexes. Abbreviated DAPT was associated with comparable NACE rates in men (hazard ratio [HR], 0.97 [95% CI, 0.75-1.24]) and women (HR, 0.87 [95% CI, 0.60-1.26]; P = .65 for interaction). There was evidence of heterogeneity of treatment effect by sex for MACCEs, with a trend toward benefit in women (HR, 0.68 [95% CI, 0.44-1.05]) but not in men (HR, 1.17 [95% CI, 0.88-1.55]; P = .04 for interaction). There was no significant interaction for MCB across sex, although the benefit with abbreviated DAPT was relatively greater in men (HR, 0.65 [95% CI, 0.50-0.84]) than in women (HR, 0.77 [95% CI, 0.53-1.12]; P = .46 for interaction). Results remained consistent in patients with acute coronary syndrome and/or complex PCI.
CONCLUSIONS AND RELEVANCE: These findings suggest that women with HBR did not experience higher rates of ischemic or bleeding events compared with men and may derive particular benefit from abbreviated compared with standard DAPT owing to these numerically lower rates of events.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03023020.

Gepubliceerd: JAMA Cardiol. 2024;9(1):35-44.
Impact factor: 14.1 ; Q1

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17. Ex vivo validation of magnetically actuated intravascular untethered robots in a clinical setting
Ligtenberg LW, Rabou NCA, Goulas C, Duinmeijer WC, Halfwerk FR, Arens J, Lomme R, Magdanz V, Klingner A, Klein Rot EAM, Nijland CHE, Wasserberg D, Liefers HR, Jonkheijm P, Susarrey-Arce A, Warlé M, Khalil ISM.

Intravascular surgical instruments require precise navigation within narrow vessels, necessitating maximum flexibility, minimal diameter, and high degrees of freedom. Existing tools often lack control during insertion due to undesirable bending, limiting vessel accessibility and risking tissue damage. Next-generation instruments aim to develop hemocompatible untethered devices controlled by external magnetic forces. Achieving this goal remains complex due to testing and implementation challenges in clinical environments. Here we assess the operational effectiveness of hemocompatible untethered magnetic robots using an ex vivo porcine aorta model. The results demonstrate a linear decrease in the swimming speed of untethered magnetic robots as arterial blood flow increases, with the capability to navigate against a maximum arterial flow rate of 67 mL/min. The untethered magnetic robots effectively demonstrate locomotion in a difficult-to-access target site, navigating through the abdominal aorta and reaching the distal end of the renal artery.

Gepubliceerd: Commun Eng. 2024;3(1):68.
Impact factor: onbekend

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18. Contemporary guideline-directed medical therapy in de novo, chronic, and worsening heart failure patients: First data from the TITRATE-HF study
Malgie J, Wilde MI, Clephas PRD, Emans ME, Koudstaal S, Schaap J, Mosterd A, van Ramshorst J, Wardeh AJ, van Wijk S, van den Heuvel M, Wierda E, Borleffs CJW, Saraber C, Beeres S, van Kimmenade R, Jansen Klomp W, Denham R, da Fonseca CA, Klip IT, Manintveld OC, van der Boon RMA, van Ofwegen CEE, Yilmaz A, Pisters R, Linssen GCM, Faber N, van Heerebeek L, van de Swaluw JEC, Bouhuijzen LJ, Post MC, Kuijper AFM, Wu KW, van Beek EA, Hesselink T, Kleijn L, Kurvers MJM, Tio RA, Langerveld J, van Dalen BM, van Eck JWM, Handoko ML, Hermans WRM, Koornstra-Wortel HJJ, Szymanski MK, Rooker D, Tandjung K, Eijsbouts SCM, Asselbergs FW, van der Meer P, Brunner-La Rocca HP, de Boer RA, Brugts JJ.

AIMS: Despite clear guideline recommendations for initiating four drug classes in all patients with heart failure (HF) with reduced ejection fraction (HFrEF) and the availability of rapid titration schemes, information on real-world implementation lags behind. Closely following the 2021 ESC HF guidelines and 2023 focused update, the TITRATE-HF study started to prospectively investigate the use, sequencing, and titration of guideline-directed medical therapy (GDMT) in HF patients, including the identification of implementation barriers.
METHODS AND RESULTS: TITRATE-HF is an ongoing long-term HF registry conducted in the Netherlands. Overall, 4288 patients from 48 hospitals were included. Among these patients, 1732 presented with de novo, 2240 with chronic, and 316 with worsening HF. The median age was 71 years (interquartile range [IQR] 63-78), 29% were female, and median ejection fraction was 35% (IQR 25-40). In total, 44% of chronic and worsening HFrEF patients were prescribed quadruple therapy. However, only 1% of HFrEF patients achieved target dose for all drug classes. In addition, quadruple therapy was more often prescribed to patients treated in a dedicated HF outpatient clinic as compared to a general cardiology outpatient clinic. In each GDMT drug class, 19% to 36% of non-use in HFrEF patients was related to side-effects, intolerances, or contraindications. In the de novo HF cohort, 49% of patients already used one or more GDMT drug classes for other indications than HF.
CONCLUSION: This first analysis of the TITRATE-HF study reports relatively high use of GDMT in a contemporary HF cohort, while still showing room for improvement regarding quadruple therapy. Importantly, the use and dose of GDMT were suboptimal, with the reasons often remaining unclear.

This underscores the urgency for further optimization of GDMT and implementation strategies within HF management.

Gepubliceerd: Eur J Heart Fail. 2024;26(7):1549-60.
Impact factor: 10.8 ; Q1

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19. Digital consults to optimize guideline-directed therapy: design of a pragmatic multicenter randomized controlled trial
Man JP, Dijkgraaf MGW, Handoko ML, de Lange FJ, Winter MM, Schijven MP, Stienen S, Meregalli P, Kok WEM, Kuipers DI, van der Harst P, Koole MAC, Chamuleau SAJ, Schuuring MJ.

AIMS: Many heart failure (HF) patients do not receive optimal guideline-directed medical therapy (GDMT) despite clear benefit on morbidity and mortality outcomes. Digital consults (DCs) have the potential to improve efficiency on GDMT optimization to serve the growing HF population. The investigator-initiated ADMINISTER trial was designed as a pragmatic multicenter randomized controlled open-label trial to evaluate efficacy and safety of DC in patients on HF treatment.
METHODS AND RESULTS: Patients (n = 150) diagnosed with HF with a reduced ejection fraction will be randomized to DC or standard care (1:1). The intervention group receives multifaceted DCs including (i) digital data sharing (e.g. exchange of pharmacotherapy use and home-measured vital signs), (ii) patient education via an e-learning, and (iii) digital guideline recommendations to treating clinicians. The consults are performed remotely unless there is an indication to perform the consult physically. The primary outcome is the GDMT prescription rate score, and secondary outcomes include time till full GDMT optimization, patient and clinician satisfaction, time spent on healthcare, and Kansas City Cardiomyopathy Questionnaire. Results will be reported in accordance to the CONSORT statement.
CONCLUSIONS: The ADMINISTER trial will offer the first randomized controlled data on GDMT prescription rates, time till full GDMT optimization, time spent on healthcare, quality of life, and patient and clinician satisfaction of the multifaceted patient- and clinician-targeted DC for GDMT optimization.

Gepubliceerd: ESC Heart Fail. 2024;11(1):560-9.
Impact factor: 3.7 ; Q1

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20. Digital Solutions to Optimize Guideline-Directed Medical Therapy Prescriptions in Heart Failure Patients: Current Applications and Future Directions
Man JP, Klopotowska J, Asselbergs FW, Handoko ML, Chamuleau SAJ, Schuuring MJ.

PURPOSEOF REVIEW: Guideline-directed medical therapy (GDMT) underuse is common in heart failure (HF) patients. Digital solutions have the potential to support medical professionals to optimize GDMT prescriptions in a growing HF population. We aimed to review current literature on the effectiveness of digital solutions on optimization of GDMT prescriptions in patients with HF.
RECENT FINDINGS: We report on the efficacy, characteristics of the study, and population of published digital solutions for GDMT optimization. The following digital solutions are discussed: teleconsultation, telemonitoring, cardiac implantable electronic devices, clinical decision support embedded within electronic health records, and multifaceted interventions. Effect of digital solutions is reported in dedicated studies, retrospective studies, or larger studies with another focus that also commented on GDMT use. Overall, we see more studies on digital solutions that report a significant increase in GDMT use. However, there is a large heterogeneity in study design, outcomes used, and populations studied, which hampers comparison of the different digital solutions. Barriers,

facilitators, study designs, and future directions are discussed. There remains a need for well-designed evaluation studies to determine safety and effectiveness of digital solutions for GDMT optimization in patients with HF. Based on this review, measuring and controlling vital signs in telemedicine studies should be encouraged, professionals should be actively alerted about suboptimal GDMT, the researchers should consider employing multifaceted digital solutions to optimize effectiveness, and use study designs that fit the unique sociotechnical aspects of digital solutions. Future directions are expected to include artificial intelligence solutions to handle larger datasets and relieve medical professional's workload.

Gepubliceerd: Curr Heart Fail Rep. 2024;21(2):147-61.
Impact factor: 3.4 ; Q2

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21. Author Correction: Digital consults in heart failure care: a randomized controlled trial
Man JP, Koole MAC, Meregalli PG, Handoko ML, Stienen S, de Lange FJ, Winter MM, Schijven MP, Kok WEM, Kuipers DI, van der Harst P, Asselbergs FW, Zwinderman AH, Dijkgraaf MGW, Chamuleau SAJ, Schuuring MJ.

