Wetenschappelijk onderzoek in Medisch Spectrum Twente

2021

Inhoudsopgave

Voorwoord

Voor u ligt de 13e editie van het jaarlijkse overzicht van de wetenschappelijke output van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2021. Dit jaaroverzicht wordt ook buiten MST verspreid onder huisartsen, apothekers, fysiotherapeuten en andere wetenschappelijke instellingen in de regio.

De publicaties zijn gegroepeerd op vakgroep of maatschap. Niet op volgorde van belangrijkheid maar alfabetisch. Hierbij is als criterium genomen dat de publicatie terug te vinden moet zijn op PubMed en de publicatiedatum moet ook in 2021 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit geïndexeerde Nederlandstalige tijdschriften opgenomen.

In 2021 zijn 334 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is bijna 100 meer vergeleken met voorgaande jaren! Zou het komen doordat veel wetenschappelijk onderzoek in 2021 stil heeft gelegen, waardoor er meer tijd overbleef om te schrijven?
De gemiddelde impact score van alle artikelen is 6,48, een nieuw record voor MST. Dit jaar hebben we 3 keer in het absolute toptijdschrift New England Journal of Medicine gestaan, 1 keer in de Lancet, 4 keer in een subtijdschrift van de Lancet, 1 maal JAMA en 8 keer in een subtijdschrift van de JAMA.

Ook wordt per publicatie ook weergegeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categorieën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden 53% in Q1, 29% in Q2, 12% in Q3 en 6% in Q4. Dat is nagenoeg identiek aan vorig jaar.
Qua promoties was 2021 een zeer matig jaar met “maar” 5 promoties in MST. Dit heeft naar alle waarschijnlijkheid te maken met het feit dat veel mensen die hun promotie uit konden stellen dat ook gedaan hebben totdat er weer meer mogelijk was qua verdediging en festiviteiten vanwege Covid.

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 2021 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

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Overzicht publicaties en de Top 3

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Unieke publicaties	191	212	245	226	216	240	232	239	334
Impact factor	4.38	4.03	5.06	4.70	4.47	5.64	6.12	5.79	6.48

2018			2019			2020			2021		
Top 3: Aantal publicaties:											
1	Cardiologie	40	1	Heelkunde	39	1	Cardiologie	40	1	Neurocentrum	52
2	Neurologie	30	2	Neurologie	33	2	Med. School	29	2	Thoraxcentrum	47
3	Longziekten	28	3	Cardiologie	27	3	Neurocentrum	29	3	Heelkunde	43
Top 3: Totale impact factor score:											
1	Cardiologie	181	1	Cardiologie	306	1	Cardiologie	433	1	Neurocentrum	442
2	Neurologie	136	2	Intensive care	197	2	Interne gnkd	169	2	Thoraxcentrum	346
3	Heelkunde	116	3	Longziekten	148	3	MDL	145	3	Intensive care	307
Top 3: Gemiddelde impact factor score:											
1	Klin. Chemie	6.9	1	MDL	16.6	1	Oogheelkunde	17.7	1	Microbiologie	25.1
2	Radiotherapie	6.7	2	Intensive care	14.2	2	Radiotherapie	11.4	2	Radiologie	17.9
3	Interne gnkd	6.1	3	Cardiologie	7.7	3	Cardiologie	10.8	3	MDL	11.2
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:											
1	Cardiologie	14	1	Cardiologie	20	1	Neurocentrum	15	1	Neurocentrum	23
2	Longziekten	14	2	Longziekten	17	2	Cardiologie	14	2	Thoraxcentrum	14
3	Heelkunde	11	3	Neurologie	13	3	Med. School	10	3	Longziekten	10
			3	Med. School	13						
Top 3: Totale impact factor score als 1e, 2e of laatste auteur:											
1	Cardiologie	63	1	Cardiologie	178	1	Interne gnkd	63	1	Neurocentrum	85
2	Neurologie	39	2	Longziekten	99	2	Neurocentrum	61	2	Thoraxcentrum	44
3	Longziekten	37	3	Med. School	44	3	Cardiologie	48	3	Klin. Chemie	33
Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:											
1	Gynaecologie	4.6	1	Cardiologie	8.9	1	Oogheelkunde	17.7	1	MDL	8.0
2	Cardiologie	4.6	2	Longziekten	5.8	2	Interne gnkd	11	2	KNO	5.4
3	Neurologie	3.9	3	Microbiologie	5.2	3	Intensive care	9.3	3	MKA chirurgie	5.4

Overzicht aantal publicaties per vakgroep:

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Anesthesiologie	1	0	0	2	0	1	0	1	4	2
Cardiologie	33	21	25	28	39	31	40	27	40	-
Dermatologie	0	0	0	0	0	0	0	1	0	1
Gynaecologie	5	5	7	6	4	13	7	6	6	5
Heelkunde	24	13	21	31	26	30	20	39	23	43
Intensive Care	16	11	13	14	13	20	15	12	11	33
Interne Geneeskunde	15	16	20	17	8	11	24	14	27	35
Kindergeneeskunde	6	5	3	11	6	6	8	3	11	8
Klinische Chemie	6	2	6	7	5	5	7	4	8	12
Klinische Farmacie	4	4	6	8	10	3	8	13	7	14
Klinische Fysica	0	0	0	2	0	2	1	0	0	2
Klinische Psychologie	4	3	4	1	0	1	2	1	0	0
KNO	0	0	1	1	1	0	0	0	0	1
Longziekten	10	11	12	16	19	24	28	14	17	22
MDL	13	6	11	5	9	10	5	14	14	16
Medical School Twente	27	24	33	35	33	26	24	24	29	19
Microbiologie	5	7	2	2	4	3	1	2	0	1
Mond- kaak-, aangez.chirurgie	1	3	0	0	1	0	1	0	0	1
Neurochirurgie	*2*	*1*	*5*	*9*	*5*	*5*	*4*	*3*	-	
Neurologie	*19*	*34*	*39*	*33*	*41*	*28*	*30*	*33*	-	
Neurocentrum	-	-	-	-	-	-	-	-	29	52
Nucleaire Geneeskunde	1	0	0	2	0	0	0	0	0	0
Oogheelkunde	0	0	0	0	0	0	1	0	1	1
Orthopedie	3	0	4	7	5	4	2	5	3	13
Pathologie	12	1	5	8	4	9	3	4	0	0
Plastische Chirurgie	0	2	0	2	4	4	13	12	11	16
Psychiatrie	0	0	0	1	0	4	0	0	1	0
Raad van Bestuur	0	0	0	0	0	0	0	9	10	7
Radiologie	7	6	11	14	10	4	11	2	4	9
Radiotherapie	10	3	5	12	10	4	5	4	5	6
Reumatologie	21	32	20	23	15	7	15	17	11	10
Revalidatiegeneeskunde	11	7	8	6	0	0	1	0	0	0
Cardiologie	*33*	*21*	*25*	*28*	*39*	*31*	*40*	*27*	*40*	-
Thoraxchirurgie	*3*	*4*	*3*	*2*	*4*	*5*	*4*	*3*	*8*	-
Thoraxcentrum	-	-	-	-	-	-	-	-	-	47
Urologie	0	0	0	0	0	0	1	0	0	1
Waardegedreven zorg	-	-	-	-	-	-	-	-	-	4

Promoties in MST in 2021
Interne geneeskunde

Caring for a patient with cancer
The psychosocial impact on informal caregivers

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen
op donderdag 30 september 2021
om 12:30 uur precies

door

Simone Marie Claire Hélène Langenberg
geboren op 30 september 1984
te Loosdrecht

Supervisor: Prof. dr. W.T.A. van der Graaf
Prof. dr. J.B. Prins
Prof. dr. C.M.L. van Herpen
Co-supervisor: Dr. A.N.M. Wymenga

Samenvatting

Inleiding

In 2018 werd in Nederland bij 116.537 inwoners de diagnose kanker gesteld en overleden 45.206 mensen aan de gevolgen van kanker. Voor kanker kunnen de volgende behandelingen worden gegeven: operatie, bestraling en/of systemische behandeling. Systemische behandeling wordt ingedeeld in chemotherapie, doelgerichte therapie, immunotherapie en/of hormonale therapie. Systemische behandeling wordt bij een curatieve, op genezing gerichte, behandeling in drie verschillende fasen gegeven , te weten 1) neoadjuvant (voorafgaan aan operatie of bestraling), 2) concomitant (tegelijk met radiotherapie) en 3) adjuvant (na operatie of bestraling). Wanneer een curatieve behandeling niet meer mogelijk is, wordt er vaak een systeembehandeling met palliatieve intentie gegeven. Het doel hiervan is levensverlenging met behoud of verbetering van de kwaliteit van leven. Tijdens deze verschillende fases in de behandeling voor kanker komt een patiënt voor vele uitdagingen te staan en de steun van (een) mantelzorger(s) is daarbij onmisbaar.

Mantelzorgers en hun uitdagingen

Er zijn in Nederland 4,4 miljoen mantelzorgers (25%) die zorg verlenen aan een naaste. Hiervan verlenen 750.000 mantelzorgers langdurige zorg (> 3 maanden) en/of voor meer dan 8 uur per dag. Het is niet precies bekend hoeveel van deze mantelzorgers zorgen voor een patiënt met kanker. Mantelzorg kan worden verleend door een partner, ouders, kind, broer of zus, maar ook door een goede vriend of buur. De zorg van mantelzorgers bestaat uit praktische en emotionele ondersteuning. Als gevolg van deze zorg kan een mantelzorger problemen ervaren, zoals overbelasting en distress, wat ook consequenties kan hebben op voor de eigen kwaliteit van leven en fysieke gezondheid. Daarnaast kunnen mantelzorgers, net als de patiënt, angst voor de terugkeer van kanker bij de patiënt ervaren.

(Over)belasting

Overbelasting ontstaat wanneer de gevolgen van de zorg voor de patiënt met kanker niet meer in balans zijn met de veerkracht van de mantelzorger en zijn of haar mogelijkheden om met de nieuwe situatie om te gaan. Risicofactoren voor overbelasting zijn divers en bestaan uit demografische factoren (vrouw, samenleven met de patiënt), psychologische factoren (depressie, beperkte coping- strategieën, stress), sociale factoren (leven in sociaal isolement), financiële factoren (onderbreking van werk, financiële zorgen) en zorg gerelateerde factoren (groter aantal uren besteed aan mantelzorgen). In Nederland zijn 380.000 mantelzorgers overbelast. Welk aandeel hiervan mantelzorger van patiënten met kanker zijn is niet bekend. Het geeft wel aan dat er een kwetsbare groep mantelzorgers is die extra ondersteuning zou kunnen gebruiken.

Distress, depressie en gecompliceerde rouw

De definitie van distress is “emotionele, sociale, spirituele of fysieke pijn of lijden dat kan leiden tot verdriet, somberheid, angst of eenzaamheid”. Distress komt vaak samen voor met overbelasting. De gevolgen van distress bij de mantelzorger kunnen zijn dat 1) patiënten op langere termijn moeite krijgen om zich aan te passen aan hun ziekte en situatie, 2) patiënten meer angst ervaren door de angst van de mantelzorger, 3) mantelzorgers niet in staat zijn om te zorgen voor de patiënt en 4) zij gevolgen ervaren op hun fysieke gezondheid, zoals het ontwikkelen van hart- en vaatziekten. De oorzaken waardoor een mantelzorger meer distress ervaart verschillen per fase waarin

de patiënt zich bevindt. Over het algemeen kan een mantelzorger distress ervaren door 1) de behandeling van de patiënt (twijfel over de effectiviteit van de behandeling, distress bij de patiënt door bijwerkingen en hoe hiermee om te gaan, onvoorbereid complexe zorg moeten leveren), 2) psychosociale factoren (sociale isolatie, veranderingen in rol in sociale leven, overspoeld voelen, de patiënt helpen emoties te verwerken, complexe verhoudingen binnen gezin/ familie), en / of 3) onvervulde behoeften (psychosociaal, medisch, financieel, kennis). Ongeveer 20% van de mantelzorgers van patiënten met kanker ervaart distress en er zijn aanwijzingen dat vrouwelijke mantelzorgers vaker distress ervaren dan mannelijke mantelzorgers. Distress kan op langere termijn leiden tot depressie. Depressie wordt gekenmerkt door gevoelens van somberheid, wanhoop, verlies van energie, gebrek aan een gevoel van eigenwaarde en hierdoor moeite hebben met het omgaan met normale dagelijkse bezigheden. Het percentage mantelzorgers van patiënten met kanker dat depressieve kenmerken heeft ligt tussen de 12 en 41% en hangt samen met de fase waarin de patiënt behandeld wordt. Nauw verbonden met distress en depressie is gecompliceerde rouw. Rouw is een normale respons op een groot verlies in het leven. Normaal gesproken neemt de intensiteit van deze rouw in de loop van de tijd af zonder dat daarvoor extra hulp nodig is. Bij gecompliceerde rouw wijkt de rouw af van normale rouw (in culturele en maatschappelijke context gezien) door de duur, intensiteit of een combinatie van beiden. Gecompliceerde rouw kenmerkt zich door een meer chronische, intensere reactie op het verlies van een naaste of juist door het ontbreken van een reactie op het verlies of door een verlate reactie op het verlies. Een natuurlijk herstel treedt niet of nauwelijks op. Het is belangrijk om te weten dat symptomen van gecompliceerde rouw overeenkomsten vertonen met symptomen van distress en depressie. Gecompliceerde rouw kan ook samen met depressie voorkomen of kan verergering van depressieve symptomen geven.

Gezondheids-gerelateerde kwaliteit van leven en vermoeidheid

Gezondheids-gerelateerde kwaliteit van leven wordt gedefinieerd als de mate waarin de gezondheid van een persoon impact heeft op zijn of haar mogelijkheid om te functioneren en hoe zijn of haar gezondheid het fysieke, mentale en sociale welzijn beïnvloedt. Er zijn studies die laten zien dat stress bij mantelzorgers een negatief effect kan hebben op hormonale- en ontstekingsprocessen. Ook lijkt er een verband te bestaan tussen mantelzorgen en een verhoogd risico op hart- en vaatziekten. Dit zal de gezondheids-gerelateerde kwaliteit van leven van mantelzorgers kunnen beïnvloeden. Onder mantelzorgers lijkt ook ernstige vermoeidheid een probleem te zijn. Bij mantelzorgers van patiënten in de palliatieve fase bleek dat 23% van deze mantelzorgers matig tot ernstig vermoeidheid zijn. Hier is echter nog weinig onderzoek naar gedaan.

Angst voor terugkeer van kanker

Onder patiënten met kanker is angst voor terugkeer van de ziekte (angst voor recidief) een belangrijk probleem. Van de patiënten die succesvol behandeld zijn voor kanker heeft ongeveer 49% last van angst voor recidief en dit percentage neemt niet af in de loop van de tijd. Ernstige angst voor terugkeer van kanker is geassocieerd met minder goede zelfzorg, distress en een hogere zorgconsumptie. Er is verder nog weinig bekend over angst voor recidief bij mantelzorgers. Er is wel een studie verricht bij partners van patiënten met prostaatkanker. Van hen had 51% angst voor ziekteprogressie (toename van ziekte).

DEEL I:
MANTELZORGERS VAN PATIËNTEN TIJDENS BEHANDELING

Mantelzorgers van patiënten die (in opzet) curatief behandeld worden
Wanneer iemand behandeld wordt voor kanker is het essentieel dat deze behandeling zo optimaal mogelijk en in zijn geheel gegeven kan worden. Mantelzorgers zijn daarbij onmisbaar en kunnen door deze zorg belast raken.

Hoofd-halskanker
In Nederland werd in 2019 bij 2839 patiënten de diagnose hoofd-halskanker gesteld, waarvan bij ongeveer de helft van hen het (ziekte) stadium III of IV betrof. Risicofactoren voor het krijgen van hoofd-halskanker zijn roken en overmatig alcoholgebruik. Daarnaast zijn er patiënten die hoofd-halskanker krijgen als gevolg van het humaan papilloma virus (HPV). Patiënten met lokaal uitgebreid hoofdhalskanker (stadium III/IV) worden curatief behandeld. Hiervoor ondergaan zij concomitant chemo- en radiotherapie gedurende 6 of 7 weken. Bijwerkingen die vaak voorkomen als gevolg van deze behandeling zijn onder andere vermoeidheid, slijmvliesschade en ontsteking van de huid. De behandeling en de gevolgen hiervan kunnen leiden tot distress en het is bekend dat het percentage depressies onder patiënten met hoofd-halskanker hoger ligt (40%) dan bij patiënten met andere soorten kanker (12.5%) en de algemene bevolking (3%). Ondersteuning tijdens de behandeling door hun mantelzorger(s) is onmisbaar. Dit kan de mantelzorger echter ook belasten.
In **hoofdstuk 2** wordt een studie beschreven over mantelzorgers van patiënten die behandeld werden met concomitant chemo- en radiotherapie in verband met lokaal uitgebreid hoofd-halskanker. Allereerst is het verloop van de belasting en vermoeidheid van de mantelzorger in relatie tot de distress en vermoeidheid van de patiënt onderzocht. Daarnaast is gekeken naar risicofactoren voor overbelasting en vermoeidheid bij de mantelzorger nadat de patiënt de behandeling heeft afgerond.
We vonden dat de vermoeidheid en belasting van mantelzorgers gemiddeld genomen het hoogste was op het moment dat de vermoeidheid en distress van patiënt ook het hoogste was, namelijk op één week na het einde van de chemoradiotherapie. Op dat moment werd bij de patiënt ook de laagste gezondheids-gerelateerde kwaliteit van leven gemeten. De gemiddelde mate van belasting en vermoeidheid van de mantelzorgers daalde weer naar het niveau van voor de start van de behandeling. Overbelaste en vermoeide vrouwelijke partners die zorgden voor een patiënt met een grote daling in zijn of haar gezondheidsgerelateerde kwaliteit van leven hadden een groter risico op overbelasting na het einde van de behandeling van de patiënt. Vermoeidheid bij de mantelzorger bij aanvang van de behandeling bleek een risicofactor te zijn voor vermoeidheid na het einde van de behandeling.
Op grond van deze resultaten lijkt het essentieel om voor het starten van de behandeling van de patiënt met lokaal vergevorderd hoofd-halskanker mantelzorgers te identificeren die bij aanvang al problemen ervaren om juist hen extra te kunnen ondersteunen en problemen op langere termijn te voorkomen.

Darmkanker
In 2019 werd in Nederland bij 9237 patiënten de diagnose darmkanker gesteld, waarvan bij ongeveer 65% stadium II of III ziekte betrof. Na resectie van de tumor zal bij een deel van deze patiënten adjuvante chemotherapie geadviseerd worden om de kans op genezing te vergroten. De meest voorkomende bijwerkingen van deze chemotherapie zijn het handvoetsyndroom, misselijkheid, braken maar vooral ook

zenuwschade aan de handen en voeten. Dit laatste is niet altijd (of veelal) niet omkeerbaar. Er is weinig bekend over mantelzorgers van patiënten die een dergelijke, in opzet curatieve, behandeling ondergaan voor darmkanker. In Nederland is wel eerder gekeken naar de ervaring(en) van naasten van darmkankerpatiënten die een operatie hadden ondergaan en die nadien tenminste een prognose van 6 maanden hadden. Jonge en vrouwelijke mantelzorgers bleken meer behoefte te hebben aan ondersteuning bij hun taken als mantelzorger. Ook werd er een relatie gevonden tussen een negatieve ervaring als mantelzorger en 1) een lager inkomen, 2) zorgen voor een meer afhankelijke patiënt, 3) spanning binnen de relatie en 4) meer zorgtaken hebben. Verder werd beschreven dat deze groep jonge en vrouwelijke mantelzorgers meer risico had op het ontwikkelen van een depressie op langere termijn. Ook mantelzorgers die een lagere sociale betrokkenheid ervaarden hadden ditzelfde risico op depressies. In **hoofdstuk 3** wordt een studie beschreven bij mantelzorgers van patiënten die in opzet curatief behandeld werden voor darmkanker. Er werd specifiek gekeken naar 1) het verloop van de belasting en distress van mantelzorgers voor, tijdens en na de behandeling van de patiënt en is er gekeken naar hoeveel mantelzorgers een hoge mate van belasting en distress ondervonden, 2) mogelijke risicofactoren voor een hoge ervaren belasting en distress tijdens en maanden na het einde van de behandeling, 3) de associatie tussen de belasting en distress van mantelzorgers en de distress van de patiënt en 4) het beloop van de gezondheids-gerelateerde kwaliteit van leven van de mantelzorgers en de associatie tussen hun belasting en distress en die van de patiënt. Gemiddeld genomen was de ervaren belasting en distress van mantelzorgers tijdens en na de behandeling laag en als het wel verhoogd was nam het ook weer af in de loop van de tijd. Er was echter een groep van mantelzorgers die voor het starten van de chemotherapie een hoge mate van belasting (12%; n=7/58) en distress (27%; n=16/60) ervaarde (12%; n=7/58). Bij respectievelijk 8% (n=4/50) en 19% (n=9/48) van de mantelzorgers werd 3 maanden na het einde van de behandeling nog een hoge mate van belasting en distress gezien. Belasting voor en tijdens de behandeling van de patiënt vormt een risicofactor voor de mate van ervaren belasting maanden na het einde van de behandeling van de patiënt. Ditzelfde werd gevonden voor distress.
Deze studie liet zien dat er een kwetsbare groep mantelzorgers is en waar het van toegevoegde waarde kan zijn om al voor het starten van de behandeling ondersteuning te bieden.

Mantelzorgers van patiënten tijdens langdurige behandeling
Mantelzorgers van patiënten die langdurig worden behandeld voor gastrointestinale stromatumor (GIST)
Een GIST is een zeldzame kwaadaardige wekedelen tumor, die meestal uitgaat van de maag- of darmwand en uit kan zaaien in de buik of naar de lever. In Nederland werd in 2018 bij ongeveer 400 patiënten een GIST vastgesteld. Deze vorm van kanker staat erom bekend dat deze ongevoelig is voor bestraling en chemotherapie, waardoor lange tijd de levensverwachting van de patiënten met een GIST beperkt was. In 2000 heeft het medicijn imatinib, een doelgericht geneesmiddel, ervoor gezorgd dat de levensverwachting van patiënten met GIST aanzienlijk verbeterde van gemiddeld minder dan een jaar naar gemiddeld meer dan 5 jaar. Daarmee werd dit medicijn de hoeksteen van de behandeling bij gemetastaseerde ziekte. Later bleek imatinib ook effectief als adjuvante behandeling van GIST, waarbij de behandelduur 3 jaar is. Inmiddels zijn er meerdere doelgerichte behandelingen voor GIST beschikbaar. Ondanks deze indrukwekkende vooruitgang in de overleving krijgen patiënten ook te maken met uitdagingen. De ervaren bijwerkingen van de jarenlange dagelijkse

medicijnen zijn vermoeidheid, diarree, misselijkheid en braken, vochtophoping rondom de ogen, spierkrampen en huiduitslag. Daarnaast hebben veel patiënten te maken met angst voor recidief of progressie van de ziekte. Dit kan ook impact hebben op het welzijn van hun naasten, zoals zorgverleners geobserveerd hebben.
In **hoofdstuk 4** wordt een studie beschreven waarin is gekeken naar 1) de mate van belasting en distress van mantelzorgers van patiënten die langdurig behandeld worden voor GIST, 2) hun gezondheids-gerelateerde kwaliteit van leven, tevredenheid over hun relatie en sociale ondersteuning en 3) mantelzorgers die een hoge mate van belasting en distress ervaarden vergeleken worden met mantelzorgers die een lage mate van belasting en distress ervaarden.
Er werd gevonden dat de mate van ervaren belasting en distress bij de mantelzorgers (n=61) in deze studie gemiddeld laag was. De ervaren gezondheidsgerelateerde kwaliteit van leven van deze mantelzorgers was vergelijkbaar met die beschreven is in de algemene bevolking. Hun mate van tevredenheid over hun relatie was hoog en ze ervaarden weinig tekortkomingen in de steun vanuit hun sociale netwerk. De helft van de patiënten ondervond hinderlijke of ernstige bijwerkingen van de behandeling en 34% ervaarde distress. Kijkend naar de mantelzorgers ervaarde 10% van hen een hoge mate van belasting en 23% een hoge mate van distress. Er is een relatie te bestaan tussen de mate van distress van de patiënt en de mate van belasting en distress van de mantelzorger. Mantelzorgers met een hoge mate van ervaren belasting gaven vaker aan een lagere mate van mentale gezondheid te ervaren, minder vitaal te zijn en meer distress te ervaren. Een hogere mate van belasting werd ook vaker gerapporteerd door 1) de nietpartner mantelzorgers, 2) mantelzorgers van patiënten die meer bijwerkingen ondervonden, 3) mantelzorgers die meer uren besteedden aan zorgen voor de patiënt en 4) mantelzorgers die voor meer dan één persoon zorgden. Mantelzorgers die meer distress ervaarden gaven vaker aan 1) een lagere mate van algehele gezondheids-gerelateerde kwaliteit van leven te ervaren, 2) meer belasting te ervaren, 3) sociaal minder te functioneren, 4) moeite te hebben met het omgaan met fysieke en emotionele problemen, 5) een lagere mate van mentale gezondheid te ervaren en 6) minder vitaal te zijn. Daarnaast werd ook gezien dat mantelzorgers met meer ervaren distress zorgden voor 1) meer afhankelijke patiënten en 2) meer dan één persoon tegelijk.
Deze studie laat zien dat het belangrijk is dat er aandacht is voor het welzijn van een kleine, maar kwetsbare groep mantelzorgers waarvan de naasten langdurig behandeld moeten worden voor kanker en dat de bewustwording hiervan een belangrijke eerste stap kan zijn.

DEEL II:
MANTELZORGERS VAN PATIËNTEN DIE KANKER OVERLEEFD HEBBEN

Mantelzorgers van patiënten die succesvol behandeld zijn voor prostaatkanker
Angst voor de recidief komt voor bij bijna de helft (49%) van de patiënten die eerder in opzet curatief zijn behandeld voor prostaatkanker. Deze angst neemt niet af in de loop van de tijd. Het is bekend dat angst voor terugkeer van kanker gepaard kan gaan met ongezond gedrag, distress en toegenomen zorgconsumptie. Het is denkbaar dat ook de mantelzorgers van deze patiënten deze angst ervaren, echter hierover is weinig bekend.
In **hoofdstuk 5** wordt een studie beschreven over partners van patiënten die eerder een in opzet curatieve behandeling van prostaatkanker ondergingen (n=168). Er werd

gekeken naar 1) hoeveel partners angst hebben voor recidief van prostaatkanker, 2) de relatie tussen de angst voor terugkeer van de ziekte tussen de partner en de patiënt, 3) de demografische gegevens van partner en patiënten die een hoge mate van angst voor recidief ervaren en 4) de relatie tussen een hoge mate van angst voor recidief bij de partners en hun gezondheids-gerelateerde kwaliteit van leven.
Er werd gevonden dat ongeveer evenveel partners (35%) en patiënten (38%) ernstige angst voor de terugkeer van de ziekte ervaarden. Een hogere mate van angst voor terugkeer van de ziekte bij de partner was geassocieerd met meer angst bij de patiënt, hetgeen ook het geval was als de partner jonger was. Vergeleken met partners met een lage angst voor recidief scoorden partners met een hoge angst voor recidief significant lager op sociaal functioneren, mentale gezondheid en vitaliteit. Zij ervaarden ook significant vaker moeite met vervullen van dagelijkse taken door moeilijkheden in hun emotioneel functioneren.
Deze studie benadrukt dat ernstige angst voor recidief ook een probleem kan zijn bij de partners van patiënten in opzet curatief behandeld zijn voor prostaatkanker. Het wordt aanbevolen om bij het vormgeven van toekomstige studies en beleid rondom angst voor recidief ook de partner te betrekken.

DEEL III:
MANTELZORGERS VAN OVERLEDEN PATIËNTEN

Nabestaanden van patiënten die deel hebben genomen aan experimentele therapie in de laatste levensfase
Wanneer een patiënt deelneemt in een fase-I experimentele studie is er geen reguliere behandeling voor de kanker meer voorhanden en is de prognose beperkt. Een patiënt die wil deelnemen aan een fase-I studie moet nog in een goede conditie verkeren. Er is een hele kleine kans dat de behandeling effect heeft op de kanker, en er kunnen wel belangrijke bijwerkingen optreden. Dit maakt de positie van de patiënt kwetsbaar in zijn of haar laatste levensfase. De meeste studies naar deze kwetsbaarheid hebben het perspectief van de patiënt en de zorgverleners belicht. Het perspectief van de mantelzorgers van de patiënt is nooit onderzocht.
In **hoofdstuk 6** wordt een studie beschreven met partners van patiënten die overleden zijn na deelname aan een experimentele behandeling in de laatste levensfase. Er is gekeken naar 1) hoe de partner van de patiënt terugkijkt op de deelname van de patiënt aan een fase-I studie en 2) naar eventuele problemen die de partner nog kan ervaren zoals distress, depressie, gecompliceerde rouw en hun gezondheids-gerelateerde kwaliteit van leven.
Wat werd gevonden is dat, 2 jaar na het overlijden van de patiënt, partners aangaven dat de deelname van de patiënt aan een fase-I studie een negatief effect had op de gezondheids-gerelateerde kwaliteit van leven van de patiënt. Daar tegenover stond dat slechts 5% (n=3/58) van de partners uiteindelijk spijt had van deze deelname. Vergeleken met de gezonde populatie, scoorden de partners gemiddeld genomen lager op sociaal en mentaal functioneren. Verder had 19% (n=11/58) van de nabestaanden symptomen van een depressie, 36% (n=21/58) ervaarde distress en 46% (n=26/57) had symptomen van gecompliceerde rouw.
Deze studie onderstreept dat verder onderzoek nodig is naar de oorzaak van deze problemen na het overlijden van de patiënt en welke relatie dit heeft met de behandeling met experimentele therapie in de laatste levensfase.

TOT SLOT

In **hoofdstuk 8** wordt de inhoud van alle hoofdstukken in relatie tot elkaar bediscussieerd, welke implicaties de bevindingen kunnen hebben voor de dagelijkste praktijk en worden aanbevelingen gedaan voor toekomstig onderzoek. De studies in dit proefschrift bevestigen hetgeen we in de praktijk zien, namelijk dat er een groep mantelzorgers is die kwetsbaar is en dat problemen bij het starten van de behandeling een risicofactor kunnen zijn voor het hebben van problemen op de langere termijn. In elke studie was een kwetsbare groep mantelzorgers te identificeren en vooral de mantelzorgers van patiënten die behandeld worden voor hoofd-halskanker en de mantelzorgers van patiënten die deelnemen aan experimentele behandeling in de laatste fase van hun leven vielen op door de mate van problemen die zij ervaarden.
Essentieel is om een onderscheid te kunnen maken tussen een normale reactie op een stressvolle situatie in het leven van de mantelzorger en wanneer dit overgaat in een probleem die het dagelijks leven van de mantelzorger dusdanig beïnvloedt dat het eigen functioneren beperkt wordt. Twee studies in dit proefschrift laten zien dat problemen voor het starten van de behandeling, zoals belasting, distress en vermoeidheid, aandacht behoeven vroeg tijdens de behandeling van de patiënt, omdat dit op langere termijn een risicofactor blijkt voor blijvende problemen. Belangrijk bij verdere ondersteuning van mantelzorgers is het samenspel tussen het herkennen van problemen van de mantelzorger door zorgprofessionals, het erkennen van de mantelzorger dat er een probleem is en de mogelijkheden om deze problemen te objectiveren en op te lossen. Net als de zorg van de patiënt die steeds verder gepersonaliseerd wordt, zal ook de zorg voor mantelzorgers maatwerk zijn. Samenwerking tussen zorgverleners in de eerste, tweede en derde lijn is daarvoor onmisbaar. De huisarts zal een centrale rol spelen, aangezien de huisarts als enige een behandelrelatie met de mantelzorger heeft. Daarnaast zal ook zijn rol als “familie dokter” van toegevoegde waarde zijn aangezien de huisarts het systeem van de patiënt en de mantelzorger goed kent, wat helpt om zorg op maat te leveren.
Er is steeds meer kennis over hoe mantelzorgers ondersteund kunnen worden. Het is bekend dat psycho-educatie, ondersteunende interventies, mindfulnessbased stress-reductie en cognitieve gedragstherapie de ervaren belasting van mantelzorgers kunnen verlichten, waar ook behoefte is aan meer kennis over copingsmechanismen van mantelzorgers en wat nader onderzocht dient te worden.
Verder zal de belasting en distress van de mantelzorger ook gevolgen kunnen hebben voor de fysieke gezondheid van de mantelzorger. Het onderzoek hiernaar is nog beperkt en kennis hierover kan een meer compleet beeld geven welke consequenties mantelzorgen kan hebben. Daarnaast kan deze kennis, samen met de verder te verwerven kennis over de mentale gevolgen van het mantelzorgen, leiden tot proactieve en preventieve interventies om problemen op langere termijn te voorkomen.
Kijkend naar nieuwe ontwikkelingen, van nieuwe behandelingen als immunotherapie tot de gevolgen die de coronapandemie heeft op het welzijn van mantelzorgers, is het belangrijk om door middel van verder onderzoek te kijken hoe welzijn van mantelzorgers zich hiertoe verhoudt.

Neurocentrum

Primary Central Nervous System Lymphoma
Diagnostic evaluation, neurocognitive functioning and health-related quality of life
Primair centraal zenuwstelsel lymfoom
Diagnostiek, neurocognitief functioneren en kwaliteit van leven

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. F.A. van der Duin Schouten
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 21 april 2021 om 15.30 uur

door

Matthijs van der Meulen
geboren te Oldebroek.

Promotor: prof. dr. M.J. van den Bent
Copromotor: dr. J.E.C. Bromberg

Samenvatting
Het primair centraal zenuwstelsel lymfoom (PCZSL) is een zeldzame vorm van een non- Hodgkin lymfoom dat zich beperkt tot de hersenen, de hersenvliezen (ofwel leptomeningen), het ruggenmerg en de ogen, zonder aanwijzingen voor ziekteactiviteit in de rest van het lichaam. De tumor presenteert zich meestal met klachten die binnen enkele weken ontstaan, zoals uitval (verlamming of niet kunnen spreken) of cognitieve veranderingen. In dit proefschrift beschrijven we aspecten van de epidemiologie, diagnostiek, neurocognitief functioneren, kwaliteit van leven en prognose van het primair centraal zenuwstelsel lymfoom.

Epidemiologie
In **hoofdstuk 2** beschrijven we onderzoek naar het voorkomen, de primaire behandeling en de overleving van patiënten met het PCZSL in Nederland tussen 1989 en 2015 gebruik makend van de data van de Nederlandse Kanker Registratie (NKR). In deze periode werden 1.673 patiënten met PCZSL gediagnosticeerd. De patiënten werden verdeeld in drie groepen: 18-60 jaar, 61-70 jaar en >70 jaar. We zagen dat het voorkomen (de incidentie) van de ziekte sterk was toegenomen, maar alleen onder patiënten >60 jaar. Deze bevinding komt overeen met bevolkingsonderzoeken in andere landen, maar de oorzaak hiervan is niet bekend. De primaire behandeling van het PCZSL is sterk veranderd in de afgelopen dertig jaar: zowel behandeling met chemotherapie in combinatie met radiotherapie als behandeling met alleen chemotherapie nam toe in de leeftijdscategorie 18-60, en behandeling met alleen radiotherapie nam juist af. In de categorieën 61-70 jaar en in mindere mate in patiënten >70 jaar nam behandeling met alleen chemotherapie toe en nam behandeling met alleen radiotherapie af. Tenslotte zagen we dat de overleving sterk was toegenomen de afgelopen dertig jaar, maar alleen in patiënten tot 70 jaar. Doordat de Nederlandse Kanker Registratie ook behandelgegevens bevat konden we vaststellen dat deze verbeterde overleving werd verklaard door veranderingen in de behandeling. Ondanks het toegenomen gebruik van chemotherapie bij patiënten ouder dan onder 70 blijft de overleving in deze groep slecht. In **hoofdstuk 3** beschrijven we de primaire behandeling en overleving van 145 ouderen (>70 jaar) met een PCZSL in Nederland, gediagnosticeerd tussen 2014 en 2016. Deze groep werd verdeeld in leeftijdsgroepen: 71-74, 75-80 en >80 jaar. In zijn algemeenheid is leeftijd een sterke prognostische factor in PCZSL patiënten, echter wij zagen geen verschil meer in overleving tussen de drie groepen die allen ouder waren dan 70 jaar. De primaire behandeling was de enige factor die significant geassocieerd was met totale overleving: diegene die kennelijk geschikt waren bevonden om chemotherapie te krijgen hadden een significant betere overleving (mediane totale overleving [mOS] 16,3 maanden, 95% betrouwbaarheidsinterval [BI]: 7,8-35,2) dan diegene die alleen radiotherapie (mOS 7,7 maanden, 95% BI 4,6-13,2) of alleen ‘supportive care’ kregen (mOS 1,4 maanden, 95% BI 1,1-1,7; p<0,001).

Diagnostiek
Het vaststellen van een zekere diagnose van een PCZSL is noodzakelijk voordat chemotherapie kan worden gestart en doordat deze patiënten vaak snel achteruit gaan is hierbij haast geboden. In veel gevallen is er een hersenbiopt nodig om de diagnose te stellen. In **hoofdstuk 4** onderzochten we de waarde van flowcytometrie op hersenbiopten in aanvulling op de gebruikelijke histologie en immuunhistochemie. Flowcytometrie had een specificiteit van 100% en een sensitiviteit van 88%. Met andere woorden, indien er een lymfoom werd gevonden met flowcytometrie, dan was

de diagnose bevestigd. Er werden wel enkele gevallen gemist. De toegevoegde waarde van flowcytometrie was de snelheid waarmee een diagnose kon worden bevestigd. In onze retrospectieve serie kon de diagnose <24uur worden gegeven in 54% van de biopten met behulp van flowcytometrie, ten opzichte van 9% met histologie en immuunhistochemie.
Na het starten van de behandeling wordt het effect van die behandeling gemonitord middels MRI beelden van de hersenen. In **hoofdstuk 5** onderzoeken we de waarde van een centrale radiologische beoordeling van MRI's die gemaakt werden in het kader van de behandeling van patiënten in de HOVON105/ ALLG NHL24 trial. Elke MRI werd beoordeeld op de mate van respons van de tumor in het ziekenhuis waar de patiënt werd behandeld door een lokale arts. De centrale radiologiebeoordeling was gebaseerd op twee ervaren beoordelaars en in geval zij van mening verschilde, besliste een derde beoordelaar. In 235 MRI's, gemaakt gedurende de behandeling, vonden we een matige overeenstemming tussen de beoordelaars (interobserver agreement) tussen de lokale en centrale beoordeling: kappa 0.46. Verrassend genoeg was de interobserver agreement tussen beide centrale beoordelaars niet beter. Dit suggereert dat de beoordeling voor de mate van respons beperkt is en dat er geen toegevoegde waarde is van een centrale radiologische beoordeling van de respons bij PCZSL in klinische studies. Bij het onderscheid tussen progressie of recidief en geen progressie of recidief was de interobserver agreement uitstekend, zowel tussen de centrale beoordelaars (kappa 0.93) als tussen de lokale en centrale beoordeling (kappa 0.87).
Daarnaast berekenden we verschillen in progressie vrije overleving en totale overleving voor erkende categorieën van de mate van respons: complete respons (CR), onbevestigde complete respons (CRu) en partiële respons (PR) op de MRI gemaakt aan het einde van de behandeling. Deze MRI moest zijn gemaakt binnen een vooraf gedefinieerde periode (zogenoemde landmark analyse) vanaf de randomisatie. In deze landmark analyse, werden alle 'end-of-treatment'-MRI's meegenomen die vóór 6,9 maanden na randomisatie waren gemaakt. Hierin vonden we geen verschillen in progressie vrije overleving en totale overleving tussen patiënten met een complete respons (CR), onbevestigde complete respons (CRu) en partiële respons (PR), zowel volgens de centrale als de lokale radiologische beoordeling. De laatste bevinding suggereert dat de verschillende response maten geen goed surrogaat eindpunt zijn, noch voor progressie vrije noch voor totale overleving.

Neurocognitief functioneren en kwaliteit van leven
In **hoofdstuk 6** geven we een uitgebreid, systematisch overzicht van de literatuur over neurocognitief functioneren en kwaliteit van leven in PCZSL patiënten, gepubliceerd vóór januari 2018. De belangrijkste conclusies waren dat de tumor zelf een grote impact heeft op zowel neurocognitief functioneren als kwaliteit van leven, en dat totale schedelbestraling in aanvulling op chemotherapie een negatief effect heeft op neurocognitief functioneren. De mate van deze impact was echter niet altijd klinisch relevant, waarbij relevantie gedefinieerd was als een verandering in z-score van >1 of >1,5 standaarddeviatie. In de HOVON 105/ ALLG NHL 24 trial werden 199 immuun competente patiënten met een nieuw gediagnosticeerde CD20+ B-cel PCZSL 1:1 gerandomiseerd tussen chemotherapie, gebaseerd op hoge dosis methotrexaat (MBVP), met of zonder rituximab. Dit werd gevolgd door consolidatie behandeling met hoge dosis cytarabine (Ara-C) en voor patiënten ≤60 jaar gevolgd door 30Gy bestraling van de gehele schedelinhoud. Er waren geen verschillen tussen

de event vrije, progressie vrije en totale overleving tussen de twee behandelarmen. In **hoofdstuk 7** en **hoofdstuk 8** beschrijven we de secundaire eindpunten van deze trial: respectievelijk neurocognitief functioneren en kwaliteit van leven. Zowel het neurocognitief functioneren als de kwaliteit van leven verbeterden significant in de tijd, vanaf baseline tot twee jaar na behandeling. De grootste verbetering trad op tussen de start en het einde van de behandeling. Doordat het PCZSL heel goed kan reageren op de behandeling impliceert dit dat de tumor zelf een grote invloed heeft op het neurocognitief functioneren en kwaliteit van leven. De verbetering in de primaire schalen die we gebruikten in de kwaliteit van leven analyse was ook klinisch relevant (≥10 punten). De scores in alle cognitieve domeinen, behalve motorsnelheid, verbeterden niet dusdanig dat dit klinisch relevant genoemd mag worden, waarbij dit gedefinieerd was als een verandering in z-score van ≥1 standaarddeviatie. Bij die patiënten die chemotherapie en totale schedelbestraling kregen, zagen we dat neurocognitief functioneren en kwaliteit van leven-scores stabiel bleven tot 2 jaar follow-up, ten opzicht van scores na WBRT. Dit is in tegenstelling tot de meeste andere studies, hetgeen mogelijk verklaard kan worden door de lagere dosis bestraling die wij hebben gebruikt (30Gy), vergeleken met de meeste andere onderzoeken (36-45Gy) en onze follow-up is mogelijk nog te kort om achteruitgang in neurocognitief functioneren te detecteren. Echter, het is eerder beschreven dat cognitieve achteruitgang al na 6-12 maanden na de bestraling kan optreden.
In **hoofdstuk 7** beschrijven we niet alleen de cognitieve veranderingen, maar ook of er een relatie is tussen cognitieve veranderingen en radiologische veranderingen: witte stof afwijkingen en breinatrofie. Er was een significante, maar zwakke relatie tussen een toename in WSA en hersenatrofie en een afname van neurocognitief functioneren.

Prognose
Veel patiënten met PCZSL hebben cognitieve stoornissen bij het debuut van de ziekte. De Mini-Mental State Examination (MMSE) is een grove screeningstool om neurocognitieve stoornissen te detecteren. In **hoofdstuk 9** is de prognostische waarde van de MMSE onderzocht in patiënten uit de HOVON105/ ALLG NHL24 studie. De MMSE-score, als continue variabele bij de start van de behandeling , voor start van de chemotherapie, bleek een onafhankelijke prognostische factor is bij het voorspellen van de progressievrije overleving en totale overleving. We zagen dat elk punt daling van de MMSE-score geassocieerd was met een slechtere prognose: voor progressievrije overleving (Hazard Ratio [HR], 95% betrouwbaarheidsinterval [BI] 1,04, 1,01-1,08) en voor totale overleving (HR, 95% BI: 1,06, 1,02-1,10). Wanneer de MMSE-score als categoriale variabele (afwijkend versus normaal) werd gebruikt voor de analyse was een baseline-score <27 (vergeleken met een score ≥ 27) opnieuw de enige factor die geassocieerd was met progressievrije (HR 1,55, 95% BI: 1,02-2,35) en totale overleving (HR 1,68 95% BI: 1,05-2,70). Leeftijd en ‘performance status’ zijn belangrijke prognostische factoren bij veel oncologische aandoeningen en beide worden gebruikt in de belangrijke prognostische modellen voor PCZSL patiënten. In ons cohort van 153 PCZSL patiënten, waarin alleen patiënten tot de leeftijd van 70 werden geïncludeerd, waren deze in multivariate analyse niet geassocieerd met progressievrije overleving en totale overleving. Echter, leeftijd vertoonde wel een trend naar significantie voor progressievrije overleving (p=0,061) en totale overleving (p=0,069). In **hoofdstuk 10** bespreken we de meest relevante resultaten van de hoofdstukken 2 tot en met 9 die in dit proefschrift werden beschreven in het licht van recente literatuur.

Orthopedie

Recovery and physiotherapy in patients with a favourable prognosis after Total Knee Arthroplasty

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens het besluit van het college van decanen
in het openbaar te verdedigen op
29 oktober 2021
om 10.30u precies

door

Karen Elisabeth Maria Harmelink
geboren op 10 november 1986
te Groningen

Promotoren	Prof. dr. M.W.G. Nijhuis - van der Sanden
	Prof. dr. P.J. van der Wees
Copromotoren	Dr. J.B. Staal
	Dr. A.V.C.M. Zeegers

Samenvatting

ACHTERGROND

Het aantal mensen dat de komende jaren een Totale Knie Prothese (TKP) zal ontvangen stijgt, mede door demografische ontwikkelingen. In Nederland worden jaarlijks ongeveer 26.000 TKP operaties verricht. Ongeveer 20% van de patiënten is ontevreden een jaar na een TKP operatie, in de meeste gevallen veroorzaakt door nog steeds bestaande slechte fysieke functie of pijn. Andere hypotheses voor ontevredenheid na een TKP operatie zijn geassocieerd met te hoge patiëntverwachtingen of onvoldoende adequate preoperatieve voorlichting over het belang van revalidatie na een TKP. Het is belangrijk om inzicht te krijgen in de factoren die de lange termijn uitkomst bepalen. Door de steeds kortere ziekenhuisopname na een TKP operatie worden post-klinische fysiotherapie programma's steeds belangrijker. Wij hebben de hypothese dat patiënten met een gunstige prognose minder intensieve begeleiding van de fysiotherapeut nodig hebben na een TKP operatie. De effectiviteit van fysiotherapeutische oefenprogramma's hangt waarschijnlijk af van de therapietrouw met betrekking tot het oefenprogramma. Het is daarom noodzakelijk dat de therapietrouw geoptimaliseerd wordt, zodat de effectiviteit van postoperatieve fysiotherapieprogramma's verbetert en hierdoor ook de uitkomst na een TKP verbetert. Een potentiële methode om therapietrouw te verbeteren zonder begeleiding is het gebruik van digitale technologieën.

DOEL VAN DE THESIS

Het doel van dit proefschrift is inzicht krijgen in het herstel bij patiënten met een gunstige prognose na een TKP en het evalueren van het effect van een activiteitencoach bij patiënten met een gunstige prognose die een thuisoefenprogramma volgen.

In **hoofdstuk 1** beginnen we met de presentatie van de epidemiologie, pathologie en behandelopties van knieartrose. Vervolgens gaan we in op de epidemiologie van de TKP, het herstel na een TKP en de mogelijkheden van postoperatieve fysiotherapie na TKP. In dit hoofdstuk beschrijven we de wetenschappelijke lacunes omtrent kennis over het herstel na TKP en de meerwaarde van postoperatieve fysiotherapie bij patiënten met een gunstige prognose. We gaan in op de doelen van dit proefschrift om de kennis rond herstel na TKP te vergroten. Aan het eind van het hoofdstuk presenteren we de onderzoeksvragen en eindigen met een overzicht van de inhoud van dit proefschrift.

In **hoofdstuk 2** onderzochten we prognostische factoren prognostische factoren voor herstel na een TKP op pijn, fysiek functioneren en kwaliteit van leven. Middels een systematische review werden prognostische studies geïncludeerd waarbij werd gekeken naar de uitkomst één jaar of langer na het moment van de operatie. Studies werden geïncludeerd als 1) werd gekeken naar preoperatieve prognostische factoren voor pijn, fysiek functioneren en/of kwaliteit van leven na een follow-up van één jaar; 2) tenminste 200 patiënten werden geïncludeerd met artrose die in aanmerking kwamen voor een TKP; 3) data analyse werd gedaan middels multivariabele analyse. De kwaliteit van bewijs per prognostische factor werd bepaald middels de GRADE methode. Achttien studies werden geïncludeerd. We vonden alleen lage kwaliteit van bewijs voor een aantal voorspellende factoren. Er is lage kwaliteit van bewijs voor de voorspelling dat er minder pijn is één jaar na TKP voor de volgende factoren: Preoperatief meer pijn, aanwezigheid van sociale support, afwezigheid van angst en aanwezigheid van meer radiografische

afwijkingen. Er is ook lage kwaliteit van bewijs dat een slechtere preoperatieve fysieke functie, minder comorbiditeiten, afwezigheid van angst, aanwezigheid van sociale support, hoger inkomen, normaal BMI en meer radiografische afwijkingen voorspellende factoren zijn voor een betere fysieke functie één jaar na een TKP operatie. Daarnaast vonden we lage kwaliteit van bewijs dat vrouwelijk geslacht en minder comorbiditeiten factoren zijn die een betere kwaliteit van leven voorspellen. De geïncludeerde studies in de systematische review keken allemaal naar herstelpunten in plaats van naar hersteltrajecten. Daarom hebben wij in **hoofdstuk 3** hersteltrajecten onderzocht voor peformance-based en zelfgerapporteerd fysiek functioneren en pijn gedurende de eerste zes weken na TKP operatie bij patiënten met een gunstige prognose voor herstel. Daarnaast hebben we gekeken of er een associatie was met deze trajecten en de uitkomst na één jaar. In deze prospectieve cohortstudie werden 218 patiënten geïncludeerd waarbij preoperatief, drie dagen, twee weken, zes weken en een jaar postoperatief metingen werden uitgevoerd. Uitkomstmaten waren fysiek functioneren (Timed Up and Go (TUG) en Knee Osteoarthritis Outcome Score – Activiteiten Dagelijks Leven (KOOS-ADL)) en pijn (Visueel Analoge Schaal (VAS)). Middels Latent Class Growth Analysis (LCGA) hebben we verschillende hersteltrajecten geïdentificeerd gedurende de eerste zes weken na operatie. Multivariabele regressie analyse werd gebruikt om associaties te vinden tussen de hersteltrajecten en uitkomsten na één jaar. De volgende hersteltrajecten werden gevonden voor TUG: 'herstel groep' (n=203), 'matig herstel groep', (n=8) en de 'vertraagd herstel groep' (n=7). De KOOS liet twee hersteltrajecten zien: 'herstel groep' (n=86) en de 'matig herstel groep' (n=132) en de VAS liet drie hersteltrajecten zien: 'geen/heel weinig pijn' (n=151), 'normale afname van pijn' (n=48) en 'blijvende pijn' (n=19). De 'vertraagd herstel groep' scoorde 3.31 [95% BI 1.52, 5.09] seconden lager op de TUG dan de 'matig herstel groep' en de KOOS 'herstel groep' scoorde 11.97 [95% BI 8.62, 15.33] punten beter dan de 'matig herstel groep' na 1 jaar. Patiënten die 'blijvende pijn' aangeven in de eerste 6 weken, hebben minder kans om pijnvrij te worden na 1 jaar dan patiënten die 'geen/heel weinig pijn' aangeven in de 6 weken revalidatie (odds ratio 0.11 [95% BI 0.03,0.42]). Deze studie geeft aan dat er verschillende hersteltrajecten bepaald kunnen worden bij patiënten na een TKP met een gunstige prognose.

De verwachting is dat patiënten na een TKP met een gunstige prognose minder fysiotherapie behandelingen nodig hebben na een intensief oefenprogramma. In **hoofdstuk 4** onderzochten we wat de verwachtingen zijn van een TKP en wat de redenen zijn voor patiënten om fysiotherapie te blijven gebruiken na een intensief oefenprogramma na TKP operatie. Dit is een studie waarbij we 15 semigestructureerde interviews hebben afgenomen. Deze zijn geanalyseerd middels een deductieve thematische analyse en gebruikt om een vragenlijst te ontwikkelen. Deze vragenlijst is verzonden naar een jaar cohort van 60 patiënten. Logistische regressie modellen zijn gebruikt om te bepalen welke factoren geassocieerd zijn met het voortzetten van fysiotherapiebehandelingen na een 10-daags intensief oefenprogramma na TKP. Van de 60 patiënten vulden 55 patiënten de vragenlijst in. Redenen voor patiënten om fysiotherapie te continueren waren: 1) blijvende klachten; 2) de verwachting dat hun fysieke gezondheid zou kunnen verbeteren; 3) voorkeur om onder begeleiding van een zorgprofessional te trainen. Patiënten die geen voorkeur voor aanvullende fysiotherapiebehandeling hadden, gaven als reden dat ze in staat waren om zelf hun oefeningen te doen. Een substantieel deel van de patiënten ging door met fysiotherapie-behandelingen ondanks dat dit qua fysieke functie niet noodzakelijk wordt geacht. De mate van

zelfredzaamheid was een belangrijke factor om wel of geen gebruik te maken van aanvullende fysiotherapiebehandelingen ongeacht of het herstel al voldoende was. Daarom concludeerden we dat de zelfmanagement capaciteiten van patiënten verbeterd zouden moeten worden. Om deze zelfmanagement capaciteiten te verbeteren kan gebruik worden gemaakt van digitale technologieën in combinatie met een thuisoefenprogramma. Thuisoefenprogramma's zijn effectief gebleken na een TKP. Wij verwachten dat de effectiviteit vergroot kan worden door de therapietrouw ten aanzien van oefeningen te vergroten.

In hoofdstuk 5 presenteren we een studie protocol voor een thuisoefenprogramma bij patiënten na een TKP met een gunstige prognose. We onderzochten hierbij het effect van een activiteitencoach op de therapietrouw ten aanzien van oefeningen en we verwachtten door de vergrootte therapietrouw een verbeterd fysiek functioneren. Deze studie is ontworpen als een gerandomiseerde, gecontroleerde studie. Patiënten in zowel de interventie- als de controlegroep ontvangen een thuisoefenprogramma van twee weken. Patiënten in de interventiegroep ontvangen daarnaast een activiteitencoach welke bestaat uit een accelerometer om activiteit te meten en een app op een smartphone welke adviezen geeft om te oefenen gedurende de dag. De primaire uitkomstmaten zijn fysiek functioneren gemeten met de TUG en de therapietrouw aan het oefenprogramma. Secundaire uitkomstmaten zijn fysiek functioneren gemeten met de KOOS, kwaliteit van leven gemeten met de SF-36 en zorgkosten gerelateerd aan de TKP tot een jaar postoperatief. Data zijn preoperatief, drie dagen, twee en zes weken en drie maanden postoperatief verzameld.

In hoofdstuk 6 presenteren we de resultaten van de gerandomiseerde, gecontroleerde studie. In totaal werden 66 patiënten geïncludeerd, 32 in de interventiegroep en 34 in de controlegroep. Alle geïncludeerde patiënten hebben de studie voltooid op alle meetmomenten. De therapietrouw ten aanzien van het activiteitenniveau was zowel in de interventie- als de controlegroep meer dan de aanbevolen tijd om actief te zijn. Er was geen statistisch significant verschil tussen de interventiegroep en de controlegroep op therapietrouw, de overige uitkomstmaten en zorgkosten. De accelerometer toonde een significant hoger activiteitenniveau in vergelijking met het activiteitendagboek. De verschillen waren te wijten aan meetverschillen gebaseerd op het registreren van kortdurende activiteiten die niet in het dagboek geregistreerd werden (bijvoorbeeld even koffie halen of de deur openen) en waren niet van verdere betekenis. Daarom is een activiteitendagboek een valide klinische keuze om therapietrouw te meten. Therapietrouw en andere uitkomstmaten verbeteren niet door het toevoegen van een activiteitencoach aan een thuisoefenprogramma bij patiënten met een gunstige prognose na een TKP operatie.

In hoofdstuk 7 presenteren we eerst de belangrijkste resultaten, vervolgens bespreken we onze bevindingen in relatie tot ander onderzoek en ten slotte hebben we de praktische implicaties van onze studies voor patiënten, fysiotherapeuten, toekomstig onderzoek en beleidsmakers uiteengezet. De indicatie voor een TKP en de selectie van de juiste patiënten is erg belangrijk voor de uitkomst na een TKP. Hiervoor bestaan geen duidelijke richtlijnen, maar er is consensus dat patiënten met 'genoeg pijn', radiologische afwijkingen en verlies van fysieke functie, waarbij andere stepped care strategieën niet hebben geholpen in aanmerking komen voor een TKP. Bovendien zijn de patiëntverwachtingen erg belangrijk voor tevredenheid na een TKP. Om de patiëntverwachtingen te optimaliseren kan gebruik worden gemaakt van 'shared decision-making'

processen. Om patiënten te informeren over hun verwachte herstel zouden zorgverleners gebruik moeten maken van individuele patiëntverwachtingen. Hersteltrajecten gebaseerd op LCGA analyses zijn bruikbaar om individueel herstel te bepalen. Een adequate voorspelling van het herstel van een individuele patiënt zorgt ervoor dat fysiotherapeut en patiënt kunnen anticiperen op het herstel en een passend fysiotherapieprogramma kunnen opstellen indien nodig.
Er is onduidelijkheid over de additionele waarde van fysiotherapie bij patiënten met een gunstige prognose na een TKP. Het natuurlijk herstel zou het herstel evengoed kunnen verklaren als het effect van de fysiotherapie. Ondanks het gebrek aan bewijs voor de effectiviteit van fysiotherapie bij patiënten na een TKP met een gunstige prognose, maken patiënten dankbaar gebruik van fysiotherapie.
Redenen voor patiënten om toch naar de fysiotherapeut te gaan na een TKP operatie zijn blijvende klachten, de verwachting dat hun fysieke fitheid kan verbeteren en verminderde zelf-managementcapaciteiten. Daarom zou bij elke patiënt preoperatief een 'shared decisionmaking' proces moeten worden doorlopen door een gespecialiseerde fysiotherapeut. Hierin moet besproken worden wat het verwachte herstel is, zodat reële verwachtingen ten aanzien van de TKP ontstaan. Daarnaast moeten de fysieke fitheid, therapietrouw, zelfmanagementcapaciteiten, verwachte fysiotherapieprogramma, financiële consequenties en opties om gebruik te maken van bijvoorbeeld digitale technologieën besproken worden. Zorgverzekeraars zouden deze preoperatieve intake moeten faciliteren. In het postoperatieve fysiotherapieprogramma dienen fysieke fitheid, zelfmanagementcapaciteiten en therapietrouw centraal te staan. In het geval van vertraagd herstel dient een individuele oplossing gevonden te worden om het herstel te verbeteren. Hierbij zou overwogen moeten worden of fysiotherapiebehandelingen van toegevoegde waarde zijn. Wij bevelen dan ook verder onderzoek aan naar de toegevoegde waarde, inhoud en duur van fysiotherapie bij alle patiënten na een TKP. Via de ‘Landelijke Database Fysiotherapie’ kunnen data op basis van herhaalde metingen verzameld worden over herstel van individuele patiënten zodat een ‘patiënt zoals mij’ verwachting van het herstel gepresenteerd kan worden. Dan kan vooraf een individueel fysiotherapieprogramma gekozen worden zodat de effectiviteit van een TKP operatie kan verbeteren. In onderzoek naar de effectiviteit van fysiotherapie moet therapietrouw meegenomen worden als uitkomstmaat omdat verbetering van fysieke functie in grote mate afhangt van de therapietrouw van de patiënt. Succes is altijd afhankelijk van een nauwkeurige voorbereiding en zonder die voorbereiding is falen een feit (Confucius 551 v C.- 479 v. C.). Dit geldt zeker ook voor het succes na een TKP operatie!

Thoraxcentrum Twente

New-generation drug-eluting stents in various patient populations

Dissertation

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Samenvatting

Voortdurende inspanningen om superieure medicijn-afgevende stents te ontwikkelen voor percutane coronaire interventies (PCI) hebben geleid tot stents die in klinische studies steeds betere uitkomsten laten zien in niet-geselecteerde patiënten populaties ('all-comers'). De innovaties in de ontwikkeling van medicijn-afgevende stents heeft geleid tot een constante aanwas van nieuwe stents die worden geïntroduceerd in de klinische praktijk. Elke nieuwe stent komt met de belofte van verbetering in klinische uitkomsten, maar of dit ook daadwerkelijk het geval is moet voortdurend getoetst worden in grootschalige gerandomiseerde studies.

Hoewel de klinische uitkomsten van all-comer patiënten na het implanteren van coronaire stents steeds beter zijn geworden, zijn er nog steeds subgroepen van patiënten die een verhoogd risico hebben op herhaalde revascularisatie, myocardinfarct of overlijden. Er is aanvullend onderzoek nodig in deze subgroepen om te ontdekken of de stentkeuze bij bepaalde patiënt karakteristieken kan leiden tot betere uitkomsten.

Dit proefschrift heeft de klinische uitkomsten onderzocht van zowel all-comer patiënten als verschillende subgroepen van patiënten met obstructief coronairlijden die behandeld zijn met nieuwe-generatie medicijn-afgevende stents.

Deel I: All-comer patiënten

Hoofdstuk 1 gaf een algemene introductie waarin de ontwikkeling van nieuwegeneratie medicijn-afgevende stents werd besproken en verschillende subgroepen werden uitgelicht.

Hoofdstuk 2 beschreef de 3-jaars uitkomsten van BIO-RESORT studie deelnemers die gerandomiseerd werden naar behandeling met medicijn-afgevende stents met oplosbare of permanente polymeer coating. De stents met oplosbare polymeer waren de sirolimus-afgevende Orsiro stent bestaande uit ultra dunne struts van kobalt-chroom legering en de everolimus-afgevende Synergy stent, die bestaat uit zeer dunne struts van platinum-chroom legering. De stent met permanente polymeer is de zotarolimusafgevende Resolute Integrity stent die bestaat uit dunne kobalt-chroom struts. Follow-up data waren beschikbaar in 3,393 van de 3,514 patiënten (96.6%). Hoewel de bestudeerde stents substantieel verschillen in onder andere stent platform en polymeer coating, werd geen verschil in uitkomsten gezien tussen patiënten die behandeld waren met 1 van de 3 stents ('target vessel failure' 8.5%, 8.8%, en 10.0%, respectievelijk). Stent trombose kwam weinig voor en was vergelijkbaar tussen de drie stent groepen (1.1%, 1.1%, en 0.9%, respectievelijk). De 3-jaars uitkomsten waren dus gunstig voor alle 3 de stentgroepen, maar langere follow-up is nodig om definitief te kunnen beantwoorden of één van de stents op lange termijn wel betere klinische uitkomsten laat zien.

Hoofdstuk 3 rapporteerde de lange termijn follow-up van de BIO-RESORT studie waarin de uitkomsten van zowel all-comer patiënten als patiënten met diabetes werden beschreven. In all-comers lieten Orsiro, Synergy en Resolute Integrity stents vergelijkbare veiligheid en effectiviteit zien na 5 jaar. Percentages van target vessel failure waren respectievelijk 12.7%, 11.5% en 14.1%. Ook in patiënten met diabetes werd geen verschil in target vessel failure gevonden tussen de stents. Cardiale mortaliteit was lager in patiënten met diabetes die behandeld waren met Orsiro versus Resolute Integrity stents (3.0% vs. 8.3%), hoewel er geen statistisch significant verschil was tussen Synergy en Resolute Integrity stents (4.2% vs. 8.3%).

Hoofdstuk 4 onderzocht all-comer patiënten die behandeld werden met de nieuwe Resolute Onyx stent ten opzichte van patiënten die behandeld werden met de Orsiro

stent in de gerandomiseerde BIONYX studie. Na 2 jaar liet de nieuwe Resolute Onyx stent, bestaande uit dunne struts van samengesteld metaal met een permanente polymeer-laag die zotarolimus afgeeft, vergelijkbare veiligheid en effectiviteit zien in all-comer patiënten ten opzichte van de Orsiro stent (target vessel failure: 7.6% vs. 7.1%). Een analyse in patiënten die in kleine vaten zijn behandeld suggereerde ook geen voordeel voor één van de twee stents.
Hoofdstuk 5 rapporteerde de behouden veiligheid en effectiviteit van behandeling met Resolute Onyx versus Orsiro stents na 3 jaar. Follow-up was beschikbaar in 2,433/2,488 (97.8%) patiënten. Deze voor het eerst gerandomiseerd onderzochte 3-jaars uitkomsten van Resolute Onyx stents lieten een gunstig percentage van target vessel failure zien (9.1%), dat overeenkwam met de uitkomsten van patiënten die behandeld werden met Orsiro stents (8.9%). We vonden een lagere mortaliteit in de Resolute Onyx groep (3.7% vs. 5.4%), maar dit kan berusten op toeval en daarom is lange termijn follow-up nodig om meer inzicht te krijgen in de betekenis van deze bevinding.
Hoofdstuk 6 beschreef een interview studie met cardiologen die coronair angiografieën uitvoeren. Het doel was om te onderzoeken in hoe verre zij zich bewust zijn van een probleem aangaande meerdere toepassingen van het gebruik van de arteria radialis die elkaar uitsluiten. Meer dan de helft van de geïnterviewde cardiologen gaf aan dat ze zich niet eerder hadden gerealiseerd dat transradiale vasculaire toegang voor coronair angiografie voorafgaand aan een coronaire bypass operatie, ervoor zorgt dat deze arterie mogelijk niet meer als graft gebruikt kan worden.
In **Hoofdstuk 7** werd een studie besproken die 5-jaars uitkomsten van 2 nieuwe generatie medicijn-afgevende stents rapporteerde en werd een alternatieve statistische methode geopperd voor het onderzoeken van uitkomsten in soortgelijke studies. De I-LOVE-IT 2 studie vond tussen 2 stents geen verschil in ischemische en bloedings uitkomsten tot 5 jaar na de behandeling. De datacollectie en analyse in die studie zijn uitgevoerd volgens de huidige internationale standaarden. Echter, onderzoekers van toekomstige studies kunnen overwegen om andere methoden te gebruiken die meer patiëntgericht zijn en die zowel de ernst als het herhaaldelijk optreden van ‘adverse events’ in overweging nemen.

Deel II. Verschillende patiënten populaties
Hoofdstuk 8 rapporteerde 2 separate analyses van de klinische uitkomsten van all-comer patiënten met diabetes die behandeld werden met nieuwe-generatie medicijn-afgevende stents in de gerandomiseerde BIO-RESORT en BIONYX studies. In BIO-RESORT werd voor 624 patiënten met diabetes geen verschil in klinische uitkomsten gevonden tussen behandeling met Orsiro, Synergy of Resolute Inregrity stents. In BIONYX werd voor 510 patiënten eveneens geen verschil in klinische uitkomsten gezien na behandeling met Orsiro versus Resolute Onyx stents. Deze bevindingen kunnen beschouwd worden als een signaal van veiligheid en effectiviteit voor het gebruik van de bestudeerde nieuwegeneratie medicijn-afgevende stents in patiënten met diabetes.
Hoofdstuk 9 onderzocht de impact van prediabetes en diabetes op 3-jaars uitkomsten van patiënten die behandeld zijn met nieuwe-generatie medicijn-afgevende stents in de BIO-RESORT en BIONYX studies. De resultaten lieten zien dat niet alleen patiënten met diabetes maar ook patiënten met prediabetes een hoog-risico PCI-populatie zijn. Na behandeling met nieuwe-generatie medicijn-afgevende stents hadden beide groepen een hoger risico op zowel bloedingen als ischemische uitkomsten dan patiënten met een normaal glucose metabolisme. De verschillen in ernstige bloedingen

konden met name verklaard worden door verschillen in patiëntkarakteristieken op baseline. Routine bepalingen van nuchter glucose of HbA1c kan helpen om patiënten met prediabetes te identificeren voor striktere controle van cardiovasculaire risicofactoren om zo het risico op ongunstige uitkomsten na PCI te verkleinen.
Hoofdstuk 10 evalueerde de klinische uitkomsten na implantatie van nieuwe-generatie medicijn-afgevende stents in patiënten zonder diabetes in wie HbA1c en nuchter plasma glucose werden bepaald en een orale glucose tolerantie test werd verricht. Op basis van deze laboratorium uitslagen werden patiënten ingedeeld in 3 groepen: normaal glucose metabolisme (normoglycemisch), prediabetes of 'stille diabetes'. Patiënten met stille diabetes op basis van HbA1c en nuchter plasma glucose hadden een hogere kans op het ontwikkelen van een nieuw myocardinfarct in het behandelde bloedvat. Daarnaast waren prediabetes en stille diabetes op basis van de orale glucose tolerantie test onafhankelijk geassocieerd met een hoger risico op target vessel failure na 3 jaar. Dit verschil werd met name gedreven door periprocedurele myocardinfarcten (myocardinfarcten binnen 48 uur na PCI) en cardiale dood. Echter, na de eerste 48 uur waren de percentages van target vessel failure, myocardinfarct en herhaalde revascularisatie laag en verschilden niet tussen de 3 groepen.
Hoofdstuk 11 toonde een analyse van gepoolde patiëntdata uit 4 grote gerandomiseerde studies (TWENTE, DUTCH PEERS, BIO-RESORT en BIONYX) om de behandeling met nieuwe-generatie medicijn-afgevende stents van patiënten boven de 80 jaar oud te evalueren. Studie deelnemers van 80 jaar en ouder hadden meer comorbiditeit en een hoger risico op target vessel failure dan jongere patiënten (7.3% vs. 5.3%). In 80-plussers was cardiale mortaliteit hoger zoals ook verwacht mag worden op basis van hun hogere leeftijd. Echter, de kans op het optreden van een myocardinfarct of herhaalde revascularisatie was niet hoger. De behandeling van 80-plussers met nieuwe-generatie medicijn-afgevende stents lijkt dan ook veilig en effectief te zijn.
Hoofdstuk 12 evalueerde 2-jaars uitkomsten van patiënten die zich presenteerden met een acuut myocardinfarct en behandeld werden met Resolute Onyx of Orsiro stents in de BIONYX studie. Twee jaar na stentimplantatie hadden patiënten die behandeld waren voor een acuut myocardinfarct een lager risico op ongunstige uitkomsten dan patiënten die voor andere coronaire syndromen werden behandeld. Deze bevindingen waren voornamelijk toe te schrijven aan verschillen in baseline patiënt- en laesie karakteristieken tussen de groepen. Ook werd er in patiënten met een acuut myocardinfarct geen verschil gezien in target vessel failure tussen behandeling met Resolute Onyx of Orsiro (6.2% vs. 6.1%) en waren de percentages van stent trombose laag en vergelijkbaar in beide stent groepen (0.2% vs. 0.9%). Concluderend kan er gesteld worden dat de behandeling van een acuut myocardinfarct met zowel Resolute Onyx als Orsiro stents gunstige en vergelijkbare uitkomsten liet zien na 2 jaar.
Hoofdstuk 13 presenteerde de algemene discussie van de bevindingen van dit proefschrift.

Conclusies
Na tientallen jaren van stent innovatie en onderzoek in gerandomiseerde klinische studies zijn nieuwe-generatie medicijn-afgevende stents de eerste keus voor percutane behandeling van patiënten met obstructief coronairlijden. In dit proefschrift zijn de initiële gunstige klinische uitkomsten bevestigd op lange termijn.
Percutane behandeling met nieuwe-generatie Resolute Integrity, Synergy, en Orsiro stents was veilig en effectief in all-comer patiënten tot en met 5 jaar follow-up. De langst beschikbare follow-up van de nieuwe Resolute Onyx, een doorontwikkelde variant van

de Resolute Integrity stent, liet gunstige en vergelijkbare 3-jaars uitkomsten zien in vergelijking met de Orsiro stent. Subgroep analyses in patiënten met kleine vaten, acuut myocardinfarct of diabetes lieten geen verschillen in veiligheid en effectiviteit zien tussen de stents. Nieuwe statistische methoden die het perspectief van patiënten meenemen over de ernst van 'adverse events' en het feit dat events vaker kunnen optreden zouden mogelijk andere uitkomsten kunnen laten zien dan de huidige standaardmethoden. Dit zou in overweging genomen moeten worden bij het opzetten van toekomstige stentstudies zodat meer patiëntgericht en beter betaalbaar onderzoek verricht kan worden. Daarnaast moeten nieuwe richtlijnen continu geëvalueerd worden aangezien meerdere gelijktijdige aanpassingen kunnen leiden tot tegenstrijdige aanbevelingen. Dit was het geval met het gebruik van de arteria radialis welke wordt aanbevolen voor percutane vasculaire toegang (voor coronair angiografie of PCI), en als arteriële graft voor een coronaire bypass operatie. Bewustwording van dit mogelijke probleem is wenselijk zodat cardiologen in sommige gevallen alternatieve vasculaire toegang kunnen overwegen om de arteria radialis te sparen en deze beschikbaar te houden als eventuele bypass graft.

De uitstekende klinische uitkomsten van all-comer patiënten zijn veelbelovend en moedigen zelfs in hoog-risico groepen het gebruik van nieuwe-generatie medicijnafgevende stents aan. Hoewel er geen verschillen tussen stents werden gevonden na behandeling van verscheidene subgroepen, hadden patiënten met prediabetes, stille diabetes en bekende diabetes nog steeds een hoger risico op ongunstige uitkomsten dan patiënten met normoglycemie na behandeling met nieuwe-generatie medicijnafgevende stents. Ook hadden patiënten die 80 jaar of ouder waren een hoger risico op cardiale dood na behandeling met nieuwe-generatie medicijn-afgevende stents dan jongere patiënten, zoals verwacht kan worden op basis van de hogere leeftijd. Echter waren de risico's op myocardinfarct, stenttrombose en herhaalde revascularisatie vergelijkbaar tussen de groepen, wat suggereert dat de behandeling van 80-plussers met nieuwe-generatie medicijn-afgevende stents veilig en effectief is. Ten slotte hebben we gezien dat gerandomiseerde studiedeelnemers die zich presenteerden met een acuut myocardinfarct een lager risico hadden op ongunstige uitkomsten dan patiënten met stabiele coronaire syndromen of instabiele angina pectoris. Dit kan hoogstwaarschijnlijk verklaard worden door de lagere leeftijd en minder comorbiditeit in patiënten met een acuut myocardinfarct. Deze bevindingen kunnen als geruststellend beschouwd worden aangezien ze suggereren dat behandeling voor een acuut myocardinfarct (in tegenstelling tot een stabiel coronair syndroom) niet per se leidt tot slechtere klinische uitkomsten.

Waardegedreven zorg

Trajectories of Health Status in Older People

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 31 maart 2021 om 11.00 uur

door

Marlies Feenstra

geboren op 21 maart 1985
te Roden

Promotoren: Prof. dr. S.E.J.A. de Rooij
Prof. dr. B.C. van Munster
Dr. N. Smidt

Samenvatting

Maatschappelijke context

Het zal u niet ontgaan zijn: kranten staan vol van de gevolgen van de zogenaamde grijze golf of, mooier verpakt, de zilveren tsunami. Met deze metafoor wordt bedoeld dat het aantal ouderen ten opzichte van de werkende bevolking toeneemt, wat niet alleen de verwachting is voor de komende decennia in Nederland, maar ook wereldwijd. De veelal negatieve connotatie van deze termen komt door de daarmee gepaard gaande verwachte problemen. Ons sociale stelsel is zo ingericht dat de werkende bevolking de lasten draagt van de niet werkende bevolking, waaronder ouderen vallen. Met een grotere niet werkenden / werkenden ratio neemt de lastendruk op de werkende bevolking toe. Een van de maatregelen om deze lastendruk te verlagen is door mensen in staat te stellen zo lang mogelijk zelfstandig en in goede gezondheid te leven. Enerzijds komt dit tegemoet aan de behoeften van de meerderheid van de ouderen zelf, anderzijds zorgt het ervoor dat de zorg beheersbaar (qua personeelsbestand) en betaalbaar blijft en draagt op die manier bij aan verlaging van de lastendruk op onze werkende bevolking. Een manier om mensen in staat te stellen zo lang mogelijk zelfstandig en in goede gezondheid te leven is door interventies te ontwerpen en te implementeren om de optimale gezondheidstoestand bij ouderen te behouden of te herwinnen. Echter om hiertoe over te kunnen gaan is het nodige voorwerk vereist: ten eerste dient onderzocht te worden welke personen tot een hoog risico groep behoren om gericht interventies te kunnen toepassen; ten tweede dient onderzocht te worden wat mensen met een hoog risico op een slechte gezondheidstoestand onderscheidt van mensen met een laag risico op een slechte gezondheidstoestand om aanknopingspunten te verkrijgen voor het ontwikkelen van gerichte interventies; ten derde is het noodzakelijk om valide, betrouwbare en responsieve instrumenten te gebruiken om de effectiviteit van interventies te beoordelen. Met dit proefschrift is beoogd om een deel van dit voorwerk te doen, door psychometrische eigenschappen te onderzoeken van verschillende bestaande instrumenten die worden gebruikt om verandering in de gezondheidstoestand van ouderen te meten (Hoofdstukken 2, 3 en 4) en door trajecten van gezondheidstoestand van ouderen in kaart te brengen en de determinanten van deze verschillende trajecten te onderzoeken (Hoofdstukken 5 en 6).

Het meten van verandering in de gezondheidstoestand van ouderen

In de ouderenzorg zijn functionele status en kwetsbaarheidsstatus (frailty status) twee belangrijke uitkomsten die gebruikt worden om gezondheidstoestand van ouderen te meten. Functionele status wordt veelal gemeten door te tellen hoeveel activiteiten van het dagelijkse leven (ADL) iemand zonder hulp kan uitvoeren. De Katz ADL Index is daarbij het meest gebruikte instrument bij oudere ziekenhuispatiënten. Om de kwetsbaarheidsstatus van ouderen in kaart te brengen worden in de wetenschap twee instrumenten veel gebruikt: 1. Het ‘Frailty Phenotype’ instrument, een screeningsinstrument om fysieke kwetsbaarheid van ouderen te meten, en 2. De ‘Frailty Index’, die de kwetsbaarheid van ouderen in kaart gemeten over meerdere domeinen, zoals fysiek functioneren, sociaal functioneren, mentaal functioneren of symptomen of ziektes. Zowel de Katz ADL Index, het Frailty Phenotype instrument als de Frailty Index worden reeds gebruikt bij wetenschappelijk onderzoek om verandering in functionele dan wel kwetsbaarheidsstatus over de tijd te meten. In de literatuur is echter nog weinig bekend over de zogeheten responsieve eigenschappen van deze instrumenten, dat wil zeggen het vermogen van een instrument om verandering over

de tijd te meten. Daarom zijn in dit proefschrift twee studies uitgevoerd om de validiteit en responsiviteit van deze instrumenten te onderzoeken.

In Hoofdstuk 2 is onderzocht of de door de patiënt ervaren verandering in functionele status overeen komt met de gemeten verandering van het aantal ADL beperkingen, gemeten met de Katz ADL Index. Hierbij werden twee tijdsbestekken meegenomen: de functionele status vóór de ziekenhuisopname tot drie maanden na ziekenhuisopname en de functionele status vóór de ziekenhuisopname tot twaalf maanden na ziekenhuisopname. Over beide tijdsbestekken was de overeenkomst laag (<50%). Deze resultaten geven reden tot twijfel over de bruikbaarheid van dit instrument om verandering in ervaren functionele status van een patiënt over de tijd te meten. In Hoofdstuk 3 zijn de reproduceerbaarheid en responsiviteit onderzocht van de Frailty Index en het Frailty Phenotype instrument. Wederom zijn de tijdsbestekken van de situatie vóór de ziekenhuisopname tot drie en twaalf maanden na de ziekenhuisopname meegenomen. De Frailty Index bleek over een goede reproduceerbaarheid en responsiviteit te beschikken over beide tijdsbestekken. De Frailty Phenotype instrument presteerde minder goed: een slechte tot matige reproduceerbaarheid en een voldoende responsiviteit over een tijdsbestek van 12 maanden.

Hoofdstuk 4 was gewijd aan een (tot nog toe) minder gebruikt instrument in de ouderenzorg: de 'Pittsburgh Fatigability Scale (PFS)'. Deze vragenlijst heeft als doel om vermoeidheid tijdens het uitvoeren van fysieke activiteiten, zogeheten vermoeibaarheid, te meten en is door ons in het Nederlands vertaald en gevalideerd bij een groep oudere ziekenhuispatiënten. De Nederlandse versie van de PFS bleek een valide en betrouwbaar instrument om mentale en fysieke vermoeibaarheid bij ziekenhuispatiënten van 70 jaar en ouder te meten. Of deze Nederlandse versie van de PFS ook geschikt is voor andere groepen, zoals thuiswonende ouderen en in hoeverre een verandering gemeten met de PFS ook betekenisvol is voor de oudere zelf zal toekomstig onderzoek moeten uitwijzen.

Op basis van de resultaten van de eerste drie hoofdstukken van dit proefschrift, aangevuld met bestaande literatuur, zijn, in Hoofdstuk 7, de algemene discussie, aanbevelingen geformuleerd voor het gebruik van de onderzochte instrumenten om verandering in gezondheid van ouderen over de tijd te meten. Ten eerste, op basis van de slechte overeenkomst tussen ervaren verandering en gemeten verandering in functionele status bij oudere ziekenhuispatiënten en omdat uit eerder onderzoek is gebleken het kleinste betekenisvolle effect voor de patiënt binnen de kleinst meetbare verandering valt bij thuiswonende ouderen, werd aanbevolen om de Katz ADL index alleen op groepsniveau te gebruiken. Ten tweede is aanbevolen om de Frailty Index boven het Frailty Phenotype instrument te verkiezen om kwetsbaarheidsstatus over de tijd te meten bij ouderen. Ook voor deze instrumenten geldt de aanbeveling ze alleen op groepsniveau te gebruiken. Ten derde hebben we geconcludeerd op basis van de resultaten van de test-hertest gegevens dat de Nederlandse PFS kan worden gebruikt om verandering in vermoeibaarheid over de tijd op groepsniveau te meten.

Trajecten en determinanten van de gezondheidstoestand van ouderen
Om mensen met een hoog risico op gezondheidsproblemen te ondersteunen om hun risico te verlagen door bijvoorbeeld gedrags interventies toe te passen, dienen we te onderzoeken welke mensen tot de hoog risico groep behoren. Traject analyse is

hiervoor een geschikte methode omdat het binnen een gegeven groep subpopulaties in kaart brengt. Zodra verschillende subpopulaties binnen een groep gemodelleerd zijn, kunnen kenmerken van individuen binnen een subpopulatie worden vergeleken met kenmerken van individuen die tot een andere subpopulatie behoren. Op deze manier worden determinanten van bijvoorbeeld personen met een 'hoog risico op gezondheidsproblemen' zichtbaar. In dit proefschrift zijn determinanten van trajecten van generieke ervaren gezondheid (general self-rated health, SRH) (Hoofdstuk 5) en trajecten van vermoeibaarheid en mobiliteit onderzocht (Hoofdstuk 6).

In Hoofdstuk 5 werden vier stabiele trajecten van SRH over een tijdsbestek van vijf jaar geïdentificeerd. Personen die toebehoorden aan het minst gunstige SRH-traject waren vaker vrouw en hadden vaker een lagere opleidingsniveau, twee of meer chronische aandoeningen, een ongezonde leefstijl en afwijkingen in drie of meer fysiologische markers, wat een indicatie is voor een voorstadium van kwetsbaarheid.

In Hoofdstuk 6 werden drie verschillende trajectcombinaties van vermoeibaarheid en mobiliteit vanaf ziekenhuisopname tot zes maanden na ontslag geïdentificeerd. Personen die toebehoorden aan de minst gunstige traject, namelijk hoge mate van vermoeibaarheid en een lage mobiliteit, hadden vaker een lagere comorbiditeitsscore en een hogere kwetsbaarheidsstatus vóór de ziekenhuisopname. De resultaten van Hoofdstuk 6 dienen echter met voorzichtigheid geïnterpreteerd te worden vanwege het kleine aantal deelnemers aan deze studie.

Gebaseerd op de resultaten van Hoofdstukken 5 en 6 is in Hoofdstuk 7, de algemene discussie, geconcludeerd dat bepaalde determinanten die terug te voeren zijn op kwetsbaarheid een negatieve invloed op gezondheidstrajecten bij ouderen hebben. De aanwezigheid van meerdere chronische aandoeningen en (een voorstadium van) kwetsbaarheid zijn geïdentificeerd als de meest voorkomende determinanten van de minst gunstige gezondheids trajecten bij zowel thuiswonende ouderen als oudere ziekenhuispatiënten. Leefstijl kan een mogelijk aanknopingspunt vormen voor de inrichting van interventies. Uit eerder onderzoek blijkt dat ouderen met multimorbiditeit of kwetsbaarheid mogelijk kunnen profiteren van interventies die gericht zijn op het verbeteren van leefstijl en daarmee de gezondheidstoestand. Om de baten en kosten van dergelijke gerichte interventies verder te optimaliseren, is het belangrijk om nog nauwkeuriger de juiste groep mensen te identificeren die het meest kunnen profiteren van dergelijke interventies. Eerder onderzoek laat een verband zien tussen vermoeibaarheid en negatieve gezondheidsuitkomsten van ouderen, zoals functionele achteruitgang. Ook uit Hoofdstuk 6 blijkt dat de mate van vermoeibaarheid geassocieerd is met het verloop van mobiliteit van oudere ziekenhuispatiënten. Op basis hiervan is aanbevolen dat toekomstig onderzoek gedaan dient te worden naar de meerwaarde van vermoeibaarheid als screeningsinstrument voor de identificatie van ouderen die mogelijk kunnen profiteren van interventies om hun kwetsbaarheidsstatus te verbeteren. Daarnaast pleiten we voor toekomstige studies die de relatie tussen vermoeibaarheid en kwetsbaarheid nader onderzoeken alsmede welke interventies het meest geschikt zijn om vermoeibaarheid bij ouderen te verbeteren.