Gepubliceerd: Nat Med. 2024;30(10):3027.
Impact factor: 50.0 ; Q1

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22. Digital consults in heart failure care: a randomized controlled trial
Man JP, Koole MAC, Meregalli PG, Handoko ML, Stienen S, de Lange FJ, Winter MM, Schijven MP, Kok WEM, Kuipers DI, van der Harst P, Asselbergs FW, Zwinderman AH, Dijkgraaf MGW, Chamuleau SAJ, Schuuring MJ.

Guideline-directed medical therapy (GDMT) has clear benefits on morbidity and mortality in patients with heart failure; however, GDMT use remains low. In the multicenter, open-label, investigator-initiated ADMINISTER trial, patients (n = 150) diagnosed with heart failure and reduced ejection fraction (HFrEF) were randomized (1:1) to receive usual care or a strategy using digital consults (DCs). DCs contained (1) digital data sharing from patient to clinician (pharmacotherapy use, home-measured vital signs and Kansas City Cardiomyopathy Questionnaires); (2) patient education via a text-based e-learning; and (3) guideline recommendations to all treating clinicians. All remotely gathered information was processed into a digital summary that was available to clinicians in the electronic health record before every consult. All patient interactions were standardly conducted remotely. The primary endpoint was change in GDMT score over 12 weeks (ΔGDMT); this GDMT score directly incorporated all non-conditional class 1 indications for HFrEF therapy with equal weights. The ADMINISTER trial met its primary outcome of achieving a higher GDMT in the DC group after a follow-up of 12 weeks (ΔGDMT score in the DC group: median 1.19, interquartile range (0.25, 2.3) arbitrary units versus 0.08 (0.00, 1.00) in usual care; $P < 0.001$). To our knowledge, this is the first multicenter randomized controlled trial that proves a DC strategy is effective to achieve GDMT optimization. ClinicalTrials.gov registration: NCT05413447 .

Gepubliceerd: Nat Med. 2024;30(10):2907-13.
Impact factor: 50.0 ; Q1

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23. Influence of utilizing hemodialysis membranes outside-in on solute clearance and filtration efficiency – One step towards a novel combined lung and kidney support device
Martins Costa A, Halfwerk FR, Thiel J-N, Wiegmann B, Neidlin M, Arens J.

Many membrane oxygenator patients suffer from renal disfunction. For these patients, a novel device integrating artificial lung and kidney support is being developed. Although outside-in blood flow is standard for membrane oxygenators, this is not typical for hemodialysis systems. The effect of outside-in blood flow on the efficiency of hemodialysis fibers for continuous hemodialysis and hemofiltration is yet unclear. This study evaluates the efficiency of commercial hemodialyzer membranes utilized outside-in compared to traditional inside-out mode regarding clearance of urea and creatinine, and ultrafiltration coefficient during in-vitro tests with porcine blood. Our results showed that dialyzers (1.2 m2, asymmetric hollow fibers) utilized outside-in had similar clearances of urea and creatinine compared to dialyzers used in the traditional mode ($p > 0.7$). However, outside-in dialyzers had an ultrafiltration coefficient four times lower than dialyzers applied in a conventional way, but adequate fluid removal could be achieved by controlling pressures in the system. This in-vitro study indicates that outside-in fibers could be sufficiently effective to maintain typical continuous renal replacement therapy doses. We regard this as one step towards a novel device with a mixed membrane fiber bundle utilizing blood flow outside both hemodialysis fibers and gas exchange fibers to provide simultaneous lung and kidney support.

Gepubliceerd: Journal of Membrane Science. 2024;698:122575.
Impact factor: 9.0 ; Q1

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24. The Therapeutic Potential of Different Surgical Approaches in the Management of Cardiac Myxoma: A Systematic Review
Mendyka D, Płonek T, Jędrasek T, Korman A, Złotowska A, Jędrasek A, Skalik R, Kustrzycki W.

BACKGROUND: Cardiac myxomas are benign tumors of the heart. They occur mostly in the left atrium. The preferred treatment is surgical resection, which can be performed via conventional median sternotomy, minimally invasive, or robotic-assisted approaches. This study aimed to evaluate the outcomes, advantages, and limitations of these surgical methods, with a focus on their safety, efficacy, and impact on patient recovery.
METHODS: This systemic review was conducted according to PRISMA guidelines. The chosen databases were systematically searched using the keywords "cardiac myxoma", "resection", "approach", "minimally invasive", and "robotic surgery". The comparison between the surgical strategies was based on thirteen articles, which met the inclusion criteria.
RESULTS: Median sternotomy remains the standard technique, providing excellent surgical access but is associated with longer hospital stays, higher blood loss, and increased risk of complications such as stroke. Minimally invasive approaches demonstrated comparable safety with shorter ICU stays, reduced blood loss, and lower postoperative pain but presented challenges, including limited exposure and longer procedure times. Robotic-assisted surgery showed potential as a safe alternative but was limited by high costs and technical demands. However, the data on minimally invasive and robotic methods are limited due to the rarity of cardiac myxomas.
CONCLUSIONS: The choice of surgical technique should be individualised by considering the tumour size, location, patient condition, and surgeon expertise. Routine postoperative echocardiographic monitoring is essential to detect residual or recurrent tumours. Further studies are needed to validate the long-term efficacy of minimally invasive and robotic approaches.

Gepubliceerd: J Clin Med. 2024;14(1).
Impact factor: 2.9 ; Q1

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25. Functional and morphological improvement of significant non-culprit coronary artery stenosis by LDL-C reduction with a PCSK9 antibody: Rationale and design of the randomized FITTER trial

Mensink FB, Los J, Oemrawsingh RM, von Birgelen C, Ijsselmuiden A, Meuwissen M, Cheng JM, van Wijk DF, Smits PC, Paradies V, van der Heijden DJ, Rai H, Ten Cate TJ, Camaro C, Damman P, van Nunen LX, Dimitriu-Leen AC, van Wely MH, Cetinyurek-Yavuz A, Byrne RA, van Royen N, van Geuns RM.

Non-culprit coronary artery lesions are commonly present in patients presenting with an acute coronary syndrome (ACS). Additional stenting of non-culprit lesions in addition to the culprit lesion intends to prevent secondary events caused by these lesions. At the same time, multiple trials have demonstrated the potential of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in reducing plaque size and changing plaque composition of non-culprit lesions. Whether intensive low-density lipoprotein cholesterol (LDL-C) reduction with PCSK9 inhibitor evolocumab improves non-culprit vessel hemodynamics, reduces the risk of plaque rupture of important non-culprit lesions, and might obviate the need for additional stenting has not been investigated. The "Functional Improvement of non-infarcT related coronary artery stenosis by Extensive LDL-C Reduction with a PCSK9 Antibody" (FITTER) trial is a multi-center, randomized, double-blind, placebo-controlled clinical trial for patients presenting with ACS and multivessel disease (MVD). After treatment of the culprit lesion, fractional flow reserve (FFR) is performed in non-culprit vessels amenable for percutaneous coronary intervention (PCI). Coronary intervention in patients with hemodynamically important non-critical lesions (FFR: 0.67-0.85) is staged after baseline imaging using near-infrared spectroscopy (NIRS) and intravascular ultrasound (IVUS). Eligible patients are randomized and treated for 12 weeks with either evolocumab or placebo, in addition to high-intensity statin therapy. Follow-up angiography with repeat FFR and IVUS-NIRS is scheduled at 12 weeks. Staged PCI is performed at the operator's discretion.The FITTER trial is the first study to evaluate the effect of maximal LDL-C reduction by the PCSK9 inhibitor evolocumab on invasively measured FFR, plaque size, and plaque composition in hemodynamically important non-culprit lesions, during a treatment period of just 12 weeks after an ACS. Currently, all patients have been included (August 2023) and data analysis is ongoing. TRIAL REGISTRATION NUMBER: clinicaltrials.gov NCT04141579.

Gepubliceerd: Heliyon. 2024;10(19):e38077.
Impact factor: 3.6 ; Q1

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26. Combination of computed tomography angiography with coronary artery calcium score for improved diagnosis of coronary artery disease: a collaborative meta-analysis of stable chest pain patients referred for invasive coronary angiography

Mohamed M, Bosserdt M, Wieske V, Dubourg B, Alkadhi H, Garcia MJ, Leschka S, Zimmermann E, Shabestari AA, Nørgaard BL, Meijs MFL, Øvrehus KA, Diederichsen ACP, Knuuti J, Halvorsen BA, Mendoza-Rodriguez V, Wan YL, Bettencourt N, Martuscelli E, Buechel RR, Mickley H, Sun K, Muraglia S, Kaufmann PA, Herzog BA, Tardif JC, Schütz GM, Laule M, Newby DE, Achenbach S, Budoff M, Haase R, Biavati F, Mézquita AV, Schlattmann P, Dewey M.