PubMed publicaties per vakgroep
Anesthesiologie

1. **Study protocol for a randomised controlled trial on the effect of local analgesia for pain relief after minimal invasive sacroiliac joint fusion: the ARTEMIS study**
Hermans SMM, Nellensteijn JM, van Santbrink H, Knoef R, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

Introduction: Chronic lower back pain is a common report in the general population. A dysfunctional sacroiliac joint (SIJ) is estimated to be responsible for one in five patients with lower back pain. Minimally invasive sacroiliac joint fusion (MISJF) is a surgical procedure to treat SIJ dysfunction. During the procedure, the SIJ is stabilised by implants inserted percutaneously under fluoroscopy guidance. Postoperatively, patients often report a lot of pain, which contributes to patients taking high doses of painkillers (opioids for example,) and preventing early mobilisation. In several orthopaedic procedures, intraoperative infiltration of the wound bed results in decreased consumption of analgesics, earlier mobilisation and shorter hospitalisation time. The aim of this study is to investigate the effectiveness of intraoperative SIJ infiltration with analgesia in reducing postoperative pain after MISJF.
Methods and analysis: We will perform a two-centre, prospective, double-blind, randomised controlled trial to determine whether SIJ infiltration with 1.5-5 cc bupivacaine 0.50% is superior to 1.5-5 cc placebo (NaCl 0.9%) in reducing postoperative pain in patients after MISJF, and to determine whether bupivacaine significantly reduces opioid use in the direct postoperative period. Patients will be randomised with 1:1 allocation for either bupivacaine (intervention) or placebo SIJ infiltration. Postoperative pain will be measured by the Visual Analogue Scale pain score at entry and exit recovery, 2, 4, 6, 24 and 48 hours postoperatively.
Ethics and dissemination: This is the first trial that investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% in reducing postoperative pain after MISJF. If intraoperative SIJ infiltration with bupivacaine 0.50% proves to be effective, this might have important clinical implications, such as postoperative analgesics (opioids for example,) consumption, earlier mobilisation and potentially shorter hospitalisation time.
Trial registration number: NL9151.

Gepubliceerd: BMJ Open. 2021;11(12):e056204.
Impact factor: 2.692; Q2

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2. **Multiple sclerosis is linked to MAPK(ERK) overactivity in microglia**
Ten Bosch GJA, Bolk J, t Hart BA, Laman JD.

Reassessment of published observations in patients with multiple sclerosis (MS) suggests a microglial malfunction due to inappropriate (over)activity of the mitogen-activated protein kinase pathway ERK (MAPK(ERK)). These observations regard biochemistry as well as epigenetics, and all indicate involvement of this pathway. Recent preclinical research on neurodegeneration already pointed towards a role of MAPK pathways, in particular MAPK(ERK). This is important as microglia with overactive MAPK have been identified to disturb local oligodendrocytes which can lead to locoregional demyelination, hallmark of MS. This constitutes a new concept on

pathophysiology of MS, besides the prevailing view, i.e., autoimmunity. Acknowledged risk factors for MS, such as EBV infection, hypovitaminosis D, and smoking, all downregulate MAPK(ERK) negative feedback phosphatases that normally regulate MAPK(ERK) activity. Consequently, these factors may contribute to inappropriate MAPK(ERK) overactivity, and thereby to neurodegeneration. Also, MAPK(ERK) overactivity in microglia, as a factor in the pathophysiology of MS, could explain ongoing neurodegeneration in MS patients despite optimized immunosuppressive or immunomodulatory treatment. Currently, for these patients with progressive disease, no effective treatment exists. In such refractory MS, targeting the cause of overactive MAPK(ERK) in microglia merits further investigation as this phenomenon may imply a novel treatment approach.

Gepubliceerd: J Mol Med (Berl). 2021;99(8):1033-42.
Impact factor: 4.599; Q2

Totale impact factor: 7.291
Gemiddelde impact factor: 3.646

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 4.599
Gemiddelde impact factor: 4.599

Dermatologie

1. **Systematic Review of the Role of Mohs Micrographic Surgery in the Management of Early-Stage Melanoma of the Head and Neck**
Theunissen CCW, Lee MH, Murad FG, Waldman AH.

Background: The role of Mohs micrographic surgery (MMS) in the management of melanoma of the head and neck (HNM) has been controversial. The authors systematically reviewed the local recurrence rate of melanoma in situ (MIS) and T1a melanomas using MMS compared with conventional wide local excision (WLE) and staged excision (SE).
Objective: To systematically review the local recurrence rate of early-stage melanomas of the HNM treated with MMS versus WLE or SE.
Methods and materials: A search of English medical literature was conducted through the common databases until November 26, 2019. Using PRISMA guidelines for the treatment of MIS and T1a melanoma with MMS, WLE, or SE, our search yielded a total of 32 articles.
Results: Mohs micrographic surgery has a lower local recurrence rate for early-stage melanomas over both SE and WLE {pooled recurrence risk 0.8% (95% confidence interval [CI] 0.4-1.1) versus 2.5% (95% CI 1.5-3.4) versus 8.7% (95% CI 5.1-12.2) ($p < .001$), respectively}.
Conclusion: Mohs micrographic surgery may offer a lower recurrence rate than SE or WLE in the management of early-stage melanomas of the face or HNM. Further clinical validation in a randomized controlled trial is required.

Gepubliceerd: Dermatol Surg. 2021;47(9):1185-9.
Impact factor: 3.398; Q2

Totale impact factor: 3.398
Gemiddelde impact factor: 3.398

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.398
Gemiddelde impact factor: 3.398

Gynaecologie

1. **Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding**

Beelen P, van den Brink MJ, Herman MC, Geomini P, Dekker JH, Duijnhoven RG, Mak N, van Meurs HS, Coppus SF, van der Steeg JW, Eising HP, Massop-Helmink DS, Klinkert ER, Nieboer TE, Timmermans A, van der Voet LF, Veersema S, Smeets NAC, Schutte JM, van Baal M, Bossuyt PM, Mol BWJ, Berger MY, Bongers MY.

Background: Heavy menstrual bleeding affects the physical functioning and social well-being of many women. The levonorgestrel-releasing intrauterine system and endometrial ablation are 2 frequently applied treatments in women with heavy menstrual bleeding.
Objective: This study aimed to compare the effectiveness of the levonorgestrel-releasing intrauterine system with endometrial ablation in women with heavy menstrual bleeding.
Study design: This multicenter, randomized controlled, noninferiority trial was performed in 26 hospitals and in a network of general practices in the Netherlands. Women with heavy menstrual bleeding, aged 34 years and older, without a pregnancy wish or intracavitary pathology were randomly allocated to treatment with either the levonorgestrel-releasing intrauterine system (Mirena) or endometrial ablation, performed with a bipolar radiofrequency device (NovaSure). The primary outcome was blood loss at 24 months, measured with a Pictorial Blood Loss Assessment Chart score. Secondary outcomes included reintervention rates, patient satisfaction, quality of life, and sexual function.
Results: We registered 645 women as eligible, of whom 270 women provided informed consent. Of these, 132 women were allocated to the levonorgestrel-releasing intrauterine system (baseline Pictorial Blood Loss Assessment Chart score, 616) and 138 women to endometrial ablation (baseline Pictorial Blood Loss Assessment Chart score, 630). At 24 months, mean Pictorial Blood Loss Assessment Chart scores were 64.8 in the levonorgestrel-releasing intrauterine system group and 14.2 in the endometrial ablation group (difference, 50.5 points; 95% confidence interval, 4.3-96.7; noninferiority, P=.87 [25 Pictorial Blood Loss Assessment Chart point margin]). Compared with 14 women (10%) in the endometrial ablation group, 34 women (27%) underwent a surgical reintervention in the levonorgestrel-releasing intrauterine system group (relative risk, 2.64; 95% confidence interval, 1.49-4.68). There was no significant difference in patient satisfaction and quality of life between the groups.
Conclusion: Both the levonorgestrel-releasing intrauterine system and endometrial ablation strategies lead to a large decrease in menstrual blood loss in women with heavy menstrual bleeding, with comparable quality of life scores after treatment. Nevertheless, there was a significant difference in menstrual blood loss in favor of endometrial ablation, and we could not demonstrate noninferiority of starting with the levonorgestrel-releasing intrauterine system. Women who start with the levonorgestrel-releasing intrauterine system, a reversible and less invasive treatment, are at an increased risk of needing additional treatment compared with women who start with endometrial ablation. The results of this study will enable physicians to provide women with heavy menstrual bleeding with the evidence to make a well-informed decision between the 2 treatments.

Gepubliceerd: Am J Obstet Gynecol. 2021;224(2):187.e1-.e10.
Impact factor: 8.661; Q1

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2. **How the Gut Microbiome Links to Menopause and Obesity, with Possible Implications for Endometrial Cancer Development**
Schreurs MPH, de Vos van Steenwijk PJ, Romano A, Dieleman S, Werner HMJ.

Background: Interest is growing in the dynamic role of gut microbiome disturbances in human health and disease. No direct evidence is yet available to link gut microbiome dysbiosis to endometrial cancer. This review aims to understand any association between microbiome dysbiosis and important risk factors of endometrial cancer, high estrogen levels, postmenopause and obesity.
Methods: A systematic search was performed with PubMed as primary database. Three separate searches were performed to identify all relevant studies.
Results: Fifteen studies were identified as highly relevant and included in the review. Eight articles focused on the relationship with obesity and eight studies focused on the menopausal change or estrogen levels. Due to the heterogeneity in patient populations and outcome measures, no meta-analysis could be performed. Both the menopausal change and obesity were noted to enhance dysbiosis by reducing microbiome diversity and increasing the Firmicutes to Bacteroidetes ratio. Both also incurred estrobolome changes, leading to increased systemic estrogen levels, especially after menopause. Furthermore, microbiome dysbiosis was reported to be related to systemic inflammation through toll-like receptor signaling deficiencies and overexpression of pro-inflammatory cytokines.
Conclusions: This review highlights that the female gut microbiome is intrinsically linked to estrogen levels, menopausal state and systemic inflammation, which indicates gut microbiome dysbiosis as a potential hallmark for risk stratification for endometrial cancer. Studies are needed to further define the role the gut microbiome plays in women at risk for endometrial cancer.

Gepubliceerd: J Clin Med. 2021;10(13).
Impact factor: 4.242; Q1

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3. **Childbirths and the Prevalence of Potential Risk Factors for Adverse Perinatal Outcomes among Asylum Seekers in The Netherlands: A Five-Year Cross-Sectional Study**
Tankink JB, Verschuuren AEH, Postma IR, van der Lans PJA, de Graaf JP, Stekelenburg J, Mesman AW.

This five-year cross-sectional study mapped the prevalence of several known risk factors for adverse perinatal outcomes in asylum-seeking women in The Netherlands. Characteristics of 2831 registered childbirths among residents of asylum seekers centers (ASCs) in The Netherlands from 2016 to 2020 were included. Results showed a high general and teenage birthrate (2.15 and 6.77 times higher compared to the Dutch, respectively). Most mothers were pregnant upon arrival, and the number of births was highest in the second month of stay in ASCs. Another peak in births between 9 and 12 months after arrival suggested that many women became pregnant shortly after arrival in The Netherlands. Furthermore, 69.5 percent of all asylum-seeking

women were relocated between ASCs at least once during pregnancy, which compromises continuity of care. The high prevalence of these risk factors in our study population might explain the increased rate of adverse pregnancy outcomes in asylum seekers compared to native women found in earlier studies. Incorporating migration-related indicators in perinatal health registration is key to support future interventions, policies, and research. Ultimately, our findings call for tailored and timely reproductive and perinatal healthcare for refugee women who simultaneously face the challenges of resettlement and pregnancy.

Gepubliceerd: Int J Environ Res Public Health. 2021;18(24).
Impact factor: 3.390; Q1

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4. **A lifestyle intervention randomized controlled trial in obese women with infertility improved body composition among those who experienced childhood adversity**
van Dammen L, Bush NR, de Rooij S, Mol BW, Mutsaerts M, van Oers A, Groen H, Hoek A, Roseboom T.

Previous research indicates that tailoring lifestyle interventions to participant characteristics optimizes intervention effectiveness. Our objective was to assess whether the effects of a preconception lifestyle intervention in obese infertile women depended on women's exposure to adversity in childhood. A follow-up of a preconception lifestyle intervention randomized controlled trial (the LIFEstyle study) was conducted in the Netherlands among 577 infertile women (age 18-39 years) with a body mass index (BMI) ≥29 kg/m(2) at time of randomization; N = 110 (19%) consented to the follow-up assessment, 6 years later. A 6-month preconception lifestyle intervention aimed weight loss through improving diet and increasing physical activity. The control group received care as usual. Outcome measures included weight, BMI, waist and hip circumference, body fat percentage, blood pressure and metabolic syndrome. The potential moderator, childhood adversity, was assessed with the Life Events Checklist-5 questionnaire. Among the 110 women in our follow-up study, n = 65 (59%) reported no childhood adverse events, n = 28 (25.5%) reported 1 type of childhood adverse events and n = 17 (15.5%) reported ≥2 types of childhood adverse events. Regression models showed significant interactions between childhood adversity and effects of lifestyle intervention at the 6-year follow-up. Among women who experienced childhood adversity, the intervention significantly reduced weight (-10.0 [95% CI -18.5 to -1.5] kg, p = 0.02), BMI (-3.2 [-6.1 to -0.2] kg/m(2) , p = 0.04) and body fat percentage (-4.5 [95% CI -7.2 to -1.9] p < 0.01). Among women without childhood adversity, the intervention did not affect these outcomes (2.7 [-3.9 to 9.4] kg, p = 0.42), (0.9 [-1.4 to 3.3] kg/m(2) , p = 0.42) and (1.7 [95% CI -0.3 to 3.7] p = 0.10), respectively. Having a history of childhood adversity modified the effect of a preconception lifestyle intervention on women's body composition. If replicated, it may be important to consider childhood adversity as a determinant of lifestyle intervention effectiveness.

Gepubliceerd: Stress Health. 2021;37(1):93-102.
Impact factor: 3.519; Q2

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5. **Birthweight and other perinatal outcomes of singletons conceived after assisted reproduction compared to natural conceived singletons in couples with unexplained subfertility: follow-up of two randomized clinical trials**
Wessel JA, Mol F, Danhof NA, Bensdorp AJ, Tjon-Kon Fat RI, Broekmans FJM, Hoek A, Mol BWJ, Mochtar MH, van Wely M, M. INeS and SUPER Study Group – includes Verberg MFG.

Study question: Does assisted reproduction, such as ovarian stimulation and/or laboratory procedures, have impact on perinatal outcomes of singleton live births compared to natural conception in couples with unexplained subfertility?
Summary answer: Compared to natural conception, singletons born after intrauterine insemination with ovarian stimulation (IUI-OS) had a lower birthweight, while singletons born after IVF had comparable birthweights, in couples with unexplained subfertility.
What is known already: Singletons conceived by assisted reproduction have different perinatal outcomes such as low birthweight and a higher risk of premature birth than naturally conceived singletons. This might be due to the assisted reproduction, such as laboratory procedures or the ovarian stimulation, or to an intrinsic factor in couples with subfertility.
Study design, size, duration: We performed a prospective cohort study using the follow-up data of two randomized clinical trials performed in couples with unexplained subfertility. We evaluated perinatal outcomes of 472 live birth singletons conceived after assisted reproduction or after natural conception within the time horizon of the studies.
Participants/materials, setting, methods: To assess the possible impact of ovarian stimulation we compared the singletons conceived after IUI with FSH or clomiphene citrate (CC) and IVF in a modified natural cycle (IVF-MNC) or standard IVF with single embryo transfer (IVF-SET) to naturally conceived singletons in the same cohorts. To further look into the possible effect of the laboratory procedures, we put both IUI and IVF groups together into IUI-OS and IVF and compared both to singletons born after natural conception. We only included singletons conceived after fresh embryo transfers. The main outcome was birthweight presented as absolute weight in grams and gestational age- and gender-adjusted percentiles. We calculated differences in birthweight using regression analyses adjusted for maternal age, BMI, smoking, parity, duration of subfertility and child gender.
Main results and the role of chance: In total, there were 472 live birth singletons. Of the 472 singleton pregnancies, 209 were conceived after IUI-OS (136 with FSH and 73 with CC as ovarian stimulation), 138 after IVF (50 after IVF-MNC and 88 after IVF-SET) and 125 were conceived naturally.Singletons conceived following IUI-FSH and IUI-CC both had lower birthweights compared to naturally conceived singletons (adjusted difference IUI-FSH -156.3 g, 95% CI -287.9 to -24.7; IUI-CC -160.3 g, 95% CI -316.7 to -3.8). When we compared IVF-MNC and IVF-SET to naturally conceived singletons, no significant difference was found (adjusted difference IVF-MNC 75.8 g, 95% CI -102.0 to 253.7; IVF-SET -10.6 g, 95% CI -159.2 to 138.1). The mean birthweight percentile was only significantly lower in the IUI-FSH group (-7.0 percentile, 95% CI -13.9 to -0.2). The IUI-CC and IVF-SET group had a lower mean percentile and the IVF-MNC group a higher mean percentile, but these groups were not significant different compared to the naturally conceived group (IUI-CC -5.1 percentile, 95% CI -13.3 to 3.0; IVF-MNC 4.4 percentile, 95% CI -4.9 to 13.6; IVF-SET -1.3 percentile, 95% CI -9.1 to 6.4).Looking at the laboratory process that took place, singletons conceived following IUI-OS had lower birthweights than naturally conceived singletons (adjusted difference -157.7 g,

95% CI -277.4 to -38.0). The IVF group had comparable birthweights with the naturally conceived group (adjusted difference 20.9 g, 95% CI -110.8 to 152.6). The mean birthweight percentile was significantly lower in the IUI-OS group compared to the natural group (-6.4 percentile, 95% CI -12.6 to -0.1). The IVF group was comparable (0.7 percentile, 95% CI -6.1 to 7.6).
Limitations, reasons for caution: The results are limited by the number of cases. The data were collected prospectively alongside the randomized controlled trials, but analyzed as treated.
Wider implications of the findings: Our data suggest IUI in a stimulated cycle may have a negative impact on the birthweight of the child and possibly on pre-eclampsia. Further research should look into the effect of different methods of ovarian stimulation on placenta pathology and pre-eclampsia in couples with unexplained subfertility using naturally conceived singletons in the unexplained population as a reference.
Trial registration number: INeS study Trial NL915 (NTR939); SUPER Trial NL3895 (NTR4057).

Gepubliceerd: Hum Reprod. 2021;36(3):817-25.
Impact factor: 6.918; Q1

Totale impact factor: 26.730
Gemiddelde impact factor: 5.346

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 4.242
Gemiddelde impact factor: 4.242

Heelkunde

1. **Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomized controlled study (PelvEx II)**
PelvEx Collaborative – includes van Duyn EB.

Background: A resection with clear margins (R0 resection) is the most important prognostic factor in patients with locally recurrent rectal cancer (LRRC). However, this is achieved in only 60 per cent of patients. The aim of this study is to investigate whether the addition of induction chemotherapy to neoadjuvant chemo(re)irradiation improves the R0 resection rate in LRRC.
Methods: This multicentre, international, open-label, phase III, parallel-arms study will enrol 364 patients with resectable LRRC after previous partial or total mesorectal resection without synchronous distant metastases or recent chemo- and/or radiotherapy treatment. Patients will be randomized to receive either induction chemotherapy (three 3-week cycles of CAPOX (capecitabine, oxaliplatin), four 2-week cycles of FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) or FOLFORI (5-fluorouracil, leucovorin, irinotecan)) followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm). Tumours will be restaged using MRI and, in the experimental arm, a further cycle of CAPOX or two cycles of FOLFOX/FOLFIRI will be administered before chemoradiotherapy in case of stable or responsive disease. The radiotherapy dose will be 25 × 2.0 Gy or 28 × 1.8 Gy in radiotherapy-naive patients, and 15 × 2.0 Gy in previously irradiated patients. The concomitant chemotherapy agent will be capecitabine administered twice daily at a dose of 825 mg/m2 on radiotherapy days. The primary endpoint of the study is the R0 resection rate. Secondary endpoints are long-term oncological outcomes, radiological and pathological response, toxicity, postoperative complications, costs, and quality of life.
Discussion: This trial protocol describes the PelvEx II study. PelvEx II, designed as a multicentre, open-label, phase III, parallel-arms study, is the first randomized study to compare induction chemotherapy followed by neoadjuvant chemo(re)irradiation and surgery with neoadjuvant chemo(re)irradiation and surgery alone in patients with locally recurrent rectal cancer, with the aim of improving the number of R0 resections.

Gepubliceerd: BJS Open. 2021;5(3).
Impact factor: 3.396; Q2

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2. **Real World Practice Deviation from Nationwide Guidelines in Patients with Intermittent Claudication**
Aaij AGL, Wermelink B, Haalboom M, Vahl AC, Meerwaldt R, Geelkerken RH.

Objective: Patients with intermittent claudication (IC) are initially treated with supervised exercise therapy (SET), as advised by national and international guidelines. Dutch health insurance companies and the Dutch National Health Care Institute suggested an 87% compliance rate with these guidelines in the Netherlands in 2017 and judged this to be undesirably low. The aim of this study was to evaluate compliance

with IC guidelines and to elaborate on the reasons for deviating from them (practice variation) in a large teaching hospital.
Methods: A retrospective single centre cohort study was conducted at a large teaching hospital in the Netherlands. In total, 420 patients with newly diagnosed IC between 1 January 2017 and 31 December 2018 were analysed. Data included risk profiles and prescribed therapies.
Results: For all 420 included patients, the compliance rate with the guidelines for SET was 80.5%. The rate of adequately motivated and defensible practice variation was 15.7%; the rate of unjustified practice variation was 3.8%. Meaningful care was seen in 96.2% of cases.
Conclusion: Deviation from IC guidelines was found in 19.5% of patients. Almost three quarters of this deviation can be explained by the decision to provide personalised, meaningful care.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2021;62(3):432-8.
Impact factor: 7.069; Q1

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3. **Outcomes in Octogenarians and the Effect of Comorbidities After Intact Abdominal Aortic Aneurysm Repair in the Netherlands: A Nationwide Cohort Study**
Alberga AJ, Karthaus EG, van Zwet EW, de Bruin JL, van Herwaarden JA, Wever JJ, Verhagen HJM. In collaboration with the Dutch Society of Vascular Surgery – includes Beuk RJ, Geelkerken RH, Meerwaldt R, Willigendael EM.

Objective: Age is an independent risk factor for mortality after both elective open surgical repair (OSR) and endovascular aneurysm repair (EVAR). As a result of an ageing population, and the less invasive nature of EVAR, the number of patients over 80 years (octogenarians) being treated is increasing. The mortality and morbidity following aneurysm surgery are increased for octogenarians. However, the mortality for octogenarians who have either low or high peri-operative risks remains unclear. The aim of this study was to provide peri-operative outcomes of octogenarians vs. non-octogenarians after OSR and EVAR for intact aneurysms, including separate subanalyses for elective and urgent intact repair, based on a nationwide cohort. Furthermore, the influence of comorbidities on peri-operative mortality was examined.
Methods: All patients registered in the Dutch Surgical Aneurysm Audit (DSAA) undergoing intact AAA repair between 2013 and 2018, were included. Patient characteristics and peri-operative outcomes (peri-operative mortality, and major complications) of octogenarians vs. non-octogenarians for both OSR and EVAR were compared using descriptive statistics. Multivariable logistic regression analyses were used to examine whether age and the presence of cardiac, pulmonary, or renal comorbidities were associated with mortality.
Results: This study included 12 054 EVAR patients (3 015 octogenarians), and 3 815 OSR patients (425 octogenarians). Octogenarians in both the EVAR and OSR treatment groups were more often female and had more comorbidities. In both treatment groups, octogenarians had significantly higher mortality rates following intact repair as well as higher major complication rates. Mortality rates of octogenarians were 1.9% after EVAR and 11.8% after OSR. Age ≥ 80 and presence of cardiac, pulmonary, and renal comorbidities were associated with mortality after EVAR and OSR.

Conclusion: Because of the high peri-operative mortality rates of octogenarians, awareness of the presence of comorbidities is essential in the decision making process before offering aneurysm repair to this cohort, especially when OSR is considered.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2021;61(6):920-8.
Impact factor: 7.069; Q1

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4. **Sacroiliac joint fusion in patients with Ehlers Danlos Syndrome: A case series**
Beijk I, Knoef R, van Vugt A, Verra W, Nellensteijn J.

Background: Sacroiliac joint dysfunction (SJD) is a known cause of lower back pain. SJD might be due to hypermobility in the Sacroiliac joint (SIJ) in patients with Ehlers Danlos Syndrome (EDS). Stabilization of the SIJ can be a highly successful treatment for lower back pain. No previous literature about EDS and SIJ fusion is available. The purpose of this study was to assess our mid-term results of SIJ fusion surgery in EDS patients suffering from SIJ dysfunction.
Methods: A case series of patients who underwent SIJ fusion for SIJ dysfunction due to EDS between January 2012 and December 2018 were analyzed in retrospect. Patients underwent surgery and the SIJ was stabilized with triangular implants bridging the joint. Pain and functional outcomes were assessed in nine agree/disagree questions and a satisfaction performance scale. Clinical data has been extracted from the patient files and in addition, we reassessed the position of the implants on the CT scans.
Results: A total of 16 patients with EDS completed the questionnaire and were available for analysis. The mean satisfaction score is 78.1 out of 100 and seven patients reported a 100% satisfaction score.
Conclusion: SIJ fusion is a safe and useful procedure to reduce pain and function levels in EDS patients with lower back pain due to SIJ dysfunction.

Gepubliceerd: N Am Spine Soc J. 2021;8:100082.
Impact factor: 0; NVT

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5. **MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): a statistical analysis plan**
Bousema JE, Annema JT, van der Heijden E, Verhagen A, Dijkgraaf MGW, van den Broek FJC, MEDIASTrial study group – includes van Duyn EB.

Background: Invasive mediastinal nodal staging is recommended by guidelines in selected patients with resectable non-small cell lung cancer (NSCLC). Endosonography is recommended as initial staging technique, followed by confirmatory mediastinoscopy in case of negative N2 or N3 cytology after endosonography. Confirmatory mediastinoscopy however is under debate owing its limited additional diagnostic value, its associated morbidity and its delay in the start of lung cancer treatment. The MEDIASTrial examines whether confirmatory mediastinoscopy can be safely omitted after negative endosonography in mediastinal nodal staging of NSCLC. The present work is the proposed statistical analysis plan of the clinical consequences of omitting mediastinoscopy, which is submitted before closure of the MEDIASTrial and

before knowledge of any results was done to enhance transparency of scientific behaviour.
Methods: The primary outcome measure of this non-inferiority trial will be unforeseen N2 disease resulting from lobe-specific mediastinal lymph node dissection. For non-inferiority, the upper limit of the 95% confidence interval of the unforeseen N2 rate in the group without mediastinoscopy should not exceed 14.3% in order to probably have no negative impact on survival. Since this is a non-inferiority trial, both an intention to treat (ITT) and a per protocol (PP) analyses will be done. The ITT and the PP analyses should both indicate non-inferiority before the diagnostic strategy omitting mediastinoscopy will be interpreted as non-inferior to the strategy with mediastinoscopy. Secondary outcome measures include 30-day major morbidity and mortality, the total number of days of hospital care, overall and disease free 2-year survival, generic and disease-specific health related quality of life and cost-effectiveness and cost-utility of staging strategies with and without mediastinoscopy.
Discussion: The MEDIASTrial will determine if confirmatory mediastinoscopy can be omitted after tumour negative systematic endosonography in invasive mediastinal staging of patients with resectable NSCLC.
Trial registrattion: Netherlands Trial Register NL6344/NTR6528 . Registered on 2017 July 06.

Gepubliceerd: Trials. 2021;22(1):168.
Impact factor: 2.279; Q4

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6. **Survival Benefit Associated With Resection of Locally Advanced Pancreatic Cancer After Upfront FOLFIRINOX Versus FOLFIRINOX Only: Multicenter Propensity Score-matched Analysis**
Brada LJH, Daamen LA, Magermans LG, Walma MS, Latifi D, van Dam RM, de Hingh IH, Liem MSL, de Meijer VE, Patijn GA, Festen S, Stommel MWJ, Bosscha K, Polée MB, Nio YC, Wessels FJ, de Vries JJJ, van Lienden KP, Bruijnen RC, Busch OR, Koerkamp BG, van Eijck C, Molenaar QI, Wilmink HJW, van Santvoort HC, Besselink MG.

Objective: This study compared median OS after resection of LAPC after upfront FOLFIRINOX versus a propensity-score matched cohort of LAPC patients treated with FOLFIRINOX-only (ie, without resection).
Background: Because the introduction of FOLFIRINOX chemotherapy, increased resection rates in LAPC patients have been reported, with improved OS. Some studies have also reported promising OS with FOLFIRINOX-only treatment in LAPC. Multicenter studies assessing the survival benefit associated with resection of LAPC versus patients treated with FOLFIRINOX-only are lacking.
Methods: Patients with non-progressive LAPC after 4 cycles of FOLFIRINOX treatment, both with and without resection, were included from a prospective multicenter cohort in 16 centers (April 2015-December 2019). Cox regression analysis identified predictors for OS. One-to-one propensity score matching (PSM) was used to obtain a matched cohort of patients with and without resection. These patients were compared for OS.
Results: Overall, 293 patients with LAPC were included, of whom 89 underwent a resection. Resection was associated with improved OS (24 vs 15 months, $P < 0.01$), as compared to patients without resection. Before PSM, resection, Charlson Comorbidity

Index, and Response Evaluation Criteria in Solid Tumors (RECIST) response were predictors for OS. After PSM, resection remained associated with improved OS [Hazard Ratio (HR) 0.344, 95% confidence interval (0.222-0.534), P < 0.01], with an OS of 24 versus 15 months, as compared to patients without resection. Resection of LAPC was associated with improved 3-year OS (31% vs 11%, P < 0.01).
Conclusions: Resection of LAPC after FOLFIRINOX was associated with increased OS and 3-year survival, as compared to propensity-score matched patients treated with FOLFIRINOX-only.

Gepubliceerd: Ann Surg. 2021;274(5):729-35.
Impact factor: 12.969; Q1

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7. **Predicting overall survival and resection in patients with locally advanced pancreatic cancer treated with FOLFIRINOX: Development and internal validation of two nomograms**
Brada LJH, Walma MS, Daamen LA, van Roessel S, van Dam RM, de Hingh IH, Liem MLS, de Meijer VE, Patijn GA, Festen S, Stommel MWJ, Bosscha K, Polée MB, Yung Nio C, Wessels FJ, de Vries JJJ, van Lienden KP, Bruijnen RC, Los M, Mohammad NH, Wilmink HW, Busch OR, Besselink MG, Quintus Molenaar I, van Santvoort HC.

Background and objectives: Patients with locally advanced pancreatic cancer (LAPC) are increasingly treated with FOLFIRINOX, resulting in improved survival and resection of tumors that were initially unresectable. It remains unclear, however, which specific patients benefit from FOLFIRINOX. Two nomograms were developed predicting overall survival (OS) and resection at the start of FOLFIRINOX for LAPC.
Methods: From our multicenter, prospective LAPC registry in 14 Dutch hospitals, LAPC patients starting first-line FOLFIRINOX (April 2015-December 2017) were included. Stepwise backward selection according to the Akaike Information Criterion was used to identify independent baseline predictors for OS and resection. Two prognostic nomograms were generated.
Results: A total of 252 patients were included, with a median OS of 14 months. Thirty-two patients (13%) underwent resection, with a median OS of 23 months. Older age, female sex, Charlson Comorbidity Index ≤1, and CA 19.9 < 274 were independent factors predicting a better OS (c-index: 0.61). WHO ps >1, involvement of the superior mesenteric artery, celiac trunk, and superior mesenteric vein ≥ 270° were independent factors decreasing the probability of resection (c-index: 0.79).
Conclusions: Two nomograms were developed to predict OS and resection in patients with LAPC before starting treatment with FOLFIRINOX. These nomograms could be beneficial in the shared decision-making process and counseling of these patients.

Gepubliceerd: J Surg Oncol. 2021;124(4):589-97.
Impact factor: 3.454; Q2

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8. **The treatment and survival of elderly patients with locally advanced pancreatic cancer: A post-hoc analysis of a multicenter registry**
Brada LJH, Walma MS, van Dam RM, de Vos-Geelen J, de Hingh IH, Creemers GJ, Liem MSL, Mekenkamp LJ, de Meijer VE, de Groot DJA, Patijn GA, de Groot JWB, Festen S, Kerver ED, Stommel MWJ, Meijerink MR, Bosscha K, Pruijt JF, Polée MB,

Ropela JA, Cirkel GA, Los M, Wilmink JW, Haj Mohammad N, van Santvoort HC, Besselink MG, Molenaar IQ.

Background: The treatment options for patients with locally advanced pancreatic cancer (LAPC) have improved in recent years and consequently survival has increased. It is unknown, however, if elderly patients benefit from these improvements in therapy. With the ongoing aging of the patient population and an increasing incidence of pancreatic cancer, this patient group becomes more relevant. This study aims to clarify the association between increasing age, treatment and overall survival in patients with LAPC.
Methods: Post-hoc analysis of a multicenter registry including consecutive patients with LAPC, who were registered in 14 centers of the Dutch Pancreatic Cancer Group (April 2015-December 2017). Patients were divided in three groups according to age (<65, 65-74 and ≥75 years). Primary outcome was overall survival stratified by primary treatment strategy. Multivariable regression analyses were performed to adjust for possible confounders.
Results: Overall, 422 patients with LAPC were included; 162 patients (38%) aged <65 years, 182 patients (43%) aged 65-74 and 78 patients (19%) aged ≥75 years. Chemotherapy was administered in 86%, 81% and 50% of the patients in the different age groups (p<0.01). Median overall survival was 12, 11 and 7 months for the different age groups (p<0.01).Patients treated with chemotherapy showed comparable median overall survival of 13, 14 and 10 months for the different age groups (p=0.11). When adjusted for confounders, age was not associated with overall survival.
Conclusion: Elderly patients are less likely to be treated with chemotherapy, but when treated with chemotherapy, their survival is comparable to younger patients.

Gepubliceerd: Pancreatology. 2021;21(1):163-9.
Impact factor: 3.996; Q2

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9. **Added value of 3D-vision during robotic pancreatoduodenectomy anastomoses in biotissue (LAEBOT 3D2D): a randomized controlled cross-over trial**

Zwart MJW, Jones LR, Balduzzi A, Takagi K, Vanlander A, van den Boezem PB, Daams F, Rosman C, Lips DJ, Moser AJ, Hogg ME, Busch ORC, Stommel MWJ, Besselink MG.

Background: We tested the added value of 3D-vision on procedure time and surgical performance during robotic pancreatoduodenectomy anastomoses in biotissue. Robotic surgery has the advantage of articulating instruments and 3D-vision. Consensus is lacking on the added value of 3D-vision during laparoscopic surgery. Given the improved dexterity with robotic surgery, the added value of 3D-vision may be even less with robotic surgery.
Methods: In this experimental randomized controlled cross-over trial, 20 surgeons and surgical residents from 5 countries performed robotic pancreaticojejunostomy and hepaticojejunostomy anastomoses in a biotissue organ model using the da Vinci® system and were randomized to start with either 3D- or 2D-vision. Primary endpoint was the time required to complete both anastomoses. Secondary endpoint was the objective structured assessment of technical skill (OSATS; range 12-60) rating; scored by two observers blinded to 3D/2D.

Results: Robotic 3D-vision reduced the combined operative time from 78.1 to 57.3 min (24.6% reduction, $p < 0.001$; 20.8 min reduction, 95% confidence intervals 12.8-28.8 min). This reduction was consistent for both anastomoses and between surgeons and residents, $p < 0.001$. Robotic 3D-vision improved OSATS performance by 6.1 points (20.8% improvement, $p = 0.003$) compared to 2D (39.4 to 45.1 points, ± 5.5).
Conclusion: 3D-vision has a considerable added value during robotic pancreatoduodenectomy anastomoses in biotissue in both time reduction and improved surgical performance as compared to 2D-vision.

Gepubliceerd: Surg Endosc. 2021;35(6):2928-35.
Impact factor: 4.584; Q1

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10. **Hypothermic oxygenated machine perfusion of the human pancreas for clinical islet isolation: a prospective feasibility study**
Doppenberg JB, Leemkuil M, Engelse MA, Krikke C, de Koning EJP, Leuvenink HGD.

Due to an increasing scarcity of pancreases with optimal donor characteristics, islet isolation centers utilize pancreases from extended criteria donors, such as from donation after circulatory death (DCD) donors, which are particularly susceptible to prolonged cold ischemia time (CIT). We hypothesized that hypothermic machine perfusion (HMP) can safely increase CIT. Five human DCD pancreases were subjected to 6 h of oxygenated HMP. Perfusion parameters, apoptosis, and edema were measured prior to islet isolation. Five human DBD pancreases were evaluated after static cold storage (SCS). Islet viability, and in vitro and in vivo functionality in diabetic mice were analyzed. Islets were isolated from HMP pancreases after 13.4 h [12.9-14.5] CIT and after 9.2 h [6.5-12.5] CIT from SCS pancreases. Histological analysis of the pancreatic tissue showed that HMP did not induce edema nor apoptosis. Islets maintained >90% viable during culture, and an appropriate in vitro and in vivo function in mice was demonstrated after HMP. The current study design does not permit to demonstrate that oxygenated HMP allows for cold ischemia extension; however, the successful isolation of functional islets from discarded human DCD pancreases after performing 6 h of oxygenated HMP indicates that oxygenated HMP may be a useful technology for better preservation of pancreases.

Gepubliceerd: Transpl Int. 2021;34(8):1397-407.
Impact factor: 3.782; Q1

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11. **Evaluation of the Berlin polytrauma definition: A Dutch nationwide observational study**
Driessen MLS, Sturms LM, van Zwet EW, Bloemers FW, Ten Duis HJ, Edwards MJR, den Hartog D, de Jongh MAC, Leenhouts PA, Poeze M, Schipper IB, Spanjersberg R, Wendt KW, de Wit RJ, van Zutphen S, Leenen LPH.

Background: The Berlin polytrauma definition (BPD) was established to identify multiple injury patients with a high risk of mortality. The definition includes injuries with an Abbreviated Injury Scale score of ≥3 in ≥2 body regions (2AIS ≥3) combined with the presence of ≥1 physiological risk factors (PRFs). The PRFs are based on age, Glasgow Coma Scale, hypotension, acidosis, and coagulopathy at specific cutoff

values. This study evaluates and compares the BPD with two other multiple injury definitions used to identify patients with high resource utilization and mortality risk, using data from the Dutch National Trauma Register (DNTR).
Methods: The evaluation was performed based on 2015 to 2018 DNTR data. First, patient characteristics for 2AIS ≥3, Injury Severity Score (ISS) of ≥16, and BPD patients were compared. Second, the PRFs prevalence and odds ratios of mortality for 2AIS ≥3 patients were compared with those from the Deutsche Gesellschaft für Unfallchirurgie Trauma Register. Subsequently, the association between PRF and mortality was assessed for 2AIS ≥3-DNTR patients and compared with those with an ISS of ≥16.
Results: The DNTR recorded 300,649 acute trauma admissions. A total of 15,711 patients sustained an ISS of ≥16, and 6,263 patients had suffered a 2AIS ≥3 injury. All individual PRFs were associated with a mortality of >30% in 2AIS ≥3-DNTR patients. The increase in PRFs was associated with a significant increase in mortality for both 2AIS ≥3 and ISS ≥16 patients. A total of 4,264 patients met the BPDs criteria. Overall mortality (27.2%), intensive care unit admission (71.2%), and length of stay were the highest for the BPD group.
Conclusion: This study confirms that the BPD identifies high-risk patients in a population-based registry. The addition of PRFs to the anatomical injury scores improves the identification of severely injured patients with a high risk of mortality. Compared with the ISS ≥16 and 2AIS ≥3 multiple injury definitions, the BPD showed to improve the accuracy of capturing patients with a high medical resource need and mortality rate. LEVEL OF EVIDENCE: Epidemiological study, level III.

Gepubliceerd: J Trauma Acute Care Surg. 2021;90(4):694-9.
Impact factor: 3.313; Q2

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12. **Surgical outcomes of laparoscopic and open resection of benign liver tumours in the Netherlands: a nationwide analysis**
Elfrink AKE, Haring MPD, de Meijer VE, Ijzermans JNM, Swijnenburg RJ, Braat AE, Erdmann JI, Terkivatan T, Te Riele WW, van den Boezem PB, Coolsen MME, Leclercq WKG, Lips DJ, de Wilde RF, Kok NFM, Grünhagen DJ, Klaase JM, Dutch Hepato Biliary Audit Group – includes Liem MSL.

Background: Data on surgical outcomes of laparoscopic liver resection (LLR) versus open liver resection (OLR) of benign liver tumour (BLT) are scarce. This study aimed to provide a nationwide overview of postoperative outcomes after LLR and OLR of BLT.
Methods: This was a nationwide retrospective study including all patients who underwent liver resection for hepatocellular adenoma, haemangioma and focal nodular hyperplasia in the Netherlands from 2014 to 2019. Propensity score matching (PSM) was applied to compare 30-day overall and major morbidity and 30-day mortality after OLR and LLR.
Results: In total, 415 patients underwent BLT resection of whom 230 (55.4%) underwent LLR. PSM for OLR and LLR resulted in 250 matched patients. Median (IQR) length of stay was shorter after LLR than OLR (4 versus 6 days, 5.0-8.0, $p < 0.001$). Postoperative 30-day overall morbidity was lower after LLR than OLR (12.0% vs. 22.4%, $p = 0.043$). LLR was associated with reduced 30-day overall morbidity in multivariable analysis (aOR:0.46, CI:0.22-0.95, $p = 0.043$). Both 30-day major morbidity and 30-day mortality were not different.

Conclusions: LLR for BLT is associated with shorter hospital stay and reduced overall morbidity and is preferred if technically feasible.

Gepubliceerd: HPB (Oxford). 2021;23(8):1230-43.
Impact factor: 3.647; Q1

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13. **Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study**
Elfrink AKE, Kok NFM, den Dulk M, Buis CI, Kazemier G, Ijzermans JNM, Lam HD, Hagendoorn J, van den Boezem PB, Ayez N, Zonderhuis BM, Lips DJ, Leclercq WKG, Kuhlmann KFD, Marsman HA, Verhoef C, Patijn GA, Grunhagen DJ, Klaase JM, Dutch Hepato Biliary Audit Group – includes Liem MSL.

Background: Liver resection is high-risk surgery in particular in elderly patients. The aim of this study was to explore postoperative outcomes after liver resection in elderly patients.
Methods: In this nationwide study, all patients who underwent liver resection for primary and secondary liver tumours in the Netherlands between 2014 and 2019 were included. Age groups were composed as younger than 70 (70-), between 70 and 80 (septuagenarians), and 80 years or older (octogenarians). Proportion of liver resections per age group and 30-day major morbidity and 30-day mortality were assessed.
Results: In total, 6587 patients were included of whom 4023 (58.9%) were younger than 70, 2135 (32.4%) were septuagenarians and 429 (6.5%) were octogenarians. The proportion of septuagenarians increased during the study period (aOR:1.06, CI:1.02-1.09, $p < 0.001$). Thirty-day major morbidity was higher in septuagenarians (11%) and octogenarians (12%) compared to younger patients (9%, $p = 0.049$). Thirty-day mortality was higher in septuagenarians (4%) and octogenarians (4%) compared to younger patients (2%, $p < 0.001$). Cardiopulmonary complications occurred more frequently with higher age, liver-specific complications did not. Higher age was associated with higher 30-day morbidity and 30-day mortality in multivariable logistic regression.
Conclusion: Thirty-day major morbidity and 30-day mortality are higher after liver resection in elderly patients, attributed mainly to non-surgical cardiopulmonary complications.

Gepubliceerd: HPB (Oxford). 2021;23(10):1506-17.
Impact factor: 3.647; Q1

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14. **Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study**
Elfrink AKE, Nieuwenhuizen S, van den Tol MP, Burgmans MC, Prevoo W, Coolsen MME, van den Boezem PB, van Delden OM, Hagendoorn J, Patijn GA, Leclercq WKG, Liem MSL, Rijken AM, Verhoef C, Kuhlmann KFD, Ruiter SJS, Grünhagen DJ, Klaase JM, Kok NFM, Meijerink MR, Swijnenburg RJ.

Background: Combining resection and thermal ablation can improve short-term postoperative outcomes in patients with colorectal liver metastases (CRLM). This study

assessed nationwide hospital variation and short-term postoperative outcomes after combined resection and ablation.
Methods: In this population-based study, all CRLM patients who underwent resection in the Netherlands between 2014 and 2018 were included. After propensity score matching for age, ASA-score, Charlson-score, diameter of largest CRLM, number of CRLM and earlier resection, postoperative outcomes were compared. Postoperative complicated course (PCC) was defined as discharge after 14 days or a major complication or death within 30 days of surgery.
Results: Of 4639 included patients, 3697 (80%) underwent resection and 942 (20%) resection and ablation. Unadjusted percentage of patients who underwent resection and ablation per hospital ranged between 4 and 44%. Hospital variation persisted after case-mix correction. After matching, 734 patients remained in each group. Hospital stay (median 6 vs. 7 days, p = 0.011), PCC (11% vs. 14.7%, p = 0.043) and 30-day mortality (0.7% vs. 2.3%, p = 0.018) were lower in the resection and ablation group. Differences faded in multivariable logistic regression due to inclusion of major hepatectomy.
Conclusion: Significant hospital variation was observed in the Netherlands. Short-term postoperative outcomes were better after combined resection and ablation, attributed to avoiding complications associated with major hepatectomy.

Gepubliceerd: HPB (Oxford). 2021;23(6):827-39.
Impact factor: Impact factor: 3.647; Q1

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15. **Factors associated with failure to rescue after liver resection and impact on hospital variation: a nationwide population-based study**
Elfrink AKE, Olthof PB, Swijnenburg RJ, den Dulk M, de Boer MT, Mieog JSD, Hagendoorn J, Kazemier G, van den Boezem PB, Rijken AM, Liem MSL, Leclercq WKG, Kuhlmann KFD, Marsman HA, Ijzermans JNM, van Duijvendijk P, Erdmann JI, Kok NFM, Grunhagen DJ, Klaase JM, Dutch Hepato Biliary Audit Group, Collaborating liver surgeons.

Background: Failure to rescue (FTR) is defined as postoperative complications leading to mortality. This nationwide study aimed to assess factors associated with FTR and hospital variation in FTR after liver surgery.
Methods: All patients who underwent liver resection between 2014 and 2017 in the Netherlands were included. FTR was defined as in-hospital or 30-day mortality after complications Dindo grade >/=3a. Variables associated with FTR and nationwide hospital variation were assessed using multivariable logistic regression.
Results: Of 4961 patients included, 3707 (74.4%) underwent liver resection for colorectal liver metastases, 379 (7.6%) for other metastases, 526 (10.6%) for hepatocellular carcinoma and 349 (7.0%) for biliary cancer. Thirty-day major morbidity was 11.5%. Overall mortality was 2.3%. FTR was 19.1%. Age 65-80 (aOR: 2.86, CI:1.01-12.0, p = 0.049), ASA 3+ (aOR:2.59, CI: 1.66-4.02, p < 0.001), liver cirrhosis (aOR:4.15, CI:1.81-9.22, p < 0.001), biliary cancer (aOR:3.47, CI: 1.73-6.96, p < 0.001), and major resection (aOR:6.46, CI: 3.91-10.9, p < 0.001) were associated with FTR. Postoperative liver failure (aOR: 26.9, CI: 14.6-51.2, p < 0.001), cardiac (aOR: 2.62, CI: 1.27-5.29, p = 0.008) and thromboembolic complications (aOR: 2.49, CI: 1.16-5.22, p = 0.017) were associated with FTR. After case-mix correction, no hospital variation in FTR was observed.

Conclusion: FTR is influenced by patient demographics, disease and procedural burden. Prevention of postoperative liver failure, cardiac and thromboembolic complications could decrease FTR.

Gepubliceerd: HPB (Oxford). 2021;23(12):1837-48.
Impact factor: 3.647; Q1

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16. **Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases**
Elfrink AKE, van Zwet EW, Swijnenburg RJ, den Dulk M, van den Boezem PB, Mieog JSD, Te Riele WW, Patijn GA, Leclercq WKG, Lips DJ, Rijken AM, Verhoef C, Kuhlmann KFD, Buis CI, Bosscha K, Belt EJT, Vermaas M, van Heek NT, Oosterling SJ, Torrenga H, Eker HH, Consten ECJ, Marsman HA, Wouters M, Kok NFM, Grünhagen DJ, Klaase JM, Dutch Hepato Biliary Audit Group – includes Liem MSL.

Background: Differences in patient demographics and disease burden can influence comparison of hospital performances. This study aimed to provide a case-mix model to compare short-term postoperative outcomes for patients undergoing liver resection for colorectal liver metastases (CRLM).
Methods: This retrospective, population-based study included all patients who underwent liver resection for CRLM between 2014 and 2018 in the Netherlands. Variation in case-mix variables between hospitals and influence on postoperative outcomes was assessed using multivariable logistic regression. Primary outcomes were 30-day major morbidity and 30-day mortality. Validation of results was performed on the data from 2019.
Results: In total, 4639 patients were included in 28 hospitals. Major morbidity was 6.2% and mortality was 1.4%. Uncorrected major morbidity ranged from 3.3% to 13.7% and mortality ranged from 0.0% to 5.0%. between hospitals. Significant differences between hospitals were observed for age higher than 80 (0.0%-17.1%, $p < 0.001$), ASA 3 or higher (3.3%-36.3%, $p < 0.001$), histopathological parenchymal liver disease (0.0%-47.1%, $p < 0.001$), history of liver resection (8.1%-36.3%, $p < 0.001$), major liver resection (6.7%-38.0%, $p < 0.001$) and synchronous metastases (35.5%-62.1%, $p < 0.001$). Expected 30-day major morbidity between hospitals ranged from 6.4% to 11.9% and expected 30-day mortality ranged from 0.6% to 2.9%. After case-mix correction no significant outliers concerning major morbidity and mortality remained. Validation on patients who underwent liver resection for CRLM in 2019 affirmed these outcomes.
Conclusion: Case-mix adjustment is a prerequisite to allow for institutional comparison of short-term postoperative outcomes after liver resection for CRLM.

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Impact factor: 4.424; Q1

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17. **Comparing practice and outcome of laparoscopic liver resection between high-volume expert centres and nationwide low-to-medium volume centres**
Görgec B, Fichtinger RS, Ratti F, Aghayan D, Van der Poel MJ, Al-Jarrah R, Armstrong T, Cipriani F, Fretland Å A, Suhool A, Bemelmans M, Bosscha K, Braat AE, De Boer MT, Dejong CHC, Doornebosch PG, Draaisma WA, Gerhards MF, Gobardhan PD,

Hagendoorn J, Kazemier G, Klaase J, Leclercq WKG, Liem MSL, Lips DJ, Marsman HA, Mieog JSD, Molenaar QI, Nieuwenhuijs VB, Nota CL, Patijn GA, Rijken AM, Slooter GD, Stommel MWJ, Swijnenburg RJ, Tanis PJ, Te Riele WW, Terkivatan T, Van den Tol PMP, Van den Boezem PB, Van der Hoeven JA, Vermaas M, Edwin B, Aldrighetti LA, Van Dam RM, Abu Hilal M, Besselink MG.

Background: Based on excellent outcomes from high-volume centres, laparoscopic liver resection is increasingly being adopted into nationwide practice which typically includes low-medium volume centres. It is unknown how the use and outcome of laparoscopic liver resection compare between high-volume centres and low-medium volume centres. This study aimed to compare use and outcome of laparoscopic liver resection in three leading European high-volume centres and nationwide practice in the Netherlands.
Method: An international, retrospective multicentre cohort study including data from three European high-volume centres (Oslo, Southampton and Milan) and all 20 centres in the Netherlands performing laparoscopic liver resection (low-medium volume practice) from January 2011 to December 2016. A high-volume centre is defined as a centre performing >50 laparoscopic liver resections per year. Patients were retrospectively stratified into low, moderate- and high-risk Southampton difficulty score groups.
Results: A total of 2425 patients were included (1540 high-volume; 885 low-medium volume). The median annual proportion of laparoscopic liver resection was 42.9 per cent in high-volume centres and 7.2 per cent in low-medium volume centres. Patients in the high-volume centres had a lower conversion rate (7.4 versus 13.1 per cent; $P < 0.001$) with less intraoperative incidents (9.3 versus 14.6 per cent; $P = 0.002$) as compared to low-medium volume centres. Whereas postoperative morbidity and mortality rates were similar in the two groups, a lower reintervention rate (5.1 versus 7.2 per cent; $P = 0.034$) and a shorter postoperative hospital stay (3 versus 5 days; $P < 0.001$) were observed in the high-volume centres as compared to the low-medium volume centres. In each Southampton difficulty score group, the conversion rate was lower and hospital stay shorter in high-volume centres. The rate of intraoperative incidents did not differ in the low-risk group, whilst in the moderate-risk and high-risk groups this rate was lower in high-volume centres (absolute difference 6.7 and 14.2 per cent; all $P < 0.004$).
Conclusion: High-volume expert centres had a sixfold higher use of laparoscopic liver resection, less conversions, and shorter hospital stay, as compared to a nationwide low-medium volume practice. Stratification into Southampton difficulty score risk groups identified some differences but largely outcomes appeared better for high-volume centres in each risk group.

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Impact factor: 6.939; Q1

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18. **Clinical added value of MRI to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): study protocol for an international multicentre prospective diagnostic accuracy study**
Görgec B, Hansen I, Kemmerich G, Syversveen T, Abu Hilal M, Belt EJT, Bisschops RHC, Bollen TL, Bosscha K, Burgmans MC, Cappendijk V, De Boer MT, D'Hondt M, Edwin B, Gielkens H, Grünhagen DJ, Gillardin P, Gobardhan PD, Hartgrink HH,

Horsthuis K, Kok NFM, Kint PAM, Kruimer JWH, Leclercq WKG, Lips DJ, Lutin B, Maas M, Marsman HA, Morone M, Pennings JP, Peringa J, Te Riele WW, Vermaas M, Wicherts D, Willemssen F, Zonderhuis BM, Bossuyt PMM, Swijnenburg RJ, Fretland Å A, Verhoef C, Besselink MG, Stoker J, CAMINO Study Group – includes Liem MSL.

Background: Abdominal computed tomography (CT) is the standard imaging method for patients with suspected colorectal liver metastases (CRLM) in the diagnostic workup for surgery or thermal ablation. Diffusion-weighted and gadoxetic-acid-enhanced magnetic resonance imaging (MRI) of the liver is increasingly used to improve the detection rate and characterization of liver lesions. MRI is superior in detection and characterization of CRLM as compared to CT. However, it is unknown how MRI actually impacts patient management. The primary aim of the CAMINO study is to evaluate whether MRI has sufficient clinical added value to be routinely added to CT in the staging of CRLM. The secondary objective is to identify subgroups who benefit the most from additional MRI.
Methods: In this international multicentre prospective incremental diagnostic accuracy study, 298 patients with primary or recurrent CRLM scheduled for curative liver resection or thermal ablation based on CT staging will be enrolled from 17 centres across the Netherlands, Belgium, Norway, and Italy. All study participants will undergo CT and diffusion-weighted and gadoxetic-acid enhanced MRI prior to local therapy. The local multidisciplinary team will provide two local therapy plans: first, based on CT-staging and second, based on both CT and MRI. The primary outcome measure is the proportion of clinically significant CRLM (CS-CRLM) detected by MRI not visible on CT. CS-CRLM are defined as liver lesions leading to a change in local therapeutical management. If MRI detects new CRLM in segments which would have been resected in the original operative plan, these are not considered CS-CRLM. It is hypothesized that MRI will lead to the detection of CS-CRLM in ≥10% of patients which is considered the minimal clinically important difference. Furthermore, a prediction model will be developed using multivariable logistic regression modelling to evaluate the predictive value of patient, tumor and procedural variables on finding CS-CRLM on MRI.
Discussion: The CAMINO study will clarify the clinical added value of MRI to CT in patients with CRLM scheduled for local therapy. This study will provide the evidence required for the implementation of additional MRI in the routine work-up of patients with primary and recurrent CRLM for local therapy.
Trial registrattion: The CAMINO study was registered in the Netherlands National Trial Register under number NL8039 on September 20th 2019.

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Impact factor: 4.430; Q2

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19. **Venous wedge and segment resection during pancreatoduodenectomy for pancreatic cancer: impact on short- and long-term outcomes in a nationwide cohort analysis**

Groen JV, Michiels N, van Roessel S, Besselink MG, Bosscha K, Busch OR, van Dam R, van Eijck CHJ, Koerkamp BG, van der Harst E, de Hingh IH, Karsten TM, Lips DJ, de Meijer VE, Molenaar IQ, Nieuwenhuijs VB, Roos D, van Santvoort HC, Wijsman JH, Wit F, Zonderhuis BM, de Vos-Geelen J, Wasser MN, Bonsing BA, Stommel MWJ, Mieog JSD, Dutch Pancreatic Cancer Group.

Background: Venous resection of the superior mesenteric or portal vein is increasingly performed in pancreatic cancer surgery, whereas results of studies on short- and long-term outcomes are contradictory. The aim of this study was to evaluate the impact of the type of venous resection in pancreatoduodenectomy for pancreatic cancer on postoperative morbidity and overall survival.
Methods: This nationwide retrospective cohort study included all patients who underwent pancreatoduodenectomy for pancreatic cancer in 18 centres (2013-2017).
Results: A total of 1311 patients were included, of whom 17 per cent underwent wedge resection and 10 per cent segmental resection. Patients with segmental resection had higher rates of major morbidity (39 versus 20 versus 23 per cent, respectively; P < 0.001) and portal or superior mesenteric vein thrombosis (18 versus 5 versus 1 per cent, respectively; P < 0.001) and worse overall survival (median 12 versus 16 versus 20 months, respectively; P < 0.001), compared to patients with wedge resection and those without venous resection. Multivariable analysis showed patients with segmental resection, but not those who had wedge resection, had higher rates of major morbidity (odds ratio = 1.93, 95 per cent c.i. 1.20 to 3.11) and worse overall survival (hazard ratio = 1.40, 95 per cent c.i. 1.10 to 1.78), compared to patients without venous resection. Among patients who received neoadjuvant therapy, there was no difference in overall survival among patients with segmental and wedge resection and those without venous resection (median 32 versus 25 versus 33 months, respectively; P = 0.470), although there was a difference in major morbidity rates (52 versus 19 versus 21 per cent, respectively; P = 0.012).
Conclusion: In pancreatic surgery, the short- and long-term outcomes are worse in patients with venous segmental resection, compared to patients with wedge resection and those without venous resection.

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Impact factor: 6.939; Q1

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20. **Compromised intestinal integrity in older adults during daily activities: a pilot study**
Hendriks S, Stokmans SC, Plas M, Buurman WA, Spoorenberg SLW, Wynia K, Heineman E, van Leeuwen BL, de Haan JJ.

Background: Malnutrition is a common and significant problem in older adults. Insight into factors underlying malnutrition is needed to develop strategies that can improve the nutritional status. Compromised intestinal integrity caused by gut wall hypoperfusion due to atherosclerosis of the mesenteric arteries in the aging gastrointestinal tract may adversely affect nutrient uptake. The presence of compromised intestinal integrity in older adults is not known. The aim of this study is to provide a proof-of-concept that intestinal integrity is compromised in older adults during daily activities.
Methods: Adults aged ≥75 years living independently without previous gastrointestinal disease or abdominal surgery were asked to complete a standardized walking test and to consume a standardized meal directly afterwards to challenge the mesenteric blood flow. Intestinal fatty acid-binding protein (I-FABP) was measured as a plasma marker of intestinal integrity, in blood samples collected before (baseline) and after the walking test, directly after the meal, and every 15 min thereafter to 75 min postprandially.

Results: Thirty-four participants (median age 81 years; 56% female) were included. Of the participants, 18% were malnourished (PG-SGA score ≥ 4), and 32% were at risk of malnutrition (PG-SGA score, 2 or 3). An I-FABP increase of ≥50% from baseline was considered a meaningful loss of intestinal integrity and was observed in 12 participants (35%; 8 females; median age 80 years). No significant differences were observed in either baseline characteristics, walking test scores, or calorie/macronutrient intake between the groups with and without a ≥ 50% I-FABP peak.
Conclusion: This study is first to indicate that intestinal integrity is compromised during daily activities in a considerable part of older adults living independently.

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Impact factor: 3.921; Q1

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21. **Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial**
Janssen QP, van Dam JL, Bonsing BA, Bos H, Bosscha KP, Coene P, van Eijck CHJ, de Hingh I, Karsten TM, van der Kolk MB, Patijn GA, Liem MSL, van Santvoort HC, Loosveld OJL, de Vos-Geelen J, Zonderhuis BM, Homs MYV, van Tienhoven G, Besselink MG, Wilmink JW, Groot Koerkamp B, Dutch Pancreatic Cancer Group.

Background: Neoadjuvant therapy has several potential advantages over upfront surgery in patients with localized pancreatic cancer; more patients receive systemic treatment, fewer patients undergo futile surgery, and R0 resection rates are higher, thereby possibly improving overall survival (OS). Two recent randomized trials have suggested benefit of neoadjuvant chemoradiotherapy over upfront surgery, both including single-agent chemotherapy regimens. Potentially, the multi-agent FOLFIRINOX regimen (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) may further improve outcomes in the neoadjuvant setting for localized pancreatic cancer, but randomized studies are needed. The PREOPANC-2 trial investigates whether neoadjuvant FOLFIRINOX improves OS compared with neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine in resectable and borderline resectable pancreatic cancer patients.
Methods: This nationwide multicenter phase III randomized controlled trial includes patients with pathologically confirmed resectable and borderline resectable pancreatic cancer with a WHO performance score of 0 or 1. Resectable pancreatic cancer is defined as no arterial and ≤ 90 degrees venous involvement; borderline resectable pancreatic cancer is defined as ≤90 degrees arterial and ≤ 270 degrees venous involvement without occlusion. Patients receive 8 cycles of neoadjuvant FOLFIRINOX chemotherapy followed by surgery without adjuvant treatment (arm A), or 3 cycles of neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions) during the second cycle, followed by surgery and 4 cycles of adjuvant gemcitabine (arm B). The primary endpoint is OS by intention-to-treat. Secondary endpoints include progression-free survival, quality of life, resection rate, and R0 resection rate. To detect a hazard ratio of 0.70 with 80% power, 252 events are needed. The number of events is expected to be reached after inclusion of 368 eligible patients assuming an accrual period of 3 years and 1.5 years follow-up.

Discussion: The PREOPANC-2 trial directly compares two neoadjuvant regimens for patients with resectable and borderline resectable pancreatic cancer. Our study will provide evidence on the neoadjuvant treatment of choice for patients with resectable and borderline resectable pancreatic cancer.
Trial registrattion: Primary registry and trial identifying number: EudraCT: 2017-002036-17 . Date of registration: March 6, 2018. Secondary identifying numbers: The Netherlands National Trial Register - NL7094 , NL61961.078.17, MEC-2018-004.

Gepubliceerd: BMC Cancer. 2021;21(1):300.
Impact factor: 4.430; Q2

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22. **Long-Term Quality of Life after Minimally Invasive vs Open Distal Pancreatectomy in the LEOPARD Randomized Trial**
Korrel M, Roelofs A, van Hilst J, Busch OR, Daams F, Festen S, Groot Koerkamp B, Klaase J, Luyer MD, van Oijen MG, Verdonck-de Leeuw IM, Besselink MG, LEOPARD Trial Collaborators – includes van Duyn EB.

Background: Minimally invasive distal pancreatectomy (MIDP) shortens time to functional recovery and improves 30-day quality of life (QoL), as compared with open distal pancreatectomy (ODP) for nonmalignant disease. The impact of MIDP on QoL, cosmetic satisfaction, and overall major complications beyond 1-year follow-up is currently unknown.
Study design: The Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD) trial randomized 108 patients to MIDP (laparoscopic or robotic) or ODP in 14 Dutch centers (April 2015 to March 2017). The primary outcome measure of this study was quality-adjusted life years (QALYs), as assessed with the EQ-5D. QoL was assessed using subscales of the EORTC QLQ-C30, PAN-26, and a body image questionnaire. The latter included a cosmetic satisfaction score (range 3-24), and a body image score (range 5-20). Differences between MIDP and ODP for QALYs, generic, and disease-specific QoL and body image were analyzed. Missing QoL data were imputed using multiple imputation.
Results: In total, 84 patients were alive, with a median follow-up of 44 months; 62 of these patients (74%) completed the questionnaires (27 MIDP, 35 ODP). There was no significant difference in QALYs between the 2 groups (mean score 2.34 vs 2.46 years, $p = 0.63$), nor on the QoL subscales. Significant overall change in EQ-5D health utilities were found for both groups over time ($p < 0.001$). Patients in the MIDP group scored higher on cosmetic satisfaction (21 vs 14, $p = 0.049$). No differences between the 2 groups were observed for clinical outcomes such as major complications, readmissions, and incisional hernias.
Conclusions: More than 3 years after distal pancreatectomy, no improvement in QALYs and overall QoL was seen after MIDP, whereas cosmetic satisfaction was higher after MIDP as compared with ODP.

Gepubliceerd: J Am Coll Surg. 2021;233(6):730-9.e9.
Impact factor: 6.113; Q1

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23. **Long-term quality of life and exocrine and endocrine insufficiency after pancreatic surgery: a multicenter, cross-sectional study**
Latenstein AEJ, Blonk L, Tjahjadi NS, de Jong N, Busch OR, de Hingh I, van Hooft JE, Liem MSL, Molenaar IQ, van Santvoort HC, de van der Schueren MAE, DeVries JH, Kazemier G, Besselink MG, Dutch Pancreatic Cancer Group.

Background: Data regarding long-term quality of life and exocrine and endocrine insufficiency after pancreatic surgery for premalignant and benign (non-pancreatitis) disease are lacking.
Methods: This cross-sectional study included patients >/=3 years after pancreatoduodenectomy or left pancreatectomy in six Dutch centers (2006-2016). Outcomes were measured with the EQ-5D-5L, the EORTC QLQ-C30, an exocrine and endocrine pancreatic insufficiency questionnaire, and PAID20.
Results: Questionnaires were completed by 153/183 patients (response rate 84%, median follow-up 6.3 years). Surgery related complaints were reported by 72/153 patients (47%) and 13 patients (8.4%) would not undergo this procedure again. The VAS (EQ-5D-5L) was 76 +/- 17 versus 82 +/- 0.4 in the general population ($p < 0.001$). The mean global health status (QLQ-C30) was 78 +/- 17 versus 78 +/- 17, $p = 1.000$. Fatigue, insomnia, and diarrhea were clinically relevantly worse in patients. Exocrine pancreatic insufficiency was reported by 62 patients (41%) with relieve of symptoms by enzyme supplementation in 48%. New-onset diabetes mellitus was present in 22 patients (14%). The median PAID20 score was 6.9/20 (IQR 2.5-17.8).
Conclusion: Although generic quality of life after pancreatic resection for pre-malignant and benign disease was similar to the general population and diabetes-related distress was low, almost half suffered from a range of symptoms highlighting the need for long-term counseling.

Gepubliceerd: HPB (Oxford). 2021;23(11):1722-31.
Impact factor: 3.647; Q1

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24. **A Clinical Decision Tool for Selection of Patients With Symptomatic Cholelithiasis for Cholecystectomy Based on Reduction of Pain and a Pain-Free State Following Surgery**
Latenstein CSS, Hannink G, van der Bilt JDW, Donkervoort SC, Eijsbouts QAJ, Heisterkamp J, Nieuwenhuijs VB, Schreinemakers JMJ, Wiering B, Boermeester MA, Drenth JPH, van Laarhoven C, Dijkgraaf MGW, de Reuver PR, SECURE trial collaborators – includes Steenvoorde P.

Importance: There is currently no consensus on the indication for cholecystectomy in patients with uncomplicated gallstone disease.
Objective: To report on the development and validation of a multivariable prediction model to better select patients for surgery.
Design, setting, and participants: This study evaluates data from 2 multicenter prospective trials (the previously published Scrutinizing (In)efficient Use of Cholecystectomy: A Randomized Trial Concerning Variation in Practice [SECURE] and the Standardized Work-up for Symptomatic Cholecystolithiasis [Success] trial) collected from the outpatient clinics of 25 Dutch hospitals between April 2014 and June 2019 and including 1561 patients with symptomatic uncomplicated cholelithiasis, defined as gallstone disease without signs of complicated cholelithiasis (ie, biliary

pancreatitis, cholangitis, common bile duct stones or cholecystitis). Data were analyzed from January 2020 to June 2020. EXPOSURES: Patient characteristics, comorbidity, surgical outcomes, pain, and symptoms measured at baseline and at 6 months' follow-up.
Main outcomes and measures: A multivariable regression model to predict a pain-free state or a clinically relevant reduction in pain after surgery. Model performance was evaluated using calibration and discrimination.
Results: A total of 1561 patients were included (494 patients in 7 hospitals in the development cohort and 1067 patients in 24 hospitals in the validation cohort; 6 hospitals included patients in both cohorts). In the development cohort, 395 patients (80.0%) underwent cholecystectomy. After surgery, 225 patients (57.0%) reported that they were pain free and 295 (74.7%) reported a clinically relevant reduction in pain. A multivariable prediction model showed that increased age, no history of abdominal surgery, increased visual analog scale pain score at baseline, pain radiation to the back, pain reduction with simple analgesics, nausea, and no heartburn were independent predictors of clinically relevant pain reduction after cholecystectomy. After internal validation, good discrimination was found (C statistic, 0.80; 95% CI, 0.74-0.84) between patients with and without clinically relevant pain reduction. The model had very good overall calibration and minimal underestimation of the probability. External validation indicated a good discrimination between patients with and without clinically relevant pain reduction (C statistic, 0.74; 95% CI, 0.70-0.78) and fair calibration with some overestimation of probability by the model.
Conclusions and relevance: The model validated in this study may help predict the probability of pain reduction after cholecystectomy and thus aid surgeons in deciding whether patients with uncomplicated cholelithiasis will benefit from cholecystectomy.

Gepubliceerd: JAMA Surg. 2021;156(10):e213706.
Impact factor: 14.766; Q1

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25. **A Completely Endovascular Solution for Transcatheter Aortic Valve Implantation Embolisation and Inversion into the Aortic Arch**
Leeuwerke SJG, Menting TP, Stoel MG, Geelkerken RH.

Introduction: Transcatheter aortic valve implantation (TAVI) has evolved into the preferred alternative to surgical valve replacement for severe aortic valve stenosis with high surgical risk. With expanding indications, life threatening complications including transcatheter aortic valve embolisation and inversion (TAVEI), in which the valve dislodges, inverts, and migrates caudally, may increase concomitantly.
Report: An 80 year old male with severe aortic valve stenosis underwent balloon expandable transcatheter aortic valve implantation (TAVI). Valve embolisation into the aortic arch inverted the bioprothesis, excluding the option of fixation in the descending aorta. Through-valve thoracic endovascular aortic repair (TEVAR) was performed after bifemoral snaring using a through-and-through wire technique and pulling the valve into the descending aorta.
Discussion: TAVI is emerging as the preferred treatment for severe aortic valve stenosis and comes with unique procedural complications, such as life threatening transcatheter aortic valve embolisation and inversion (TAVEI). Although some authors prefer treating embolisation of a non-inverted balloon expandable valve into the aorta by using the valvuloplasty balloon to pull the valve distally and fixing it in the descending

aorta, this risks further expansion of the valve and consequently fixing it in an undesirable position and is not possible if the valve inverts. Downstream placement of the valve by snaring with a guiding catheter covering/protecting a through-and-through wire technique, combined with through-valve TEVAR, provides a new bail out strategy for this serious complication and may reduce TAVEI associated mortality and morbidity.

Gepubliceerd: EJVES Vasc Forum. 2021;52:13-6.
Impact factor: 0; NVT

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26. **Nationwide Study to Predict Colonic Ischemia after Abdominal Aortic Aneurysm Repair in The Netherlands**

Willemsen SI, Ten Berge MG, Statius van Eps RG, Veger HTC, van Overhagen H, van Dijk LC, Putter H, Wever JJ. In collaboration with the Dutch Society of Vascular Surgery, the Steering Committee of the Dutch Surgical Aneurysm Audit and the Dutch Institute for Clinical Auditing – includes Beuk RJ, Geelkerken RH, Meerwaldt R, Willigendael EM.

Background: Colonic ischemia remains a severe complication after abdominal aortic aneurysm (AAA) repair and is associated with a high mortality. With open repair being one of the main risk factors of colonic ischemia, deciding between endovascular or open aneurysm repair should be based on tailor-made medicine. This study aims to identify high-risk patients of colonic ischemia, a risk that can be taken into account while deciding on AAA treatment strategy.
Methods: A nationwide population-based cohort study of 9,433 patients who underwent an AAA operation between 2014 and 2016 was conducted. Potential risk factors were determined by reviewing prior studies and univariate analysis. With logistic regression analysis, independent predictors of intestinal ischemia were established. These variables were used to form a prediction model.
Results: Intestinal ischemia occurred in 267 patients (2.8%). Occurrence of intestinal ischemia was seen significantly more in open repair versus endovascular aneurysm repair (7.6% vs. 0.9%; P < 0.001). This difference remained significant after stratification by urgency of the procedure, in both intact open (4.2% vs. 0.4%; P < 0.001) and ruptured open repair (15.0% vs. 6.2%); P < 0.001). Rupture of the AAA was the most important predictor of developing intestinal ischemia (odds ratio [OR], 5.9, 95% confidence interval [CI] 4.4-8.0), followed by having a suprarenal AAA (OR 3.4; CI 1.1-10.6). Associated procedural factors were open repair (OR 2.8; 95% CI 1.9-4.2), blood loss >1L (OR 3.6; 95% CI 1.7-7.5), and prolonged operating time (OR 2.0; 95% CI 1.4-2.8). Patient characteristics included having peripheral arterial disease (OR 2.4; 95% CI 1.3-4.4), female gender (OR 1.7; 95% CI 1.2-2.4), renal insufficiency (OR 1.7; 1.3-2.2), and pulmonary history (OR 1.6; 95% CI 1.2-2.2). Age <68 years proved to be a protective factor (OR 0.5; 95% CI 0.4-0.8). Associated mortality was higher in patients with intestinal ischemia versus patients without (50.6% vs. 5.1%, P < 0.001). Each predictor was given a score between 1 and 4. Patients with a score of ≥10 proved to be at high risk. A prediction model with an excellent AUC = 0.873 (95% CI 0.855-0.892) could be formed.
Conclusions: One of the main risk factors is open repair. Several other risk factors can contribute to developing colonic ischemia after AAA repair. The proposed prediction model can be used to identify patients at high risk for developing colonic ischemia. With the current trend in AAA repair leaning toward open repair for better

long-term results, our prediction model allows a better informed decision can be made in AAA treatment strategy.

Gepubliceerd: Ann Vasc Surg. 2021;73:407-16.
Impact factor: 1.466; Q4

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27. **Risk of conversion to open surgery during robotic and laparoscopic pancreatoduodenectomy and effect on outcomes: international propensity score-matched comparison study**
Lof S, Vissers FL, Klompmaker S, Berti S, Boggi U, Coratti A, Dokmak S, Fara R, Festen S, D'Hondt M, Khatkov I, Lips DJ, Luyer M, Manzoni A, Rosso E, Saint-Marc O, Besselink MG, Abu Hilal M.

Background: Minimally invasive pancreatoduodenectomy (MIPD) is increasingly being performed because of perceived patient benefits. Whether conversion of MIPD to open pancreatoduodenectomy worsens outcome, and which risk factors are associated with conversion, is unclear.
Methods: This was a post hoc analysis of a European multicentre retrospective cohort study of patients undergoing MIPD (2012-2017) in ten medium-volume (10-19 MIPDs annually) and four high-volume (at least 20 MIPDs annually) centres. Propensity score matching (1 : 1) was used to compare outcomes of converted and non-converted MIPD procedures. Multivariable logistic regression analysis was performed to identify risk factors for conversion, with results presented as odds ratios (ORs) with 95 per cent confidence intervals (c.i).
Results: Overall, 65 of 709 MIPDs were converted (9.2 per cent) and the overall 30-day mortality rate was 3.8 per cent. Risk factors for conversion were tumour size larger than 40 mm (OR 2.7, 95 per cent c.i.1.0 to 6.8; P = 0.041), pancreatobiliary tumours (OR 2.2, 1.0 to 4.8; P = 0.039), age at least 75 years (OR 2.0, 1.0 to 4.1; P = 0.043), and laparoscopic pancreatoduodenectomy (OR 5.2, 2.5 to 10.7; P < 0.001). Medium-volume centres had a higher risk of conversion than high-volume centres (15.2 versus 4.1 per cent, P < 0.001; OR 4.1, 2.3 to 7.4, P < 0.001). After propensity score matching (56 converted MIPDs and 56 completed MIPDs) including risk factors, rates of complications with a Clavien-Dindo grade of III or higher (32 versus 34 per cent; P = 0.841) and 30-day mortality (12 versus 6 per cent; P = 0.274) did not differ between converted and non-converted MIPDs.
Conclusion: Risk factors for conversion during MIPD include age, large tumour size, tumour location, laparoscopic approach, and surgery in medium-volume centres. Although conversion during MIPD itself was not associated with worse outcomes, the outcome in these patients was poor in general which should be taken into account during patient selection for MIPD.

Gepubliceerd: Br J Surg. 2021;108(1):80-7.
Impact factor: 6.939; Q1

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28. **High prevalence of non-accidental trauma among deceased children presenting at Level I trauma centers in the Netherlands**
Loos MHJ, Bakx R, Duijst W, Aarts F, de Blaauw I, Bloemers FW, Bosch JAT, Evers M, Greeven APA, Hondius MJ, van Hooren R, Huisman E, Hulscher JBF, Keyzer-

Dekker CMG, Krug E, Menke J, Naujocks T, Reijnders UJL, de Ridder VA, Spanjersberg WR, Teeuw AH, Theeuwes HP, Vervoort-Steenbakkers W, de Vries S, de Wit R, van Rijn RR.

Purpose: Between 0.1-3% of injured children who present at a hospital emergency department ultimately die as a result of their injuries. These events are typically reported as unnatural causes of death and may result from either accidental or non-accidental trauma (NAT). Examples of the latter include trauma that is inflicted directly or resulting from neglect. Although consultation with a forensic physician is mandatory for all deceased children, the prevalence of fatal inflicted trauma or neglect among children is currently unclear.
Methods: This is a retrospective study that included children (0-18 years) who presented and died at one of the 11 Level I trauma centers in the Netherlands between January 1, 2014, and January 1, 2019. Outcomes were classified based on the conclusions of the Child Abuse and Neglect team or those of forensic pathologists and/or the court in cases referred for legally mandated autopsies. Cases in which conclusions were unavailable and there was no clear accidental cause of death were reviewed by an expert panel.
Results: The study included 175 cases of childhood death. Seventeen (9.7%) of these children died due to inflicted trauma (9.7%), 18 (10.3%) due to neglect, and 140 (80%) due to accidents. Preschool children (< 5 years old) were significantly more likely to present with injuries due to inflicted trauma and neglect compared to older children (44% versus 6%, $p < 0.001$, odds ratio [OR] 5.80, 95% confidence interval [CI] 2.66-12.65). Drowning accounted for 14 of the 18 (78%) pediatric deaths due to neglect, representing 8% of the total cases. Postmortem radiological studies and autopsies were performed on 37 (21%) of all cases of childhood death.
Conclusion: One of every five pediatric deaths in our nationwide Level I trauma center study was attributed to NAT; 44% of these deaths were the result of trauma experienced by preschool-aged children. A remarkable number of fatal drownings were due to neglect. Postmortem radiological studies and autopsies were performed in only one-fifth of all deceased children. The limited use of postmortem investigations may have resulted in missed cases of NAT, which will result in an overall underestimation of fatal NAT experienced by children.

Gepubliceerd: Forensic Sci Med Pathol. 2021;17(4):621-33.
Impact factor: 2.007; Q2

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29. **Recipient age and outcome after pancreas transplantation: a retrospective dual-center analysis**
Messner F, Leemkuil M, Yu Y, Massie AB, Krendl FJ, Benjamens S, Bösmüller C, Weissenbacher A, Schneeberger S, Pol RA, Margreiter C.

With a later onset of diabetes complications and thus increasing age of transplant candidates, many centers have extended upper age limits for pancreas transplantation. This study investigates the effect of recipient and donor age on outcomes after pancreas transplantation.We retrospectively analyzed 565 pancreas transplants performed at two Eurotransplant centers. The cohort was split at a recipient and donor age of 50 and 40 years, respectively. Median recipient age in old patients (≥50 years; 27.2%) was 54 years and 40 years in young patients (<50 years). Compared to young

recipients, old recipients had an inferior patient survival rate (≥50: 5yr, 82.8%; 10yr, 65.6%; <50: 5yr, 93.3%; 10yr, 82.0%; P < 0.0001). Old recipients demonstrated comparable death-censored pancreas (≥50: 1yr, 80.6%; 5yr, 70.2%; <50: 1yr, 87.3%; 5yr, 77.8%; P = 0.35) and kidney graft survival (≥50: 1yr, 97.4%; 5yr, 90.6%; <50: 1yr, 97.8%; 5yr, 90.2%; P = 0.53) compared to young recipients. Besides a lower rate of kidney rejection, similar relative risks for postoperative complications were detected in old and young patients. This study shows that despite an increased mortality in old recipients, excellent graft survival can be achieved similar to that of young patients. Age alone should not exclude patients from receiving a pancreas transplant.

Gepubliceerd: Transpl Int. 2021;34(4):657-68.
Impact factor: 3.782; Q1

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30. **Objectively measured preoperative physical activity is associated with time to functional recovery after hepato-pancreato-biliary cancer surgery: a pilot study**
Mylius CF, Krijnen WP, Takken T, Lips DJ, Eker H, van der Schans CP, Klaase JM.

Background: Surgical resection is currently the cornerstone of hepato-pancreato-biliary (HPB) cancer treatment. A low preoperative aerobic fitness level has been identified as a modifiable risk factor associated with complications after major abdominal surgery. A person's aerobic fitness is influenced by performing moderate to vigorous physical activity (MVPA). This study aims to determine the activity monitor measured levels of MVPA performed among patients on the waiting list for HPB cancer surgery and their association with postoperative outcomes.
Methods: A prospective, observational multi-center cohort pilot study was conducted. Patients enlisted for resection surgery on suspicion of HPB (pre)malignancy were enrolled. Performed MVPA was measured by an Actigraph wGT3X-BT. Additionally, aerobic fitness was measured via the Incremental Shuttle Walk Test, and (post)operative variables were collected from the electronic patient files. The association between MVPA and the pre- and postoperative variables was determined by univariate and multivariable (logistic) robust regression.
Results: A total of 38 participants, median age 66.0 (IQR 58.25-74.75) years, were enrolled. The median daily MVPA was 10.7 (IQR 6.9-18.0) min; only 8 participants met the Dutch MVPA guidelines. Participant's age and aerobic fitness were associated with MVPA by multivariable statistical analysis. Time to functional recovery was 8 (IQR 5-12) days and was associated with MVPA and type of surgery (major/minor) in multivariable analysis.
Conclusion: Seventy-six percent of patients enlisted for resection of HPB (pre)malignancy performed insufficient MVPA. A higher level of MVPA was associated with a shorter time to functional recovery.

Gepubliceerd: Perioper Med (Lond). 2021;10(1):33.
Impact factor: 3.535; Q2

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31. **A complete magnetic sentinel lymph node biopsy procedure in oral cancer patients: A pilot study**
Nieuwenhuis ER, Kolenaar B, van Bemmel AJM, Hof JJ, van Baarlen J, Christenhusz A, Pouw JJ, Ten Haken B, Alic L, de Bree R.

Objectives: To assess the feasibility and merits of a complete magnetic approach for a sentinel lymph node biopsy (SLNB) procedure in oral cancer patients.
Materials and methods: This study included ten oral cancer patients (stage cT1-T2N0M0) scheduled for elective neck dissection (END). Superparamagnetic iron oxide nanoparticles (SPIO) were administered peritumorally prior to surgery. A preoperative MRI was acquired to identify lymph nodes (LNs) with iron uptake. A magnetic detector was used to identify magnetic hotspots prior, during, and after the SLNB procedure. The resected sentinel LNs (SLNs) were evaluated using step-serial sectioning, and the neck dissection specimen was assessed by routine histopathological examination. A postoperative MRI was acquired to observe any residual iron.
Results: Of ten primary tumors, eight were located in the tongue, one floor-of-mouth (FOM), and one tongue-FOM transition. SPIO injections were experienced as painful by nine patients, two of whom developed a tongue swelling. In eight patients, magnetic SLNs were successfully detected and excised during the magnetic SLNB procedure. During the END procedure, additional magnetic SLNs were identified in three patients. Histopathology confirmed iron deposits in sinuses of excised SLNs. Three SLNs were harboring metastases, of which one was identified only during the END procedure. The END specimens revealed no further metastases.
Conclusion: A complete magnetic SLNB procedure was successfully performed in eight of ten patients (80% success rate), therefore the procedure seems feasible. Recommendations for further investigation are made including: use of anesthetics, magnetic tracer volume, planning preoperative MRI, comparison to conventional technique and follow-up.

Gepubliceerd: Oral Oncol. 2021;121:105464.
Impact factor: 5.337; Q1

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32. **Pancreatic resection in the pediatric, adolescent and young adult population: nationwide analysis on complications**
Pranger BK, van Dam JL, Groen JV, van Eijck CH, Koerkamp BG, Bonsing BA, Mieog JSD, Besselink MG, Busch OR, Kazemier G, de Jong KP, de Kleine RHJ, Molenaar IQ, Stommel MWJ, Gerhards MF, Coolsen MME, van Santvoort HC, van der Harst E, Klaase JM, de Meijer VE, Dutch Pancreatic Cancer Group.

Background: The aim of this study was to determine pancreatic surgery specific short- and long-term complications of pediatric, adolescent and young adult (PAYA) patients who underwent pancreatic resection, as compared to a comparator cohort of adults.
Methods: A nationwide retrospective cohort study was performed in PAYA patients who underwent pancreatic resection between 2007 and 2016. PAYA was defined as all patients <40 years at time of surgery. Pancreatic surgery-specific complications were assessed according to international definitions and textbook outcome was determined.
Results: A total of 230 patients were included in the PAYA cohort (112 distal pancreatectomies, 99 pancreatoduodenectomies), and 2526 patients in the comparator

cohort. For pancreatoduodenectomy, severe morbidity (29.3% vs. 28.6%; P = 0.881), in-hospital mortality (1% vs. 4%; P = 0.179) and textbook outcome (62% vs. 58%; P = 0.572) were comparable between the PAYA and the comparator cohort. These outcomes were also similar for distal pancreatectomy. After pancreatoduodenectomy, new-onset diabetes mellitus (8% vs. 16%) and exocrine pancreatic insufficiency (27% vs. 73%) were lower in the PAYA cohort when compared to adult literature.
Conclusion: Pancreatic surgery-specific complications were comparable with patients >/=40 years. Development of endocrine and exocrine insufficiency in PAYA patients who underwent pancreatoduodenectomy, however, was substantially lower compared to adult literature.

Gepubliceerd: HPB (Oxford). 2021;23(8):1175-84.
Impact factor: 3.647; Q1

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33. **Does oncological outcome differ between restorative and nonrestorative low anterior resection in patients with primary rectal cancer?**
Roodbeen SX, Blok RD, Borstlap WA, Bemelman WA, Hompes R, Tanis PJ, Dutch Snapshot Research Group – includes van Duyn EB

Aim: Nonrestorative low anterior resection (n-rLAR) (also known as low Hartmann's) is performed for rectal cancer when a poor functional outcome is anticipated or there have been problems when constructing the anastomosis. Compared with restorative LAR (rLAR), little oncological outcome data are available for n-rLAR. The aim of this study was to compare oncological outcomes between rLAR and n-rLAR for primary rectal cancer.
Method: This was a nationwide cross-sectional comparative study including all elective sphincter-saving LAR procedures for nonmetastatic primary rectal cancer performed in 2011 in 71 Dutch hospitals. Oncological outcomes of patients undergoing rLAR and n-rLAR were collected in 2015; the data were evaluated using Kaplan-Meier survival analysis and the results compared using log-rank testing. Uni- and multivariable Cox regression analysis was used to evaluate the association between the type of LAR and oncological outcome measures.
Results: A total of 1197 patients were analysed, of whom 892 (75%) underwent rLAR and 305 (25%) underwent n-rLAR. The 3-year local recurrence (LR) rate was 3% after rLAR and 8% after n-rLAR (P < 0.001). The 3-year disease-free survival and overall survival rates were 77% (rLAR) vs 62% (n-rLAR) (P < 0.001) and 90% (rLAR) vs 75% (n-rLAR) (P < 0.001), respectively. In multivariable Cox analysis, n-rLAR was independently associated with a higher risk of LR (OR = 2.95) and worse overall survival (OR = 1.72).
Conclusion: This nationwide study revealed that n-rLAR for rectal cancer was associated with poorer oncological outcome than r-LAR. This is probably a noncausal relationship, and might reflect technical difficulties during low pelvic dissection in a subset of those patients, with oncological implications.

Gepubliceerd: Colorectal Dis. 2021;23(4):843-52.
Impact factor: 3.788; Q1

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34. **Perioperative Systemic Therapy vs Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Alone for Resectable Colorectal Peritoneal Metastases: A Phase 2 Randomized Clinical Trial**

Rovers KP, Bakkers C, Nienhuijs SW, Burger JWA, Creemers GM, Thijs AMJ, Brandt-Kerkhof ARM, Madsen EVE, van Meerten E, Tuynman JB, Kusters M, Versteeg KS, Aalbers AGJ, Kok NFM, Buffart TE, Wiezer MJ, Boerma D, Los M, de Reuver PR, Bremers AJA, Verheul HMW, Kruijff S, de Groot DJA, Witkamp AJ, van Grevenstein WMU, Koopman M, Nederend J, Lahaye MJ, Kranenburg O, Fijneman RJA, van 't Erve I, Snaebjornsson P, Hemmer PHJ, Dijkgraaf MGW, Punt CJA, Tanis PJ, de Hingh I, Dutch Peritoneal Oncology Group and the Dutch Colorectal Cancer Group – includes van Duyn EB, Mastboom WJ

Importance: To date, no randomized clinical trials have investigated perioperative systemic therapy relative to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) alone for resectable colorectal peritoneal metastases (CPM).
Objective: To assess the feasibility and safety of perioperative systemic therapy in patients with resectable CPM and the response of CPM to neoadjuvant treatment.
Design, setting, and participants: An open-label, parallel-group phase 2 randomized clinical trial in all 9 Dutch tertiary centers for the surgical treatment of CPM enrolled participants between June 15, 2017, and January 9, 2019. Participants were patients with pathologically proven isolated resectable CPM who did not receive systemic therapy within 6 months before enrollment.
Interventions: Randomization to perioperative systemic therapy or CRS-HIPEC alone. Perioperative systemic therapy comprised either four 3-week neoadjuvant and adjuvant cycles of CAPOX (capecitabine and oxaliplatin), six 2-week neoadjuvant and adjuvant cycles of FOLFOX (fluorouracil, leucovorin, and oxaliplatin), or six 2-week neoadjuvant cycles of FOLFIRI (fluorouracil, leucovorin, and irinotecan) and either four 3-week adjuvant cycles of capecitabine or six 2-week adjuvant cycles of fluorouracil with leucovorin. Bevacizumab was added to the first 3 (CAPOX) or 4 (FOLFOX/FOLFIRI) neoadjuvant cycles.
Main outcomes and measures: Proportions of macroscopic complete CRS-HIPEC and Clavien-Dindo grade 3 or higher postoperative morbidity. Key secondary outcomes were centrally assessed rates of objective radiologic and major pathologic response of CPM to neoadjuvant treatment. Analyses were done modified intention-to-treat in patients starting neoadjuvant treatment (experimental arm) or undergoing upfront surgery (control arm).
Results: In 79 patients included in the analysis (43 [54%] men; mean [SD] age, 62 [10] years), experimental (n = 37) and control (n = 42) arms did not differ significantly regarding the proportions of macroscopic complete CRS-HIPEC (33 of 37 [89%] vs 36 of 42 [86%] patients; risk ratio, 1.04; 95% CI, 0.88-1.23; P = .74) and Clavien-Dindo grade 3 or higher postoperative morbidity (8 of 37 [22%] vs 14 of 42 [33%] patients; risk ratio, 0.65; 95% CI, 0.31-1.37; P = .25). No treatment-related deaths occurred. Objective radiologic and major pathologic response rates of CPM to neoadjuvant treatment were 28% (9 of 32 evaluable patients) and 38% (13 of 34 evaluable patients), respectively.
Conclusions and relevance: In this randomized phase 2 trial in patients diagnosed with resectable CPM, perioperative systemic therapy seemed feasible, safe, and able to induce response of CPM, justifying a phase 3 trial.
Trial registrattion: ClinicalTrials.gov Identifier: NCT02758951.

Gepubliceerd: JAMA Surg. 2021;156(8):710-20.
Impact factor: 14.766; Q1

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35. **Up to 10-year follow-up after EVAR with the Endurant stent graft system: a single-center experience**
Salemans PB, Lind RC, van der Linde RA, Pierie MP, Fritschy WM.

Background: Endovascular aneurysm repair (EVAR) has become the preferred treatment for infrarenal abdominal aortic aneurysms (AAA) over open surgical repair. The Endurant stent graft is widely used, and large registries report low rates of aneurysm-related mortality and reinterventions at midterm follow-up. Reports of long-term follow-up are limited. The aim of this study is to report our experiences and share our results, reintervention rate and mortality at long-term follow-up after using the Endurant stent graft.
Methods: All consecutive patients treated between 2009 and 2013 with the Medtronic Endurant I and II stent graft for an infrarenal AAA in an elective setting were included. Primary outcomes were overall and aneurysm-related survival and reintervention rates.
Results: One hundred sixty-five consecutive patients (median age 74; IQR: 68-79) with an aneurysm diameter of 62 mm (IQR: 58-70) and neck length of 29 mm (IQR: 21-40) were electively treated with the Endurant I or II stent graft. One hundred thirty-four patients (81.2%) were treated inside IFU (instructions for use) and 31 (18.8%) outside IFU. At median follow-up of 76 months (IQR: 50-97), 60 patients (36.4%) were deceased. Kaplan-Meier estimates at 10 years follow-up of overall survival and freedom from aneurysm-related mortality were respectively 48.5% (CI: 43.7-53.3%) and 97.3% (CI: 95.7-98.9%). Freedom from reintervention was 86.0% with an CI: 83.1-88.9% at 5 years follow-up and 75.6% with a CI: 70.2-81.0% at 10 years follow-up. A total of 25 (15.2%) patients had an EVAR-related reintervention; indications were endoleak (EL) type 1A (N.=11), EL type 1B (N.=3), EL type 2 (N.=6), EL type 3 (N.=1) and limb occlusion (N.=4). We found no significant differences in outcome between the inside and outside IFU groups. At 5 years follow-up 92.6% of patients had stable or decreased diameter, and 7.4% had an increased diameter.
Conclusions: This large cohort single-center study demonstrates the effectiveness and safety of the Endurant stent graft system at long-term follow-up with low reintervention rates and aneurysm-related mortality.

Gepubliceerd: J Cardiovasc Surg (Torino). 2021;62(3):242-9.
Impact factor: 1.888; Q3

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36. **Dutch trauma system performance: Are injured patients treated at the right place?**
Sturms LM, Driessen MLS, van Klaveren D, Ten Duis HJ, Kommer GJ, Bloemers FW, den Hartog D, Edwards MJ, Leenhouts PA, van Zutphen S, Schipper IB, Spanjersberg R, Wendt KW, de Wit RJ, Poeze M, Leenen LP, de Jongh M.

Background: The goal of trauma systems is to match patient care needs to the capabilities of the receiving centre. Severely injured patients have shown better outcomes if treated in a major trauma centre (MTC). We aimed to evaluate patient distribution in the Dutch trauma system. Furthermore, we sought to identify factors

associated with the undertriage and transport of severely injured patients (Injury Severity Score (ISS) >15) to the MTC by emergency medical services (EMS).
Methods: Data on all acute trauma admissions in the Netherlands (2015-2016) were extracted from the Dutch national trauma registry. An ambulance driving time model was applied to calculate MTC transport times and transport times of ISS >15 patients to the closest MTC and non-MTC. A multivariable logistic regression analysis was performed to identify factors associated with ISS >15 patients' EMS undertriage to an MTC.
Results: Of the annual average of 78,123 acute trauma admissions, 4.9% had an ISS >15. The nonseverely injured patients were predominantly treated at non-MTCs (79.2%), and 65.4% of patients with an ISS >15 received primary MTC care. This rate varied across the eleven Dutch trauma networks (36.8%-88.4%) and was correlated with the transport times to an MTC (Pearson correlation -0.753, p=0.007). The trauma networks also differed in the rates of secondary transfers of ISS >15 patients to MTC hospitals (7.8% - 59.3%) and definitive MTC care (43.6% - 93.2%). Factors associated with EMS undertriage of ISS >15 patients to the MTC were female sex, older age, severe thoracic and abdominal injury, and longer additional EMS transport times.
Conclusions: Approximately one-third of all severely injured patients in the Netherlands are not initially treated at an MTC. Special attention needs to be directed to identifying patient groups with a high risk of undertriage. Furthermore, resources to overcome longer transport times to an MTC, including the availability of ambulance and helicopter services, may improve direct MTC care and result in a decrease in the variation of the undertriage of severely injured patients to MTCs among the Dutch trauma networks. Furthermore, attention needs to be directed to improving primary triage guidelines and instituting uniform interfacility transfer agreements.

Gepubliceerd: Injury. 2021;52(7):1688-96.
Impact factor: 2.586; Q2

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37. **Can 3D-printing avoid discomfort-related implant removal in midshaft clavicle fractures? A four-year follow-up**
van Doremalen RFM, van der Linde RA, Kootstra JJ, van Helden SH, Hekman EEG.

Introduction: Due to the variation in shape and curvature of the clavicle, plates often have to be adjusted during surgery to acquire a good fit. Poorly fitted plates can cause discomfort, eventually requiring implant removal. 3D-printed replicas of the fractured clavicle can assist in planning of the surgical approach, plate selection and, if necessary, adjustment of the plate prior to surgery. We hypothesized this method of preoperative preparation would reduce implant-related discomfort resulting in a reduced reoperation rate
Materials and methods: In a prospective cohort study, perioperative plate handling and clavicle fixation were timed and follow-up data were collected from participants undergoing operative treatment for a midshaft clavicle fracture. The control group (n = 7) received conventional surgery with standard precontoured plates. For the intervention group (n = 7), 3D-printed replicas of the fractured clavicle and a mirrored version of the healthy contralateral clavicle were available prior to surgery for planning of the surgical approach, and for plate selection and contouring. Primary outcome was reoperation rate due to implant-related discomfort. Secondary outcomes were

complications and time differences in the different surgical phases (reduction, fixation and overall operation time)
Results: More participants in the control group had the plate removed due to discomfort compared to the intervention group (5/7 vs. 0/6; P = 0.012). One participant was excluded from the intervention group due to a postoperative complication; an infection occurred at the implant site. No relevant time difference in surgical plate handling was found between both groups.
Conclusions: Preoperative preparation using 3D-printed replicas of the clavicle fracture may reduce implant removal caused by plated-related discomfort. No relevant effect on surgery time was found.
Trial registrattion: Registered with 'toetsingonline.nl', trial number NL51269.075/14, 17-02-2015.

Gepubliceerd: Arch Orthop Trauma Surg. 2021;141(11):1899-907.
Impact factor: 3.067; Q2

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38. **Minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma (DIPLOMA): study protocol for a randomized controlled trial**
van Hilst J, Korrel M, Lof S, de Rooij T, Vissers F, Al-Sarireh B, Alseidi A, Bateman AC, Björnsson B, Boggi U, Bratlie SO, Busch O, Butturini G, Casadei R, Dijk F, Dokmak S, Edwin B, van Eijck C, Esposito A, Fabre JM, Falconi M, Ferrari G, Fuks D, Groot Koerkamp B, Hackert T, Keck T, Khatkov I, de Kleine R, Kokkola A, Kooby DA, Lips DJ, Luyer M, Marudanayagam R, Menon K, Molenaar Q, de Pastena M, Pietrabissa A, Rajak R, Rosso E, Sanchez Velazquez P, Saint Marc O, Shah M, Soonawalla Z, Tomazic A, Verbeke C, Verheij J, White S, Wilmink HW, Zerbi A, Dijkgraaf MG, Besselink MG, Abu Hilal M.

Background: Recently, the first randomized trials comparing minimally invasive distal pancreatectomy (MIDP) with open distal pancreatectomy (ODP) for non-malignant and malignant disease showed a 2-day reduction in time to functional recovery after MIDP. However, for pancreatic ductal adenocarcinoma (PDAC), concerns have been raised regarding the oncologic safety (i.e., radical resection, lymph node retrieval, and survival) of MIDP, as compared to ODP. Therefore, a randomized controlled trial comparing MIDP and ODP in PDAC regarding oncological safety is warranted. We hypothesize that the microscopically radical resection (R0) rate is non-inferior for MIDP, as compared to ODP.
Methods/design: DIPLOMA is an international randomized controlled, patient- and pathologist-blinded, non-inferiority trial performed in 38 pancreatic centers in Europe and the USA. A total of 258 patients with an indication for elective distal pancreatectomy with splenectomy because of proven or highly suspected PDAC of the pancreatic body or tail will be randomly allocated to MIDP (laparoscopic or robot-assisted) or ODP in a 1:1 ratio. The primary outcome is the microscopically radical resection margin (R0, distance tumor to pancreatic transection and posterior margin ≥ 1 mm), which is assessed using a standardized histopathology assessment protocol. The sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1-β), expected R0 rate in the open group of 58%, expected R0 resection rate in the minimally invasive group of 67%, and a non-inferiority margin of 7%. Secondary outcomes include time to functional recovery, operative outcomes (e.g., blood loss, operative time, and conversion to open surgery), other

histopathology findings (e.g., lymph node retrieval, perineural- and lymphovascular invasion), postoperative outcomes (e.g., clinically relevant complications, hospital stay, and administration of adjuvant treatment), time and site of disease recurrence, survival, quality of life, and costs. Follow-up will be performed at the outpatient clinic after 6, 12, 18, 24, and 36 months postoperatively.
Discussion: The DIPLOMA trial is designed to investigate the non-inferiority of MIDP versus ODP regarding the microscopically radical resection rate of PDAC in an international setting.
Trial registrattion: ISRCTN registry ISRCTN44897265 . Prospectively registered on 16 April 2018.

Gepubliceerd: Trials. 2021;22(1):608.
Impact factor: 2.279; Q4

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39. **Risk factors for surgery-related muscle quantity and muscle quality loss and their impact on outcome**
van Wijk L, van Duinhoven S, Liem MSL, Bouman DE, Viddeleer AR, Klaase JM.

Background: Surgery-related loss of muscle quantity negatively affects postoperative outcomes. However, changes of muscle quality have not been fully investigated. A perioperative intervention targeting identified risk factors could improve postoperative outcome. This study investigated risk factors for surgery-related loss of muscle quantity and quality and outcomes after liver resection for colorectal liver metastasis (CRLM).
Methods: Data of patients diagnosed with CRLM who underwent liver resection between 2006 and 2016 were analysed. Muscle quantity (psoas muscle index [PMI]), and muscle quality, (average muscle radiation attenuation [AMA] of the psoas), were measured using computed tomography. Changes in PMI and AMA of psoas after surgery were assessed.
Results: A total of 128 patients were analysed; 67 (52%) had surgery-related loss of muscle quantity and 83 (65%) muscle quality loss. Chronic obstructive pulmonary disease (COPD) (P = 0.045) and diabetes (P = 0.003) were risk factors for surgery-related loss of muscle quantity. A higher age (P = 0.002), open resection (P = 0.003) and longer operation time (P = 0.033) were associated with muscle quality loss. Overall survival was lower in patients with both muscle quantity and quality loss compared to other categories (P = 0.049). The rate of postoperative complications was significantly higher in the group with surgery-related loss of muscle quality.
Conclusions: Risk factors for surgery-related muscle loss were identified. Overall survival was lowest in patients with both muscle quantity and quality loss. Complication rate was higher in patients with surgery-related loss of muscle quality.

Gepubliceerd: Eur J Med Res. 2021;26(1):36.
Impact factor: 2.175; Q4

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40. **Comparing the signal enhancement of a gadolinium based and an iron-oxide based contrast agent in low-field MRI**
van Zandwijk JK, Simonis FFJ, Heslinga FG, Hofmeijer EIS, Geelkerken RH, Ten Haken B.

Recently, there has been a renewed interest in low-field MRI. Contrast agents (CA) in MRI have magnetic behavior dependent on magnetic field strength. Therefore, the optimal contrast agent for low-field MRI might be different from what is used at higher fields. Ultra-small superparamagnetic iron-oxides (USPIOs), commonly used as negative CA, might also be used for generating positive contrast in low-field MRI. The purpose of this study was to determine whether an USPIO or a gadolinium based contrast agent is more appropriate at low field strengths. Relaxivity values of ferumoxytol (USPIO) and gadoterate (gadolinium based) were used in this research to simulate normalized signal intensity (SI) curves within a concentration range of 0-15 mM. Simulations were experimentally validated on a 0.25T MRI scanner. Simulations and experiments were performed using spin echo (SE), spoiled gradient echo (SGE), and balanced steady-state free precession (bSSFP) sequences. Maximum achievable SIs were assessed for both CAs in a range of concentrations on all sequences. Simulations at 0.25T showed a peak in SIs at low concentrations ferumoxytol versus a wide top at higher concentrations for gadoterate in SE and SGE. Experiments agreed well with the simulations in SE and SGE, but less in the bSSFP sequence due to overestimated relaxivities in simulations. At low magnetic field strengths, ferumoxytol generates similar signal enhancement at lower concentrations than gadoterate.

Gepubliceerd: PLoS One. 2021;16(8):e0256252.
Impact factor: 3.240; Q2

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41. **Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort**

Walma MS, Brada LJ, Patuleia SIS, Blomjous JG, Bollen TL, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam R, Festen S, Jan de Groot D, Willem de Groot J, Mohammad NH, Hermans JJ, de Hingh IH, Kerver ED, van Leeuwen MS, van der Leij C, Liem MSL, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nederend J, Nio CY, Patijn GA, Polée MB, Pruijt JF, Renken NS, Rombouts SJ, Schouten TJ, Stommel MWJ, Verweij ME, de Vos-Geelen J, de Vries JJJ, Vulink A, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ.

Introduction: Since current studies on locally advanced pancreatic cancer (LAPC) mainly report from single, high-volume centers, it is unclear if outcomes can be translated to daily clinical practice. This study provides treatment strategies and clinical outcomes within a multicenter cohort of unselected patients with LAPC.
Materials and methods: Consecutive patients with LAPC according to Dutch Pancreatic Cancer Group criteria, were prospectively included in 14 centers from April 2015 until December 2017. A centralized expert panel reviewed response according to RECIST v1.1 and potential surgical resectability. Primary outcome was median overall survival (mOS), stratified for primary treatment strategy.
Results: Overall, 422 patients were included, of whom 77% (n = 326) received chemotherapy. The majority started with FOLFIRINOX (77%, 252/326) with a median of six cycles (IQR 4-10). Gemcitabine monotherapy was given to 13% (41/326) of patients and nab-paclitaxel/gemcitabine to 10% (33/326), with a median of two (IQR 3-5) and three (IQR 3-5) cycles respectively. The mOS of the entire cohort was 10 months (95%CI 9-11). In patients treated with FOLFIRINOX, gemcitabine monotherapy, or nab-paclitaxel/gemcitabine, mOS was 14 (95%CI 13-15), 9 (95%CI 8-10), and 9 months

(95%CI 8-10), respectively. A resection was performed in 13% (32/252) of patients after FOLFIRINOX, resulting in a mOS of 23 months (95%CI 12-34).
Conclusion: This multicenter unselected cohort of patients with LAPC resulted in a 14 month mOS and a 13% resection rate after FOLFIRINOX. These data put previous results in perspective, enable us to inform patients with more accurate survival numbers and will support decision-making in clinical practice.

Gepubliceerd: Eur J Surg Oncol. 2021;47(3 Pt B):699-707.
Impact factor: 4.424; Q1

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42. **Radiofrequency ablation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer (PELICAN): study protocol for a randomized controlled trial**
Walma MS, Rombouts SJ, Brada LJH, Borel Rinkes IH, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam RM, van Delden OM, Festen S, Ghorbani P, de Groot DJ, de Groot JWB, Haj Mohammad N, van Hillegersberg R, de Hingh IH, D'Hondt M, Kerver ED, van Leeuwen MS, Liem MSL, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nio CY, Oulad Abdennabi I, Pando E, Patijn GA, Polée MB, Pruijt JF, Roeyen G, Ropela JA, Stommel MWJ, de Vos-Geelen J, de Vries JJ, van der Waal EM, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ.

Background: Approximately 80% of patients with locally advanced pancreatic cancer (LAPC) are treated with chemotherapy, of whom approximately 10% undergo a resection. Cohort studies investigating local tumor ablation with radiofrequency ablation (RFA) have reported a promising overall survival of 26-34 months when given in a multimodal setting. However, randomized controlled trials (RCTs) investigating the effect of RFA in combination with chemotherapy in patients with LAPC are lacking.
Methods: The "Pancreatic Locally Advanced Unresectable Cancer Ablation" (PELICAN) trial is an international multicenter superiority RCT, initiated by the Dutch Pancreatic Cancer Group (DPCG). All patients with LAPC according to DPCG criteria, who start with FOLFIRINOX or (nab-paclitaxel/)gemcitabine, are screened for eligibility. Restaging is performed after completion of four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine (i.e., 2 months of treatment), and the results are assessed within a nationwide online expert panel. Eligible patients with RECIST stable disease or objective response, in whom resection is not feasible, are randomized to RFA followed by chemotherapy or chemotherapy alone. In total, 228 patients will be included in 16 centers in The Netherlands and four other European centers. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, RECIST response, CA 19.9 and CEA response, toxicity, quality of life, pain, costs, and immunomodulatory effects of RFA.
Discussion: The PELICAN RCT aims to assess whether the combination of chemotherapy and RFA improves the overall survival when compared to chemotherapy alone, in patients with LAPC with no progression of disease following 2 months of systemic treatment.

Gepubliceerd: Trials. 2021;22(1):313.
Impact factor: 2.279; Q4

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43. **A Systematic Review and Critical Appraisal of Peri-Procedural Tissue Perfusion Techniques and their Clinical Value in Patients with Peripheral Arterial Disease**
Wermelink B, Ma KF, Haalboom M, El Moumni M, de Vries JPM, Geelkerken RH.

Objective: Many techniques have been introduced to enable quantification of tissue perfusion in patients with peripheral arterial disease (PAD). Currently, none of these techniques is widely used to analyse real time tissue perfusion changes during endovascular or surgical revascularisation procedures. The aim of this systematic review was to provide an up to date overview of the peri-procedural applicability of currently available techniques, diagnostic accuracy of assessing tissue perfusion and the relationship with clinical outcomes.
Data sources: MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials.
Review methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines. Four electronic databases were searched up to 31 12 2020 for eligible articles: MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. Eligible articles describing a perfusion measurement technique, used in a peri-procedural setting before and within 24 hours after the revascularisation procedure, with the aim of determining the effect of intervention in patients with PAD, were assessed for inclusion. The QUADAS-2 tool was used to assess the risk of bias and applicability of the studies.
Results: An overview of 10 techniques found in 26 eligible articles focused on study protocols, research goals, and clinical outcomes is provided. Non-invasive techniques included laser speckle contrast imaging, micro-lightguide spectrophotometry, magnetic resonance imaging perfusion, near infrared spectroscopy, skin perfusion pressure, and plantar thermography. Invasive techniques included two dimensional perfusion angiography, contrast enhanced ultrasound, computed tomography perfusion imaging, and indocyanine green angiography. The results of the 26 eligible studies, which were mostly of poor quality according to QUADAS-2, were without exception, not sufficient to substantiate implementation in daily clinical practice.
Conclusion: This systematic review provides an overview of 10 tissue perfusion assessment techniques for patients with PAD. It seems too early to appoint one of them as a reference standard. The scope of future research in this domain should therefore focus on clinical accuracy, reliability, and validation of the techniques.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2021;62(6):896-908.
Impact factor: 7.069; Q1

Totale impact factor: 196.382
Gemiddelde impact factor: 4.567

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 30.865
Gemiddelde impact factor: 3.858

Intensive care

1. **Clinically relevant potential drug-drug interactions in intensive care patients: A large retrospective observational multicenter study**

Bakker T, Abu-Hanna A, Dongelmans DA, Vermeijden WJ, Bosman RJ, de Lange DW, Klopotowska JE, de Keizer NF, Hendriks S, Ten Cate J, Schutte PF, van Balen D, Duyvendak M, Karakus A, Sigtermans M, Kuck EM, Hunfeld NGM, van der Sijs H, de Feiter PW, Wils EJ, Spronk PE, van Kan HJM, van der Steen MS, Purmer IM, Bosma BE, Kieft H, van Marum RJ, de Jonge E, Beishuizen A, Movig K, Mulder F, Franssen EJF, van den Bergh WM, Bult W, Hoeksema M, Wesselink E.

Purpose: Potential drug-drug interactions (pDDIs) may harm patients admitted to the Intensive Care Unit (ICU). Due to the patient's critical condition and continuous monitoring on the ICU, not all pDDIs are clinically relevant. Clinical decision support systems (CDSSs) warning for irrelevant pDDIs could result in alert fatigue and overlooking important signals. Therefore, our aim was to describe the frequency of clinically relevant pDDIs (crpDDIs) to enable tailoring of CDSSs to the ICU setting.
Materials & methods: In this multicenter retrospective observational study, we used medication administration data to identify pDDIs in ICU admissions from 13 ICUs. Clinical relevance was based on a Delphi study in which intensivists and hospital pharmacists assessed the clinical relevance of pDDIs for the ICU setting.
Results: The mean number of pDDIs per 1000 medication administrations was 70.1, dropping to 31.0 when considering only crpDDIs. Of 103,871 ICU patients, 38% was exposed to a crpDDI. The most frequently occurring crpDDIs involve QT-prolonging agents, digoxin, or NSAIDs.
Conclusions: Considering clinical relevance of pDDIs in the ICU setting is important, as only half of the detected pDDIs were crpDDIs. Therefore, tailoring CDSSs to the ICU may reduce alert fatigue and improve medication safety in ICU patients.

Gepubliceerd: J Crit Care. 2021;62:124-30.
Impact factor: 3.425; Q2

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2. **Monitoring circulating dipeptidyl peptidase 3 (DPP3) predicts improvement of organ failure and survival in sepsis: a prospective observational multinational study**

Blet A, Deniau B, Santos K, van Lier DPT, Azibani F, Wittebole X, Chousterman BG, Gayat E, Hartmann O, Struck J, Bergmann A, Antonelli M, Beishuizen A, Constantin JM, Damoisel C, Deye N, Di Somma S, Dugernier T, François B, Gaudry S, Huberlant V, Lascarrou JB, Marx G, Mercier E, Oueslati H, Pickkers P, Sonneville R, Legrand M, Laterre PF, Mebazaa A.

Background: Dipeptidyl peptidase 3 (DPP3) is a cytosolic enzyme involved in the degradation of various cardiovascular and endorphin mediators. High levels of circulating DPP3 (cDPP3) indicate a high risk of organ dysfunction and mortality in cardiogenic shock patients.
Methods: The aim was to assess relationships between cDPP3 during the initial intensive care unit (ICU) stay and short-term outcome in the AdrenOSS-1, a prospective observational multinational study in twenty-four ICU centers in five countries. AdrenOSS-1 included 585 patients admitted to the ICU with severe sepsis

or septic shock. The primary outcome was 28-day mortality. Secondary outcomes included organ failure as defined by the Sequential Organ Failure Assessment (SOFA) score, organ support with focus on vasopressor/inotropic use and need for renal replacement therapy. cDPP3 levels were measured upon admission and 24 h later.
Results: Median [IQR] cDPP3 concentration upon admission was 26.5 [16.2-40.4] ng/mL. Initial SOFA score was 7 [5-10], and 28-day mortality was 22%. We found marked associations between cDPP3 upon ICU admission and 28-day mortality (unadjusted standardized HR 1.8 [CI 1.6-2.1]; adjusted HR 1.5 [CI 1.3-1.8]) and between cDPP3 levels and change in renal and liver SOFA score ($p = 0.0077$ and 0.0009, respectively). The higher the initial cDPP3 was, the greater the need for organ support and vasopressors upon admission; the longer the need for vasopressor(s), mechanical ventilation or RRT and the higher the need for fluid load (all $p < 0.005$). In patients with cDPP3 > 40.4 ng/mL upon admission, a decrease in cDPP3 below 40.4 ng/mL after 24 h was associated with an improvement of organ function at 48 h and better 28-day outcome. By contrast, persistently elevated cDPP3 at 24 h was associated with worsening organ function and high 28-day mortality.
Conclusions: Admission levels and rapid changes in cDPP3 predict outcome during sepsis. Trial Registration ClinicalTrials.gov, NCT02393781. Registered on March 19, 2015.

Gepubliceerd: Crit Care. 2021;25(1):61.
Impact factor: 9.097; Q1

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3. **Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury**
Bossers SM, Loer SA, Bloemers FW, Den Hartog D, Van Lieshout EMM, Hoogerwerf N, van der Naalt J, Absalom AR, Peerdeman SM, Schwarte LA, Boer C, Schober P, BRAIN-PROTECT collaborators - includes Beishuizen A.

Importance: The development and expansion of intracranial hematoma are associated with adverse outcomes. Use of tranexamic acid might limit intracranial hematoma formation, but its association with outcomes of severe traumatic brain injury (TBI) is unclear.
Objective: To assess whether prehospital administration of tranexamic acid is associated with mortality and functional outcomes in a group of patients with severe TBI.
Design, setting, and participants: This multicenter cohort study is an analysis of prospectively collected observational data from the Brain Injury: Prehospital Registry of Outcome, Treatments and Epidemiology of Cerebral Trauma (BRAIN-PROTECT) study in the Netherlands. Patients treated for suspected severe TBI by the Dutch Helicopter Emergency Medical Services between February 2012 and December 2017 were included. Patients were followed up for 1 year after inclusion. Data were analyzed from January 10, 2020, to September 10, 2020.
Exposures: Administration of tranexamic acid during prehospital treatment.
Main outcomes and measures: The primary outcome was 30-day mortality. Secondary outcomes included mortality at 1 year, functional neurological recovery at discharge (measured by Glasgow Outcome Scale), and length of hospital stay. Data were also collected on demographic factors, preinjury medical condition, injury characteristics, operational characteristics, and prehospital vital parameters.

Results: A total of 1827 patients were analyzed, of whom 1283 (70%) were male individuals and the median (interquartile range) age was 45 (23-65) years. In the unadjusted analysis, higher 30-day mortality was observed in patients who received prehospital tranexamic acid (odds ratio [OR], 1.34; 95% CI, 1.16-1.55; P < .001), compared with patients who did not receive prehospital tranexamic acid. After adjustment for confounders, no association between prehospital administration of tranexamic acid and mortality was found across the entire cohort of patients. However, a substantial increase in the odds of 30-day mortality persisted in patients with severe isolated TBI who received prehospital tranexamic acid (OR, 4.49; 95% CI, 1.57-12.87; P = .005) and after multiple imputations (OR, 2.05; 95% CI, 1.22-3.45; P = .007).
Conclusions and relevance: This study found that prehospital tranexamic acid administration was associated with increased mortality in patients with isolated severe TBI, suggesting the judicious use of the drug when no evidence for extracranial hemorrhage is present.

Gepubliceerd: JAMA Neurol. 2021;78(3):338-45.
Impact factor: 18.302; Q1

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4. **Lactate is associated with mortality in very old intensive care patients suffering from COVID-19: results from an international observational study of 2860 patients**
Bruno RR, Wernly B, Flaatten H, Fjølner J, Artigas A, Bollen Pinto B, Schefold JC, Binnebössel S, Baldia PH, Kelm M, Beil M, Sigal S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Wollborn J, Arche Banzo MJ, Fuest K, Marsh B, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Jung C, COVIP Study Group - includes Cornet AD.

Purpose: Lactate is an established prognosticator in critical care. However, there still is insufficient evidence about its role in predicting outcome in COVID-19. This is of particular concern in older patients who have been mostly affected during the initial surge in 2020.
Methods: This prospective international observation study (The COVIP study) recruited patients aged 70 years or older (ClinicalTrials.gov ID: NCT04321265) admitted to an intensive care unit (ICU) with COVID-19 disease from March 2020 to February 2021. In addition to serial lactate values (arterial blood gas analysis), we recorded several parameters, including SOFA score, ICU procedures, limitation of care, ICU- and 3-month mortality. A lactate concentration ≥ 2.0 mmol/L on the day of ICU admission (baseline) was defined as abnormal. The primary outcome was ICU-mortality. The secondary outcomes 30-day and 3-month mortality.
Results: In total, data from 2860 patients were analyzed. In most patients (68%), serum lactate was lower than 2 mmol/L. Elevated baseline serum lactate was associated with significantly higher ICU- and 3-month mortality (53% vs. 43%, and 71% vs. 57%, respectively, p < 0.001). In the multivariable analysis, the maximum lactate concentration on day 1 was independently associated with ICU mortality (aOR 1.06 95% CI 1.02-1.11; p = 0.007), 30-day mortality (aOR 1.07 95% CI 1.02-1.13; p = 0.005) and 3-month mortality (aOR 1.15 95% CI 1.08-1.24; p < 0.001) after adjustment for age, gender, SOFA score, and frailty. In 826 patients with baseline lactate ≥ 2 mmol/L sufficient data to calculate the difference between maximal levels on days 1 and 2 (Δ serum lactate) were available. A decreasing lactate concentration over time was

inversely associated with ICU mortality after multivariate adjustment for SOFA score, age, Clinical Frailty Scale, and gender (aOR 0.60 95% CI 0.42-0.85; p = 0.004).
Conclusion: In critically ill old intensive care patients suffering from COVID-19, lactate and its kinetics are valuable tools for outcome prediction.
Trial registration number: NCT04321265.

Gepubliceerd: Ann Intensive Care. 2021;11(1):128.
Impact factor: 6.925; Q1

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5. **Management and outcomes in critically ill nonagenarian versus octogenarian patients**
Bruno RR, Wernly B, Kelm M, Boumendil A, Morandi A, Andersen FH, Artigas A, Finazzi S, Cecconi M, Christensen S, Faraldi L, Lichtenauer M, Muessig JM, Marsh B, Moreno R, Oeyen S, Öhman CA, Pinto BB, Soliman IW, Szczeklik W, Valentin A, Watson X, Leaver S, Boulanger C, Walther S, Schefold JC, Joannidis M, Nalapko Y, Elhadi M, Fjølner J, Zafeiridis T, De Lange DW, Guidet B, Flaatten H, Jung C, VIP2 study group - includes Cornet AD.

Background: Intensive care unit (ICU) patients age 90 years or older represent a growing subgroup and place a huge financial burden on health care resources despite the benefit being unclear. This leads to ethical problems. The present investigation assessed the differences in outcome between nonagenarian and octogenarian ICU patients.
Methods: We included 7900 acutely admitted older critically ill patients from two large, multinational studies. The primary outcome was 30-day-mortality, and the secondary outcome was ICU-mortality. Baseline characteristics consisted of frailty assessed by the Clinical Frailty Scale (CFS), ICU-management, and outcomes were compared between octogenarian (80-89.9 years) and nonagenarian (> 90 years) patients. We used multilevel logistic regression to evaluate differences between octogenarians and nonagenarians.
Results: The nonagenarians were 10% of the entire cohort. They experienced a higher percentage of frailty (58% vs 42%; p < 0.001), but lower SOFA scores at admission (6 + 5 vs. 7 + 6; p < 0.001). ICU-management strategies were different. Octogenarians required higher rates of organ support and nonagenarians received higher rates of life-sustaining treatment limitations (40% vs. 33%; p < 0.001). ICU mortality was comparable (27% vs. 27%; p = 0.973) but a higher 30-day-mortality (45% vs. 40%; p = 0.029) was seen in the nonagenarians. After multivariable adjustment nonagenarians had no significantly increased risk for 30-day-mortality (aOR 1.25 (95% CI 0.90-1.74; p = 0.19)).
Conclusion: After adjustment for confounders, nonagenarians demonstrated no higher 30-day mortality than octogenarian patients. In this study, being age 90 years or more is no particular risk factor for an adverse outcome. This should be considered-together with illness severity and pre-existing functional capacity - to effectively guide triage decisions.
Trial registrattion: NCT03134807 and NCT03370692 .

Gepubliceerd: BMC Geriatr. 2021;21(1):576.
Impact factor: 3.921; Q1

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6. **Some Patients Are More Equal Than Others: Variation in Ventilator Settings for Coronavirus Disease 2019 Acute Respiratory Distress Syndrome**
Dam TA, de Grooth HJ, Klausch T, Fleuren LM, de Bruin DP, Entjes R, Rettig TCD, Dongelmans DA, Boelens AD, Rigter S, Hendriks SHA, de Jong R, Kamps MJA, Peters M, Karakus A, Gommers D, Ramnarain D, Wils EJ, Achterberg S, Nowitzky R, van den Tempel W, de Jager CPC, Nooteboom F, Oostdijk E, Koetsier P, Cornet AD, Reidinga AC, de Ruijter W, Bosman RJ, Frenzel T, Urlings-Strop LC, de Jong P, Smit EGM, Cremer OL, Mehagnoul-Schipper DJ, Faber HJ, Lens J, Brunnekreef GB, Festen-Spanjer B, Dormans T, Dijkstra A, Simons B, Rijkeboer AA, Arbous S, Aries M, Beukema M, Pretorius D, van Raalte R, van Tellingen M, Gritters van den Oever NC, Lalisang RCA, Tonutti M, Girbes ARJ, Hoogendoorn M, Thoral PJ, Elbers PWG.

Objectives: As coronavirus disease 2019 is a novel disease, treatment strategies continue to be debated. This provides the intensive care community with a unique opportunity as the population of coronavirus disease 2019 patients requiring invasive mechanical ventilation is relatively homogeneous compared with other ICU populations. We hypothesize that the novelty of coronavirus disease 2019 and the uncertainty over its similarity with noncoronavirus disease 2019 acute respiratory distress syndrome resulted in substantial practice variation between hospitals during the first and second waves of coronavirus disease 2019 patients. DESIGN: Multicenter retrospective cohort study.
Setting: Twenty-five hospitals in the Netherlands from February 2020 to July 2020, and 14 hospitals from August 2020 to December 2020. PATIENTS: One thousand two hundred ninety-four critically ill intubated adult ICU patients with coronavirus disease 2019 were selected from the Dutch Data Warehouse. Patients intubated for less than 24 hours, transferred patients, and patients still admitted at the time of data extraction were excluded.
Measurements and main results: We aimed to estimate between-ICU practice variation in selected ventilation parameters (positive end-expiratory pressure, Fio(2), set respiratory rate, tidal volume, minute volume, and percentage of time spent in a prone position) on days 1, 2, 3, and 7 of intubation, adjusted for patient characteristics as well as severity of illness based on Pao(2)/Fio(2) ratio, pH, ventilatory ratio, and dynamic respiratory system compliance during controlled ventilation. Using multilevel linear mixed-effects modeling, we found significant ($p \leq 0.001$) variation between ICUs in all ventilation parameters on days 1, 2, 3, and 7 of intubation for both waves.
Conclusions: This is the first study to clearly demonstrate significant practice variation between ICUs related to mechanical ventilation parameters that are under direct control by intensivists. Their effect on clinical outcomes for both coronavirus disease 2019 and other critically ill mechanically ventilated patients could have widespread implications for the practice of intensive care medicine and should be investigated further by causal inference models and clinical trials.

Gepubliceerd: Crit Care Explor. 2021;3(10):e0555.
Impact factor: 0; NVT

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7. **The value of open-source clinical science in pandemic response: lessons from ISARIC**
ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

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8. **The Dutch Data Warehouse, a multicenter and full-admission electronic health records database for critically ill COVID-19 patients**
Fleuren LM, Dam TA, Tonutti M, de Bruin DP, Lalisang RCA, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, Dongelmans DA, de Jong R, Peters M, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Faber HJ, Karakus A, Entjes R, de Jong P, Rettig TCD, Arbous S, Vonk SJJ, Fornasa M, Machado T, Houwert T, Hovenkamp H, Noorduijn-Londono R, Quintarelli D, Scholtemeijer MG, de Beer AA, Cina G, Beudel M, Herter WE, Girbes ARJ, Hoogendoorn M, Thoral PJ, Elbers PWG.

Background: The Coronavirus disease 2019 (COVID-19) pandemic has underlined the urgent need for reliable, multicenter, and full-admission intensive care data to advance our understanding of the course of the disease and investigate potential treatment strategies. In this study, we present the Dutch Data Warehouse (DDW), the first multicenter electronic health record (EHR) database with full-admission data from critically ill COVID-19 patients.
Methods: A nation-wide data sharing collaboration was launched at the beginning of the pandemic in March 2020. All hospitals in the Netherlands were asked to participate and share pseudonymized EHR data from adult critically ill COVID-19 patients. Data included patient demographics, clinical observations, administered medication, laboratory determinations, and data from vital sign monitors and life support devices. Data sharing agreements were signed with participating hospitals before any data transfers took place. Data were extracted from the local EHRs with prespecified queries and combined into a staging dataset through an extract-transform-load (ETL) pipeline. In the consecutive processing pipeline, data were mapped to a common concept vocabulary and enriched with derived concepts. Data validation was a continuous process throughout the project. All participating hospitals have access to the DDW. Within legal and ethical boundaries, data are available to clinicians and researchers.
Results: Out of the 81 intensive care units in the Netherlands, 66 participated in the collaboration, 47 have signed the data sharing agreement, and 35 have shared their data. Data from 25 hospitals have passed through the ETL and processing pipeline. Currently, 3464 patients are included in the DDW, both from wave 1 and wave 2 in the Netherlands. More than 200 million clinical data points are available. Overall ICU mortality was 24.4%. Respiratory and hemodynamic parameters were most frequently measured throughout a patient's stay. For each patient, all administered medication and their daily fluid balance were available. Missing data are reported for each descriptive.

Conclusions: In this study, we show that EHR data from critically ill COVID-19 patients may be lawfully collected and can be combined into a data warehouse. These initiatives are indispensable to advance medical data science in the field of intensive care medicine.

Gepubliceerd: Crit Care. 2021;25(1):304.
Impact factor: 9.097; Q1

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9. **Predictors for extubation failure in COVID-19 patients using a machine learning approach**
Fleuren LM, Dam TA, Tonutti M, de Bruin DP, Lalisang RCA, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, Dongelmans DA, de Jong R, Peters M, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Faber HJ, Karakus A, Entjes R, de Jong P, Rettig TCD, Arbous S, Vonk SJJ, Fornasa M, Machado T, Houwert T, Hovenkamp H, Noorduijn Londono R, Quintarelli D, Scholtemeijer MG, de Beer AA, Cinà G, Kantorik A, de Ruijter T, Herter WE, Beudel M, Girbes ARJ, Hoogendoorn M, Thoral PJ, Elbers PWG, Dutch ICU Data Sharing Against Covid-19 Collaborators – includes Beishuizen A.

Introduction: Determining the optimal timing for extubation can be challenging in the intensive care. In this study, we aim to identify predictors for extubation failure in critically ill patients with COVID-19.
Methods: We used highly granular data from 3464 adult critically ill COVID patients in the multicenter Dutch Data Warehouse, including demographics, clinical observations, medications, fluid balance, laboratory values, vital signs, and data from life support devices. All intubated patients with at least one extubation attempt were eligible for analysis. Transferred patients, patients admitted for less than 24 h, and patients still admitted at the time of data extraction were excluded. Potential predictors were selected by a team of intensive care physicians. The primary and secondary outcomes were extubation without reintubation or death within the next 7 days and within 48 h, respectively. We trained and validated multiple machine learning algorithms using fivefold nested cross-validation. Predictor importance was estimated using Shapley additive explanations, while cutoff values for the relative probability of failed extubation were estimated through partial dependence plots.
Results: A total of 883 patients were included in the model derivation. The reintubation rate was 13.4% within 48 h and 18.9% at day 7, with a mortality rate of 0.6% and 1.0% respectively. The grandient-boost model performed best (area under the curve of 0.70) and was used to calculate predictor importance. Ventilatory characteristics and settings were the most important predictors. More specifically, a controlled mode duration longer than 4 days, a last fraction of inspired oxygen higher than 35%, a mean tidal volume per kg ideal body weight above 8 ml/kg in the day before extubation, and a shorter duration in assisted mode (< 2 days) compared to their median values. Additionally, a higher C-reactive protein and leukocyte count, a lower thrombocyte count, a lower Glasgow coma scale and a lower body mass index compared to their medians were associated with extubation failure.

Conclusion: The most important predictors for extubation failure in critically ill COVID-19 patients include ventilatory settings, inflammatory parameters, neurological status, and body mass index. These predictors should therefore be routinely captured in electronic health records.

Gepubliceerd: Crit Care. 2021;25(1):448.
Impact factor: 9.097; Q1

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10. **Large-scale ICU data sharing for global collaboration: the first 1633 critically ill COVID-19 patients in the Dutch Data Warehouse**
Fleuren LM, de Bruin DP, Tonutti M, Lalisang RCA, Elbers PWG, Dutch ICU Data Sharing Collaborators - includes Cornet AD, Beishuizen A.

Gepubliceerd: Intensive Care Med. 2021;47(4):478-81.
Impact factor: 17.440; Q1

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11. **Risk factors for adverse outcomes during mechanical ventilation of 1152 COVID-19 patients: a multicenter machine learning study with highly granular data from the Dutch Data Warehouse**
Fleuren LM, Tonutti M, de Bruin DP, Lalisang RCA, Dam TA, Gommers D, Cremer OL, Bosman RJ, Vonk SJJ, Fornasa M, Machado T, van der Meer NJM, Rigter S, Wils EJ, Frenzel T, Dongelmans DA, de Jong R, Peters M, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef G, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Achterberg S, Faber HJ, Karakus A, Beukema M, Entjes R, de Jong P, Houwert T, Hovenkamp H, Noorduijn Londono R, Quintarelli D, Scholtemeijer MG, de Beer AA, Cinà G, Beudel M, de Keizer NF, Hoogendoorn M, Girbes ARJ, Herter WE, Elbers PWG, Thoral PJ, Dutch ICU Data Sharing Against Covid-19 Collaborators – includes Beishuizen A.

Background: The identification of risk factors for adverse outcomes and prolonged intensive care unit (ICU) stay in COVID-19 patients is essential for prognostication, determining treatment intensity, and resource allocation. Previous studies have determined risk factors on admission only, and included a limited number of predictors. Therefore, using data from the highly granular and multicenter Dutch Data Warehouse, we developed machine learning models to identify risk factors for ICU mortality, ventilator-free days and ICU-free days during the course of invasive mechanical ventilation (IMV) in COVID-19 patients.
Methods: The DDW is a growing electronic health record database of critically ill COVID-19 patients in the Netherlands. All adult ICU patients on IMV were eligible for inclusion. Transfers, patients admitted for less than 24 h, and patients still admitted at time of data extraction were excluded. Predictors were selected based on the literature, and included medication dosage and fluid balance. Multiple algorithms were trained and validated on up to three sets of observations per patient on day 1, 7, and 14 using fivefold nested cross-validation, keeping observations from an individual patient in the same split.

Results: A total of 1152 patients were included in the model. XGBoost models performed best for all outcomes and were used to calculate predictor importance. Using Shapley additive explanations (SHAP), age was the most important demographic risk factor for the outcomes upon start of IMV and throughout its course. The relative probability of death across age values is visualized in Partial Dependence Plots (PDPs), with an increase starting at 54 years. Besides age, acidaemia, low P/F-ratios and high driving pressures demonstrated a higher probability of death. The PDP for driving pressure showed a relative probability increase starting at 12 cmH(2)O.
Conclusion: Age is the most important demographic risk factor of ICU mortality, ICU-free days and ventilator-free days throughout the course of invasive mechanical ventilation in critically ill COVID-19 patients. pH, P/F ratio, and driving pressure should be monitored closely over the course of mechanical ventilation as risk factors predictive of these outcomes.

Gepubliceerd: Intensive Care Med Exp. 2021;9(1):32.
Impact factor: 0; NVT

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12. **Relationship between the Clinical Frailty Scale and short-term mortality in patients ≥ 80 years old acutely admitted to the ICU: a prospective cohort study**
Fronczek J, Polok K, de Lange DW, Jung C, Beil M, Rhodes A, Fjølner J, Górka J, Andersen FH, Artigas A, Cecconi M, Christensen S, Joannidis M, Leaver S, Marsh B, Morandi A, Moreno R, Oeyen S, Agvald-Öhman C, Bollen Pinto B, Schefold JC, Valentin A, Walther S, Watson X, Zafeiridis T, Sviri S, van Heerden PV, Flaatten H, Guidet B, Szczeklik W, VIP1; VIP2 study group - includes Cornet AD.

Background: The Clinical Frailty Scale (CFS) is frequently used to measure frailty in critically ill adults. There is wide variation in the approach to analysing the relationship between the CFS score and mortality after admission to the ICU. This study aimed to evaluate the influence of modelling approach on the association between the CFS score and short-term mortality and quantify the prognostic value of frailty in this context.
Methods: We analysed data from two multicentre prospective cohort studies which enrolled intensive care unit patients ≥ 80 years old in 26 countries. The primary outcome was mortality within 30-days from admission to the ICU. Logistic regression models for both ICU and 30-day mortality included the CFS score as either a categorical, continuous or dichotomous variable and were adjusted for patient's age, sex, reason for admission to the ICU, and admission Sequential Organ Failure Assessment score.
Results: The median age in the sample of 7487 consecutive patients was 84 years (IQR 81-87). The highest fraction of new prognostic information from frailty in the context of 30-day mortality was observed when the CFS score was treated as either a categorical variable using all original levels of frailty or a nonlinear continuous variable and was equal to 9% using these modelling approaches ($p < 0.001$). The relationship between the CFS score and mortality was nonlinear ($p < 0.01$).
Conclusion: Knowledge about a patient's frailty status adds a substantial amount of new prognostic information at the moment of admission to the ICU. Arbitrary simplification of the CFS score into fewer groups than originally intended leads to a loss of information and should be avoided. Trial registration NCT03134807 (VIP1), NCT03370692 (VIP2).

Gepubliceerd: Crit Care. 2021;25(1):231.
Impact factor: 9.097; Q1

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13. **Frailty is associated with long-term outcome in patients with sepsis who are over 80 years old: results from an observational study in 241 European ICUs**
Haas LEM, Boumendil A, Flaatten H, Guidet B, Ibarz M, Jung C, Moreno R, Morandi A, Andersen FH, Zafeiridis T, Walther S, Oeyen S, Leaver S, Watson X, Boulanger C, Szczeklik W, Schefold JC, Cecconi M, Marsh B, Joannidis M, Nalapko Y, Elhadi M, Fjølner J, Artigas A, de Lange DW, VIP2 study group - includes Cornet AD.

Background: Sepsis is one of the most frequent reasons for acute intensive care unit (ICU) admission of very old patients and mortality rates are high. However, the impact of pre-existing physical and cognitive function on long-term outcome of ICU patients ≥ 80 years old (very old intensive care patients (VIPs)) with sepsis is unclear.
Objective: To investigate both the short- and long-term mortality of VIPs admitted with sepsis and assess the relation of mortality with pre-existing physical and cognitive function. DESIGN: Prospective cohort study.
Setting: 241 ICUs from 22 European countries in a six-month period between May 2018 and May 2019. SUBJECTS: Acutely admitted ICU patients aged ≥80 years with sequential organ failure assessment (SOFA) score ≥ 2.
Methods: Sepsis was defined according to the sepsis 3.0 criteria. Patients with sepsis as an admission diagnosis were compared with other acutely admitted patients. In addition to patients' characteristics, disease severity, information about comorbidity and polypharmacy and pre-existing physical and cognitive function were collected.
Results: Out of 3,596 acutely admitted VIPs with SOFA score ≥ 2, a group of 532 patients with sepsis were compared to other admissions. Predictors for 6-month mortality were age (per 5 years): Hazard ratio (HR, 1.16 (95% confidence interval (CI), 1.09-1.25, P < 0.0001), SOFA (per one-point): HR, 1.16 (95% CI, 1.14-1.17, P < 0.0001) and frailty (CFS > 4): HR, 1.34 (95% CI, 1.18-1.51, P < 0.0001).
Conclusions: There is substantial long-term mortality in VIPs admitted with sepsis. Frailty, age and disease severity were identified as predictors of long-term mortality in VIPs admitted with sepsis.

Gepubliceerd: Age Ageing. 2021;50(5):1719-27.
Impact factor: 10.668; Q1

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14. **Duration of antibiotic treatment using procalcitonin-guided treatment algorithms in older patients: a patient-level meta-analysis from randomized controlled trials**
Heilmann E, Gregoriano C, Annane D, Reinhart K, Bouadma L, Wolff M, Chastre J, Luyt CE, Tubach F, Branche AR, Briel M, Christ-Crain M, Welte T, Corti C, de Jong E, Nijsten M, de Lange DW, van Oers JAH, Beishuizen A, Girbes ARJ, Deliberato RO, Schroeder S, Kristoffersen KB, Layios N, Damas P, Lima SSS, Nobre V, Wei L, Oliveira CF, Shehabi Y, Stolz D, Tamm M, Verduri A, Wang JX, Drevet S, Gavazzi G, Mueller B, Schuetz P.

Background: Older patients have a less pronounced immune response to infection, which may also influence infection biomarkers. There is currently insufficient data

regarding clinical effects of procalcitonin (PCT) to guide antibiotic treatment in older patients.
Objective and design: We performed an individual patient data meta-analysis to investigate the association of age on effects of PCT-guided antibiotic stewardship regarding antibiotic use and outcome.
Subjects and methods: We had access to 9,421 individual infection patients from 28 randomized controlled trials comparing PCT-guided antibiotic therapy (intervention group) or standard care. We stratified patients according to age in four groups (<75 years [n = 7,079], 75-80 years [n = 1,034], 81-85 years [n = 803] and >85 years [n = 505]). The primary endpoint was the duration of antibiotic treatment and the secondary endpoints were 30-day mortality and length of stay.
Results: Compared to control patients, mean duration of antibiotic therapy in PCT-guided patients was significantly reduced by 24, 22, 26 and 24% in the four age groups corresponding to adjusted differences in antibiotic days of -1.99 (95% confidence interval [CI] -2.36 to -1.62), -1.98 (95% CI -2.94 to -1.02), -2.20 (95% CI -3.15 to -1.25) and - 2.10 (95% CI -3.29 to -0.91) with no differences among age groups. There was no increase in the risk for mortality in any of the age groups. Effects were similar in subgroups by infection type, blood culture result and clinical setting (P interaction >0.05).
Conclusions: This large individual patient data meta-analysis confirms that, similar to younger patients, PCT-guided antibiotic treatment in older patients is associated with significantly reduced antibiotic exposures and no increase in mortality.

Gepubliceerd: Age Ageing. 2021;50(5):1546-56.
Impact factor: 10.668; Q1

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15. **Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe**
Jung C, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, Wolff G, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Joannidis M, Oeyen S, Zafeiridis T, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Flaatten H, COVIP study group - includes Cornet AD.

Background: The primary aim of this study was to assess the outcome of elderly intensive care unit (ICU) patients treated during the spring and autumn COVID-19 surges in Europe.
Methods: This was a prospective European observational study (the COVIP study) in ICU patients aged 70 years and older admitted with COVID-19 disease from March to December 2020 to 159 ICUs in 14 European countries. An electronic database was used to register a number of parameters including: SOFA score, Clinical Frailty Scale, co-morbidities, usual ICU procedures and survival at 90 days. The study was registered at ClinicalTrials.gov (NCT04321265).
Results: In total, 2625 patients were included, 1327 from the first and 1298 from the second surge. Median age was 74 and 75 years in surge 1 and 2, respectively. SOFA score was higher in the first surge (median 6 versus 5, $p < 0.0001$). The PaO(2)/FiO(2) ratio at admission was higher during surge 1, and more patients received invasive mechanical ventilation (78% versus 68%, $p < 0.0001$). During the first 15 days of treatment, survival was similar during the first and the second surge. Survival was lower

in the second surge after day 15 and differed after 30 days (57% vs 50%) as well as after 90 days (51% vs 40%).
Conclusion: An unexpected, but significant, decrease in 30-day and 90-day survival was observed during the second surge in our cohort of elderly ICU patients. The reason for this is unclear. Our main concern is whether the widespread changes in practice and treatment of COVID-19 between the two surges have contributed to this increased mortality in elderly patients. Further studies are urgently warranted to provide more evidence for current practice in elderly patients.
Trial registration number: NCT04321265 , registered March 19th, 2020.

Gepubliceerd: Crit Care. 2021;25(1):344.
Impact factor: 9.097; Q1

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16. **A challenging case of undifferentiated shock**
Kats I, Schraverus PJ, Hazewinkel MJ, Cornet AD.

Gepubliceerd: Oxf Med Case Reports. 2021;2021(11):omab106.
Impact factor: 0; NVT

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17. **Prevalence, associated factors and outcomes of pressure injuries in adult intensive care unit patients: the DecubICUs study**
Labeau SO, Afonso E, Benbenishty J, Blackwood B, Boulanger C, Brett SJ, Calvino-Gunther S, Chaboyer W, Coyer F, Deschepper M, François G, Honore PM, Jankovic R, Khanna AK, Llaurado-Serra M, Lin F, Rose L, Rubulotta F, Saager L, Williams G, Blot SI, DecubICUs Study Team; European Society of Intensive Care Medicine (ESICM) Trails Group Collaborators – includes Vermeijden JW.

Purpose: Intensive care unit (ICU) patients are particularly susceptible to developing pressure injuries. Epidemiologic data is however unavailable. We aimed to provide an international picture of the extent of pressure injuries and factors associated with ICU-acquired pressure injuries in adult ICU patients.
Methods: International 1-day point-prevalence study; follow-up for outcome assessment until hospital discharge (maximum 12 weeks). Factors associated with ICU-acquired pressure injury and hospital mortality were assessed by generalised linear mixed-effects regression analysis.
Results: Data from 13,254 patients in 1117 ICUs (90 countries) revealed 6747 pressure injuries; 3997 (59.2%) were ICU-acquired. Overall prevalence was 26.6% (95% confidence interval [CI] 25.9-27.3). ICU-acquired prevalence was 16.2% (95% CI 15.6-16.8). Sacrum (37%) and heels (19.5%) were most affected. Factors independently associated with ICU-acquired pressure injuries were older age, male sex, being underweight, emergency surgery, higher Simplified Acute Physiology Score II, Braden score < 19, ICU stay > 3 days, comorbidities (chronic obstructive pulmonary disease, immunodeficiency), organ support (renal replacement, mechanical ventilation on ICU admission), and being in a low or lower-middle income-economy. Gradually increasing associations with mortality were identified for increasing severity of pressure injury: stage I (odds ratio [OR] 1.5; 95% CI 1.2-1.8), stage II (OR 1.6; 95% CI 1.4-1.9), and stage III or worse (OR 2.8; 95% CI 2.3-3.3).

Conclusion: Pressure injuries are common in adult ICU patients. ICU-acquired pressure injuries are associated with mainly intrinsic factors and mortality. Optimal care standards, increased awareness, appropriate resource allocation, and further research into optimal prevention are pivotal to tackle this important patient safety threat.

Gepubliceerd: Intensive Care Med. 2021;47(2):160-9.
Impact factor: 17.440; Q1

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18. **Safety and tolerability of non-neutralizing adrenomedullin antibody adrecizumab (HAM8101) in septic shock patients: the AdrenOSS-2 phase 2a biomarker-guided trial**
Laterre PF, Pickkers P, Marx G, Wittebole X, Meziani F, Dugernier T, Huberlant V, Schuerholz T, François B, Lascarrou JB, Beishuizen A, Oueslati H, Contou D, Hoiting O, Lacherade JC, Chousterman B, Pottecher J, Bauer M, Godet T, Karakas M, Helms J, Bergmann A, Zimmermann J, Richter K, Hartmann O, Pars M, Mebazaa A, AdrenOSS-2 study participants – includes Vermeijden JW.

Purpose: Investigate safety and tolerability of adrecizumab, a humanized monoclonal adrenomedullin antibody, in septic shock patients with high adrenomedullin.
Methods: Phase-2a, double-blind, randomized, placebo-controlled biomarker-guided trial with a single infusion of adrecizumab (2 or 4 mg/kg b.w.) compared to placebo. Patients with adrenomedullin above 70 pg/mL, < 12 h of vasopressor start for septic shock were eligible. Randomization was 1:1:2. Primary safety (90-day mortality, treatment emergent adverse events (TEAE)) and tolerability (drug interruption, hemodynamics) endpoints were recorded. Efficacy endpoints included the Sepsis Support Index (SSI, reflecting ventilator- and shock-free days alive), change in Sequential-related Organ Failure Assessment (SOFA) and 28-day mortality.
Results: 301 patients were enrolled (median time of 8.5 h after vasopressor start). Adrecizumab was well tolerated (one interruption, no hemodynamic alteration) with no differences in frequency and severity in TEAEs between treatment arms (TEAE of grade 3 or higher: 70.5% in the adrecizumab group and 71.1% in the placebo group) nor in 90-day mortality. Difference in change in SSI between adrecizumab and placebo was 0.72 (CI -1.93-0.49, p = 0.24). Among various secondary endpoints, delta SOFA score (defined as maximum versus minimum SOFA) was more pronounced in the adrecizumab combined group compared to placebo [difference at 0.76 (95% CI 0.18-1.35); p = 0.007]. 28-day mortality in the adrecizumab group was 23.9% and 27.7% in placebo with a hazard ratio of 0.84 (95% confidence interval 0.53-1.31, log-rank p = 0.44).
Conclusions: Overall, we successfully completed a randomized trial evaluating selecting patients for enrolment who had a disease-related biomarker. There were no overt signals of harm with using two doses of the adrenomedullin antibody adrecizumab; however, further randomized controlled trials are required to confirm efficacy and safety of this agent in septic shock patients.

Gepubliceerd: Intensive Care Med. 2021;47(11):1284-94.
Impact factor: 17.440; Q1

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19. **The effect of immediate coronary angiography after cardiac arrest without ST-segment elevation on left ventricular function. A sub-study of the COACT randomised trial**
Lemkes JS, Spoormans EM, Demirkiran A, Leutscher S, 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, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van de Ven PM, van Loon RB, van Royen N.

Background: The effect of immediate coronary angiography and percutaneous coronary intervention (PCI) in patients who are successfully resuscitated after cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) on left ventricular function is currently unknown.
Methods: This prespecified sub-study of a multicentre trial evaluated 552 patients, successfully resuscitated from out-of-hospital cardiac arrest without signs of STEMI. Patients were randomized to either undergo immediate coronary angiography or delayed coronary angiography, after neurologic recovery. All patients underwent PCI if indicated. The main outcomes of this analysis were left ventricular ejection fraction and end-diastolic and systolic volumes assessed by cardiac magnetic resonance imaging or echocardiography.
Results: Data on left ventricular function was available for 397 patients. The mean (± standard deviation) left ventricular ejection fraction was 45.2% (±12.8) in the immediate angiography group and 48.4% (±13.2) in the delayed angiography group (mean difference: -3.19; 95% confidence interval [CI], -6.75 to 0.37). Median left ventricular end-diastolic volume was 177 ml in the immediate angiography group compared to 169 ml in the delayed angiography group (ratio of geometric means: 1.06; 95% CI, 0.95-1.19). In addition, mean left ventricular end-systolic volume was 90 ml in the immediate angiography group compared to 78 ml in the delayed angiography group (ratio of geometric means: 1.13; 95% CI 0.97-1.32).
Conclusion: In patients successfully resuscitated after out-of-hospital cardiac arrest and without signs of STEMI, immediate coronary angiography was not found to improve left ventricular dimensions or function compared with a delayed angiography strategy.
Clinical Trial registrattion: Netherlands Trial Register number, NTR4973.

Gepubliceerd: Resuscitation. 2021;164:93-100.
Impact factor: 5.262; Q1

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20. **Elevated methaemoglobin in a critically ill patient as a result of hydrogen peroxide exposure: A case study**
Mian P, Krabbe H, van Drie-Pierik R, Silderhuis V, Beishuizen A.

What is known and objective: Formation of methaemoglobinaemia (MetHb) decreases oxygen capacity in the blood, leading to tissue hypoxia. This condition may be acquired following exposure to certain drugs.
Case summary: A critically ill patient with necrotizing fasciitis unexpectedly developed marked and unexplained MetHb (6.7%). Her digital medication list did not reveal the

causative factor. However, deeper exploration showed the use of other compounds (acetone, hydrogen peroxide) not routinely visible on the medication list.
What is new and conclusion: Elevated MetHb likely resulted from high-volume hydrogen peroxide 3% exposure. Clinicians should be cautious rinsing large open wounds with hydrogen peroxide. When MetHb is diagnosed, less familiar compounds, usually not on the medication list, should be considered in the differential diagnosis and extensive hetero-anamnesis is mandatory.

Gepubliceerd: J Clin Pharm Ther. 2021;46(5):1473-5.
Impact factor: 2.512; Q3

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21. **External Validation of the DCD-N Score and a Linear Prediction Model to Identify Potential Candidates for Organ Donation After Circulatory Death: A Nationwide Multicenter Cohort Study**
Nijhoff MF, Pol RA, Volbeda M, Kotsopoulos AMM, Sonneveld JPC, Otterspoor L, Abdo WF, Silderhuis VM, El Moumni M, Moers C.

Background: Donation after circulatory death (DCD) is a procedure in which after planned withdrawal of life-sustaining treatment (WLST), the dying process is monitored. A DCD procedure can only be continued if the potential organ donor dies shortly after WLST. This study performed an external validation of 2 existing prediction models to identify potentially DCD candidates, using one of the largest cohorts.
Methods: This multicenter retrospective study analyzed all patients eligible for DCD donation from 2010 to 2015. The first model (DCD-N score) assigned points for absence of neurological reflexes and oxygenation index. The second model, a linear prediction model (LPDCD), yielded the probability of death within 60 min. This study determined discrimination (c-statistic) and calibration (Hosmer and Lemeshow test) for both models.
Results: This study included 394 patients, 283 (72%) died within 60 min after WLST. The DCD-N score had a c-statistic of 0.77 (95% confidence intervals, 0.71-0.83) and the LPDCD model 0.75 (95% confidence intervals, 0.68-0.81). Calibration of the LPDCD 60-min model proved to be poor (Hosmer and Lemeshow test, $P < 0.001$).
Conclusions: The DCD-N score and the LPDCD model showed good discrimination but poor calibration for predicting the probability of death within 60 min. Construction of a new prediction model on a large data set is needed to obtain better calibration.

Gepubliceerd: Transplantation. 2021;105(6):1311-6.
Impact factor: 4.939; Q1

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22. **How are rapid diagnostic tests for infectious diseases used in clinical practice: a global survey by the International Society of Antimicrobial Chemotherapy (ISAC)**
Poole S, Townsend J, Wertheim H, Kidd SP, Welte T, Schuetz P, Luyt CE, Beishuizen A, Jensen JS, Del Castillo JG, Plebani M, Saeed K.

Novel rapid diagnostic tests (RDTs) offer huge potential to optimise clinical care and improve patient outcomes. In this study, we aim to assess the current patterns of use around the world, identify issues for successful implementation and suggest best

practice advice on how to introduce new tests. An electronic survey was devised by the International Society of Antimicrobial Chemotherapy (ISAC) Rapid Diagnostics and Biomarkers working group focussing on the availability, structure and impact of RDTs around the world. It was circulated to ISAC members in December 2019. Results were collated according to the UN human development index (HDI). 81 responses were gathered from 31 different countries. 84% of institutions reported the availability of any test 24/7. In more developed countries, this was more for respiratory viruses, whereas in high and medium/low developed countries, it was for HIV and viral hepatitis. Only 37% of those carrying out rapid tests measured the impact. There is no 'one-size fits all' solution to RDTs: the requirements must be tailored to the healthcare setting in which they are deployed and there are many factors that should be considered prior to this.

Gepubliceerd: Eur J Clin Microbiol Infect Dis. 2021;40(2):429-34.
Impact factor: 3.267; Q3

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23. **The Impact of Nursing Delirium Preventive Interventions in the ICU: A Multicenter Cluster-randomized Controlled Clinical Trial**
Rood PJT, Zegers M, Ramnarain D, Koopmans M, Klarenbeek T, Ewalds E, van der Steen MS, Oldenbeuving AW, Kuiper MA, Teerenstra S, Adang E, van Loon LM, Wassenaar A, Vermeulen H, Pickkers P, van den Boogaard M, UNDERPIN-ICU Study Investigators - includes Beishuizen A.

Rationale: Delirium is common in critically ill patients and is associated with deleterious outcomes. Nonpharmacological interventions are recommended in current delirium guidelines, but their effects have not been unequivocally established. Objectives: To determine the effects of a multicomponent nursing intervention program on delirium in the ICU.
Methods: A stepped-wedge cluster-randomized controlled trial was conducted in ICUs of 10 centers. Adult critically ill surgical, medical, or trauma patients at high risk of developing delirium were included. A multicomponent nursing intervention program focusing on modifiable risk factors was implemented as standard of care. The primary outcome was the number of delirium-free and coma-free days alive in 28 days after ICU admission. Measurements and Main
Results: A total of 1,749 patients were included. Time spent on interventions per 8-hour shift was median (interquartile range) 38 (14-116) minutes in the intervention period and median 32 (13-73) minutes in the control period (P = 0.44). Patients in the intervention period had a median of 23 (4-27) delirium-free and coma-free days alive compared with a median of 23 (5-27) days for patients in the control group (mean difference, -1.21 days; 95% confidence interval, -2.84 to 0.42 d; P = 0.15). In addition, the number of delirium days was similar: median 2 (1-4) days (ratio of medians, 0.90; 95% confidence interval, 0.75 to 1.09; P = 0.27).
Conclusions: In this large randomized controlled trial in adult ICU patients, a limited increase in the use of nursing interventions was achieved, and no change in the number of delirium-free and coma-free days alive in 28 days could be determined. Clinical trial registered with www.clinicaltrials.gov (NCT03002701).

Gepubliceerd: Am J Respir Crit Care Med. 2021;204(6):682-91.
Impact factor: 21.405; Q1

24. **In-depth assessment of health-related quality of life after in-hospital cardiac arrest**
Schluep M, Endeman H, Gravesteijn BY, Kuijs C, Blans MJ, van den Bogaard B, Van Gemert A, Hukshorn CJ, van der Meer BJM, Knook AHM, van Melsen T, Peters R, Simons KS, Spijkers G, Vermeijden JW, Wils EJ, Stolker RJ, Hoeks SE.

Introduction: Evidence on physical and psychological well-being of in-hospital cardiac arrest (IHCA) survivors is scarce. The aim of this study is to describe long-term health-related quality of life (HRQoL), functional independence and psychological distress 3 and 12 months post-IHCA.
Methods: A multicenter prospective cohort study in 25 hospitals between January 2017 - May 2018. Adult IHCA survivors were included. HRQoL (EQ-5D-5L, SF-12), psychological distress (HADS, CSI) and functional independence (mRS) were assessed at 3 and 12 months post-IHCA.
Results: At 3-month follow-up 136 of 212 survivors responded to the questionnaire and at 12 months 110 of 198 responded. The median (IQR) EQ-utility Index score was 0.77 (0.65-0.87) at 3 months and 0.81 (0.70-0.91) at 12 months. At 3 months, patients reported a median SF-12 (IQR) physical component scale (PCS) of 38.9 (32.8-46.5) and mental component scale (MCS) of 43.5 (34.0-39.7) and at 12 months a PCS of 43.1 (34.6-52.3) and MCS 46.9 (38.5-54.5).
Discussion: Using various tools most IHCA survivors report an acceptable HRQoL and a substantial part experiences lower HRQoL compared to population norms. Our data suggest that younger (male) patients and those with poor functional status prior to admission are at highest risk of impaired HRQoL.

Gepubliceerd: J Crit Care. 2021;68:22-30.
Impact factor: 3.425; Q2

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25. **Long-term survival and health-related quality of life after in-hospital cardiac arrest**
Schluep M, Hoeks SE, Blans M, van den Bogaard B, Koopman-van Gemert A, Kuijs C, Hukshorn C, van der Meer N, Knook M, van Melsen T, Peters R, Perik P, Simons K, Spijkers G, Vermeijden JW, Wils EJ, Robert Jan Stolker RJ, Rik Endeman H.

Introduction: In-hospital cardiac arrest (IHCA) is an adverse event associated with high mortality. Because of the impact of IHCA more data is needed on incidence, outcomes and associated factors that are present prior to cardiac arrest. The aim was to assess one-year survival, patient-centred outcomes after IHCA and their associated pre-arrest factors.
Methods: A multicentre prospective cohort study in 25 hospitals between January 1st 2017 and May 31st 2018. Patients >/= 18 years receiving cardiopulmonary resuscitation (CPR) for IHCA were included. Data were collected using Utstein and COSCA-criteria, supplemented by pre-arrest Modified Rankin Scale (MRS, functional status) and morbidity through the Charlson Comorbidity Index (CCI). Main outcomes were survival, health-related quality of life (HRQoL, EuroQoL) and functional status (MRS) after one-year.
Results: A total of 713 patients were included, 64.5% was male, median age was 63 years (IQR 52-72) and 72.8% had a non-shockable rhythm, 394 (55.3%) achieved ROSC, 231 (32.4%) survived to hospital discharge and 198 (27.8%) survived one year

after cardiac arrest. Higher pre-arrest MRS, age and CCI were associated with mortality. At one year, patients rated HRQoL 72/100 points on the EQ-VAS and 69.7% was functionally independent.
Conclusion: One-year survival after IHCA in this study is 27.8%, which is relatively high compared to previous studies. Survival is associated with a patient's pre-arrest functional status and morbidity. HRQoL appears acceptable, however functional rehabilitation warrants attention. These findings provide a comprehensive insight in in-hospital cardiac arrest prognosis.

Gepubliceerd: Resuscitation. 2021;167:297-306.
Impact factor: 5.262; Q1

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26. **[Communication about in hospital resuscitation orders]**
Schluep M, Hoeks SE, Endeman HR, S IJ, Romijn TMM, Alsma J, Bosch FH, Cornet AD, Knook A, Koopman-van Gemert A, van Melsen T, Peters R, Simons KS, Wils EJ, Stolker RJ, van Dijk M.

Background: The decision to attempt or refrain from resuscitation is preferably based on prognostic factors for outcome and subsequently communicated with patients. Both patients and physicians consider good communication important, however little is known about patient involvement in and understanding of cardiopulmonary resuscitation (CPR) directives. AIM: To determine the prevalence of Do Not Resuscitate (DNR)-orders, to describe recollection of CPR-directive conversations and factors associated with patient recollection and understanding.
Methods: This was a two-week nationwide multicentre cross-sectional observational study using a study-specific survey. The study population consisted of patients admitted to non-monitored wards in 13 hospitals. Data were collected from the electronic medical record (EMR) concerning CPR-directive, comorbidity and at-home medication. Patients reported their perception and expectations about CPR-counselling through a questionnaire.
Results: A total of 1136 patients completed the questionnaire. Patients' CPR-directives were documented in the EMR as follows: 63.7% full code, 27.5% DNR and in 8.8% no directive was documented. DNR was most often documented for patients >80 years (66.4%) and in patients using >10 medications (45.3%). Overall, 55.8% of patients recalled having had a conversation about their CPR-directive and 48.1% patients reported the same CPR-directive as the EMR. Most patients had a good experience with the CPR-directive conversation in general (66.1%), as well as its timing (84%) and location (94%) specifically.
Conclusions: The average DNR-prevalence is 27.5%. Correct understanding of their CPR-directive is lowest in patients aged ≥80 years and multimorbid patients. CPR-directive counselling should focus more on patient involvement and their correct understanding.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021;165.
Impact factor: 0; NVT

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27. **Sex differences in patients with out-of-hospital cardiac arrest without ST-segment elevation: A COACT trial substudy**
Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, van de Ven PM, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, der Harst PV, 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, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Appelman Y, van Royen N.

Background: Whether sex is associated with outcomes of out-of-hospital cardiac arrest (OHCA) is unclear.
Objectives: This study examined sex differences in survival in patients with OHCA without ST-segment elevation myocardial infarction (STEMI).
Methods: Using data from the randomized controlled Coronary Angiography after Cardiac Arrest (COACT) trial, the primary point of interest was sex differences in OHCA-related one-year survival. Secondary points of interest included the benefit of immediate coronary angiography compared to delayed angiography until after neurologic recovery, angiographic and clinical outcomes.
Results: In total, 522 patients (79.1% men) were included. Overall one-year survival was 59.6% in women and 63.4% in men (HR 1.18; 95% CI: 0.76-1.81;p = 0.47). No cardiovascular risk factors were found that modified survival. Women less often had significant coronary artery disease (CAD) (37.0% vs. 71.3%;p < 0.001), but when present, they had a worse prognosis than women without CAD (HR 3.06; 95% CI 1.31-7.19;p = 0.01). This was not the case for men (HR 1.05; 95% CI 0.67-1.65;p = 0.83). In both sexes, immediate coronary angiography did not improve one-year survival compared to delayed angiography (women, odds ratio (OR) 0.87; 95% CI 0.58-1.30;p = 0.49; vs. men, OR 0.97; 95% CI 0.45-2.09;p = 0.93).
Conclusion: In OHCA patients without STEMI, we found no sex differences in overall one-year survival. Women less often had significant CAD, but when CAD was present they had worse survival than women without CAD. This was not the case for men. Both sexes did not benefit from a strategy of immediate coronary angiography as compared to delayed strategy with respect to one-year survival. **Clinical Trial registration number:** Netherlands trial register (NTR) 4973.

Gepubliceerd: Resuscitation. 2021;158:14-22.
Impact factor: 5.262; Q1

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28. **Evolution Over Time of Ventilatory Management and Outcome of Patients With Neurologic Disease**
Tejerina EE, Pelosi P, Robba C, Peñuelas O, Muriel A, Barrios D, Frutos-Vivar F, Raymondos K, Du B, Thille AW, Ríos F, González M, Del-Sorbo L, Marín MDC, Valle Pinheiro B, Soares MA, Nin N, Maggiore SM, Bersten A, Amin P, Cakar N, Young Suh G, Abroug F, Jibaja M, Matamis D, Ali Zeggwagh A, Sutherasan Y, Anzueto A, Esteban A, B. VENTILA Group - includes Beishuizen A.

Objectives: To describe the changes in ventilator management over time in patients with neurologic disease at ICU admission and to estimate factors associated with 28-

day hospital mortality. DESIGN: Secondary analysis of three prospective, observational, multicenter studies.
Setting: Cohort studies conducted in 2004, 2010, and 2016. PATIENTS: Adult patients who received mechanical ventilation for more than 12 hours.
Interventions: None.
Measurements and main results: Among the 20,929 patients enrolled, we included 4,152 (20%) mechanically ventilated patients due to different neurologic diseases. Hemorrhagic stroke and brain trauma were the most common pathologies associated with the need for mechanical ventilation. Although volume-cycled ventilation remained the preferred ventilation mode, there was a significant ($p < 0.001$) increment in the use of pressure support ventilation. The proportion of patients receiving a protective lung ventilation strategy was increased over time: 47% in 2004, 63% in 2010, and 65% in 2016 ($p < 0.001$), as well as the duration of protective ventilation strategies: 406 days per 1,000 mechanical ventilation days in 2004, 523 days per 1,000 mechanical ventilation days in 2010, and 585 days per 1,000 mechanical ventilation days in 2016 ($p < 0.001$). There were no differences in the length of stay in the ICU, mortality in the ICU, and mortality in hospital from 2004 to 2016. Independent risk factors for 28-day mortality were age greater than 75 years, Simplified Acute Physiology Score II greater than 50, the occurrence of organ dysfunction within first 48 hours after brain injury, and specific neurologic diseases such as hemorrhagic stroke, ischemic stroke, and brain trauma.
Conclusions: More lung-protective ventilatory strategies have been implemented over years in neurologic patients with no effect on pulmonary complications or on survival. We found several prognostic factors on mortality such as advanced age, the severity of the disease, organ dysfunctions, and the etiology of neurologic disease.

Gepubliceerd: Crit Care Med. 2021;49(7):1095-106.
Impact factor: 7.598; Q1

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29. **Significant interference on specific point-of-care glucose measurements due to high dose of intravenous vitamin C therapy in critically ill patients**
Ten Berge D, Muller W, Beishuizen A, Cornet AD, Slingerland R, Krabbe J.

Gepubliceerd: Clin Chem Lab Med. 2021;59(5):e197-e9.
Impact factor: 3.694; Q2

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30. **Infarct-related chronic total coronary occlusion and the risk of ventricular tachyarrhythmic events in out-of-hospital cardiac arrest survivors**
van der Graaf M, Jewbali LSD, Lemkes JS, Spoormans EM, van der Ent M, Meuwissen M, Blans MJ, van der Harst P, Henriques JP, Beishuizen A, Camaro C, Bleeker GB, van Royen N, Yap SC.

Introduction: Chronic total coronary occlusion (CTO) has been identified as a risk factor for ventricular arrhythmias, especially a CTO in an infarct-related artery (IRA). This study aimed to evaluate the effect of an IRA-CTO on the occurrence of ventricular tachyarrhythmic events (VTEs) in out-of-hospital cardiac arrest survivors without ST-segment elevation.

Methods: We conducted a post hoc analysis of the COACT trial, a multicentre randomised controlled trial. Patients were included when they survived index hospitalisation after cardiac arrest and demonstrated coronary artery disease on coronary angiography. The primary endpoint was the occurrence of a VTE, defined as appropriate implantable cardioverter-defibrillator (ICD) therapy, sustained ventricular tachyarrhythmia or sudden cardiac death.
Results: A total of 163 patients from ten centres were included. Unrevascularised IRA-CTO in a main vessel was present in 43 patients (26%). Overall, 61% of the study population received an ICD for secondary prevention. During a follow-up of 1 year, 12 patients (7.4%) experienced at least one VTE. The cumulative incidence rate of VTEs was higher in patients with an IRA-CTO compared to patients without an IRA-CTO (17.4% vs 5.6%, log-rank p = 0.03). However, multivariable analysis only identified left ventricular ejection fraction < 35% as an independent factor associated with VTEs (adjusted hazard ratio 8.7, 95% confidence interval 2.2-35.4). A subanalysis focusing on CTO, with or without an infarct in the CTO territory, did not change the results.
Conclusion: In out-of-hospital cardiac arrest survivors with coronary artery disease without ST-segment elevation, an IRA-CTO was not an independent factor associated with VTEs in the 1st year after the index event.

Gepubliceerd: Neth Heart J. 2021;29(10):500-5.
Impact factor: 2.380; Q3

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31. **Mid-Regional Proadrenomedullin and Mid-Regional Proatrial Natriuretic Peptide Clearance Predicts Poor Outcomes Better Than Single Baseline Measurements in Critically Ill Patients With Pneumonia: A Retrospective Cohort Study**
Van Oers J, Krabbe J, Kemna E, Kluiters Y, Vos P, De Lange D, Girbes A, Beishuizen A.