OBJECTIVES: Coronary computed tomography angiography (CCTA) has higher diagnostic accuracy than coronary artery calcium (CAC) score for detecting obstructive coronary artery disease (CAD) in patients with stable chest pain, while the added diagnostic value of combining CCTA with CAC is unknown. We investigated whether combining coronary CCTA with CAC score can improve the diagnosis of obstructive CAD compared with CCTA alone.
METHODS: A total of 2315 patients (858 women, 37%) aged 61.1 ± 10.2 from 29 original studies were included to build two CAD prediction models based on either CCTA alone or CCTA combined with the CAC score. CAD was defined as at least 50% coronary diameter stenosis on invasive coronary angiography. Models were built by using generalized linear mixed-effects models with a random

intercept set for the original study. The two CAD prediction models were compared by the likelihood ratio test, while their diagnostic performance was compared using the area under the receiver-operating-characteristic curve (AUC). Net benefit (benefit of true positive versus harm of false positive) was assessed by decision curve analysis.
RESULTS: CAD prevalence was 43.5% (1007/2315). Combining CCTA with CAC improved CAD diagnosis compared with CCTA alone (AUC: 87% [95% CI: 86 to 89%] vs. 80% [95% CI: 78 to 82%]; $p < 0.001$), likelihood ratio test 236.3, df: 1, $p < 0.001$, showing a higher net benefit across almost all threshold probabilities.
CONCLUSION: Adding the CAC score to CCTA findings in patients with stable chest pain improves the diagnostic performance in detecting CAD and the net benefit compared with CCTA alone.
CLINICAL RELEVANCE STATEMENT: CAC scoring CT performed before coronary CTA and included in the diagnostic model can improve obstructive CAD diagnosis, especially when CCTA is non-diagnostic.
KEY POINTS:
• The combination of coronary artery calcium with coronary computed tomography angiography showed significantly higher AUC (87%, 95% confidence interval [CI]: 86 to 89%) for diagnosis of coronary artery disease compared to coronary computed tomography angiography alone (80%, 95% CI: 78 to 82%, $p < 0.001$).
• Diagnostic improvement was mostly seen in patients with non-diagnostic C.
• The improvement in diagnostic performance and the net benefit was consistent across age groups, chest pain types, and genders.

Gepubliceerd: Eur Radiol. 2024;34(4):2426-36.
Impact factor: 4.7 ; Q1

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27. Explainable machine learning using echocardiography to improve risk prediction in patients with chronic coronary syndrome
Molenaar MA, Bouma BJ, Asselbergs FW, Verouden NJ, Selder JL, Chamuleau SAJ, Schuuring MJ.

AIMS: The European Society of Cardiology guidelines recommend risk stratification with limited clinical parameters such as left ventricular (LV) function in patients with chronic coronary syndrome (CCS). Machine learning (ML) methods enable an analysis of complex datasets including transthoracic echocardiography (TTE) studies. We aimed to evaluate the accuracy of ML using clinical and TTE data to predict all-cause 5-year mortality in patients with CCS and to compare its performance with traditional risk stratification scores.
METHODS AND RESULTS: Data of consecutive patients with CCS were retrospectively collected if they attended the outpatient clinic of Amsterdam UMC location AMC between 2015 and 2017 and had a TTE assessment of the LV function. An eXtreme Gradient Boosting (XGBoost) model was trained to predict all-cause 5-year mortality. The performance of this ML model was evaluated using data from the Amsterdam UMC location VUmc and compared with the reference standard of traditional risk scores. A total of 1253 patients (775 training set and 478 testing set) were included, of which 176 patients (105 training set and 71 testing set) died during the 5-year follow-up period. The ML model demonstrated a superior performance [area under the receiver operating characteristic curve (AUC) 0.79] compared with traditional risk stratification tools (AUC 0.62-0.76) and showed good external performance. The most important TTE risk predictors included in the ML model were LV dysfunction and significant tricuspid regurgitation.
CONCLUSION: This study demonstrates that an explainable ML model using TTE and clinical data can accurately identify high-risk CCS patients, with a prognostic value superior to traditional risk scores.

Gepubliceerd: Eur Heart J Digit Health. 2024;5(2):170-82.
Impact factor: 4.4 ; Q1

28. Validation of machine learning-based risk stratification scores for patients with acute coronary syndrome treated with percutaneous coronary intervention
Molenaar MA, Selder JL, Schmidt AF, Asselbergs FW, Nieuwendijk JD, van Dalfsen B, Schuuring MJ, Bouma BJ, Chamuleau SAJ, Verouden NJ.

AIMS: This study aimed to validate the machine learning-based Global Registry of Acute Coronary Events (GRACE) 3.0 score and PRAISE (Prediction of Adverse Events following an Acute Coronary Syndrome) in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI) for predicting mortality.
METHODS AND RESULTS: Data of consecutive patients with ACS treated with PCI in a tertiary centre in the Netherlands between 2014 and 2021 were used for external validation. The GRACE 3.0 score for predicting in-hospital mortality was evaluated in 2759 patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated with PCI. The PRAISE score for predicting one-year mortality was evaluated in 4347 patients with ACS treated with PCI. Both risk scores were compared with the GRACE 2.0 score. The GRACE 3.0 score showed excellent discrimination [c-statistic 0.90 (95% CI 0.84, 0.94)] for predicting in-hospital mortality, with well-calibrated predictions (calibration-in-the large [CIL] -0.19 [95% CI -0.45, 0.07]). The PRAISE score demonstrated moderate discrimination [c-statistic 0.75 (95% CI 0.70, 0.80)] and overestimated the one-year risk of mortality [CIL -0.56 (95% CI -0.73, -0.39)]. Decision curve analysis demonstrated that the GRACE 3.0 score offered improved risk prediction compared with the GRACE 2.0 score, while the PRAISE score did not.
CONCLUSION: This study in ACS patients treated with PCI provides suggestive evidence that the GRACE 3.0 score effectively predicts in-hospital mortality beyond the GRACE 2.0 score. The PRAISE score demonstrated limited potential for predicting one-year mortality risk. Further external validation studies in larger cohorts including patients without PCI are warranted.

Gepubliceerd: Eur Heart J Digit Health. 2024;5(6):702-11.
Impact factor: 4.4 ; Q1

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29. Inappropriate Therapy and Shock Rates Between the Subcutaneous and Transvenous Implantable Cardiac Defibrillator: A Secondary Analysis of the PRAETORIAN Trial
Olde Nordkamp LRA, Pepplinkhuizen S, Ghani A, Boersma LVA, Kuschyk J, El-Chami MF, Behr ER, Brouwer TF, Kääb S, Mittal S, Quast ABE, van der Stuijt W, Smeding L, de Veld JA, Tijssen JGP, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Jansen WPJ, Whinnett ZI, Nordbeck P, Knaut M, Philbert BT, van Opstal JM, Chicos AB, Allaart CP, Borger van der Burg AE, Dizon JM, Miller MA, Nemirovsky D, Surber R, Upadhyay GA, Weiss R, de Weger A, Wilde AAM, Knops RE.

BACKGROUND: Inappropriate therapy (IAT) is an undesirable side effect of implantable cardiac defibrillator (ICD) therapy. Early studies with the subcutaneous ICD (S-ICD) showed relatively high inappropriate shock (IAS) rates. The PRAETORIAN (Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy) trial demonstrated that the S-ICD is noninferior to the transvenous ICD (TV-ICD) with regard to the combined end point of IAS and complications. This secondary analyses evaluates all IAT in the PRAETORIAN trial.
METHODS: This international, multicenter trial randomized 849 patients with an indication for ICD therapy between S-ICD (n=426) and TV-ICD therapy (n=423). ICD programming was mandated by protocol. All analysis were performed in the modified intention-to-treat population.
RESULTS: In both groups 42 patients experienced IAT (48-month Kaplan-Meier estimated cumulative incidence, 9.9% and 10.1%, respectively; hazard ratio (HR), 0.99 [95% CI, 0.65-1.52]; P=0.97). There

was no significant difference in patients experiencing IAS between both groups (P=0.14). In the S-ICD group, 81 IAT episodes with 124 IAS and 1 inappropriate antitachycardia pacing occurred versus 89 IAT episodes with 130 IAS and 124 inappropriate antitachycardia pacing in the TV-ICD group. IAT episodes were most frequently caused by supraventricular tachycardias in the TV-ICD group (n=83/89) versus cardiac oversensing in the S-ICD group (n=40/81). In the TV-ICD group, a baseline heart rate >80 bpm (HR, 1.99 [95% CI, 1.05-3.76]; P=0.03), a history of atrial fibrillation (HR, 2.66 [95% CI, 1.41-5.02]; P=0.003), and smoking (HR, 2.46 [95% CI, 1.31-4.09]; P=0.005) were independent predictors for IAT. A QRS duration >120 ms was an independent predictor for IAT caused by cardiac oversensing in the S-ICD group (HR, 3.13 [95% CI, 1.34-7.31]; P=0.008). Post-IAS interventions significantly reduced IAS recurrence in both groups (P=0.046).
CONCLUSIONS: There was no significant difference in IAT and IAS rates between the S-ICD and TV-ICD in a conventional ICD population, but causes and predictors for IAT differed between the devices. After the first IAS, an intervention significantly reduced the recurrence rate of IAS.
REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01296022.