Background: We assessed the ability of baseline and serial measurements of mid-regional proadrenomedullin (MR-proADM) and mid-regional proatrial natriuretic peptide (MR-proANP) to predict 28-day mortality in critically ill patients with pneumonia compared with Acute Physiological and Chronic Health Evaluation IV (APACHE IV) model and Sequential Organ Failure Assessment (SOFA) score.
Methodology: Biomarkers were collected for the first five days in this retrospective observational cohort study. Biomarker clearance (as a percentage) was presented as biomarker decline in five days. We investigated the relationship between biomarkers and mortality in a multivariable Cox regression model. APACHE IV and SOFA were calculated after 24 hours from intensive care unit admission.
Results: In 153 critically ill patients with pneumonia, 28-day mortality was 26.8%. Values of baseline MR-proADM, MR-proANP, and APACHE IV were significantly higher in 28-day nonsurvivors, but not significantly different for SOFA score. Baseline MR-proADM and MR-proANP, APACHE IV, and SOFA had a low area under the curve in receiver operating characteristics (ROC) curves. No optimal cut-off points could be calculated. Biomarkers and severity scores were divided into tertiles. The highest tertiles baseline MR-proADM and MR-proANP were not significant predictors for 28-day mortality in a multivariable model with age and APACHE IV. SOFA was not a significant predictor in univariable analysis. Clearances of MR-proADM and MR-proANP were significantly higher in 28-day survivors. MR-proADM and MR-proANP

clearances had similar low accuracy to identify nonsurvivors in ROC curves and were divided into tertiles. Low clearances of MR-proADM and MR-proANP (first tertiles) were significant predictors for 28-day mortality (hazard ratio [HR]: 2.38; 95% confidence interval [CI]: 1.21-4.70; p = 0.013 and HR: 2.27; 95% CI: 1.16-4.46; p = 0.017) in a model with age and APACHE IV.
Conclusions: MR-proADM and MR-proANP clearance performed better in predicting 28-day mortality in a model with age and APACHE IV compared with single baseline measurements in a mixed population of critically ill with pneumonia.

Gepubliceerd: Cureus. 2021;13(5):e15285.
Impact factor: 0; NVT

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32. **Antimicrobial Lessons From a Large Observational Cohort on Intra-abdominal Infections in Intensive Care Units**
Vogelaers D, Blot S, Van den Berge A, Montravers P, Abdominal Sepsis Study ('AbSeS') Group - includes Cornet AD, Vermeijden JW.

Severe intra-abdominal infection commonly requires intensive care. Mortality is high and is mainly determined by disease-specific characteristics, i.e. setting of infection onset, anatomical barrier disruption, and severity of disease expression. Recent observations revealed that antimicrobial resistance appears equally common in community-acquired and late-onset hospital-acquired infection. This challenges basic principles in anti-infective therapy guidelines, including the paradigm that pathogens involved in community-acquired infection are covered by standard empiric antimicrobial regimens, and second, the concept of nosocomial acquisition as the main driver for resistance involvement. In this study, we report on resistance profiles of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecalis and Enterococcus faecium in distinct European geographic regions based on an observational cohort study on intra-abdominal infections in intensive care unit (ICU) patients. Resistance against aminopenicillins, fluoroquinolones, and third-generation cephalosporins in E. coli, K. pneumoniae and P. aeruginosa is problematic, as is carbapenem-resistance in the latter pathogen. For E. coli and K. pneumoniae, resistance is mainly an issue in Central Europe, Eastern and South-East Europe, and Southern Europe, while resistance in P. aeruginosa is additionally problematic in Western Europe. Vancomycin-resistance in E. faecalis is of lesser concern but requires vigilance in E. faecium in Central and Eastern and South-East Europe. In the subcohort of patients with secondary peritonitis presenting with either sepsis or septic shock, the appropriateness of empiric antimicrobial therapy was not associated with mortality. In contrast, failure of source control was strongly associated with mortality. The relevance of these new insights for future recommendations regarding empiric antimicrobial therapy in intra-abdominal infections is discussed.

Gepubliceerd: Drugs. 2021;81(9):1065-78.
Impact factor: 9.546; Q1

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33. **Ventilator Weaning and Discontinuation Practices for Critically Ill Patients**
Burns KEA, Rizvi L, Cook DJ, Lebovic G, Dodek P, Villar J, Slutsky AS, Jones A, Kapadia FN, Gattas DJ, Epstein SK, Pelosi P, Kefala K, Meade MO, the Canadian

Critical Care Trials Group, reseach collaborators – includes Beishuizen A, Vermeijden JW.

Importance: Although most critically ill patients receive invasive mechanical ventilation (IMV), few studies have characterized how IMV is discontinued in practice. Objective: To describe practice variation in IMV discontinuation internationally, associations between initial discontinuation events and outcomes, and factors associated with the use of select discontinuation strategies and failed initial spontaneous breathing trials (SBTs).
Design, setting, and participants: Prospective, multinational, observational study of critically ill adults who received IMV for at least 24 hours from 142 intensive care units (ICUs) in 19 countries within 6 regions (27 in Canada, 23 in India, 22 in the UK, 26 in Europe, 21 in Australia/New Zealand, and 23 in the US).
Exposures: Receiving IMV.
Main outcomes and measures: Primary analyses characterized types of initial IMV discontinuation events (extubation, SBT, or tracheostomy) and associations with clinical outcomes (including duration of ventilation, ICU and hospital mortality, and ICU and hospital length of stay). Secondary analyses examined the associations between SBT outcome and SBT timing and clinical outcomes.
Results: Among 1868 patients (median [interquartile range] age, 61.8 [48.9-73.1] years; 1173 [62.8%] men) 424 (22.7%) underwent direct extubation, 930 (49.8%) had an initial SBT (761 [81.8%] successful), 150 (8.0%) underwent direct tracheostomy, and 364 (19.5%) died before a weaning attempt. Across regions, there was variation in the use of written directives to guide care, daily screening, SBT techniques, ventilator modes, and the roles played by clinicians involved in weaning. Compared with initial direct extubation, patients who had an initial SBT had higher ICU mortality (20 [4.7%] vs 96 [10.3%]; absolute difference, 5.6% [95% CI, 2.6%-8.6%]), longer duration of ventilation (median of 2.9 vs 4.1 days; absolute difference, 1.2 days [95% CI, 0.7-1.6]), and longer ICU stay (median of 6.7 vs 8.1 days; absolute difference, 1.4 days [95% CI, 0.8-2.4]). Patients whose initial SBT failed (vs passed) had higher ICU mortality (29 [17.2%] vs 67 [8.8%]; absolute difference, 8.4% [95% CI, 2.0%-14.7%]), longer duration of ventilation (median of 6.1 vs 3.5 days; absolute difference, 2.6 days [95% CI, 1.6-3.6]), and longer ICU stay (median of 10.6 vs 7.7 days; absolute difference, 2.8 days [95% CI, 1.1-5.2]). Compared with patients who underwent early initial SBTs, patients who underwent late initial SBTs (>2.3 days after intubation) had longer duration of ventilation (median of 2.1 vs 6.1 days; absolute difference, 4.0 days [95% CI, 3.7-4.5]), longer ICU stay (median of 5.9 vs 10.8 days; absolute difference, 4.9 days [95% CI, 4.0-6.3]), and longer hospital stay (median of 14.3 vs 22.8 days; absolute difference, 8.5 days [95% CI, 6.0-11.0]).
Conclusions and relevance: In this observational study of invasive mechanical ventilation discontinuation in 142 ICUs in Canada, India, the UK, Europe, Australia/New Zealand, and the US from 2013 to 2016, weaning practices varied internationally.

Gepubliceerd: JAMA. 2021;325(12):1173-84.
Impact factor: 56.274; Q1

Totale impact factor: 307.611
Gemiddelde impact factor: 9.322

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 2.512
Gemiddelde impact factor: 0.837

Interne Geneeskunde

1. **Circulating adrenomedullin and B-type natriuretic peptide do not predict blood pressure fluctuations during pheochromocytoma resection: a cross-sectional study**

Berends AMA, Buitenwerf E, Riphagen IJ, Lenders JWM, Timmers H, Kruijff S, Links TP, van der Horst-Schrivers ANA, Stegeman CA, Eekhoff EMW, Feelders RA, Corssmit EPM, Groote Veldman R, Haak HR, Muller Kobold AC, Kerstens MN.

Background: Despite adequate presurgical management, blood pressure fluctuations are common during resection of pheochromocytoma or sympathetic paraganglioma (PPGL). To a large extent, the variability in blood pressure control during PPGL resection remains unexplained. Adrenomedullin and B-type natriuretic peptide, measured as MR-proADM and NT-proBNP, respectively, are circulating biomarkers of cardiovascular dysfunction. We investigated whether plasma levels of MR-proADM and NT-proBNP are associated with blood pressure fluctuations during PPGL resection.
Methods: Study subjects participated in PRESCRIPT, a randomized controlled trial in patients undergoing PPGL resection. MR-proADM and NT-proBNP were determined in a single plasma sample drawn before surgery. Multivariable linear and logistic regression analyses were used to explore associations between these biomarkers and blood pressure fluctuations, use of vasoconstrictive agents during surgery as well as the occurrence of perioperative cardiovascular events.
Results: A total of 126 PPGL patients were included. Median plasma concentrations of MR-proADM and NT-proBNP were 0.51 (0.41-0.63) nmol/L and 68.7 (27.9-150.4) ng/L, respectively. Neither MR-proADM nor NT-proBNP were associated with blood pressure fluctuations. There was a positive correlation between MR-proADM concentration and the cumulative dose of vasoconstrictive agents (03B2 0.44, P =0.001). Both MR-proADM and NT-proBNP were significantly associated with perioperative cardiovascular events (OR: 5.46, P =0.013 and OR: 1.54, P =0.017, respectively).
Conclusions: plasma MR-proADM or NT-proBNP should not be considered as biomarkers for the presurgical risk assessment of blood pressure fluctuations during PPGL resection. Future studies are needed to explore the potential influence of these biomarkers on the intraoperative requirement of vasoconstrictive agents and the perioperative cardiovascular risk.

Gepubliceerd: Eur J Endocrinol. 2021;185(4):507-14.
Impact factor: 6.664; Q1

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2. **Checkpoint inhibitor induced hepatitis and the relation with liver metastasis and outcome in advanced melanoma patients**

Biewenga M, van der Kooij MK, Wouters M, Aarts MJB, van den Berkmortel F, de Groot JWB, Boers-Sonderen MJ, Hospers GAP, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Haanen J, van der Eertwegh AJM, van Hoek B, Kapiteijn E.

Background: Checkpoint inhibitor-induced hepatitis is an immune-related adverse event of programmed cell death protein 1 (PD-1) inhibition, cytotoxic T-lymphocyte associated 4 (CTLA-4) inhibition or the combination of both. Aim of this study was to

assess whether checkpoint inhibitor-induced hepatitis is related to liver metastasis and outcome in a real-world nationwide cohort.
Methods: Data from the prospective nationwide Dutch Melanoma Treatment Registry (DMTR) was used to analyze incidence, risk factors of checkpoint inhibitor-induced grade 3-4 hepatitis and outcome.
Results: 2561 advanced cutaneous melanoma patients received 3111 treatments with checkpoint inhibitors between May 2012 and January 2019. Severe hepatitis occurred in 30/1620 (1.8%) patients treated with PD-1 inhibitors, in 29/1105 (2.6%) patients treated with ipilimumab and in 80/386 (20.7%) patients treated with combination therapy. Patients with hepatitis had a similar prevalence of liver metastasis compared to patients without hepatitis (32% vs. 27%; p = 0.58 for PD-1 inhibitors; 42% vs. 29%; p = 0.16 for ipilimumab; 38% vs. 43%; p = 0.50 for combination therapy). There was no difference in median progression free and overall survival between patients with and without hepatitis (6.0 months vs. 5.4 months progression-free survival; p = 0.61; 17.0 vs. 16.2 months overall survival; p = 0.44).
Conclusion: Incidence of hepatitis in a real-world cohort is 1.8% for PD-1 inhibitor, 2.6% for ipilimumab and 20.7% for combination therapy. Checkpoint inhibitor-induced hepatitis had no relation with liver metastasis and had no negative effect on the outcome.

Gepubliceerd: Hepatol Int. 2021;15(2):510-9.
Impact factor: 6.047; Q2

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3. **Health-related quality of life of long-term advanced melanoma survivors treated with anti-CTLA-4 immune checkpoint inhibition compared to matched controls**
Boekhout AH, Rogiers A, Jozwiak K, Boers-Sonderen MJ, van den Eertwegh AJ, Hospers GA, de Groot JWB, Aarts MJB, Kapiteijn E, Ten Tije AJ, Piersma D, Vreugdenhil G, van der Veldt AA, Suijkerbuijk KPM, Rozeman EA, Neyns B, Janssen KJ, van de Poll-Franse LV, Blank CU.

Background: Checkpoint inhibitors have changed overall survival for patients with advanced melanoma. However, there is a lack of data on health-related quality of life (HRQoL) of long-term advanced melanoma survivors, years after treatment. Therefore, we evaluated HRQoL in long-term advanced melanoma survivors and compared the study outcomes with matched controls without cancer.
Materian and methods: Ipilimumab-treated advanced melanoma survivors without evidence of disease and without subsequent systemic therapy for a minimum of two years following last administration of ipilimumab were eligible for this study. The European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30 (EORTC QLQ-C30), the Multidimensional Fatigue Inventory (MFI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Melanoma questionnaire (FACT-M) were administered. Controls were individually matched for age, gender, and educational status. Outcomes of survivors and controls were compared using generalized estimating equations, and differences were interpreted as clinically relevant according to published guidelines.
Results: A total of 89 survivors and 265 controls were analyzed in this study. After a median follow-up of 39 (range, 17-121) months, survivors scored significantly lower on

physical (83.7 vs. 89.8, difference (diff) = -5.80, p=.005), role (83.5 vs. 90, diff = -5.97, p=.02), cognitive (83.7 vs. 91.9, diff = -8.05, p=.001), and social functioning (86.5 vs. 95.1, diff = -8.49, p= <.001) and had a higher symptom burden of fatigue (23.0 vs. 15.5, diff = 7.48, p=.004), dyspnea (13.3 vs. 6.7, diff = 6.47 p=.02), diarrhea (7.9 vs. 4.0, diff = 3.78, p=.04), and financial impact (10.5 vs. 2.5, diff = 8.07, p=.001) than matched controls. Group differences were indicated as clinically relevant.
Discussion: Compared to matched controls, long-term advanced melanoma survivors had overall worse functioning scores, more physical symptoms, and financial difficulties. These data may contribute to the development of appropriate survivorship care.

Gepubliceerd: Acta Oncol. 2021;60(1):69-77.
Impact factor: 4.089; Q3

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4. **Genome-Wide Meta-analysis Identifies Genetic Variants Associated With Glycemic Response to Sulfonylureas**
Dawed AY, Yee SW, Zhou K, van Leeuwen N, Zhang Y, Siddiqui MK, Etheridge A, Innocenti F, Xu F, Li JH, Beulens JW, van der Heijden AA, Slieker RC, Chang YC, Mercader JM, Kaur V, Witte JS, Lee MTM, Kamatani Y, Momozawa Y, Kubo M, Palmer CNA, Florez JC, Hedderson MM, t Hart LM, Giacomini KM, Pearson ER, DIRECT Consortium; MetGen Plus investigators - includes Out M.

Objective: Sulfonylureas, the first available drugs for the management of type 2 diabetes, remain widely prescribed today. However, there exists significant variability in glycemic response to treatment. We aimed to establish heritability of sulfonylurea response and identify genetic variants and interacting treatments associated with HbA(1c) reduction.
Research design and methods: As an initiative of the Metformin Genetics Plus Consortium (MetGen Plus) and the DIabetes REsearCh on patient straTification (DIRECT) consortium, 5,485 White Europeans with type 2 diabetes treated with sulfonylureas were recruited from six referral centers in Europe and North America. We first estimated heritability using the generalized restricted maximum likelihood approach and then undertook genome-wide association studies of glycemic response to sulfonylureas measured as HbA(1c) reduction after 12 months of therapy followed by meta-analysis. These results were supported by acute glipizide challenge in humans who were naïve to type 2 diabetes medications, cis expression quantitative trait loci (eQTL), and functional validation in cellular models. Finally, we examined for possible drug-drug-gene interactions.
Results: After establishing that sulfonylurea response is heritable (mean ± SEM 37 ± 11%), we identified two independent loci near the GXYLT1 and SLCO1B1 genes associated with HbA(1c) reduction at a genome-wide scale (P < 5 × 10(-8)). The C allele at rs1234032, near GXYLT1, was associated with 0.14% (1.5 mmol/mol), P = 2.39 × 10(-8)), lower reduction in HbA(1c). Similarly, the C allele was associated with higher glucose trough levels (β = 1.61, P = 0.005) in healthy volunteers in the SUGAR-MGH given glipizide (N = 857). In 3,029 human whole blood samples, the C allele is a cis eQTL for increased expression of GXYLT1 (β = 0.21, P = 2.04 × 10(-58)). The C allele of rs10770791, in an intronic region of SLCO1B1, was associated with 0.11% (1.2 mmol/mol) greater reduction in HbA(1c) (P = 4.80 × 10(-8)). In 1,183 human liver samples, the C allele at rs10770791 is a cis eQTL for reduced SLCO1B1 expression

(P = 1.61 × 10(-7)), which, together with functional studies in cells expressing SLCO1B1, supports a key role for hepatic SLCO1B1 (encoding OATP1B1) in regulation of sulfonylurea transport. Further, a significant interaction between statin use and SLCO1B1 genotype was observed (P = 0.001). In statin nonusers, C allele homozygotes at rs10770791 had a large absolute reduction in HbA(1c) (0.48 ± 0.12% [5.2 ± 1.26 mmol/mol]), equivalent to that associated with initiation of a dipeptidyl peptidase 4 inhibitor.
Conclusions: We have identified clinically important genetic effects at genome-wide levels of significance, and important drug-drug-gene interactions, which include commonly prescribed statins. With increasing availability of genetic data embedded in clinical records these findings will be important in prescribing glucose-lowering drugs.

Gepubliceerd: Diabetes Care. 2021;44(12):2673-82.
Impact factor: 19.112; Q1

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5. **Toxicity, Response and Survival in Older Patients with Metastatic Melanoma Treated with Checkpoint Inhibitors**
de Glas NA, Bastiaannet E, van den Bos F, Mooijaart SP, van der Veldt AAM, Suijkerbuijk KPM, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, van den Eertwegh AJM, de Groot JB, Haanen J, Hospers GAP, Jalving H, Piersma D, van Rijn RS, Ten Tije AJ, Vreugdenhil G, Wouters M, Portielje JEA, Kapiteijn EW.

Background: Previous trials suggest no differences in immunotherapy treatment between older and younger patients, but mainly young patients with a good performance status were included. The aim of this study was to describe the treatment patterns and outcomes of "real-world" older patients with metastatic melanoma and to identify predictors of outcome.
Methods: We included patients aged ≥65 years with metastatic melanoma from the Dutch Melanoma Treatment Registry. We described the reasons for hospital admissions and treatment discontinuation. Additionally, we assessed predictors of toxicity and response using logistic regression models and survival using Cox regression models.
Results: We included 2216 patients. Grade ≥3 toxicity was not associated with age, comorbidities or WHO status. Patients aged ≥75 discontinued treatment due to toxicity more often, resulting in fewer treatment cycles. Response rates were similar to previous trials (40.3% and 43.6% in patients aged 65-75 and ≥75, respectively, for anti-PD1 treatment) and did not decrease with age or comorbidity. Melanoma-specific survival was not affected by age or comorbidity.
Conclusion: Response rates and toxicity outcomes of checkpoint inhibitors did not change with increasing age or comorbidity. However, the impact of grade I-II toxicity on quality of life deserves further study as older patients discontinue treatment more frequently.

Gepubliceerd: Cancers (Basel). 2021;13(11).
Impact factor: 6.639; Q1

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6. **Adjuvant treatment for melanoma in clinical practice - Trial versus reality**

de Meza MM, Ismail RK, Rauwerdink D, van Not OJ, van Breeschoten J, Blokx WAM, de Boer A, van Dartel M, Hilarius DL, Ellebaek E, Bonenkamp HJ, Blank CU, Aarts MJB, van Akkooi ACJ, van den Berkmortel F, Boers-Sonderen MJ, de Groot JWB, Haanen JB, Hospers GAP, Kapiteijn EW, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil A, Westgeest HM, van den Eertwegh AJM, Suijkerbuijk KPM, Wouters M.

Background: Little is known about outcomes of adjuvant-treated melanoma patients beyond the clinical trial setting. Since 2019, adjuvant-treated melanoma patients have been registered in the DMTR, a population-based registry to monitor the quality and safety of melanoma care in the Netherlands. This study aims to describe treatment patterns, relapse, and toxicity rates of adjuvant-treated melanoma patients beyond the clinical trial setting.
Methods: Analyses were performed on adjuvant-treated melanoma patients included in the DMTR. Descriptive statistics were used to analyse patient-, and treatment characteristics. A baseline registration completeness analysis was performed, and an analysis on trial eligibility in clinical practice patients. Recurrence-free survival (RFS) at 12-months was estimated with the Kaplan-Meier method.
Results: A total of 641 patients were treated with adjuvant anti-PD-1 therapy. RFS at 12-months was 70.6% (95% CI, 66.9-74.6) with a median follow-up of 12.8 months. Sex, stage of disease and Breslow thickness were associated with a higher hazard for RFS. Eighteen per cent of the anti-PD-1-treated patients developed grade ≥3 toxicity. Sixty-one per cent of patients prematurely discontinued anti-PD-1 therapy.
Conclusion: Adjuvant anti-PD-1 treatment of resected stage III/IV melanoma in daily practice showed slightly higher toxicity rates and more frequent premature discontinuation but similar RFS rates compared to trials.

Gepubliceerd: Eur J Cancer. 2021;158:234-45.
Impact factor: 9.162; Q1

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7. **The value of open-source clinical science in pandemic response: lessons from ISARIC**
ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

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8. **Trends in survival and costs in metastatic melanoma in the era of novel targeted and immunotherapeutic drugs**
Franken MG, Leeneman B, Aarts MJB, van Akkooi ACJ, van den Berkmortel F, Boers-Sonderen MJ, van den Eertwegh AJM, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, van der Veldt AAM, Westgeest HM, Wouters M, Haanen J, Uyl-de Groot CA.

Background: The objective of this study was to evaluate trends in survival and health care costs in metastatic melanoma in the era of targeted and immunotherapeutic drugs.

Materials and methods: Data on survival and health care resource use were retrieved from the Dutch Melanoma Treatment Registry. The Kaplan-Meier method was used to estimate overall survival. Health care costs and budget impact were computed by applying unit costs to individual patient resource use. All outcomes were stratified by year of diagnosis.
Results: Baseline characteristics were balanced across cohort years. The percentage of patients receiving systemic treatment increased from 73% in 2013 to 90% in 2018. Patients received on average 1.85 [standard deviation (SD): 1.14] lines of treatment and 41% of patients received at least two lines of treatment. Median survival increased from 11.8 months in 2013 [95% confidence interval (CI): 10.7-13.7 months] to 21.1 months in 2018 (95% CI: 18.2 months-not reached). Total mean costs were €100 330 (SD: €103 699); systemic treatments accounted for 84% of the total costs. Costs for patients who received systemic treatment [€118 905 (SD: €104 166)] remained reasonably stable over the years even after the introduction of additional (combination of) novel drugs. From mid-2013 to 2018, the total budget impact for all patients was €452.79 million.
Conclusion: Our study shows a gain in survival in the era of novel targeted and immunotherapeutic drugs. These novel drugs came, however, along with substantial health care costs. Further insights into the cost-effectiveness of the novel drugs are crucial for ensuring value for money in the treatment of patients with metastatic melanoma.

Gepubliceerd: ESMO Open. 2021;6(6):100320.
Impact factor: 6.540; Q1

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9. **Watchful waiting for small non-functional pancreatic neuroendocrine tumours: nationwide prospective cohort study (PANDORA)**
Heidsma CM, Engelsman AF, van Dieren S, Stommel MWJ, de Hingh I, Vriens M, Hol L, Festen S, Mekenkamp L, Hoogwater FJH, Daams F, Klümpen HJ, Besselink MG, van Eijck CH, Nieveen van Dijkum EJ.

Gepubliceerd: Br J Surg. 2021;108(8):888-91.
Impact factor: 6.939; Q1

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10. **Postapproval trials versus patient registries: comparability of advanced melanoma patients with brain metastases**
Ismail RK, Sikkes NO, Wouters M, Hilarius DL, Pasmooij AMG, van den Eertwegh AJM, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, de Groot JWB, Haanen J, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije BJ, van der Veldt AAM, Vreugdenhil A, van Dartel M, de Boer A.

Postapproval trials and patient registries have their pros and cons in the generation of postapproval data. No direct comparison between clinical outcomes of these data sources currently exists for advanced melanoma patients. We aimed to investigate whether a patient registry can complement or even replace postapproval trials. Postapproval single-arm clinical trial data from the Medicines Evaluation Board and real-world data from the Dutch Melanoma Treatment Registry were used. The study population consisted of advanced melanoma patients with brain metastases treated

with targeted therapies (BRAF- or BRAF-MEK inhibitors) in the first line. A Cox hazard regression model and a propensity score matching (PSM) model were used to compare the two patient populations. Compared to patients treated in postapproval trials (n = 467), real-world patients (n = 602) had significantly higher age, higher ECOG performance status, more often ≥3 organ involvement and more symptomatic brain metastases. Lactate dehydrogenase levels were similar between both groups. The unadjusted median overall survival (mOS) in postapproval clinical trial patients was 8.7 (95% CI, 8.1-10.4) months compared to 7.2 (95% CI, 6.5-7.7) months (P < 0.01) in real-world patients. With the Cox hazard regression model, survival was adjusted for prognostic factors, which led to a statistically insignificant difference in mOS for trial and real-world patients of 8.7 (95% CI, 7.9-10.4) months compared to 7.3 (95% CI, 6.3-7.9) months, respectively. The PSM model resulted in 310 matched patients with similar survival (P = 0.9). Clinical outcomes of both data sources were similar. Registries could be a complementary data source to postapproval clinical trials to establish information on clinical outcomes in specific subpopulations.

Gepubliceerd: Melanoma Res. 2021;31(1):58-66.
Impact factor: 3.599; Q2

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11. **Inferior Outcome of Addition of the Aminopeptidase Inhibitor Tosedostat to Standard Intensive Treatment for Elderly Patients with AML and High Risk MDS**
Janssen J, Löwenberg B, Manz M, Bargetzi M, Biemond B, Borne PVD, Breems D, Brouwer R, Chalandon Y, Deeren D, Efthymiou A, Gjertsen BT, Graux C, Gregor M, Heim D, Hess U, Hoogendoorn M, Jaspers A, Jie A, Jongen-Lavrencic M, Klein S, Klift MV, Kuball J, Lammeren-Venema DV, Legdeur MC, Loosdrecht AV, Maertens J, Kooy MVM, Moors I, Nijziel M, Obbergh FV, Oosterveld M, Pabst T, Poel MV, Sinnige H, Spertini O, Terpstra W, Tick L, Velden WV, Vekemans MC, Vellenga E, Weerdt O, Westerweel P, Stüssi G, Norden YV, Ossenkoppele G.

Treatment results of AML in elderly patients are unsatisfactory. We hypothesized that addition of tosedostat, an aminopeptidase inhibitor, to intensive chemotherapy may improve outcome in this population. After establishing a safe dose in a run-in phase of the study in 22 patients, 231 eligible patients with AML above 65 years of age (median 70, range 66-81) were randomly assigned in this open label randomized Phase II study to receive standard chemotherapy (3+7) with or without tosedostat at the selected daily dose of 120 mg (n = 116), days 1-21. In the second cycle, patients received cytarabine 1000 mg/m(2) twice daily on days 1-6 with or without tosedostat. CR/CRi rates in the 2 arms were not significantly different (69% (95% C.I. 60-77%) vs 64% (55-73%), respectively). At 24 months, event-free survival (EFS) was 20% for the standard arm versus 12% for the tosedostat arm (Cox-p = 0.01) and overall survival (OS) 33% vs 18% respectively (p = 0.006). Infectious complications accounted for an increased early death rate in the tosedostat arm. Atrial fibrillation was more common in the tosedostat arm as well. The results of the present study show that the addition of tosedostat to standard chemotherapy does negatively affect the therapeutic outcome of elderly AML patients.

Gepubliceerd: Cancers (Basel). 2021;13(4).
Impact factor: 6.639; Q1

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12. **Outcomes for systemic therapy in older patients with metastatic melanoma: Results from the Dutch Melanoma Treatment Registry**
Jochems A, Bastiaannet E, Aarts MJB, van Akkooi ACJ, van den Berkmortel F, Boers-Sonderen MJ, van den Eertwegh AJM, de Glas NG, de Groot JWB, Haanen J, Hospers GAP, van der Hoeven JJM, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van Zeijl MCT, Kapiteijn E, Wouters M.

Background: The incidence of metastatic melanoma is increasing in all ages. Multiple trials with targeted drugs and immune checkpoint inhibitors showed improved survival in metastatic melanoma. However, patients aged ≥75 years are often under-represented in clinical trials, therefore raising questions on safety and efficacy of treatment.
Patients and methods: We analyzed a real-world cohort of 3054 patients with metastatic melanoma stratified for age (≤65 years, 66-74 years and ≥ 75 years), and BRAF status, providing data on treatment strategies, toxicity, and survival. Kaplan Meier curves and Cox Proportional Hazard Models were used to present overall survival (OS) and Melanoma Specific Survival (MSS).
Results: Overall, 52.2% of patients were ≤ 65 years and 18.4% of patients ≥75 years. BRAF mutated tumors were found less often in patients ≥75 years: 34.5% versus 65% in patients ≤65 years. Patients ≥75 years received systemic therapy less frequently compared to their younger counterparts independent of the BRAF status. When receiving treatment, no statistical significant difference in grade 3 or 4 toxicity was observed. Three year Overall Survival rate was 13.7% (9.1-19.3) in patients ≥75 years versus 26.7% (23.1-30.4) in patients ≤65 years, with a Hazard Ratio (HR) of 1.71 (95%CI 1.50-1.95), $p < 0.001$. Three year Melanoma Specific Survival was 30.4% (22.0-39.2) versus 34.0% (29.7-38.2), HR 1.26 (95% CI 1.07-1.49), $p = 0.005$ with an adjusted HR of 1.21 (1.00-1.47), $p = 0.049$.
Conclusion: Patients with metastatic melanoma ≥75 years are less frequently treated, but when treated there is no statistical significant increase in toxicity and only a borderline statistical significant difference in Melanoma Specific Survival was seen, compared to younger patients.

Gepubliceerd: J Geriatr Oncol. 2021;12(7):1031-8.
Impact factor: 3.599; Q3

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13. **Informal caregiver well-being during and after patients' treatment with adjuvant chemotherapy for colon cancer: a prospective, exploratory study**
Langenberg S, Poort H, Wymenga ANM, de Groot JW, Muller EW, van der Graaf WTA, Prins JB, van Herpen CML.

Introduction: Caring for a significant other during cancer treatment can be demanding. Little is known about the well-being of informal caregivers of patients with colon cancer. This study aims to examine informal caregiver well-being during adjuvant chemotherapy for colon cancer.
Materian and methods: This exploratory longitudinal, prospective study measured the course of informal caregiver burden (Self-Perceived Pressure of Informal Care), distress (Hospital Anxiety and Depression Scale), health-related quality of life (RAND-36), marital satisfaction (Maudsley Marital Questionnaire), social support (Social Support List - Discrepancies), fatigue (Abbreviated Fatigue Questionnaire), and self-

esteem (Caregiver Reaction Assessment) before (T0), during (T1), and after (T2) patients' treatment.
Results: Baseline data of 60 out of 76 eligible dyads (79%) were analyzed. Mean levels of informal caregiver burden and distress improved significantly over time, as did their health-related quality of life and perceived social support. At baseline, 30% and 26.7% of informal caregivers reported moderate-to-high levels of burden and clinically relevant levels of distress, respectively, which changed to 20% and 18.8% at T2. Informal caregiver burden and distress at baseline were the strongest predictors of informal caregiver burden and distress during and following patients' treatment, respectively.
Conclusion: When informal caregivers and patients experience problems before start of adjuvant chemotherapy, problems seem to improve over time. Approximately 20% of informal caregivers remain burdened and distressed after patients' end of treatment. Paying attention to baseline distress and burden seems indicated, as these were strong predictors of informal caregivers' well-being during and after treatment.

Gepubliceerd: Support Care Cancer. 2021;29(5):2481-91.
Impact factor: 3.603; Q2

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14. **Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial**
Löwenberg B, Pabst T, Maertens J, Gradowska P, Biemond BJ, Spertini O, Vellenga E, Griskevicius L, Tick LW, Jongen-Lavrencic M, van Marwijk Kooy M, Vekemans MC, van der Velden W, Beverloo B, Michaux L, Graux C, Deeren D, de Weerdt O, van Esser JWJ, Bargetzi M, Klein SK, Gadisseur A, Westerweel PE, Veelken H, Gregor M, Silzle T, van Lammeren-Venema D, Moors I, Breems DA, Hoogendoorn M, Legdeur MJC, Fischer T, Kuball J, Cornelissen J, Porkka K, Juliusson G, Meyer P, Höglund M, Gjertsen BT, Janssen J, Huls G, Passweg J, Cloos J, Valk PJM, van Elssen C, Manz MG, Floisand Y, Ossenkoppele GJ.

Lenalidomide, an antineoplastic and immunomodulatory drug, has therapeutic activity in acute myeloid leukemia (AML), but definitive studies about its therapeutic utility have been lacking. In a phase 3 study, we compared 2 induction regimens in newly diagnosed patients age 18 to 65 years with AML: idarubicine-cytarabine (cycle 1) and daunorubicin and intermediate-dose cytarabine (cycle 2) without or with lenalidomide (15 mg orally on days 1-21). One final consolidation cycle of chemotherapy or autologous stem cell transplantation (auto-SCT) or allogeneic SCT (allo-SCT) was provided according to a prognostic risk and minimal residual disease (MRD)-adapted approach. Event-free survival (EFS; primary end point) and other clinical end points were assessed. A second random assignment in patients in complete response or in complete response with incomplete hematologic recovery after cycle 3 or auto-SCT involved 6 cycles of maintenance with lenalidomide (10 mg on days 1-21) or observation. In all, 392 patients were randomly assigned to the control group, and 388 patients were randomly assigned to lenalidomide induction. At a median follow-up of 41 months, the study revealed no differences in outcome between the treatments (EFS, 44% ± 2% standard error and overall survival, 54% ± 2% at 4 years for both arms) although in an exploratory post hoc analysis, a lenalidomide benefit was suggested in SRSF2-mutant AML. In relation to the previous Dutch-Belgian Hemato-Oncology Cooperative Group and Swiss Group for Clinical Cancer Research (HOVON-SAKK) studies that used a similar 3-cycle regimen but did not pursue an MRD-guided

approach, these survival estimates compare markedly more favorably. MRD status after cycle 2 lost prognostic value in intermediate-risk AML in the risk-adjusted treatment context. Maintenance with lenalidomide showed no apparent effect on relapse probability in 88 patients randomly assigned for this part of the study.

Gepubliceerd: Blood Adv. 2021;5(4):1110-21.
Impact factor: 6.799; Q1

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15. **Prospective practice survey of management of cetuximab-related skin reactions**
Lugtenberg RT, Boers-Doets CB, Witteveen PO, van Herpen CML, Wymenga ANM, de Groot JWB, Hoeben A, Del Grande C, van Doorn B, Koldenhof JJ, Driessen CML, Gelderblom H.

Purpose: Evidence-based guidelines on how to prevent or treat cetuximab-related skin reactions are lacking and multiple care and management strategies are used. The main purpose of the present study is to gain information about the different skincare products being used against skin reactions in metastatic colorectal cancer (mCRC) and recurrent/metastatic (R/M) or locally advanced (LA) squamous cell cancer of the head and neck (SCCHN) patients treated with cetuximab.
Methods: An open-label, prospective observational study conducted in the Netherlands. The occurrence of skin reactions and the care and management options taken were documented for 16 weeks, starting from the first administration of cetuximab.
Results: A total of 103 patients were included in 7 hospitals. 38 patients (37%) developed a grade >/= 2 skin reaction. Eighty-six patients could be analysed for the primary endpoint (73.3% males, mean age 62.4 years, n = 44 LA SCCHN, n = 16 R/M SCCHN, n = 26 mCRC). The most frequently used skin products at some point during the observation period were moisturizing products (70%), systemic antibiotics (64%), topical antibiotics (58%), lipid-regenerating (28%) and other topical products (28%). The overall use of products gradually increased from baseline to week 6-10, reducing by week 16. Hospital protocols were the primary reason (> 50%) for choice of the skincare products and medications.
Conclusion: A variety of skin care products and antibiotics were commonly used. Only few patients developed severe cutaneous reactions. For patients, the occurrence of skin reactions did not influence their willingness to continue cetuximab therapy.

Gepubliceerd: Support Care Cancer. 2021;29(7):3497-506.
Impact factor: 3.603; Q2

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16. **Relatively mild symptoms after chronic overdose with a double-dose encorafenib: a case report**
Mian P, Meussen E, Piersma D, Lankheet NAG.

Encorafenib (Braftovi) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with binimetinib (Mektovi). According to the product label of encorafenib, there are no specific treatment recommendations in case of an overdose. We report on a 63-year-old man who

ingested a double dose (900 mg) of encorafenib for 16 days. He developed overall minor chronic overdose symptoms such as nausea and vomiting grade 1 and muscle pain. Based on the most occurring adverse events of encorafenib, liver values, kidney function parameters and QTc interval were measured. Kidney function parameters were normal, whereas liver values were slightly increased (grade 1) and QTc slightly prolonged. The plasma concentration 3 h after the last dose was 2110 ng/mL. We describe the course of a case with a chronic overdose during 16 days of the double dose of encorafenib as well as the followed approach, which could be taken into account when observing an encorafenib overdose. Providing information in times of Covid-19 is challenging, but remains necessary for good clinical care.

Gepubliceerd: Anticancer Drugs. 2021;32(5):589-91.
Impact factor: 2.248; Q4

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17. **Acute teriflunomide overdose with relatively mild symptoms: A case report**
Mian P, van Haaften WT, Assink M, van Drie-Pierik R.

What is know and objective: Teriflunomide is indicated for the treatment of adult patients with relapsing-remitting multiple sclerosis.
Case summary: We present a rare intoxication with a high dose (672 mg) of teriflunomide. According to its product label, the only known treatment is the administration of colestyramine and activated carbon (charcoal). No serious adverse events occurred during the time the patient was admitted (<24 h). No long-term overdose-related symptoms or complaints were reported.
What is new and conclusion: The fact that after the acute overdose both adverse events and laboratory parameters were acceptable, prescribing colestyramine and activated carbon, as well as monitoring of laboratory parameters such as full blood count, liver and kidney values and QTc, seems sufficient during the early stage (<24 h after intake) of teriflunomide overdose.

Gepubliceerd: J Clin Pharm Ther. 2021;46(6):1784-6.
Impact factor: 2.512; Q3

18**. Early discontinuation of PD-1 blockade upon achieving a complete or partial response in patients with advanced melanoma: the multicentre prospective Safe Stop trial**
Mulder EEAP, de Joode K, Litière S, Ten Tije AJ, Suijkerbuijk KPM, Boers-Sonderen MJ, Hospers GAP, de Groot JWB, van den Eertwegh AJM, Aarts MJB, Piersma D, van Rijn RS, Kapiteijn E, Vreugdenhil G, van den Berkmortel F, Hoop EO, Franken MG, Ryll B, Rutkowski P, Sleijfer S, Haanen JBAG, van der Veldt AAM.

Background: The introduction of programmed cell death protein 1 (PD-1) blockers (i.e. nivolumab and pembrolizumab) has significantly improved the prognosis of patients with advanced melanoma. However, the long treatment duration (i.e. two years or longer) has a high impact on patients and healthcare systems in terms of (severe) toxicity, health-related quality of life (HRQoL), resource use, and healthcare costs. While durable tumour responses have been observed and PD-1 blockade is discontinued on an individual basis, no consensus has been reached on the optimal

treatment duration. The objective of the Safe Stop trial is to evaluate whether early discontinuation of first-line PD-1 blockade is safe in patients with advanced and metastatic melanoma who achieve a radiological response.
Methods: The Safe Stop trial is a nationwide, multicentre, prospective, single-arm, interventional study in the Netherlands. A total of 200 patients with advanced and metastatic cutaneous melanoma and a confirmed complete response (CR) or partial response (PR) according to response evaluation criteria in solid tumours (RECIST) v1.1 will be included to early discontinue first-line monotherapy with nivolumab or pembrolizumab. The primary objective is the rate of ongoing responses at 24 months after discontinuation of PD-1 blockade. Secondary objectives include best overall and duration of response, need and outcome of rechallenge with PD-1 blockade, and changes in (serious) adverse events and HRQoL. The impact of treatment discontinuation on healthcare resource use, productivity losses, and hours of informal care will also be assessed. Results will be compared to those from patients with CR or PR who completed 24 months of treatment with PD-1 blockade and had an ongoing response at treatment discontinuation. It is hypothesised that it is safe to early stop first-line nivolumab or pembrolizumab at confirmed tumour response while improving HRQoL and reducing costs.
Discussion: From a patient, healthcare, and economic perspective, shorter treatment duration is preferred and overtreatment should be prevented. If early discontinuation of first-line PD-1 blockade appears to be safe, early discontinuation of PD-1 blockade may be implemented as the standard of care in a selected group of patients.
Trial registrattion: The Safe Stop trial has been registered in the Netherlands Trial Register (NTR), Trial NL7293 (old NTR ID: 7502), https://www.trialregister.nl/trial/7293 . Date of registration September 30, 2018.

Gepubliceerd: BMC Cancer. 2021;21(1):323.
Impact factor: 4.430; Q2

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19. **Phase I/II Study of LDE225 in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Metastatic Pancreatic Cancer**
Pijnappel EN, Wassenaar NPM, Gurney-Champion OJ, Klaassen R, van der Lee K, Pleunis-van Empel MCH, Richel DJ, Legdeur MC, Nederveen AJ, van Laarhoven HWM, Wilmink JW.

Background: Desmoplasia is a central feature of the tumor microenvironment in pancreatic ductal adenocarcinoma (PDAC). LDE225 is a pharmacological Hedgehog signaling pathway inhibitor and is thought to specifically target tumor stroma. We investigated the combined use of LDE225 and chemotherapy to treat PDAC patients.
Methods: This was a multi-center, phase I/II study for patients with metastatic PDAC establishing the maximum tolerated dose of LDE225 co-administered with gemcitabine and nab-paclitaxel (phase I) and evaluating the efficacy and safety of the treatment combination after prior FOLFIRINOX treatment (phase II). Tumor microenvironment assessment was performed with quantitative MRI using intra-voxel incoherent motion diffusion weighted MRI (IVIM-DWI) and dynamic contrast-enhanced (DCE) MRI.
Results: The MTD of LDE225 was 200 mg once daily co-administered with gemcitabine 1000 mg/m(2) and nab-paclitaxel 125 mg/m(2). In phase II, six therapy-related grade 4 adverse events (AE) and three grade 5 were observed. In 24 patients, the target lesion response was evaluable. Three patients had partial response (13%),

14 patients showed stable disease (58%), and 7 patients had progressive disease (29%). Median overall survival (OS) was 6 months (IQR 3.9-8.1). Blood plasma fraction (DCE) and diffusion coefficient (IVIM-DWI) significantly increased during treatment. Baseline perfusion fraction could predict OS (>222 days) with 80% sensitivity and 85% specificity.
Conclusion: LDE225 in combination with gemcitabine and nab-paclitaxel was well-tolerated in patients with metastatic PDAC and has promising efficacy after prior treatment with FOLFIRINOX. Quantitative MRI suggested that LDE225 causes increased tumor diffusion and works particularly well in patients with poor baseline tumor perfusion.

Gepubliceerd: Cancers (Basel). 2021;13(19).
Impact factor: 6.639; Q1

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20. **HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study**
Smit C, Boyd A, Rijnders BJA, van de Laar TJW, Leyten EM, Bierman WF, Brinkman K, Claassen MAA, den Hollander J, Boerekamps A, Newsum AM, Schinkel J, Prins M, Arends JE, Op de Coul ELM, van der Valk M, Reiss P, ATHENA observational cohort - Includes Delsing C, Kootstra GJ.

Background: In the Netherlands, access to direct-acting antivirals (DAAs) against hepatitis C virus (HCV) has been unrestricted for chronic infection since 2015. We evaluated whether the nationwide incidence of HCV infections in individuals with HIV has changed since 2015.
Methods: In this retrospective cohort study, data from the ATHENA cohort of people with HIV aged 18 years or older attending any of the 24 HIV treatment centres in the Netherlands between 2000 and 2019 were assessed. We used parametric proportional hazards models with a piecewise exponential survival function to model HCV primary infection and reinfection incidence per 1000 person-years.
Findings: Of the 23 590 individuals without previous HCV infection, 1269 cases of HCV primary infection were documented (incidence 5·2 per 1000 person-years [95% CI 5·0-5·5]). The highest incidence was observed in men who have sex with men (MSM; 7·7 per 1000 person-years [7·3-8·2]) and was lower in people who inject drugs (PWID; 1·7 per 1000 person-years [0·7-4·1]) and other key populations (1·0 per 1000 person-years [0·8-1·2]). In MSM, incidence increased in 2007 to 14·3 per 1000 person-years and fluctuated between 8·7 and 13·0 per 1000 person-years from 2008 to 2015. In 2016, incidence declined to 6·1 cases per 1000 person-years and remained steady between 4·1 and 4·9 per 1000 person-years from 2017 to 2019. Of the 1866 individuals with a previous HCV infection, 274 reinfections were documented (incidence 26·9 per 1000 person-years [95% CI 23·9-30·3]). The highest incidence rate was observed in MSM (38·5 per 1000 person-years [33·9-43·7]) and was lower in PWID (10·9 per 1000 person-years [3·5-33·8]) and other key populations (8·9 per 1000 person-years [6·3-12·5]). In MSM, reinfection incidence fluctuated between 38·0 and 88·9 per 1000 person-years from 2006 to 2015, reaching 55·6 per 1000 person-years in 2015. In 2016, reinfection incidence declined to 41·4 per 1000 person-years, followed by further decreases to 24·4 per 1000 person-years in 2017 and 11·4 per 1000 person-years in 2019.

Interpretation: The sharp decline in HCV incidence in MSM with HIV shortly after restrictions on DAAs were lifted suggests a treatment-as-prevention effect. HCV incidence was already low in PWID and other groups before unrestricted access. Ongoing HCV transmission is occurring in MSM, as illustrated by a declining but high rate of reinfection, stressing the need for additional preventive measures. FUNDING: Dutch Ministry of Health, Welfare, and Sport.

Gepubliceerd: Lancet HIV. 2021;8(2):e96-e105.
Impact factor: 12.767; Q1

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21. **Hospital Variation in Cancer Treatments and Survival OutComes of Advanced Melanoma Patients: Nationwide Quality Assurance in The Netherlands**
van Breeschoten J, van den Eertwegh AJM, de Wreede LC, Hilarius DL, van Zwet EW, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Stevense-den Boer MAM, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Suijkerbuijk KPM, Wouters M.

Background: To assure a high quality of care for patients treated in Dutch melanoma centers, hospital variation in treatment patterns and outcomes is evaluated in the Dutch Melanoma Treatment Registry. The aim of this study was to assess center variation in treatments and 2-year survival probabilities of patients diagnosed between 2013 and 2017 in the Netherlands.
Methods: We selected patients diagnosed between 2013 and 2017 with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry. Centers' performance on 2-year survival was evaluated using Empirical Bayes estimates calculated in a random effects model. Treatment patterns of the centers with the lowest and highest estimates for 2-year survival were compared.
Results: For patients diagnosed between 2014 and 2015, significant center variation in 2-year survival probabilities was observed even after correcting for case-mix and treatment with new systemic therapies. The different use of new systemic therapies partially explained the observed variation. From 2016 onwards, no significant difference in 2-year survival was observed between centers.
Conclusion: Our data suggest that between 2014 and 2015, after correcting for patient case-mix, significant variation in 2-year survival probabilities between Dutch melanoma centers existed. The use of new systemic therapies could partially explain this variation. In 2013 and between 2016 and 2017, no significant variation between centers existed.

Gepubliceerd: Cancers (Basel). 2021;13(20).
Impact factor: 6.639; Q1

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22. **Nationwide Outcomes of Advanced Melanoma According to BRAFV600 Status**
van Breeschoten J, Wouters M, de Wreede LC, Hilarius DH, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Blokx WAM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Boers MJ, van den Eertwegh AJM.

Objective: The aim of this study was to evaluate treatment patterns and overall survival (OS) of patients with BRAFV600 wild-type and BRAFV600-mutant advanced melanoma in the Netherlands.
Methods: We selected patients of 18 years and over, diagnosed between 2016 and 2017 with unresectable stage IIIC or IV melanoma, registered in the Dutch Melanoma Treatment Registry. To assess the association of BRAFV600-mutation status with OS we used the Cox proportional-hazards model.
Results: A total of 642 BRAFV600 wild-type and 853 mutant patients were included in the analysis. Median OS did not differ significantly between both groups, 15.2 months (95% confidence interval [CI]: 13.2-19.2) versus 20.6 months (95% CI: 18.3-25.0). Survival rates at 6 and 12 months were significantly lower for BRAFV600 wild-type patients compared with BRAFV600-mutant patients, 72.0% (95% CI: 68.6-75.6) and 56.0% (95% CI: 52.2-60.0) versus 83.4% (95% CI: 80.9-85.9) and 65.7% (95% CI: 62.6-69.0). Two-year survival was not significantly different between both groups, 41.1% (95% CI: 37.2-45.3) versus 47.0% (95% CI: 43.6-60.6). Between 0 and 10 months, BRAFV600 wild-type patients had a decreased survival with a hazard ratio for OS of 2.00 (95% CI: 1.62-2.46) but this effect disappeared after 10 months. At 12 months, BRAFV600-mutant patients had started with second-line systemic treatment more often compared with BRAFV600 wild-type patients (50% vs. 19%).
Conclusion: These results suggest that advanced BRAFV600 wild-type melanoma patients have worse survival than BRAFV600-mutated patients during the first 10 months after diagnosis because of less available treatment options.

Gepubliceerd: Am J Clin Oncol. 2021;44(2):82-9.
Impact factor: 2.339; Q4

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23. **First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAF(V600)-mutant advanced melanoma patients: a propensity-matched survival analysis**
van Breeschoten J, Wouters M, Hilarius DL, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Blokx WAM, Tije BJT, Veldt A, Vreugdenhil A, Boers-Sonderen MJ, van den Eertwegh AJM.

Background: Anti-PD-1 antibodies and BRAF/MEK inhibitors are the two main groups of systemic therapy in the treatment of BRAF(V600)-mutant advanced melanoma. Until now, data are inconclusive on which therapy to use as first-line treatment. The aim of this study was to use propensity score matching to compare first-line anti-PD-1 monotherapy vs. BRAF/MEK inhibitors in advanced BRAF(V600)-mutant melanoma patients.
Methods: We selected patients diagnosed between 2014 and 2017 with advanced melanoma and a known BRAF(V600)-mutation treated with first-line BRAF/MEK inhibitors or anti-PD-1 antibodies, registered in the Dutch Melanoma Treatment Registry. Patients were matched based on their propensity scores using the nearest neighbour and the optimal matching method.
Results: Between 2014 and 2017, a total of 330 and 254 advanced melanoma patients received BRAF/MEK inhibitors and anti-PD-1 monotherapy as first-line systemic therapy. In the matched cohort, patients receiving anti-PD-1 antibodies as a first-line treatment had a higher median and 2-year overall survival compared to patients treated

with first-line BRAF/MEK inhibitors, 42.3 months (95% CI: 37.3-NE) vs. 19.8 months (95% CI: 16.7-24.3) and 65.4% (95% CI: 58.1-73.6) vs. 41.7% (95% CI: 34.2-51.0).
Conclusions: Our data suggest that in the matched BRAF(V600)-mutant advanced melanoma patients, anti-PD-1 monotherapy is the preferred first-line treatment in patients with relatively favourable patient and tumour characteristics.

Gepubliceerd: Br J Cancer. 2021;124(7):1222-30.
Impact factor: 7.640; Q1

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24. **Not all ground-glass opacifications reflect COVID-19; the hidden danger of a pandemic**
van Dalfsen MT, Delsing CE.

We present a 30-year-old male, an 82-year-old male and a 71-year-old female who presented with fever, cough and dyspnea during de COVID-19 pandemic. Chest CT showed a ground-glass opacification and/or crazy paving. In all of these patients the PCR for SARS-CoV-2 was negative, but the COVID-19 pandemic caused a delay in diagnosis and treatment of these patients with big consequences for these patients. We show the risk of being fixated on COVID-19, the need for a careful examination respecting the medical history of the patient. Don't conclude too quickly on a CORADS-4 or 5, but do additional tests and consult other specialists when the PCR for SARS-CoV-2 is negative.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021;165.
Impact factor: 0; NVT

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25. **Sex-Based Differences in Treatment with Immune Checkpoint Inhibition and Targeted Therapy for Advanced Melanoma: A Nationwide Cohort Study**
van der Kooij MK, Dekkers OM, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, de Groot JWB, Hospers GAP, Piersma D, van Rijn RS, Suijkerbuijk KPM, Westgeest HM, van der Veldt AAM, Vreugdenhil G, Wilgenhof S, Wouters M, Haanen J, van den Eertwegh AJM, Kapiteijn E.

Recent meta-analyses show conflicting data on sex-dependent benefit following systemic treatment for advanced melanoma patients. We examined the nationwide Dutch Melanoma Treatment Registry (July 2013-July 2018), assessing sex-dependent differences in advanced melanoma patients (stage IIIC/IV) with respect to clinical characteristics, mutational profiles, treatments initiated, grade 3-4 adverse events (AEs), treatment responses, and mortality. We included 3985 patients, 2363 men (59%) and showed that although men and women with advanced melanoma differ in clinical and tumor characteristics, the safety profile of immune checkpoint inhibition (ICI) is comparable. The data suggest a 10% survival advantage for women, mainly seen in patients ≥60 years of age and patients with BRAF V600 mutant melanoma. Following ICI there was no survival difference.

Gepubliceerd: Cancers (Basel). 2021;13(18).
Impact factor: 6.639; Q1

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26. **Safety and Efficacy of Checkpoint Inhibition in Patients With Melanoma and Preexisting Autoimmune Disease : A Cohort Study**

van der Kooij MK, Suijkerbuijk KPM, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, van Breeschoten J, van den Eertwegh AJM, de Groot JWB, Haanen J, Hospers GAP, Piersma D, van Rijn RS, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van Zeijl MCT, Wouters M, Dekkers OM, Kapiteijn E.

Background: Because immune checkpoint inhibition (ICI) can cause immune-related adverse events (irAEs) mimicking immunologic diseases, patients with preexisting autoimmune disease (AID) have been excluded from clinical trials.
Objective: To evaluate the safety and efficacy of ICI in patients with advanced melanoma with and without AID. DESIGN: Nationwide cohort study.
Setting: The Netherlands. PATIENTS: 4367 patients with advanced melanoma enrolled in the Dutch Melanoma Treatment Registry (DMTR) between July 2013 and July 2018 and followed through February 2019. MEASUREMENTS: Patient, clinical, and treatment characteristics; irAEs of grade 3 or higher; treatment response; and survival.
Results: A total of 415 patients (9.5%) had AID, categorized as rheumatologic AID (n = 227), endocrine AID (n = 143), inflammatory bowel disease (IBD) (n = 55), or "other" (n = 8). Of these, 228 patients (55%) were treated with ICI (vs. 2546 [58%] without AID); 87 were treated with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4), 187 with anti-programmed cell death 1 (PD-1), and 34 with the combination. The incidences of irAEs of grade 3 or higher in patients with AID were 30% (95% CI, 21% to 41%) with anti-CTLA-4, 17% (CI, 12% to 23%) with anti-PD-1, and 44% (CI, 27% to 62%) with combination therapy; for patients without AID, the incidences were 30% (CI, 27% to 33%) (n = 916), 13% (CI, 12% to 15%) (n = 1540), and 48% (CI, 43% to 53%) (n = 388), respectively. Patients with AID more often discontinued anti-PD-1 treatment because of toxicity than patients without AID (17% [CI, 12% to 23%] vs. 9% [CI, 8% to 11%]). Patients with IBD were more prone to anti-PD-1-induced colitis (6/31 = 19% [CI, 7% to 37%]) than patients with other AIDs (3% [CI, 0% to 6%]) and patients without AID (2% [CI, 2% to 3%]).The objective response rate was similar in patients with versus without AID who were treated with anti-CTLA-4 (10% [CI, 5% to 19%] vs. 16% [CI, 14% to 19%]), anti-PD-1 (40% [CI, 33% to 47%] vs. 44% [CI, 41% to 46%]), or the combination (39% [CI, 20% to 59%] vs. 43% [CI, 38% to 49%]). Survival did not differ between patients with and those without AID (median, 13 months [CI, 10 to 16 months] vs. 14 months [CI, 13 to 15 months]).
Limitation: Information was limited on AID severity and immunosuppressive treatment.
Conclusion: Response to ICI with anti-CTLA-4, anti-PD-1, or their combination for advanced melanoma and overall incidence of any irAEs of grade 3 or higher were similar in patients with and without preexisting AID. However, severe colitis and toxicity requiring early discontinuation of treatment occurred more frequently among patients with preexisting IBD, warranting close follow-up.
Primary funding source: The Netherlands Organization for Health Research and Development.

Gepubliceerd: Ann Intern Med. 2021;174(5):641-8.
Impact factor: 25.391; Q1

27**. Circulating TP53 mutations are associated with early tumor progression and poor survival in pancreatic cancer patients treated with FOLFIRINOX**
van der Sijde F, Azmani Z, Besselink MG, Bonsing BA, de Groot JWB, Groot Koerkamp B, Haberkorn BCM, Homs MYV, van IWFJ, Janssen QP, Lolkema MP, Luelmo SAC, Mekenkamp LJM, Mustafa DAM, van Schaik RHN, Wilmink JW, Vietsch EE, van Eijck CHJ.

Background: Biomarkers predicting treatment response may be used to stratify pancreatic ductal adenocarcinoma (PDAC) patients for therapy. The aim of this study was to identify circulating tumor DNA (ctDNA) mutations that associate with tumor progression during FOLFIRINOX chemotherapy, and overall survival (OS).
Methods: Circulating cell-free DNA was analyzed with a 57 gene next-generation sequencing panel using plasma samples of 48 PDAC patients of all disease stages. Patients received FOLFIRINOX as initial treatment. Chemotherapy response was determined on CT scans as disease control (n = 30) or progressive disease (n = 18) within eight cycles of FOLFIRINOX, based on RECIST 1.1 criteria.
Results: Detection of a TP53 ctDNA mutation before start of FOLFIRINOX [odds ratio (OR) 10.51, 95% confidence interval (CI) 1.40-79.14] and the presence of a homozygous TP53 Pro72Arg germline variant (OR 6.98, 95% CI 1.31-37.30) were predictors of early tumor progression during FOLFIRINOX in multivariable analysis. Five patients presented with the combination of a TP53 ctDNA mutation before start of FOLFIRINOX and the homozygous Pro72Arg variant. All five patients showed progression during FOLFIRINOX. The combination of the TP53 mutation and TP53 germline variant was associated with shorter survival (median OS 4.4 months, 95% CI 2.6-6.2 months) compared with patients without any TP53 alterations (median OS 13.0 months, 95% CI 8.6-17.4 months).
Conclusion: The combination of a TP53 ctDNA mutation before start of FOLFIRINOX and a homozygous TP53 Pro72Arg variant is a promising biomarker, associated with early tumor progression during FOLFIRINOX and poor OS. The results of this exploratory study need to be validated in an independent cohort.

Gepubliceerd: Ther Adv Med Oncol. 2021;13:17588359211033704.
Impact factor: 8.168; Q1

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28. **Serum miR-373-3p and miR-194-5p Are Associated with Early Tumor Progression during FOLFIRINOX Treatment in Pancreatic Cancer Patients: A Prospective Multicenter Study**
van der Sijde F, Homs MYV, van Bekkum ML, van den Bosch TPP, Bosscha K, Besselink MG, Bonsing BA, de Groot JWB, Karsten TM, Groot Koerkamp B, Haberkorn BCM, Luelmo SAC, Mekenkamp LJM, Mustafa DAM, Wilmink JW, van Eijck CHJ, Vietsch EE, on behalf of The Dutch Pancreatic Cancer Group.

In this study, we explored the predictive value of serum microRNA (miRNA) expression for early tumor progression during FOLFIRINOX chemotherapy and its association with overall survival (OS) in patients with pancreatic ductal adenocarcinoma (PDAC). A total of 132 PDAC patients of all disease stages were included in this study, of whom 25% showed progressive disease during FOLFIRINOX according to the RECIST criteria. MiRNA expression was analyzed in serum collected before the start and after one cycle of chemotherapy. In the discovery cohort (n = 12), a 352-miRNA RT-qPCR panel was

used. In the validation cohorts (total n = 120), miRNA expression was detected using individual RT-qPCR miRNA primers. Before the start of FOLFIRINOX, serum miR-373-3p expression was higher in patients with progressive disease compared to patients with disease control after FOLFIRINOX (Log2 fold difference (FD) 0.88, p = 0.006). MiR-194-5p expression after one cycle of FOLFIRINOX was lower in patients with progressive disease (Log2 FD -0.29, p = 0.044). Both miRNAs were predictors of early tumor progression in a multivariable model including disease stage and baseline CA19-9 level (miR-373-3p odds ratio (OR) 3.99, 95% CI 1.10-14.49; miR-194-5p OR 0.91, 95% CI 0.83-0.99). MiR-373-3p and miR-194-5p did not show an association with OS after adjustment for disease stage, baseline CA19-9, and chemotherapy response. In conclusion, high serum miR-373-3p before the start and low serum miR-194-5p after one cycle are associated with early tumor progression during FOLFIRINOX.

Gepubliceerd: Int J Mol Sci. 2021;22(20).
Impact factor: 5.924; Q1

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29. **Trends in Use and Perceptions About Triplet Chemotherapy Plus Bevacizumab for Metastatic Colorectal Cancer**
van Nassau SC, Bond MJ, Scheerman I, van Breeschoten J, Kessels R, Valkenburg-van Iersel LB, Verheul HM, Buffart TE, Mekenkamp LJ, Lemmens VE, Koopman M, Bol GM.

Importance: Triplet chemotherapy with fluorouracil, folinic acid, oxaliplatin, and irinotecan plus bevacizumab (FOLFOXIRI-B) is an effective first-line treatment option for patients with metastatic colorectal cancer (mCRC). However, the degree of implementation of FOLFOXIRI-B in daily practice is unknown.
Objectives: To evaluate the current adoption rate of FOLFOXIRI-B in patients with mCRC and investigate the perspectives of medical oncologists toward this treatment option.
Design, setting, and participants: This 1-week, multicenter, cross-sectional study in the Netherlands used a flash mob design, which facilitates ultrafast data generation (flash) through the engagement of numerous researchers (mob). During the study week (March 1-5, 2021), patient data were retrieved from electronic health records of 47 hospitals on patients with mCRC who were referred to a medical oncologist between November 1, 2020, and January 31, 2021. Interviews were simultaneously conducted with 101 medical oncologists from 52 hospitals who regularly treat patients with mCRC.
Exposure: First-line systemic treatment as determined by the treating physician.
Main outcomes and measures: The FOLFOXIRI-B prescription rate was the main outcome. Current practice was compared with prescription rates in 2015 to 2018. Eligibility for treatment with FOLFOXIRI-B was estimated. An exploratory outcome was medical oncologists' reported perspectives on FOLFOXIRI-B.
Results: A total of 5948 patients in the Netherlands (median age [interquartile range], 66 [57-73] years; 3503 [59%] male; and 3712 [62%] with left-sided or rectal tumor) were treated with first-line systemic therapy for synchronous mCRC. A total of 282 patients with mCRC underwent systemic therapy during the study period (2021). Of these 282 patients, 199 (71%) were treated with intensive first-line therapy other than FOLFOXIRI-B, of whom 184 (65%) were treated with oxaliplatin doublets with or without bevacizumab; 14 (5%) with irinotecan doublets with or without bevacizumab, panitumumab, or cetuximab; and 1 (0.4%) with irinotecan with bevacizumab. Fifty-four

patients (19%) were treated with fluoropyrimidine monotherapy with or without bevacizumab, 1 patient (0.4%) with panitumumab monotherapy, and 3 (1%) with immune checkpoint inhibitors. In total, 25 patients (9%; 95% CI, 6%-12%) were treated with first-line FOLFOXIRI-B compared with 142 (2%; 95% CI, 2%-3%) in 2015 to 2018. During the study period, 21 of 157 eligible patients (13.4%) in the Netherlands were treated with FOLFOXIRI-B. A total of 87 medical oncologists (86%) reported discussing FOLFOXIRI-B as a treatment option with eligible patients. A total of 47 of 85 (55%) generally communicated a preference for a chemotherapy doublet to patients. These oncologists reported a significantly lower awareness of guidelines and trial results. Toxic effects were the most reported reason to prefer an alternative regimen.
Conclusions and relevance: The findings of this study suggest that FOLFOXIRI-B prescription rates have marginally increased in the last 5 years. Considering that most medical oncologists discuss this treatment option, the prescription rate found in this study was below expectations. Awareness of guidelines and trial data seems to contribute to the discussion of available treatment options by medical oncologists, and the findings of this study suggest a need for repeated and continuing medical education.

Gepubliceerd: JAMA Netw Open. 2021;4(9):e2124766.
Impact factor: 8.485; Q1

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30. **Survival outcomes of patients with advanced melanoma from 2013 to 2017: Results of a nationwide population-based registry**
van Zeijl MCT, de Wreede LC, van den Eertwegh AJM, Wouters M, Jochems A, Schouwenburg MG, Aarts MJB, van Akkooi ACJ, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van der Hoeven JJM, Haanen J.

Background: The treatment landscape has completely changed for advanced melanoma. We report survival outcomes and the differential impact of prognostic factors over time in daily clinical practice.
Methods: From a Dutch nationwide population-based registry, patients with advanced melanoma diagnosed from 2013 to 2017 were analysed (n = 3616). Because the proportional hazards assumption was violated, a multivariable Cox model restricted to the first 6 months and a multivariable landmark Cox model from 6 to 48 months were used to assess overall survival (OS) of cases without missing values. The 2017 cohort was excluded from this analysis because of the short follow-up time.
Results: Median OS of the 2013 and 2016 cohort was 11.7 months (95% confidence interval [CI]: 10.4-13.5) and 17.7 months (95% CI: 14.9-19.8), respectively. Compared with the 2013 cohort, the 2016 cohort had superior survival in the Cox model from 0 to 6 months (hazard ratio [HR] = 0.55 [95% CI: 0.43-0.72]) and in the Cox model from 6 to 48 months (HR = 0.68 [95% CI: 0.57-0.83]). Elevated lactate dehydrogenase levels, distant metastases in ≥3 organ sites, brain and liver metastasis and Eastern Cooperative Oncology Group performance score of ≥1 had stronger association with inferior survival from 0 to 6 months than from 6 to 48 months. BRAF-mutated melanoma had superior survival in the first 6 months (HR = 0.50 [95% CI: 0.42-0.59]).
Conclusion(s): Prognosis for advanced melanoma in the Netherlands has improved from 2013 to 2016. Prognostic importance of most evaluated factors was higher in the

first 6 months after diagnosis. BRAF-mutated melanoma was only associated with superior survival in the first 6 months.

Gepubliceerd: Eur J Cancer. 2021;144:242-51.
Impact factor: 9.162; Q1

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31. **Clinical outcome of patients with metastatic melanoma of unknown primary in the era of novel therapy**
Verver D, Grunhagen DJ, van Akkooi ACJ, Aarts MJB, van den Berkmortel F, van den Eertwegh AJM, de Groot JWB, Boers-Sonderen MJ, Haanen J, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Tije AJT, Vreugdenhil G, Verhoef C, van der Veldt AAM.

Melanoma of unknown primary (MUP) is considered different from melanoma of known primary (MKP), and it is unclear whether these patients benefit equally from novel therapies. In the current study, characteristics and overall survival (OS) of patients with advanced and metastatic MUP and MKP were compared in the era of novel therapy. Patients were selected from the prospective nation-wide Dutch Melanoma Treatment Registry (DMTR). The following criteria were applied: diagnosis of stage IIIc unresectable or IV cutaneous MKP (cMKP) or MUP between July 2012 and July 2017 and treatment with immune checkpoint inhibition and/or targeted therapy. OS was estimated using the Kaplan-Meier method. The stratified multivariable Cox regression model was used for adjusted analysis. A total of 2706 patients were eligible including 2321 (85.8%) patients with cMKP and 385 (14.2%) with MUP. In comparative analysis, MUP patients more often presented with advanced and metastatic disease at primary diagnosis with poorer performance status, higher LDH, and central nervous system metastases. In crude analysis, median OS of cMKP or MUP patients was 12 months (interquartile range [IQR] 5 - 44) and 14 months (IQR 5 - not reached), respectively (P = 0.278). In adjusted analysis, OS in MUP patients was superior (hazard rate 0.70, 95% confidence interval 0.58-0.85; P < 0.001). As compared to patients with advanced and metastatic cMKP, MUP patients have superior survival in adjusted analysis, but usually present with poorer prognostic characteristics. In crude analysis, OS was comparable indicating that patients with MUP benefit at least equally from treatment with novel therapies.

Gepubliceerd: Cancer Immunol Immunother. 2021;70(11):3123-35.
Impact factor: 6.968; Q1

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32. **Impact of malnourishment on the pharmacokinetics of acetaminophen and susceptibility to acetaminophen hepatotoxicity**
Zillen D, Movig KLL, Kant G, Masselink JB, Mian P.

Background: Acetaminophen hepatotoxicity is thought to be primarily caused by formation of the specific reactive metabolite N-acetyl-para-benzo-quinone imine (NAPQI). Malnourished individuals are at increased risk of acetaminophen-related hepatotoxicity. We report a case of low acetaminophen clearance in a severely underweight young woman, and elaborate on the possible effects of malnutrition on the

total clearance of acetaminophen as well as on the separate contributions of the different metabolic pathways.
Case report: An 18-year-old Caucasian woman weighing 43 kg with a history of eating disorder-related hospital admissions presented at the emergency department after having ingested 33 tablets of acetaminophen 500 mg two hours earlier. She then received intravenous N-acetylcysteine for 33 h. Nine hours after ingestion, the acetaminophen elimination half-life (t½) was estimated to be >100 h.
Discussion: While decreased total acetaminophen clearance (twofold) due to malnutrition has been reported in literature, the extremely low clearance in this specific patient cannot be explained. Malnourished individuals generally have reduced antioxidant reserves, coinciding with a shift in metabolic routes toward oxidative metabolism. This may result in increased formation of NAPQI and reduced neutralizing capacity, thereby increasing the risk of acetaminophen-induced hepatotoxicity. Evidence for this observation can be found in animal and to a lesser extent in human studies.

Gepubliceerd: Clin Case Rep. 2021;9(11):e04611.
Impact factor: 0; NVT

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33. **Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort**
Walma MS, Brada LJ, Patuleia SIS, Blomjous JG, Bollen TL, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam R, Festen S, Jan de Groot D, Willem de Groot J, Mohammad NH, Hermans JJ, de Hingh IH, Kerver ED, van Leeuwen MS, van der Leij C, Liem MSL, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nederend J, Nio CY, Patijn GA, Polée MB, Pruijt JF, Renken NS, Rombouts SJ, Schouten TJ, Stommel MWJ, Verweij ME, de Vos-Geelen J, de Vries JJJ, Vulink A, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ.

Introduction: Since current studies on locally advanced pancreatic cancer (LAPC) mainly report from single, high-volume centers, it is unclear if outcomes can be translated to daily clinical practice. This study provides treatment strategies and clinical outcomes within a multicenter cohort of unselected patients with LAPC.
Materials and methods: Consecutive patients with LAPC according to Dutch Pancreatic Cancer Group criteria, were prospectively included in 14 centers from April 2015 until December 2017. A centralized expert panel reviewed response according to RECIST v1.1 and potential surgical resectability. Primary outcome was median overall survival (mOS), stratified for primary treatment strategy.
Results: Overall, 422 patients were included, of whom 77% (n = 326) received chemotherapy. The majority started with FOLFIRINOX (77%, 252/326) with a median of six cycles (IQR 4-10). Gemcitabine monotherapy was given to 13% (41/326) of patients and nab-paclitaxel/gemcitabine to 10% (33/326), with a median of two (IQR 3-5) and three (IQR 3-5) cycles respectively. The mOS of the entire cohort was 10 months (95%CI 9-11). In patients treated with FOLFIRINOX, gemcitabine monotherapy, or nab-paclitaxel/gemcitabine, mOS was 14 (95%CI 13-15), 9 (95%CI 8-10), and 9 months (95%CI 8-10), respectively. A resection was performed in 13% (32/252) of patients after FOLFIRINOX, resulting in a mOS of 23 months (95%CI 12-34).
Conclusion: This multicenter unselected cohort of patients with LAPC resulted in a 14 month mOS and a 13% resection rate after FOLFIRINOX. These data put previous

results in perspective, enable us to inform patients with more accurate survival numbers and will support decision-making in clinical practice.

Gepubliceerd: Eur J Surg Oncol. 2021;47(3 Pt B):699-707.
Impact factor: 4.424; Q1

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34. **Radiofrequency ablation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer (PELICAN): study protocol for a randomized controlled trial**
Walma MS, Rombouts SJ, Brada LJH, Borel Rinkes IH, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam RM, van Delden OM, Festen S, Ghorbani P, de Groot DJ, de Groot JWB, Haj Mohammad N, van Hillegersberg R, de Hingh IH, D'Hondt M, Kerver ED, van Leeuwen MS, Liem MSL, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nio CY, Oulad Abdennabi I, Pando E, Patijn GA, Polée MB, Pruijt JF, Roeyen G, Ropela JA, Stommel MWJ, de Vos-Geelen J, de Vries JJ, van der Waal EM, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ.

Background: Approximately 80% of patients with locally advanced pancreatic cancer (LAPC) are treated with chemotherapy, of whom approximately 10% undergo a resection. Cohort studies investigating local tumor ablation with radiofrequency ablation (RFA) have reported a promising overall survival of 26-34 months when given in a multimodal setting. However, randomized controlled trials (RCTs) investigating the effect of RFA in combination with chemotherapy in patients with LAPC are lacking.
Methods: The "Pancreatic Locally Advanced Unresectable Cancer Ablation" (PELICAN) trial is an international multicenter superiority RCT, initiated by the Dutch Pancreatic Cancer Group (DPCG). All patients with LAPC according to DPCG criteria, who start with FOLFIRINOX or (nab-paclitaxel/)gemcitabine, are screened for eligibility. Restaging is performed after completion of four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine (i.e., 2 months of treatment), and the results are assessed within a nationwide online expert panel. Eligible patients with RECIST stable disease or objective response, in whom resection is not feasible, are randomized to RFA followed by chemotherapy or chemotherapy alone. In total, 228 patients will be included in 16 centers in The Netherlands and four other European centers. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, RECIST response, CA 19.9 and CEA response, toxicity, quality of life, pain, costs, and immunomodulatory effects of RFA.
Discussion: The PELICAN RCT aims to assess whether the combination of chemotherapy and RFA improves the overall survival when compared to chemotherapy alone, in patients with LAPC with no progression of disease following 2 months of systemic treatment.
Trial registrattion: Dutch Trial Registry NL4997 . Registered on December 29, 2015. ClinicalTrials.gov NCT03690323 . Retrospectively registered on October 1, 2018.

Gepubliceerd: Trials. 2021;22(1):313.
Impact factor: 2.279; Q4

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35. **The treatment and survival of elderly patients with locally advanced pancreatic cancer: A post-hoc analysis of a multicenter registry**
Brada LJH, Walma MS, van Dam RM, de Vos-Geelen J, de Hingh IH, Creemers GJ, Liem MSL, Mekenkamp LJ, de Meijer VE, de Groot DJA, Patijn GA, de Groot JWB, Festen S, Kerver ED, Stommel MWJ, Meijerink MR, Bosscha K, Pruijt JF, Polée MB, Ropela JA, Cirkel GA, Los M, Wilmink JW, Haj Mohammad N, van Santvoort HC, Besselink MG, Molenaar IQ.

Background: The treatment options for patients with locally advanced pancreatic cancer (LAPC) have improved in recent years and consequently survival has increased. It is unknown, however, if elderly patients benefit from these improvements in therapy. With the ongoing aging of the patient population and an increasing incidence of pancreatic cancer, this patient group becomes more relevant. This study aims to clarify the association between increasing age, treatment and overall survival in patients with LAPC.
Methods: Post-hoc analysis of a multicenter registry including consecutive patients with LAPC, who were registered in 14 centers of the Dutch Pancreatic Cancer Group (April 2015-December 2017). Patients were divided in three groups according to age (<65, 65-74 and ≥75 years). Primary outcome was overall survival stratified by primary treatment strategy. Multivariable regression analyses were performed to adjust for possible confounders.
Results: Overall, 422 patients with LAPC were included; 162 patients (38%) aged <65 years, 182 patients (43%) aged 65-74 and 78 patients (19%) aged ≥75 years. Chemotherapy was administered in 86%, 81% and 50% of the patients in the different age groups (p<0.01). Median overall survival was 12, 11 and 7 months for the different age groups (p<0.01).Patients treated with chemotherapy showed comparable median overall survival of 13, 14 and 10 months for the different age groups (p=0.11). When adjusted for confounders, age was not associated with overall survival.
Conclusion: Elderly patients are less likely to be treated with chemotherapy, but when treated with chemotherapy, their survival is comparable to younger patients.

Gepubliceerd: Pancreatology. 2021;21(1):163-9.
Impact factor: 3.996; Q2

Totale impact factor: 244.809
Gemiddelde impact factor: 6.995

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 4.760
Gemiddelde impact factor: 1.587

Kindergeneeskunde

1. **[Myocardial Infarction and resuscitation of an adolescent: consequences of an unexplained disease]**
de Jong JJD, Slenter RHJ, van Lierop P, Wagenaar LJ.

Background: Morbus Kawasaki is defined by unexplained fever combined with at least 4 out of 5 classic symptoms: bilateral conjunctivitis, polymorphic exanthema, strawberry tongue and red swollen lips, extremity changes and cervical lymphadenopathy. However, these symptoms do not always occur completely or simultaneously.
Case description: An 18-year old man was admitted after an out of hospital cardiac arrest caused by an occluded aneurysmatic LAD, which was treated with a percutanious coronary intervention. Coronary angiogram however also revealed coronary aneurysms of all coronaries, identifying an episode of unexplained fever and vasculitis 4 years prior as Morbus Kawasaki.
Conclusion: Echocardiogram, CTA and MRA can reveal coronary malformations and thus identify M. Kawasaki when there is an incomplete M. Kawasaki. An early diagnosis and treatment with high dose aspirin and intravenous immunoglobulines is essential to reduce the risk of cardiovascular complications later in life.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021;165.
Impact factor: 0; NVT

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2. **The Need for Testing-The Exercise Challenge Test to Disentangle Causes of Childhood Exertional Dyspnea**
Hengeveld VS, van der Kamp MR, Thio BJ, Brannan JD.

Exertional dyspnea is a common symptom in childhood which can induce avoidance of physical activity, aggravating the original symptom. Common causes of exertional dyspnea are exercise induced bronchoconstriction (EIB), dysfunctional breathing, physical deconditioning and the sensation of dyspnea when reaching the physiological limit. These causes frequently coexist, trigger one another and have overlapping symptoms, which can impede diagnoses and treatment. In the majority of children with exertional dyspnea, EIB is not the cause of symptoms, and in asthmatic children it is often not the only cause. An exercise challenge test (ECT) is a highly specific tool to diagnose EIB and asthma in children. Sensitivity can be increased by simulating real-life environmental circumstances where symptoms occur, such as environmental factors and exercise modality. An ECT reflects daily life symptoms and impairment, and can in an enjoyable way disentangle common causes of exertional dyspnea.

Gepubliceerd: Front Pediatr. 2021;9:773794.
Impact factor: 3.418; Q1

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3. **Question 6: What is the use of allergy testing in children with asthma?**
Klok T, Ottink MD, Brand PLP.

Disagreement exists between asthma guidelines on the routine use of allergy testing in the diagnostic work-up of a child with persistent asthma, although the important role of inhalant allergy in the pathophysiology of asthma and allergic rhinitis is undisputed. The usefulness of screening for inhalant allergies in asthma is connected to the efficacy of allergen reduction measures and specific immunotherapy, both of which appear to be more effective in children than in adults. Allergen-specific exposure reduction recommendations are therefore an essential part of childhood asthma management. Such recommendations should be guided by appropriate diagnosis of inhalant allergy, based on a structured allergy history and results of sensitization tests. Specific IgE testing and skin prick testing show comparable results in identifying clinically important sensitizations. Although a therapeutic medication trial can be started pragmatically in children with asthma without diagnosing their inhalant allergy, we recommend making or excluding an accurate diagnosis of inhalant allergy.

Gepubliceerd: Paediatr Respir Rev. 2021;37:57-63.
Impact factor: 2.726; Q2

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4. **Food or medication? The therapeutic effects of food on the duration and incidence of upper respiratory tract infections: a Review of the literature**
van der Gaag EJ, Hummel TZ.

Purpose: Upper respiratory tract infections are common in children and adults. Antiviral treatments are only available for specific groups of patients, stimulating the distribution of over-the-counter medication to relieve the symptoms for the other patients. Studies about whole foods and their effect on the incidence and duration of upper respiratory tract infections were reviewed.
Methods: Randomized controlled trials and case-control studies available on MEDLINE, Web of Science, Cochrane Library and Embase were included.
Results and conclusions: Thirty-three studies were included. The incidence of respiratory infections or symptoms was shown to be reduced in some studies when probiotics, prebiotics, growing-up milk, fish oil, kiwi, garlic and xylitol were taken. Duration was favorably influenced by the intake of elderberry, kiwi, probiotics and fish oil. When the risk of bias and repetition is taken into account, probiotics and elderberry repeatedly show favorable effects. Prudent conclusions can be made in selective patient groups. However, the studies were diverse and were only performed by a few study groups.

Gepubliceerd: Crit Rev Food Sci Nutr. 2021;61(16):2691-704.
Impact factor: 11.176; Q1

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5. **Feasibility, Efficacy, and Efficiency of eHealth-Supported Pediatric Asthma Care: Six-Month Quasi-Experimental Single-Arm Pretest-Posttest Study**
van der Kamp M, Reimering Hartgerink P, Driessen JMM, Thio B, Hermens H, Tabak M.

Background: Early detection of loss of asthma control can effectively reduce the burden of the disease. However, broad implementation in clinical practice has not been accomplished so far. We are in need of research investigating the operationalization of eHealth pediatric asthma care in practice, which can provide the most potential benefits in terms of adoption, efficiency, and effectiveness.
Objective: The aim of this study was to investigate the technical and clinical feasibility, including an exploration of the efficacy and cost-efficiency, of an eHealth program implemented in daily clinical pediatric asthma practice.
Methods: We designed an eHealth-supported pediatric asthma program facilitating early detection of loss of asthma control while increasing symptom awareness and self-management. In the 6-month program, asthma control was monitored by 4 health care professionals (HCPs) by using objective home measurements and the web-based Puffer app to allow timely medical anticipation and prevent treatment delay. Technical feasibility was assessed by technology use, system usability, and technology acceptance. Clinical feasibility was assessed by participation and patient-reported health and care outcomes and via a focus group with HCPs regarding their experiences of implementing eHealth in daily practice. The efficacy and cost-efficiency were explored by comparing pretest-posttest program differences in asthma outcomes (asthma control, lung function, and therapy adherence) and medical consumption.
Results: Of 41 children, 35 children with moderate-to-severe asthma volunteered for participation. With regard to technical feasibility, the Puffer app scored a good usability score of 78 on the System Usability Scale and a score of 70 for technology acceptance on a scale of 1 to 100. Approximately 75% (18/24) of the children indicated that eHealth helped them to control their asthma during the program. HCPs indicated that home measurements and real time communication enabled them to make safe and substantiated medical decisions during symptom manifestations. With an average time commitment of 15 minutes by patients, eHealth care led to a 80% gross reduction (from €71,784 to €14,018, US $1=€0.85) in health care utilization, 8.6% increase (from 18.6 to 20.2, P=.40) in asthma control, 25.0% increase (from 2.8 to 3.5, P=.04) in the self-management level, and 20.4% improved (from 71.2 to 76.8, P=.02) therapy adherence.
Conclusions: eHealth asthma care seems to be technically and clinically feasible, enables safe remote care, and seems to be beneficial for pediatric asthma care in terms of health outcomes and health care utilization. Follow-up research should focus on targeted effectiveness studies with the lessons learned, while also enabling individualization of eHealth for personalized health care.

Gepubliceerd: JMIR Form Res. 2021;5(7):e24634.
Impact factor: 0; NVT

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6. **Volatile organic breath components and exercise induced bronchoconstriction in asthmatic children**
van der Kamp MR, Driessen JMM, van der Schee MP, Thio BJ, de Jongh FHC.

Introduction: Asthma is one of the most common chronic diseases in childhood and is generally characterized by exercise induced bronchoconstriction (EIB). Assessing EIB is time consuming and expensive as it requires a fully equipped pulmonary function laboratory. Analysis of volatile organic compounds (VOCs) in breath is a novel technique for examining biomarkers which may associate with asthma features. The

aim of this pilot study was to identify potential markers in the relationship between EIB and VOCs.
Methods: Children between four and 14 years old were asked to provide a breath sample prior to undergoing an exercise challenge test to assess for EIB.
Results: Breath samples were collected and analyzed in 46 asthmatic children, 21 with EIB and 25 without EIB (NO-EIB). Molecular features (MFs) were not significantly different between EIB and NO-EIB controls. 29 of the 46 children were corticosteroid naïve, 10 with EIB and 13 without. In the corticosteroid naïve group EIB was associated with increased MF23 and MF14 in the lower breath sample (p-value < 0.05).
Conclusion: This pilot study shows that EIB was related to an increased MF14 and MF23 in corticosteroid naïve children. The tentative identities of these compounds are octanal and dodecane/tetradecane respectively. These candidate biomarkers have a potential to enable non-invasive diagnosis of EIB in steroid-naïve children. Trial registration This study is registered in the Netherlands trial register (trial no. NL6087) at 14 February 2017.

Gepubliceerd: Allergy Asthma Clin Immunol. 2021;17(1):121.
Impact factor: 3.406; Q3

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7. **Can the Childhood Physical Activity Questionnaire Be Used to Identify Physical Activity Levels in Children With Asthma?**
van der Kamp MR, Nieuwdorp BW, Thio BJ, Tabak M, Kamps AWA, Hermens HJ, Driessen JMM.

Objective: Children with asthma who are physically active have a better quality of life, emphasizing the importance of activity monitoring and promotion in daily life. The validity of self-reported activity measurements has been questioned in pediatric populations. In this study, we aim to compare the Physical Activity Questionnaire for Children (PAQ-C) with objectively measured PA using accelerometry.
Design: In this comparison study, the pooled dataset of two cross-sectional studies was used, which prospectively home-monitored PA using the alternative self-report PAQ-C questionnaire as well as with the criterion standard accelerometry (Actigraph wGT3X-BT and GT1M). Participants:Ninety children with pediatrician-diagnosed asthma participated in the study.
Main Outcome Measures: Correlation coefficients were calculated to determine the relation between the PAQ-C and accelerometer data. The predictive value of the PAQ-C in differentiating between achieving and failing the recommended daily level of moderate-to-vigorous activity (MVPA) was evaluated with receiver operator characteristic (ROC) analysis.
Results: The results showed weak to moderate correlations of the PAQ-C with the accelerometer data (r = 0.29-0.47). A PAQ-C cutoff of 3.09 showed the best performance on predicting whether the recommended level of MVPA was achieved. With this cutoff, 21 of the 39 children that did achieve their daily MVPA level (53.8% sensitivity) and 33 of the 46 children that did fail their daily MVPA level (71.7% specificity) were correctly classified. A PAQ-C score of 3.5 revealed a negative predictive value of 100% for assessing physical inactivity.
Conclusion: This study revealed a weak relation between the PAQ-C and PA assessed with accelerometry. However, a PAQ-C score of 3.5 or higher might be used

as a low-cost and easy-to-use PA screening tool for ruling out physical inactivity in a portion of the pediatric asthma population.
Clinical Trial Registration: Netherlands Trial Register: Trial NL6087.

Gepubliceerd: Front Pediatr. 2021;9:726695.
Impact factor: 3.418; Q1

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8. **Comparison of inhalation technique with the Diskus and Autohaler in asthmatic children at home**
van der Kolk A, Lammers N, Brusse-Keizer M, van der Palen J, Faber J, Spenkelink-Visser R, Thio BJ.

Objective: Asthma is the most common chronic disease in childhood and anti-inflammatory medication is the cornerstone of treatment. Inhalers are frequently used incorrectly when demonstrated in the hospital, suggesting poor technique at home. We aimed to 1) compare daily inhalation technique with the Diskus and Autohaler in asthmatic children by filming inhalations at home and 2) compare daily inhalation technique with technique demonstrated in the hospital.
Methods: We performed a randomised study in asthmatic children (aged 6-18 years) from the outpatient clinic of Medisch Spectrum Twente hospital (Enschede, The Netherlands) from July 2014 to April 2016. Children received inhalation instructions for the Diskus and Autohaler and were randomised to use one device in the morning and the other in the evening. During the 28-day study period, inhalations were filmed at home and subsequently demonstrated in the hospital. All inhalations were checked for seven critical errors per device.
Results: 636 videos with the Diskus and 663 with the Autohaler were provided by 27 children. The most common critical error in daily life was an incorrect device position during preparation of the Diskus (n=271) and an insufficiently deep inhalation (n=39) using the Autohaler. Percentage of correct days using the Diskus was 44%, compared to 96% with the Autohaler ($p<0.001$). The two most common errors with the Diskus were made at least twice as often at home than in the hospital.
Conclusion: Inhalation technique at home was markedly better with the Autohaler than with the Diskus. Paediatricians should be aware that hospital-based demonstrations can overestimate daily inhalation technique with the Diskus.

Gepubliceerd: ERJ Open Res. 2021;7(2).
Impact factor: 0; NVT

Totale impact factor: 24.144
Gemiddelde impact factor: 3.018

Aantal artikelen 1e, 2e of laatste auteur: 7
Totale impact factor: 24.144
Gemiddelde impact factor: 3.449

Klinische chemie

1. **Comparison of three methods to stabilize bronchoalveolar lavage cells for flowcytometric analysis**
Eidhof HHM, Gratama JW, Mulder AHL.

Background: Flowcytometric analysis of lymphocytes and their subpopulations in bronchoalveolar lavages (BAL) can support the diagnosis of interstitial lung diseases. This analysis should be done within 4 hr after lavage due to rapid cell deterioration. We tested three methods in order to stabilize for at least 28 days the BAL cell populations to allow delayed flowcytometric analysis in order to facilitate external quality assurance (EQA).
Methods: We compared an in-house, dual-step stabilization method for BAL cells with results of two different commercial available stabilization reagents: TransFix(R) and Streck Cell Preservative. All three methods were compared with native BAL cells as reference. BAL samples from six patients were tested on six occasions following stabilization from 1 to 28 days by flow cytometry.
Results: Following stabilization and storage at 4 degrees C, BAL cell suspensions had stable light scatter patterns and lymphocyte subsets. As expected, rapid deterioration of cells was seen with native BAL cells. The stabilized lavages showed more stable counts of WBC and lymphocyte populations with only minor differences found between the three methods.
Conclusions: If analysis of the BAL cells is performed more than 24 hr after the lavage, stabilized BAL cells are superior to native cells. The in-house method can be used for EQA purposes with stability for at least 28 days. The TransFix and Streck methods might be useful for postponed diagnostic analysis of lavage cells but did not meet our 28 days criterion defined needed for EQA purposes.

Gepubliceerd: Cytometry B Clin Cytom. 2021;100(3):377-83.
Impact factor: 3.058; Q2

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2. **A comparison of two LC-MS/MS methods and one radioimmunoassay for the analysis of salivary melatonin**
Karel P, Schutten E, van Faassen M, Wanschers H, Brouwer R, Mulder AL, Kema IP, Reichman LJ, Krabbe JG.

Gepubliceerd: Ann Clin Biochem. 2021;58(4):387-8.
Impact factor: 2.057; Q3

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3. **Performance of commercially-available cholesterol self-tests**
Kurstjens S, Gemen E, Walk S, Njo T, Krabbe J, Gijzen K, Elisen MG, Kusters R.

Background: Hypercholesterolemia (plasma cholesterol concentration ≥5.2 mmol/L) is a risk factor for cardiovascular disease and stroke. Many different cholesterol self-tests are readily available at general stores, pharmacies and web shops. However, there is limited information on their analytical and diagnostic performance.
Methods: We included 62 adult patients who required a lipid panel measurement (cholesterol, high-density lipoprotein (HDL), triglycerides and LDL(calc)) for routine

care. The performance of five different cholesterol self-tests, three quantitative meters (Roche Accutrend Plus, Mission 3-in-1 and Qucare) and two semi-quantitative strip tests (Veroval and Mylan MyTest), was assessed according to the manufacturers' protocol.
Results: The average plasma cholesterol concentration was 5.2 ± 1.2 mmol/L. The mean absolute relative difference (MARD) of the five cholesterol self-tests ranged from 6 ± 5% (Accutrend Plus) to 20 ± 12% (Mylan Mytest). The Accutrend Plus cholesterol meter showed the best diagnostic performance with a 92% sensitivity and 89% specificity. The Qucare and Mission 3-in-1 are able to measure HDL concentrations and can thus provide a cholesterol:HDL ratio. The Passing-Bablok regression analyses for the ratio showed poor performance in both self-tests (Mission 3-in-1: y = 1.62x-1.20; Qucare: y = 0.61x + 1.75). The Accutrend Plus is unable to measure the plasma high-density lipoprotein concentration.
Conclusions/interpretation: The Accutrend Plus cholesterol meter (Roche) had excellent diagnostic and analytic performance. However, several of the commercially-available self-tests had considerably poor accuracy and diagnostic performance and therefore do not meet the required qualifications, potentially leading to erroneous results. Better regulation, standardization and harmonization of cholesterol self-tests is warranted.

Gepubliceerd: Ann Clin Biochem. 2021;58(4):289-96.
Impact factor: 2.057; Q3

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4. **Elevated methaemoglobin in a critically ill patient as a result of hydrogen peroxide exposure: A case study**
Mian P, Krabbe H, van Drie-Pierik R, Silderhuis V, Beishuizen A.

What is known and objective: Formation of methaemoglobinaemia (MetHb) decreases oxygen capacity in the blood, leading to tissue hypoxia. This condition may be acquired following exposure to certain drugs.
Case summary: A critically ill patient with necrotizing fasciitis unexpectedly developed marked and unexplained MetHb (6.7%). Her digital medication list did not reveal the causative factor. However, deeper exploration showed the use of other compounds (acetone, hydrogen peroxide) not routinely visible on the medication list.
What is new and conclusion: Elevated MetHb likely resulted from high-volume hydrogen peroxide 3% exposure. Clinicians should be cautious rinsing large open wounds with hydrogen peroxide. When MetHb is diagnosed, less familiar compounds, usually not on the medication list, should be considered in the differential diagnosis and extensive hetero-anamnesis is mandatory.

Gepubliceerd: J Clin Pharm Ther. 2021;46(5):1473-5.
Impact factor: 2.512; Q3

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5. **Harmonizing light transmission aggregometry in the Netherlands by implementation of the SSC-ISTH guideline**
Munnix ICA, Van Oerle R, Verhezen P, Kuijper P, Hackeng CM, Hopman-Kerkhoff HIJ, Hudig F, Van De Kerkhof D, Leyte A, De Maat MPM, Oude Elferink RFM, Ruinemans-Koerts J, Schoorl M, Slomp J, Soons H, Stroobants A, Van Wijk E, Henskens YMC.

Light transmission aggregometry (LTA) is considered the gold standard method for evaluation of platelet function. However, there are a lot of variation in protocols (pre-analytical procedures and agonist concentrations) and results. The aim of our study was to establish a national LTA protocol, to investigate the effect of standardization and to define national reference values for LTA. The SSC guideline was used as base for a national procedure. Almost all recommendations of the SSC were followed e.g. no adjustment of PRP, citrate concentration of 109 mM, 21 needle gauge, fasting, resting time for whole blood and PRP, centrifugation time, speed and agonists concentrations. LTA of healthy volunteers was measured in a total of 16 hospitals with 5 hospitals before and after standardization. Results of more than 120 healthy volunteers (maximum aggregation %) were collected, with participating laboratories using 4 different analyzers with different reagents. Use of low agonist concentrations showed high variation before and after standardization, with the exception of collagen. For most high agonist concentrations (ADP, collagen, ristocetin, epinephrine and arachidonic acid) variability in healthy subjects decreased after standardization. We can conclude that a standardized Dutch protocol for LTA, based on the SSC guideline, does not result in smaller variability in healthy volunteers for all agonist concentrations.

Gepubliceerd: Platelets. 2021;32(4):516-23.
Impact factor: 3.862; Q2

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6. **Plasma mineral (selenium, zinc or copper) concentrations in the general pregnant population, adjusted for supplement intake, in relation to thyroid function**
Pop V, Krabbe J, Maret W, Rayman M.

The present study reports on first-trimester reference ranges of plasma mineral Se/Zn/Cu concentration in relation to free thyroxine (FT4), thyrotropin (TSH) and thyroid peroxidase antibodies (TPO-Ab), assessed at 12 weeks' gestation in 2041 pregnant women, including 544 women not taking supplements containing Se/Zn/Cu. The reference range (2·5th-97·5th percentiles) in these 544 women was 0·72-1·25 μmol/l for Se, 17·15-35·98 μmol/l for Cu and 9·57-16·41 μmol/l for Zn. These women had significantly lower mean plasma Se concentration (0·94 (sd 0·12) μmol/l) than those (n 1479) taking Se/Zn/Cu supplements (1·03 (sd 0·14) μmol/l; $P < 0·001$), while the mean Cu (26·25 μmol/l) and Zn (12·55 μmol/l) concentrations were almost identical in these sub-groups. Women with hypothyroxinaemia (FT4 below reference range with normal TSH) had significantly lower plasma Zn concentrations than euthyroid women. After adjusting for covariates including supplement intake, plasma Se (negatively), Zn and Cu (positively) concentrations were significantly related to logFT4; Se and Cu (but not Zn) were positively and significantly related to logTSH. Women taking additional Se/Zn/Cu supplements were 1·46 (95 % CI 1·09, 2·04) times less likely to have elevated titres of TPO-Ab at 12 weeks of gestation. We conclude that first-trimester Se reference ranges are influenced by Se-supplement intake, while Cu and Zn ranges are not. Plasma mineral Se/Zn/Cu concentrations are associated with thyroid FT4 and TSH concentrations. Se/Zn/Cu supplement intake affects TPO-Ab status. Future research should focus on the impact of trace mineral status during gestation on thyroid function.

Gepubliceerd: Br J Nutr. 2021;125(1):71-8.

Impact factor: 3.718; Q3

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7. **High throughput surface plasmon resonance imaging method for clinical detection of presence and strength of binding of IgM, IgG and IgA antibodies against SARS-CoV-2 during CoViD-19 infection**
Schasfoort RBM, van Weperen J, van Amsterdam M, Parisot J, Hendriks J, Koerselman M, Karperien M, Mentink A, Bennink M, Krabbe H, Terstappen LW, Mulder AHL.

Surface Plasmon Resonance imaging (SPRi) was used to determine the presence and strength of binding of IgG, IgM and IgA against the Receptor Binding Domain (RBD) of SARS-CoV-2 in sera of 102 CoViD-19 and non-CoViD-19 patients. The SPRi assay simultaneously measures the antibody isotype levels and the strength of binding to the RBD of ultimate 384 patient samples in one run. It turns out that during the course of the disease, the IgG levels and strength of binding increased while generally the IgM and IgA levels go down. Recovered patients all show high strength of binding of the IgG type to the RBD protein. The anti-RBD immunoglobulins SPRi assay provides additional insights in the immune status of patients recovering from CoViD-19. This new high throughput method can be applied for the assessment of the quality of the immune reaction of healthy individuals to SARS-CoV-2 and its mutants in vaccination programs.•Surface Plasmon Resonance imaging is an unprecedented technology for high throughput screening of antibody profiling of CoViD19 patients.•Fingerprinting of isotypes IgM, IgG and IgA can be performed for 384 patients in one run.•An affinity maturation effect was shown for patients recovering from CoViD19.

Gepubliceerd: MethodsX. 2021;8:101432.
Impact factor: 0; NVT

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8. **Presence and strength of binding of IgM, IgG and IgA antibodies against SARS-CoV-2 during CoViD-19 infection**
Schasfoort RBM, van Weperen J, van Amsterdam M, Parisot J, Hendriks J, Koerselman M, Karperien M, Mentink A, Bennink M, Krabbe H, Terstappen LW, Mulder AHL.

Surface Plasmon Resonance imaging (SPRi) was used to determine the presence and strength of binding of IgG, IgM and IgA against the Receptor Binding Domain (RBD) of SARS-CoV-2 in sera of 119 CoViD-19 patients. The SPRi assay measures the antibody isotype levels and the strength of binding to the RBD of ultimate 384 patient samples in one run. It turns out that during the course of the disease, the IgG levels and strength of binding increased while generally the IgM and IgA levels go down. Recovered patients all show high strength of binding of the IgG type to the RBD protein. The anti-RBD immunoglobulins SPRi assay provides additional insights in the immune status of patients recovering from CoViD-19 and this new method can furthermore be applied for the assessment of the quality of the immune reaction of healthy individuals to SARS-CoV-2 in vaccination programs.

Gepubliceerd: Biosens Bioelectron. 2021;183:113165.
Impact factor: 10.618; Q1

9. **Significant interference on specific point-of-care glucose measurements due to high dose of intravenous vitamin C therapy in critically ill patients**
Ten Berge D, Muller W, Beishuizen A, Cornet AD, Slingerland R, Krabbe J.

Gepubliceerd: Clin Chem Lab Med. 2021;59(5):e197-e9.
Impact factor: 3.694; Q2

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10. **Clinical usefulness of drug-laboratory test interaction alerts: a multicentre survey**
van Balveren JA, Verboeket-van de Venne W, Doggen CJM, Cornelissen AS, Erdem-Eraslan L, de Graaf AJ, Krabbe JG, Musson REA, Oosterhuis WP, de Rijke YB, van der Sijs H, Tintu AN, Verheul RJ, Hoedemakers RMJ, Kusters R.

Objectives: Knowledge of possible drug-laboratory test interactions (DLTIs) is important for the interpretation of laboratory test results. Failure to recognize these interactions may lead to misinterpretation, a delayed or erroneous diagnosis, or unnecessary extra diagnostic tests or therapy, which may harm patients. The aim of this multicentre survey was to evaluate the clinical value of DLTI alerts.
Methods: A survey was designed with six predefined clinical cases selected from the clinical laboratory practice with a potential DLTI. Physicians from several departments, including internal medicine, cardiology, intensive care, surgery and geriatrics in six participating hospitals were recruited to fill in the survey. The survey addressed their knowledge of DLTIs, motivation to receive an alert and opinion on the potential influence on medical decision making.
Results: A total of 210 physicians completed the survey. Of these respondents 93% had a positive attitude towards receiving DLTI alerts; however, the reported value differed per case and per respondent's background. In each clinical case, medical decision making was influenced as a consequence of the reported DLTI message (ranging from 3 to 45% of respondents per case).
Conclusions: In this multicentre survey, most physicians stated DLTI messages to be useful in laboratory test interpretation. Medical decision making was influenced by reporting DLTI alerts in each case. Alerts should be adjusted according to the needs and preferences of the receiving physicians.

Gepubliceerd: Clin Chem Lab Med. 2021;59(7):1239-45.
Impact factor: 3.694; Q2

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11. **Mid-Regional Proadrenomedullin and Mid-Regional Proatrial Natriuretic Peptide Clearance Predicts Poor Outcomes Better Than Single Baseline Measurements in Critically Ill Patients With Pneumonia: A Retrospective Cohort Study**
Van Oers J, Krabbe J, Kemna E, Kluiters Y, Vos P, De Lange D, Girbes A, Beishuizen A.

Background: We assessed the ability of baseline and serial measurements of mid-regional proadrenomedullin (MR-proADM) and mid-regional proatrial natriuretic peptide

(MR-proANP) to predict 28-day mortality in critically ill patients with pneumonia compared with Acute Physiological and Chronic Health Evaluation IV (APACHE IV) model and Sequential Organ Failure Assessment (SOFA) score.
Methodology: Biomarkers were collected for the first five days in this retrospective observational cohort study. Biomarker clearance (as a percentage) was presented as biomarker decline in five days. We investigated the relationship between biomarkers and mortality in a multivariable Cox regression model. APACHE IV and SOFA were calculated after 24 hours from intensive care unit admission.
Results: In 153 critically ill patients with pneumonia, 28-day mortality was 26.8%. Values of baseline MR-proADM, MR-proANP, and APACHE IV were significantly higher in 28-day nonsurvivors, but not significantly different for SOFA score. Baseline MR-proADM and MR-proANP, APACHE IV, and SOFA had a low area under the curve in receiver operating characteristics (ROC) curves. No optimal cut-off points could be calculated. Biomarkers and severity scores were divided into tertiles. The highest tertiles baseline MR-proADM and MR-proANP were not significant predictors for 28-day mortality in a multivariable model with age and APACHE IV. SOFA was not a significant predictor in univariable analysis. Clearances of MR-proADM and MR-proANP were significantly higher in 28-day survivors. MR-proADM and MR-proANP clearances had similar low accuracy to identify nonsurvivors in ROC curves and were divided into tertiles. Low clearances of MR-proADM and MR-proANP (first tertiles) were significant predictors for 28-day mortality (hazard ratio [HR]: 2.38; 95% confidence interval [CI]: 1.21-4.70; p = 0.013 and HR: 2.27; 95% CI: 1.16-4.46; p = 0.017) in a model with age and APACHE IV.
Conclusions: MR-proADM and MR-proANP clearance performed better in predicting 28-day mortality in a model with age and APACHE IV compared with single baseline measurements in a mixed population of critically ill with pneumonia.

Gepubliceerd: Cureus. 2021;13(5):e15285.
Impact factor: 0; NVT

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12. **Guideline development for prevention of transfusion-associated graft-versus-host disease: reduction of indications for irradiated blood components after prestorage leukodepletion of blood components**
Wiersum-Osselton JC, Slomp J, Frederik Falkenburg JH, Geltink T, van Duijnhoven HLP, Netelenbos T, Schipperus MR.

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, commonly fatal complication of transfusion preventable by irradiation of blood units. The revision of the Dutch transfusion guideline addressed the question whether irradiation is still necessary if blood components are prestorage leukodepleted. We searched for published cases of TA-GVHD following transfusion of prestorage leukodepleted blood and through contacting haemovigilance systems. Six presumed cases were found, dating from 1998 to 2013. Four out of six patients had received one or more non-irradiated units despite recognised indications for irradiated blood components. In the countries providing information, over 50 million prestorage leukodepleted, non-irradiated, non-pathogen-reduced cellular components were transfused in a 10-year period. Potential benefits of lifting indications for irradiation were considered. These include reduced irradiation costs (euro 1.5 million annually in the Netherlands) and less donor exposure for neonates. Findings were presented in an invitational expert

meeting. Recommendations linked to human leukocyte antigen similarity between donor and recipient or intra-uterine transfusion were left unchanged. Indications linked to long-lasting deep T-cell suppression were defined with durations of 6 or 12 months after end of treatment (e.g. autologous or allogeneic stem cell transplantation). Need for continued alertness to TA-GVHD and haemovigilance reporting of erroneous non-irradiated transfusions was emphasised.

Gepubliceerd: Br J Haematol. 2021;195(5):681-8.
Impact factor: 6.998; Q1

Totale impact factor: 42.268
Gemiddelde impact factor: 3.522

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 32.655
Gemiddelde impact factor: 3.628

Klinische farmacie

1. **Clinically relevant potential drug-drug interactions in intensive care patients: A large retrospective observational multicenter study**

Bakker T, Abu-Hanna A, Dongelmans DA, Vermeijden WJ, Bosman RJ, de Lange DW, Klopotowska JE, de Keizer NF, Hendriks S, Ten Cate J, Schutte PF, van Balen D, Duyvendak M, Karakus A, Sigtermans M, Kuck EM, Hunfeld NGM, van der Sijs H, de Feiter PW, Wils EJ, Spronk PE, van Kan HJM, van der Steen MS, Purmer IM, Bosma BE, Kieft H, van Marum RJ, de Jonge E, Beishuizen A, Movig K, Mulder F, Franssen EJF, van den Bergh WM, Bult W, Hoeksema M, Wesselink E.

Purpose: Potential drug-drug interactions (pDDIs) may harm patients admitted to the Intensive Care Unit (ICU). Due to the patient's critical condition and continuous monitoring on the ICU, not all pDDIs are clinically relevant. Clinical decision support systems (CDSSs) warning for irrelevant pDDIs could result in alert fatigue and overlooking important signals. Therefore, our aim was to describe the frequency of clinically relevant pDDIs (crpDDIs) to enable tailoring of CDSSs to the ICU setting.
Materials & methods: In this multicenter retrospective observational study, we used medication administration data to identify pDDIs in ICU admissions from 13 ICUs. Clinical relevance was based on a Delphi study in which intensivists and hospital pharmacists assessed the clinical relevance of pDDIs for the ICU setting.
Results: The mean number of pDDIs per 1000 medication administrations was 70.1, dropping to 31.0 when considering only crpDDIs. Of 103,871 ICU patients, 38% was exposed to a crpDDI. The most frequently occurring crpDDIs involve QT-prolonging agents, digoxin, or NSAIDs.
Conclusions: Considering clinical relevance of pDDIs in the ICU setting is important, as only half of the detected pDDIs were crpDDIs. Therefore, tailoring CDSSs to the ICU may reduce alert fatigue and improve medication safety in ICU patients.

Gepubliceerd: J Crit Care. 2021;62:124-30.
Impact factor: 3.425; Q2

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2. **Modelling Tools to Characterize Acetaminophen Pharmacokinetics in the Pregnant Population**

Brookhuis SAM, Allegaert K, Hanff LM, Lub-de Hooge MN, Dallmann A, Mian P.

This review describes acetaminophen pharmacokinetics (PK) throughout pregnancy, as analyzed by three methods (non-compartmental analyses (NCA), population PK, and physiologically based PK (PBPK) modelling). Eighteen studies using NCA were reported in the scientific literature. These studies reported an increase in the volume of distribution (3.5-60.7%) and an increase in the clearance (36.8-84.4%) of acetaminophen in pregnant women compared to non-pregnant women. Only two studies using population PK modelling as a technique were available in the literature. The largest difference in acetaminophen clearance (203%) was observed in women at delivery compared to non-pregnant women. One study using the PBPK technique was found in the literature. This study focused on the formation of metabolites, and the toxic metabolite N-acetyl-p-benzoquinone imine was the highest in the first trimester, followed by the second and third trimester, compared with non-pregnant women. In conclusion, this review gave an overview on acetaminophen PK changes in pregnancy.

Also, knowledge gaps, such as fetal and placenta PK parameters, have been identified, which should be explored further before dosing adjustments can be suggested on an evidence-based basis.

Gepubliceerd: Pharmaceutics. 2021;13(8).
Impact factor: 6.321; Q1

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3. **Impact of enantiomer-specific changes in pharmacokinetics between infants and adults on the target concentration of racemic ketorolac: A pooled analysis**
Cloesmeijer ME, van Esdonk MJ, Lynn AM, Smits A, Tibboel D, Daali Y, Olkkola KT, Allegaert K, Mian P.

Aims: Ketorolac is a nonsteroidal anti-inflammatory racemic drug with analgesic effects only attributed to its S-enantiomer. The aim of this study is to quantify enantiomer-specific maturational pharmacokinetics (PK) of ketorolac and investigate if the contribution of both enantiomers to the total ketorolac concentration remains equal between infants and adults or if a change in target racemic concentration should be considered when applied to infants.
Methods: Data were pooled from 5 different studies in adults, children and infants, with 1020 plasma concentrations following single intravenous ketorolac administration. An allometry-based enantiomer-specific population PK model was developed with NONMEM 7.3. Simulations were performed in typical adults and infants to investigate differences in S- and R-ketorolac exposure.
Results: S- and R-ketorolac PK were best described with a 3- and a 2-compartment model, respectively. The allometry-based PK parameters accounted for changes between populations. No maturation function of ketorolac clearance could be identified. All model parameters were estimated with adequate precision (relative standard error <50%). Single dose simulations showed that a previously established analgesic concentration at half maximal effect in adults of 0.37 mg/L, had a mean S-ketorolac concentration of 0.057 mg/L, but a mean S-ketorolac concentration of 0.046 mg/L in infants. To match the effective adult S-ketorolac-concentration (0.057 mg/L) in typical infants, the EC(50-racemic) should be increased to 0.41 mg/L.
Conclusion: Enantiomer-specific changes in ketorolac PK yield different concentrations and S- and R-ketorolac ratios between infants and adults at identical racemic concentrations. These PK findings should be considered when studies on maturational pharmacodynamics are considered.

Gepubliceerd: Br J Clin Pharmacol. 2021;87(3):1443-54.
Impact factor: 4.340; Q2

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4. **Study protocol for a randomised controlled trial on the effect of local analgesia for pain relief after minimal invasive sacroiliac joint fusion: the ARTEMIS study**
Hermans SMM, Nellensteijn JM, van Santbrink H, Knoef R, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

Introduction: Chronic lower back pain is a common report in the general population. A dysfunctional sacroiliac joint (SIJ) is estimated to be responsible for one in five patients with lower back pain. Minimally invasive sacroiliac joint fusion (MISJF) is a

surgical procedure to treat SIJ dysfunction. During the procedure, the SIJ is stabilised by implants inserted percutaneously under fluoroscopy guidance. Postoperatively, patients often report a lot of pain, which contributes to patients taking high doses of painkillers (opioids for example,) and preventing early mobilisation. In several orthopaedic procedures, intraoperative infiltration of the wound bed results in decreased consumption of analgesics, earlier mobilisation and shorter hospitalisation time. The aim of this study is to investigate the effectiveness of intraoperative SIJ infiltration with analgesia in reducing postoperative pain after MISJF.
Methods and analysis: We will perform a two-centre, prospective, double-blind, randomised controlled trial to determine whether SIJ infiltration with 1.5-5 cc bupivacaine 0.50% is superior to 1.5-5 cc placebo (NaCl 0.9%) in reducing postoperative pain in patients after MISJF, and to determine whether bupivacaine significantly reduces opioid use in the direct postoperative period. Patients will be randomised with 1:1 allocation for either bupivacaine (intervention) or placebo SIJ infiltration. Postoperative pain will be measured by the Visual Analogue Scale pain score at entry and exit recovery, 2, 4, 6, 24 and 48 hours postoperatively.
Ethics and dissemination: This is the first trial that investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% in reducing postoperative pain after MISJF. If intraoperative SIJ infiltration with bupivacaine 0.50% proves to be effective, this might have important clinical implications, such as postoperative analgesics (opioids for example,) consumption, earlier mobilisation and potentially shorter hospitalisation time.
Trial registration number: NL9151.

Gepubliceerd: BMJ Open. 2021;11(12):e056204.
Impact factor: 2.692; Q2

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5. **Switching TNFα inhibitors: Patterns and determinants**
Meijboom RW, Gardarsdottir H, Becker ML, de Groot MCH, Movig KLL, Kuijvenhoven J, Egberts TCG, Leufkens HGM, Giezen TJ.

The aim of this study was to assess switching patterns and determinants for switching in patients initiating TNFα inhibitor (TNFα-i) treatment. Patients were included who started TNFα-i treatment between July 1, 2012 and December 31, 2017, from three Dutch hospitals, and were diagnosed with rheumatic diseases (RD), inflammatory bowel disease (IBD), or psoriasis. Outcomes were switching, defined as initiating another biological; switching patterns including multiple switches until the end of follow-up; determinants for first switch, assessed using multivariate logistic regression. A total of 2228 patients were included (median age 43.3 years, 57% female), of which 52% (n = 1155) received TNFα-i for RD, 43% (n = 967) for IBD, and 5% (n = 106) for psoriasis. About 16.6% of RD patients, 14.5% of IBD patients, and 16.0% of psoriasis patients switched at least once, mainly to another TNFα-i. TNFα-i dose escalation (OR 13.78, 95% CI 1.40-135.0) and high-dose corticosteroids initiation (OR 3.62, 95% CI 1.10-12.15) were determinants for switching in RD patients. TNFα-i dose escalation (OR 8.22, 95% CI 3.76-17.93), immunomodulator initiation/dose escalation (OR 2.13, 95% CI 1.04-4.34), high-dose corticosteroids initiation (OR 6.91, 95% CI 2.81-17.01) and serum concentration measurement (OR 5.44, 95% CI 2.74-10.79) were determinants for switching in IBD patients. Switching biological treatment occurred in about one in six patients. RD patients with TNFα-i dose escalation and/or high-dose

corticosteroids initiation were more likely to switch. IBD patients with TNFα-i or immunomodulator initiation/dose escalation, high-dose corticosteroids initiation or serum concentration measurement were more likely to switch. These findings might help clinicians anticipating switching in TNFα-i treatment.

Gepubliceerd: Pharmacol Res Perspect. 2021;9(4):e00843.
Impact factor: 2.794; Q3

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6. **Elevated methaemoglobin in a critically ill patient as a result of hydrogen peroxide exposure: A case study**
Mian P, Krabbe H, van Drie-Pierik R, Silderhuis V, Beishuizen A.

What is known and objective: Formation of methaemoglobinaemia (MetHb) decreases oxygen capacity in the blood, leading to tissue hypoxia. This condition may be acquired following exposure to certain drugs.
Case summary: A critically ill patient with necrotizing fasciitis unexpectedly developed marked and unexplained MetHb (6.7%). Her digital medication list did not reveal the causative factor. However, deeper exploration showed the use of other compounds (acetone, hydrogen peroxide) not routinely visible on the medication list.
What is new and conclusion: Elevated MetHb likely resulted from high-volume hydrogen peroxide 3% exposure. Clinicians should be cautious rinsing large open wounds with hydrogen peroxide. When MetHb is diagnosed, less familiar compounds, usually not on the medication list, should be considered in the differential diagnosis and extensive hetero-anamnesis is mandatory.

Gepubliceerd: J Clin Pharm Ther. 2021;46(5):1473-5.
Impact factor: 2.512; Q3

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7. **Relatively mild symptoms after chronic overdose with a double-dose encorafenib: a case report**
Mian P, Meussen E, Piersma D, Lankheet NAG.

Encorafenib (Braftovi) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with binimetinib (Mektovi). According to the product label of encorafenib, there are no specific treatment recommendations in case of an overdose. We report on a 63-year-old man who ingested a double dose (900 mg) of encorafenib for 16 days. He developed overall minor chronic overdose symptoms such as nausea and vomiting grade 1 and muscle pain. Based on the most occurring adverse events of encorafenib, liver values, kidney function parameters and QTc interval were measured. Kidney function parameters were normal, whereas liver values were slightly increased (grade 1) and QTc slightly prolonged. The plasma concentration 3 h after the last dose was 2110 ng/mL. We describe the course of a case with a chronic overdose during 16 days of the double dose of encorafenib as well as the followed approach, which could be taken into account when observing an encorafenib overdose. Providing information in times of Covid-19 is challenging, but remains necessary for good clinical care.

Gepubliceerd: Anticancer Drugs. 2021;32(5):589-91.

Impact factor: 2.248; Q4

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8. **Mechanistic Coupling of a Novel in silico Cotyledon Perfusion Model and a Physiologically Based Pharmacokinetic Model to Predict Fetal Acetaminophen Pharmacokinetics at Delivery**
Mian P, Nolan B, van den Anker JN, van Calsteren K, Allegaert K, Lakhi N, Dallmann A.

Little is known about placental drug transfer and fetal pharmacokinetics despite increasing drug use in pregnant women. While physiologically based pharmacokinetic (PBPK) models can help in some cases to shed light on this knowledge gap, adequate parameterization of placental drug transfer remains challenging. A novel in silico model with seven compartments representing the ex vivo cotyledon perfusion assay was developed and used to describe placental transfer and fetal pharmacokinetics of acetaminophen. Unknown parameters were optimized using observed data. Thereafter, values of relevant model parameters were copied to a maternal-fetal PBPK model and acetaminophen pharmacokinetics were predicted at delivery after oral administration of 1,000 mg. Predictions in the umbilical vein were evaluated with data from two clinical studies. Simulations from the in silico cotyledon perfusion model indicated that acetaminophen accumulates in the trophoblasts; simulated steady state concentrations in the trophoblasts were 4.31-fold higher than those in the perfusate. The whole-body PBPK model predicted umbilical vein concentrations with a mean prediction error of 24.7%. Of the 62 concentration values reported in the clinical studies, 50 values (81%) were predicted within a 2-fold error range. In conclusion, this study presents a novel in silico cotyledon perfusion model that is structurally congruent with the placenta implemented in our maternal-fetal PBPK model. This allows transferring parameters from the former model into our PBPK model for mechanistically exploring whole-body pharmacokinetics and concentration-effect relationships in the placental tissue. Further studies should investigate acetaminophen accumulation and metabolism in the placenta as the former might potentially affect placental prostaglandin synthesis and subsequent fetal exposure.

Gepubliceerd: Front Pediatr. 2021;9:733520.
Impact factor: 3.418; Q1

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9. **Acute teriflunomide overdose with relatively mild symptoms: A case report**
Mian P, van Haaften WT, Assink M, van Drie-Pierik R.

What is know and objective: Teriflunomide is indicated for the treatment of adult patients with relapsing-remitting multiple sclerosis.
Case summary: We present a rare intoxication with a high dose (672 mg) of teriflunomide. According to its product label, the only known treatment is the administration of colestyramine and activated carbon (charcoal). No serious adverse events occurred during the time the patient was admitted (<24 h). No long-term overdose-related symptoms or complaints were reported.
What is new and conclusion: The fact that after the acute overdose both adverse events and laboratory parameters were acceptable, prescribing colestyramine and activated carbon, as well as monitoring of laboratory parameters such as full blood

count, liver and kidney values and QTc, seems sufficient during the early stage (<24 h after intake) of teriflunomide overdose.

Gepubliceerd: J Clin Pharm Ther. 2021;46(6):1784-6.
Impact factor: 2.512; Q3

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10. **The Impact of Non-dopaminergic Medication on Quality of Life in Parkinson's Disease**
Oonk NGM, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background and objectives: Quality of life (QoL) in Parkinson's disease (PD) depends on multiple factors. Due to PD treatment and accompanying, age-related or independent comorbidities, pill burden is often high. The relation of QoL and pharmacotherapy for comorbidities in PD has not been widely studied. This study investigated if and to what extent non-dopaminergic drugs are related to QoL in PD. Second, the impact of demographics and non-motor symptoms were evaluated. A better understanding of the impact of different non-dopaminergic drugs and polypharmacy on QoL will have added value in selecting appropriate (medication) interventions.
Methods: In a cross-sectional analysis, medication prescription data of 209 PD patients were analyzed and grouped according to the Rx-Risk comorbidity index. QoL was measured using the PDQ-39 questionnaire. Non-motor symptoms were analyzed with the Non-Motor Symptoms questionnaire. Independent factors associated with a reduced QoL were identified with a multivariate linear regression analysis.
Results: Non-dopaminergic drugs, subdivided into Rx-Risk comorbidity categories, were not associated with reduced QoL, except for the use of anti-epileptic drugs. However, using more daily non-dopaminergic drugs was also negatively associated with QoL, as well as female sex, increased PD severity, and more non-motor symptoms. Contraindicated non-dopaminergic medication was barely prescribed (0.4%).
Conclusion: Non-dopaminergic drugs are frequently prescribed, and higher numbers are associated with impaired QoL in PD. However, when divided in drug types, only anti-epileptic drugs were negatively associated with QoL. In these patients, physicians might improve QoL by further optimizing the condition it was prescribed for (e.g., pain or anxiety), or managing of side effects.
Trial registrattion: Netherlands Trial Register; NL4360.

Gepubliceerd: Clin Drug Investig. 2021;41(9):809-16.
Impact factor: 2.859; Q3

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11. **Population Pharmacokinetics and Bayesian Dose Adjustment to Advance TDM of Anti-TB Drugs**
Sturkenboom MGG, Märtson AG, Svensson EM, Sloan DJ, Dooley KE, van den Elsen SHJ, Denti P, Peloquin CA, Aarnoutse RE, Alffenaar JC.

Tuberculosis (TB) is still the number one cause of death due to an infectious disease. Pharmacokinetics and pharmacodynamics of anti-TB drugs are key in the optimization

of TB treatment and help to prevent slow response to treatment, acquired drug resistance, and adverse drug effects. The aim of this review was to provide an update on the pharmacokinetics and pharmacodynamics of anti-TB drugs and to show how population pharmacokinetics and Bayesian dose adjustment can be used to optimize treatment. We cover aspects on preclinical, clinical, and population pharmacokinetics of different drugs used for drug-susceptible TB and multidrug-resistant TB. Moreover, we include available data to support therapeutic drug monitoring of these drugs and known pharmacokinetic and pharmacodynamic targets that can be used for optimization of therapy. We have identified a wide range of population pharmacokinetic models for first- and second-line drugs used for TB, which included models built on NONMEM, Pmetrics, ADAPT, MWPharm, Monolix, Phoenix, and NPEM2 software. The first population models were built for isoniazid and rifampicin; however, in recent years, more data have emerged for both new anti-TB drugs, but also for defining targets of older anti-TB drugs. Since the introduction of therapeutic drug monitoring for TB over 3 decades ago, further development of therapeutic drug monitoring in TB next steps will again depend on academic and clinical initiatives. We recommend close collaboration between researchers and the World Health Organization to provide important guideline updates regarding therapeutic drug monitoring and pharmacokinetics/pharmacodynamics.

Gepubliceerd: Clin Pharmacokinet. 2021;60(6):685-710.
Impact factor: 6.447; Q1

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12. **Tricyclic antidepressants for major depressive disorder: a comprehensive evaluation of current practice in the Netherlands**
Vos CF, Aarnoutse RE, Op de Coul MJM, Spijker J, Groothedde-Kuyvenhoven MM, Mihaescu R, Wessels-Basten SJW, Rovers JJE, Ter Hark SE, Schene AH, Hulscher M, Janzing JGE.

Background: Traditionally tricyclic antidepressants (TCAs) have an important place in treatment of major depressive disorder (MDD). Today, often other antidepressant medications are considered as first step in the pharmacological treatment of MDD, mainly because they are associated with less adverse effects, whereby the position of TCAs appears unclear. In this study we aimed to examine the current practice of TCAs in treatment of unipolar MDD.
Methods: A mixed methods approach was applied. First, a selection of leading international and national guidelines was reviewed. Second, actual TCA prescription was examined by analyzing health records of 75 MDD patients treated with the TCAs nortriptyline, clomipramine or imipramine in different centers in the Netherlands. Third, promotors and barriers influencing the choice for TCAs and dosing strategies were explored using semi-structured interviews with 24 Dutch psychiatrists.
Results: Clinical practice guidelines were sometimes indirective and inconsistent with each other. Health records revealed that most patients (71%) attained therapeutic plasma concentrations within two months of TCA use. Patients who achieved therapeutic plasma concentrations reached them on average after 19.6 days (SD 10.9). Both health records and interviews indicated that therapeutic nortriptyline concentrations were attained faster compared to other TCAs. Various factors were identified influencing the choice for TCAs and dosing by psychiatrists.

Conclusions: Guideline recommendations and clinical practice regarding TCA prescription for MDD vary. To increase consistency in clinical practice we recommend development of an up-to-date guideline integrating selection and dosing of TCAs, including the roles of therapeutic drug monitoring and pharmacogenetics. Such a guideline is currently lacking and would contribute to optimal TCA treatment, whereby efficacy and tolerability may be increased.

Gepubliceerd: BMC Psychiatry. 2021;21(1):481.
Impact factor: 3.630; Q2

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13. **Impact of malnourishment on the pharmacokinetics of acetaminophen and susceptibility to acetaminophen hepatotoxicity**
Zillen D, Movig KLL, Kant G, Masselink JB, Mian P.

Background: Acetaminophen hepatotoxicity is thought to be primarily caused by formation of the specific reactive metabolite N-acetyl-para-benzo-quinone imine (NAPQI). Malnourished individuals are at increased risk of acetaminophen-related hepatotoxicity. We report a case of low acetaminophen clearance in a severely underweight young woman, and elaborate on the possible effects of malnutrition on the total clearance of acetaminophen as well as on the separate contributions of the different metabolic pathways.
Case report: An 18-year-old Caucasian woman weighing 43 kg with a history of eating disorder-related hospital admissions presented at the emergency department after having ingested 33 tablets of acetaminophen 500 mg two hours earlier. She then received intravenous N-acetylcysteine for 33 h. Nine hours after ingestion, the acetaminophen elimination half-life (t½) was estimated to be >100 h.
Discussion: While decreased total acetaminophen clearance (twofold) due to malnutrition has been reported in literature, the extremely low clearance in this specific patient cannot be explained. Malnourished individuals generally have reduced antioxidant reserves, coinciding with a shift in metabolic routes toward oxidative metabolism. This may result in increased formation of NAPQI and reduced neutralizing capacity, thereby increasing the risk of acetaminophen-induced hepatotoxicity. Evidence for this observation can be found in animal and to a lesser extent in human studies.

Gepubliceerd: Clin Case Rep. 2021;9(11):e04611.
Impact factor: 0; NVT

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14. **Verkorting van de huidige 21-uurs-behandeling met N-acetylcysteïne - Meer kennis nodig voor 12-uurs-regime bij overdosering van paracetamol**
Mian P, Movig K, Touwen DJ, Sturkenboom MGG.

(Inter)nationaal is een discussie gaande of de kortere behandelingsduur (12 in plaats van 21 uur) met N-acetylcysteine, bij patiënten met een overdosering paracetamol, effectief en veilig is. Uitkomsten van een internationale studie zijn veelbelovend. Het is nu zaak deze verkorte behandeling ook toepasbaar te maken voor de Nederlandse situatie.

Gepubliceerd: Pharmaceutisch Weekblad, 156(12), 20-23
Impact factor: 0; NVT

Totale impact factor: 43.198
Gemiddelde impact factor: 3.086

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 24.210
Gemiddelde impact factor: 2.690

Klinische fysica

1. **Tunable blood oxygenation in the vascular anatomy of a semi-anthropomorphic photoacoustic breast phantom**
Dantuma M, Kruitwagen S, Ortega-Julia J, Pompe van Meerdervoort RP, Manohar S.

Significance: Recovering accurate oxygenation estimations in the breast with quantitative photoacoustic tomography (QPAT) is not straightforward. Accurate light fluence models are required, but the unknown ground truth of the breast makes it difficult to validate them. Phantoms are often used for the validation, but most reported phantoms have a simple architecture. Fluence models developed in these simplistic objects are not accurate for application on the complex tissues of the breast.
Aim: We present a sophisticated breast phantom platform for photoacoustic (PA) and ultrasound (US) imaging in general, and specifically for QPAT. The breast phantom is semi-anthropomorphic in distribution of optical and acoustic properties and contains wall-less channels with blood.
Approach: 3D printing approaches are used to develop the solid 3D breast phantom from custom polyvinyl chloride plastisol formulations and additives for replicating the tissue optical and acoustic properties. A flow circuit was developed to flush the channels with bovine blood with a controlled oxygen saturation level. To showcase the phantom's functionality, PA measurements were performed on the phantom with two oxygenation levels. Image reconstructions with and without fluence compensation from Monte Carlo simulations were analyzed for the accuracy of oxygen saturation estimations.
Results: We present design aspects of the phantom, demonstrate how it is developed, and present its breast-like appearance in PA and US imaging. The oxygen saturations were estimated in two regions of interest with and without using the fluence models. The fluence compensation positively influenced the SO2 estimations in all cases and confirmed that highly accurate fluence models are required to minimize estimation errors.
Conclusions: This phantom allows studies to be performed in PA in carefully controlled laboratory settings to validate approaches to recover both qualitative and quantitative features sought after in in-vivo studies. We believe that testing with phantoms of this complexity can streamline the transition of new PA technologies from the laboratory to studies in the clinic.

Gepubliceerd: J Biomed Opt. 2021;26(3).
Impact factor: 3.170; Q2

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2. **Suite of 3D test objects for performance assessment of hybrid photoacoustic-ultrasound breast imaging systems**
Dantuma M, Kruitwagen SC, Weggemans MJ, Op't Root T, Manohar S.

Significance: During the development and early testing phases of new photoacoustic (PA) breast imaging systems, several choices need to be made in aspects of system design and measurement sequences. Decision-making can be complex for state-of-the-art systems such as 3D hybrid photoacoustic-ultrasound (PA-US) breast imagers intended for multispectral quantitative imaging. These systems have a large set of design choices and system settings that affect imaging performance in different ways

and often require trade-offs. Decisions have to be made carefully as they can strongly influence the imaging performance.
Aim: A systematic approach to assess the influence of various choices on the imaging performance in carefully controlled laboratory situations is crucial before starting with human studies. Test objects and phantoms are used for first imaging studies, but most reported structures have a 2D geometry and are not suitable to assess all the image quality characteristics (IQCs) of 3D hybrid PA-US systems.
Approach: Our work introduces a suite of five test objects designed for hybrid PA-US systems with a 3D detection aperture. We present the test object designs and production protocols and explain how they can be used to study various performance measures. To demonstrate the utility of the developed objects, measurements are made with an existing tomographic PA system.
Results: Two test objects were developed for measurements of the US detectors' impulse responses and light distribution on the breast surface. Three others were developed to assess image quality and quantitative accuracy of the PA and US modes. Three of the five objects were imaged to demonstrate their use.
Conclusions: The developed test objects allow one to study influences of various choices in design and system settings. With this, IQCs can be assessed as a function of measurement sequence settings for the PA and US modes in a controlled way. Systematic studies and measurements using these objects will help to optimize various system settings and measurement protocols in laboratory situations before embarking on human studies.

Gepubliceerd: J Biomed Opt. 2021;27(7).
Impact factor: 3.170; Q2

Totale impact factor: 6.340
Gemiddelde impact factor: 3.170

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 6.340
Gemiddelde impact factor: 3.170

KNO

1. **A complete magnetic sentinel lymph node biopsy procedure in oral cancer patients: A pilot study**

Nieuwenhuis ER, Kolenaar B, van Bemmel AJM, Hof JJ, van Baarlen J, Christenhusz A, Pouw JJ, Ten Haken B, Alic L, de Bree R.

Objectives: To assess the feasibility and merits of a complete magnetic approach for a sentinel lymph node biopsy (SLNB) procedure in oral cancer patients.
Materials and methods: This study included ten oral cancer patients (stage cT1-T2N0M0) scheduled for elective neck dissection (END). Superparamagnetic iron oxide nanoparticles (SPIO) were administered peritumorally prior to surgery. A preoperative MRI was acquired to identify lymph nodes (LNs) with iron uptake. A magnetic detector was used to identify magnetic hotspots prior, during, and after the SLNB procedure. The resected sentinel LNs (SLNs) were evaluated using step-serial sectioning, and the neck dissection specimen was assessed by routine histopathological examination. A postoperative MRI was acquired to observe any residual iron.
Results: Of ten primary tumors, eight were located in the tongue, one floor-of-mouth (FOM), and one tongue-FOM transition. SPIO injections were experienced as painful by nine patients, two of whom developed a tongue swelling. In eight patients, magnetic SLNs were successfully detected and excised during the magnetic SLNB procedure. During the END procedure, additional magnetic SLNs were identified in three patients. Histopathology confirmed iron deposits in sinuses of excised SLNs. Three SLNs were harboring metastases, of which one was identified only during the END procedure. The END specimens revealed no further metastases.
Conclusion: A complete magnetic SLNB procedure was successfully performed in eight of ten patients (80% success rate), therefore the procedure seems feasible. Recommendations for further investigation are made including: use of anesthetics, magnetic tracer volume, planning preoperative MRI, comparison to conventional technique and follow-up.

Gepubliceerd: Oral Oncol. 2021;121:105464.
Impact factor: 5.337; Q1

Totale impact factor: 5.337
Gemiddelde impact factor: 5.337

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 5.337
Gemiddelde impact factor: 5.337

Longgeneeskunde

1. **Validation of a Novel Compact System for the Measurement of Lung Volumes**
Berger KI, Adam O, Dal Negro RW, Kaminsky DA, Shiner RJ, Burgos F, de Jongh FHC, Cohen I, Fredberg JJ.

Background: Current techniques for measuring absolute lung volumes rely on bulky and expensive equipment and are complicated to use for the operator and the patient. A novel method for measurement of absolute lung volumes, the MiniBox method, is presented.
Research question: Across a population of patients and healthy participants, do values for total lung capacity (TLC) determined by the novel compact device (MiniBox, PulmOne Advanced Medical Devices, Ltd.) compare favorably with measurements determined by traditional whole body plethysmography? STUDY **design and methods:** A total of 266 participants (130 men) and respiratory patients were recruited from five global centers (three in Europe and two in the United States). The study population comprised individuals with obstructive (n = 197) and restrictive (n = 33) disorders as well as healthy participants (n = 36). TLC measured by conventional plethysmography (TLC(Pleth)) was compared with TLC measured by the MiniBox (TLC(MB)).
Results: TLC values ranged between 2.7 and 10.9 L. The normalized root mean square difference (NSD) between TLC(Pleth) and TLC(MB) was 7.0% in healthy participants. In obstructed patients, the NSD was 7.9% in mild obstruction and 9.1% in severe obstruction. In restricted patients, the NSD was 7.8% in mild restriction and 13.9% in moderate and severe restriction. No significant differences were found between TLC values obtained by the two measurement techniques. Also no significant differences were found in results obtained among the five centers.
Interpretation: TLC as measured by the novel MiniBox system is not significantly different from TLC measured by conventional whole body plethysmography, thus validating the MiniBox method as a reliable method to measure absolute lung volumes.

Gepubliceerd: Chest. 2021;159(6):2356-65.
Impact factor: 9.410; Q1

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2. **Stability in eosinophil categorisation during subsequent severe exacerbations of COPD**
Citgez E, van der Palen J, van der Valk P, Kerstjens HAM, Brusse-Keizer M.

Background: The blood eosinophil count has been shown to be a promising biomarker for establishing personalised treatment strategies to reduce corticosteroid use, either inhaled or systemic, in chronic obstructive pulmonary disease (COPD). Eosinophil levels seem relatively stable over time in stable state, but little is known whether this is also true in subsequent severe acute exacerbations of COPD (AECOPD).
Aims and objectives: To determine the stability in eosinophil categorisation between two subsequent severe AECOPDs employing frequently used cut-off levels.
Methods: During two subsequent severe AECOPDs, blood eosinophil counts were determined at admission to the hospital in 237 patients in the Cohort of Mortality and Inflammation in COPD Study. The following four cut-off levels were analysed: absolute counts of eosinophils ≥0.2×10⁹/L (200 cells/μL) and ≥0.3×10⁹/L (300 cells/μL) and

relative eosinophil percentage of ≥2% and ≥3% of total leucocyte count. Categorisations were considered stable if during the second AECOPD their blood eosinophil status led to the same classification: eosinophilic or not.
Results: Depending on the used cut-off, the overall stability in eosinophil categorisation varied between 70% and 85% during two subsequent AECOPDs. From patients who were eosinophilic at the first AECOPD, 34%-45% remained eosinophilic at the subsequent AECOPD, while 9%-21% of patients being non-eosinophilic at the first AECOPD became eosinophilic at the subsequent AECOPD.
Conclusions: The eosinophil variability leads to category changes in subsequent AECOPDs, which limits the eosinophil categorisation stability. Therefore, measurement of eosinophils at each new exacerbation seems warranted.

Gepubliceerd: BMJ Open Respir Res. 2021;8(1).
Impact factor: 0; NVT

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3. **Real-world outcomes versus clinical trial results of immunotherapy in stage IV non-small cell lung cancer (NSCLC) in the Netherlands**
Cramer-van der Welle CM, Verschueren MV, Tonn M, Peters BJM, Schramel F, Klungel OH, Groen HJM, van de Garde EMW, Santeon NSCLC Study Group, includes Schouwink JH.

This study aims to assess how clinical outcomes of immunotherapy in real-world (effectiveness) correspond to outcomes in clinical trials (efficacy) and to look into factors that might explain an efficacy-effectiveness (EE) gap. All patients diagnosed with stage IV non-small cell lung cancer (NSCLC) in 2015-2018 in six Dutch large teaching hospitals (Santeon network) were identified and followed-up from date of diagnosis until death or end of data collection. Progression-free survival (PFS) and overall survival (OS) from first-line (1L) pembrolizumab and second-line (2L) nivolumab were compared with clinical trial data by calculating hazard ratios (HRs). From 1950 diagnosed patients, 1005 (52%) started with any 1L treatment, of which 83 received pembrolizumab. Nivolumab was started as 2L treatment in 141 patients. For both settings, PFS times were comparable between real-world and trials (HR 1.08 (95% CI 0.75-1.55), and HR 0.91 (95% CI 0.74-1.14), respectively). OS was significantly shorter in real-world for 1L pembrolizumab (HR 1.55; 95% CI 1.07-2.25). Receiving subsequent lines of treatment was less frequent in real-world compared to trials. There is no EE gap for PFS from immunotherapy in patients with stage IV NSCLC. However, there is a gap in OS for 1L pembrolizumab. Fewer patients proceeding to a subsequent line of treatment in real-world could partly explain this.

Gepubliceerd: Sci Rep. 2021;11(1):6306.
Impact factor: 4.380; Q1

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4. **A contrast-enhanced-CT-based classification tree model for classifying malignancy of solid lung tumors in a Chinese clinical population**
Cui X, Heuvelmans MA, Sidorenkov G, Zhao Y, Fan S, Groen HJM, Dorrius MD, Oudkerk M, de Bock GH, Vliegenthart R, Ye Z.

Background: To develop and validate a contrast-enhanced CT based classification tree model for classifying solid lung tumors in clinical patients into malignant or benign.
Methods: Between January 2015 and October 2017, 827 pathologically confirmed solid lung tumors (487 malignant, 340 benign; median size, 27.0 mm, IQR 18.0-39.0 mm) from 827 patients from a dedicated Chinese cancer hospital were identified. Nodules were divided randomly into two groups, a training group (575 cases) and a testing group (252 cases). CT characteristics were collected by two radiologists, and analyzed using a classification and regression tree (CART) model. For validation, we used the decision analysis threshold to evaluate the classification performance of the CART model and radiologist's diagnosis (benign; malignant) in the testing group.
Results: Three out of 19 characteristics [margin (smooth; slightly lobulated/lobulated/spiculated), and shape (round/oval; irregular), subjective enhancement (no/uniform enhancement; heterogeneous enhancement)] were automatically generated by the CART model for classifying solid lung tumors. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the CART model is 98.5%, 58.1%, 80.6%, 98.6%, 79.8%, and 90.4%, 54.7%, 82.4% 98.5%, 74.2% for the radiologist's diagnosis by using three-threshold decision analysis.
Conclusions: Tumor margin and shape, and subjective tumor enhancement were the most important CT characteristics in the CART model for classifying solid lung tumors as malignant. The CART model had higher discriminatory power than radiologist's diagnosis. The CART model could help radiologists making recommendations regarding follow-up or surgery in clinical patients with a solid lung tumor.

Gepubliceerd: J Thorac Dis. 2021;13(7):4407-17.
Impact factor: 2.895; Q3

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5. **The value of open-source clinical science in pandemic response: lessons from ISARIC**
ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

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6. **Computed Tomography Screening for Early Lung Cancer, COPD and Cardiovascular Disease in Shanghai: Rationale and Design of a Population-based Comparative Study**
Du Y, Li Q, Sidorenkov G, Vonder M, Cai J, de Bock GH, Guan Y, Xia Y, Zhou X, Zhang D, Rook M, Vliegenthart R, Heuvelmans MA, Dorrius MD, van Ooijen PMA, Groen HJM, van der Harst P, Xiao Y, Ye Z, Xie X, Wang W, Oudkerk M, Fan L, Liu S.

Rationale and objectives: To describe the rational and design of a population-based comparative study. The objective of the study is to assess the screening performance of volume-based management of CT-detected lung nodule in comparison to diameter-based management, and to improve the effectiveness of CT screening for chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD), in addition

to lung cancer, based on quantitative measurement of CT imaging biomarkers in a Chinese screening setting.
Materials and methods: A population-based comparative study is being performed, including 10,000 asymptomatic participants between 40 and 74 years old from Shanghai urban population. Participants in the intervention group undergo a low-dose chest and cardiac CT scan at baseline and 1 year later, and are managed according to NELCIN-B3 protocol. Participants in the control group undergo a low-dose chest CT scan according to the routine CT protocol and are managed according to the clinical practice. Epidemiological data are collected through questionnaires. In the fourth year from baseline, the diagnosis of the three diseases will be collected.
Results: The unnecessary referral rate will be compared between NELCIN-B3 and standard protocol for managing early-detected lung nodules. The effectiveness of quantitative measurement of CT imaging biomarkers for early detection of lung cancer, COPD and CVD will be evaluated.
Conclusion: We expect that the quantitative assessment of the CT imaging biomarkers will reduce the number of unnecessary referrals for early detected lung nodules, and will improve the early detection of COPD and CVD in a Chinese urban population.
Trial registrattion: ClinicalTrials.gov, NCT03988322. Registered on 14 June 2019.

Gepubliceerd: Acad Radiol. 2021;28(1):36-45.
Impact factor: 3.173; Q2

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7. **Comparison of National Comprehensive Cancer Network and European Position Statement protocols for nodule management in low-dose computed tomography lung cancer screening in a general Chinese population**
Du Y, Li Y, Dorrius MD, Sidorenkov G, Vonder M, Vliegenthart R, Heuvelmans MA, Cui X, Ye Z, de Bock GH.

Background: Low-dose computed tomography (LDCT) lung cancer screening often refers individuals to unnecessary examinations. This study aims to compare the European Position Statement (EUPS) and National Comprehensive Cancer Network (NCCN) protocols in management of participants at baseline screening round.
Methods: LDCT lung cancer screening was prospectively performed in a Chinese asymptomatic population aged 40-74 years. A total of 1,000 consecutive baseline LDCT scans were read twice independently. All screen-detected lung nodules by the first reader were included. The first reader manually measured the diameter of lung nodules (NCCN protocol), and the second reader semi-automatically measured the volume and diameter (EUPS volume and diameter protocols). The protocols were used to classify the participants into three management groups: next screening round, short-term repeat LDCT scan and referral to a pulmonologist. Groups were compared using Wilcoxon test for paired samples. Number of lung cancers by protocols was provided.
Results: Of the 1,000 participants (61.4±6.7 years old), 168 lung nodules in 124 participants were visually detected and manually measured in the first reading, and re-measured semi-automatically. Applying the NCCN protocol, EUPS volume and diameter protocol, the proportion of referrals among all participants was 0.6%, 1.9%, and 1.4%, respectively. The proportion of short-term repeat scans was 4.5%, 9.7% and 4.5%, respectively. Among the 10 lung cancer patients, one would have been diagnosed earlier if the EUPS volume protocol would have been followed.

Conclusions: In a first round screening in a Chinese general population, the lower threshold for referral in the EUPS protocol as compared to the NCCN protocol, leads to more referrals to a pulmonologist, with the potential of earlier cancer diagnosis. The EUPS volume protocol recommends fewer participants to short-term repeat LDCT scan than the EUPS diameter protocol. Follow-up studies should show the impact of both protocols on (interval) cancer diagnosis.

Gepubliceerd: J Thorac Dis. 2021;13(12):6855-65.
Impact factor: 2.895; Q3

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8. **Evaluation of a novel deep learning-based classifier for perifissural nodules**
Han D, Heuvelmans M, Rook M, Dorrius M, van Houten L, Price NW, Pickup LC, Novotny P, Oudkerk M, Declerck J, Gleeson F, van Ooijen P, Vliegenthart R.

Objectives: To evaluate the performance of a novel convolutional neural network (CNN) for the classification of typical perifissural nodules (PFN).
Methods: Chest CT data from two centers in the UK and The Netherlands (1668 unique nodules, 1260 individuals) were collected. Pulmonary nodules were classified into subtypes, including "typical PFNs" on-site, and were reviewed by a central clinician. The dataset was divided into a training/cross-validation set of 1557 nodules (1103 individuals) and a test set of 196 nodules (158 individuals). For the test set, three radiologically trained readers classified the nodules into three nodule categories: typical PFN, atypical PFN, and non-PFN. The consensus of the three readers was used as reference to evaluate the performance of the PFN-CNN. Typical PFNs were considered as positive results, and atypical PFNs and non-PFNs were grouped as negative results. PFN-CNN performance was evaluated using the ROC curve, confusion matrix, and Cohen's kappa.
Results: Internal validation yielded a mean AUC of 91.9% (95% CI 90.6-92.9) with 78.7% sensitivity and 90.4% specificity. For the test set, the reader consensus rated 45/196 (23%) of nodules as typical PFN. The classifier-reader agreement (k = 0.62-0.75) was similar to the inter-reader agreement (k = 0.64-0.79). Area under the ROC curve was 95.8% (95% CI 93.3-98.4), with a sensitivity of 95.6% (95% CI 84.9-99.5), and specificity of 88.1% (95% CI 81.8-92.8).
Conclusion: The PFN-CNN showed excellent performance in classifying typical PFNs. Its agreement with radiologically trained readers is within the range of inter-reader agreement. Thus, the CNN-based system has potential in clinical and screening settings to rule out perifissural nodules and increase reader efficiency. KEY POINTS: * Agreement between the PFN-CNN and radiologically trained readers is within the range of inter-reader agreement. * The CNN model for the classification of typical PFNs achieved an AUC of 95.8% (95% CI 93.3-98.4) with 95.6% (95% CI 84.9-99.5) sensitivity and 88.1% (95% CI 81.8-92.8) specificity compared to the consensus of three readers.

Gepubliceerd: Eur Radiol. 2021;31(6):4023-30.
Impact factor: 5.315; Q1

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9. **Lung cancer prediction by Deep Learning to identify benign lung nodules**
Heuvelmans MA, van Ooijen PMA, Ather S, Silva CF, Han D, Heussel CP, Hickes W, Kauczor HU, Novotny P, Peschl H, Rook M, Rubtsov R, von Stackelberg O, Tsakok MT, Arteta C, Declerck J, Kadir T, Pickup L, Gleeson F, Oudkerk M.

Introduction: Deep Learning has been proposed as promising tool to classify malignant nodules. Our aim was to retrospectively validate our Lung Cancer Prediction Convolutional Neural Network (LCP-CNN), which was trained on US screening data, on an independent dataset of indeterminate nodules in an European multicentre trial, to rule out benign nodules maintaining a high lung cancer sensitivity.
Methods: The LCP-CNN has been trained to generate a malignancy score for each nodule using CT data from the U.S. National Lung Screening Trial (NLST), and validated on CT scans containing 2106 nodules (205 lung cancers) detected in patients from from the Early Lung Cancer Diagnosis Using Artificial Intelligence and Big Data (LUCINDA) study, recruited from three tertiary referral centers in the UK, Germany and Netherlands. We pre-defined a benign nodule rule-out test, to identify benign nodules whilst maintaining a high sensitivity, by calculating thresholds on the malignancy score that achieve at least 99 % sensitivity on the NLST data. Overall performance per validation site was evaluated using Area-Under-the-ROC-Curve analysis (AUC).
Results: The overall AUC across the European centers was 94.5 % (95 %CI 92.6-96.1). With a high sensitivity of 99.0 %, malignancy could be ruled out in 22.1 % of the nodules, enabling 18.5 % of the patients to avoid follow-up scans. The two false-negative results both represented small typical carcinoids.
Conclusion: The LCP-CNN, trained on participants with lung nodules from the US NLST dataset, showed excellent performance on identification of benign lung nodules in a multi-center external dataset, ruling out malignancy with high accuracy in about one fifth of the patients with 5-15 mm nodules.

Gepubliceerd: Lung Cancer. 2021;154:1-4.
Impact factor: 5.705; Q1

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10. **Seasonal prevalence and characteristics of low-dose CT detected lung nodules in a general Dutch population**
Lancaster HL, Heuvelmans MA, Pelgrim GJ, Rook M, Kok MGJ, Aown A, de Bock GH, van den Berge M, Groen HJM, Vliegenthart R.

We investigated whether presence and characteristics of lung nodules in the general population using low-dose computed tomography (LDCT) varied by season. Imaging in Lifelines (ImaLife) study participants who underwent chest LDCT-scanning between October 2018 and October 2019 were included in this sub-study. Hay fever season (summer) was defined as 1st April to 30th September and Influenza season (winter) as 1st October to 31st March. All lung nodules with volume of ≥ 30 mm(3) (approximately 3 mm in diameter) were registered. In total, 2496 lung nodules were found in 1312 (38%) of the 3456 included participants (nodules per participant ranging from 1 to 21, median 1). In summer, 711 (54%) participants had 1 or more lung nodule(s) compared to 601 (46%) participants in winter (p = 0.002). Of the spherical, perifissural and left-upper-lobe nodules, relatively more were detected in winter, whereas of the polygonal-, irregular-shaped and centrally-calcified nodules, relatively more were detected in summer. Various seasonal diseases with inflammation as underlying pathophysiology

may influence presence and characteristics of lung nodules. Further investigation into underlying pathophysiology using short-term LDCT follow-up could help optimize the management strategy for CT-detected lung nodules in clinical practice.

Gepubliceerd: Sci Rep. 2021;11(1):9139.
Impact factor: 4.380; Q1

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11. **Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives**
Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK.

In the past decade, the introduction of molecularly targeted agents and immune-checkpoint inhibitors has led to improved survival outcomes for patients with advanced-stage lung cancer; however, this disease remains the leading cause of cancer-related mortality worldwide. Two large randomized controlled trials of low-dose CT (LDCT)-based lung cancer screening in high-risk populations - the US National Lung Screening Trial (NLST) and NELSON - have provided evidence of a statistically significant mortality reduction in patients. LDCT-based screening programmes for individuals at a high risk of lung cancer have already been implemented in the USA. Furthermore, implementation programmes are currently underway in the UK following the success of the UK Lung Cancer Screening (UKLS) trial, which included the Liverpool Health Lung Project, Manchester Lung Health Check, the Lung Screen Uptake Trial, the West London Lung Cancer Screening pilot and the Yorkshire Lung Screening trial. In this Review, we focus on the current evidence on LDCT-based lung cancer screening and discuss the clinical developments in high-risk populations worldwide; additionally, we address aspects such as cost-effectiveness. We present a framework to define the scope of future implementation research on lung cancer screening programmes referred to as Screening Planning and Implementation RAtionale for Lung cancer (SPIRAL).

Gepubliceerd: Nat Rev Clin Oncol. 2021;18(3):135-51.
Impact factor: 66.675; Q1

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12. **Predictors of patient adherence to COPD self-management exacerbation action plans**
Schrijver J, Effing TW, Brusse-Keizer M, van der Palen J, van der Valk P, Lenferink A.

Objective: Identifying patient characteristics predicting categories of patient adherence to Chronic Obstructive Pulmonary Disease (COPD) exacerbation action plans.
Methods: Data were obtained from self-treatment intervention groups of two COPD self-management trials. Patients with ≥1 exacerbation and/or ≥1 self-initiated prednisolone course during one-year follow-up were included. Optimal treatment was defined as 'self-initiating prednisolone treatment ≤2 days from the onset of a COPD exacerbation'. Predictors of adherence categories were identified by multinomial logistic regression analysis using patient characteristics.
Results: 145 COPD patients were included and allocated to four adherence categories: 'optimal treatment' (26.2 %), 'sub optimal treatment' (11.7 %), 'significant delay or no treatment' (31.7 %), or 'treatment outside the actual exacerbation period'

(30.3 %). One unit increase in baseline dyspnoea score (mMRC scale 0-4) increased the risk of 'significant delay or no treatment' (OR 1.64 (95 % CI 1.07-2.50)). Cardiac comorbidity showed a borderline significant increased risk of 'treatment outside the actual exacerbation period' (OR 2.40 (95 % CI 0.98-5.85)).
Conclusion: More severe dyspnoea and cardiac comorbidity may lower adherence to COPD exacerbation action plans. PRACTICE IMPLICATIONS: Tailored self-management support with more focus on dyspnoea and cardiac disease symptoms may help patients to better act upon increased exacerbation symptoms and improve adherence to COPD exacerbation action plans.

Gepubliceerd: Patient Educ Couns. 2021;104(1):163-70.
Impact factor: 2.940; Q1

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13. **Adherence to an eHealth Self-Management Intervention for Patients with Both COPD and Heart Failure: Results of a Pilot Study**
Sloots J, Bakker M, van der Palen J, Eijsvogel M, van der Valk P, Linssen G, van Ommeren C, Grinovero M, Tabak M, Effing T, Lenferink A.

Background: Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) often coexist and share periods of symptom deterioration. Electronic health (eHealth) might play an important role in adherence to interventions for the self-management of COPD and CHF symptoms by facilitating and supporting home-based care.
Methods: In this pilot study, an eHealth self-management intervention was developed based on paper versions of multi-morbid exacerbation action plans and evaluated in patients with both COPD and CHF. Self-reporting of increased symptoms in diaries was linked to an automated decision support system that generated self-management actions, which was communicated via an eHealth application on a tablet. After participating in self-management training sessions, patients used the intervention for a maximum of four months. Adherence to daily symptom diary completion and follow-up of actions were analyzed. An add-on sensorized (Respiro(®)) inhaler was used to analyze inhaled medication adherence and inhalation technique.
Results: In total, 1148 (91%) of the daily diaries were completed on the same day by 11 participating patients (mean age 66.8 ± 2.9 years; moderate (55%) to severe (45%) COPD; 46% midrange left ventricular function (LVF) and 27% reduced LVF). Seven patients received a total of 24 advised actions because of increased symptoms of which 11 (46%) were followed-up. Of the 13 (54%) unperformed advised actions, six were "call the case manager". Adherence to inhaled medication was 98.4%, but 51.9% of inhalations were performed incorrectly, with "inhaling too shortly" (<1.25 s) being the most frequent error (79.6%).
Discussion: Whereas adherence to completing daily diaries was high, advised actions were inadequately followed-up, particularly the action "call the case manager". Inhaled medication adherence was high, but inhalations were poorly performed. Future research is needed to identify adherence barriers, further tailor the intervention to the individual patient and analyse the intervention effects on health outcomes.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2021;16:2089-103.
Impact factor: 3.355; Q2

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14. **An Embodied Conversational Agent in an eHealth Self-management Intervention for Chronic Obstructive Pulmonary Disease and Chronic Heart Failure: Exploratory Study in a Real-life Setting**
Ter Stal S, Sloots J, Ramlal A, Op den Akker H, Lenferink A, Tabak M.

Background: Embodied conversational agents (ECAs) have the potential to stimulate actual use of eHealth apps. An ECA's design influences the user's perception during short interactions, but daily life evaluations of ECAs in health care are scarce.
Objective: This is an exploratory, long-term study on the design of ECAs for eHealth. The study investigates how patients perceive the design of the ECA over time with regard to the ECA's characteristics (friendliness, trustworthiness, involvement, expertise, and authority), small talk interaction, and likeliness of following the agent's advice.
Methods: We developed an ECA within an eHealth self-management intervention for patients with both chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF), which we offered for 4 months. Patients rated 5 agent characteristics and likeliness of following the agent's advice before use and after 3 and 9 weeks of use. The amount of patients' small talk interaction was assessed by log data. Lastly, individual semistructured interviews were used to triangulate results.
Results: Eleven patients (7 male and 4 female) with COPD and CHF participated (median age 70 years). Patients' perceptions of the agent characteristics did not change over time (P>.05 for all characteristics) and only 1 participant finished all small talk dialogues. After 3 weeks of use, the patients were less likely to follow the agent's advice (P=.01). The agent's messages were perceived as nonpersonalized and the feedback as inappropriate, affecting the agent's perceived reliability.
Conclusions: This exploratory study provides first insights into ECA design for eHealth. The first impression of an ECA's design seems to remain during long-term use. To investigate future added value of ECAs in eHealth, perceived reliability should be improved by managing users' expectations of the ECA's capabilities and creating ECA designs fitting individual needs.
Trial registrattion: Netherlands Trial Register NL6480;

Gepubliceerd: JMIR Hum Factors. 2021;8(4):e24110.
Impact factor: 0; NVT

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15. **Volatile organic breath components and exercise induced bronchoconstriction in asthmatic children**
van der Kamp MR, Driessen JMM, van der Schee MP, Thio BJ, de Jongh FHC.

Introduction: Asthma is one of the most common chronic diseases in childhood and is generally characterized by exercise induced bronchoconstriction (EIB). Assessing EIB is time consuming and expensive as it requires a fully equipped pulmonary function laboratory. Analysis of volatile organic compounds (VOCs) in breath is a novel technique for examining biomarkers which may associate with asthma features. The aim of this pilot study was to identify potential markers in the relationship between EIB and VOCs.
Methods: Children between four and 14 years old were asked to provide a breath sample prior to undergoing an exercise challenge test to assess for EIB.

Results: Breath samples were collected and analyzed in 46 asthmatic children, 21 with EIB and 25 without EIB (NO-EIB). Molecular features (MFs) were not significantly different between EIB and NO-EIB controls. 29 of the 46 children were corticosteroid naïve, 10 with EIB and 13 without. In the corticosteroid naïve group EIB was associated with increased MF23 and MF14 in the lower breath sample (p-value < 0.05).
Conclusion: This pilot study shows that EIB was related to an increased MF14 and MF23 in corticosteroid naïve children. The tentative identities of these compounds are octanal and dodecane/tetradecane respectively. These candidate biomarkers have a potential to enable non-invasive diagnosis of EIB in steroid-naïve children. Trial registration This study is registered in the Netherlands trial register (trial no. NL6087) at 14 February 2017.

Gepubliceerd: Allergy Asthma Clin Immunol. 2021;17(1):121.
Impact factor: 3.406; Q3

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16. **Opioids in patients with COPD and refractory dyspnea: literature review and design of a multicenter double blind study of low dosed morphine and fentanyl (MoreFoRCOPD)**
van Dijk M, Mooren KJM, van den Berg JK, van Beurden-Moeskops WJC, Heller-Baan R, de Hosson SM, Lam-Wong WY, Peters L, Pool K, Kerstjens HAM.

Background: Refractory dyspnea or breathlessness is a common symptom in patients with advanced chronic obstructive pulmonary disease (COPD), with a high negative impact on quality of life (QoL). Low dosed opioids have been investigated for refractory dyspnea in COPD and other life-limiting conditions, and some positive effects were demonstrated. However, upon first assessment of the literature, the quality of evidence in COPD seemed low or inconclusive, and focused mainly on morphine which may have more side effects than other opioids such as fentanyl. For the current publication we performed a systematic literature search. We searched for placebo-controlled randomized clinical trials investigating opioids for refractory dyspnea caused by COPD. We included trials reporting on dyspnea, health status and/or QoL. Three of fifteen trials demonstrated a significant positive effect of opioids on dyspnea. Only one of four trials reporting on QoL or health status, demonstrated a significant positive effect. Two-thirds of included trials investigated morphine. We found no placebo-controlled RCT on transdermal fentanyl. Subsequently, we hypothesized that both fentanyl and morphine provide a greater reduction of dyspnea than placebo, and that fentanyl has less side effects than morphine.
Methods: We describe the design of a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl 12 mcg/h and morphine sustained-release 10 mg b.i.d. The primary endpoint is change in daily mean dyspnea sensation measured on a numeric rating scale. Secondary endpoints are change in daily worst dyspnea, QoL, anxiety, sleep quality, hypercapnia, side effects, patient preference, and continued opioid use. Sixty patients with severe stable COPD and refractory dyspnea (FEV(1) < 50%, mMRC ≥ 3, on optimal standard therapy) will be included.
Discussion: Evidence for opioids for refractory dyspnea in COPD is not as robust as usually appreciated. We designed a study comparing both the more commonly used opioid morphine, and transdermal fentanyl to placebo. The cross-over design will help to get a better impression of patient preferences. We believe our study design to

investigate both sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information for better treatment of refractory dyspnea in COPD. Trial registration NCT03834363 (ClinicalTrials.gov), registred at 7 Feb 2019.

Gepubliceerd: BMC Pulm Med. 2021;21(1):289.
Impact factor: 3.317; Q2

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17. **Pre-admission anticoagulant therapy and mortality in hospitalized COVID-19 patients: A retrospective cohort study**
van Haaps TF, Collard D, van Osch FHM, Middeldorp S, Coppens M, de Kruif MD, Vlot EA, Douma RA, Ten Cate H, Juffermans NP, Gritters N, Vlaar AP, Reidinga AC, Heuvelmans MA, Oudkerk M, Büller HR, van den Bergh JPW, Maas A, Ten Wolde M, Simsek S, Beudel M, van Es N.

Gepubliceerd: Thromb Res. 2021;208:35-8.
Impact factor: 3.944; Q2

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18. **Diaphragm Activity Pre and Post Extubation in Ventilated Critically Ill Infants and Children Measured With Transcutaneous Electromyography**
van Leuteren RW, de Waal CG, de Jongh FH, Bem RA, van Kaam AH, Hutten G.

Objectives: Swift extubation is important to prevent detrimental effects of invasive mechanical ventilation but carries the risk of extubation failure. Accurate tools to assess extubation readiness are lacking. This study aimed to describe the effect of extubation on diaphragm activity in ventilated infants and children. Our secondary aim was to compare diaphragm activity between failed and successfully extubated patients.
Design: Prospective, observational study.
Setting: Single-center tertiary neonatal ICU and PICU.
Patients: Infants and children receiving invasive mechanical ventilation longer than 24 hours.
Interventions: None.
Measurements and main results: Diaphragm activity was measured with transcutaneous electromyography, from 15 minutes before extubation till 180 minutes thereafter. Peak and tonic activity, inspiratory amplitude, inspiratory area under the curve, and respiratory rate were calculated from the diaphragm activity waveform. One hundred forty-seven infants and children were included (median postnatal age, 1.9; interquartile range, 0.9-6.7 wk). Twenty patients (13.6%) failed extubation within 72 hours. Diaphragm activity increased rapidly after extubation and remained higher throughout the measurement period. Pre extubation, peak (end-inspiratory) diaphragm activity and tonic (end-inspiratory) diaphragm activity were significantly higher in failure, compared with success cases (5.6 vs 7.0 μV; p = 0.04 and 2.8 vs 4.1 μV; p = 0.04, respectively). Receiver operator curve analysis showed the highest area under the curve for tonic (end-inspiratory) diaphragm activity (0.65), with a tonic (end-inspiratory) diaphragm activity greater than 3.4 μV having a combined sensitivity and specificity of 55% and 77%, respectively, to predict extubation outcome. After extubation, diaphragm activity remained higher in patients failing extubation.
Conclusions: Diaphragm activity rapidly increased after extubation. Patients failing extubation had a higher level of diaphragm activity, both pre and post extubation. The

predictive value of the diaphragm activity variables alone was limited. Future studies are warranted to assess the additional value of electromyography of the diaphragm in combined extubation readiness assessment.

Gepubliceerd: Pediatr Crit Care Med. 2021;22(11):950-9.
Impact factor: 3.624; Q1

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19. **Transcutaneous monitoring of diaphragm activity as a measure of work of breathing in preterm infants**
van Leuteren RW, de Waal CG, Hutten GJ, de Jongh FH, van Kaam AH.

Objective: Monitoring work of breathing (WOB) is important to assess the pulmonary condition and adjust respiratory support in preterm infants. Conventional WOB measurement (esophageal pressure, tidal volume) is invasive and we hypothesized that monitoring diaphragm activity could be a noninvasive alternative to estimate WOB. The objective was to determine the correlation between conventional WOB measures and diaphragm activity, in preterm infants.
Methods: WOB and diaphragm activity, measured with transcutaneous electromyography (dEMG), were simultaneously recorded at different nasal continuous positive airway pressure (nCPAP) levels. During a 30-s recording at each nCPAP level, dEMG parameters, inspiratory WOB (WOB(i)), and pressure time product (PTP(in)) were calculated per breath. The correlation coefficient between WOB- and dEMG-measures was calculated using single breaths and after aggregating all breaths into deciles of incremental WOB(i) .
Results: Fifteen preterm infants were included (median gestational age, 28 weeks). Single-breath analysis showed a poor median correlation of 0.27 (interquartile range [IQR], 0.03 to 0.33) and 0.08 (IQR, -0.03 to 0.28), respectively, for WOB(i) and PTP(in) with peak diaphragmatic activity (dEMG(peak)). A modest median correlation coefficient of 0.65 (IQR, 0.13 to 0.79) and 0.43 (IQR, -0.33 to 0.69) was found for, respectively, WOB(i) and PTP(in) with dEMG(peak) in the aggregated analysis.
Conclusion: Diaphragm activity showed a modest correlation with WOB(i) and PTP(in) in an aggregated analysis. This finding warrants further studies in infants with more significant lung disease.

Gepubliceerd: Pediatr Pulmonol. 2021;56(6):1593-600.
Impact factor: 3.039; Q2

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20. **Cardiorespiratory monitoring in the delivery room using transcutaneous electromyography**
van Leuteren RW, Kho E, de Waal CG, Te Pas AB, Salverda HH, de Jongh FH, van Kaam AH, Hutten GJ.

Objective: To assess feasibility of transcutaneous electromyography of the diaphragm (dEMG) as a monitoring tool for vital signs and diaphragm activity in the delivery room (DR).
Design: Prospective observational study.
Setting: Delivery room.
Patients: Newborn infants requiring respiratory stabilisation after birth.

Interventions: In addition to pulse oximetry (PO) and ECG, dEMG was measured with skin electrodes for 30 min after birth.
Outcome measures: We assessed signal quality of dEMG and ECG recording, agreement between heart rate (HR) measured by dEMG and ECG or PO, time between sensor application and first HR read-out and agreement between respiratory rate (RR) measured with dEMG and ECG, compared with airway flow. Furthermore, we analysed peak, tonic and amplitude diaphragmatic activity from the dEMG-based respiratory waveform.
Results: Thirty-three infants (gestational age: 31.7+/-2.8 weeks, birth weight: 1525+/-661 g) were included.18%+/-14% and 22%+/-21% of dEMG and ECG data showed poor quality, respectively. Monitoring HR with dEMG was fast (median 10 (IQR 10-11) s) and accurate (intraclass correlation coefficient (ICC) 0.92 and 0.82 compared with ECG and PO, respectively). RR monitoring with dEMG showed moderate (ICC 0.49) and ECG low (ICC 0.25) agreement with airway flow. Diaphragm activity started high with a decreasing trend in the first 15 min and subsequent stabilisation.
Conclusion: Monitoring vital signs with dEMG in the DR is feasible and fast. Diaphragm activity can be detected and described with dEMG, making dEMG promising for future DR studies.

Gepubliceerd: Arch Dis Child Fetal Neonatal Ed. 2021;106(4):352-6.
Impact factor: 5.747; Q1

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21. **The Effect of Initial Oxygen Exposure on Diaphragm Activity in Preterm Infants at Birth**
van Leuteren RW, Scholten AWJ, Dekker J, Martherus T, de Jongh FH, van Kaam AH, Te Pas AB, Hutten J.