Gepubliceerd: Circ Arrhythm Electrophysiol. 2024;17(12):e012836.
Impact factor: 9.8 ; Q1

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30. Permanent pacemaker implantation after combined mitral- and tricuspid valve surgery: a nationwide multicentre study
Olsthoorn JR, Tjon Joek Tjien A, Heuts S, Bouwmeester S, Houterman S, Roefs MM, Koene B, Singh S, Boon R, Tonino P, Verberkmoes N, Cardiothoracic Surgery and Pacemaker/ICD Registration Committees of the Netherlands Heart Registration; Speekenbrink RGH.

OBJECTIVES: The threshold to perform concomitant tricuspid valve (TV) repair during primary mitral valve (MV) surgery has decreased, based on recent randomized evidence. Based on these developments, the indication for TV repair during MV surgery is expected to increase further. However, concerns have been raised regarding the risk of permanent pacemaker implantation (PPI) during a concomitant procedure. Therefore, we aim to assess the incidence of PPI in combined MV and TV surgery in a nationwide registry.
METHODS: The current study uniquely cross-linked the Cardiothoracic and Pacemaker/ICD registry of the Netherlands Heart Registration. Patients undergoing primary MV and TV surgery (± atrial septal defect closure, rhythm surgery, coronary artery bypass grafting) between 1 January and 31 December2021 were included. The primary outcome was PPI within 30 days after surgery. Subgroup analyses were performed for isolated MV and TV surgery and MV repair. The association between concomitant TV surgery and PPI was assessed using multivariable binary logistic regression analyses.
RESULTS: A total of 1060 patients (n = 833 MV, n = 227 MV + TV) were included. The overall incidence of PPI was 4.3%. No significant difference in PPI between MV and MV + TV surgery were found (3.7% vs 6.6%, P = 0.06). Concomitant TV surgery was not an independent risk factor for PPI after surgery after adjustment for covariates. These results were robust after sensitivity analyses.
CONCLUSIONS: The current study was not able to find a statistical difference between the PPI rate in MV surgery patients and MV + TV surgery patients. Extension of the waiting period prior to PPI, may result in decreased PPI rates.

Gepubliceerd: Eur J Cardiothorac Surg. 2024;66(4).
Impact factor: 3.0 ; Q2

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31. Invasiveness of previous treatment for peripheral arterial disease and risk of adverse cardiac events after coronary stenting
Pinxterhuis TH, von Birgelen C, Geelkerken RH, Doggen CJM, Menting TP, van Houwelingen KG, Linssen GCM, Ploumen EH.

Patients with peripheral arterial disease (PADs), undergoing percutaneous coronary intervention (PCI), have higher adverse event risks. The effect of invasiveness of PADs treatment on PCI outcome is unknown. This study assessed the impact of the invasiveness of previous PADs treatment (invasive or non-invasive) on event risks after PCI with contemporary drug-eluting stents. This post-hoc analysis pooled 3-year patient-level data of PCI all-comer patients living in the eastern Netherlands, previously treated for PADs. PADs included symptomatic atherosclerotic lesion in the lower or upper extremities; carotid or vertebral arteries; mesenteric arteries or aorta. Invasive PADs treatment comprised endarterectomy, bypass surgery, percutaneous transluminal angioplasty, stenting or amputation; non-invasive treatment consisted of medication and participation in exercise programs. Primary endpoint was (coronary) target vessel failure: composite of cardiac mortality, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. Of 461 PCI patients with PADs, information on PADs treatment was available in 357 (77.4%) patients; 249 (69.7%) were treated invasively and 108 (30.3%) non-invasively. Baseline and PCI procedural characteristics showed no between-group difference. Invasiveness of PADs treatment was not associated with adverse event risks, including target vessel failure (20.5% vs. 16.0%; HR: 1.30, 95%-CI 0.75-2.26, p = 0.35), major adverse cardiac events (23.3% vs. 20.4%; HR: 1.16, 95%-CI 0.71-1.90, p = 0.55), and all-cause mortality (12.1% vs. 8.3%; HR: 1.48, 95%-CI 0.70-3.13, p = 0.30). In PADs patients participating in PCI trials, we found no significant relation between the invasiveness of previous PADs treatment and 3-year outcome after PCI. Consequently, high-risk PCI patients can be identified by consulting medical records, searching for PADs, irrespective of the invasiveness of PADs treatment.

Gepubliceerd: Cardiovasc Interv Ther. 2024;39(2):173-82.
Impact factor: 5.8 ; Q1

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32. Ethnic minorities treated with new-generation drug-eluting coronary stents in two European randomised clinical trials
Ploumen EH, Semedo E, Doggen CJM, Schotborgh CE, Anthonio RL, Danse PW, Benit E, Aminian A, Stoel MG, Hartmann M, van Houwelingen KG, Scholte M, Roguin A, Linssen GCM, Zocca P, von Birgelen C.

BACKGROUND: Several ethnic minorities have an increased risk of cardiovascular events, but previous European trials that investigated clinical outcome after coronary stenting did not assess the patients' ethnic background.
AIMS: To compare ethnic minority and Western European trial participants in terms of both cardiovascular risk profile and 1-year clinical outcome after percutaneous coronary intervention.
METHODS: In the BIO-RESORT and BIONYX randomised trials, which assessed new-generation drug-eluting stents, information on patients' self-reported ethnic background was prospectively collected. Pooled patient-level data of 5803 patients, enrolled in the Netherlands and Belgium, were analysed in this prespecified analysis. The main endpoint was target vessel failure after 1 year.
RESULTS: Patients were classified as belonging to an ethnic minority (n = 293, 5%) or of Western European origin (n = 5510, 95%). Follow-up data were available in 5772 of 5803 (99.5%) patients. Ethnic minority patients were younger, less often female, more often current smokers, more often medically treated for diabetes, and more often had a positive family history of coronary artery disease. The main endpoint target vessel failure did not differ between ethnic minority and Western European patients (3.5% vs 4.9%, hazard ratio 0.71, 95% confidence interval 0.38-1.33; p = 0.28). There was also no difference in mortality, myocardial infarction, and repeat revascularisation rates.

CONCLUSIONS: Despite the unfavourable cardiovascular risk profile of ethnic minority patients, short-term clinical outcome after treatment with contemporary drug-eluting stents was highly similar to that in Western European patients. Further efforts should be made to ensure the enrolment of more ethnic minority patients in future coronary stent trials.

Gepubliceerd: Neth Heart J. 2024;32(6):254-61.
Impact factor: 2.0 ; Q3

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33. Hospital infections and health-related quality of life after cardiac surgery: a multicenter survey
Rijnhart-de Jong HG, Haenen J, Porta F, Timmermans M, Boerma EC, de Jong K, participating centers of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration; Speekenbrink RGH.

BACKGROUND: Recent research suggested that hospital infections are a predictive marker for physical non-recovery one year after cardiothoracic surgery. The purpose of this study was to explore whether this risk factor is etiologic. Additional, the influence of a potential effect modifying factor, diabetes mellitus, was investigated.
METHODS: In this multicenter study, patients underwent elective or urgent cardiothoracic surgery between 01-01-2015 and 31-12-2019, and completed pre- and one year post-operative Short Form Health Survey 36/12 quality of life questionnaires. A binary logistic regression model, in which the inverse of the propensity score for infection risk was included as a weight variable, was used. Second, this analysis was stratified for diabetes mellitus status.
RESULTS: 8577 patients were included. After weighing for the propensity score, the standardized mean differences of all variables decreased and indicated sufficient balance between the infection and non-infection groups. Hospital infections were found to be a risk factor for non-recovery after cardiothoracic surgery in the original and imputed dataset before weighting. However, after propensity score weighing, hospital infections did not remain significantly associated with recovery (OR for recovery = 0.79; 95% CI [0.60-1.03]; p = 0.077). No significant interaction between diabetes mellitus and hospital infections on recovery was found (p = 0.845).
CONCLUSIONS: This study could not convincingly establish hospital infections as an etiologic risk factor for non-improvement of physical recovery in patients who underwent cardiothoracic surgery. In addition, there was no differential effect of hospital infections on non-improvement of physical recovery for patients with and without diabetes mellitus. Trial registration International Clinical Trials Registry Platform ID NL9818; date of registration, 22-10-2021 (https://trialsearch.who.int/).

Gepubliceerd: J Cardiothorac Surg. 2024;19(1):84.
Impact factor: 1.5 ; Q3

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34. The effectiveness of coronary computed tomography angiography and functional testing for the diagnosis of obstructive coronary artery disease: results from the individual patient data Collaborative Meta-Analysis of Cardiac CT (COME-CCT)
Schlattmann P, Wieske V, Bressem KK, Götz T, Schuetz GM, Andreini D, Pontone G, Alkadhi H, Hausleiter J, Zimmermann E, Gerber B, Shabestari AA, Meijs MFL, Sato A, Øvrehus KA, Jenkins SMM, Knuuti J, Hamdan A, Halvorsen BA, Mendoza-Rodriguez V, Rixe J, Wan YL, Langer C, Leschka S, Martuscelli E, Ghostine S, Tardif JC, Sánchez AR, Haase R, Dewey M.

AIM: To determine the effectiveness of functional stress testing and computed tomography angiography (CTA) for diagnosis of obstructive coronary artery disease (CAD).