Background: The initial FiO(2) that should be used for the stabilization of preterm infants in the delivery room (DR) is still a matter of debate as both hypoxia and hyperoxia should be prevented. A recent randomized controlled trial showed that preterm infants [gestational age (GA) < 30 weeks] stabilized with an initial high FiO(2) (1.0) had a significantly higher breathing effort than infants stabilized with a low FiO(2) (0.3). As the diaphragm is the main respiratory muscle in these infants, we aimed to describe the effects of the initial FiO(2) on diaphragm activity.
Methods: In a subgroup of infants from the original bi-center randomized controlled trial diaphragm activity was measured with transcutaneous electromyography of the diaphragm (dEMG), using three skin electrodes that were placed directly after birth. Diaphragm activity was compared in the first 5 min after birth. From the dEMG respiratory waveform several outcome measures were determined for comparison of the groups: average peak- and tonic inspiratory activity (dEMG(peak) and dEMG(ton), respectively), inspiratory amplitude (dEMG(amp)), area under the curve (dEMG(AUC)) and the respiratory rate (RR).
Results: Thirty-one infants were included in this subgroup, of which 29 could be analyzed [n = 15 (median GA 28.4 weeks) and n = 14 (median GA 27.9 weeks) for the 100 and 30% oxygen group, respectively]. Tonic diaphragm activity was significantly higher in the high FiO(2)-group (4.3 ± 2.1 μV vs. 2.9 ± 1.1 μV; p = 0.047). The other dEMG-parameters (dEMG(peak), dEMG(amp), dEMG(AUC)) showed consistently higher values in the high FiO(2) group, but did not reach statistical significance.

Average RR showed similar values in both groups (34 ± 9 vs. 32 ± 10 breaths/min for the high and low oxygen group, respectively).
Conclusion: Preterm infants stabilized with an initial high FiO(2) showed significantly more tonic diaphragm activity and an overall trend toward a higher level of diaphragm activity than those stabilized with an initial low FiO(2). These results confirm that a high initial FiO(2) after birth stimulates breathing effort, which can be objectified with dEMG.

Gepubliceerd: Front Pediatr. 2021;9:640491.
Impact factor: 3.418; Q1

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22. **Predicting Mortality in COPD with Validated and Sensitive Biomarkers; Fibrinogen and Mid-Range-Proadrenomedullin (MR-proADM)**
Zuur-Telgen MC, Citgez E, Zuur AT, van der Valk P, van der Palen J, Kerstjens HAM, Brusse-Keizer M.

Although fibrinogen is a FDA qualified prognostic biomarker in COPD, it still lacks sufficient resolution to be clinically useful. Next to replication of findings in different cohorts also the combination with other validated biomarkers should be investigated. Therefore, the aim of this study was to confirm in a large well-defined population of COPD patients whether fibrinogen can predict mortality and whether a combination with the biomarker MR-proADM can increase prognostic accuracy. From the COMIC cohort study we included COPD patients with a blood sample obtained in stable state (n = 640) and/or at hospitalization for an acute exacerbation of COPD (n = 262). Risk of death during 3 years of follow up for the separate and combined biomarker models was analyzed with Cox regression. Furthermore, logistic regression models for death after one year were constructed. When both fibrinogen and MR-proADM were included in the survival model, a doubling in fibrinogen and MR-proADM levels gave a 2.2 (95% CI 1.3-3.7) and 2.1 (95% CI 1.5-3.0) fold increased risk of dying, respectively. The prediction model for death after 1 year improved significantly when MR-proADM was added to the model with fibrinogen (AUC increased from 0.78 to 0.83; p = 0.02). However, the combined model was not significantly more adequate than the model with solely MR-proADM (AUC 0.83 vs 0.82; p = 0.34). The study suggests that MR-proADM is more promising than fibrinogen in prediciting mortality. Adding fibrinogen to a model containing MR-proADM does not significantly increase the predictive capacity of the model.

Gepubliceerd: Copd. 2021;18(6):643-9.
Impact factor: 2.409; Q4

Totale impact factor: 165.293
Gemiddelde impact factor: 7.513

Aantal artikelen 1e, 2e of laatste auteur: 10
Totale impact factor: 30.600
Gemiddelde impact factor: 3.060

MDL

1. **Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis**
Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, Bouwense SAW, Bruno MJ, Cappendijk VC, Dejong CHC, van Duijvendijk P, van Eijck CHJ, Fockens P, Francken MFG, van Goor H, Hadithi M, Hallensleben NDL, Haveman JW, Jacobs M, Jansen JM, Kop MPM, van Lienden KP, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, van de Poll M, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Stommel MWJ, Straathof JWA, Timmerhuis HC, Venneman NG, Voermans RP, van de Vrie W, Witteman BJ, Dijkgraaf MGW, van Santvoort HC, Besselink MG.

Background: Infected necrotizing pancreatitis is a potentially lethal disease that is treated with the use of a step-up approach, with catheter drainage often delayed until the infected necrosis is encapsulated. Whether outcomes could be improved by earlier catheter drainage is unknown.
Methods: We conducted a multicenter, randomized superiority trial involving patients with infected necrotizing pancreatitis, in which we compared immediate drainage within 24 hours after randomization once infected necrosis was diagnosed with drainage that was postponed until the stage of walled-off necrosis was reached. The primary end point was the score on the Comprehensive Complication Index, which incorporates all complications over the course of 6 months of follow-up.
Results: A total of 104 patients were randomly assigned to immediate drainage (55 patients) or postponed drainage (49 patients). The mean score on the Comprehensive Complication Index (scores range from 0 to 100, with higher scores indicating more severe complications) was 57 in the immediate-drainage group and 58 in the postponed-drainage group (mean difference, -1; 95% confidence interval [CI], -12 to 10; P = 0.90). Mortality was 13% in the immediate-drainage group and 10% in the postponed-drainage group (relative risk, 1.25; 95% CI, 0.42 to 3.68). The mean number of interventions (catheter drainage and necrosectomy) was 4.4 in the immediate-drainage group and 2.6 in the postponed-drainage group (mean difference, 1.8; 95% CI, 0.6 to 3.0). In the postponed-drainage group, 19 patients (39%) were treated conservatively with antibiotics and did not require drainage; 17 of these patients survived. The incidence of adverse events was similar in the two groups.
Conclusions: This trial did not show the superiority of immediate drainage over postponed drainage with regard to complications in patients with infected necrotizing pancreatitis. Patients randomly assigned to the postponed-drainage strategy received fewer invasive interventions. (Funded by Fonds NutsOhra and Amsterdam UMC; POINTER ISRCTN Registry number, ISRCTN33682933.).

Gepubliceerd: N Engl J Med. 2021;385(15):1372-81.
Impact factor: 91.253; Q1

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2. **Complete Resolution of Mucosal Neutrophils May Predict Nonfatigue in Ulcerative Colitis**
Braat H, Parikh K, Peppelenbosch MP.

Gepubliceerd: Clin Gastroenterol Hepatol. 2021;19(11):2455-6.
Impact factor: 11.382; Q1

3. **Cross-cultural translation and validation of the IBD-control questionnaire in The Netherlands: a patient-reported outcome measure in inflammatory bowel disease**
de Jong ME, Taal E, Thomas PWA, Römkens TEH, Jansen JM, West RL, Slotman E, Hoentjen F, Russel M.

Background: There is a need for easy-to-use patient-reported outcome measures (PROMS) in inflammatory bowel disease (IBD) practice. The 'IBD-control' is a short IBD-specific questionnaire capturing disease control from the patient's perspective. The International Consortium for Health Outcomes Measurement (ICHOM) recommends the use of the IBD-control even though it has only been validated in the United Kingdom. We aimed to cross-culturally translate and validate the IBD-control in the Netherlands using IBDREAM, a prospective multicentre IBD registry.
Methods: Lack of ambiguity and acceptability were verified in a pilot patient group (n = 5) after forward-backward translation of the IBD-control. Prospective validation involved completion of the IBD-control, Short Form-36, short IBDQ and disease activity measurement by Physician Global Assessment (PGA) and Simple Clinical Colitis Activity Index or Harvey-Bradshaw Index. Test-retest (2-week repeat) was used for measuring reliability.
Results: Questionnaires were completed by 998 IBD patients (674 Crohn's disease, 324 ulcerative colitis). Internal consistency (Cronbach's alpha) was 0.82 for the sub-group of 8 questions (IBD-control-8-sub-score). Mean completion time was 105 s. Construct validity analyses demonstrated moderate-to-strong correlations of the IBD-control-8-subscore and the other instruments (0.49-0.81). Test-retest reliability for stable patients was high (intraclass correlation coefficient 0.95). The IBD-control-8-subscore showed good discriminant ability between the PGA categories (ANOVA, p<.001). Sensitivity to change analyses showed large effect sizes of 0.81-1.87 for the IBD-control-8 subscore.
Conclusions: These results support the IBD-control as a rapid, reliable, valid and sensitive instrument for measuring disease control from an IBD patient's perspective in the Netherlands.

Gepubliceerd: Scand J Gastroenterol. 2021;56(2):155-61.
Impact factor: 2.425; Q4

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4. **Clinical Outcomes of Covid-19 in Patients With Inflammatory Bowel Disease: A Nationwide Cohort Study**
Derikx L, Lantinga MA, de Jong DJ, van Dop WA, Creemers RH, Römkens TEH, Jansen JM, Mahmmod N, West RL, Tan A, Bodelier AGL, Gorter MHP, Boekema PJ, Halet ERC, Horjus CS, van Dijk MA, Hirdes MMC, Epping Stippel LSM, Jharap B, Lutgens M, Russel MG, Gilissen LPL, Nauta S, van Bodegraven AA, Hoentjen F.

Background and aims: The COVID-19 risk and disease course in inflammatory bowel disease [IBD] patients remains uncertain. Therefore, we aimed to assess the clinical presentation, disease course, and outcomes of COVID-19 in IBD patients. Second, we determined COVID-19 incidences in IBD patients and compared this with the general population.

Methods: We conducted a multicentre, nationwide IBD cohort study in The Netherlands and identified patients with COVID-19. First, we assessed the COVID-19 disease course and outcomes. Second, we compared COVID-19 incidences between our IBD study cohort and the general Dutch population.
Results: We established an IBD cohort of 34 763 patients. COVID-19 was diagnosed in 100/34 763 patients [0.29%]; 20/100 of these patients [20%] had severe COVID-19 defined as admission to the intensive care unit, mechanical ventilation, and/or death. Hospitalisation occurred in 59/100 [59.0%] patients and 13/100 [13.0%] died. All patients who died had comorbidities and all but one were ≥65 years old. In line, we identified ≥1 comorbidity as an independent risk factor for hospitalisation (odds ratio [OR] 4.20, 95% confidence interval [CI] 1.58-11.17,; p = 0.004). Incidences of COVID-19 between the IBD study cohort and the general population were comparable (287.6 [95% CI 236.6-349.7] versus 333.0 [95% CI 329.3-336.7] per 100000 patients, respectively; p = 0.15).
Conclusions: Of 100 cases with IBD and COVID-19, 20% developed severe COVID-19, 59% were hospitalised and 13% died. A comparable COVID-19 risk was found between the IBD cohort [100/34 763 = 0.29%] and the general Dutch population. The presence of ≥1 comorbidities was an independent risk factor for hospitalisation due to COVID-19.

Gepubliceerd: J Crohns Colitis. 2021;15(4):529-39.
Impact factor: 9.071; Q1

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5. **Adverse Drug Reactions from Real-World Data in Inflammatory Bowel Disease Patients in the IBDREAM Registry**
Giraud EL, Thomas PWA, van Lint JA, van Puijenbroek EP, Römkens TEH, West RL, Russel M, Jansen JM, Jessurun NT, Hoentjen F.

Introduction: Inflammatory bowel disease (IBD) frequently requires chronic immunosuppressive treatment and active involvement from patients during treatment decision making. Information about the risk of developing adverse drug reactions (ADRs) to IBD therapies is required in this process.
Objective: The aim of this study was to describe the ADRs reported in IBD patients from real-world data, using the Dutch nationwide IBDREAM registry, and compare the occurrence and cumulative incidences with the Summary of Product Characteristics (SmPC) of the associated drugs.
Methods: In this retrospective multicentre study, ADRs related to IBD medication were assessed. Only reports associated with the use of drugs used for the maintenance treatment of IBD were included. All ADRs were verified by healthcare professionals and coded by trained pharmacovigilance assessors.
Results: In total, 3080 ADRs were reported in 1179 patients. Twenty-three new drug-ADR associations related to the use of azathioprine, mercaptopurine, infliximab, oral mesalamine and thioguanine were reported in the IBDREAM registry that were not mentioned in the corresponding SmPCs. The most frequently reported new association was pyrexia for azathioprine (3.1%) and mercaptopurine (4.9%). In addition, there were seven ADRs with a higher cumulative incidence in IBDREAM compared with the SmPC, and included, among others, arthralgia during mercaptopurine use (2.5%), and diarrhoea (1.4%), alopecia (1.2%) and infections (1.6%) during azathioprine use.

Conclusions: Based on real-world data, ADR reporting demonstrated new ADRs and higher incidences of ADRs to IBD therapies. This information will contribute to drug safety by updating the SmPCs, allowing better risk assessment and communication towards patients.

Gepubliceerd: Drug Saf. 2021;44(5):581-8.
Impact factor: 5.606; Q1

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6. **Polygenetic risk scores do not add predictive power to clinical models for response to anti-TNFα therapy in inflammatory bowel disease**
Karmi N, Bangma A, Spekhorst LM, van Dullemen HM, Visschedijk MC, Dijkstra G, Weersma RK, Voskuil MD, Festen EAM.

Background: Anti-tumour necrosis factor alpha (TNFα) therapy is widely used in the management of Crohn's disease (CD) and ulcerative colitis (UC). However, up to a third of patients do not respond to induction therapy and another third of patients lose response over time. To aid patient stratification, polygenetic risk scores have been identified as predictors of response to anti-TNFα therapy. We aimed to replicate the association between polygenetic risk scores and response to anti-TNFα therapy in an independent cohort of patients, to establish its clinical validity.
Materials and methods: Primary non-response, primary response, durable response and loss of response to anti-TNFα therapy was retrospectively assessed for each patient using stringent definitions. Genome wide genotyping was performed and previously described polygenetic risk scores for primary non-response and durable response were calculated. We compared polygenetic risk scores between patients with primary response and primary non-response, and between patients with durable response and loss of response, using separate analyses for CD and UC.
Results: Out of 334 patients with CD, 15 (4%) patients met criteria for primary non-response, 221 (66%) for primary response, 115 (34%) for durable response and 35 (10%) for loss of response. Out of 112 patients with UC, 12 (11%) met criteria for primary non-response, 68 (61%) for primary response, 19 (17%) for durable response and 20 (18%) for loss of response. No significant differences in polygenetic risk scores were found between primary non-responders and primary responders, and between durable responders and loss of responders.
Conclusions: We could not replicate the previously reported association between polygenetic risk scores and response to anti-TNFα therapy in an independent cohort of patients with CD or UC. Currently, there is insufficient evidence to use polygenetic risk scores to predict response to anti-TNFα therapy in patients with IBD.

Gepubliceerd: PLoS One. 2021;16(9):e0256860.
Impact factor: 3.240; Q2

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7. **Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer**
Latenstein AEJ, Mackay TM, van Huijgevoort NCM, Bonsing BA, Bosscha K, Hol L, Bruno MJ, van Coolsen MME, Festen S, van Geenen E, Groot Koerkamp B, Hemmink GJM, de Hingh I, Kazemier G, Lubbinge H, de Meijer VE, Molenaar IQ, Quispel R, van

Santvoort HC, Seerden TCJ, Stommel MWJ, Venneman NG, Verdonk RC, Besselink MG, van Hooft JE.

Background: Guidelines advise self-expanding metal stents (SEMS) over plastic stents in preoperative endoscopic biliary drainage (EBD) for malignant extrahepatic biliary obstruction. This study aims to assess nationwide practice and outcomes.
Methods: Patients with pancreatic head and periampullary cancer who underwent EBD before pancreatoduodenectomy were included from the Dutch Pancreatic Cancer Audit (2017-2018). Multivariable logistic and linear regression models were performed.
Results: In total, 575/1056 patients (62.0%) underwent preoperative EBD: 246 SEMS (42.8%) and 329 plastic stents (57.2%). EBD-related complications were comparable between the groups (44/246 (17.9%) vs. 64/329 (19.5%), p = 0.607), including pancreatitis (22/246 (8.9%) vs. 25/329 (7.6%), p = 0.387). EBD-related cholangitis was reduced after SEMS placement (10/246 (4.1%) vs. 32/329 (9.7%), p = 0.043), which was confirmed in multivariable analysis (OR 0.36 95%CI 0.15-0.87, p = 0.023). Major postoperative complications did not differ (58/246 (23.6%) vs. 90/329 (27.4%), p = 0.316), whereas postoperative pancreatic fistula (24/246 (9.8%) vs. 61/329 (18.5%), p = 0.004; OR 0.50 95%CI 0.27-0.94, p = 0.031) and hospital stay (14.0 days vs. 17.4 days, p = 0.005; B 2.86 95%CI -5.16 to -0.57, p = 0.014) were less after SEMS placement.
Conclusion: This study found that preoperative EBD frequently involved plastic stents. SEMS seemed associated with lower risks of cholangitis and less postoperative pancreatic fistula, but without an increased pancreatitis risk.

Gepubliceerd: HPB (Oxford). 2021;23(2):270-8.
Impact factor: 3.647; Q1

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8. **[Pancreatic panniculitis with polyarthritis: PPP syndrome]**
Lichtenbeld EA, Ter Borg EJ, Venneman NG, Janssens RWA, Eijken EJE, van Kempen G.

Background: Diseases of the pancreas may present with extrapancreatic symptoms, such as (poly)arthritis or necrosis of subcutaneous fat. A combination of pancreatitis, panniculitis and (poly)arthritis is referred to as the PPP syndrome, which is associated with acute and chronic pancreatitis, as well as pancreatic malignancies.
Case description: This article describes a patient which was admitted to our hospital with severe polyarthritis and panniculitis. A meticulous work-up revealed an underlying focal alcoholic pancreatitis. The clinical course in our patient illustrates the severity of the PPP syndrome and emphasizes the need of a multidisciplinary approach.
Conclusion: Panniculitis and/or (poly)arthritis may be the first symptom of underlying pancreatic disease. Timely recognition and diagnosis is imperative for successful treatment and outcome. The multi-organ involvement in the PPP syndrome requires close collaboration across different medical departments.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021;165.
Impact factor: 0; NVT

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9. **Do endosonographers agree on the presence of bile duct sludge and the subsequent need for intervention?**
Quispel R, Schutz HM, Hallensleben ND, Bhalla A, Timmer R, van Hooft JE, Venneman NG, Erler NS, Veldt BJ, van Driel L, Bruno MJ.

Background and study aims: Endoscopic ultrasonography (EUS) is a tool widely used to diagnose bile duct lithiasis. In approximately one out of five patients with positive findings at EUS, sludge is detected in the bile duct instead of stones. The objective of this study was to establish the agreement among endosonographers regarding: 1. presence of common bile duct (CBD) stones, microlithiasis and sludge; and 2. the need for subsequent treatment.
Patients and methods: 30 EUS videos of patients with an intermediate probability of CBD stones were evaluated by 41 endosonographers. Experience in EUS and endoscopic retrograde cholangiopancreatography, and the endosonographers' type of practices were recorded. Fleiss' kappa statistics were used to quantify the agreement. Associations between levels of experience and both EUS ratings and treatment decisions were investigated using mixed effects models.
Results: A total of 1230 ratings and treatment decisions were evaluated. The overall agreement on EUS findings was fair (Fleiss' κ 0.32). The agreement on presence of stones was moderate (κ 0.46). For microlithiasis it was fair (κ 0.25) and for sludge it was slight (κ 0.16). In cases with CBD stones there was an almost perfect agreement for the decision to subsequently perform an ERC+ES.In case of presumed microlithiasis or sludge an ERC was opted for in 78% and 51% of cases, respectively. Differences in experience and types of practice appear unrelated to the agreement on both EUS findings and the decision for subsequent treatment.
Conclusions: There is only slight agreement among endosonographers regarding the presence of bile duct sludge. Regarding the need for subsequent treatment of bile duct sludge there is no consensus.

Gepubliceerd: Endosc Int Open. 2021;9(6):E911-e7.
Impact factor: 0; NVT

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10. **Increased Use of Prophylactic Measures in Preventing Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis**
Sperna Weiland CJ, Engels MML, Poen AC, Bhalla A, Venneman NG, van Hooft JE, Bruno MJ, Verdonk RC, Fockens P, Drenth JPH, van Geenen EJM, Dutch Pancreatitis Study Group.

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs), pancreatic duct stenting, and intensive intravenous hydration have been proven to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Trial participation and guideline changes demanded an assessment of the clinical practice of post-ERCP pancreatitis prophylaxis.
Aims: The surveys aim to identify points of improvement to inform and educate ERCPists about current evidence-based practice.
Methods: Two anonymous surveys were conducted among Dutch gastroenterologists in 2013 (n = 408) and 2020 (n = 575) for longitudinal views and attitudes pertaining to post-ERCP pancreatitis prophylaxis and recognition of post-ERCP pancreatitis risk factors.

Results: In 2013 and 2020, respectively, 121 and 109 ERCPists responded. In the 2013 survey, 98% of them utilized NSAID prophylaxis and 62% pancreatic duct stent prophylaxis in specific cases. In the 2020 survey, the use of NSAIDs (100%), pancreatic duct stents (78%), and intensive intravenous hydration (33%) increased among ERCPists. NSAID prophylaxis was the preferred prophylactic measure for all risk factors in the 2020 survey, except for ampullectomy, pancreatic duct contrast injection, and pancreatic duct cannulation, for which NSAID prophylaxis and pancreatic duct stent combined was equally favored or preferred.
Conclusion: Rectal NSAIDs are the most applied post-ERCP pancreatitis prophylaxis in the Netherlands, followed by pancreatic duct stents and intensive intravenous hydration. Additionally, there is reason to believe that recent guideline updates and active research participation have led to increased prophylaxis implementation.

Gepubliceerd: Dig Dis Sci. 2021;66(12):4457-66.
Impact factor: 3.199; Q3

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11. **Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT): a multicentre, open-label, randomised, controlled trial**
Sperna Weiland CJ, Smeets X, Kievit W, Verdonk RC, Poen AC, Bhalla A, Venneman NG, Witteman BJM, da Costa DW, van Eijck BC, Schwartz MP, Römkens TEH, Vrolijk JM, Hadithi M, Voorburg A, Baak LC, Thijs WJ, van Wanrooij RL, Tan A, Seerden TCJ, Keulemans YCA, de Wijkerslooth TR, van de Vrie W, van der Schaar P, van Dijk SM, Hallensleben NDL, Sperna Weiland RL, Timmerhuis HC, Umans DS, van Hooft JE, van Goor H, van Santvoort HC, Besselink MG, Bruno MJ, Fockens P, Drenth JPH, van Geenen EJM.

Background: Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Prophylactic rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs) is considered as standard of care to reduce the risk of post-ERCP pancreatitis. It has been suggested that aggressive hydration might further reduce this risk. Guidelines already recommend aggressive hydration in patients who are unable to receive rectal NSAIDs, although it is laborious and time consuming. We aimed to evaluate the added value of aggressive hydration in patients receiving prophylactic rectal NSAIDs.
Methods: FLUYT, a multicentre, open-label, randomised, controlled trial done across 22 Dutch hospitals, included patients aged between 18 and 85 years with moderate to high risk of post-ERCP pancreatitis. Patients were randomly assigned (1:1) by a web-based module with varying block sizes to a combination of aggressive hydration and rectal NSAIDs (100 mg diclofenac or indomethacin; aggressive hydration group) or rectal NSAIDs (100 mg diclofenac or indomethacin) alone (control group). Randomisation was stratified according to treatment centre. Aggressive hydration comprised 20 mL/kg intravenous Ringer's lactate solution within 60 min from the start of ERCP, followed by 3 mL/kg per h for 8 h. The control group received normal intravenous saline with a maximum of 1·5 mL/kg per h and 3 L per 24 h. The primary endpoint was post-ERCP pancreatitis and was analysed on a modified intention-to-treat basis (including all patients who underwent randomisation and an ERCP and for

whom data regarding the primary outcome were available). The trial is registered with the ISRCTN registry, ISRCTN13659155.
Findings: Between June 5, 2015, and June 6, 2019, 826 patients were randomly assigned, of whom 388 in the aggressive hydration group and 425 in the control group were included in the modified intention-to-treat analysis. Post-ERCP pancreatitis occurred in 30 (8%) patients in the aggressive hydration group and in 39 (9%) patients in the control group (relative risk 0·84, 95% CI 0·53-1·33, p=0·53). There were no differences in serious adverse events, including hydration-related complications (relative risk 0·99, 95% CI 0·59-1·64; p=1·00), ERCP-related complications (0·90, 0·62-1·31; p=0·62), intensive care unit admission (0·37, 0·07-1·80; p=0·22), and 30-day mortality (0·95, 0·50-1·83; p=1·00).
Interpretation: Aggressive periprocedural hydration did not reduce the incidence of post-ERCP pancreatitis in patients with moderate to high risk of developing this complication who routinely received prophylactic rectal NSAIDs. Therefore, the burden of laborious and time-consuming aggressive periprocedural hydration to further reduce the risk of post-ERCP pancreatitis is not justified. FUNDING: Netherlands Organisation for Health Research and Development and Radboud University Medical Center.

Gepubliceerd: Lancet Gastroenterol Hepatol. 2021;6(5):350-8.
Impact factor: 18.486; Q1

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12. **Gut Microbiota-Derived Propionate Production May Explain Beneficial Effects of Intermittent Fasting in Experimental Colitis**
Su J, Braat H, Peppelenbosch MP.

Gepubliceerd: J Crohns Colitis. 2021;15(6):1081-2.
Impact factor: 9.071; Q1

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13. **Non-classical clinical presentation at diagnosis by male celiac disease patients of older age**
Tan IL, Withoff S, Kolkman JJ, Wijmenga C, Weersma RK, Visschedijk MC.

Background: In a biopsy-proven adult celiac disease (CeD) cohort from the Netherlands, male patients were diagnosed with CeD at significantly older ages than female patients. **Objectives:** To identify which factors contribute to diagnosis later in life and whether diagnostic delay influences improvement of symptoms after starting a gluten-free diet (GFD).
Methods: We performed a questionnaire study in 211 CeD patients (67:144, male:female) with median age at diagnosis of 41.8 years (interquartile range: 25-58) and at least Marsh 2 histology.
Results: Classical symptoms (diarrhea, fatigue, abdominal pain and/or weight loss) were more frequent in women than men, but sex was not significantly associated with age at diagnosis. In a multivariate analysis, a non-classical presentation (without any classical symptoms) and a negative family history of CeD were significant predictors of older age at diagnosis (coefficients of 8 and 12 years, respectively). A delay of >3 years between first symptom and diagnosis was associated with slower improvement of symptoms after start of GFD, but not with sex, presentation of classical symptoms or age at diagnosis.

Conclusion: Non-classical CeD presentation is more prevalent in men and is associated with a diagnosis of CeD later in life. Recognizing CeD sooner after onset of symptoms is important because a long diagnostic delay is associated with a slower improvement of symptoms after starting a GFD.

Gepubliceerd: Eur J Intern Med. 2021;83:28-33.
Impact factor: 4.624; Q1

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14. **Discrepancy between patient- and healthcare provider-reported adverse drug reactions in inflammatory bowel disease patients on biological therapy**
Thomas PWA, Romkens TEH, West RL, Russel M, Jansen JM, van Lint JA, Jessurun NT, Hoentjen F.

Background: Only limited data is available on the extent and burden of adverse drug reactions (ADRs) to biological therapy in inflammatory bowel disease (IBD) patients in daily practice, especially from a patient's perspective.
Objective: The aim of this study was to systematically assess patient-reported ADRs during biological therapy in IBD patients and compare these with healthcare provider (HCP)-reported ADRs.
Methods: This multicentre, prospective, event monitoring study enrolled IBD patients on biological therapy. Patients completed bimonthly comprehensive web-based questionnaires regarding description of biological induced ADRs, follow-up of previous ADRs and experienced burden of the ADR using a five-point Likert scale. The relationship between patient-reported ADRs and biological therapy was assessed. HCP-reported ADRs were extracted from the electronic healthcare records.
Results: In total, 182 patients (female 51%, mean age 42.2 [standard deviation 14.2] years, Crohn's disease 77%) were included and completed 728 questionnaires. At baseline, 60% of patients used infliximab, 30% adalimumab, 9% vedolizumab and 1% ustekinumab. Fifty percent of participants reported at least one ADR with a total of 239 unique ADRs. Fatigue (n = 26) and headache (n = 20) resulted in the highest burden and a correlation in time with the administration of the biological was described in 56% and 85% respectively. Out of 239 ADRs, 115 were considered biological-related. HCPs reported 119 ADRs. Agreement between patient-reported ADRs and HCP-reported ADRs was only 13%.
Conclusion: IBD patients often report ADRs during biological therapy. We observed an important significant difference between the type and frequency of patient-reported ADRs versus HCP-reported ADRs, leading to an underestimation of more subjective ADRs and patients' ADR-related burden.

Gepubliceerd: United European Gastroenterol J. 2021;9(8):919-28.
Impact factor: 4.623; Q2

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15. **Inflammatory bowel disease patients provide reliable self-reported medical information: A multicentre prospective pharmacovigilance monitoring system**
Thomas PWA, West RL, Russel M, Jansen JM, Kosse LJ, Jessurun NT, Römkens TEH, Hoentjen F.

Purpose: To assess the agreement between patient-reported and health care provider-reported medical information in inflammatory bowel disease (IBD).
Methods: This multicentre, prospective, event monitoring study enrolled adult Crohn's disease (CD) and ulcerative colitis (UC) patients treated with a biological in four medical centers in the Netherlands. At two-monthly intervals, patients completed questionnaires on biological use, combination therapy and indication. The patient-reported information was compared with their electronic health records (EHRs) and analysed for percentage agreement and Cohen's kappa. A reference population from a prospective IBD registry was used to assess the representativeness of the study population.
Results: In total, 182 patients (female 50.5%, mean age 42.2 years, CD 76.9%) were included in the analysis. At baseline, 51.0% of the patients were prescribed an immunomodulator (43.9% thiopurines, 7.1% methotrexate), and patients were prescribed biologicals as follows: 59.3% infliximab, 30.2% adalimumab, 9.3% vedolizumab, and 1.1% ustekinumab. Agreement on patient-reported indication and biological use was almost perfect ($\kappa = 0.878$ and $\kappa = 1.000$, respectively); substantial for combination therapy ($\kappa = 0.672$). Gender, age, type of IBD, biological use and combination therapy were comparable with the reference population.
Conclusion: Systematic patient-reporting by questionnaires was reliable in retrieving indication and treatment specific information from IBD patients. These results indicate that the use of patient-reporting outcomes in daily IBD practice can ensure reliable information collection.

Gepubliceerd: Pharmacoepidemiol Drug Saf. 2021;30(4):520-4.
Impact factor: 2.890; Q2

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16. **Genetic Risk Scores Identify Genetic Aetiology of Inflammatory Bowel Disease Phenotypes**
Voskuil MD, Spekhorst LM, van der Sloot KWJ, Jansen BH, Dijkstra G, van der Woude CJ, Hoentjen F, Pierik MJ, van der Meulen AE, de Boer NKH, Lowenberg M, Oldenburg B, Festen EAM, Weersma RK.

Background and aims: Inflammatory bowel disease [IBD] phenotypes are very heterogeneous between patients, and current clinical and molecular classifications do not accurately predict the course that IBD will take over time. Genetic determinants of disease phenotypes remain largely unknown but could aid drug development and allow for personalised management. We used genetic risk scores [GRS] to disentangle the genetic contributions to IBD phenotypes.
Methods: Clinical characteristics and imputed genome-wide genetic array data of patients with IBD were obtained from two independent cohorts [cohort A, n = 1097; cohort B, n = 2156]. Genetic risk scoring [GRS] was used to assess genetic aetiology shared across traits and IBD phenotypes. Significant GRS-phenotype (false-discovery rate [FDR] corrected $p < 0.05$) associations identified in cohort A were put forward for replication in cohort B.
Results: Crohn's disease [CD] GRS were associated with fibrostenotic CD [R2 = 7.4%, FDR = 0.02] and ileocaecal resection [R2 = 4.1%, FDR = 1.6E-03], and this remained significant after correcting for previously identified clinical and genetic risk factors. Ulcerative colitis [UC] GRS [R2 = 7.1%, FDR = 0.02] and primary sclerosing cholangitis [PSC] GRS [R2 = 3.6%, FDR = 0.03] were associated with colonic CD, and these two

associations were largely driven by genetic variation in MHC. We also observed pleiotropy between PSC genetic risk and smoking behaviour [R2 = 1.7%, FDR = 0.04]. **Conclusions:** Patients with a higher genetic burden of CD are more likely to develop fibrostenotic disease and undergo ileocaecal resection, whereas colonic CD shares genetic aetiology with PSC and UC that is largely driven by variation in MHC. These results further our understanding of specific IBD phenotypes.

Gepubliceerd: J Crohns Colitis. 2021;15(6):930-7.
Impact factor: 9.071; Q1

Totale impact factor: 178.588
Gemiddelde impact factor: 11.162

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 31.949
Gemiddelde impact factor: 7.987

Medical School

1. **Real World Practice Deviation from Nationwide Guidelines in Patients with Intermittent Claudication**
Aaij AGL, Wermelink B, Haalboom M, Vahl AC, Meerwaldt R, Geelkerken RH.

Objective: Patients with intermittent claudication (IC) are initially treated with supervised exercise therapy (SET), as advised by national and international guidelines. Dutch health insurance companies and the Dutch National Health Care Institute suggested an 87% compliance rate with these guidelines in the Netherlands in 2017 and judged this to be undesirably low. The aim of this study was to evaluate compliance with IC guidelines and to elaborate on the reasons for deviating from them (practice variation) in a large teaching hospital.
Methods: A retrospective single centre cohort study was conducted at a large teaching hospital in the Netherlands. In total, 420 patients with newly diagnosed IC between 1 January 2017 and 31 December 2018 were analysed. Data included risk profiles and prescribed therapies.
Results: For all 420 included patients, the compliance rate with the guidelines for SET was 80.5%. The rate of adequately motivated and defensible practice variation was 15.7%; the rate of unjustified practice variation was 3.8%. Meaningful care was seen in 96.2% of cases.
Conclusion: Deviation from IC guidelines was found in 19.5% of patients. Almost three quarters of this deviation can be explained by the decision to provide personalised, meaningful care.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2021;62(3):432-8.
Impact factor: 7.069; Q1

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2. **Stability in eosinophil categorisation during subsequent severe exacerbations of COPD**
Citgez E, van der Palen J, van der Valk P, Kerstjens HAM, Brusse-Keizer M.

Background: The blood eosinophil count has been shown to be a promising biomarker for establishing personalised treatment strategies to reduce corticosteroid use, either inhaled or systemic, in chronic obstructive pulmonary disease (COPD). Eosinophil levels seem relatively stable over time in stable state, but little is known whether this is also true in subsequent severe acute exacerbations of COPD (AECOPD).
Aims and objectives: To determine the stability in eosinophil categorisation between two subsequent severe AECOPDs employing frequently used cut-off levels.
Methods: During two subsequent severe AECOPDs, blood eosinophil counts were determined at admission to the hospital in 237 patients in the Cohort of Mortality and Inflammation in COPD Study. The following four cut-off levels were analysed: absolute counts of eosinophils ≥0.2×10⁹/L (200 cells/μL) and ≥0.3×10⁹/L (300 cells/μL) and relative eosinophil percentage of ≥2% and ≥3% of total leucocyte count. Categorisations were considered stable if during the second AECOPD their blood eosinophil status led to the same classification: eosinophilic or not.
Results: Depending on the used cut-off, the overall stability in eosinophil categorisation varied between 70% and 85% during two subsequent AECOPDs. From patients who were eosinophilic at the first AECOPD, 34%-45% remained eosinophilic at the

subsequent AECOPD, while 9%-21% of patients being non-eosinophilic at the first AECOPD became eosinophilic at the subsequent AECOPD.
Conclusions: The eosinophil variability leads to category changes in subsequent AECOPDs, which limits the eosinophil categorisation stability. Therefore, measurement of eosinophils at each new exacerbation seems warranted.

Gepubliceerd: BMJ Open Respir Res. 2021;8(1).
Impact factor: 0; NVT

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3. **The value of open-source clinical science in pandemic response: lessons from ISARIC**
ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

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4. **Does EMDR Therapy Have an Effect on Memories of Emotional Abuse, Neglect and Other Types of Adverse Events in Patients with a Personality Disorder? Preliminary Data**
Hafkemeijer L, Starrenburg A, van der Palen J, Slotema K, de Jongh A.

Background: Little is known about the effectiveness of trauma-focused therapies for memories of events not meeting the A-criterion of post-traumatic stress disorder (PTSD).
Objective: Determining the effect of EMDR therapy on memories of emotional abuse, neglect and other types of adverse events in patients with a personality disorder (PD).
Method: We conducted a secondary analysis of the data from our study, which aimed to determine the effectiveness of five sessions of EMDR therapy in 49 patients with a PD. Patients were divided into three different groups depending on their most prevalent type of adverse event. Data were analyzed with Generalized Estimating Equations.
Results: Of all patients, 49% reported emotional neglect, 22.4% emotional abuse and 26.5% other types. Only one patient reported memories that predominantly fulfilled the A-criterion of PTSD. After five sessions of EMDR therapy, medium to large treatment effects for memories related to neglect (ds between 0.52 and 0.79), medium treatment effects for memories involving emotional abuse (ds between 0.18 and 0.59) and other types of adverse events were found (ds between 0.18 and 0.53). No significant differences in symptom reduction associated with the application of EMDR therapy among memories involving these three different types of adverse events could be revealed.
Conclusions: The results support the notion that EMDR therapy is not only an effective therapy for memories related to A-criteria-worthy events, but that it also has a symptom-reducing effect on memories involving other types of adverse events. This suggests that EMDR might be a valuable addition to the treatment of PD without PTSD.

Gepubliceerd: J Clin Med. 2021;10(19).
Impact factor: 4.242; Q1

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5. **Functional and morphological lumbar multifidus characteristics in subgroups with low back pain in primary care**
Hofste A, Soer R, Groen GJ, van der Palen J, Geerdink FJB, Oosterveld FGJ, Kiers H, Wolff AP, Hermens H.

Background: Since the contribution of the lumbar multifidus(LM) is not well understood in relation to non-specific low back pain(LBP), this may limit physiotherapists in choosing the most appropriate treatment strategy. **Objectives:** This study aims to compare clinical characteristics, in terms of LM function and morphology, between subacute and chronic LBP patients from a large clinical practice cohort compared to healthy controls. DESIGN: Multicenter case control study.
Method: Subacute and chronic LBP patients and healthy controls between 18 and 65 years of age were included. Several clinical tests were performed: primary outcomes were the LM thickness from ultrasound measurements, trunk range of motion(ROM) from 3D kinematic tests, and median frequency and root mean square values of LM by electromyography measurements. The secondary outcomes Numeric Rating Scale for Pain(NRS) and the Oswestry Disability Index(ODI) were administered. Comparisons between groups were made with ANOVA, p-values<0.05, with Tukey's HSD post-hoc test were considered significant.
Results: A total of 161 participants were included, 50 healthy controls, 59 chronic LBP patients, and 52 subacute LBP patients. Trunk ROM and LM thickness were significantly larger in healthy controls compared to all LBP patients($p < 0.01$). A lower LM thickness was found between subacute and chronic LBP patients although not significant($p = 0.11$-0.97). All between-group comparisons showed no statistically significant differences in electromyography outcomes ($p = 0.10$-0.32). NRS showed no significant differences between LBP subgroups($p = 0.21$). Chronic LBP patients showed a significant higher ODI score compared to subacute LBP patients($p = 0.03$).
Conclusions: Trunk ROM and LM thickness show differences between LBP patients and healthy controls.

Gepubliceerd: Musculoskelet Sci Pract. 2021;55:102429.
Impact factor: 2.520; Q2

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6. **Optimizing the risk threshold of lymph node involvement for performing extended pelvic lymph node dissection in prostate cancer patients: a cost-effectiveness analysis**
Hueting TA, Cornel EB, Korthorst RA, Pleijhuis RG, Somford DM, van Basten JA, van der Palen J, Koffijberg H.

Background: Extended pelvic lymph node dissection (ePLND) may be omitted in prostate cancer (CaP) patients with a low predicted risk of lymph node involvement (LNI). The aim of the current study was to quantify the cost-effectiveness of using different risk thresholds for predicted LNI in CaP patients to inform decision making on omitting ePLND.

Methods: Five different thresholds (2%, 5%, 10%, 20%, and 100%) used in practice for performing ePLND were compared using a decision analytic cohort model with the 100% threshold (i.e., no ePLND) as reference. Compared outcomes consisted of quality-adjusted life years (QALYs) and costs. Baseline characteristics for the hypothetical cohort were based on an actual Dutch patient cohort containing 925 patients who underwent ePLND with risks of LNI predicted by the Memorial Sloan Kettering Cancer Center web-calculator. The best strategy was selected based on the incremental cost effectiveness ratio when applying a willingness to pay (WTP) threshold of €20,000 per QALY gained. Probabilistic sensitivity analysis was performed with Monte Carlo simulation to assess the robustness of the results.
Results: Costs and health outcomes were lowest (€4,858 and 6.04 QALYs) for the 100% threshold, and highest (€10,939 and 6.21 QALYs) for the 2% threshold, respectively. The incremental cost effectiveness ratio for the 2%, 5%, 10%, and 20% threshold compared with the first threshold above (i.e., 5%, 10%, 20%, and 100%) were €189,222/QALY, €130,689/QALY, €51,920/QALY, and €23,187/QALY respectively. Applying a WTP threshold of €20.000 the probabilities for the 2%, 5%, 10%, 20%, and 100% threshold strategies being cost-effective were 0.0%, 0.3%, 4.9%, 30.3%, and 64.5% respectively.
Conclusion: Applying a WTP threshold of €20.000, completely omitting ePLND in CaP patients is cost-effective compared to other risk-based strategies. However, applying a 20% threshold for probable LNI to the Briganti 2012 nomogram or the Memorial Sloan Kettering Cancer Center web-calculator, may be a feasible alternative, in particular when higher WTP values are considered.

Gepubliceerd: Urol Oncol. 2021;39(1):72.e7-.e14.
Impact factor: 0; NVT

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7. **Effectiveness and safety of cervical catheter tip placement in intrathecal baclofen treatment of spasticity: A systematic review**
Jacobs NW, Maas EM, Brusse-Keizer M, Rietman HJS.

Objective: To evaluate the effectiveness and safety of intrathecal baclofen treatment of spasticity, administered via a cervical catheter tip. DESIGN: A review of PubMed and the Cochrane Library up to September 2020. No restriction in study design. Two reviewers independently evaluated eligibility, extracted data and evaluated risk of bias. Studies were included in which patients were treated with intrathecal baclofen for spasticity, with the catheter tip at or above the first thoracic level, independent of diagnosis and age.
Results: Thirteen studies were eligible, with a moderate to critical risk of bias. Improvement in spasticity was seen only in the upper extremity in 6% of subjects, only in the lower extremity in 2%, in both upper and lower extremities in 50% and without specification of location in 41%. Upper extremity function improved in 88% of cases. Neither drug-related (1%) nor technical (21%) complications occurred more often than in lower placement of the tip. Effects on respiratory function and sleep apnoea were not investigated.
Conclusion: Cervically administered intrathecal baclofen seems to improve upper extremity spasticity and function, without causing more complications than thoracolumbar intrathecal baclofen. However, the mainly drug-related complications have not been thoroughly investigated and the available literature is of poor

methodological quality. Further research is needed to confirm the efficacy and safety of this procedure.

Gepubliceerd: J Rehabil Med. 2021;53(7):jrm00215.
Impact factor: 2.912; Q2

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8. **Functional or not functional; that's the question: Can we predict the diagnosis functional movement disorder based on associated features?**
Lagrand T, Tuitert I, Klamer M, van der Meulen A, van der Palen J, Kramer G, Tijssen M.

Background and Purpose: Functional movement disorders (FMDs) pose a diagnostic challenge for clinicians. Over the years several associated features have been shown to be suggestive for FMDs. Which features mentioned in the literature are discriminative between FMDs and non-FMDs were examined in a large cohort. In addition, a preliminary prediction model distinguishing these disorders was developed based on differentiating features.
Method: Medical records of all consecutive patients who visited our hyperkinetic outpatient clinic from 2012 to 2019 were retrospectively reviewed and 12 associated features in FMDs versus non-FMDs were compared. An independent t test for age of onset and Pearson chi-squared analyses for all categorical variables were performed. Multivariate logistic regression analysis was performed to develop a preliminary predictive model for FMDs.
Results: A total of 874 patients were eligible for inclusion, of whom 320 had an FMD and 554 a non-FMD. Differentiating features between these groups were age of onset, sex, psychiatric history, family history, more than one motor phenotype, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day. Based on these a preliminary predictive model was computed with a discriminative value of 91%.
Discussion: Ten associated features are shown to be not only suggestive but also discriminative between hyperkinetic FMDs and non-FMDs. Clinicians can use these features to identify patients suspected for FMDs and can subsequently alert them to test for positive symptoms at examination. Although a first preliminary model has good predictive accuracy, further validation should be performed prospectively in a multi-center study.

Gepubliceerd: Eur J Neurol. 2021;28(1):33-9.
Impact factor: 6.089; Q1

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9. **The Impact of Non-dopaminergic Medication on Quality of Life in Parkinson's Disease**
Oonk NGM, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background and objectives: Quality of life (QoL) in Parkinson's disease (PD) depends on multiple factors. Due to PD treatment and accompanying, age-related or independent comorbidities, pill burden is often high. The relation of QoL and pharmacotherapy for comorbidities in PD has not been widely studied. This study

investigated if and to what extent non-dopaminergic drugs are related to QoL in PD. Second, the impact of demographics and non-motor symptoms were evaluated. A better understanding of the impact of different non-dopaminergic drugs and polypharmacy on QoL will have added value in selecting appropriate (medication) interventions.
Methods: In a cross-sectional analysis, medication prescription data of 209 PD patients were analyzed and grouped according to the Rx-Risk comorbidity index. QoL was measured using the PDQ-39 questionnaire. Non-motor symptoms were analyzed with the Non-Motor Symptoms questionnaire. Independent factors associated with a reduced QoL were identified with a multivariate linear regression analysis.
Results: Non-dopaminergic drugs, subdivided into Rx-Risk comorbidity categories, were not associated with reduced QoL, except for the use of anti-epileptic drugs. However, using more daily non-dopaminergic drugs was also negatively associated with QoL, as well as female sex, increased PD severity, and more non-motor symptoms. Contraindicated non-dopaminergic medication was barely prescribed (0.4%).
Conclusion: Non-dopaminergic drugs are frequently prescribed, and higher numbers are associated with impaired QoL in PD. However, when divided in drug types, only anti-epileptic drugs were negatively associated with QoL. In these patients, physicians might improve QoL by further optimizing the condition it was prescribed for (e.g., pain or anxiety), or managing of side effects.
Trial registrattion: Netherlands Trial Register; NL4360.

Gepubliceerd: Clin Drug Investig. 2021;41(9):809-16.
Impact factor: 2.859; Q3

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10. **Use and usability of the dr. Bart app and its relation with health care utilisation and clinical outcomes in people with knee and/or hip osteoarthritis**
Pelle T, van der Palen J, de Graaf F, van den Hoogen FHJ, Bevers K, van den Ende CHM.

Background: Self-management is of paramount importance in the non-surgical treatment of knee/hip osteoarthritis (OA). Modern technologies offer the possibility of 24/7 self-management support. We developed an e-self-management application (dr. Bart app) for people with knee/hip OA. The aim of this study was to document the use and usability of the dr. Bart app and its relation with health care utilisation and clinical outcomes in people with knee/hip OA.
Methods: For this study we used backend data for the first 26 weeks of use by the intervention group (N = 214) of an RCT examining the effectiveness of the dr. Bart app. A central element of the dr. Bart app is that it proposes a selection of 72 preformulated goals for health behaviours based on the 'tiny habits method' (e.g. after lunch I rise 12 times from my chair to train my leg muscles). The usability of the app was measured using the System Usability Scale questionnaire (SUS), on a scale of 0-100. To assess the association between the intensity of use of the app and health care utilisation (i.e., consultations in primary or secondary health care) and clinical outcomes (i.e., self-management behaviour, physical activity, health-related quality of life, illness perceptions, symptoms, pain, activities of daily living) we calculated Spearman rank correlation coefficients.

Results: Of the 214 participants, 171 (80%) logged in at least once with 151 (71%) choosing at least one goal and 114 (53%) completing at least one goal during the 26 weeks. Of those who chose at least one goal, 56 participants (37%) continued to log in for up to 26 weeks, 12 (8%) continued to select new goals from the offered goals and 37 (25%) continued to complete goals. Preformulated goals in the themes of physical activity (e.g., performing an exercise from the exercises library in the app) and nutrition (e.g., 'eat two pieces of fruit today') were found to be most popular with users. The mean usability scores (standard deviation) at the three and six month follow-ups were 65.9 (16.9) and 64.5 (17.5), respectively. The vast majority of associations between the intensity of use of the dr. Bart app and target outcomes were weak at $\rho < (-) 0.25$.
Conclusions: More than one-third of people with knee/hip OA who started using the app, continued to use it up to 26 weeks, though usability could be improved. Patients appear to have preferences for goals related to physical activity and nutrition, rather than for goals related to vitality and education. We found weak/no associations between the intensity of use of the dr. Bart app and health care utilisation and clinical outcomes.
Trial registrattion: Dutch Trial Register (Trial Number NTR6693/NL6505).

Gepubliceerd: BMC Health Serv Res. 2021;21(1):444.
Impact factor: 2.655; Q3

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11. **Predictors of patient adherence to COPD self-management exacerbation action plans**
Schrijver J, Effing TW, Brusse-Keizer M, van der Palen J, van der Valk P, Lenferink A.

Objective: Identifying patient characteristics predicting categories of patient adherence to Chronic Obstructive Pulmonary Disease (COPD) exacerbation action plans.
Methods: Data were obtained from self-treatment intervention groups of two COPD self-management trials. Patients with ≥1 exacerbation and/or ≥1 self-initiated prednisolone course during one-year follow-up were included. Optimal treatment was defined as 'self-initiating prednisolone treatment ≤2 days from the onset of a COPD exacerbation'. Predictors of adherence categories were identified by multinomial logistic regression analysis using patient characteristics.
Results: 145 COPD patients were included and allocated to four adherence categories: 'optimal treatment' (26.2 %), 'sub optimal treatment' (11.7 %), 'significant delay or no treatment' (31.7 %), or 'treatment outside the actual exacerbation period' (30.3 %). One unit increase in baseline dyspnoea score (mMRC scale 0-4) increased the risk of 'significant delay or no treatment' (OR 1.64 (95 % CI 1.07-2.50)). Cardiac comorbidity showed a borderline significant increased risk of 'treatment outside the actual exacerbation period' (OR 2.40 (95 % CI 0.98-5.85)).
Conclusion: More severe dyspnoea and cardiac comorbidity may lower adherence to COPD exacerbation action plans. PRACTICE IMPLICATIONS: Tailored self-management support with more focus on dyspnoea and cardiac disease symptoms may help patients to better act upon increased exacerbation symptoms and improve adherence to COPD exacerbation action plans.

Gepubliceerd: Patient Educ Couns. 2021;104(1):163-70.
Impact factor: 2.940; Q1

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12. **Adherence to an eHealth Self-Management Intervention for Patients with Both COPD and Heart Failure: Results of a Pilot Study**
Sloots J, Bakker M, van der Palen J, Eijsvogel M, van der Valk P, Linssen G, van Ommeren C, Grinovero M, Tabak M, Effing T, Lenferink A.

Background: Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) often coexist and share periods of symptom deterioration. Electronic health (eHealth) might play an important role in adherence to interventions for the self-management of COPD and CHF symptoms by facilitating and supporting home-based care.
Methods: In this pilot study, an eHealth self-management intervention was developed based on paper versions of multi-morbid exacerbation action plans and evaluated in patients with both COPD and CHF. Self-reporting of increased symptoms in diaries was linked to an automated decision support system that generated self-management actions, which was communicated via an eHealth application on a tablet. After participating in self-management training sessions, patients used the intervention for a maximum of four months. Adherence to daily symptom diary completion and follow-up of actions were analyzed. An add-on sensorized (Respiro(®)) inhaler was used to analyze inhaled medication adherence and inhalation technique.
Results: In total, 1148 (91%) of the daily diaries were completed on the same day by 11 participating patients (mean age 66.8 ± 2.9 years; moderate (55%) to severe (45%) COPD; 46% midrange left ventricular function (LVF) and 27% reduced LVF). Seven patients received a total of 24 advised actions because of increased symptoms of which 11 (46%) were followed-up. Of the 13 (54%) unperformed advised actions, six were "call the case manager". Adherence to inhaled medication was 98.4%, but 51.9% of inhalations were performed incorrectly, with "inhaling too shortly" (<1.25 s) being the most frequent error (79.6%).
Discussion: Whereas adherence to completing daily diaries was high, advised actions were inadequately followed-up, particularly the action "call the case manager". Inhaled medication adherence was high, but inhalations were poorly performed. Future research is needed to identify adherence barriers, further tailor the intervention to the individual patient and analyse the intervention effects on health outcomes.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2021;16:2089-103.
Impact factor: 3.355; Q2

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13. **Long-term effectiveness of web-based cognitive behavioral therapy for patients with eating disorders**
Ter Huurne ED, de Haan HA, Postel MG, DeJong CAJ, VanDerNagel JEL, van der Palen J.

Purpose: To evaluate the long-term effectiveness of a web-based therapist-delivered cognitive behavioral therapy (CBT) for patients with eating disorders (ED).
Methods: We used follow-up data from a randomized controlled trial that evaluated a web-based CBT on ED psychopathology and related health, compared to a waiting list control (WL) condition. As participants of the WL condition started the intervention after their waiting period, follow-up data included participants from both groups. The primary outcome was change from baseline, at 3, 6, and 12-month intervals in ED psychopathology, analyzed using mixed models for repeated measures. Secondary

outcomes included body dissatisfaction, BMI, physical health, mental health, self-esteem, quality of life, and social functioning.
Results: The population comprised 212 participants in total, in three subgroups: bulimia nervosa (BN; n = 44), binge eating disorder (BED; n = 83), and ED not otherwise specified (EDNOS; n = 85). Treatment effects were sustained during follow-up, with generally large effect sizes for the reduction of ED psychopathology and body dissatisfaction, and small to moderate effect sizes for physical and mental health, self-esteem, social functioning, and quality of life. Most effects were found for all three subgroups, except for long-term improvements in self-esteem and quality of life among participants with BN and EDNOS.
Conclusion: This study showed long-term sustainability of treatment effects up to 1-year post-treatment of a web-based therapist-delivered CBT for patients with various ED.
Level of evidence: Level IV, evidence obtained from multiple time series analysis, with intervention. UNIQUE CLINICAL TRIAL NUMBER: NTR2415-Dutch Trial Registry (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2415).

Gepubliceerd: Eat Weight Disord. 2021;26(3):911-9.
Impact factor: 4.652; Q2

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14. **Comparison of inhalation technique with the Diskus and Autohaler in asthmatic children at home**
van der Kolk A, Lammers N, Brusse-Keizer M, van der Palen J, Faber J, Spenkelink-Visser R, Thio BJ.

Objective: Asthma is the most common chronic disease in childhood and anti-inflammatory medication is the cornerstone of treatment. Inhalers are frequently used incorrectly when demonstrated in the hospital, suggesting poor technique at home. We aimed to 1) compare daily inhalation technique with the Diskus and Autohaler in asthmatic children by filming inhalations at home and 2) compare daily inhalation technique with technique demonstrated in the hospital.
Methods: We performed a randomised study in asthmatic children (aged 6-18 years) from the outpatient clinic of Medisch Spectrum Twente hospital (Enschede, The Netherlands) from July 2014 to April 2016. Children received inhalation instructions for the Diskus and Autohaler and were randomised to use one device in the morning and the other in the evening. During the 28-day study period, inhalations were filmed at home and subsequently demonstrated in the hospital. All inhalations were checked for seven critical errors per device.
Results: 636 videos with the Diskus and 663 with the Autohaler were provided by 27 children. The most common critical error in daily life was an incorrect device position during preparation of the Diskus (n=271) and an insufficiently deep inhalation (n=39) using the Autohaler. Percentage of correct days using the Diskus was 44%, compared to 96% with the Autohaler ($p<0.001$). The two most common errors with the Diskus were made at least twice as often at home than in the hospital.
Conclusion: Inhalation technique at home was markedly better with the Autohaler than with the Diskus. Paediatricians should be aware that hospital-based demonstrations can overestimate daily inhalation technique with the Diskus.

Gepubliceerd: ERJ Open Res. 2021;7(2).
Impact factor: 0; NVT

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15. **Cardiac imaging in ischemic stroke or transient ischemic attack of undetermined cause: Systematic review & meta-analysis**
van der Maten G, Dijkstra S, Meijs MFL, von Birgelen C, van der Palen J, den Hertog HM.

Background: Patients with ischemic stroke or transient ischemic attack (TIA) of undetermined cause often undergo cardiac imaging in search of a cardioembolic source. As the choice of the most appropriate imaging approach is controversial and therapeutic implications have changed over time, we aimed to identify in patients with "cryptogenic stroke or TIA" the yield of transthoracic or transesophageal echocardiography (TTE or TEE) and cardiac computed tomography (CT).
Methods and results: We performed a systematic review and meta-analysis according to the PRISMA guidelines. Included were studies that assessed consecutive patients with ischemic stroke or TIA of undetermined cause to evaluate the yield of TTE, TEE, or cardiac CT for detecting cardioembolic sources. For each type of cardioembolic source the pooled prevalence was calculated. Only six out of 1458 studies fulfilled the inclusion criteria (1022 patients). One study reported the yield of TTE, four of TEE, and one of both TTE and TEE; no study assessed cardiac CT. Mean patient age ranged from 44.3-71.2 years, 49.2-59.7% were male. TTE detected 43 cardioembolic sources in 316 patients (4 (1.3%) major, 39 (12.3%) minor), and TEE 248 in 937 patients (55 (5.9%) major, 193 (20.6%) minor). The most prevalent major cardioembolic source was left atrial appendage thrombus, yet results were heterogeneous among studies.
Conclusions: TTE and TEE infrequently detect major cardioembolic sources that require a change of therapy. Findings should be interpreted with caution due to the limited number of studies. A large-sized prospective clinical trial is warranted to support evidence-based decision-making.

Gepubliceerd: Int J Cardiol. 2021;339:211-8.
Impact factor: 4.164; Q2

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16. **Detection of Major Cardioembolic Sources in Real-World Patients with Ischemic Stroke or Transient Ischemic Attack of Undetermined Cause**
van der Maten G, Reimer JMB, Meijs MFL, von Birgelen C, Brusse-Keizer M, den Hertog HM.

Background/Aim: Current guidelines recommend transthoracic echocardiography (TTE) and ambulatory rhythm monitoring following ischemic stroke or transient ischemic attack (TIA) of undetermined cause for identifying cardioembolic sources (CES). Due to ongoing controversies about this routine strategy, we evaluated its yield in a real-world setting.
Methods: In a tertiary medical center, we retrospectively evaluated consecutive patients with ischemic stroke or TIA of undetermined cause, who (after standard work-up) underwent TTE, ambulatory rhythm monitoring, or both. CES were classified as major if probably related to ischemic events and warranting a change of therapy.

Results: Between January 2014 and December 2017, 674 patients had ischemic stroke or TIA of undetermined cause. Of all 484 patients (71.8%) who underwent TTE, 9 (1.9%) had a major CES. However, 7 of them had already been identified for cardiac evaluation due to new major electrocardiographic abnormalities or cardiac symptoms. Thus, only 2 patients (0.4%) truly benefitted from unselected TTE screening. Ambulatory rhythm monitoring was performed in 411 patients (61.0%) and revealed AF in 10 patients (2.4%).
Conclusion: Detecting a major CES is essential because appropriate treatment lowers the risk of recurrent stroke. Nonetheless, in this real-world study that aimed at routine use of TTE and ambulatory rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause, the prevalence of major CES was low. Most patients with major CES on TTE already had an indication for referral to a cardiologist, suggesting that major CES might also have been identified with a much more selective use of TTE.

Gepubliceerd: Cerebrovasc Dis Extra. 2021;11(1):22-8.
Impact factor: 0; NVT

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17. **A Systematic Review and Critical Appraisal of Peri-Procedural Tissue Perfusion Techniques and their Clinical Value in Patients with Peripheral Arterial Disease**
Wermelink B, Ma KF, Haalboom M, El Moumni M, de Vries JPM, Geelkerken RH.

Objective: Many techniques have been introduced to enable quantification of tissue perfusion in patients with peripheral arterial disease (PAD). Currently, none of these techniques is widely used to analyse real time tissue perfusion changes during endovascular or surgical revascularisation procedures. The aim of this systematic review was to provide an up to date overview of the peri-procedural applicability of currently available techniques, diagnostic accuracy of assessing tissue perfusion and the relationship with clinical outcomes.
Data sources: MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials. REVIEW
Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines. Four electronic databases were searched up to 31 12 2020 for eligible articles: MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. Eligible articles describing a perfusion measurement technique, used in a peri-procedural setting before and within 24 hours after the revascularisation procedure, with the aim of determining the effect of intervention in patients with PAD, were assessed for inclusion. The QUADAS-2 tool was used to assess the risk of bias and applicability of the studies.
Results: An overview of 10 techniques found in 26 eligible articles focused on study protocols, research goals, and clinical outcomes is provided. Non-invasive techniques included laser speckle contrast imaging, micro-lightguide spectrophotometry, magnetic resonance imaging perfusion, near infrared spectroscopy, skin perfusion pressure, and plantar thermography. Invasive techniques included two dimensional perfusion angiography, contrast enhanced ultrasound, computed tomography perfusion imaging, and indocyanine green angiography. The results of the 26 eligible studies, which were mostly of poor quality according to QUADAS-2, were without exception, not sufficient to substantiate implementation in daily clinical practice.

Conclusion: This systematic review provides an overview of 10 tissue perfusion assessment techniques for patients with PAD. It seems too early to appoint one of them as a reference standard. The scope of future research in this domain should therefore focus on clinical accuracy, reliability, and validation of the techniques.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2021;62(6):896-908.
Impact factor: 7.069; Q1

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18. **Applying the electronic nose for pre-operative SARS-CoV-2 screening**
Wintjens A, Hintzen KFH, Engelen SME, Lubbers T, Savelkoul PHM, Wesseling G, van der Palen J, Bouvy ND.

Background: Infection with SARS-CoV-2 causes corona virus disease (COVID-19). The most standard diagnostic method is reverse transcription-polymerase chain reaction (RT-PCR) on a nasopharyngeal and/or an oropharyngeal swab. The high occurrence of false-negative results due to the non-presence of SARS-CoV-2 in the oropharyngeal environment renders this sampling method not ideal. Therefore, a new sampling device is desirable. This proof-of-principle study investigated the possibility to train machine-learning classifiers with an electronic nose (Aeonose) to differentiate between COVID-19-positive and negative persons based on volatile organic compounds (VOCs) analysis.
Methods: Between April and June 2020, participants were invited for breath analysis when a swab for RT-PCR was collected. If the RT-PCR resulted negative, the presence of SARS-CoV-2-specific antibodies was checked to confirm the negative result. All participants breathed through the Aeonose for five minutes. This device contains metal-oxide sensors that change in conductivity upon reaction with VOCs in exhaled breath. These conductivity changes are input data for machine learning and used for pattern recognition. The result is a value between - 1 and + 1, indicating the infection probability.
Results: 219 participants were included, 57 of which COVID-19 positive. A sensitivity of 0.86 and a negative predictive value (NPV) of 0.92 were found. Adding clinical variables to machine-learning classifier via multivariate logistic regression analysis, the NPV improved to 0.96.
Conclusions: The Aeonose can distinguish COVID-19 positive from negative participants based on VOC patterns in exhaled breath with a high NPV. The Aeonose might be a promising, non-invasive, and low-cost triage tool for excluding SARS-CoV-2 infection in patients elected for surgery.

Gepubliceerd: Surg Endosc. 2021;35(12):6671-8.
Impact factor: 4.584; Q1

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19. **Predicting Mortality in COPD with Validated and Sensitive Biomarkers; Fibrinogen and Mid-Range-Proadrenomedullin (MR-proADM)**
Zuur-Telgen MC, Citgez E, Zuur AT, van der Valk P, van der Palen J, Kerstjens HAM, Brusse-Keizer M.

Although fibrinogen is a FDA qualified prognostic biomarker in COPD, it still lacks sufficient resolution to be clinically useful. Next to replication of findings in different

cohorts also the combination with other validated biomarkers should be investigated. Therefore, the aim of this study was to confirm in a large well-defined population of COPD patients whether fibrinogen can predict mortality and whether a combination with the biomarker MR-proADM can increase prognostic accuracy. From the COMIC cohort study we included COPD patients with a blood sample obtained in stable state (n = 640) and/or at hospitalization for an acute exacerbation of COPD (n = 262). Risk of death during 3 years of follow up for the separate and combined biomarker models was analyzed with Cox regression. Furthermore, logistic regression models for death after one year were constructed. When both fibrinogen and MR-proADM were included in the survival model, a doubling in fibrinogen and MR-proADM levels gave a 2.2 (95% CI 1.3-3.7) and 2.1 (95% CI 1.5-3.0) fold increased risk of dying, respectively. The prediction model for death after 1 year improved significantly when MR-proADM was added to the model with fibrinogen (AUC increased from 0.78 to 0.83; p = 0.02). However, the combined model was not significantly more adequate than the model with solely MR-proADM (AUC 0.83 vs 0.82; p = 0.34). The study suggests that MR-proADM is more promising than fibrinogen in prediciting mortality. Adding fibrinogen to a model containing MR-proADM does not significantly increase the predictive capacity of the model.

Gepubliceerd: Copd. 2021;18(6):643-9.
Impact factor: 2.409; Q4

Totale impact factor: 82.590
Gemiddelde impact factor: 4.347

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 9.716
Gemiddelde impact factor: 2.429

Microbiologie

1. **The value of open-source clinical science in pandemic response: lessons from ISARIC**

ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

Totale impact factor: 25.071
Gemiddelde impact factor: 25.071

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

Mond- Kaak- en Aangezichtschirurgie

1. **A complete magnetic sentinel lymph node biopsy procedure in oral cancer patients: A pilot study**

Nieuwenhuis ER, Kolenaar B, van Bemmel AJM, Hof JJ, van Baarlen J, Christenhusz A, Pouw JJ, Ten Haken B, Alic L, de Bree R.

Objectives: To assess the feasibility and merits of a complete magnetic approach for a sentinel lymph node biopsy (SLNB) procedure in oral cancer patients.
Materials and methods: This study included ten oral cancer patients (stage cT1-T2N0M0) scheduled for elective neck dissection (END). Superparamagnetic iron oxide nanoparticles (SPIO) were administered peritumorally prior to surgery. A preoperative MRI was acquired to identify lymph nodes (LNs) with iron uptake. A magnetic detector was used to identify magnetic hotspots prior, during, and after the SLNB procedure. The resected sentinel LNs (SLNs) were evaluated using step-serial sectioning, and the neck dissection specimen was assessed by routine histopathological examination. A postoperative MRI was acquired to observe any residual iron.
Results: Of ten primary tumors, eight were located in the tongue, one floor-of-mouth (FOM), and one tongue-FOM transition. SPIO injections were experienced as painful by nine patients, two of whom developed a tongue swelling. In eight patients, magnetic SLNs were successfully detected and excised during the magnetic SLNB procedure. During the END procedure, additional magnetic SLNs were identified in three patients. Histopathology confirmed iron deposits in sinuses of excised SLNs. Three SLNs were harboring metastases, of which one was identified only during the END procedure. The END specimens revealed no further metastases.
Conclusion: A complete magnetic SLNB procedure was successfully performed in eight of ten patients (80% success rate), therefore the procedure seems feasible. Recommendations for further investigation are made including: use of anesthetics, magnetic tracer volume, planning preoperative MRI, comparison to conventional technique and follow-up.

Gepubliceerd: Oral Oncol. 2021;121:105464.
Impact factor: 5.337; Q1

Totale impact factor: 5.337
Gemiddelde impact factor: 5.337

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 5.337
Gemiddelde impact factor: 5.337

Neurocentrum

1. **Importance of Occlusion Site for Thrombectomy Technique in Stroke: Comparison Between Aspiration and Stent Retriever**

Bernsen MLE, Goldhoorn RB, Lingsma HF, van Oostenbrugge RJ, van Zwam WH, Uyttenboogaart M, Roos Y, Martens JM, Hofmeijer J, MR CLEAN Registry investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background and Purpose: Thrombectomy with stent retriever and direct aspiration are equally effective in the endovascular treatment of anterior circulation acute ischemic stroke. We report efficacy and safety of initial treatment technique per occlusion segment.
Methods: For this study, we analyzed data from the MR CLEAN Registry, a prospective, observational study in all centers that perform endovascular therapy in the Netherlands. We used ordinal logistic regression analysis to compare clinical and technical results of first line direct aspiration treatment with that of stent retriever thrombectomy stratified for occlusion segment. Primary outcome measure was functional outcome at 3 months. Secondary outcome measures included reperfusion grade expressed as the extended Thrombolysis in Cerebral Infarction score, periprocedural complication risk, time to reperfusion, and mortality.
Results: Of the 2282 included patients, 1658 (73%) were initially treated with stent retriever and 624 (27%) with aspiration. Four hundred sixty-two patients had an occlusion of the intracranial part of the carotid artery, 1349 of the proximal middle cerebral artery, and 471 of the distal parts of the middle cerebral artery. There was no difference in functional outcome between aspiration and stent retriever thrombectomy (odds ratio, 1.0 [95% CI, 0.9-1.2]) in any of the occlusion segments (P value for interaction=0.2). Reperfusion rate was higher in the aspiration group (odds ratio, 1.4 [95% CI, 1.1-1.6]) and did not differ between occlusion segments (P value for interaction=0.6). Procedure times were shorter in the aspiration group (minutes 50 versus 65 minutes; P<0.0001). There was no difference in periprocedural complications or mortality.
Conclusions: In unselected patients with anterior circulation infarcts, we observed equal functional outcome of aspiration and stent retriever thrombectomy in all occlusion segments. When aspiration was the first line treatment modality, reperfusion rates were higher and procedure times shorter in all occlusion segments.

Gepubliceerd: Stroke. 2021;52(1):80-90.
Impact factor: 7.914; Q1

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2. **EEG functional connectivity contributes to outcome prediction of postanoxic coma**

Carrasco-Gómez M, Keijzer HM, Ruijter BJ, Bruña R, Tjepkema-Cloostermans MC, Hofmeijer J, van Putten M.

Objective: To investigate the additional value of EEG functional connectivity features, in addition to non-coupling EEG features, for outcome prediction of comatose patients after cardiac arrest.
Methods: Prospective, multicenter cohort study. Coherence, phase locking value, and mutual information were calculated in 19-channel EEGs at 12 h, 24 h and 48 h after

cardiac arrest. Three sets of machine learning classification models were trained and validated with functional connectivity, EEG non-coupling features, and a combination of these. Neurological outcome was assessed at six months and categorized as "good" (Cerebral Performance Category [CPC] 1-2) or "poor" (CPC 3-5).
Results: We included 594 patients (46% good outcome). A sensitivity of 51% (95% CI: 34-56%) at 100% specificity in predicting poor outcome was achieved by the best functional connectivity-based classifier at 12 h after cardiac arrest, while the best non-coupling-based model reached a sensitivity of 32% (0-54%) at 100% specificity using data at 12 h and 48 h. Combination of both sets of features achieved a sensitivity of 73% (50-77%) at 100% specificity.
Conclusion: Functional connectivity measures improve EEG based prediction models for poor outcome of postanoxic coma. SIGNIFICANCE: Functional connectivity features derived from early EEG hold potential to improve outcome prediction of coma after cardiac arrest.

Gepubliceerd: Clin Neurophysiol. 2021;132(6):1312-20.
Impact factor: 3.708; Q2

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3. **Efficient use of clinical EEG data for deep learning in epilepsy**
da Silva Lourenço C, Tjepkema-Cloostermans MC, van Putten M.

Objective: Automating detection of Interictal Epileptiform Discharges (IEDs) in electroencephalogram (EEG) recordings can reduce the time spent on visual analysis for the diagnosis of epilepsy. Deep learning has shown potential for this purpose, but the scarceness of expert annotated data creates a bottleneck in the process.
Methods: We used EEGs from 50 patients with focal epilepsy, 49 patients with generalized epilepsy (IEDs were visually labeled by experts) and 67 controls. The data was filtered, downsampled and cut into two second epochs. We increased the number of input samples containing IEDs through temporal shifting and using different montages. A VGG C convolutional neural network was trained to detect IEDs.
Results: Using the dataset with more samples, we reduced the false positive rate from 2.11 to 0.73 detections per minute at the intersection of sensitivity and specificity. Sensitivity increased from 63% to 96% at 99% specificity. The model became less sensitive to the position of the IED in the epoch and montage.
Conclusions: Temporal shifting and use of different EEG montages improves performance of deep neural networks in IED detection. SIGNIFICANCE: Dataset augmentation can reduce the need for expert annotation, facilitating the training of neural networks, potentially leading to a fundamental shift in EEG analysis.

Gepubliceerd: Clin Neurophysiol. 2021;132(6):1234-40.
Impact factor: 3.708; Q2

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4. **Machine learning for detection of interictal epileptiform discharges**
da Silva Lourenço C, Tjepkema-Cloostermans MC, van Putten M.

The electroencephalogram (EEG) is a fundamental tool in the diagnosis and classification of epilepsy. In particular, Interictal Epileptiform Discharges (IEDs) reflect an increased likelihood of seizures and are routinely assessed by visual analysis of the

EEG. Visual assessment is, however, time consuming and prone to subjectivity, leading to a high misdiagnosis rate and motivating the development of automated approaches. Research towards automating IED detection started 45 years ago. Approaches range from mimetic methods to deep learning techniques. We review different approaches to IED detection, discussing their performance and limitations. Traditional machine learning and deep learning methods have yielded the best results so far and their application in the field is still growing. Standardization of datasets and outcome measures is necessary to compare models more objectively and decide which should be implemented in a clinical setting.

Gepubliceerd: Clin Neurophysiol. 2021;132(7):1433-43.
Impact factor: 3.708; Q2

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5. **Subacute neurological deficits and respiratory insufficiency due to intrathecal methotrexate**
de Faber S, Mutsaers P, van den Bent MJ, van der Meulen M.

Background and aim: We present a case of a 22-year-old male diagnosed with B-cell acute lymphoblastic leukemia who received intrathecal (IT) methotrexate (MTX) in addition to his systemic chemotherapy regime. During induction treatment, he presented with a rapidly progressive bilateral paresis, anarthria, and respiratory insufficiency requiring intubation. The brain magnetic resonance imaging showed bilateral lesions with diffusion restriction of the corona radiata/centrum semi-ovale without other abnormalities. He recovered spontaneously without neurological sequelae. The clinical course combined with the radiological findings is suspect for an IT-MTX-induced leukoencephalopathy.
Relevance for patients: Although neurological deficits after IT-MTX are rare and in most cases self-limiting, it should be recognized as a cause for rapid neurological decline after excluding other causes.

Gepubliceerd: J Clin Transl Res. 2021;7(6):809-10.
Impact factor: 0; NVT

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6. **Endovascular treatment in anterior circulation stroke beyond 6.5 hours after onset or time last seen well: results from the MR CLEAN Registry**
Dekker L, Venema E, Pirson FAV, Majoie C, Emmer BJ, Jansen IGH, Mulder M, Lemmens R, Goldhoorn RB, Wermer MJH, Boiten J, Lycklama À Nijeholt GJ, Roos Y, van Es A, Lingsma HF, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ, van den Wijngaard IR, MR CLEAN Registry investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background: Randomised controlled trials with perfusion selection have shown benefit of endovascular treatment (EVT) for ischaemic stroke between 6 and 24 hours after symptom onset or time last seen well. However, outcomes after EVT in these late window patients without perfusion imaging are largely unknown. We assessed their characteristics and outcomes in routine clinical practice.
Methods: The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry, a prospective, multicentre study in

the Netherlands, included patients with an anterior circulation occlusion who underwent EVT between 2014 and 2017. CT perfusion was no standard imaging modality. We used adjusted ordinal logistic regression analysis to compare patients treated within versus beyond 6.5 hours after propensity score matching on age, prestroke modified Rankin Scale (mRS), National Institutes of Health Stroke Scale, Alberta Stroke Programme Early CT Score (ASPECTS), collateral status, location of occlusion and treatment with intravenous thrombolysis. Outcomes included 3-month mRS score, functional independence (defined as mRS 0-2), and death.
Results: Of 3264 patients who underwent EVT, 106 (3.2%) were treated beyond 6.5 hours (median 8.5, IQR 6.9-10.6), of whom 93 (87.7%) had unknown time of stroke onset. CT perfusion was not performed in 87/106 (80.2%) late window patients. Late window patients were younger (mean 67 vs 70 years, p<0.04) and had slightly lower ASPECTS (median 8 vs 9, p<0.01), but better collateral status (collateral score 2-3: 68.3% vs 57.7%, p=0.03). No differences were observed in proportions of functional independence (43.3% vs 40.5%, p=0.57) or death (24.0% vs 28.9%, p=0.28). After matching, outcomes remained similar (adjusted common OR for 1 point improvement in mRS 1.04, 95% CI 0.56 to 1.93).
Conclusions: Without the use of CT perfusion selection criteria, EVT in the 6.5-24-hour time window was not associated with poorer outcome in selected patients with favourable clinical and CT/CT angiography characteristics. randomised controlled trials with lenient inclusion criteria are needed to identify more patients who can benefit from EVT in the late window.

Gepubliceerd: Stroke Vasc Neurol. 2021;6(4):572-80.
Impact factor: 4.081; Q2

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7. **Effect of First-Pass Reperfusion on Outcome After Endovascular Treatment for Ischemic Stroke**
den Hartog SJ, Zaidat O, Roozenbeek B, van Es A, Bruggeman AAE, Emmer BJ, Majoie C, van Zwam WH, van den Wijngaard IR, van Doormaal PJ, Lingsma HF, Burke JF, Dippel DWJ, MR CLEAN Registry investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background: First-pass reperfusion (FPR) is associated with favorable outcome after endovascular treatment. It is unknown whether this effect is independent of patient characteristics and whether FPR has better outcomes compared with excellent reperfusion (Expanded Thrombolysis in Cerebral Infarction [eTICI] 2C-3) after multiple-passes reperfusion. We aimed to evaluate the association between FPR and outcome with adjustment for patient, imaging, and treatment characteristics to single out the contribution of FPR.
Methods and Results: FPR was defined as eTICI 2C-3 after 1 pass. Multivariable regression models were used to investigate characteristics associated with FPR and to investigate the effect of FPR on outcomes. We included 2686 patients of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry. Factors associated with FPR were as follows: history of hyperlipidemia (adjusted odds ratio [OR], 1.05; 95% CI, 1.01-1.10), middle cerebral artery versus intracranial carotid artery occlusion (adjusted OR, 1.11; 95% CI, 1.06-1.16), and aspiration versus stent thrombectomy (adjusted OR, 1.07; 95% CI, 1.03-1.11). Interventionist experience increased the likelihood of FPR (adjusted OR,

1.03 per 50 patients previously treated; 95% CI, 1.01-1.06). Adjusted for patient, imaging, and treatment characteristics, FPR remained associated with a better 24-hour National Institutes of Health Stroke Scale (NIHSS) score (-37%; 95% CI, -43% to -31%) and a better modified Rankin Scale (mRS) score at 3 months (adjusted common OR, 2.16; 95% CI, 1.83-2.54) compared with no FPR (multiple-passes reperfusion+no excellent reperfusion), and compared with multiple-passes reperfusion alone (24-hour NIHSS score, (-23%; 95% CI, -31% to -14%), and mRS score (adjusted common OR, 1.45; 95% CI, 1.19-1.78)).
Conclusions: FPR compared with multiple-passes reperfusion is associated with favorable outcome, independently of patient, imaging, and treatment characteristics. Factors associated with FPR were the experience of the interventionist, history of hyperlipidemia, location of occluded artery, and use of an aspiration device compared with stent thrombectomy.

Gepubliceerd: J Am Heart Assoc. 2021;10(7):e019988.
Impact factor: 5.501; Q1

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8. **Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data**
Duarte RV, Nevitt S, Maden M, Meier K, Taylor RS, Eldabe S, de Vos CC.

Spinal cord stimulation (SCS) has been suggested as a treatment option for patients with painful diabetic neuropathy (PDN). We conducted a systematic review and undertook a meta-analysis on individual patient data from randomised controlled trials (RCTs) to assess the effectiveness of SCS for the management of PDN. Electronic databases were searched from inception to May 2020 for RCTs of SCS for PDN. Searches identified 2 eligible RCTs (total of 93 patients with PDN) and 2 long-term follow-up studies of one of the RCTs. Individual patient data were obtained from the authors of one of these RCTs. Meta-analysis showed significant and clinically meaningful reductions in pain intensity for SCS compared with best medical therapy alone, pooled mean difference (MD) -3.13 (95% confidence interval [CI]: -4.19 to -2.08) on a 10-point scale at the 6-month follow-up. More patients receiving SCS achieved at least a 50% reduction in pain intensity compared with best medical therapy, pooled risk ratio 0.08 (95% CI: 0.02-0.38). Increases were observed for health-related quality of life assessed as EQ-5D utility score (pooled MD 0.16, 95% CI: 0.02-0.30) and visual analogue scale (pooled MD 11.21, 95% CI: 2.26-20.16). Our findings demonstrate that SCS is an effective therapeutic adjunct to best medical therapy in reducing pain intensity and improving health-related quality of life in patients with PDN. Large well-reported RCTs with long-term follow-up are required to confirm these results.

Gepubliceerd: Pain. 2021;162(11):2635-43.
Impact factor: 6.961; Q1

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9. **Glial Chloride Homeostasis Under Transient Ischemic Stress**
Engels M, Kalia M, Rahmati S, Petersilie L, Kovermann P, van Putten M, Rose CR, Meijer HGE, Gensch T, Fahlke C.

High water permeabilities permit rapid adjustments of glial volume upon changes in external and internal osmolarity, and pathologically altered intracellular chloride concentrations ([Cl(-)](int)) and glial cell swelling are often assumed to represent early events in ischemia, infections, or traumatic brain injury. Experimental data for glial [Cl(-)](int) are lacking for most brain regions, under normal as well as under pathological conditions. We measured [Cl(-)](int) in hippocampal and neocortical astrocytes and in hippocampal radial glia-like (RGL) cells in acute murine brain slices using fluorescence lifetime imaging microscopy with the chloride-sensitive dye MQAE at room temperature. We observed substantial heterogeneity in baseline [Cl(-)](int), ranging from 14.0 ± 2.0 mM in neocortical astrocytes to 28.4 ± 3.0 mM in dentate gyrus astrocytes. Chloride accumulation by the Na(+)-K(+)-2Cl(-) cotransporter (NKCC1) and chloride outward transport (efflux) through K(+)-Cl(-) cotransporters (KCC1 and KCC3) or excitatory amino acid transporter (EAAT) anion channels control [Cl(-)](int) to variable extent in distinct brain regions. In hippocampal astrocytes, blocking NKCC1 decreased [Cl(-)](int), whereas KCC or EAAT anion channel inhibition had little effect. In contrast, neocortical astrocytic or RGL [Cl(-)](int) was very sensitive to block of chloride outward transport, but not to NKCC1 inhibition. Mathematical modeling demonstrated that higher numbers of NKCC1 and KCC transporters can account for lower [Cl(-)](int) in neocortical than in hippocampal astrocytes. Energy depletion mimicking ischemia for up to 10 min did not result in pronounced changes in [Cl(-)](int) in any of the tested glial cell types. However, [Cl(-)](int) changes occurred under ischemic conditions after blocking selected anion transporters. We conclude that stimulated chloride accumulation and chloride efflux compensate for each other and prevent glial swelling under transient energy deprivation.

Gepubliceerd: Front Cell Neurosci. 2021;15:735300.
Impact factor: 5.505; Q1

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10. **Detecting multiple sclerosis via breath analysis using an eNose, a pilot study**
Ettema AR, Lenders M, Vliegen J, Slettenaar A, Tjepkema-Cloostermans MC, de Vos CC.

In the present study we investigated whether multiple sclerosis (MS) can be detected via exhaled breath analysis using an electronic nose (eNose). The Aeonose(TM)(an eNose, The eNose Company, Zutphen, the Netherlands) is a diagnostic test device to detect patterns of volatile organic compounds in exhaled breath. We evaluated whether the Aeonose(TM)can make a distinction between the breath patterns of patients with MS and healthy control subjects. In this mono-center, prospective, non-invasive study, 124 subjects with a confirmed diagnosis of MS and 129 control subjects each breathed into the Aeonose(TM)for 5 min. Exhaled breath data was used to train an artificial neural network (ANN) predictive model. To investigate the influence of medication intake we created a second predictive model with a subgroup of MS patients without medication prescribed for MS. The ANN model based on the entire dataset was able to distinguish MS patients from healthy controls with a sensitivity of 0.75 (95% CI: 0.66-0.82) and specificity of 0.60 (0.51-0.69). The model created with the subgroup of MS patients not using medication and the healthy control subjects had a sensitivity of 0.93 (0.82-0.98) and a specificity of 0.74 (0.65-0.81). The study showed that the Aeonose(TM)is able to make a distinction between MS patients and healthy control subjects, and could potentially provide a quick screening test to assist in diagnosing

MS. Further research is needed to determine whether the Aeonose(TM)is able to differentiate new MS patients from subjects who will not get the diagnosis.