METHODS AND RESULTS: Two-thousand nine-hundred twenty symptomatic stable chest pain patients were included in the international Collaborative Meta-Analysis of Cardiac CT consortium to compare CTA with exercise electrocardiography (exercise-ECG) and single-photon emission computed tomography (SPECT) for diagnosis of CAD defined as ≥ 50% diameter stenosis by invasive coronary angiography (ICA) as reference standard. Generalised linear mixed models were used for calculating the diagnostic accuracy of each diagnostic test including non-diagnostic results as dependent variables in a logistic regression model with random intercepts and slopes. Covariates were the reference standard ICA, the type of diagnostic method, and their interactions. CTA showed significantly better diagnostic performance ($p < 0.0001$) with a sensitivity of 94.6% (95% CI 92.7-96) and a specificity of 76.3% (72.2-80) compared to exercise-ECG with 54.9% (47.9-61.7) and 60.9% (53.4-66.3), SPECT with 72.9% (65-79.6) and 44.9% (36.8-53.4), respectively. The positive predictive value of CTA was ≥ 50% in patients with a clinical pretest probability of 10% or more while this was the case for ECG and SPECT at pretest probabilities of ≥ 40 and 28%. CTA reliably excluded obstructive CAD with a post-test probability of below 15% in patients with a pretest probability of up to 74%.
CONCLUSION: In patients with stable chest pain, CTA is more effective than functional testing for the diagnosis as well as for reliable exclusion of obstructive CAD. CTA should become widely adopted in patients with intermediate pretest probability.
SYSTEMATIC REVIEW REGISTRATION: PROSPERO Database for Systematic Reviews-CRD42012002780.
CRITICAL RELEVANCE STATEMENT: In symptomatic stable chest pain patients, coronary CTA is more effective than functional testing for diagnosis and reliable exclusion of obstructive CAD in intermediate pretest probability of CAD.
KEY POINTS: Coronary computed tomography angiography showed significantly better diagnostic performance ($p < 0.0001$) for diagnosis of coronary artery disease compared to exercise-ECG and SPECT. The positive predictive value of coronary computed tomography angiography was ≥ 50% in patients with a clinical pretest probability of at least 10%, for ECG ≥ 40%, and for SPECT 28%. Coronary computed tomography angiography reliably excluded obstructive coronary artery disease with a post-test probability of below 15% in patients with a pretest probability of up to 74%.

Gepubliceerd: Insights Imaging. 2024;15(1):208.
Impact factor: 4.5 ; Q1

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35. Social media for cardiac imagers: a review
Schuuring MJ, Anwer S, Petersen SE, Moharem-Elgamal S, Muraru D.

Cardiac imaging plays a pivotal role in the diagnosis and management of cardiovascular diseases. In the burgeoning landscape of digital technology and social media platforms, it becomes essential for cardiac imagers to know how to effectively increase the visibility and the impact of their activity. With the availability of social sites like X (formerly Twitter), Instagram, and Facebook, cardiac imagers can now reach a wider audience and engage with peers, sharing their findings, insights, and discussions. The integration of persistent identifiers, such as digital object identifiers (DOIs), facilitates traceability and citation of cardiac imaging publications across various digital platforms, further enhancing their discoverability. To maximize visibility, practical advice is provided, including the use of visually engaging infographics and videos, as well as the strategic implementation of relevant hashtags and keywords. These techniques can significantly improve the discoverability of cardiac imaging research through search engine optimization and social media algorithms. Tracking impact and engagement is crucial in the digital age, and this review discusses various metrics and tools to gauge the reach and influence of cardiac imaging publications. This includes traditional citation-based metrics and altmetrics. Moreover, this review underscores the importance of creating and updating professional profiles on social platforms and participating in relevant scientific communities online. The adoption of digital technology, social platforms, and a strategic approach to publication sharing can empower

cardiac imaging professionals to enhance the visibility and impact of their research, ultimately advancing the field and improving patient care.

Gepubliceerd: Eur Heart J Cardiovasc Imaging. 2024;25(9):1177-82.
Impact factor: 6.6 ; Q1

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36. Digital solutions to optimize guideline-directed medical therapy prescription rates in patients with heart failure: a clinical consensus statement from the ESC Working Group on e-Cardiology, the Heart Failure Association of the European Society of Cardiology, the Association of Cardiovascular Nursing & Allied Professions of the European Society of Cardiology, the ESC Digital Health Committee, the ESC Council of Cardio-Oncology, and the ESC Patient Forum
Schuuring MJ, Treskes RW, Castiello T, Jensen MT, Casado-Arroyo R, Neubeck L, Lyon AR, Keser N, Rucinski M, Marketou M, Lambrinou E, Volterrani M, Hill L.

The 2021 European Society of Cardiology guideline on diagnosis and treatment of acute and chronic heart failure (HF) and the 2023 Focused Update include recommendations on the pharmacotherapy for patients with New York Heart Association (NYHA) class II-IV HF with reduced ejection fraction. However, multinational data from the EVOLUTION HF study found substantial prescribing inertia of guideline-directed medical therapy (GDMT) in clinical practice. The cause was multifactorial and included limitations in organizational resources. Digital solutions like digital consultation, digital remote monitoring, digital interrogation of cardiac implantable electronic devices, clinical decision support systems, and multifaceted interventions are increasingly available worldwide. The objectives of this Clinical Consensus Statement are to provide (i) examples of digital solutions that can aid the optimization of prescription of GDMT, (ii) evidence-based insights on the optimization of prescription of GDMT using digital solutions, (iii) current evidence gaps and implementation barriers that limit the adoption of digital solutions in clinical practice, and (iv) critically discuss strategies to achieve equality of access, with reference to patient subgroups. Embracing digital solutions through the use of digital consults and digital remote monitoring will future-proof, for example alerts to clinicians, informing them of patients on suboptimal GDMT. Researchers should consider employing multifaceted digital solutions to optimize effectiveness and use study designs that fit the unique sociotechnical aspects of digital solutions. Artificial intelligence solutions can handle larger data sets and relieve medical professionals' workloads, but as the data on the use of artificial intelligence in HF are limited, further investigation is warranted.

Gepubliceerd: Eur Heart J Digit Health. 2024;5(6):670-82.
Impact factor: 4.4 ; Q1

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37. Three-Dimensional Heart Modeling of Hypertrophic Obstructive Cardiomyopathy for In Situ Patient-Specific Simulation to Optimize Septal Myectomy
Smits KC, Speekenbrink RGH, Hekman EEG, Koenrades MA, Heeringa TJP, Arens J, Halfwerk FR.

OBJECTIVE: Hypertrophic obstructive cardiomyopathy (HOCM) develops in at least 1 out of 715 young adults. Patients who are refractory to medical therapy qualify for septal myectomy. Due to anatomy, serious complications such as ventricular septal defect and heart block may occur. Establishing cardiovascular magnetic resonance (CMR)-based 3-dimensional (3D) models as part of preoperative planning and training has the potential to decrease procedure-related complications and improve results.
METHODS: CMR images were used to segment cardiac structures. Left ventricular wall thickness was calculated and projected on top of the in silico model. A 3D model was printed with a red layer

indicating a wall thickness exceeding 15 mm and used for preoperative resection planning and patient counseling. To provide preoperative patient-specific in situ simulation, the planned resection volume was replaced with silicone in a second model. For perioperative quality control, resected silicone was compared with resected myocardial tissue. The impact of the models was evaluated descriptively through consultation of both the cardiothoracic surgeon and patients and through patient outcomes.
RESULTS: Three-dimensional in silico and 3D-printed heart models of 5 patients were established preoperatively. Since the introduction of the models in October 2020, the surgeon feels better prepared, more confident, and less difficulty with making decisions. In addition, patients feel better informed preoperatively.
CONCLUSIONS: Using 3D heart models optimized preoperative planning and training, intraoperative quality control, and patient consultation. Reduction of procedure-related complications and clinical outcome should be studied in larger cohorts.

Gepubliceerd: Innovations (Phila). 2024;19(5):532-40.
Impact factor: 1.6 ; Q2

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38. A Nationwide Study on Mitral Valve Repair vs Replacement for Active Endocarditis
Tomšič A, de Weger A, van der Stoel M, Klautz RJM, Palmen M, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration; Speekenbrink RGH.

BACKGROUND: Real-world evidence supporting the reproducibility and superiority of valve repair over replacement in active mitral valve infective endocarditis is lacking.
METHODS: Data from a prospective nationwide database, including all cardiac surgical procedures in The Netherlands, were used. Adult patients undergoing primary mitral valve intervention who had a diagnosis of active infective endocarditis and who underwent surgery between 2013 and 2020 were included. Survival analysis was performed for the whole follow-up period as well as after applying the landmark of 90 days.
RESULTS: Of 715 patients who met the inclusion criteria, 294 (41.1%) underwent valve repair. Mitral valve repair rates decreased slightly over the course of the study. The early mortality rate was 13.0%, and a trend of steadily declining early mortality rates over the course of the study, despite a steady increase in patient complexity, was observed. On risk-adjusted analysis, mitral valve replacement demonstrated inferior results when compared with valve repair (adjusted hazard ratio, 2.216; 95% CI, 1.425-3.448; P < .001), even after a landmark analysis was performed (adjusted hazard ratio 2.489; 95% CI, 1.124-5.516; P = .025). These results were confirmed by a propensity score-adjusted analysis (adjusted hazard ratio 2.251; 95% CI, 1.029-4.21; P = .042).
CONCLUSIONS: Contemporary trends in mitral valve surgery for active infective endocarditis suggest growing patient complexity but slightly declining early mortality rates. A trend of decreasing mitral valve repair rates was seen. The results of this study suggest improved late outcomes of valve repair compared with valve replacement.