Gepubliceerd: J Breath Res. 2021;15(2).
Impact factor: 3.262; Q2

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11. **Assessment of Recurrent Stroke Risk in Patients With a Carotid Web**
Guglielmi V, Compagne KCJ, Sarrami AH, Sluis WM, van den Berg LA, van der Sluijs PM, Mandell DM, van der Lugt A, Roos Y, Majoie C, Dippel DWJ, Emmer BJ, van Es A, Coutinho JM, MR CLEAN trial and MR CLEAN Registry investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Importance: A carotid web (CW) is a shelf-like lesion along the posterior wall of the internal carotid artery bulb and an underrecognized cause of young stroke. Several studies suggest that patients with symptomatic CW have a high risk of recurrent stroke, but high-quality data are lacking.
Objective: To assess the 2-year risk of recurrent stroke in patients with a symptomatic CW.
Design, setting, and participants: A comparative cohort study used data from the MR CLEAN trial (from 2010-2014) and MR CLEAN Registry (from 2014-2017). Data were analyzed in September 2020. The MR CLEAN trial and MR CLEAN Registry were nationwide prospective multicenter studies on endovascular treatment (EVT) of large vessel occlusion (LVO) stroke in the Netherlands. Baseline data were from 3439 consecutive adult patients with anterior circulation LVO stroke and available computed tomography (CT)-angiography of the carotid bulb. Two neuroradiologists reevaluated CT-angiography images for presence or absence of CW and identified 30 patients with CW ipsilateral to the index stroke. For these 30 eligible CW participants, detailed follow-up data regarding stroke recurrence within 2 years were acquired. These 30 patients with CW ipsilateral to the index stroke were compared with 168 patients without CW who participated in the MR CLEAN extended follow-up trial and who were randomized to the EVT arm.
Main outcomes and measures: The primary outcome was recurrent stroke occurring within 2 years after the index stroke. Cox proportional hazards regression models were used to compare recurrent stroke rates within 2 years for patients with and without CW, adjusted for age and sex. The research question was formulated prior to data collection.
Results: Of 3439 patients with baseline CT-angiography assessed, the median age was 72 years (interquartile range, 61-80 years) and 1813 (53%) were men. Patients with CW were younger (median age, 57 [interquartile range, 46-66] years vs 66 [interquartile range, 56-77] years; P = .02 and more often women (22 of 30 [73%] vs 67 of 168 [40%]; P = .001) than patients without CW. Twenty-eight of 30 patients (93%) received medical management after the index stroke (23 with antiplatelet therapy and 5 with anticoagulant therapy). During 2 years of follow-up, 5 of 30 patients (17%) with CW had a recurrent stroke compared with 5 of 168 patients (3%) without CW (adjusted hazard ratio, 4.9; 95% CI, 1.4-18.1).
Conclusions and relevance: In this study, 1 of 6 patients with a symptomatic CW had a recurrent stroke within 2 years, suggesting that medical management alone may not provide sufficient protection for patients with CW.

Gepubliceerd: JAMA Neurol. 2021;78(7):826-33.

Impact factor: 18.302; Q1

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12. **Prognostic factors for relapse and outcome in pediatric acute transverse myelitis**
Helfferich J, Bruijstens AL, Wong YYM, Danielle van Pelt E, Boon M, Neuteboom RF, Dutch Study Group for Pediatric Multiple Sclerosis and Acute Disseminated Encephalomyelitis – includes Portier RP.

Objective: It may be difficult for clinicians to estimate the prognosis of pediatric acute transverse myelitis (ATM). The aim of this study was to define prognostic factors for relapsing disease and poor outcome in pediatric ATM.
Methods: This prospective cohort study included 49 children, 18 boys and 31 girls (median age 13.1 years, IQR 6.5-16.2) with a first episode of ATM. Factors associated with relapsing disease and poor outcome (Expanded Disability Status Scale (EDSS) ≥ 4) were assessed during a median follow-up of 37 months (IQR 18-75).
Results: In total, 14 patients (29%) experienced ≥ 1 relapse(s) and nine patients (18%) had a poor outcome. Factors at onset associated with relapsing disease included higher age (16.1 vs. 11.6 years, p = 0.002), longer time to maximum severity of symptoms (5.5 vs. 3 days, p = 0.01), lower maximum EDSS score (4.0 vs. 6.5, p = 0.003), short lesion on spinal MRI (64 vs. 21%, p = 0.006), abnormalities on brain MRI (93 vs. 44%, p = 0.002) and presence of oligoclonal bands in cerebrospinal fluid (67 vs. 14%, p = 0.004). The only factor associated with poor outcome was presence of a spinal cord lesion on MRI without cervical involvement (56 vs. 14%, p = 0.02).
Conclusion: Pediatric ATM patients presenting with clinical, radiological and laboratory features associated with multiple sclerosis (MS) are at risk for relapsing disease. In absence of these known MS risk factors at onset of disease these patients are at low risk for relapses. Only a minority of pediatric ATM patients in this cohort have a poor outcome.

Gepubliceerd: Brain Dev. 2021;43(5):626-36.
Impact factor: 1.961; Q3

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13. **American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version**
Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, Gerard EE, Herman ST, Haider HA, Osman G, Rodriguez-Ruiz A, Maciel CB, Gilmore EJ, Fernandez A, Rosenthal ES, Claassen J, Husain AM, Yoo JY, So EL, Kaplan PW, Nuwer MR, van Putten M, Sutter R, Drislane FW, Trinka E, Gaspard N.

Gepubliceerd: J Clin Neurophysiol. 2021;38(1):1-29.
Impact factor: 2.177; Q4

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14. **Ion dynamics at the energy-deprived tripartite synapse**
Kalia M, Meijer HGE, van Gils SA, van Putten M, Rose CR.

The anatomical and functional organization of neurons and astrocytes at 'tripartite synapses' is essential for reliable neurotransmission, which critically depends on ATP. In low energy conditions, synaptic transmission fails, accompanied by a breakdown of ion gradients, changes in membrane potentials and cell swelling. The resulting cellular damage and cell death are causal to the often devastating consequences of an ischemic stroke. The severity of ischemic damage depends on the age and the brain region in which a stroke occurs, but the reasons for this differential vulnerability are far from understood. In the present study, we address this question by developing a comprehensive biophysical model of a glutamatergic synapse to identify key determinants of synaptic failure during energy deprivation. Our model is based on fundamental biophysical principles, includes dynamics of the most relevant ions, i.e., Na+, K+, Ca2+, Cl- and glutamate, and is calibrated with experimental data. It confirms the critical role of the Na+/K+-ATPase in maintaining ion gradients, membrane potentials and cell volumes. Our simulations demonstrate that the system exhibits two stable states, one physiological and one pathological. During energy deprivation, the physiological state may disappear, forcing a transit to the pathological state, which can be reverted when blocking voltage-gated Na+ and K+ channels. Our model predicts that the transition to the pathological state is favoured if the extracellular space fraction is small. A reduction in the extracellular space volume fraction, as, e.g. observed with ageing, will thus promote the brain's susceptibility to ischemic damage. Our work provides new insights into the brain's ability to recover from energy deprivation, with translational relevance for diagnosis and treatment of ischemic strokes.

Gepubliceerd: PLoS Comput Biol. 2021;17(6):e1009019.
Impact factor: 4.475; Q1

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15. **Dynamic functional connectivity of the EEG in relation to outcome of postanoxic coma**

Keijzer HM, Tjepkema-Cloostermans MC, Klijn CJM, Blans M, van Putten M, Hofmeijer J.

Objective: Early EEG contains reliable information for outcome prediction of comatose patients after cardiac arrest. We introduce dynamic functional connectivity measures and estimate additional predictive values.
Methods: We performed a prospective multicenter cohort study on continuous EEG for outcome prediction of comatose patients after cardiac arrest. We calculated Link Rates (LR) and Link Durations (LD) in the α, δ, and θ band, based on similarity of instantaneous frequencies in five-minute EEG epochs, hourly, during 3 days after cardiac arrest. We studied associations of LR and LD with good (Cerebral Performance Category (CPC) 1-2) or poor outcome (CPC 3-5) with univariate analyses. With random forest classification, we established EEG-based predictive models. We used receiver operating characteristics to estimate additional values of dynamic connectivity measures for outcome prediction.
Results: Of 683 patients, 369 (54%) had poor outcome. Patients with poor outcome had significantly lower LR and longer LD, with largest differences 12 h after cardiac arrest (LR(θ) 1.87 vs. 1.95 Hz and LD(α) 91 vs. 82 ms). Adding these measures to a model with classical EEG features increased sensitivity for reliable prediction of poor outcome from 34% to 38% at 12 h after cardiac arrest.

Conclusion: Poor outcome is associated with lower dynamics of connectivity after cardiac arrest.
Significance: Dynamic functional connectivity analysis may improve EEG based outcome prediction.

Gepubliceerd: Clin Neurophysiol. 2021;132(1):157-64.
Impact factor: 3.708; Q2

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16. **Between-hospital variation in rates of complications and decline of patient performance after glioblastoma surgery in the dutch Quality Registry Neuro Surgery**
Kommers I, Ackermans L, Ardon H, van den Brink WA, Bouwknegt W, Balvers RK, van der Gaag N, Bosscher L, Kloet A, Koopmans J, Laan MT, Tewarie RN, Robe PA, van der Veer O, Wagemakers M, Zwinderman AH, De Witt Hamer PC.

Introduction: For decisions on glioblastoma surgery, the risk of complications and decline in performance is decisive. In this study, we determine the rate of complications and performance decline after resections and biopsies in a national quality registry, their risk factors and the risk-standardized variation between institutions.
Methods: Data from all 3288 adults with first-time glioblastoma surgery at 13 hospitals were obtained from a prospective population-based Quality Registry Neuro Surgery in the Netherlands between 2013 and 2017. Patients were stratified by biopsies and resections. Complications were categorized as Clavien-Dindo grades II and higher. Performance decline was considered a deterioration of more than 10 Karnofsky points at 6 weeks. Risk factors were evaluated in multivariable logistic regression analysis. Patient-specific expected and observed complications and performance declines were summarized for institutions and analyzed in funnel plots.
Results: For 2271 resections, the overall complication rate was 20 % and 16 % declined in performance. For 1017 biopsies, the overall complication rate was 11 % and 30 % declined in performance. Patient-related characteristics were significant risk factors for complications and performance decline, i.e. higher age, lower baseline Karnofsky, higher ASA classification, and the surgical procedure. Hospital characteristics, i.e. case volume, university affiliation and biopsy percentage, were not. In three institutes the observed complication rate was significantly less than expected. In one institute significantly more performance declines were observed than expected, and in one institute significantly less.
Conclusions: Patient characteristics, but not case volume, were risk factors for complications and performance decline after glioblastoma surgery. After risk-standardization, hospitals varied in complications and performance declines.

Gepubliceerd: J Neurooncol. 2021;152(2):289-98.
Impact factor: 4.130; Q2

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17. **A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke**
LeCouffe NE, Kappelhof M, Treurniet KM, Rinkel LA, Bruggeman AE, Berkhemer OA, Wolff L, van Voorst H, Tolhuisen ML, Dippel DWJ, van der Lugt A, van Es A, Boiten J, Lycklama À Nijeholt GJ, Keizer K, Gons RAR, Yo LSF, van Oostenbrugge RJ, van

Zwam WH, Roozenbeek B, van der Worp HB, Lo RTH, van den Wijngaard IR, de Ridder IR, Costalat V, Arquizan C, Lemmens R, Demeestere J, Hofmeijer J, Martens JM, Schonewille WJ, Vos JA, Uyttenboogaart M, Bokkers RPH, van Tuijl JH, Kortman H, Schreuder F, Boogaarts HD, de Laat KF, van Dijk LC, den Hertog HM, van Hasselt B, Brouwers PJAM, Bulut T, Remmers MJM, van Norden A, Imani F, Rozeman AD, Elgersma OEH, Desfontaines P, Brisbois D, Samson Y, Clarençon F, Krietemeijer GM, Postma AA, van Doormaal PJ, van den Berg R, van der Hoorn A, Beenen LFM, Nieboer D, Lingsma HF, Emmer BJ, Coutinho JM, Majoie C, Roos Y, MR CLEAN-NO IV Investigators – includes Lodico J, Droste H.

Background: The value of administering intravenous alteplase before endovascular treatment (EVT) for acute ischemic stroke has not been studied extensively, particularly in non-Asian populations.
Methods: We performed an open-label, multicenter, randomized trial in Europe involving patients with stroke who presented directly to a hospital that was capable of providing EVT and who were eligible for intravenous alteplase and EVT. Patients were randomly assigned in a 1:1 ratio to receive EVT alone or intravenous alteplase followed by EVT (the standard of care). The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability] to 6 [death]) at 90 days. We assessed the superiority of EVT alone over alteplase plus EVT, as well as noninferiority by a margin of 0.8 for the lower boundary of the 95% confidence interval for the odds ratio of the two trial groups. Death from any cause and symptomatic intracerebral hemorrhage were the main safety end points.
Results: The analysis included 539 patients. The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) with EVT alone and 2 (interquartile range, 2 to 5) with alteplase plus EVT. The adjusted common odds ratio was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P = 0.28), which showed neither superiority nor noninferiority of EVT alone. Mortality was 20.5% with EVT alone and 15.8% with alteplase plus EVT (adjusted odds ratio, 1.39; 95% CI, 0.84 to 2.30). Symptomatic intracerebral hemorrhage occurred in 5.9% and 5.3% of the patients in the respective groups (adjusted odds ratio, 1.30; 95% CI, 0.60 to 2.81).
Conclusions: In a randomized trial involving European patients, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with regard to disability outcome at 90 days after stroke. The incidence of symptomatic intracerebral hemorrhage was similar in the two groups. (Funded by the Collaboration for New Treatments of Acute Stroke consortium and others; MR CLEAN-NO IV ISRCTN number, ISRCTN80619088.).

Gepubliceerd: N Engl J Med. 2021;385(20):1833-44.
Impact factor: 91.253; Q1

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18. **Diagnostic value of serum biomarkers FGF21 and GDF15 compared to muscle sample in mitochondrial disease**
Lehtonen JM, Auranen M, Darin N, Sofou K, Bindoff L, Hikmat O, Uusimaa J, Vieira P, Tulinius M, Lönnqvist T, de Coo IF, Suomalainen A, Isohanni P.

The aim of this study was to compare the value of serum biomarkers, fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15), with histological analysis of muscle in the diagnosis of mitochondrial disease. We collected 194 serum

samples from patients with a suspected or known mitochondrial disease. Biomarkers were analyzed blinded using enzyme-labeled immunosorbent assay. Clinical data were collected using a structured questionnaire. Only 39% of patients with genetically verified mitochondrial disease had mitochondrial pathology in their muscle histology. In contrast, biomarkers were elevated in 62% of patients with genetically verified mitochondrial disease. Those with both biomarkers elevated had a muscle manifesting disorder and a defect affecting mitochondrial DNA expression. If at least one of the biomarkers was induced and the patient had a myopathic disease, a mitochondrial DNA expression disease was the cause with 94% probability. Among patients with biomarker analysis and muscle biopsy taken <12 months apart, a mitochondrial disorder would have been identified in 70% with analysis of FGF21 and GDF15 compared to 50% of patients whom could have been identified with muscle biopsy alone. Muscle findings were nondiagnostic in 72% (children) and 45% (adults). Induction of FGF21 and GDF15 suggest a mitochondrial etiology as an underlying cause of a muscle manifesting disease. Normal biomarker values do not, however, rule out a mitochondrial disorder, especially if the disease does not manifest in muscle. We suggest that FGF21 and GDF15 together should be first-line diagnostic investigations in mitochondrial disease complementing muscle biopsy.

Gepubliceerd: J Inherit Metab Dis. 2021;44(2):469-80.
Impact factor: 4.982; Q1

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19. **Dr. Jan Holsheimer 1941-2021**
Lenders MWPM, Kho KH, de Vos CC, Elands A.

Gepubliceerd: Neuromodulation. 2021;24(4):609.
Impact factor: 4.722; Q2

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20. **Effect of intravenous low-dose S-ketamine on pain in patients with Complex Regional Pain Syndrome: A retrospective cohort study**
Mangnus TJP, Dirckx M, Bharwani KD, de Vos CC, Frankema SPG, Stronks DL, Huygen F.

Objective: The objective of this study was to assess the effectiveness of a low-dose intravenous S-ketamine treatment on refractory pain in patients with Complex Regional Pain Syndrome (CRPS).
Methods: In this retrospective study, patients with CRPS who received intravenous S-ketamine from March 2010 to April 2019 were included. According to our inpatient protocol, S-ketamine dose was increased until pain reduction was achieved or side effects were observed. Maximum dose was 14 mg/h and treatment duration was 7 days. Primary outcome parameters were pain scores (Numeric Rating Scale) at baseline (T0), end of infusion (T1), and approximately 4 weeks postinfusion (T2). Patients were categorized as responder/nonresponder at T1 and T2. Patients were considered a responder in case there was pain score reduction of greater than or equal to 2 points or if treatment was reported as successful.
Results: Forty-eight patients were included. Mean disease duration was 5 years (interquartile range [IQR] = 6 years). Median pain score significantly decreased from 8 (IQR = 2) at T0 to 6 (IQR = 4) at T1 ($p < 0.001$). At T1, 62% of the patients were

responders. At T2, 48% of the patients remained a responder. A significant proportion of the responders at T1 turned into nonresponders at T2 ($p = 0.03$).
Conclusion: In a group of patients with CRPS with refractory pain, low-dose intravenous S-ketamine treatment resulted in effective pain relief during infusion. Although a significant proportion of initial responders became nonresponders at follow-up, half of the patients were still a responder at ~ 4 weeks postinfusion. Further research is needed to investigate mechanisms responsible for pain relief by S-ketamine infusions and to ascertain possible predictors of response to the treatment.

Gepubliceerd: Pain Pract. 2021;21(8):890-7.
Impact factor: 3.183; Q3

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21. **Underlying genetic variation in familial frontotemporal dementia: sequencing of 198 patients**
Mol MO, van Rooij JGJ, Wong TH, Melhem S, Verkerk A, Kievit AJA, van Minkelen R, Rademakers R, Pottier C, Kaat LD, Seelaar H, van Swieten JC, Dopper EGP.

Frontotemporal dementia (FTD) presents with a wide variability in clinical syndromes, genetic etiologies, and underlying pathologies. Despite the discovery of pathogenic variants in several genes, many familial cases remain unsolved. In a large FTD cohort of 198 familial patients, we aimed to determine the types and frequencies of variants in genes related to FTD. Pathogenic or likely pathogenic variants were revealed in 74 (37%) patients, including 4 novel variants. The repeat expansion in C9orf72 was most common (21%), followed by variants in MAPT (6%), GRN (4.5%), and TARDBP (3.5%). Other pathogenic variants were found in VCP, TBK1, PSEN1, and a novel homozygous variant in OPTN. Furthermore, we identified 15 variants of uncertain significance, including a promising variant in TUBA4A and a frameshift in VCP, for which additional research is needed to confirm pathogenicity. The patients without identified genetic cause demonstrated a wide clinical and pathological variety. Our study contributes to the clinical characterization of the genetic subtypes and confirms the value of whole-exome sequencing in identifying novel genetic variants.

Gepubliceerd: Neurobiol Aging. 2021;97:148.e9-.e16.
Impact factor: 4.673; Q2

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22. **Novel TUBA4A Variant Associated With Familial Frontotemporal Dementia**
Mol MO, Wong TH, Melhem S, Basu S, Viscusi R, Galjart N, Rozemuller AJM, Fallini C, Landers JE, Kaat LD, Seelaar H, van Rooij JGJ, van Swieten JC.

Objective: Despite the strong genetic component of frontotemporal dementia (FTD), a substantial proportion of patients remain genetically unresolved. We performed an in-depth study of a family with an autosomal dominant form of FTD to investigate the underlying genetic cause.
Methods: Following clinical and pathologic characterization of the family, genetic studies included haplotype sharing analysis and exome sequencing. Subsequently, we performed immunohistochemistry, immunoblotting, and a microtubule repolymerization assay to investigate the potential impact of the candidate variant in tubulin alpha 4a (TUBA4A).

Results: The clinical presentation in this family is heterogeneous, including behavioral changes, parkinsonian features, and uncharacterized dementia. Neuropathologic examination of 2 patients revealed TAR DNA binding protein 43 (TDP-43) pathology with abundant dystrophic neurites and neuronal intranuclear inclusions, consistent with frontotemporal lobar degeneration-TDP type A. We identified a likely pathogenic variant in TUBA4A segregating with disease. TUBA4A encodes for α-tubulin, which is a major component of the microtubule network. Variants in TUBA4A have been suggested as a rare genetic cause of amyotrophic lateral sclerosis (ALS) and have sporadically been reported in patients with FTD without supporting genetic segregation. A decreased trend of TUBA4A protein abundance was observed in patients compared with controls, and a microtubule repolymerization assay demonstrated disrupted α-tubulin function. As opposed to variants found in ALS, TUBA4A variants associated with FTD appear more localized to the N-terminus, indicating different pathogenic mechanisms.
Conclusions: Our findings support the role of TUBA4A variants as rare genetic cause of familial FTD.

Gepubliceerd: Neurol Genet. 2021;7(3):e596.
Impact factor: 3.485; Q2

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23. **Stroke patient's alarm choice: General practitioner or emergency medical services**
Nguyen TTM, Kruyt ND, Pierik JGJ, Doggen CJM, van der Lugt P, Ramessersing SAV, Wijers NT, Brouwers PJAM, Wermer MJH, den Hertog HM.

Objectives: Stroke patients should be treated as soon as possible since the benefit of reperfusion therapies is highly time-dependent. The proportion of patients eligible for reperfusion therapy is still limited, as many patients do not immediately alarm healthcare providers. The choice of healthcare system entrance influences the time of arrival in the hospital. Therefore, we assessed differences in these choices to obtain insight for strategies to reduce time delays in acute stroke patients.
Materials and methods: Patients with suspected acute stroke admitted to the participating hospitals received a questionnaire. We assessed differences between patients who initially alarmed the general practitioner (GP) and patients who directly alarmed the emergency medical services (EMS). Additionally, we assessed regional differences and patient trajectories after medical help was sought.
Results: We included 163 patients. Most patients alarmed the GP as primary healthcare provider (n = 104; 64%), and median onset-to-door times were longer in these patients (466 minutes [IQR 149-1586]) compared to patients directly alarming the EMS (n = 59; 36%) (90 minutes [IQR 45-286]). This was even more pronounced in less densely populated areas. Patients who alarmed the GP first, more often had patient delay >15 minutes, hesitated to burden healthcare providers and underestimated symptomatology.
Conclusions: Our results showed that patients who alarmed the GP first instead of the EMS differed in several factors that are potentially modifiable. Strategies to achieve reduction of vital prehospital time delays and to improve patient outcome are optimizing public awareness campaigns and GP triage along with adjusting current guidelines by enabling and focusing on immediate involvement of the EMS once acute stroke is suspected.

Gepubliceerd: Acta Neurol Scand. 2021;143(2):164-70.
Impact factor: 3.209;Q2

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24. **Modulation of the Somatosensory Evoked Potential by Attention and Spinal Cord Stimulation**
Niso G, Tjepkema-Cloostermans MC, Lenders MWPM, de Vos CC.

Introduction: Spinal Cord Stimulation (SCS) is a last-resort treatment for patients with intractable chronic pain in whom pharmacological and other treatments have failed. Conventional tonic SCS is accompanied by tingling sensations. More recent stimulation protocols like burst SCS are not sensed by the patient while providing similar levels of pain relief. It has been previously reported that conventional tonic SCS can attenuate sensory-discriminative processing in several brain areas, but that burst SCS might have additional effects on the medial, motivational-affective pain system. In this explorative study we assessed the influence of attention on the somatosensory evoked brain responses under conventional tonic SCS as well as burst SCS regime.
Methods: Twelve chronic pain patients with an implanted SCS device had 2-weeks evaluation periods with three different SCS settings (conventional tonic SCS, burst SCS, and sham SCS). At the end of each period, an electro-encephalography (EEG) measurement was done, at which patients received transcutaneous electrical pulses at the tibial nerve to induce somatosensory evoked potentials (SEP). SEP data was acquired while patients were attending the applied pulses and while they were mind wandering. The effects of attention as well as SCS regimes on the SEP were analyzed by comparing amplitudes of early and late latencies at the vertex as well as brain activity at full cortical maps.
Results: Pain relief obtained by the various SCS settings varied largely among patients. Early SEP responses were not significantly affected by attention nor SCS settings (i.e., burst, tonic, and sham). However, late SEP responses (P300) were reduced with tonic and burst SCS: conventional tonic SCS reduced P300 brain activity in the unattended condition, while burst SCS reduced P300 brain activity in both attended and unattended conditions.
Conclusion: Burst spinal cord stimulation for the treatment of chronic pain seems to reduce cortical attention that is or can be directed to somatosensory stimuli to a larger extent than conventional spinal cord stimulation treatment. This is a first step in understanding why in selected chronic pain patients burst SCS is more effective than tonic SCS and how neuroimaging could assist in personalizing SCS treatment.

Gepubliceerd: Front Neurol. 2021;12:694310.
Impact factor: 4.003; Q2

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25. **Anticoagulant selection in relation to the SAMe-TT(2)R(2) score in patients with atrial fibrillation: The GLORIA-AF registry**
Ntaios G, Huisman MV, Diener HC, Halperin JL, Teutsch C, Marler S, Gurusamy VK, Thompson M, Lip GYH, Olshansky B, GLORIA-AF Investigators – includes Brouwers PJAM.

Aim: The SAMe-TT(2)R(2) score helps identify patients with atrial fibrillation (AF) likely to have poor anticoagulation control during anticoagulation with vitamin K antagonists (VKA) and those with scores >2 might be better managed with a target-specific oral

anticoagulant (NOAC). We hypothesized that in clinical practice, VKAs may be prescribed less frequently to patients with AF and SAMe-TT(2)R(2) scores >2 than to patients with lower scores.
Methods and results: We analyzed the Phase III dataset of the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF), a large, global, prospective global registry of patients with newly diagnosed AF and ≥1 stroke risk factor. We compared baseline clinical characteristics and antithrombotic prescriptions to determine the probability of the VKA prescription among anticoagulated patients with the baseline SAMe-TT(2)R(2) score >2 and ≤ 2. Among 17,465 anticoagulated patients with AF, 4,828 (27.6%) patients were prescribed VKA and 12,637 (72.4%) patients an NOAC: 11,884 (68.0%) patients had SAMe-TT(2)R(2) scores 0-2 and 5,581 (32.0%) patients had scores >2. The proportion of patients prescribed VKA was 28.0% among patients with SAMe-TT(2)R(2) scores >2 and 27.5% in those with scores ≤2.
Conclusions: The lack of a clear association between the SAMe-TT(2)R(2) score and anticoagulant selection may be attributed to the relative efficacy and safety profiles between NOACs and VKAs as well as to the absence of trial evidence that an SAMe-TT(2)R(2)-guided strategy for the selection of the type of anticoagulation in NVAF patients has an impact on clinical outcomes of efficacy and safety. The latter hypothesis is currently being tested in a randomized controlled trial. **Clinical Trial registrattion:** URL: https://www.clinicaltrials.gov//Unique identifier: NCT01937377, NCT01468701, and NCT01671007.

Gepubliceerd: Hellenic J Cardiol. 2021;62(2):152-7.
Impact factor: 0; NVT

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26. **Neuroprotective Treatment of Postanoxic Encephalopathy: A Review of Clinical Evidence**
Nutma S, le Feber J, Hofmeijer J.

Postanoxic encephalopathy is the key determinant of death or disability after successful cardiopulmonary resuscitation. Animal studies have provided proof-of-principle evidence of efficacy of divergent classes of neuroprotective treatments to promote brain recovery. However, apart from targeted temperature management (TTM), neuroprotective treatments are not included in current care of patients with postanoxic encephalopathy after cardiac arrest. We aimed to review the clinical evidence of efficacy of neuroprotective strategies to improve recovery of comatose patients after cardiac arrest and to propose future directions. We performed a systematic search of the literature to identify prospective, comparative clinical trials on interventions to improve neurological outcome of comatose patients after cardiac arrest. We included 53 studies on 21 interventions. None showed unequivocal benefit. TTM at 33 or 36°C and adrenaline (epinephrine) are studied most, followed by xenon, erythropoietin, and calcium antagonists. Lack of efficacy is associated with heterogeneity of patient groups and limited specificity of outcome measures. Ongoing and future trials will benefit from systematic collection of measures of baseline encephalopathy and sufficiently powered predefined subgroup analyses. Outcome measurement should include comprehensive neuropsychological follow-up, to show treatment effects that are not detectable by gross measures of functional recovery. To enhance translation from animal models to

patients, studies under experimental conditions should adhere to strict methodological and publication guidelines.

Gepubliceerd: Front Neurol. 2021;12:614698.
Impact factor: 4.003; Q2

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27. **The Impact of Non-dopaminergic Medication on Quality of Life in Parkinson's Disease**
Oonk NGM, Movig KLL, van der Palen J, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background and objectives: Quality of life (QoL) in Parkinson's disease (PD) depends on multiple factors. Due to PD treatment and accompanying, age-related or independent comorbidities, pill burden is often high. The relation of QoL and pharmacotherapy for comorbidities in PD has not been widely studied. This study investigated if and to what extent non-dopaminergic drugs are related to QoL in PD. Second, the impact of demographics and non-motor symptoms were evaluated. A better understanding of the impact of different non-dopaminergic drugs and polypharmacy on QoL will have added value in selecting appropriate (medication) interventions.
Methods: In a cross-sectional analysis, medication prescription data of 209 PD patients were analyzed and grouped according to the Rx-Risk comorbidity index. QoL was measured using the PDQ-39 questionnaire. Non-motor symptoms were analyzed with the Non-Motor Symptoms questionnaire. Independent factors associated with a reduced QoL were identified with a multivariate linear regression analysis.
Results: Non-dopaminergic drugs, subdivided into Rx-Risk comorbidity categories, were not associated with reduced QoL, except for the use of anti-epileptic drugs. However, using more daily non-dopaminergic drugs was also negatively associated with QoL, as well as female sex, increased PD severity, and more non-motor symptoms. Contraindicated non-dopaminergic medication was barely prescribed (0.4%).
Conclusion: Non-dopaminergic drugs are frequently prescribed, and higher numbers are associated with impaired QoL in PD. However, when divided in drug types, only anti-epileptic drugs were negatively associated with QoL. In these patients, physicians might improve QoL by further optimizing the condition it was prescribed for (e.g., pain or anxiety), or managing of side effects.
Trial registrattion: Netherlands Trial Register; NL4360.

Gepubliceerd: Clin Drug Investig. 2021;41(9):809-16.
Impact factor: 2.859; Q3

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28. **Safety, feasibility and efficacy of metformin and sitagliptin in patients with a TIA or minor ischaemic stroke and impaired glucose tolerance**
Osei E, Zandbergen A, Brouwers PJAM, Mulder L, Koudstaal P, Lingsma H, Dippel DWJ, den Hertog H.

Introduction: Impaired glucose tolerance (IGT) is highly prevalent after stroke and is associated with recurrent stroke and unfavourable outcome. **Objectives:** We aimed to assess the feasibility, safety and effects on glucose metabolism of metformin or

sitagliptin in patients with transient ischaemic attack (TIA) or minor ischaemic stroke and IGT. DESIGN: We performed a multicentre, randomised, controlled, open-label phase II trial with blinded outcome assessment.
Interventions: Patients were randomised in a 2:1:1 ratio to 'no medication', sitagliptin or metformin.
Primary and secondary outcome measures: Primary outcome measures were baseline adjusted differences of 2-hour postload glucose; secondary outcome measures fasting glucose, glycosylated haemoglobin 1c (HbA1c) levels, tolerability and safety of metformin and sitagliptin at 6 months. Patients on metformin or sitagliptin were contacted by telephone for recording of possible adverse events and to support continuation of treatment at 2 weeks, 6 weeks and 3 months after inclusion. These events were not analysed as outcome measures.
Results: Fifty-three patients were randomised to control group, 26 to metformin and 22 to sitagliptin. We found no significant differences in 2-hour postload glucose between patients on antidiabetic drugs and controls ((-0.04 mmol/L (95% CI -0.53 to 0.45)). Patients in the treatment arms had reduced fasting glucose: ((-0.21 mmol/L (95% CI -0.36 to -0.06)) and HbA1c levels ((-1.16 mmol/mol (95% CI -1.84 to -0.49)). Thirteen patients (50%) on metformin and 7 (32%) on sitagliptin experienced side effects. Sixteen patients (61%) in the metformin and 13 (59%) in the sitagliptin group were still on treatment after 6 months.
Conclusions: Metformin and sitagliptin were both effective in reducing fasting glucose and HbA1c levels in patients with recent TIA or minor ischaemic stroke and IGT. However, the reduction of glucose levels and sample size was relatively small. The clinical relevance, therefore, needs to be tempered. A phase III trial is needed to investigate whether medical treatment, compared with lifestyle intervention or a combination of both, not only improves glucose metabolism in IGT, but also leads to reduction of recurrent TIA or ischaemic stroke in these patients.
Trial registration number: NL3048.

Gepubliceerd: BMJ Open. 2021;11(9):e046113.
Impact factor: 2.692; Q2

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29. **STQS: Interpretable multi-modal Spatial-Temporal-seQuential model for automatic Sleep scoring**
Pathak S, Lu C, Nagaraj SB, van Putten M, Seifert C.

Sleep scoring is an important step for the detection of sleep disorders and usually performed by visual analysis. Since manual sleep scoring is time consuming, machine-learning based approaches have been proposed. Though efficient, these algorithms are black-box in nature and difficult to interpret by clinicians. In this paper, we propose a deep learning architecture for multi-modal sleep scoring, investigate the model's decision making process, and compare the model's reasoning with the annotation guidelines in the AASM manual. Our architecture, called STQS, uses convolutional neural networks (CNN) to automatically extract spatio-temporal features from 3 modalities (EEG, EOG and EMG), a bidirectional long short-term memory (Bi-LSTM) to extract sequential information, and residual connections to combine spatio-temporal and sequential features. We evaluated our model on two large datasets, obtaining an accuracy of 85% and 77% and a macro F1 score of 79% and 73% on SHHS and an in-house dataset, respectively. We further quantify the contribution of various architectural

components and conclude that adding LSTM layers improves performance over a spatio-temporal CNN, while adding residual connections does not. Our interpretability results show that the output of the model is well aligned with AASM guidelines, and therefore, the model's decisions correspond to domain knowledge. We also compare multi-modal models and single-channel models and suggest that future research should focus on improving multi-modal models.

Gepubliceerd: Artif Intell Med. 2021;114:102038.
Impact factor: 5.326; Q1

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30. **Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial**
Post R, Germans MR, Tjerkstra MA, Vergouwen MDI, Jellema K, Koot RW, Kruyt ND, Willems PWA, Wolfs JFC, de Beer FC, Kieft H, Nanda D, van der Pol B, Roks G, de Beer F, Halkes PHA, Reichman LJA, Brouwers PJAM, van den Berg-Vos RM, Kwa VIH, van der Ree TC, Bronner I, van de Vlekkert J, Bienfait HP, Boogaarts HD, Klijn CJM, van den Berg R, Coert BA, Horn J, Majoie C, Rinkel GJE, Roos Y, Vandertop WP, Verbaan D.

Background: In patients with aneurysmal subarachnoid haemorrhage, short-term antifibrinolytic therapy with tranexamic acid has been shown to reduce the risk of rebleeding. However, whether this treatment improves clinical outcome is unclear. We investigated whether ultra-early, short-term treatment with tranexamic acid improves clinical outcome at 6 months.
Methods: In this multicentre prospective, randomised, controlled, open-label trial with masked outcome assessment, adult patients with spontaneous CT-proven subarachnoid haemorrhage in eight treatment centres and 16 referring hospitals in the Netherlands were randomly assigned to treatment with tranexamic acid in addition to care as usual (tranexamic acid group) or care as usual only (control group). Tranexamic acid was started immediately after diagnosis in the presenting hospital (1 g bolus, followed by continuous infusion of 1 g every 8 h, terminated immediately before aneurysm treatment, or 24 h after start of the medication, whichever came first). The primary endpoint was clinical outcome at 6 months, assessed by the modified Rankin Scale, dichotomised into a good (0-3) or poor (4-6) clinical outcome. Both primary and safety analyses were according to intention to treat. This trial is registered at ClinicalTrials.gov, NCT02684812.
Findings: Between July 24, 2013, and July 29, 2019, we enrolled 955 patients; 480 patients were randomly assigned to tranexamic acid and 475 patients to the control group. In the intention-to-treat analysis, good clinical outcome was observed in 287 (60%) of 475 patients in the tranexamic acid group, and 300 (64%) of 470 patients in the control group (treatment centre adjusted odds ratio 0·86, 95% CI 0·66-1·12). Rebleeding after randomisation and before aneurysm treatment occurred in 49 (10%) patients in the tranexamic acid and in 66 (14%) patients in the control group (odds ratio 0·71, 95% CI 0·48-1·04). Other serious adverse events were comparable between groups.
Interpretation: In patients with CT-proven subarachnoid haemorrhage, presumably caused by a ruptured aneurysm, ultra-early, short-term tranexamic acid treatment did not improve clinical outcome at 6 months, as measured by the modified Rankin Scale.
Funding: Fonds NutsOhra.

Gepubliceerd: Lancet. 2021;397(10269):112-8.
Impact factor: 79.323; Q1

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31. **Seizures induced in electroconvulsive therapy as a human epilepsy model: A comparative case study**
Pottkamper JCM, Verdijk J, Hofmeijer J, van Waarde JA, van Putten M.

Objective: Standardized investigation of epileptic seizures and the postictal state may contribute to a better understanding of ictal and postictal phenomena. This comparative case study aims to assess whether electrically induced seizures in electroconvulsive therapy (ECT) show sufficient similarities with spontaneous seizures to serve as a human epilepsy model.
Methods: We compared six EEG recordings, three ECT-induced seizures and three generalized tonic-clonic seizures, using quantitative electroencephalography (EEG) analyses. EEG recordings during and after ECT sessions (under general anesthesia and muscle paralysis) were collected prospectively, whereas epilepsy data were selected retrospectively. Time-frequency representations, dominant ictal frequencies, and postictal alpha-delta ratios were calculated.
Results: In all EEG recordings, a decrease in dominant ictal frequency was observed, as well as postictal suppression. Postictal alpha-delta ratio indicated the same trend for all: a gradual increase from predominantly delta to alpha frequencies on timescales of hours after the seizure. Postictal spectral representation was similar. Muscle artifacts were absent in ECT-induced seizures and present in spontaneous seizures. Ictal amplitude was higher in epileptic than in ECT-induced seizures. Temporospectral ictal dynamics varied slightly between groups.
Significance: We show that ictal and postictal characteristics in ECT and patients with generalized tonic-clonic seizures are essentially similar. ECT-induced seizures may be used to investigate aspects of ictal and postictal states in a highly predictable manner and well-controlled environment. This suggests that clinical and electrophysiological observations during ECT may be extrapolated to epilepsy with generalized tonic-clonic seizures.

Gepubliceerd: Epilepsia Open. 2021;6(4):672-84.
Impact factor: 0; NVT

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32. **Trajectories of Fatigue, Psychological Distress, and Coping Styles After Mild Traumatic Brain Injury: A 6-Month Prospective Cohort Study**
Rakers SE, Timmerman ME, Scheenen ME, de Koning ME, van der Horn HJ, van der Naalt J, Spikman JM.

Objective: To analyze fatigue after mild traumatic brain injury (TBI) with latent class growth analysis (LCGA) to determine distinct recovery trajectories and investigate influencing factors, including emotional distress and coping styles.
Design: An observational cohort study design with validated questionnaires assessing fatigue, anxiety, depression, posttraumatic stress, and coping at 2 weeks and 3 and 6 months postinjury.
Setting: Three level 1 trauma centers.
Participants: Patients with mild TBI (N=456).

Interventions: Not applicable.
Main outcome measures: Fatigue was measured with the fatigue severity subscale of the Checklist Individual Strength, including 8 items (sum score, 8-56). Subsequently, 3 clinical categories were created: high (score, 40-56), moderate (score, 26-38), and low (score, 8-25).
Results: From the entire mild TBI group, 4 patient clusters with distinct patterns for fatigue, emotional distress, and coping styles were found with LCGA. Clusters 1 and 2 showed favorable recovery from fatigue over time, with low emotional distress and the predominant use of active coping in cluster 1 (30%) and low emotional distress and decreasing passive coping in cluster 2 (25%). Clusters 3 and 4 showed unfavorable recovery, with persistent high fatigue and increasing passive coping together with low emotional distress in cluster 3 (27%) and high emotional distress in cluster 4 (18%). Patients with adverse trajectories were more often women and more often experiencing sleep disturbances and pain.
Conclusions: The prognosis for recovery from posttraumatic fatigue is favorable for 55% of mild TBI patients. Patients at risk for chronic fatigue can be signaled in the acute phase postinjury based on the presence of high fatigue, high passive coping, and, for a subgroup of patients, high emotional distress. LCGA proved to be a highly valuable and multipurpose statistical method to map distinct courses of disease-related processes over time.

Gepubliceerd: Arch Phys Med Rehabil. 2021;102(10):1965-71 e2.
Impact factor: 3.966; Q1

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33. **Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial**
Schreuder F, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, Luijckx GJ, Messchendorp GP, van Tuijl J, Bienfait HP, Booij SJ, van den Wijngaard IR, Remmers MJM, Schreuder A, Dippel DW, Staals J, Brouwers PJAM, Wermer MJH, Coutinho JM, Kwa VIH, van Gelder IC, Schutgens REG, Zweedijk B, Algra A, van Dalen JW, Jaap Kappelle L, Rinkel GJE, van der Worp HB, Klijn CJM.

Background: In patients with atrial fibrillation who survive an anticoagulation-associated intracerebral haemorrhage, a decision must be made as to whether restarting or permanently avoiding anticoagulation is the best long-term strategy to prevent recurrent stroke and other vascular events. In APACHE-AF, we aimed to estimate the rates of non-fatal stroke or vascular death in such patients when treated with apixaban compared with when anticoagulation was avoided, to inform the design of a larger trial.
Methods: APACHE-AF was a prospective, randomised, open-label, phase 2 trial with masked endpoint assessment, done at 16 hospitals in the Netherlands. Patients who survived intracerebral haemorrhage while treated with anticoagulation for atrial fibrillation were eligible for inclusion 7-90 days after the haemorrhage. Participants also had a CHA(2)DS(2)-VASc score of at least 2 and a score on the modified Rankin scale (mRS) of 4 or less. Participants were randomly assigned (1:1) to receive oral apixaban (5 mg twice daily or a reduced dose of 2·5 mg twice daily) or to avoid anticoagulation (oral antiplatelet agents could be prescribed at the discretion of the treating physician) by a central computerised randomisation system, stratified by the intention to start or

withhold antiplatelet therapy in participants randomised to avoiding anticoagulation, and minimised for age and intracerebral haemorrhage location. The primary outcome was a composite of non-fatal stroke or vascular death, whichever came first, during a minimum follow-up of 6 months, analysed using Cox proportional hazards modelling in the intention-to-treat population. APACHE-AF is registered with ClinicalTrials.gov (NCT02565693) and the Netherlands Trial Register (NL4395), and the trial is closed to enrolment at all participating sites.
Findings: Between Jan 15, 2015, and July 6, 2020, we recruited 101 patients (median age 78 years [IQR 73-83]; 55 [54%] were men and 46 [46%] were women; 100 [99%] were White and one [1%] was Black) a median of 46 days (IQR 21-74) after intracerebral haemorrhage. 50 were assigned to apixaban and 51 to avoid anticoagulation (of whom 26 [51%] started antiplatelet therapy). None were lost to follow-up. Over a median follow-up of 1·9 years (IQR 1·0-3·1; 222 person-years), non-fatal stroke or vascular death occurred in 13 (26%) participants allocated to apixaban (annual event rate 12·6% [95% CI 6·7-21·5]) and in 12 (24%) allocated to avoid anticoagulation (11·9% [95% CI 6·2-20·8]; adjusted hazard ratio 1·05 [95% CI 0·48-2·31]; p=0·90). Serious adverse events that were not outcome events occurred in 29 (58%) of 50 participants assigned to apixaban and 29 (57%) of 51 assigned to avoid anticoagulation.
Interpretation: Patients with atrial fibrillation who had an intracerebral haemorrhage while taking anticoagulants have a high subsequent annual risk of non-fatal stroke or vascular death, whether allocated to apixaban or to avoid anticoagulation. Our data underline the need for randomised controlled trials large enough to allow identification of subgroups in whom restarting anticoagulation might be either beneficial or hazardous. FUNDING: Dutch Heart Foundation (grant 2012T077).

Gepubliceerd: Lancet Neurol. 2021;20(11):907-16.
Impact factor: 44.182; Q1

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34. **Risk, Clinical Course, and Outcome of Ischemic Stroke in Patients Hospitalized With COVID-19: A Multicenter Cohort Study**
Sluis WM, Linschoten M, Buijs JE, Biesbroek JM, den Hertog HM, Ribbers T, Nieuwkamp DJ, van Houwelingen RC, Dias A, van Uden IWM, Kerklaan JP, Bienfait HP, Vermeer SE, de Jong SW, Ali M, Wermer MJH, de Graaf MT, Brouwers PJAM, Asselbergs FW, Kappelle LJ, van der Worp HB, Algra AM.

Background and Purpose: The frequency of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) varies in the current literature, and risk factors are unknown. We assessed the incidence, risk factors, and outcomes of acute ischemic stroke in hospitalized patients with COVID-19.
Methods: We included patients with a laboratory-confirmed SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) infection admitted in 16 Dutch hospitals participating in the international CAPACITY-COVID registry between March 1 and August 1, 2020. Patients were screened for the occurrence of acute ischemic stroke. We calculated the cumulative incidence of ischemic stroke and compared risk factors, cardiovascular complications, and in-hospital mortality in patients with and without ischemic stroke.
Results: We included 2147 patients with COVID-19, of whom 586 (27.3%) needed treatment at an intensive care unit. Thirty-eight patients (1.8%) had an ischemic stroke.

Patients with stroke were older but did not differ in sex or cardiovascular risk factors. Median time between the onset of COVID-19 symptoms and diagnosis of stroke was 2 weeks. The incidence of ischemic stroke was higher among patients who were treated at an intensive care unit (16/586; 2.7% versus nonintensive care unit, 22/1561; 1.4%; P=0.039). Pulmonary embolism was more common in patients with (8/38; 21.1%) than in those without stroke (160/2109; 7.6%; adjusted risk ratio, 2.08 [95% CI, 1.52-2.84]). Twenty-seven patients with ischemic stroke (71.1%) died during admission or were functionally dependent at discharge. Patients with ischemic stroke were at a higher risk of in-hospital mortality (adjusted risk ratio, 1.56 [95% CI, 1.13-2.15]) than patients without stroke.
Conclusions: In this multicenter cohort study, the cumulative incidence of acute ischemic stroke in hospitalized patients with COVID-19 was ≈2%, with a higher risk in patients treated at an intensive care unit. The majority of stroke patients had a poor outcome. The association between ischemic stroke and pulmonary embolism warrants further investigation.

Gepubliceerd: Stroke. 2021;52(12):3978-86.
Impact factor: 7.914; Q1

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35. **How to Identify Responders and Nonresponders to Dorsal Root Ganglion-Stimulation Aimed at Eliciting Motor Responses in Chronic Spinal Cord Injury: Post Hoc Clinical and Neurophysiological Tests in a Case Series of Five Patients**
Soloukey S, Drenthen J, Osterthun R, de Vos CC, De Zeeuw CI, Huygen F, Harhangi BS.

Objective: While integrity of spinal pathways below injury is generally thought to be an important factor in the success-rate of neuromodulation strategies for spinal cord injury (SCI), it is still unclear how the integrity of these pathways conveying the effects of stimulation should be assessed. In one of our institutional case series of five patients receiving dorsal root ganglion (DRG)-stimulation for elicitation of immediate motor response in motor complete SCI, only two out of five patients presented as responders, showing immediate muscle activation upon DRG-stimulation. The current study focuses on post hoc clinical-neurophysiological tests performed within this patient series to illustrate their use for prediction of spinal pathway integrity, and presumably, responder-status.
Materials and methods: In a series of three nonresponders and two responders (all male, American Spinal Injury Association [ASIA] impairment scale [AIS] A/B), a test-battery consisting of questionnaires, clinical measurements, as well as a series of neurophysiological measurements was performed less than eight months after participation in the initial study.
Results: Nonresponders presented with a complete absence of spasticity and absence of leg reflexes. Additionally, nonresponders presented with close to no compound muscle action potentials (CMAPs) or Hofmann(H)-reflexes. In contrast, both responders presented with clear spasticity, elicitable leg reflexes, CMAPs, H-reflexes, and sensory nerve action potentials, although not always consistent for all tested muscles.
Conclusions: Post hoc neurophysiological measurements were limited in clearly separating responders from nonresponders. Clinically, complete absence of spasticity-related complaints in the nonresponders was a distinguishing factor between

responders and nonresponders in this case series, which mimics prior reports of epidural electrical stimulation, potentially illustrating similarities in mechanisms of action between the two techniques. However, the problem remains that explicit use and report of preinclusion clinical-neurophysiological measurements is missing in SCI literature. Identifying proper ways to assess these criteria might therefore be unnecessarily difficult, especially for nonestablished neuromodulation techniques.

Gepubliceerd: Neuromodulation. 2021;24(4):719-28.
Impact factor: 4.722; Q2

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36. **Coping with stress before and after mild traumatic brain injury: a pilot hair cortisol study**
Spikman JM, van der Horn HJ, Scheenen ME, de Koning ME, Savas M, Langerak T, van Rossum EFC, van der Naalt J.

Background: Cortisol is a crucial hormone for adaptation to challenging and stressful situations. Hair cortisol measurement is used to determine chronic stress; the growth rate of hair allows to determine averaged cortisol levels for a longer period.
Objective: Pre- and post-injury measures of hair cortisol were compared in patients with mild traumatic brain injury (mTBI), and related to their coping styles.
Methods: For 46 patients with mTBI, 3 cm scalp hair samples were collected 4-6 weeks post-injury, resulting in two 1 cm segments, pre- and post-injury. Hair samples were also collected for 11 healthy controls. Hair cortisol was quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Complaints, anxiety, depression and coping style were measured two weeks post-injury and long term (six-twelve months), added with measures for post-traumatic stress and functional outcome.
Results: There were no differences between patients' pre- and post-injury cortisol levels, nor between cortisol levels of patients and controls. However, pre- and post-injury cortisol levels of patients were negatively correlated with both passive and an avoidant coping style.
Conclusions: Our findings suggest that mTBI has no separate impact on chronic long-term cortisol levels, possibility indicating that variability in cortisol levels reflects individuals' premorbid characteristics determining coping with stress in general.

Gepubliceerd: Brain Inj. 2021;35(8):871-9.
Impact factor: 2.311; Q2

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37. **White Matter Lesions and Outcomes After Endovascular Treatment for Acute Ischemic Stroke: MR CLEAN Registry Results**
Uniken Venema SM, Postma AA, van den Wijngaard IR, Vos JA, Lingsma HF, Bokkers RPH, Hofmeijer J, Dippel DWJ, Majoie CB, van der Worp HB, MR CLEAN Registry Investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background: Cerebral white matter lesions (WMLs) have been associated with a greater risk of poor functional outcome after ischemic stroke. We assessed the relations between WML burden and radiological and clinical outcomes in patients treated with endovascular treatment in routine practice.

Methods: We analyzed data from the MR CLEAN Registry (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands)—a prospective, multicenter, observational cohort study of patients treated with endovascular treatment in the Netherlands. WMLs were graded on baseline noncontrast computed tomography using a visual grading scale. The primary outcome was the score on the modified Rankin Scale at 90 days. Secondary outcomes included early neurological recovery, successful reperfusion (extended Thrombolysis in Cerebral Infarction ≥2b), futile recanalization (modified Rankin Scale score ≥3 despite successful reperfusion), and occurrence of symptomatic intracranial hemorrhage. We used multivariable logistic regression models to assess associations between WML severity and outcomes, taking the absence of WML on noncontrast computed tomography as the reference category.
Results: Of 3180 patients included in the MR CLEAN Registry between March 2014 and November 2017, WMLs were graded for 3046 patients and categorized as none (n=1855; 61%), mild (n=608; 20%), or moderate to severe (n=588; 19%). Favorable outcome (modified Rankin Scale score, 0–2) was achieved in 838 patients (49%) without WML, 192 patients (34%) with mild WML, and 130 patients (24%) with moderate-to-severe WML. Increasing WML grades were associated with a shift toward poorer functional outcome in a dose-dependent manner (adjusted common odds ratio, 1.34 [95% CI, 1.13–1.60] for mild WML and 1.67 [95% CI, 1.39–2.01] for moderate-to-severe WML; Ptrend, <0.001). Increasing WML grades were associated with futile recanalization (Ptrend, <0.001) and were inversely associated with early neurological recovery (Ptrend, 0.041) but not with the probability of successful reperfusion or symptomatic intracranial hemorrhage.
Conclusions: An increasing burden of WML at baseline is associated with poorer clinical outcomes after endovascular treatment for acute ischemic stroke but not with the probability of successful reperfusion or symptomatic intracranial hemorrhage.

Gepubliceerd: Stroke. 2021;52(9):2849-57.
Impact factor: 7.914; Q1

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38. **Cardiac imaging in ischemic stroke or transient ischemic attack of undetermined cause: Systematic review & meta-analysis**
van der Maten G, Dijkstra S, Meijs MFL, von Birgelen C, van der Palen J, den Hertog HM.

Background: Patients with ischemic stroke or transient ischemic attack (TIA) of undetermined cause often undergo cardiac imaging in search of a cardioembolic source. As the choice of the most appropriate imaging approach is controversial and therapeutic implications have changed over time, we aimed to identify in patients with "cryptogenic stroke or TIA" the yield of transthoracic or transesophageal echocardiography (TTE or TEE) and cardiac computed tomography (CT).
Methods and results: We performed a systematic review and meta-analysis according to the PRISMA guidelines. Included were studies that assessed consecutive patients with ischemic stroke or TIA of undetermined cause to evaluate the yield of TTE, TEE, or cardiac CT for detecting cardioembolic sources. For each type of cardioembolic source the pooled prevalence was calculated. Only six out of 1458 studies fulfilled the inclusion criteria (1022 patients). One study reported the yield of TTE, four of TEE, and one of both TTE and TEE; no study assessed cardiac CT. Mean patient age ranged

from 44.3-71.2 years, 49.2-59.7% were male. TTE detected 43 cardioembolic sources in 316 patients (4 (1.3%) major, 39 (12.3%) minor), and TEE 248 in 937 patients (55 (5.9%) major, 193 (20.6%) minor). The most prevalent major cardioembolic source was left atrial appendage thrombus, yet results were heterogeneous among studies.
Conclusions: TTE and TEE infrequently detect major cardioembolic sources that require a change of therapy. Findings should be interpreted with caution due to the limited number of studies. A large-sized prospective clinical trial is warranted to support evidence-based decision-making.

Gepubliceerd: Int J Cardiol. 2021;339:211-8.
Impact factor: 4.164; Q2

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39. **Detection of Major Cardioembolic Sources in Real-World Patients with Ischemic Stroke or Transient Ischemic Attack of Undetermined Cause**
van der Maten G, Reimer JMB, Meijs MFL, von Birgelen C, Brusse-Keizer MGJ, den Hertog HM.

Background/Aim: Current guidelines recommend transthoracic echocardiography (TTE) and ambulatory rhythm monitoring following ischemic stroke or transient ischemic attack (TIA) of undetermined cause for identifying cardioembolic sources (CES). Due to ongoing controversies about this routine strategy, we evaluated its yield in a real-world setting.
Methods: In a tertiary medical center, we retrospectively evaluated consecutive patients with ischemic stroke or TIA of undetermined cause, who (after standard work-up) underwent TTE, ambulatory rhythm monitoring, or both. CES were classified as major if probably related to ischemic events and warranting a change of therapy.
Results: Between January 2014 and December 2017, 674 patients had ischemic stroke or TIA of undetermined cause. Of all 484 patients (71.8%) who underwent TTE, 9 (1.9%) had a major CES. However, 7 of them had already been identified for cardiac evaluation due to new major electrocardiographic abnormalities or cardiac symptoms. Thus, only 2 patients (0.4%) truly benefitted from unselected TTE screening. Ambulatory rhythm monitoring was performed in 411 patients (61.0%) and revealed AF in 10 patients (2.4%).
Conclusion: Detecting a major CES is essential because appropriate treatment lowers the risk of recurrent stroke. Nonetheless, in this real-world study that aimed at routine use of TTE and ambulatory rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause, the prevalence of major CES was low. Most patients with major CES on TTE already had an indication for referral to a cardiologist, suggesting that major CES might also have been identified with a much more selective use of TTE.
Gepubliceerd: Cerebrovasc Dis Extra. 2021;11(1):22-8.
Impact factor: 0; NVT

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40. **Primary therapy and survival in patients aged over 70-years-old with primary central nervous system lymphoma: a contemporary, nationwide, population-based study in the Netherlands**
van der Meulen M, Bromberg JEC, Nijland M, Visser O, Doorduijn JK, Dinmohamed AG.

Gepubliceerd: Haematologica. 2021;106(2):597-600.
Impact factor: 9.941; Q1

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41. **MMSE is an independent prognostic factor for survival in primary central nervous system lymphoma**
van der Meulen M, Dirven L, Bakunina K, van den Bent MJ, Issa S, Doorduijn JK, Bromberg JEC.

Introduction: To assess the value of the Mini-Mental State Examination (MMSE)-score at baseline in predicting survival in adult primary central nervous system lymphoma (PCNSL) patients.
Methods: In the HOVON 105/ ALLG NHL 24 phase III study patients with newly-diagnosed PCNSL were randomized between high-dose methotrexate-based chemotherapy with or without rituximab. Data on potential (MMSE-score), and known baseline prognostic factors (age, performance status, serum LDH, cerebrospinal fluid total protein, involvement of deep brain structures, multiple cerebral lesions, and the IELSG-score) were collected prospectively. Multivariable stepwise Cox regression analyses were used to assess the prognostic value of all factors on progression-free survival (PFS) and overall survival (OS) among patients with available MMSE score at baseline. Age was analyzed as continuous variable, the MMSE-score both as a continuous and as a categorical variable.
Results: In univariable analysis, age, MMSE-score and whether the patient received rituximab were statistically significantly prognostic factors for PFS. Age and MMSE-score were statistically significantly associated with OS. In a multivariable analysis of the univariately significant factors only MMSE-score was independently associated with the survival endpoints, as a continuous variable (HR for PFS 1.04, 95% CI 1.01-1.08; OS 1.06 (95% CI 1.02-1.10) and as categorical variable HR (< 27 versus ≥ 27 for PFS 1.55 (1.02-2.35); OS 1.68 (1.05-2.70). In our population, performance status, serum LDH, and CSF protein level were not of prognostic value.
Conclusion: Neurocognitive disturbances, measured with the MMSE at baseline, are an unfavorable prognostic factor for both PFS and OS in adult PCNSL patients up to 70 years-old.

Gepubliceerd: J Neurooncol. 2021;152(2):357-62.
Impact factor: 4.130; Q2

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42. **Neurocognitive functioning and radiologic changes in primary CNS lymphoma patients: results from the HOVON 105/ALLG NHL 24 randomized controlled trial**
van der Meulen M, Dirven L, Habets EJJ, Bakunina K, Smits M, Achterberg HC, Seute T, Cull G, Schouten H, Zijlstra JM, Brandsma D, Enting RH, Beijert M, Taphoorn MJB, van den Bent MJ, Issa S, Doorduijn JK, Bromberg JEC.

Background: To analyze the effect of treatment on neurocognitive functioning and the association of neurocognition with radiological abnormalities in primary central nervous system lymphoma (PCNSL).
Methods: One hundred and ninety-nine patients from a phase III trial (HOVON 105/ALLG NHL 24), randomized to standard chemotherapy with or without rituximab,

followed in patients ≤60 years old by 30-Gy whole-brain radiotherapy (WBRT), were asked to participate in a neuropsychological evaluation before and during treatment, and up to 2 years posttreatment. Scores were transformed into a standardized z-score; clinically relevant changes were defined as a change in z-score of ≥1 SD. The effect of WBRT was analyzed in irradiated patients. All MRIs were centrally assessed for white matter abnormalities and cerebral atrophy, and their relation with neurocognitive scores over time in each domain was calculated.
Results: 125/199 patients consented to neurocognitive evaluation. Statistically significant improvements in neurocognition were seen in all domains. A clinically relevant improvement was seen only in the motor speed domain, without differences between the arms. In the follow-up of irradiated patients (n = 43), no change was observed in any domain score, compared to after WBRT. Small but significant inverse correlations were found between neurocognitive scores over time and changes in white matter abnormalities (regression coefficients: -0.048 to -0.347) and cerebral atrophy (-0.212 to -1.774).
Conclusions: Addition of rituximab to standard treatment in PCNSL patients did not impact neurocognitive functioning up to 2 years posttreatment, nor did treatment with 30-Gy WBRT in patients ≤60 years old. Increased white matter abnormalities and brain atrophy showed weak associations with neurocognition.

Gepubliceerd: Neuro Oncol. 2021;23(8):1315-26.
Impact factor: 12.300; Q1

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43. **Extent of radiological response does not reflect survival in primary central nervous system lymphoma**
van der Meulen M, Postma AA, Smits M, Bakunina K, Minnema MC, Seute T, Cull G, Enting RH, van der Poel M, Stevens WBC, Brandsma D, Beeker A, Doorduijn JK, Issa S, van den Bent MJ, Bromberg JEC.

Background: In primary central nervous system lymphoma (PCNSL), small enhancing lesions can persist after treatment. It is unknown whether a difference in response category (complete response [CR], complete response unconfirmed [CRu], or partial response [PR]) reflects survival. We aimed to determine the value of a central radiology review on response assessment and whether the extent of response influenced progression-free and/or overall survival.
Methods: All patients in the HOVON 105/ALLG NHL 24 study with at least a baseline MRI and one MRI made for response evaluation available for central review were included. Tumor measurements were done by 2 independent central reviewers, disagreements were adjudicated by a third reviewer. Crude agreement and interobserver agreement (Cohen's kappa) were calculated. Differences in progression-free and overall survival between different categories of response at the end-of-protocol-treatment were assessed by the log-rank test in a landmark survival-analysis.
Results: Agreement between the central reviewers was 61.7% and between local and central response assessment was 63.0%. Cohen's kappa's, which corrects for expected agreement, were 0.44 and 0.46 (moderate), respectively. Progression agreement or not was 93.3% (kappa 0.87) between local and central response assessment. There were no significant differences in progression-free and overall survival between patients with CR, CRu, or PR at the end-of-protocol-treatment, according to both local and central response assessment.

Conclusions: Reliability of response assessment (CR/CRu/PR) is moderate even by central radiology review and these response categories do not reliably predict survival. Therefore, primary outcome in PCNSL studies should be survival rather than CR or CR/CRu-rate.

Gepubliceerd: Neurooncol Adv. 2021;3(1):vdab007.
Impact factor: 0; NVT

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44. **EEG biomarker informed prescription of antidepressants in MDD: a feasibility trial**
van der Vinne N, Vollebregt MA, Rush AJ, Eebes M, van Putten MJAM, Arns M.

Using pre-treatment biomarkers to guide patients to the preferred antidepressant medication treatment could be a promising approach to enhance its current modest response and remission rates. This open-label prospective study assessed the feasibility of using such pre-treatment biomarkers, by using previously identified EEG features (paroxysmal activity; alpha peak frequency; frontal alpha asymmetry) to inform the clinician in selecting among three different antidepressants (ADs; escitalopram, sertraline, venlafaxine) as compared to Treatment As Usual (TAU). EEG data were obtained from 195 outpatients with major depressive disorder prior to eight weeks of AD treatment. Primary outcome measure was the percentage change between before and after treatment on the Beck Depression Inventory-II (BDI-II). We compared TAU and EEG-informed prescription through AN(C)OVAs. Recruitment started with patients receiving TAU to establish baseline effectiveness, after which we recruited patients receiving EEG-informed prescription. 108 patients received EEG-informed prescription and 87 patients received TAU. Clinicians and patients were satisfied with the protocol. Overall, 70 (65%) of the EEG-informed clinicians followed recommendations (compared to 52 (60%) following prescriptions in the TAU group), establishing feasibility. We here confirm that treatment allocation informed by EEG variables previously reported in correlational studies, was feasible.

Gepubliceerd: Eur Neuropsychopharmacol. 2021;44:14-22.
Impact factor: 4.600; Q2

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45. **Dysregulation of Astrocyte Ion Homeostasis and Its Relevance for Stroke-Induced Brain Damage**
van Putten M, Fahlke C, Kafitz KW, Hofmeijer J, Rose CR.

Ischemic stroke is a leading cause of mortality and chronic disability. Either recovery or progression towards irreversible failure of neurons and astrocytes occurs within minutes to days, depending on remaining perfusion levels. Initial damage arises from energy depletion resulting in a failure to maintain homeostasis and ion gradients between extra- and intracellular spaces. Astrocytes play a key role in these processes and are thus central players in the dynamics towards recovery or progression of stroke-induced brain damage. Here, we present a synopsis of the pivotal functions of astrocytes at the tripartite synapse, which form the basis of physiological brain functioning. We summarize the evidence of astrocytic failure and its consequences under ischemic conditions. Special emphasis is put on the homeostasis and stroke-

induced dysregulation of the major monovalent ions, namely Na(+), K(+), H(+), and Cl(-), and their involvement in maintenance of cellular volume and generation of cerebral edema.

Gepubliceerd: Int J Mol Sci. 2021;22(11).
Impact factor: 5.924; Q1

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46. **Quantified health and cost effects of faster endovascular treatment for large vessel ischemic stroke patients in the Netherlands**
van Voorst H, Kunz WG, van den Berg LA, Kappelhof M, Pinckaers FME, Goyal M, Hunink MGM, Emmer BJ, Mulder M, Dippel DWJ, Coutinho JM, Marquering HA, Boogaarts HD, van der Lugt A, van Zwam WH, Roos Y, Buskens E, Dijkgraaf MGW, Majoie C, MR CLEAN Registry Investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background: The effectiveness of endovascular treatment (EVT) for large vessel occlusion (LVO) stroke severely depends on time to treatment. However, it remains unclear what the value of faster treatment is in the years after index stroke. The aim of this study was to quantify the value of faster EVT in terms of health and healthcare costs for the Dutch LVO stroke population.
Methods: A Markov model was used to simulate 5-year follow-up functional outcome, measured with the modified Rankin Scale (mRS), of 69-year-old LVO patients. Post-treatment mRS was extracted from the MR CLEAN Registry (n=2892): costs per unit of time and Quality-Adjusted Life Years (QALYs) per mRS sub-score were retrieved from follow-up data of the MR CLEAN trial (n=500). Net Monetary Benefit (NMB) at a willingness to pay of €80 000 per QALY was reported as primary outcome, and secondary outcome measures were days of disability-free life gained and costs.
Results: EVT administered 1 min faster resulted in a median NMB of €309 (IQR: 226;389), 1.3 days of additional disability-free life (IQR: 1.0;1.6), while cumulative costs remained largely unchanged (median: -€15, IQR: -65;33) over a 5-year follow-up period. As costs over the follow-up period remained stable while QALYs decreased with longer time to treatment, which this results in a near-linear decrease of NMB. Since patients with faster EVT lived longer, they incurred more healthcare costs.
Conclusion: One-minute faster EVT increases QALYs while cumulative costs remain largely unaffected. Therefore, faster EVT provides better value of care at no extra healthcare costs.

Gepubliceerd: J Neurointerv Surg. 2021;13(12):1099-105.
Impact factor: 5.836; Q1

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47. **Prediction of Outcome and Endovascular Treatment Benefit: Validation and Update of the MR PREDICTS Decision Tool**
Venema E, Roozenbeek B, Mulder M, Brown S, Majoie C, Steyerberg EW, Demchuk AM, Muir KW, Dávalos A, Mitchell PJ, Bracard S, Berkhemer OA, Lycklama À Nijeholt GJ, van Oostenbrugge RJ, Roos Y, van Zwam WH, van der Lugt A, Hill MD, White P, Campbell BCV, Guillemin F, Saver JL, Jovin TG, Goyal M, Dippel DWJ, Lingsma HF, HERMES collaborators and MR CLEAN Registry Investigators – includes Brouwers PJAM, Kleijn S, Lodico J, Droste H.

Background and Purpose: Benefit of early endovascular treatment (EVT) for ischemic stroke varies considerably among patients. The MR PREDICTS decision tool, derived from MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), predicts outcome and treatment benefit based on baseline characteristics. Our aim was to externally validate and update MR PREDICTS with data from international trials and daily clinical practice.
Methods: We used individual patient data from 6 randomized controlled trials within the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration to validate the original model. Then, we updated the model and performed a second validation with data from the observational MR CLEAN Registry. Primary outcome was functional independence (defined as modified Rankin Scale score 0–2) 3 months after stroke. Treatment benefit was defined as the difference between the probability of functional independence with and without EVT. Discriminative performance was evaluated using a concordance (C) statistic.
Results: We included 1242 patients from HERMES (633 assigned to EVT, 609 assigned to control) and 3156 patients from the MR CLEAN Registry (all of whom underwent EVT within 6.5 hours). The C-statistic for functional independence was 0.74 (95% CI, 0.72–0.77) in HERMES and, after model updating, 0.80 (0.78–0.82) in the Registry. Median predicted treatment benefit of routinely treated patients (Registry) was 10.3% (interquartile range, 5.8%–14.4%). Patients with low (<1%) predicted treatment benefit (n=135/3156 [4.3%]) had low rates of functional independence, irrespective of reperfusion status, suggesting potential absence of treatment benefit. The updated model was made available online for clinicians and researchers at www.mrpredicts.com.
Conclusions: Because of the substantial treatment effect and small potential harm of EVT, most patients arriving within 6 hours at an endovascular-capable center should be treated regardless of their clinical characteristics. MR PREDICTS can be used to support clinical judgement when there is uncertainty about the treatment indication, when resources are limited, or before a patient is to be transferred to an endovascular-capable center.

Gepubliceerd: Stroke. 2021;52(9):2764-72.
Impact factor: 7.914; Q1

48. **Biallelic variants in HPDL cause pure and complicated hereditary spastic paraplegia**

Wiessner M, Maroofian R, Ni MY, Pedroni A, Müller JS, Stucka R, Beetz C, Efthymiou S, Santorelli FM, Alfares AA, Zhu C, Uhrova Meszarosova A, Alehabib E, Bakhtiari S, Janecke AR, Otero MG, Chen JYH, Peterson JT, Strom TM, De Jonghe P, Deconinck T, De Ridder W, De Winter J, Pasquariello R, Ricca I, Alfadhel M, van de Warrenburg BP, Portier R, Bergmann C, Ghasemi Firouzabadi S, Jin SC, Bilguvar K, Hamed S, Abdelhameed M, Haridy NA, Maqbool S, Rahman F, Anwar N, Carmichael J, Pagnamenta A, Wood NW, Tran Mau-Them F, Haack T, Di Rocco M, Ceccherini I, Iacomino M, Zara F, Salpietro V, Scala M, Rusmini M, Xu Y, Wang Y, Suzuki Y, Koh K, Nan H, Ishiura H, Tsuji S, Lambert L, Schmitt E, Lacaze E, Küpper H, Dredge D, Skraban C, Goldstein A, Willis MJH, Grand K, Graham JM, Lewis RA, Millan F, Duman Ö, Dündar N, Uyanik G, Schöls L, Nürnberg P, Nürnberg G, Catala Bordes A, Seeman P, Kuchar M, Darvish H, Rebelo A, Bouçanova F, Medard JJ, Chrast R, Auer-Grumbach M, Alkuraya FS, Shamseldin H, Al Tala S, Rezazadeh Varaghchi J, Najafi M, Deschner S, Gläser D, Hüttel W, Kruer MC, Kamsteeg EJ, Takiyama Y, Züchner S,

Baets J, Synofzik M, Schüle R, Horvath R, Houlden H, Bartesaghi L, Lee HJ, Ampatzis K, Pierson TM, Senderek J.

Human 4-hydroxyphenylpyruvate dioxygenase-like (HPDL) is a putative iron-containing non-heme oxygenase of unknown specificity and biological significance. We report 25 families containing 34 individuals with neurological disease associated with biallelic HPDL variants. Phenotypes ranged from juvenile-onset pure hereditary spastic paraplegia to infantile-onset spasticity and global developmental delays, sometimes complicated by episodes of neurological and respiratory decompensation. Variants included bona fide pathogenic truncating changes, although most were missense substitutions. Functionality of variants could not be determined directly as the enzymatic specificity of HPDL is unknown; however, when HPDL missense substitutions were introduced into 4-hydroxyphenylpyruvate dioxygenase (HPPD, an HPDL orthologue), they impaired the ability of HPPD to convert 4-hydroxyphenylpyruvate into homogentisate. Moreover, three additional sets of experiments provided evidence for a role of HPDL in the nervous system and further supported its link to neurological disease: (i) HPDL was expressed in the nervous system and expression increased during neural differentiation; (ii) knockdown of zebrafish hpdl led to abnormal motor behaviour, replicating aspects of the human disease; and (iii) HPDL localized to mitochondria, consistent with mitochondrial disease that is often associated with neurological manifestations. Our findings suggest that biallelic HPDL variants cause a syndrome varying from juvenile-onset pure hereditary spastic paraplegia to infantile-onset spastic tetraplegia associated with global developmental delays.

Gepubliceerd: Brain. 2021;144(5):1422-34.
Impact factor: 13.501; Q1

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49. **Predicting neurological outcome in comatose patients after cardiac arrest with multiscale deep neural networks**
Zheng WL, Amorim E, Jing J, Ge W, Hong S, Wu O, Ghassemi M, Lee JW, Sivaraju A, Pang T, Herman ST, Gaspard N, Ruijter BJ, Sun J, Tjepkema-Cloostermans MC, Hofmeijer J, van Putten M, Westover MB.
Objective: Electroencephalography (EEG) is an important tool for neurological outcome prediction after cardiac arrest. However, the complexity of continuous EEG data limits timely and accurate interpretation by clinicians. We develop a deep neural network (DNN) model to leverage complex EEG trends for early and accurate assessment of cardiac arrest coma recovery likelihood.
Methods: We developed a multiscale DNN combining convolutional neural networks (CNN) and recurrent neural networks (long short-term memory [LSTM]) using EEG and demographic information (age, gender, shockable rhythm) from a multicenter cohort of 1,038 cardiac arrest patients. The CNN learns EEG feature representations while the multiscale LSTM captures short-term and long-term EEG dynamics on multiple time scales. Poor outcome is defined as a Cerebral Performance Category (CPC) score of 3-5 and good outcome as CPC score 1-2 at 3-6 months after cardiac arrest. Performance is evaluated using area under the receiver operating characteristic curve (AUC) and calibration error.
Results: Model performance increased with EEG duration, with AUC increasing from 0.83 (95% Confidence Interval [CI] 0.79-0.87 at 12h to 0.91 (95%CI 0.88-0.93) at 66h.

Sensitivity of good and poor outcome prediction was 77% and 75% at a specificity of 90%, respectively. Sensitivity of poor outcome was 50% at a specificity of 99%. Predicted probability was well matched to the observation frequency of poor outcomes, with a calibration error of 0.11 [0.09-0.14].
Conclusions: These results demonstrate that incorporating EEG evolution over time improves the accuracy of neurologic outcome prediction for patients with coma after cardiac arrest.

Gepubliceerd: Resuscitation. 2021;169:86-94.
Impact factor: 5.262; Q1

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50. **Ancestral Origin of the First Indian Families with Myotonic Dystrophy Type 2**
Damen MJ, Schijvenaars MMVAP, Schimmel-Naber AM, Groothuismink JM, Coenen MJC, Tieleman AA

Background: Myotonic dystrophy type 2 (DM2) is caused by a CCTG repeat expansion in intron 1 of the CCHC-Type Zinc Finger Nucleic Acid Binding Protein (CNBP) gene. Previous studies indicated that this repeat expansion originates from separate founders.
Objective: This study was set out to determine whether or not patients with DM2 originating from European and non-European countries carry the previously described European founder haplotypes.
Methods: Haplotype analysis was performed in 59 DM2 patients from 29 unrelated families. Twenty-three families were from European descent and 6 families originated from non-European countries (India, Suriname and Morocco). Seven short tandem repeats (CL3N122, CL3N99, CL3N59, CL3N117, CL3N119, CL3N19 and CL3N23) and 4 single nucleotide polymorphisms (SNP) (rs1871922, rs1384313, rs4303883 and CGAP_886192) in and around the CNBP gene were used to construct patients' haplotypes. These haplotypes were compared to the known DM2 haplotypes to determine the ancestral origin of the CNBP repeat expansion.
Results: Of 41 patients, the haplotype could be assigned to the previously described Caucasian haplotypes. Three patients from Morocco and Portugal had a haplotype identical to the earlier reported Moroccan haplotype. Twelve patients from India and Suriname, however, carried a haplotype that seems distinct from the previously reported haplotypes. Three individuals could not be assigned to a specific haplotype.
Conclusion: The ancestral origin of DM2 in India might be distinct from the Caucasian families and the solely described Japanese patient. However, we were unable to establish this firmly due to the limited genetic variation in the region surrounding the CNBP gene.

Gepubliceerd: J. Neuromuscul. Dis. 2021;8(4):715-722.
Impact factor: 4.440 ;Q1

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51. **Cerebral amyloid angiopathy: an easily missed diagnosis in patients with transient neurological deficitis**
Reimer JMB, Deodatus JA, Nguyen TKM, den Hertog HM

Cerebral amyloid angiopathy (CAA) is a degenerative neurovascular disease in which the protein amyloid-beta accumulates in the vessel wall of cortical and leptomeningeal arteries. This may lead to acute lobar cerebral haemorrhage, which in case of CAA is fatal in 10-30% of cases. CAA may also present with transient focal neurological episodes (TFNE), the symptoms of which may mimic a transient ischaemic attack (TIA). Distinction between the two has important implications for therapy, as antithrombotics are relatively contra-indicated in CAA, but indicated after a TIA. We describe a patient with transient focal neurological deficits who was initially treated with antithrombotic therapy for a suspected TIA. Eventually, the diagnosis CAA was made and antithrombotic treatment was ceased. This case stresses the importance of considering the diagnosis CAA with TFNE in patients presenting with transient neurological deficits, in order to avoid an unnecessarily increased risk of symptomatic and possibly fatal cerebral haemorrhage.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021 Feb 18;165:D5337.
Impact factor: 0; NVT

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52. **Parainfectieuze myoclonieën bij een COVID-19-infectie**
NGM Oonk, AEJ Sijben, JPP van Vugt, JPM van der Vegt

Een 87-jarige patiënt ontwikkelde gegeneraliseerde, actie-geïnduceerde myoclonieën op basis van een auto-immuungemedieerde, parainfectieuze reactie bij een SARS-CoV-2-infectie. Met aanvullend onderzoek waren reeds overige oorzaken uitgesloten. De patiënt werd symptomatisch behandeld met anti-epileptica en aanvullend een methylprednisolonkuur. De behandeling had een goed effect. Na 3 maanden resteerden nog subtiele myoclonieën en was er nog sprake van lichte cognitieve en fysieke klachten. Het klinisch spectrum van COVID-19-geassocieerde myoclonieën beschreven in de recente literatuur reikt van geïsoleerde myoclonieën tot een opsoclonus-myoclonussyndroom met encefalopathie. Bij het merendeel van de patiënten blijkt hieraan een para- of postinfectieuze oorzaak ten grondslag te liggen. De behandeling bestaat uit symptoombestrijding met anti-epileptica, eventueel in combinatie met immunosuppressiva. De prognose van parainfectieuze myoclonus bij COVID-19 lijkt tot nu toe gunstig, hoewel over de langetermijngevolgen nog geen harde uitspraken kunnen worden gedaan.

Gepubliceerd: Tijdschrift voor Neurologie en Neurochirurgie. 2021;122(3):127-31
Impact factor: 0; NVT

Totale impact factor: 441.835
Gemiddelde impact factor: 8.497

Aantal artikelen 1e, 2e of laatste auteur: 23
Totale impact factor: 85.026
Gemiddelde impact factor: 3.697

Oogheelkunde

1. **Association of Smoking, Alcohol Consumption, Blood Pressure, Body Mass Index, and Glycemic Risk Factors With Age-Related Macular Degeneration: A Mendelian Randomization Study**

Kuan V, Warwick A, Hingorani A, Tufail A, Cipriani V, Burgess S, Sofat R, International AMD Genomics Consortium International – includes Saksens NTM.

Importance: Advanced age-related macular degeneration (AMD) is a leading cause of blindness in Western countries. Causal, modifiable risk factors need to be identified to develop preventive measures for advanced AMD.
Objective: To assess whether smoking, alcohol consumption, blood pressure, body mass index, and glycemic traits are associated with increased risk of advanced AMD.
Design, Setting, Participants: This study used 2-sample mendelian randomization. Genetic instruments composed of variants associated with risk factors at genome-wide significance (P < 5 x 10-8) were obtained from published genome-wide association studies. Summary-level statistics for these instruments were obtained for advanced AMD from the International AMD Genomics Consortium 2016 data set, which consisted of 16144 individuals with AMD and 17832 control individuals. Data were analyzed from July 2020 to September 2021.
Exposures: Smoking initiation, smoking cessation, lifetime smoking, age at smoking initiation, alcoholic drinks per week, body mass index, systolic and diastolic blood pressure, type 2 diabetes, glycated hemoglobin, fasting glucose, and fasting insulin. Main Outcomes and Measures: Advanced AMD and its subtypes, geographic atrophy (GA), and neovascular AMD.
Results: A 1-SD increase in logodds of genetically predicted smoking initiation was associated with higher risk of advanced AMD (odds ratio [OR], 1.26; 95% CI, 1.13-1.40; P < .001), while a 1-SD increase in logodds of genetically predicted smoking cessation (former vs current smoking) was associated with lower risk of advanced AMD (OR, 0.66; 95% CI, 0.50-0.87; P = .003). Genetically predicted increased lifetime smoking was associated with increased risk of advanced AMD (OR per 1-SD increase in lifetime smoking behavior, 1.32; 95% CI, 1.09-1.59; P = .004). Genetically predicted alcohol consumption was associated with higher risk of GA (OR per 1-SD increase of log-transformed alcoholic drinks per week, 2.70; 95% CI, 1.48-4.94; P = .001). There was insufficient evidence to suggest that genetically predicted blood pressure, body mass index, and glycemic traits were associated with advanced AMD.
Conclusions and Relevance: This study provides genetic evidence that increased alcohol intake may be a causal risk factor for GA. As there are currently no known treatments for GA, this finding has important public health implications. These results also support previous observational studies associating smoking behavior with risk of advanced AMD, thus reinforcing existing public health messages regarding the risk of blindness associated with smoking.

Gepubliceerd: JAMA Ophthalmol. 2021;139(12):1299-306.
Impact factor: 7.389; Q1

Totale impact factor: 7.389
Gemiddelde impact factor: 7.389
Aantal artikelen 1e, 2e of laatste auteur: 0

Totale impact factor: NVT
Gemiddelde impact factor: NVT

Orthopedie

1. **Sacroiliac joint fusion in patients with Ehlers Danlos Syndrome: A case series**
Beijk I, Knoef R, van Vugt A, Verra W, Nellensteijn J.

Background: Sacroiliac joint dysfunction (SJD) is a known cause of lower back pain. SJD might be due to hypermobility in the Sacroiliac joint (SIJ) in patients with Ehlers Danlos Syndrome (EDS). Stabilization of the SIJ can be a highly successful treatment for lower back pain. No previous literature about EDS and SIJ fusion is available. The purpose of this study was to assess our mid-term results of SIJ fusion surgery in EDS patients suffering from SIJ dysfunction.
Methods: A case series of patients who underwent SIJ fusion for SIJ dysfunction due to EDS between January 2012 and December 2018 were analyzed in retrospect. Patients underwent surgery and the SIJ was stabilized with triangular implants bridging the joint. Pain and functional outcomes were assessed in nine agree/disagree questions and a satisfaction performance scale. Clinical data has been extracted from the patient files and in addition, we reassessed the position of the implants on the CT scans.
Results: A total of 16 patients with EDS completed the questionnaire and were available for analysis. The mean satisfaction score is 78.1 out of 100 and seven patients reported a 100% satisfaction score.
Conclusion: SIJ fusion is a safe and useful procedure to reduce pain and function levels in EDS patients with lower back pain due to SIJ dysfunction.

Gepubliceerd: N Am Spine Soc J. 2021;8:100082.
Impact factor: 0; NVT

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2. **Customized treatment for an oncologic lesion near a joint: case report of a custom-made 3D-printed prosthesis for a grade II chondrosarcoma of the proximal ulna**
Brandsma ASE, Veen EJD, Glaudemans A, Jutte PC, Ploegmakers JJW.

Gepubliceerd: JSES Int. 2021;5(1):42-5.
Impact factor: 0; NVT

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3. **All-Arthroscopic Muscle Slide and Advancement Technique to Repair Massive Retracted Posterosuperior Rotator Cuff Tears**
Gupta A, Ker AM, Maharaj JC, Veen EJD, Cutbush K.

Symptomatic massive posterosuperior rotator cuff tears without glenohumeral joint arthritis and chronic medial retraction often are deemed "irreparable." These patients often are treated with alternative joint-sparing procedures including superior capsular reconstruction or tendon transfer procedures. Open and arthroscopic-assisted muscle advancement techniques allow maximal lateral tendon mobilisation during rotator cuff repair. In this report, we present an all-arthroscopic technique of complete supraspinatus and infraspinatus muscle scapular detachment and advancement in retracted massive posterosuperior rotator cuff tears. This allows for an anatomical tendon footprint reduction and tension-free repair.

Gepubliceerd: Arthrosc Tech. 2021;10(6):e1439-e46.
Impact factor: 0; NVT

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4. **Reasons for continuing physiotherapy treatment after a high-intensity physyiotherapy program in patients after total knee arthroplasty: a mixed-methods study**
Harmelink K, Nijhuis-van der Sanden R, Zeegers E, Hullegie W, Van der Wees P, Staal B.