Gepubliceerd: Ann Thorac Surg. 2024;117(1):120-6.
Impact factor: 3.9 ; Q1

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39. Event Prediction in HFpEF Using Machine Learning: Will This Promising Model Be Applied in Practice?
Valk JG, John A, Schuuring MJ.

Gepubliceerd: JACC Asia. 2024;4(12):969-71.
Impact factor onbekend

40. The impact of patient-reported frailty on cardiovascular outcomes in elderly patients after non-ST-acute coronary syndrome

van den Broek WWA, Gimbel ME, Hermanides RS, Runnett C, Storey RF, Knaapen P, Emans ME, Oemrawsingh RM, Cooke J, Galasko G, Walhout R, Stoel MG, von Birgelen C, van Bergen P, Brinckman SL, Aksoy I, Liem A, Van't Hof AWJ, Jukema JW, Heestermans A, Nicastia D, Alber H, Austin D, Nasser A, Deneer V, Ten Berg JM.

BACKGROUND: As life expectancy increases, the population of older individuals with coronary artery disease and frailty is growing. We aimed to assess the impact of patient-reported frailty on the treatment and prognosis of elderly early survivors of non-ST-elevation acute coronary syndrome (NSTE-ACS).
METHODS: Frailty data were obtained from two prospective trials, POPular Age and the POPular Age Registry, which both assessed elderly NSTE-ACS patients. Frailty was assessed one month after admission with the Groningen Frailty Indicator (GFI) and was defined as a GFI-score of 4 or higher. In these early survivors of NSTE-ACS, we assessed differences in treatment and 1-year outcomes between frail and non-frail patients, considering major adverse cardiovascular events (MACE, including cardiovascular mortality, myocardial infarction, and stroke) and major bleeding.
RESULTS: The total study population consisted of 2192 NSTE-ACS patients, aged ≥70 years. The GFI-score was available in 1320 patients (79 ± 5 years, 37% women), of whom 712 (54%) were considered frail. Frail patients were at higher risk for MACE than non-frail patients (9.7% vs. 5.1%, adjusted hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.01-2.43, p = 0.04), but not for major bleeding (3.7% vs. 2.8%, adjusted HR 1.23, 95% CI 0.65-2.32, p = 0.53). Cubic spline analysis showed a gradual increase of the risk for clinical outcomes with higher GFI-scores.
CONCLUSIONS: In elderly NSTE-ACS patients who survived 1-month follow-up, patient-reported frailty was independently associated with a higher risk for 1-year MACE, but not with major bleeding. These findings emphasize the importance of frailty screening for risk stratification in elderly NSTE-ACS patients.

Gepubliceerd: Int J Cardiol. 2024;405:131940.
Impact factor: 3.2 ; Q2

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41. Routine transthoracic echocardiography in ischaemic stroke or transient ischaemic attack of undetermined cause: a prospective multicentre study

van der Maten G, Meijs MFL, Timmer JR, Brouwers P, von Birgelen C, Coutinho JM, Bouma BJ, Kerkhoff H, Helming AM, van Tuijl JH, van der Meer NA, Saxena R, Ebink C, van der Palen J, den Hertog HM.

BACKGROUND: Guidelines recommend routine transthoracic echocardiography (TTE) after ischaemic stroke or transient ischaemic attack of undetermined cause; yet, only limited scientific evidence exists. Therefore, we aimed to determine in these patients the prevalence of TTE-detected major cardiac sources of embolism (CSE), which are abnormalities leading to therapeutic changes.
METHODS: Six Dutch hospitals conducted a prospective observational study that enrolled patients with ischaemic stroke or transient ischaemic attack of undetermined cause. Patients underwent TTE after comprehensive diagnostic evaluation on stroke units, including blood chemistry, 12-lead electrocardiogram (ECG), ≥ 24 h continuous ECG monitoring, brain imaging and cervical artery imaging. Primary outcome measure was the proportion of patients with TTE-detected major CSE.
RESULTS: From March 2018 to October 2020, 1084 patients, aged 66.6 ± 12.5 years, were enrolled; 456 (42.1%) patients were female and 869 (80.2%) had ischaemic stroke. TTE detected major CSE in

only 11 (1.0%) patients. Ten (90.9%) of these patients also had major ECG abnormalities (previous infarction, major repolarisation abnormalities, or previously unknown left bundle branch block) that would have warranted TTE assessment regardless of stroke evaluation. Such ECG abnormalities were present in 11.1% of the total study population. A single patient (0.1%) showed a major CSE despite having no ECG abnormality.
CONCLUSIONS: This multicentre cross-sectional study in patients who-after workup on contemporary stroke units-were diagnosed with ischaemic stroke or transient ischaemic attack of undetermined cause found TTE-detected major CSE in only 1% of all patients. Most of these patients also had major ECG abnormalities. These findings question the value of routine TTE assessment in this clinical setting.

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Impact factor: 2.0 ; Q3

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42. Cost-effectiveness analysis of transthoracic echocardiographic assessment in patients with ischemic stroke or TIA of undetermined cause
van der Maten G, Pouwels X, Meijs MFL, von Birgelen C, den Hertog HM, Koffijberg H.

BACKGROUND: The multicenter ATTEST study recently assessed 1084 patients with ischemic stroke or transient ischemic attack (TIA) of undetermined cause and found that routine transthoracic echocardiography (TTE) detects abnormalities with treatment implications (i.e., major cardiac sources of embolism) in only 1 % of patients, of whom most (91 %) also had major electrocardiographic (ECG)-abnormalities. In this study, we performed a cost-effectiveness analysis of different TTE strategies.
METHODS: We compared the cost-effectiveness of three strategies of TTE assessment: (1) TTE in all patients; (2) TTE only in patients with major ECG-abnormalities; and (3) TTE not performed. Input data were derived from ATTEST and systematic literature reviews. A Markov model was developed that simulated recurrent ischemic stroke or TIA and intracranial and gastro-intestinal bleeding complications in patients with ischemic stroke or TIA of undetermined cause. Primary outcome was the additional costs per additional quality-adjusted life-year (QALY) from a Dutch societal perspective.
RESULTS: Performing TTE only in patients with major ECG-abnormalities led to 0.0083 additional QALYs and €108 additional costs per patient as compared with not performing TTE (€12,987/QALY). Performing TTE in all patients resulted in 0.0005 additional QALYs and €422 additional costs per patient as compared with performing TTE only in case of major ECG-abnormalities (€805,336/QALY).
CONCLUSIONS: In patients with ischemic stroke or TIA of undetermined cause, a strategy of performing TTE only in patients who also had major ECG-abnormalities resulted in the most favorable ratio of additional costs per additional QALY. This supports performing TTE only in patients, who also have major ECG-abnormalities.

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Impact factor: 1.8 ; Q3

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43. Percutaneous left stellate ganglion block for refractory ventricular tachycardia in structural heart disease: our single-centre experience
van der Pas VR, van Opstal JM, Scholten MF, Monteiro de Oliveira NP, Speekenbrink RGH, van Dessel P.

INTRODUCTION: When electrical storm (ES) is amenable to neither antiarrhythmic drugs, nor deep sedation or catheter ablation, autonomic modulation may be considered. We report our experience

with percutaneous left stellate ganglion block (PSGB) to temporarily suppress refractory ventricular arrhythmia (VA) in patients with structural heart disease.
METHODS: A retrospective analysis was performed at our institution of patients with structural heart disease and an implantable cardioverter defibrillator (ICD) who had undergone PSGB for refractory VA between January 2018 and October 2021. The number of times antitachycardia pacing (ATP) was delivered and the number of ICD shocks/external cardioversions performed in the week before and after PSGB were evaluated. Charts were checked for potential complications. RESULTS: Twelve patients were identified who underwent a combined total of 15 PSGB and 5 surgical left cardiac sympathetic denervation procedures. Mean age was 73 ± 5.8 years and all patients were male. Nine of 12 (75%) had ischaemic cardiomyopathy, with the remainder having non-ischaemic dilated cardiomyopathy. Mean left ventricular ejection fraction was 35% (± 12.2%). Eight of 12 (66.7%) patients were already being treated with both amiodarone and beta-blockers. The reduction in ATP did not reach statistical significance (p = 0.066); however, ICD shocks (p = 0.028) and ATP/shocks combined were significantly reduced (p = 0.04). At our follow-up electrophysiology meetings PSGB was deemed ineffective in 4 of 12 patients (33%). Temporary anisocoria was seen in 2 of 12 (17%) patients, and temporary hypotension and hoarseness were reported in a single patient. DISCUSSION: In this limited series, PSGB showed promise as a method for temporarily stabilising refractory VA and ES in a cohort of male patients with structural heart disease. The side effects observed were mild and temporary.

Gepubliceerd: Neth Heart J. 2024;32(7-8):283-9.
Impact factor: 2.0 ; Q3

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44. Cardioversion strategy impacts rate control during recurrences in patients with paroxysmal atrial fibrillation: A subanalysis of the RACE 7 ACWAS trial
van der Velden RMJ, Pluymaekers N, Dudink E, Luermans J, Meeder JG, Heesen WF, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, van Opstal JM, Kirchhof C, van Dijk VF, Swart HP, Alings M, Van Gelder IC, Crijns H, Linz D.

BACKGROUND: In the Rate Control versus Electrical Cardioversion Trial 7-Acute Cardioversion versus Wait and See, patients with recent-onset atrial fibrillation (AF) were randomized to either early or delayed cardioversion.
AIM: This prespecified sub-analysis aimed to evaluate heart rate during AF recurrences after an emergency department (ED) visit identified by an electrocardiogram (ECG)-based handheld device.
METHODS: After the ED visit, included patients (n = 437) were asked to use an ECG-based handheld device to monitor for recurrences during the 4-week follow-up period. 335 patients used the handheld device and were included in this analysis. Recordings from the device were collected and assessed for heart rhythm and rate. Optimal rate control was defined as a target resting heart rate of <110 beats per minute (bpm).
RESULTS: In 99 patients (29.6%, mean age 67 ± 10 years, 39.4% female, median 6 [3-12] AF recordings) a total of 314 AF recurrences (median 2 [1-3] per patient) were identified during follow-up. The average median resting heart rate at recurrence was 100 ± 21 bpm in the delayed vs 112 ± 25 bpm in the early cardioversion group (p = .011). Optimal rate control was seen in 68.4% [21.3%-100%] and 33.3% [0%-77.5%] of recordings (p = .01), respectively. Randomization group [coefficient -12.09 (-20.55 to -3.63, p = .006) for delayed vs. early cardioversion] and heart rate on index ECG [coefficient 0.46 (0.29-0.63, p < .001) per bpm increase] were identified on multivariable analysis as factors associated with lower median heart rate during AF recurrences.
CONCLUSION: A delayed cardioversion strategy translated into a favorable heart rate profile during AF recurrences.

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Impact factor: 2.3 ; Q2

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45. ECMOve: A Mobilization Device for Extracorporeal Membrane Oxygenation Patients
van Galen DJM, Meinders Q, Halfwerk FR, Arens J.

Extracorporeal membrane oxygenation (ECMO) is a temporary lifesaving treatment for critically ill patients with severe respiratory or cardiac failure. Studies demonstrated the feasibility of in-hospital mobilizing during and after ECMO treatment preventing neuromuscular weakness and impaired physical functioning. Despite more compact mobile ECMO devices, implementation of ambulatory ECMO remains labor-intensive, complex, and challenging. It requires a large multidisciplinary team to carry equipment, monitor and physically support the patient, and to provide a back-up wheelchair in case of fatigue. Moreover, there is no adequate solution to ensure the stability of the patient's cannula and circuit management during ambulation. We developed a system contributing to improvement and innovation of current ambulatory ECMO patient programs. Our modular cart-in-cart system carries necessary ECMO equipment, features an extendable walking frame, and contains a folding seat for patient transport. An adjustable shoulder brace with lockable tubing-connectors enables safe fixation of the blood tubing. ECMOve provides safety, support, and accessibility while performing ambulatory ECMO for both patient and caregiver. Prototype evaluation in a simulated intensive care unit showed feasibility of our design, but needs to be evaluated in clinical care.

Gepubliceerd: Asaio j. 2024;70(5):377-86.
Impact factor: 2.3 ; Q2

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46. Final 5-year report of BIONYX comparing the thin-composite wire-strut zotarolimus-eluting stent versus ultrathin-strut sirolimus-eluting stent
van Vliet D, Ploumen EH, Pinxterhuis TH, Buiten RA, Aminian A, Schotborgh CE, Danse PW, Roguin A, Anthonio RL, Benit E, Zocca P, Doggen CJM, von Birgelen C.

BACKGROUND: The BIONYX randomized trial is the first study to evaluate the Resolute Onyx durable polymer-coated zotarolimus-eluting stent (ZES) in all-comers. Furthermore, it is the first trial to assess safety and efficacy of this stent versus the Orsiro biodegradable-polymer sirolimus-eluting stent (SES) in all-comers, paying particular attention to patients with diabetes. It has previously shown promising results until 3 years of follow-up. AIMS: We aimed to assess long-term clinical outcome after percutaneous coronary intervention (PCI) with Onyx ZES versus Orsiro SES at 5-year follow-up.
METHODS: The main composite endpoint was target vessel failure (TVF): cardiac death, target vessel myocardial infarction, or target vessel revascularization. Time to primary and secondary endpoints was assessed using Kaplan-Meier methods, applying the log-rank test for between-group comparison.
RESULTS: Follow-up was available in 2414/2488 (97.0%) patients. After 5 years, TVF showed no significant difference between Onyx ZES and Orsiro SES (12.7% vs. 13.7%, hazard ratio [HR] 0.94, 95% confidence interval [CI] [0.75-1.17], p(log-rank) = 0.55). Landmark analysis between 3- and 5-year follow-up found a lower target lesion revascularization rate for Onyx ZES (1.1% vs. 2.4%, HR 0.47, 95% CI [0.24-0.93], p(log-rank) = 0.026). A prespecified subgroup analysis showed no significant between-stent difference in clinical outcome among patients with diabetes. After treatment with Onyx ZES, patients aged ≥75 years had significantly lower rates of TVF (13.8% vs. 21.9%, HR 0.60, 95% CI [0.39-0.93], p(log-rank) = 0.023).
CONCLUSIONS: The final 5-year analysis of the randomized BIONYX trial showed favorable and similar long-term outcomes of safety and efficacy for Onyx ZES and Orsiro SES in both all-comers and patients with diabetes.

Gepubliceerd: Catheter Cardiovasc Interv. 2024;104(1):1-9.
Impact factor: 1.9 ; Q3

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47. Mitral annular disjunction in idiopathic ventricular fibrillation patients: just a bystander or a potential cause?
Verheul LM, Guglielmo M, Groeneveld SA, Kirkels FP, Scrocco C, Cramer MJ, Bootsma M, Kapel GFL, Alings M, Evertz R, Mulder BA, Prakken NHJ, Balt JC, Volders PGA, Hirsch A, Yap SC, Postema PG, Nijveldt R, Velthuis BK, Behr ER, Wilde AAM, Hassink RJ.

AIMS: Previously, we demonstrated that inferolateral mitral annular disjunction (MAD) is more prevalent in patients with idiopathic ventricular fibrillation (IVF) than in healthy controls. In the present study, we advanced the insights into the prevalence and ventricular arrhythmogenicity by inferolateral MAD in an even larger IVF cohort.
METHODS AND RESULTS: This retrospective multi-centre study included 185 IVF patients [median age 39 (27, 52) years, 40% female]. Cardiac magnetic resonance images were analyzed for mitral valve and annular abnormalities and late gadolinium enhancement. Clinical characteristics were compared between patients with and without MAD. MAD in any of the 4 locations was present in 112 (61%) IVF patients and inferolateral MAD was identified in 24 (13%) IVF patients. Mitral valve prolapse (MVP) was found in 13 (7%) IVF patients. MVP was more prevalent in patients with inferolateral MAD compared with patients without inferolateral MAD (42 vs. 2%, $P < 0.001$). Pro-arrhythmic characteristics in terms of a high burden of premature ventricular complexes (PVCs) and non-sustained ventricular tachycardia (VT) were more prevalent in patients with inferolateral MAD compared to patients without inferolateral MAD (67 vs. 23%, $P < 0.001$ and 63 vs. 41%, $P = 0.046$, respectively). Appropriate implantable cardioverter defibrillator therapy during follow-up was comparable for IVF patients with or without inferolateral MAD (13 vs. 18%, $P = 0.579$).
CONCLUSION: A high prevalence of inferolateral MAD and MVP is a consistent finding in this large IVF cohort. The presence of inferolateral MAD is associated with a higher PVC burden and non-sustained VTs. Further research is needed to explain this potential interplay.

Gepubliceerd: Eur Heart J Cardiovasc Imaging. 2024;25(6):764-70.
Impact factor: 6.6 ; Q1

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48. Body mass index and pulmonary vein isolation: real-world data on outcomes and quality of life
Vermeer J, Houterman S, Medendorp N, van der Voort P, Dekker L, Ablation Registration Committee of the Netherlands Heart Registration; van Dessel PFHM.

AIMS: Increasing numbers of overweight and obese patients undergo pulmonary vein isolation (PVI), despite the association between higher body mass index (BMI) and adverse PVI outcomes. Evidence on complications and quality of life in different bodyweight groups is limited. This study aims to clarify the impact of BMI on repeat ablations, periprocedural complications, and changes in quality of life.
METHODS AND RESULTS: This multi-centre study analysed prospectively collected data from 15 ablation centres, covering all first-time PVI patients in the Netherlands from 2015 to 2021. Patients were categorized by BMI: normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), and obesity (≥30 kg/m2). Quality of life was assessed using the Atrial Fibrillation Effect on QualiTy-of-life questionnaire at baseline and 1-year post-PVI. Among 20 725 patients, 30% were of normal weight, 47% overweight, and 23% obese. Within the first year after PVI, obese patients had a higher incidence of repeat ablations than normal-weighing and overweight patients (17.8 vs. 15.6 and 16.1%, $P < 0.05$). Obesity was independently associated with repeat ablations (odds ratio 1.15; 95%

confidence interval 1.01-1.31, P = 0.03). This association remained apparent after 3 years. Complication rates were 3.8% in normal weight, 3.0% in overweight, and 4.6% in obese, with weight class not being an independent predictor. Quality of life improved in all weight groups post-PVI but remained lowest in obese patients.
CONCLUSION: Obesity is independently associated with a higher rate of repeat ablations. Pulmonary vein isolation is equally safe in all weight classes. Despite lower quality of life among obese individuals, substantial improvements occur for all weight groups after PVI.

Gepubliceerd: Europace. 2024;26(6).
Impact factor: 7.4 ; Q1

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49. Intra- and interobserver reliability in measuring aortic root rotation with cardiac magnetic resonance imaging
Voortman M, Fitski W, van Es J, Doggen CJM, Plonek T, von Birgelen C, Wagenaar LJ.

BACKGROUND: The rotational position of the aortic root (AoR) is of substantial clinical interest as it has been associated with severe aortic complications, such as aortic dissections. We described a cardiac magnetic resonance (CMR)-based method for measuring AoR rotation and evaluated the reliability of measurements.
METHODS: CMR was used for measuring AoR rotation in 50 consecutive healthy subjects. Intra- and interobserver reliability were assessed by comparing repeated measurements by the same analyst and by three independent analysts. The angles of the non-coronary sinus (NCS), right coronary sinus (RCS), and left coronary sinus (LCS) were measured relative to the interatrial septum (IAS). The angle between IAS and posterior atrial wall was measured to examine the reliability of the IAS as a key anatomical landmark. Intra- and interobserver agreement were determined using intraclass correlation coefficients (ICCs).
RESULTS: Images of 47/50 (94%) subjects were analyzed; three were excluded due to insufficient image quality. The mean ± standard deviation (SD) AoR rotation angles of NCS, RCS, and LCS were 25.9°±12.9°, 37.5°±15.2°, and 97.0°±13.1°, respectively. For measurements of AoR rotation, both intraobserver [NCS: ICC =0.94, 95% confidence interval (CI): 0.88-0.96; RCS: ICC =0.93, 95% CI: 0.87-0.96; LCS: ICC =0.91, 95% CI: 0.84-0.95] and interobserver agreement (NCS: ICC =0.90, 95% CI: 0.84-0.94; RCS: ICC =0.86, 95% CI: 0.77-0.92; LCS: ICC =0.87, 95% CI: 0.80-0.92) were excellent. The IAS angle was 79.2°±8.9°; its intraobserver agreement was somewhat higher (ICC =0.94, 95% CI: 0.88-0.96) than the interobserver agreement (ICC =0.76, 95% CI: 0.63-0.85).
CONCLUSIONS: The present study in healthy subjects reports a CMR-based approach for measuring AoR rotation. CMR allows to quantify AoR rotation with excellent intra- and interobserver agreement.

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Impact factor: 2.1 ; Q3

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50. Rationale and design of the STOP-IMH randomised trial: Safety of ticagrelor monotherapy after primary percutaneous coronary intervention for ST-elevation myocardial infarction and the effect on intramyocardial haemorrhage
Woelders ECI, Yosofi B, Peeters DAM, Konijnenberg LSF, von Birgelen C, van Rees JB, van den Oord SCH, Heestermans A, Claessen B, van Royen N, van Geuns RJM, Nijveldt R, Damman P.

BACKGROUND: Ticagrelor monotherapy after 1-3 months of dual antiplatelet therapy (DAPT) has shown to be effective and safe after percutaneous coronary intervention (PCI), including in patients with an ST elevation myocardial infarction (STEMI). Direct omission of aspirin could further reduce

bleeding complications and may reduce the incidence and expansion of intramyocardial haemorrhage (IMH), a frequent complication after revascularisation for a STEMI.
METHODS: This multicentre open label pilot study randomises 200 STEMI patients within 24 hours after primary PCI and before the first subsequent dose of aspirin to ticagrelor monotherapy or ticagrelor plus aspirin for twelve months. As IMH is more frequently observed after an anterior STEMI, IMH and infarct size will be determined with cardiac magnetic resonance (CMR) imaging in 60 anterior STEMI patients. In this subgroup, blood samples will be analysed for biochemical outcomes.
RESULTS: The primary safety endpoint consists of major adverse cardiac and cerebral events, and the primary efficacy endpoint is infarct size on CMR. Secondary efficacy endpoints consist of the incidence and extent of IMH determined by CMR, and of clinical bleeding events. Other endpoints include all-cause mortality and biochemical outcomes.
CONCLUSION: The STOP-IMH pilot study compares ticagrelor monotherapy with ticagrelor plus aspirin directly after primary PCI in 200 STEMI patients. We aim to provide a signal of safety regarding ischemic events for the direct omission of aspirin after primary PCI, and to compare the infarct size by CMR between the two treatment strategies in the first week after primary PCI.

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Impact factor: 2.5 ; Q2

Totale impact factor: 469.0
Gemiddelde impact factor: 9.4

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 19
Totale impact factor: 164.6
Gemiddelde impact factor: 8.7

Urologie

1. The psychosocial impact of prostate cancer screening for BRCA1 and BRCA2 carriers
Bancroft EK, Page EC, Brook MN, Pope J, Thomas S, Myhill K, Helfand BT, Talaty P, Ong KR, Douglas E, Cook J, Rosario DJ, Salinas M, Buys SS, Anson J, Davidson R, Longmuir M, Side L, Eccles DM, Tischkowitz M, Taylor A, Cruellas M, Ballestero EP, Cleaver R, Varughese M, Barwell J, LeButt M, Greenhalgh L, Hart R, Azzabi A, Jobson I, Cogley L, Evans DG, Rothwell J, Taylor N, Hogben M, Saya S, Eeles RA, Aaronson NK, IMPACT Study Steering Committee and IMPACT Collaborators; Asselman M.

OBJECTIVES: To report the long-term outcomes from a longitudinal psychosocial study that forms part of the 'Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted Screening in men at higher genetic risk and controls' (IMPACT) study. The IMPACT study is a multi-national study of targeted prostate cancer (PrCa) screening in individuals with a known germline pathogenic variant (GPV) in either the BReast CAncer gene 1 (BRCA1) or the BReast CAncer gene 2 (BRCA2).
SUBJECTS AND METHODS: Participants enrolled in the IMPACT study were invited to complete a psychosocial questionnaire prior to each annual screening visit for a minimum of 5 years. The questionnaire included questions on sociodemographics and the following measures: Hospital Anxiety and Depression Scale, Impact of Event Scale, 36-item Short-Form Health Survey, Memorial Anxiety Scale for PrCa, Cancer Worry Scale, risk perception and knowledge.
RESULTS: A total of 760 participants completed questionnaires: 207 participants with GPV in BRCA1, 265 with GPV in BRCA2 and 288 controls (non-carriers from families with a known GPV). We found no evidence of clinically concerning levels of general or cancer-specific distress or poor health-related quality of life in the cohort as a whole. Individuals in the control group had significantly less worry about PrCa compared with the carriers; however, all mean scores were low and within reported general population norms, where available. BRCA2 carriers with previously high prostate-specific antigen (PSA) levels experience a small but significant increase in PrCa anxiety ($P = 0.01$) and PSA-specific anxiety ($P < 0.001$). Cancer risk perceptions reflected information provided during genetic counselling and participants had good levels of knowledge, although this declined over time.
CONCLUSION: This is the first study to report the longitudinal psychosocial impact of a targeted PrCa screening programme for BRCA1 and BRCA2 carriers. The results reassure that an annual PSA-based screening programme does not have an adverse impact on psychosocial health or health-related quality of life in these higher-risk individuals. These results are important as more PrCa screening is targeted to higher-risk groups.

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Impact factor: 4.4 ; Q1

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2. The effect of enhanced recovery after surgery (ERAS) in renal surgery
Elferink SEM, Bretveld R, Kwast ABG, Asselman M, Essink JGJ, Potters JW, van der Palen J.

OBJECTIVE: To study the effect of ERAS on a textbook outcome (TO) after elective renal surgery.
PATIENTS AND METHODS: Retrospective study of all patients who underwent a robot-assisted laparoscopic partial or radical nephrectomy or robot-assisted laparoscopic radical nephroureterectomy in Medisch Spectrum Twente (MST), Enschede, the Netherlands. In total, 277 patients were included. 66 patients from 2018 to 2021 (pre-ERAS group) and 211 patients from 2021 to 2023 (ERAS group). TO is a maximum of two nights in the hospital after surgery, no severe complications during or after surgery ≥ grade IIIb, no blood transfusions, no intensive care, no readmissions, and no mortality within 30 days after surgery. Comparisons were made between the pre-ERAS and ERAS groups using unpaired t-test, Mann-Whitney U test, the chi-squared test or

Fisher's exact test. Multivariate logistic regression was used to adjust for possible confounding.
RESULTS: TO was significantly (p = 0.005) better in the ERAS group (TO = 76.8%) compared to the pre-ERAS group (TO = 59.1%). Compared to a pre-ERAS patient, the adjusted odds ratio for achieving a TO as an ERAS patient is 2.1 (95% CI 1.15-3.78).
CONCLUSIONS: The implementation of ERAS showed a positive effect on the TO of elective renal surgery patients.

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Totale impact factor: 7.3
Gemiddelde impact factor: 3.7

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

Waardegedreven zorg

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Impact factor: 2.9 ; Q2

Totale impact factor: 2.9
Gemiddelde impact factor: 2.9

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Totale impact factor: 2.9
Gemiddelde impact factor: 2.9