Background: Patients after total knee arthroplasty treated with a 10-day high-intensity physiotherapy program in a resort were expected to recover fast without need for a longer physiotherapy treatment period.
Objective: To explore the expectations and experiences of patients with total knee arthroplasty following the high-intensity physiotherapy program, including the perceived recovery level at discharge, and reasons for (not) adhering to the given advice at discharge (being either continuing with or refraining from further physiotherapy treatment).
Design: A mixed-methods approach: semi-structured interviews were held and were then used to develop items and answer categories for a survey.Methods: Fifteen patients participated in semi-structured interviews, which focused on expectations and experiences related to the total knee arthroplasty and physiotherapy program, the perceived recovery level at the moment of discharge, and the reasons for the advice at discharge (continuing with or refraining from physiotherapy treatment) being followed. A deductive thematic analysis of those interviews was used to develop a survey, which was sent to the total cohort of 60 patients. Logistic regression models were estimated to determine which factors were associated with the continuation of physiotherapy treatment and (not) following the advice.
Results: Four themes were identified: (1) confidence of independent recovery; (2) experiencing residual complaints; (3) expecting further improvement of physical fitness; and (4) preferring to be supervised by a healthcare professional. These themes were covered by 14 items in the survey. In total, 55 out of 60 patients completed the survey. Out of 36 patients, 23 continued with physiotherapy treatment despite an adequate level of recovery. Five out of 19 patients, who were advised to continue with physiotherapy treatment, decided to refrain. Advice to continue with physiotherapy treatment was followed more often than advice to refrain from physiotherapy treatment (OR 0.09; 95%CI 0.01-0.85). Reasons for continuing with physiotherapy treatment were residual complaints, the expectation that their physical fitness could be improved and preferring to be supervised by a healthcare professional. In contrast, patients who refrained from physiotherapy, despite being advised to continue, were self-confident that they could do exercises by themselves.
Conclusions: A substantial proportion of patients continued with physiotherapy treatment because they expected that a higher level of recovery could be reached. The level of self-confidence to recover on their own seemed to be an important factor in deciding to continue with or refrain from physiotherapy treatment. It would be helpful to focus on self-management skills during the high-intensity physiotherapy program following total knee arthroplasty.

Gepubliceerd: Physiother Theory Pract. 2021;37(12):1321-36.

Impact factor: 2.279; Q3

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5. **Recovery trajectories over six weeks in patients selected for a high-intensity physiotherapy program after Total knee Arthroplasty: a latent class analysis**
Harmelink KEM, Dandis R, J. Van der Wees PJ, Zeegers A, der Sanden MWN, Staal JB.

Background: Recovery trajectories differ between individual patients and it is hypothesizes that they can be used to predict if an individual patient is likely to recover earlier or later. Primary aim of this study was to determine if it is possible to identify recovery trajectories for physical functioning and pain during the first six weeks in patients after TKA. Secondary aim was to explore the association of these trajectories with one-year outcomes.
Methods: Prospective cohort study of 218 patients with the following measurement time points: preoperative, and at three days, two weeks, six weeks, and one year post-surgery (no missings). Outcome measures were performance-based physical functioning (Timed Up and Go [TUG]), self-reported physical functioning (Knee injury and Osteoarthritis Outcome Score-Activities of Daily Living [KOOS-ADL]), and pain (Visual Analogue Scale [VAS]). Latent Class Analysis was used to distinguish classes based on recovery trajectories over the first six weeks postoperatively. Multivariable regression analyses were used to identify associations between classes and one year outcomes.
Results: TUG showed three classes: "gain group" (n = 203), "moderate gain group" (n = 8) and "slow gain group" (n = 7), KOOS showed two classes: "gain group" (n = 86) and "moderate gain group" (n = 132), and VAS-pain three classes: "no/very little pain" (n = 151), "normal decrease of pain" (n = 48) and "sustained pain" (n = 19). The" low gain group" scored 3.31 [95% CI 1.52, 5.09] seconds less on the TUG than the "moderate gain group" and the KOOS "gain group" scored 11.97 [95% CI 8.62, 15.33] points better than the "moderate gain group" after one year. Patients who had an early trajectory of "sustained pain" had less chance to become free of pain at one year than those who reported "no or little pain" (odds ratio 0.11 [95% CI 0.03,0.42].
Conclusion: The findings of this study indicate that different recovery trajectories can be detected. These recovery trajectories can distinguish outcome after one year.

Gepubliceerd: BMC Musculoskelet Disord. 2021;22(1):179.
Impact factor: 2.355; Q3

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6. **Study protocol for a randomised controlled trial on the effect of local analgesia for pain relief after minimal invasive sacroiliac joint fusion: the ARTEMIS study**
Hermans SMM, Nellensteijn JM, van Santbrink H, Knoef R, Reinders MK, Hoofwijk DMN, Potters JW, Movig KLL, Curfs I, van Hemert WLW.

Introduction: Chronic lower back pain is a common report in the general population. A dysfunctional sacroiliac joint (SIJ) is estimated to be responsible for one in five patients with lower back pain. Minimally invasive sacroiliac joint fusion (MISJF) is a surgical procedure to treat SIJ dysfunction. During the procedure, the SIJ is stabilised by implants inserted percutaneously under fluoroscopy guidance. Postoperatively, patients often report a lot of pain, which contributes to patients taking high doses of

painkillers (opioids for example,) and preventing early mobilisation. In several orthopaedic procedures, intraoperative infiltration of the wound bed results in decreased consumption of analgesics, earlier mobilisation and shorter hospitalisation time. The aim of this study is to investigate the effectiveness of intraoperative SIJ infiltration with analgesia in reducing postoperative pain after MISJF.
Methods and analysis: We will perform a two-centre, prospective, double-blind, randomised controlled trial to determine whether SIJ infiltration with 1.5-5 cc bupivacaine 0.50% is superior to 1.5-5 cc placebo (NaCl 0.9%) in reducing postoperative pain in patients after MISJF, and to determine whether bupivacaine significantly reduces opioid use in the direct postoperative period. Patients will be randomised with 1:1 allocation for either bupivacaine (intervention) or placebo SIJ infiltration. Postoperative pain will be measured by the Visual Analogue Scale pain score at entry and exit recovery, 2, 4, 6, 24 and 48 hours postoperatively.
Ethics and dissemination: This is the first trial that investigates the effectiveness of intraoperative SIJ infiltration with bupivacaine 0.50% in reducing postoperative pain after MISJF. If intraoperative SIJ infiltration with bupivacaine 0.50% proves to be effective, this might have important clinical implications, such as postoperative analgesics (opioids for example,) consumption, earlier mobilisation and potentially shorter hospitalisation time.
Trial registration number: NL9151.

Gepubliceerd: BMJ Open. 2021;11(12):e056204.
Impact factor: 2.692; Q2

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7. **Knee Joint Distraction as Treatment for Osteoarthritis Results in Clinical and Structural Benefit: A Systematic Review and Meta-Analysis of the Limited Number of Studies and Patients Available**
Jansen MP, Boymans T, Custers RJH, Van Geenen RCI, Van Heerwaarden RJ, Huizinga MR, Nellensteijn JM, Sollie R, Spruijt S, Mastbergen SC.

Objective: Knee joint distraction (KJD) is a joint-preserving osteoarthritis treatment that may postpone a total knee arthroplasty (TKA) in younger patients. This systematic review and meta-analysis evaluates short- and long-term clinical benefit and tissue structure changes after KJD.
Design: MEDLINE, EMBASE, and Web of Science were searched for eligible clinical studies evaluating at least one of the primary parameters: WOMAC, VAS-pain, KOOS, EQ5D, radiographic joint space width or MRI cartilage thickness after KJD. Random effects models were applied on all outcome parameters and outcomes were compared with control groups found in the included studies.
Results: Eleven articles reporting on 7 different KJD cohorts with in total 127 patients and 5 control groups with multiple follow-up moments were included, of which 2 were randomized controlled trials. Significant improvements in all primary parameters were found and benefit lasted up to at least 9 years. Overall, outcomes were comparable with control groups, including high tibial osteotomy, although TKA showed better clinical response.
Conclusions: Current, still limited, evidence shows KJD causes clear benefit in clinical and structural parameters, both short- and long-term. Longer follow-up with more patients is necessary, to validate outcome and to potentially improve patient selection

for this intensive treatment. Thus far, for younger knee osteoarthritis patients, KJD may be an option to consider.

Gepubliceerd: Cartilage. 2021;13(1_suppl):1113S-23S.
Impact factor: 4.634; Q1

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8. **Effect of the Sharrard procedure on hip instability in children with Down syndrome: a retrospective study**
Mulder F, Bok LA, van Douveren F, Pruijs HEH, Zeegers A.

Purpose: The aim of this study was to retrospectively analyze the effect of the Sharrard procedure on hip instability in children with Down syndrome (DS), as measured by the migration index.
Methods: In total, 17 children (21 hips) were included from six hospitals in the Netherlands between 2003 and 2019. The primary outcome, hip instability, was assessed with the Reimers' migration index on preoperative and postoperative plain anteroposterior pelvic radiographs. The mean age at surgery was 8.1 years, the majority of children were male (64.7%) and the mean follow-up time was 7.3 years.
Results: The mean preoperative migration index was 46% (sd 23.5) and the mean postoperative migration index was 37% (sd 28.4). The mean Delta migration index (the difference in pre-operative migration index and most recent post-operative migration index) showed an improvement of 9.3% (sd 22.7). An improvement in migration index was observed in 52%, no change in 29% and deterioration in 19% of hips. No (re)dislocations occurred in 91% of the hips. No major complications were observed during the follow-up period.
Conclusion: Early intervention is warranted in children with DS showing hip instability or hip migration, in order to succeed with less complex procedures. The Sharrard procedure should be considered in children with DS showing hip instability or hip migration, since it aims to rebalance the muscles of the hip joint, is less complex than bony procedures of the femur and acetabulum, surgery time is often shorter, there are fewer major complications and the rehabilitation period is shorter.
Level of evidence: IV - retrospective case series.

Gepubliceerd: J Child Orthop. 2021;15(5):488-95.
Impact factor: 1.548; Q4

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9. **Bilateral massive osteolysis of uncertain origin after total knee arthroplasty: A case report and review of literature**
Rassir R, Nellensteijn JM, Saouti R, Nolte PA.

Introduction and importance: Periprosthetic osteolysis (PPOL) is a common complication after total knee arthroplasty (TKA) and is most commonly caused by wear-induced particles.
Case presentation: We report an unusual case of massive bilateral PPOL in the posterior flanges of the femur and patellae 4 years after bilateral uncemented TKA without patellar resurfacing in a 71-year old female. Bilateral staged revision surgery including polyethylene exchange and allograft morselized bone impaction was

performed to treat the osteolytic lesions. There were no signs of implant malalignment, polyethylene wear or component loosening.
Clinical discussion: Several factors are associated with an increased risk on PPOL (e.g. polyethylene sterilization method, patient age, male gender). Surgical intervention in the context of massive PPOL should include replacement of a potential particle generator (most often polyethylene), correction of potential malalignment, treatment of bone defects and assessment of implant anchorage.
Conclusion: This report highlights the available evidence on clinical presentation, associated risk factors and preferred treatment strategy of massive osteolytic lesions after TKA according to available evidence.

Gepubliceerd: Int J Surg Case Rep. 2021;80:105678.
Impact factor: 0; NVT

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10. **Patient-Specific Guided Osteotomy to Correct a Symptomatic Malunion of the Left Forearm**
Schröder FF, de Graaff F, Vochteloo AJH.

We present a case report of a 12-year old female with a midshaft forearm fracture. Initial conservative treatment with a cast failed, resulting in a malunion. The malunion resulted in functional impairment for which surgery was indicated. A corrective osteotomy was planned using 3D analyses of the preoperative CT-scan. Subsequently, patient-specific guides were printed and used during the procedure to precisely correct the malunion. Three months after surgery, the radiographs showed full consolidation and the patient was pain-free with full range of motion and comparable strength in both forearms. The current case report shows that a corrective osteotomy with patient-specific guides based on preoperative 3D analyses can help surgeons to plan and precisely correct complex malunions resulting in improved functional outcomes.

Gepubliceerd: Children (Basel). 2021;8(8).
Impact factor: 2.863; Q2

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11. **Dislocation after Posterior Stabilized Primary Total Knee Replacement: A Rare Complication in Four Cases**
Spierenburg W, Mutsaerts E, van Raay J.

Introduction: Dislocation of a total knee arthroplasty is a rare complication that has rarely been described, while the total knee arthroplasty is frequently performed. From literature, we know patient-related factors, like obesity, neuropsychiatric disease, and severe valgus or varus deformity, are associated with higher risk of dislocation. We show our cases for awareness of the risk factors for surgeons.
Case Presentations. We present four patients with a dislocation after a total knee arthroplasty. We compare these case reports with previous literature and show the most important risk factors for these dislocations. In our cases, three of them suffered from obesity, which possibly has contributed to the dislocation. Three patients did have instability which emphasizes the importance of ligament balancing while performing a total knee replacement. In all cases, an exchange of the polyethylene liner was performed.

Conclusion: Implant-related factors and surgical technique as well as patient-related factors can contribute to this uncommon complication. Obesity, neuropsychiatric disorders, and a severe valgus or varus deformity are important patient-related risk factors. Our cases show these risk factors too. Some of these risk factors were encountered as well as other comorbidity factors. Such risk factors must be taken into consideration when deciding whether to perform a total knee arthroplasty. This stresses the importance of patient education and shared decision-making before performing a total knee replacement.

Gepubliceerd: Case Rep Orthop. 2021;2021:9935401.
Impact factor: 0; NVT

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12. **Arthroscopic isolated long head of biceps tenotomy in patients with degenerative rotator cuff tears: mid-term clinical results and prognostic factors**
Veen EJD, Boeddha AV, Diercks RL, Kleinlugtenbelt YV, Landman EBM, Koorevaar CT.

Introduction: The long head of biceps tendon is frequently involved in degenerative rotator cuff tears. Therefore, this study explored the clinical results of an isolated biceps tenotomy and identified prognostic factors for improvement in pain and function.
Materials and methods: Between 2008 and 2017, an arthroscopic isolated biceps tenotomy was performed on 64 patients with a degenerative rotator cuff tear (> 65 years). Primary outcome was patient-perceived improvement in pain and function. Potential prognostic factors for improvement in pain and function were identified.
Results: A perceived improvement in pain was reported in 78% of the patients at three months after surgery and in 75% at a mean follow-up of 4.2 years (1-7 years; n = 55). A perceived improvement in function was observed in 49% of patients at three months and in 76% of patients at follow-up. Patients with a preoperatively normal acromiohumeral distance (> 10 mm) reported an improvement in pain and function significantly more often. Retraction of the supraspinatus tendon Patte 3 was significantly associated with worse functional outcome.
Conclusions: A biceps tenotomy can be a reliable treatment option for patients with symptomatic degenerative cuff tears who fail conservative treatment and have a normal acromiohumeral distance (> 10 mm).

Gepubliceerd: Eur J Orthop Surg Traumatol. 2021;31(3):441-8.
Impact factor: 0; NVT

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13. **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 T, van der Hoeven JH, Diercks RL, Stevens M.

Background: Abnormal movement patterns due to compensatory mechanisms have been reported in patients with rotator cuff tears. The long head of the biceps tendon may especially be overactive and a source of pain and could induce abnormal muscle

activation in these patients. It is still unknown why some patients with a rotator cuff tear develop complaints and others do not.
Questions/purposes: (1) Which shoulder muscles show a different activation pattern on electromyography (EMG) while performing the Functional Impairment Test-Hand and Neck/Shoulder/Arm (FIT-HaNSA) in patients with a symptomatic rotator cuff tear compared with age-matched controls with an intact rotator cuff? (2) Which shoulder muscles are coactivated on EMG while performing the FIT-HaNSA?
Methods: This comparative study included two groups of people aged 50 years and older: a group of patients with chronic symptomatic rotator cuff tears (confirmed by MRI or ultrasound with the exclusion of Patte stage 3 and massive rotator cuff tears) and a control group of volunteers without shoulder conditions. Starting January 2019, 12 patients with a chronic rotator cuff tear were consecutively recruited at the outpatient orthopaedic clinic. Eleven age-matched controls (randomly recruited by posters in the hospital) were included after assuring the absence of shoulder complaints and an intact rotator cuff on ultrasound imaging. The upper limb was examined using the FIT-HaNSA (score: 0 [worst] to 300 seconds [best]), shoulder-specific instruments, health-related quality of life, and EMG recordings of 10 shoulder girdle muscles while performing a tailored FIT-HaNSA.
Results: EMG (normalized root mean square amplitudes) revealed hyperactivity of the posterior deltoid and biceps brachii muscles during the upward phase in patients with rotator cuff tears compared with controls (posterior deltoid: 111% ± 6% versus 102% ± 10%, mean difference -9 [95% confidence interval -17 to -1]; p = 0.03; biceps brachii: 118% ± 7% versus 111% ± 6%, mean difference -7 [95% CI -13 to 0]; p = 0.04), and there was decreased activity during the downward phase in patients with rotator cuff tears compared with controls (posterior deltoid: 89% ± 6% versus 98% ± 10%, mean difference 9 [95% CI 1 to 17]; p = 0.03; biceps brachii: 82% ± 7% versus 89% ± 6%, mean difference 7 [95% CI 0 to 14]; p = 0.03). The posterior deltoid functioned less in conjunction with the other deltoid muscles, and lower coactivation was seen in the remaining intact rotator cuff muscles in the rotator cuff tear group than in the control group.
Conclusion: Patients with a symptomatic rotator cuff tear show compensatory movement patterns based on abnormal activity of the biceps brachii and posterior deltoid muscles when compared with age-matched controls. The posterior deltoid functions less in conjunction with the other deltoid muscles, and lower coactivation was seen in the remaining intact rotator cuff muscles in the rotator cuff tear group than the control group.
Clinical relevance: This study supports the potential benefit of addressing the long head biceps tendon in the treatment of patients with a symptomatic rotator cuff tear. Moreover, clinicians might use these findings for conservative treatment; the posterior deltoid can be specifically trained to help compensate for the deficient rotator cuff.

Gepubliceerd: Clin Orthop Relat Res. 2021;479(2):378-88.
Impact factor: 4.291; Q1

Totale impact factor: 20.085
Gemiddelde impact factor: 1.545

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 10.817
Gemiddelde impact factor: 1.202

Plastische chirurgie

1. **Moving breast implant registries forward: Are they FAIR and Functional?**
Bargon CA, Becherer BE, Young-Afat DA, van Bommel A, Hommes J, Hoornweg MJ, Keuter X, de Fazio S, Melnikov D, Monton Echeverria J, Perks G, Lumenta DB, Couturaud B, von Fritschen U, Stark B, Hölmich LR, Crosbie A, Lispi L, Campanale A, Cooter RD, Pusic AL, Hopper I, Mureau M, Rakhorst HA.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2021;74(1):4-12.
Impact factor: 2.740; Q2

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2. **Standards for treatment of open lower limb fractures maintained in spite of the COVID-19 pandemic: Results from an international, multi-centric, retrospective cohort study**
Berner JE, Chan JK, Gardiner MD, Rakhorst H, Ortega-Briones A, Nanchahal J, Jain A, Covid Intellect Collaborative.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2021;74(7):1633-701.
Impact factor: 2.740; Q2

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3. **Are Patient Expectations and Illness Perception Associated with Patient-reported Outcomes from Surgical Decompression in de Quervain's Tenosynovitis?**
Blackburn J, van der Oest MJW, Chen NC, Feitz R, Duraku LS, Zuidam JM, Vranceanu AM, Selles RW, Hand-Wrist Study Group – includes Blomme RAM.

Background: Psychological factors such as depression, pain catastrophizing, kinesiophobia, pain anxiety, and more negative illness perceptions are associated with worse pain and function in patients at the start of treatment for de Quervain's tenosynovitis. Longitudinal studies have found symptoms of depression and pain catastrophizing at baseline were associated with worse pain after treatment. It is important to study patients opting for surgery for their condition because patients should choose surgical treatment based on their values rather than misconceptions. Psychological factors associated with worse patient-reported outcomes from surgery for de Quervain's tenosynovitis should be identified and addressed preoperatively so surgeons can correct any misunderstandings about the condition.
Question/purpose: What preoperative psychosocial factors (depression, anxiety, pain catastrophizing, illness perception, and patient expectations) are associated with pain and function 3 months after surgical treatment of de Quervain's tenosynovitis after controlling for demographic characteristics?
Methods: This was a prospective cohort study of 164 patients who underwent surgery for de Quervain's tenosynovitis between September 2017 and October 2018 performed by 20 hand surgeons at 18 centers. Our database included 326 patients who underwent surgery for de Quervain's tenosynovitis during the study period. Of these, 62% (201 of 326) completed all baseline questionnaires and 50% (164 of 326) also completed patient-reported outcomes at 3 months postoperatively. We found no difference between those included and those not analyzed in terms of age, sex, duration of symptoms, smoking status, and workload. The mean ± SD age of the patients was 52

± 14 years, 86% (141 of 164) were women, and the mean duration of symptoms was 13 ± 19 months. Patients completed the Patient-Rated Wrist Evaluation (PRWE), the VAS for pain and function, the Patient Health Questionnaire for symptoms of anxiety and depression, the Pain Catastrophizing Scale, the Credibility/Expectations Questionnaire, and the Brief Illness Perceptions questionnaire at baseline. Patients also completed the PRWE and VAS for pain and function at 3 months postoperatively. We used a hierarchical multivariable linear regression model to investigate the relative contribution of patient demographics and psychosocial factors to the pain and functional outcome at 3 months postoperatively.
Results: After adjusting for demographic characteristics, psychosocial factors, and baseline PRWE score, we found that only the patient's expectations of treatment and how long their illness would last were associated with the total PRWE score at 3 months postoperatively. More positive patient expectations of treatment were associated with better patient-reported pain and function at 3 months postoperatively (ß = -2.0; $p < 0.01$), while more negative patient perceptions of how long their condition would last were associated with worse patient-reported pain and function (timeline ß = 2.7; $p < 0.01$). The final model accounted for 31% of the variance in the patient-reported outcome at 3 months postoperatively.
Conclusion: Patient expectations and illness perceptions are associated with patient-reported pain and functional outcomes after surgical decompression for de Quervain's tenosynovitis. Addressing misconceptions about de Quervain's tenosynovitis in terms of the consequences for patients and how long their symptoms will last should allow patients to make informed decisions about the treatment that best matches their values. Prospective studies are needed to investigate whether addressing patient expectations and illness perceptions, with decision aids for example, can improve patient-reported pain and function postoperatively in those patients who still choose surgery for de Quervain's tenosynovitis. LEVEL OF EVIDENCE: Level III, therapeutic study.

Gepubliceerd: Clin Orthop Relat Res. 2021;479(5):1147-55.
Impact factor: 4.291; Q1

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4. **Testing for Implicit Gender Bias among Plastic Surgeons**
Bucknor A, Ngaage LM, Taylor KJ, Kamali P, Rakhorst HA, Mathijssen IMJ, Furnas H.

The aim of this study was to examine for the presence of implicit bias within the field of plastic surgery using a gender-specific Implicit Association Test (IAT), specifically looking at gender and career stereotypes.
Methods: A Gender-Career/Family Implicit Association Test was developed and distributed to the international plastic surgery community. Mean scores were calculated. Respondents were provided with an automated summary interpretation of their results, categorizing association for a particular grouping of gender and career/family as a little or no, slight, moderate, or strong. Respondents were also asked a series of demographic and post-IAT questions.
Results: Ninety-five responses were available for analysis. Overall, respondents showed a moderate-to-strong association of male + career / female + family compared with the reverse, which was statistically significant. Nearly half of the respondents thought they might have an implicit gender-related bias; however, 50% post-test would not change their behavior based on results, while 9.5% would.

Conclusions: Plastics surgeons may have an unconscious tendency to associate men with a career and women with a family. Further steps must be taken to increase awareness and mitigate the impact of implicit gender bias.

Gepubliceerd: Plast Reconstr Surg Glob Open. 2021;9(6):e3612.
Impact factor: 0; NVT

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5. **Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma: Report of the scientific committee on health, emerging and environmental risks (SCHEER)**
De Jong WH, Panagiotakos D, Proykova A, Samaras T, Clemens MW, De Jong D, Hopper I, Rakhorst HA, Santanelli di Pompeo F, Turner SD.

The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) was requested by the European Commission (EC) to provide a scientific opinion on the safety of breast implants in relation to anaplastic large cell lymphoma (ALCL). There are several types of textured breast implants; surface textures of breast implants are not all manufactured in the same way, and breast implants with diverse surface textures may also present different benefits. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of the breast implants associated anaplastic large cell lymphoma (BIA-ALCL). Therefore, risk assessments per implant type are needed. Overall SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and BIA-ALCL, particularly in relation to implants with an intermediate to high surface roughness.The pathogenic mechanisms are not fully elucidated; current hypotheses include genetic drivers, chronic inflammation resulting either from bacterial contamination, shell shedding of particulates, or shell surface characteristics leading to friction, or by implant associated reactive compounds. Reporting of new BIA-ALCL cases by the national clinical registries is critically important to obtain a better estimate of the risk of BIA-ALCL for patients with a breast implant.

Gepubliceerd: Regul Toxicol Pharmacol. 2021;125:104982.
Impact factor: 3.271; Q1

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6. **Test-retest Reliability and Construct Validity of the Satisfaction with Treatment Result Questionnaire in Patients with Hand and Wrist Conditions: A Prospective Study**
De Ridder WA, van Kooij YE, Vermeulen GM, Slijper HP, Selles RW, Wouters RM, Hand-Wrist Study Group – includes Blomme RAM.

Background: A patient's satisfaction with a treatment result is an important outcome domain as clinicians increasingly focus on patient-centered, value-based healthcare. However, to our knowledge, there are no validated satisfaction metrics focusing on treatment results for hand and wrist conditions.
Questions/purposes: Among patients who were treated for hand and wrist conditions, we asked: (1) What is the test-retest reliability of the Satisfaction with Treatment Result Questionnaire? (2) What is the construct validity of that outcomes tool?

Methods: This was a prospective study using two samples: a test-retest reliability sample and a construct validity sample. For the test-retest sample, data collection took place between February 2020 and May 2020, and we included 174 patients at the end of their treatment with complete baseline data that included both the primary test and the retest. Test-retest reliability was evaluated with a mean time difference of 7.2 ± 1.6 days. For the construct validity sample, data collection took place between January 2012 and May 2020. We included 3742 patients who completed the Satisfaction with Treatment Result Questionnaire, VAS, and the Net Promotor Score (NPS) at 3 months. Construct validity was evaluated using hypothesis testing in which we correlated the patients' level of satisfaction to the willingness to undergo the treatment again, VAS scores, and the NPS. We performed additional hypothesis testing on 2306 patients who also completed the Michigan Hand Outcomes Questionnaire (MHQ). Satisfaction with the treatment result was measured as the patients' level of satisfaction on a 5-point Likert scale and their willingness to undergo the treatment again under similar circumstances.
Results: We found high reliability for level of satisfaction measured on Likert scale (intraclass correlation coefficient 0.86 [95% CI 0.81 to 0.89]) and almost-perfect agreement for both level of satisfaction measured on the Likert scale (weighted kappa 0.86 [95% CI 0.80 to 0.91]) and willingness to undergo the treatment again (kappa 0.81 [95% CI 0.70 to 0.92]) of the Satisfaction with Treatment Result Questionnaire. Construct validity was good to excellent as seven of the eight hypotheses were confirmed. In the confirmed hypotheses, there was a moderate-to-strong correlation with VAS pain, VAS function, NPS, MHQ pain, and MHQ general hand function (Spearman rho ranged from 0.43 to 0.67; all $p < 0.001$) and a strong to very strong correlation with VAS satisfaction and MHQ satisfaction (Spearman rho 0.73 and 0.71; both $p < 0.001$). The rejected hypothesis indicated only a moderate correlation between the level of satisfaction on a 5-point Likert scale and the willingness to undergo the treatment again under similar circumstances (Spearman rho 0.44; $p < 0.001$).
Conclusion: The Satisfaction with Treatment Result Questionnaire has good-to-excellent construct validity and very high test-retest reliability in patients with hand and wrist conditions. CLINICAL RELEVANCE: This questionnaire can be used to reliably and validly measure satisfaction with treatment result in striving for patient-centered care and value-based healthcare. Future research should investigate predictors of variation in satisfaction with treatment results.

Gepubliceerd: Clin Orthop Relat Res. 2021;479(9):2022-32.
Impact factor: 4.291; Q1

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7. **Prognostic Factors in Open Triangular Fibrocartilage Complex (TFCC) Repair**
Feitz R, Stip D, van der Oest M, Souer S, Hovius S, Selles R, Hand-Wrist Study Group – includes Blomme RAM.

Purpose: Patients with triangular fibrocartilage complex (TFCC) injury report ulnar-sided wrist pain and impaired function. Open TFCC repair aims to improve the condition of these patients. Patients have shown reduction in pain and improvement in function at 12 months after surgery; however, results are highly variable. The purpose of this study was to relate patient (eg, age and sex), disease (eg, trauma history and arthroscopic findings), and surgery factors (type of bone anchor) associated with pain and functional outcomes at 12 months after surgery.

Methods: This study included patients who underwent an open TFCC repair between December 2011 and December 2018 in various Xpert Clinics in the Netherlands. All patients were asked to complete Patient-Rated Wrist Evaluation (PRWE) questionnaires at baseline as well as at 12 months after surgery. Patient, disease, and surgery factors were extracted from digital patient records. All factors were analyzed by performing a multivariable hierarchical linear regression.
Results: We included 274 patients who had received open TFCC repair and completed PRWE questionnaires. Every extra month of symptoms before surgery was correlated with an increase of 0.14 points on the PRWE total score at 12 months after surgery. In addition, an increase of 0.28 points in the PRWE total score at 12 months was seen per extra point of PRWE total score at baseline.
Conclusions: Increased preoperative pain, less preoperative function, and a longer duration of complaints are factors that were associated with more pain and less function at 12 months after open surgery for TFCC. This study arms surgeons with data to predict outcomes for patients undergoing open TFCC repair.
Type of study/level of evidence: Prognostic II.

Gepubliceerd: J Hand Surg Glob Online. 2021;3(4):176-81.
Impact factor: 0; NVT

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8. **Factors associated with return to work after open reinsertion of the triangular fibrocartilage**
Feitz R, Teunissen JS, van der Oest MJW, van der Heijden EPA, Selles RW, Hovius SER, Hand-Wrist Study Group – includes Blomme RAM.

The aim of this study was to assess return to work (RTW) after open Triangular Fibrocartilage Complex (TFCC) reinsertion. RTW after open surgery for TFCC injury was assessed by questionnaires at 6 weeks, 3 months, 6 months, and 12 months post-operatively. Median RTW time was assessed on inverted Kaplan-Meier curves and hazard ratios were calculated with Cox regression models. 310 patients with a mean age of 38 years were included. By 1 year, 91% of the patients had returned to work, at a median 12 weeks (25%-75%: 6-20 weeks). Light physical labor (HR 3.74) was associated with RTW within the first 15 weeks; this association altered from 23 weeks onward: light (HR 0.59) or moderate physical labor (HR 0.25) was associated with lower RTW rates. Patients with poorer preoperative Patient-Rated Wrist Evaluation (PRWE) total score returned to work later (HR 0.91 per 10 points). Overall cost of loss of productivity per patient was €13,588. In the first year after open TFCC reinsertion, 91% of the patients returned to work, including 50% within 12 weeks. Factors associated with RTW were age, gender, work intensity, and PRWE score at baseline.

Gepubliceerd: Hand Surg Rehabil. 2021;40(4):405-12.
Impact factor: 0.969; Q4

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9. **ESPRAS Survey on Breast Reconstruction in Europe**
Giunta RE, Hansson E, Andresen C, Athanasopoulos E, Benedetto GD, Celebic AB, Caulfield R, Costa H, Demirdöver C, Georgescu A, Hemelryck TV, Henley M, Kappos EA, Karabeg R, Karhunen-Enckell U, Korvald C, Mortillet S, Murray DJ, Palenčár D, Piatkowski A, Pompeo FSD, Psaras G, Rakhorst H, Rogelj K, Rosenkrantz Hölmich L,

Schaefer DJ, Spendel S, Stepic N, Vandevoort M, Vasar O, Waters R, Zic R, Moellhoff N, Elander A.

Background: The European Leadership Forum (ELF) of the European Society of Plastic, Reconstructive and Aesthetic Surgery (ESPRAS) previously identified the need for harmonisation of breast reconstruction standards in Europe, in order to strengthen the role of plastic surgeons. This study aims to survey the status, current trends and potential regional differences in the practice of breast reconstruction in Europe, with emphasis on equity and access.
Materials and methods: A largescale web-based questionnaire was sent to consultant plastic and reconstructive surgeons, who are experienced in breast reconstruction and with understanding of the national situation in their country. Suitable participants were identified via the Executive Committee (ExCo) of ESPRAS and national delegates of ESPRAS. The results were evaluated and related to evidence-based literature.
Results: A total of 33 participants from 29 European countries participated in this study. Overall, the incidence of breast reconstruction was reported to be relatively low across Europe, comparable to other large geographic regions, such as North America. Equity of provision and access to breast reconstruction was distributed evenly within Europe, with geographic regions potentially affecting the type of reconstruction offered. Standard practices with regard to radiotherapy differed between countries and a clear demand for European guidelines on breast reconstruction was reported.
Conclusion: This study identified distinct lack of consistency in international practice patterns across European countries and a strong demand for consistent European guidance. Large-scale and multi-centre European clinical trials are required to further elucidate the presented areas of interest and to define European standard operating procedures.

Gepubliceerd: Handchir Mikrochir Plast Chir. 2021;53(4):340-8.
Impact factor: 1.018; Q4

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10. **The anterior LICAP flap: a design option for oncoplastic breast reconstruction**
Jacobs JED, Al Shaer S, Schmidbauer U, de Leeuw DM, Rakhorst HA, Zöphel OT.

The purpose was to describe the operation technique of an anterior lateral intercostal artery perforator (LICAP) flap and analyse outcomes and complications. An anterior LICAP flap is a good and safe alternative for direct oncoplastic breast reconstruction. It is a reliable flap that provides sufficient volume and good esthetic outcomes.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2021;8(1):158-63.
Impact factor: 0; NVT

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11. **The Influence of Illness Perception and Mental Health on Return to Work After Carpal Tunnel Release Surgery**
Jansen MC, van der Oest MJW, de Haas NP, Selles RW, Zuidam JM, Hand-Wrist Study Group – includes Blomme RAM.

Purpose: Although multiple factors influencing return to work after a carpal tunnel release (CTR) have been identified, little is known about the influence of psychological patient factors on return to work. Therefore, this study aimed to identify the psychological factors that play a role in the return to work after a CTR surgery.
Methods: Patients who planned to undergo a CTR were asked to fill out the Brief Illness Perception Questionnaire and the Patient Health Questionnaire before surgery to measure their illness perceptions and mental health status, respectively. Return to work was defined as the time until returning to work for 50% of normal hours and was measured using a questionnaire at 6 weeks, 3 months, and 6 months. To identify associations between nonpsychological and psychological patient factors and the return to work after CTR surgery, a Cox proportional hazards model was constructed.
Results: In total, 615 patients were included in our study. Six months after surgery, 91% of the patients returned to work. For the psychological patient factors, we found that increases of 1 point on the items of worrying about carpal tunnel syndrome and having faith preoperatively in a beneficial effect of the CTR surgery were associated with hazard ratios of 0.92 (95% confidence interval, 0.88-0.96) and 1.10 (95% confidence interval, 1.02-1.19), respectively, for returning to work in the first 6 months after surgery. An increase of 1 point on the depression subscale of the Patient Health Questionnaire was associated with a hazard ratio of 0.88 (95% confidence interval, 0.78-0.99) for returning to work in the first 6 months after surgery.
Conclusions: Our study showed that multiple psychological patient factors are associated with return to work after a CTR surgery. Addressing these psychological factors before surgery might be a low-cost intervention to improve return to work after the CTR surgery.
Type of study/level of evidence: Prognostic II.

Gepubliceerd: J Hand Surg Am. 2021;46(9):748-57.
Impact factor: 2.230; Q3

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12. **Cost-utility analysis of four common surgical treatment pathways for breast cancer**
Kouwenberg CAE, Mureau MAM, Kranenburg LW, Rakhorst H, de Leeuw D, Klem T, Koppert LB, Ramos IC, Busschbach JJ.

Background: The aim was to evaluate the cost-utility of four common surgical treatment pathways for breast cancer: mastectomy, breast-conserving therapy (BCT), implant breast reconstruction (BR) and autologous-BR.
Methods: Patient-level healthcare consumption data and results of a large quality of life (QoL) study from five Dutch hospitals were combined. The cost-effectiveness was assessed in terms of incremental costs and quality adjusted life years (QALYs) over a 10-year follow-up period. Costs were assessed from a healthcare provider perspective.
Results: BCT resulted in comparable QoL with lower costs compared to implant-BR and autologous-BR and showed better QoL with higher costs than mastectomy (euro17,246/QALY). QoL outcomes and costs of especially autologous-BR were affected by the relatively high occurrence of complications. If reconstruction following mastectomy was performed, implant-BR was more cost-effective than autologous-BR.
Conclusion: The occurrence of complications had a substantial effect on costs and QoL outcomes of different surgical pathways for breast cancer. When this was taken into account, BCT was most the cost-effective treatment. Even with higher costs and a

higher risk of complications, implant-BR and autologous-BR remained cost-effective over mastectomy. This pleas for adapting surgical pathways to individual patient preferences in the trade-off between the risks of complications and expected outcomes.

Gepubliceerd: Eur J Surg Oncol. 2021;47(6):1299-308.
Impact factor: 4.424; Q1

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13. **International Confederation of Societies of Plastic Surgery Trainees: Connecting and Empowering Plastic Surgery Trainees Worldwide**
Lindqvist EK, Navia A, Cappuyns L, Chopra S, Khalaf A, Noordzij N, Perks G, Rakhorst H, Kirschbaum J.

Gepubliceerd: Plast Reconstr Surg. 2021;147(5):924e-5e.
Impact factor: 4.763; Q1

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14. **ICOPLAST trainees Europe: Uniting plastic surgery trainees around training, research and sustainability**
Noordzij NA, Lindqvist EK, Gardiner MD, Smits ES, Perks G, Baur EM, Rakhorst H.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2021;74(4):890-930.
Impact factor: 2.740; Q2

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15. **Reoperation After Operative Fixation of Proximal Interphalangeal Joint Fractures**
Oflazoglu K, Wilkens SC, Rakhorst H, Ring D, Chen NC.

Background: The purpose of this study was to determine the reoperation rate and what factors are associated with reoperation of proximal interphalangeal (PIP) joint fractures.
Methods: We identified 161 surgically treated PIP joint fractures between 2004 and 2015 at 2 academic medical systems. Demographic, injury, radiographic, and treatment data that might be associated with reoperation were collected. Bivariate analysis was performed. Factors identified during bivariate analysis with a $P < .10$ were entered into a multivariable logistic regression analysis.
Results: Of the 161 fingers, 25 underwent revision surgery. Open fracture was independently associated with revision surgery. The most common indication for reoperation was joint stiffness (35%). In a subanalysis of 111 closed fractures, no factors were associated with revision surgery.
Conclusions: Soft tissue injury is a major factor in reoperation after PIP joint fracture dislocation. Specific attention should be paid to persistent subluxation because this may predispose to early arthrosis.

Gepubliceerd: Hand (N Y). 2021;16(3):338-47.
Impact factor: 0; NVT

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16. **BREAST trial study protocol: evaluation of a non-invasive technique for breast reconstruction in a multicentre, randomised controlled trial**
Schop SSJ, Hommes JE, Krastev TK, Derks D, Larsen M, Rakhorst H, Schmidbauer U, Smit JM, Tan T, Wehrens K, de Wit T, van der Hulst R, Piatkowski de Grzymala AA.

Introduction: Pioneers have shown that it is possible to reconstruct a full breast using just autologous fat harvested by liposuction or autologous fat transfer (AFT). This study describes the first multicentre randomised study protocol to thoroughly investigate the effectiveness of AFT to reconstruct full breasts following mastectomy procedures (primarily and delayed).
Methods and analysis: This study is designed as a multicentre, randomised controlled clinical superiority trial with a 1:1 allocation ratio. A total of 196 patients (98 patients per treatment arm) are aimed to be included. Patients who wish to undergo breast reconstruction with either one of the two techniques are randomly allocated into the AFT group (intervention) or the tissue-expander/prosthesis group (control). The primary outcome measure for the quality of life is measured by the validated BREAST-Q questionnaire.
Ethics and dissemination: Approval for this study was obtained from the medical ethics committee of Maastricht University Medical Centre/Maastricht University; the trial has been registered at ClinicalTrials.gov. The results of this randomised controlled trial will be presented at scientific meetings as abstracts for poster or oral presentations and published in peer-reviewed journals.
Trial status: Enrolment into the trial has started in October 2015. Data collection and data analysis are expected to be completed in December 2021.
Trial registration number: NCT02339779.

Gepubliceerd: BMJ Open. 2021;11(9):e051413.
Impact factor: 2.692; Q2

Totale impact factor: 36.169
Gemiddelde impact factor: 2.261

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.480
Gemiddelde impact factor: 2.740

Raad van Bestuur

1. **Screening instruments for cognitive impairment in older patients in the Emergency Department: a systematic review and meta-analysis**
Calf AH, Pouw MA, van Munster BC, Burgerhof JGM, de Rooij SE, Smidt N.

Background: cognitive impairment is highly prevalent among older patients attending the Emergency Department (ED) and is associated with adverse outcomes.
Methods: we conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of cognitive screening instruments to rule out cognitive impairment in older patients in the ED. A comprehensive literature search was performed in MEDLINE, EMBASE, CINAHL and CENTRAL. A risk of bias assessment using QUADAS-2 was performed.
Results: 23 articles, examining 18 different index tests were included. Only seven index tests could be included in the meta-analysis. For ruling out cognitive impairment irrespective of aetiology, Ottawa 3 Day Year (O3DY) (pooled sensitivity 0.90; (95% CI) 0.71-0.97) had the highest sensitivity. Fourteen articles focused on screening for cognitive impairment specifically caused by delirium. For ruling out delirium, the 4 A's Test (4AT) showed highest sensitivity (pooled sensitivity 0.87, 95% confidence interval (95% CI) 0.74-0.94).
Conclusions: high clinical and methodological heterogeneity was found between included studies. Therefore, it is a challenge to recommend one diagnostic test for use as a screening instrument for cognitive impairment in the ED. The 4AT and O3DY seem most promising for ruling out cognitive impairment in older patients attending the ED.The review protocol was registered in PROSPERO (CRD42018082509).

Gepubliceerd: Age Ageing. 2021;50(1):105-12.
Impact factor: 10.668; Q1

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2. **Reproducibility and responsiveness of the Frailty Index and Frailty Phenotype in older hospitalized patients**
Feenstra M, Oud FMM, Jansen CJ, Smidt N, van Munster BC, de Rooij SE.

Background: There is growing interest for interventions aiming at preventing frailty progression or even to reverse frailty in older people, yet it is still unclear which frailty instrument is most appropriate for measuring change scores over time to determine the effectiveness of interventions. The aim of this prospective cohort study was to determine reproducibility and responsiveness properties of the Frailty Index (FI) and Frailty Phenotype (FP) in acutely hospitalized medical patients aged 70 years and older.
Methods: Reproducibility was assessed by Intra-Class Correlation Coefficients (ICC), standard error of measurement (SEM) and smallest detectable change (SDC); Responsiveness was assessed by the standardized response mean (SRM), and area under the receiver operating characteristic curve (AUC).
Results: At baseline, 243 patients were included with a median age of 76 years (range 70-98). The analytic samples included 192 and 187 patients in the three and twelve months follow-up analyses, respectively. ICC of the FI were 0.85 (95 % confidence interval [CI]: 0.76; 0.91) and 0.84 (95% CI: 0.77; 0.90), and 0.65 (95% CI: 0.49; 0.77) and 0.77 (95% CI: 0.65; 0.84) for the FP. SEM ranged from 5 to 13 %; SDC from 13 to

37 %. SRMs were good in patients with unchanged frailty status (< 0.50), and doubtful to good for deteriorated and improved patients (0.43-1.00). AUC's over three months were 0.77 (95% CI: 0.69; 0.86) and 0.71 (95% CI: 0.62; 0.79) for the FI, and 0.68 (95% CI: 0.58; 0.77) and 0.65 (95% CI: 0.55; 0.74) for the FP. Over twelve months, AUCs were 0.78 (95% CI: 0.69; 0.87) and 0.82 (95% CI: 0.73; 0.90) for the FI, and 0.78 (95% CI: 0.69; 0.87) and 0.75 (95% CI: 0.67; 0.84) for the FP.
Conclusions: The Frailty Index showed better reproducibility and responsiveness properties compared to the Frailty Phenotype among acutely hospitalized older patients.

Gepubliceerd: BMC Geriatr. 2021;21(1):499.
Impact factor: 3.921; Q1

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3. **Reliability and validity of the Patient Benefit Assessment Scale for Hospitalised Older Patients (P-BAS HOP)**
van der Kluit MJ, Dijkstra GJ, de Rooij SE.

Background: The Patient Benefit Assessment Scale for Hospitalised Older Patients (P-BAS HOP) is a tool which is capable of both identifying the priorities of the individual patient and measuring the outcomes relevant to him/her, resulting in a Patient Benefit Index (PBI) with range 0-3, indicating how much benefit the patient had experienced from the admission. The aim of this study was to evaluate the reliability, validity, responsiveness and interpretability of the P-BAS HOP.
Methods: A longitudinal study among hospitalised older patients with a baseline interview during hospitalisation and a follow-up by telephone 3 months after discharge. Test-retest reliability of the baseline and follow-up questionnaire were tested. Percentage of agreement, Cohen's kappa with quadratic weighting and maximum attainable kappa were calculated per item. The PBI was calculated for both test and retest of baseline and follow-up and compared with Intraclass Correlation Coefficient (ICC). Construct validity was tested by evaluating pre-defined hypotheses comparing the priority of goals with experienced symptoms or limitations at admission and the achievement of goals with progression or deterioration of other constructs. Responsiveness was evaluated by correlating the PBI with the anchor question 'How much did you benefit from the admission?'. This question was also used to evaluate the interpretability of the PBI with the visual anchor-based minimal important change distribution method.
Results: Reliability was tested with 53 participants at baseline and 72 at follow-up. Mean weighted kappa of the baseline items was 0.38. ICC between PBI of the test and retest was 0.77. Mean weighted kappa of the follow-up items was 0.51. ICC between PBI of the test and retest was 0.62. For the construct validity, tested in 451 participants, all baseline hypotheses were confirmed. From the follow-up hypotheses, tested in 344 participants, five of seven were confirmed. The Spearman's correlation coefficient between the PBI and the anchor question was 0.51. The optimal cut-off point was 0.7 for 'no important benefit' and 1.4 points for 'important benefit' on the PBI.
Conclusions: Although the concept seems promising, the reliability and validity of the P-BAS HOP appeared to be not yet satisfactory. We therefore recommend adapting the P-BAS HOP.

Gepubliceerd: BMC Geriatr. 2021;21(1):149.

Impact factor: 3.921; Q1

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4. **Association between dementia parental family history and mid-life modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort**
Vrijsen J, Abu-Hanna A, de Rooij SE, Smidt N.

Objective: Individuals with a parental family history (PFH) of dementia have an increased risk to develop dementia, regardless of genetic risks. The aim of this study is to investigate the association between a PFH of dementia and currently known modifiable risk factors for dementia among middle-aged individuals using propensity score matching (PSM). DESIGN: A cross-sectional study.
Setting and participants: A subsample of Lifelines (35-65 years), a prospective population-based cohort study in the Netherlands was used.
Outcome measures: Fourteen modifiable risk factors for dementia and the overall Lifestyle for Brain Health (LIBRA) score, indicating someone's potential for dementia risk reduction (DRR).
Results: The study population included 89 869 participants of which 10 940 (12.2%) had a PFH of dementia (mean (SD) age=52.95 (7.2)) and 36 389 (40.5%) without a PFH of dementia (mean (SD) age=43.19 (5.5)). Of 42 540 participants (47.3%), PFH of dementia was imputed. After PSM, potential confounding variables were balanced between individuals with and without PFH of dementia. Individuals with a PFH of dementia had more often hypertension (OR=1.19; 95% CI 1.14 to 1.24), high cholesterol (OR=1.24; 95% CI 1.18 to 1.30), diabetes (OR=1.26; 95% CI 1.11 to 1.42), cardiovascular diseases (OR=1.49; 95% CI 1.18 to 1.88), depression (OR=1.23; 95% CI 1.08 to 1.41), obesity (OR=1.14; 95% CI 1.08 to 1.20) and overweight (OR=1.10; 95% CI 1.05 to 1.17), and were more often current smokers (OR=1.20; 95% CI 1.14 to 1.27) and ex-smokers (OR=1.21; 95% CI 1.16 to 1.27). However, they were less often low/moderate alcohol consumers (OR=0.87; 95% CI 0.83 to 0.91), excessive alcohol consumers (OR=0.93; 95% CI 0.89 to 0.98), socially inactive (OR=0.84; 95% CI 0.78 to 0.90) and physically inactive (OR=0.93; 95% CI 0.91 to 0.97). Having a PFH of dementia resulted in a higher LIBRA score (RC=0.15; 95% CI 0.11 to 0.19).
Conclusion: We found that having a PFH of dementia was associated with several modifiable risk factors. This suggests that middle-aged individuals with a PFH of dementia are a group at risk and could benefit from DRR. Further research should explore their knowledge, beliefs and attitudes towards DRR, and whether they are willing to assess their risk and change their lifestyle to reduce dementia risk.

Gepubliceerd: BMJ Open. 2021;11(12):e049918.
Impact factor: 2.692; Q2

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5. **Knowledge, health beliefs and attitudes towards dementia and dementia risk reduction among descendants of people with dementia: a qualitative study using focus group discussions**
Vrijsen J, Maeckelberghe ELM, Broekstra R, de Vries JJ, Abu-Hanna A, De Deyn PP, Voshaar RCO, Reesink FE, Buskens E, de Rooij SE, Smidt N.

Background: Individuals with a parental family history of dementia have an increased risk of developing dementia because they share their genes as well as their psychosocial behaviour. Due to this increased risk and their experience with dementia, they may be particularly eager to receive information regarding dementia risk reduction (DRR). This study evaluated the knowledge, beliefs and attitudes towards dementia and DRR among descendants of people with dementia.
Method: Using a semi-structured topic guide, three focus group discussions were conducted consisting of 12 female (80%) and 3 male (20%) descendants of people with dementia with a mean (± SD) age of 48.8 (± 12) years. Focus group discussions were audio recorded and transcribed. Each transcript was analysed thoroughly, and where appropriate, a code was generated and assigned by two researchers independently. Then, similar codes were grouped together and categorized into themes.
Results: The items in the topic guide could only be addressed after participants had been given the opportunity to share their experiences of having a parent with dementia. Participants were unaware or uncertain about the possibility of reducing the risk of developing dementia and therefore hesitant to assess their dementia risk without treatment options in sight. Moreover, participants indicated that their general practitioner only gave some information on heritability, not on DRR. Although participants identified a large number of modifiable risk factors as a group during the group discussions, they were eager to receive more information on dementia and DRR. In the end, participants adopted a more positive attitude towards a DRR programme and provided suggestions for the development of future DRR programmes.
Conclusions: Although the research aim was to evaluate the knowledge, beliefs and attitudes towards dementia and DRR, sharing experiences of having a parent with dementia seemed a prerequisite for considering participants' own risk of developing dementia and participating in a DRR programme. Knowledge of dementia and DRR was limited. Due to unawareness of the possibility of reducing dementia risk, participants were hesitant about assessing their dementia risk. Group discussions positively changed the perception of dementia risk assessment and participants' willingness to participate in a DRR programme.

Gepubliceerd: BMC Public Health. 2021;21(1):1344.
Impact factor: 3.295; Q2

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6. **Knowledge, health beliefs and attitudes towards dementia and dementia risk reduction among the Dutch general population: a cross-sectional study**
Vrijsen J, Matulessij TF, Joxhorst T, de Rooij SE, Smidt N.

Background: Positive health beliefs and attitudes towards dementia and dementia risk reduction may encourage adopting a healthy behaviour. Therefore, we aimed to investigate the knowledge, health beliefs and attitudes towards dementia and dementia risk reduction among the Dutch general population and its association with the intention to change health behaviours.
Methods: A random sample of Dutch residents (30 to 80 years) was invited to complete an online survey. We collected data on knowledge, health beliefs and attitudes towards dementia (risk reduction) and the intention to change health behaviours. Multivariable logistic regression analyses were used to obtain effect estimates.
Results: Six hundred fifty-five participants completed the survey. In general, participants had insufficient knowledge about dementia and dementia risk reduction.

Participants had relatively high scores on general health motivation and perceived benefits, but low scores on perceived susceptibility, perceived severity, perceived barriers, cues to action and self-efficacy. Individuals with higher scores on perceived benefits and cues to action had more often the intention to change their behaviour with regard to physical activity (OR = 1.33, 95%-CI:1.11-1.58; OR = 1.13, 95%-CI:1.03-1.24, respectively) and alcohol consumption (OR = 1.30, 95%-CI:1.00-1.69; OR = 1.17, 95%-CI:1.02-1.35, respectively). Younger excessive alcohol consumers with higher perceived severity scores had more often the intention to change their alcohol consumption behaviour (OR = 2.70, 95%-CI:1.04-6.97) compared to older excessive alcohol consumers. Opposite results were found for middle-aged excessive alcohol consumers (OR = 0.81, 95%-CI:0.67-0.99). Individuals who perceived more barriers had more often the intention to change their diet (OR = 1.10, 95%-CI:1.01-1.21), but less often the intention to change their smoking behaviour (OR = 0.78, 95%-CI:0.63-0.98). Moreover, less educated individuals with higher perceived benefits scores had less often the intention to change their diet (OR = 0.78, 95%-CI:0.60-0.99), while highly educated individuals with higher perceived benefits scores had more often the intention to change their diet (OR = 1.41, 95%-CI:1.12-1.78).
Conclusions: The knowledge, beliefs and attitudes towards dementia and dementia risk reduction among the Dutch general population is insufficient to support dementia risk reduction. More education about dementia and dementia risk reduction is needed to improve health beliefs and attitudes towards dementia and dementia risk reduction in order to change health behaviour.

Gepubliceerd: BMC Public Health. 2021;21(1):857.
Impact factor: 3.295; Q2

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7. **The validity and reliability of a digital Ruff Figural Fluency Test (RFFT)**
Vrijsen J, van Erpecum CL, de Rooij SE, Niebuur J, Smidt N.

Background: The Ruff Figural Fluency Test (RFFT) is a valid but time-consuming and labour-intensive cognitive paper-and-pencil test. A digital RFFT was developed that can be conducted independently using an iPad and Apple Pencil and RFFT scores are computed automatically. We investigated the validity and reliability of this digital RFFT.
Methods: We randomly allocated participants to the digital or paper-and-pencil RFFT. After the first test, the other test was performed immediately (cross-over). Participants were invited for a second digital RFFT 1 week later. For the digital RFFT, an (automatic) algorithm and two independent raters (criterion standard) assessed the number of unique designs (UD) and perseverative errors (PE). These raters also assessed the paper-and-pencil RFFT. We used Intraclass correlation coefficients (ICC), sensitivity, specificity, %-agreement, Kappa, and Bland-Altman plots.
Results: We included 94 participants (mean (SD) age 39.9 (14.8), 73.4% follow-up). Mean (SD) UD and median (IQR) PE of the digital RFFT were 84.2 (26.0) and 4 (2-7.3), respectively. Agreement between manual and automatic scoring of the digital RFFT was high for UD (ICC = 0.99, 95% CI 0.98, 0.99, sensitivity = 0.98; specificity = 0.96) and PE (ICC = 0.99, 95% CI 0.98, 0.99; sensitivity = 0.90, specificity = 1.00), indicating excellent criterion validity. Small but significant differences in UD were found between the automatic and manual scoring (mean difference: - 1.12, 95% CI - 1.92, - 0.33). Digital and paper-and-pencil RFFT had moderate agreement for UD (ICC = 0.73, 95% CI 0.34, 0.87) and poor agreement for PE (ICC = 0.47, 95% CI

0.30, 0.62). Participants had fewer UD on the digital than paper-and-pencil RFFT (mean difference: - 7.09, 95% CI - 11.80, - 2.38). The number of UD on the digital RFFT was associated with higher education (Spearman's $r = 0.43$, $p < 0.001$), and younger age (Pearson's $r = - 0.36$, $p < 0.001$), showing its ability to discriminate between different age categories and levels of education. Test-retest reliability was moderate (ICC = 0.74, 95% CI 0.61, 0.83).
Conclusions: The automatic scoring of the digital RFFT has good criterion and convergent validity. There was low agreement between the digital RFFT and paper-and-pencil RFFT and moderate test-retest reliability, which can be explained by learning effects. The digital RFFT is a valid and reliable instrument to measure executive cognitive function among the general population and is a feasible alternative to the paper-and-pencil RFFT in large-scale studies. However, its scores cannot be used interchangeably with the paper-and-pencil RFFT scores.

Gepubliceerd: BMC Psychol. 2021;9(1):65.
Impact factor: 0; NVT

Totale impact factor: 27.792
Gemiddelde impact factor: 3.970

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.921
Gemiddelde impact factor: 3.921

Radiologie

1. **Healthy Life-Year Costs of Treatment Speed From Arrival to Endovascular Thrombectomy in Patients With Ischemic Stroke: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials**

Almekhlafi MA, Goyal M, Dippel DWJ, Majoie C, Campbell BCV, Muir KW, Demchuk AM, Bracard S, Guillemin F, Jovin TG, Mitchell P, White P, Hill MD, Brown S, Saver JL, Hermes Trialists Collaboration – includes Gerrits DG.

Importance: The benefits of endovascular thrombectomy (EVT) are time dependent. Prior studies may have underestimated the time-benefit association because time of onset is imprecisely known.
Objective: To assess the lifetime outcomes associated with speed of endovascular thrombectomy in patients with acute ischemic stroke due to large-vessel occlusion (LVO).
Data Sources: PubMed was searched for randomized clinical trials of stent retriever thrombectomy devices vs medical therapy in patients with anterior circulation LVO within 12 hours of last known well time, and for which a peer-reviewed, complete primary results article was published by August 1, 2020.
Study Selection: All randomized clinical trials of stent retriever thrombectomy devices vs medical therapy in patients with anterior circulation LVO within 12 hours of last known well time were included.
Data Extraction/Synthesis: Patient-level data regarding presenting clinical and imaging features and functional outcomes were pooled from the 7 retrieved randomized clinical trials of stent retriever thrombectomy devices (entirely or predominantly) vs medical therapy. All 7 identified trials published in a peer-reviewed journal (by August 1, 2020) contributed data. Detailed time metrics were collected including last known well-to-door (LKWTD) time; last known well/onset-to-puncture (LKWTP) time; last known well-to-reperfusion (LKWR) time; door-to-puncture (DTP) time; and door-to-reperfusion (DTR) time.
Main Outcomes and Measures: Change in healthy life-years measured as disability-adjusted life-years (DALYs). DALYs were calculated as the sum of years of life lost (YLL) owing to premature mortality and years of healthy life lost because of disability (YLD). Disability weights were assigned using the utility-weighted modified Rankin Scale. Age-specific life expectancies without stroke were calculated from 2017 US National Vital Statistics.
Results: Among the 781 EVT-treated patients, 406 (52.0%) were early-treated (LKWTP </=4 hours) and 375 (48.0%) were late-treated (LKWTP >4-12 hours). In early-treated patients, LKWTD was 188 minutes (interquartile range, 151.3-214.8 minutes) and DTP 105 minutes (interquartile range, 76-135 minutes). Among the 298 of 380 (78.4%) patients with substantial reperfusion, median DTR time was 145.0 minutes (interquartile range, 111.5-185.5 minutes). Care process delays were associated with worse clinical outcomes in LKW-to-intervention intervals in early-treated patients and in door-to-intervention intervals in early-treated and late-treated patients, and not associated with LKWTD intervals, eg, in early-treated patients, for each 10-minute delay, healthy life-years lost were DTP 1.8 months vs LKWTD 0.0 months; P < .001. Considering granular time increments, the amount of healthy life-time lost associated with each 1 second of delay was DTP 2.2 hours and DTR 2.4 hours.
Conclusions and Relevance: In this study, care delays were associated with loss of healthy life-years in patients with acute ischemic stroke treated with EVT, particularly

in the postarrival time period. The finding that every 1 second of delay was associated with loss of 2.2 hours of healthy life may encourage continuous quality improvement in door-to-treatment times.

Gepubliceerd: JAMA Neurol. 2021;78(6):709-17.
Impact factor: 18.302; Q1

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2. **Importance of Occlusion Site for Thrombectomy Technique in Stroke: Comparison Between Aspiration and Stent Retriever**
Bernsen MLE, Goldhoorn RB, Lingsma HF, van Oostenbrugge RJ, van Zwam WH, Uyttenboogaart M, Roos Y, Martens JM, Hofmeijer J, MR CLEAN Registry Investigators – includes Bulut T, Gerrits DG.

Background and Purpose: Thrombectomy with stent retriever and direct aspiration are equally effective in the endovascular treatment of anterior circulation acute ischemic stroke. We report efficacy and safety of initial treatment technique per occlusion segment.
Methods: For this study, we analyzed data from the MR CLEAN Registry, a prospective, observational study in all centers that perform endovascular therapy in the Netherlands. We used ordinal logistic regression analysis to compare clinical and technical results of first line direct aspiration treatment with that of stent retriever thrombectomy stratified for occlusion segment. Primary outcome measure was functional outcome at 3 months. Secondary outcome measures included reperfusion grade expressed as the extended Thrombolysis in Cerebral Infarction score, periprocedural complication risk, time to reperfusion, and mortality.
Results: Of the 2282 included patients, 1658 (73%) were initially treated with stent retriever and 624 (27%) with aspiration. Four hundred sixty-two patients had an occlusion of the intracranial part of the carotid artery, 1349 of the proximal middle cerebral artery, and 471 of the distal parts of the middle cerebral artery. There was no difference in functional outcome between aspiration and stent retriever thrombectomy (odds ratio, 1.0 [95% CI, 0.9-1.2]) in any of the occlusion segments (P value for interaction=0.2). Reperfusion rate was higher in the aspiration group (odds ratio, 1.4 [95% CI, 1.1-1.6]) and did not differ between occlusion segments (P value for interaction=0.6). Procedure times were shorter in the aspiration group (minutes 50 versus 65 minutes; P<0.0001). There was no difference in periprocedural complications or mortality.
Conclusions: In unselected patients with anterior circulation infarcts, we observed equal functional outcome of aspiration and stent retriever thrombectomy in all occlusion segments. When aspiration was the first line treatment modality, reperfusion rates were higher and procedure times shorter in all occlusion segments.

Gepubliceerd: Stroke. 2021;52(1):80-90.
Impact factor: 7.914; Q1

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3. **Assessment of Recurrent Stroke Risk in Patients With a Carotid Web**
Guglielmi V, Compagne KCJ, Sarrami AH, Sluis WM, van den Berg LA, van der Sluijs PM, Mandell DM, van der Lugt A, Roos Y, Majoie C, Dippel DWJ, Emmer BJ, van Es A, Coutinho JM, MR CLEAN trial and MR CLEAN Registry Investigators – includes Bulut T, Gerrits DG.

Importance: A carotid web (CW) is a shelf-like lesion along the posterior wall of the internal carotid artery bulb and an underrecognized cause of young stroke. Several studies suggest that patients with symptomatic CW have a high risk of recurrent stroke, but high-quality data are lacking.
Objective: To assess the 2-year risk of recurrent stroke in patients with a symptomatic CW.
Design, setting, and participants: A comparative cohort study used data from the MR CLEAN trial (from 2010-2014) and MR CLEAN Registry (from 2014-2017). Data were analyzed in September 2020. The MR CLEAN trial and MR CLEAN Registry were nationwide prospective multicenter studies on endovascular treatment (EVT) of large vessel occlusion (LVO) stroke in the Netherlands. Baseline data were from 3439 consecutive adult patients with anterior circulation LVO stroke and available computed tomography (CT)-angiography of the carotid bulb. Two neuroradiologists reevaluated CT-angiography images for presence or absence of CW and identified 30 patients with CW ipsilateral to the index stroke. For these 30 eligible CW participants, detailed follow-up data regarding stroke recurrence within 2 years were acquired. These 30 patients with CW ipsilateral to the index stroke were compared with 168 patients without CW who participated in the MR CLEAN extended follow-up trial and who were randomized to the EVT arm.
Main outcomes and measures: The primary outcome was recurrent stroke occurring within 2 years after the index stroke. Cox proportional hazards regression models were used to compare recurrent stroke rates within 2 years for patients with and without CW, adjusted for age and sex. The research question was formulated prior to data collection.
Results: Of 3439 patients with baseline CT-angiography assessed, the median age was 72 years (interquartile range, 61-80 years) and 1813 (53%) were men. Patients with CW were younger (median age, 57 [interquartile range, 46-66] years vs 66 [interquartile range, 56-77] years; P = .02 and more often women (22 of 30 [73%] vs 67 of 168 [40%]; P = .001) than patients without CW. Twenty-eight of 30 patients (93%) received medical management after the index stroke (23 with antiplatelet therapy and 5 with anticoagulant therapy). During 2 years of follow-up, 5 of 30 patients (17%) with CW had a recurrent stroke compared with 5 of 168 patients (3%) without CW (adjusted hazard ratio, 4.9; 95% CI, 1.4-18.1).
Conclusions and relevance: In this study, 1 of 6 patients with a symptomatic CW had a recurrent stroke within 2 years, suggesting that medical management alone may not provide sufficient protection for patients with CW.

Gepubliceerd: JAMA Neurol. 2021;78(7):826-33.
Impact factor: 18.302; Q1

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4. **A challenging case of undifferentiated shock**
Kats I, Schraverus PJ, Hazewinkel MJ, Cornet AD.

Gepubliceerd: Oxf Med Case Reports. 2021;2021(11):omab106.
Impact factor: 0; NVT

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5. **A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke**

LeCouffe NE, Kappelhof M, Treurniet KM, Rinkel LA, Bruggeman AE, Berkhemer OA, Wolff L, van Voorst H, Tolhuisen ML, Dippel DWJ, van der Lugt A, van Es A, Boiten J, Lycklama À Nijeholt GJ, Keizer K, Gons RAR, Yo LSF, van Oostenbrugge RJ, van Zwam WH, Roozenbeek B, van der Worp HB, Lo RTH, van den Wijngaard IR, de Ridder IR, Costalat V, Arquizan C, Lemmens R, Demeestere J, Hofmeijer J, Martens JM, Schonewille WJ, Vos JA, Uyttenboogaart M, Bokkers RPH, van Tuijl JH, Kortman H, Schreuder F, Boogaarts HD, de Laat KF, van Dijk LC, den Hertog HM, van Hasselt B, Brouwers P, Bulut T, Remmers MJM, van Norden A, Imani F, Rozeman AD, Elgersma OEH, Desfontaines P, Brisbois D, Samson Y, Clarençon F, Krietemeijer GM, Postma AA, van Doormaal PJ, van den Berg R, van der Hoorn A, Beenen LFM, Nieboer D, Lingsma HF, Emmer BJ, Coutinho JM, Majoie C, Roos Y.

Background: The value of administering intravenous alteplase before endovascular treatment (EVT) for acute ischemic stroke has not been studied extensively, particularly in non-Asian populations.
Methods: We performed an open-label, multicenter, randomized trial in Europe involving patients with stroke who presented directly to a hospital that was capable of providing EVT and who were eligible for intravenous alteplase and EVT. Patients were randomly assigned in a 1:1 ratio to receive EVT alone or intravenous alteplase followed by EVT (the standard of care). The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability] to 6 [death]) at 90 days. We assessed the superiority of EVT alone over alteplase plus EVT, as well as noninferiority by a margin of 0.8 for the lower boundary of the 95% confidence interval for the odds ratio of the two trial groups. Death from any cause and symptomatic intracerebral hemorrhage were the main safety end points.
Results: The analysis included 539 patients. The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) with EVT alone and 2 (interquartile range, 2 to 5) with alteplase plus EVT. The adjusted common odds ratio was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P = 0.28), which showed neither superiority nor noninferiority of EVT alone. Mortality was 20.5% with EVT alone and 15.8% with alteplase plus EVT (adjusted odds ratio, 1.39; 95% CI, 0.84 to 2.30). Symptomatic intracerebral hemorrhage occurred in 5.9% and 5.3% of the patients in the respective groups (adjusted odds ratio, 1.30; 95% CI, 0.60 to 2.81).
Conclusions: In a randomized trial involving European patients, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with regard to disability outcome at 90 days after stroke. The incidence of symptomatic intracerebral hemorrhage was similar in the two groups. (Funded by the Collaboration for New Treatments of Acute Stroke consortium and others; MR CLEAN-NO IV ISRCTN number, ISRCTN80619088.).

Gepubliceerd: N Engl J Med. 2021;385(20):1833-44.
Impact factor: 91.253; Q1

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6. **Association of White Matter Lesions and Outcome After Endovascular Stroke Treatment**
Luijten SPR, Bos D, Compagne KCJ, Wolff L, Majoie C, Roos Y, van Zwam WH, van Oostenbrugge RJ, Dippel DWJ, van der Lugt A, van Es A, MR CLEAN trial investigators – includes Bulut T, Gerrits DG.

Objective: To investigate the association between white matter lesions (WML) and functional outcome in patients with acute ischemic stroke (AIS) and the modification of the effect of endovascular treatment (EVT) by WML.
Methods: We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial and assessed severity of WML on baseline noncontrast CT imaging (NCCT; n = 473) according to the Van Swieten Scale. Poststroke functional outcome was assessed with the modified Rankin Scale. We investigated the association of WML with functional outcome using ordinal logistic regression models adjusted for age, sex, and other relevant cardiovascular and prognostic risk factors. In addition, an interaction term between treatment allocation and WML severity was used to assess treatment effect modification by WML.
Results: We found an independent negative association between more severe WML and functional outcome (adjusted common odds ratio [acOR] 0.77 [95% confidence interval (CI) 0.66-0.90]). Patients with absent to moderate WML had similar benefit of EVT on functional outcome (acOR 1.93 [95% CI 1.31-2.84]) as patients with severe WML (acOR 1.95 [95% CI 0.90-4.20]). No treatment effect modification of WML was found (p for interaction = 0.85).
Conclusions: WML are associated with poor functional outcome after AIS, but do not modify the effect of EVT. CLASSIFICATION OF EVIDENCE: Prognostic accuracy. This study provides Class II evidence that for patients with AIS, the presence of WML on baseline NCCT is associated with worse functional outcomes.

Gepubliceerd: Neurology. 2021;96(3):e333-e42.
Impact factor: 9.910; Q1

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7. **A complete magnetic sentinel lymph node biopsy procedure in oral cancer patients: A pilot study**
Nieuwenhuis ER, Kolenaar B, van Bemmel AJM, Hof JJ, van Baarlen J, Christenhusz A, Pouw JJ, Ten Haken B, Alic L, de Bree R.

Objectives: To assess the feasibility and merits of a complete magnetic approach for a sentinel lymph node biopsy (SLNB) procedure in oral cancer patients.
Materials and methods: This study included ten oral cancer patients (stage cT1-T2N0M0) scheduled for elective neck dissection (END). Superparamagnetic iron oxide nanoparticles (SPIO) were administered peritumorally prior to surgery. A preoperative MRI was acquired to identify lymph nodes (LNs) with iron uptake. A magnetic detector was used to identify magnetic hotspots prior, during, and after the SLNB procedure. The resected sentinel LNs (SLNs) were evaluated using step-serial sectioning, and the neck dissection specimen was assessed by routine histopathological examination. A postoperative MRI was acquired to observe any residual iron.
Results: Of ten primary tumors, eight were located in the tongue, one floor-of-mouth (FOM), and one tongue-FOM transition. SPIO injections were experienced as painful

by nine patients, two of whom developed a tongue swelling. In eight patients, magnetic SLNs were successfully detected and excised during the magnetic SLNB procedure. During the END procedure, additional magnetic SLNs were identified in three patients. Histopathology confirmed iron deposits in sinuses of excised SLNs. Three SLNs were harboring metastases, of which one was identified only during the END procedure. The END specimens revealed no further metastases.
Conclusion: A complete magnetic SLNB procedure was successfully performed in eight of ten patients (80% success rate), therefore the procedure seems feasible. Recommendations for further investigation are made including: use of anesthetics, magnetic tracer volume, planning preoperative MRI, comparison to conventional technique and follow-up.

Gepubliceerd: Oral Oncol. 2021;121:105464.
Impact factor: 5.337; Q1

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8. **Risk factors for surgery-related muscle quantity and muscle quality loss and their impact on outcome**
van Wijk L, van Duinhoven S, Liem MSL, Bouman DE, Viddeleer AR, Klaase JM.

Background: Surgery-related loss of muscle quantity negatively affects postoperative outcomes. However, changes of muscle quality have not been fully investigated. A perioperative intervention targeting identified risk factors could improve postoperative outcome. This study investigated risk factors for surgery-related loss of muscle quantity and quality and outcomes after liver resection for colorectal liver metastasis (CRLM).
Methods: Data of patients diagnosed with CRLM who underwent liver resection between 2006 and 2016 were analysed. Muscle quantity (psoas muscle index [PMI]), and muscle quality, (average muscle radiation attenuation [AMA] of the psoas), were measured using computed tomography. Changes in PMI and AMA of psoas after surgery were assessed.
Results: A total of 128 patients were analysed; 67 (52%) had surgery-related loss of muscle quantity and 83 (65%) muscle quality loss. Chronic obstructive pulmonary disease (COPD) (P = 0.045) and diabetes (P = 0.003) were risk factors for surgery-related loss of muscle quantity. A higher age (P = 0.002), open resection (P = 0.003) and longer operation time (P = 0.033) were associated with muscle quality loss. Overall survival was lower in patients with both muscle quantity and quality loss compared to other categories (P = 0.049). The rate of postoperative complications was significantly higher in the group with surgery-related loss of muscle quality.
Conclusions: Risk factors for surgery-related muscle loss were identified. Overall survival was lowest in patients with both muscle quantity and quality loss. Complication rate was higher in patients with surgery-related loss of muscle quality.

Gepubliceerd: Eur J Med Res. 2021;26(1):36.
Impact factor: 2.175; Q4

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9. **Prediction of Outcome and Endovascular Treatment Benefit: Validation and Update of the MR PREDICTS Decision Tool**
Venema E, Roozenbeek B, Mulder M, Brown S, Majoie C, Steyerberg EW, Demchuk AM, Muir KW, Dávalos A, Mitchell PJ, Bracard S, Berkhemer OA, Lycklama À Nijeholt

GJ, van Oostenbrugge RJ, Roos Y, van Zwam WH, van der Lugt A, Hill MD, White P, Campbell BCV, Guillemin F, Saver JL, Jovin TG, Goyal M, Dippel DWJ, Lingsma HF, Hermes collaborators and MR CLEAN Registry Investigators – includes Bulut T, Gerrits DG.

Background and Purpose: Benefit of early endovascular treatment (EVT) for ischemic stroke varies considerably among patients. The MR PREDICTS decision tool, derived from MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), predicts outcome and treatment benefit based on baseline characteristics. Our aim was to externally validate and update MR PREDICTS with data from international trials and daily clinical practice.
Methods: We used individual patient data from 6 randomized controlled trials within the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration to validate the original model. Then, we updated the model and performed a second validation with data from the observational MR CLEAN Registry. Primary outcome was functional independence (defined as modified Rankin Scale score 0–2) 3 months after stroke. Treatment benefit was defined as the difference between the probability of functional independence with and without EVT. Discriminative performance was evaluated using a concordance (C) statistic.
Results: We included 1242 patients from HERMES (633 assigned to EVT, 609 assigned to control) and 3156 patients from the MR CLEAN Registry (all of whom underwent EVT within 6.5 hours). The C-statistic for functional independence was 0.74 (95% CI, 0.72–0.77) in HERMES and, after model updating, 0.80 (0.78–0.82) in the Registry. Median predicted treatment benefit of routinely treated patients (Registry) was 10.3% (interquartile range, 5.8%–14.4%). Patients with low (<1%) predicted treatment benefit (n=135/3156 [4.3%]) had low rates of functional independence, irrespective of reperfusion status, suggesting potential absence of treatment benefit. The updated model was made available online for clinicians and researchers at www.mrpredicts.com.
Conclusions: Because of the substantial treatment effect and small potential harm of EVT, most patients arriving within 6 hours at an endovascular-capable center should be treated regardless of their clinical characteristics. MR PREDICTS can be used to support clinical judgement when there is uncertainty about the treatment indication, when resources are limited, or before a patient is to be transferred to an endovascular-capable center.

Gepubliceerd: Stroke. 2021;52(9):2764-72.
Impact factor: 7.914; Q1

Totale impact factor: 161.107
Gemiddelde impact factor: 17.901

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

Radiotherapie

1. **Limited Impact of Breast Cancer and Non-breast Malignancies on Survival in Older Patients with Early-Stage Breast Cancer: Results of a Large, Single-Centre, Population-Based Study**

Jobsen JJ, van der Palen J, Siemerink E, Struikmans H.

Aims: To analyse the disease-free survival and overall survival in older adults with breast cancer after breast-conserving therapy, focusing on the relevance of non-breast malignancy (NBM) with respect to survival rates.
Materials and methods: Analyses were based on 1205 women aged 65 years and older with breast cancer treated with breast-conserving therapy between 1999 and 2015. Patients were divided into three age categories: 65-70, 71-75 and >75 years. Multivariate survival analysis was carried out using Cox regression analysis.
Results: The two youngest age categories showed excellent results, with a 12-year disease-free survival of 84.6 and 86.3%, respectively. We noted a 17.2% incidence of NBM, particularly for colon cancer and lung cancer. Most (72.9%) occurred after a diagnosis of breast cancer. Of those 72.9%, about 50% died as a result of NBM within 2 years of the diagnosis of NBM. The overall 12-year NBM-specific survival was 92.0%. The 12-year overall survival was 60.0% for all and for the three abovementioned age categories was 73.3, 54.4 and 28.4%, respectively. The cause of death for all was predominantly non-malignancy-related morbidity.
Conclusion: The impact of breast cancer on life expectancy was limited, in particularly for women aged 65-75 years. The relevance of NBM on survival was limited.

Gepubliceerd: Clin Oncol (R Coll Radiol). 2022;34(6):355-62.
Impact factor: 4.126; Q3

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2. **The Dutch-Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases**

Méndez Romero A, Schillemans W, van Os R, Koppe F, Haasbeek CJ, Hendriksen EM, Muller K, Ceha HM, Braam PM, Reerink O, Intven MPM, Joye I, Jansen EPM, Westerveld H, Koedijk MS, Heijmen BJM, Buijsen J.

Purpose: Although various studies have reported that stereotactic body radiation therapy (SBRT) for liver metastases has high local control rates and relatively low toxicity, most series included a small number of patients. We aimed to validate these outcomes in a large multi-institution patient cohort treated in accordance with a common protocol.
Methods and materials: A shared web-based registry of patients with liver metastases treated with SBRT was developed by 13 centers (12 in the Netherlands and 1 in Belgium). All the centers had previously agreed on the items to be collected, the fractionation schemes, and the organs-at-risk constraints to be applied. Follow-up was performed at the discretion of the centers. Patient, tumor, and treatment characteristics were entered in the registry. Only liver metastases treated individually as independent targets and with at least 1 radiologic follow-up examination were considered for local control analysis. Toxicity of grade 3 or greater was scored according to the Common Terminology Criteria of Adverse Events (v4.03).

Results: Between January 1, 2013, and July 31, 2019, a total of 515 patients were entered in the web-based registry. The median age was 71 years. In total, 668 liver metastases were registered, and 447 were included for local control analysis. The most common primary tumor origin was colorectal cancer (80.3%), followed by lung cancer (8.9%) and breast cancer (4%). The most-used fractionation scheme was 3x18-20 Gy (36.0%), followed by 8x7.5 Gy (31.8%), 5x11-12 Gy (25.5%), and 12x5 Gy (6.7%). The median follow-up time was 1.1 years for local control and 2.3 years for survival. Actuarial 1-year local control was 87%; 1-year overall survival was 84%. Toxicity of grade 3 or greater was found in 3.9% of the patients.
Conclusions: This multi-institutional study confirms the high rates of local control and limited toxicity in a large patient cohort. Stereotactic body radiation therapy should be considered a valuable part of the multidisciplinary approach to treating liver metastases.

Gepubliceerd: Int J Radiat Oncol Biol Phys. 2021;109(5):1377-86.
Impact factor: 7.038; Q1

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3. **Impaired Geriatric 8 Score is Associated with Worse Survival after Radiotherapy in Older Patients with Cancer**
Middelburg JG, Middelburg RA, van Zwienen M, Mast ME, Bhawanie A, Jobsen JJ, Rozema T, Maas H, Geijsen ED, van der Leest AH, van den Bongard D, van Loon J, Budiharto T, Aarts MJ, Terhaard CHJ, Struikmans H.

Aims: To investigate whether the Geriatric 8 (G8) score and the Timed Get Up and Go Test (TGUGT), together with clinical and demographic patient characteristics, are associated with survival and late toxicity after (chemo)radiation therapy, administered with curative intent in older patients with cancer.
Materials and methods: Four hundred and two patients aged ≥65 years (median age 72 years, range 65-96 years), diagnosed with either breast, non-small cell lung, prostate, head and neck, rectal or oesophageal cancer, and referred for curative (chemo)radiation therapy, took part in a multicentre prospective cohort study in eight radiotherapy centres in the Netherlands. The G8 and TGUGT scores were assessed before starting treatment. Other potential predictors and late toxicity were also recorded. Survival status and date of death, if applicable, were ascertained at the Dutch national death registry.
Results: After 2.5 years, the overall survival was 83%. Survival was 87% for patients with high G8 scores and 55% for patients with low G8 scores (Log-rank P value < 0.0001). Survival was 77% for patients with good TGUGT results and 50% for patients with poor TGUGT results (Log-rank P value < 0.001). In multivariable analysis, in addition to age and type of primary tumour, the association of the G8 score with overall survival remained, with a hazard ratio of 2.1 (95% confidence interval 1.2-3.8) for low versus high scores.
Conclusions: G8 was associated with overall survival in older patients with cancer irradiated with curative intent. This association was independent of the predictive value of age and primary tumour.

Gepubliceerd: Clin Oncol (R Coll Radiol). 2021;33(4):e203-e10.
Impact factor: 4.126; Q3

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4. **Side Effects 15 Years After Lymph Node Irradiation in Breast Cancer: Randomized EORTC Trial 22922/10925**
Poortmans PM, Struikmans H, De Brouwer P, Weltens C, Fortpied C, Kirkove C, Budach V, Peignaux-Casasnovas K, van der Leij F, Vonk E, Valli M, vanTienhoven G, Weidner N, Noel G, Guckenberger M, Koiter E, van Limbergen E, Engelen A, Fourquet A, Bartelink H, Eortc Radiation Oncology Group, Breast Cancer, Groups.

Background: Uncertainty about the benefit-risk ratio of regional lymph node irradiation led to varying clinical protocols. We investigated long-term late side effects after internal mammary and medial supraclavicular (IM-MS) lymph node irradiation to improve shared decision making.
Methods: The multicenter European Organization for Research and Treatment of Cancer trial (ClinicalTrials.gov, NCT00002851) randomly assigned stage I-III breast cancer patients with involved axillary nodes and/or a medially located primary tumor. We analyzed late side effects both longitudinally at every follow-up and cross-sectionally at 5-year intervals. All statistical tests were 2-sided.
Results: Between 1996 and 2004, 46 departments from 13 countries accrued 4004 patients. Median follow-up was 15.7 years. Longitudinal follow-up data showed cumulative incidence rates at 15 years of 2.9% (95% confidence interval [CI] = 2.2% to 3.8%) vs 5.7% (95% CI = 4.7% to 6.9%) (P < .001) for lung fibrosis, 1.1% (95% CI = 0.7% to 1.7%) vs 1.9% (95% CI = 1.3% to 2.6%) (P = .07) for cardiac fibrosis, and 9.4% (95% CI = 8.0% to 10.8%) vs 11.1% (95% CI = 9.6% to 12.7%) (P = .04) for any cardiac disease when treated without or with IM-MS lymph node irradiation. There was no evidence for differences between left- and right-sided breast cancer (Wald chi2 test of treatment by breast side interaction, P = .33 and P = .35, for cardiac fibrosis and for any cardiac disease, respectively). The cumulative incidence probabilities of cross-sectionally reported side effects with a score of 2 or greater at 15 years were 0.1% (95% CI = 0.0% to 0.5%) vs 0.8% (95% CI = 0.4% to 1.4%) for pulmonary (P = .02), 1.8% (95% CI = 1.1% to 2.8%) vs 2.6% (95% CI = 1.8% to 3.7%) for cardiac (P = .15), and 0.0% (95% CI not evaluated) vs 0.1% (95% CI = 0.0% to 0.4%) for esophageal (P = .16), respectively. No difference was observed in the incidence of second malignancies, contralateral breast cancer, or cardiovascular deaths.
Conclusions: The incidence of late pulmonary side effects was statistically significantly higher after IM-MS lymph node irradiation, as were some of the cardiac events, without a difference between left- and right-sided treatments. Absolute rates and differences were very low, without increased non-breast cancer-related mortality, even before introducing heart-sparing techniques.

Gepubliceerd: J Natl Cancer Inst. 2021;113(10):1360-8.
Impact factor: 13.506; Q1

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5. **Prevalence and Prognosis of Lynch Syndrome and Sporadic Mismatch Repair Deficiency in Endometrial Cancer**
Post CCB, Stelloo E, Smit V, Ruano D, Tops CM, Vermij L, Rutten TA, Jürgenliemk-Schulz IM, Lutgens L, Jobsen JJ, Nout RA, Crosbie EJ, Powell ME, Mileshkin L, Leary A, Bessette P, Putter H, de Boer SM, Horeweg N, Nielsen M, Wezel TV, Bosse T, Creutzberg CL.

Background: Standard screening of endometrial cancer (EC) for Lynch syndrome (LS) is gaining traction; however, the prognostic impact of an underlying hereditary etiology is unknown. We established the prevalence, prognosis, and subsequent primary cancer incidence of patients with LS-associated EC in relation to sporadic mismatch repair deficient (MMRd)-EC in the large combined Post Operative Radiation Therapy in Endometrial Carcinoma-1, -2, and -3 trial cohort.
Methods: After MMR-immunohistochemistry, MLH1-promoter methylation testing, and next-generation sequencing, tumors were classified into 3 groups according to the molecular cause of their MMRd-EC. Kaplan-Meier method, log-rank test, and Cox model were used for survival analysis. Competing risk analysis was used to estimate the subsequent cancer probability. All statistical tests were 2-sided.
Results: Among the 1336 ECs, 410 (30.7%) were MMRd. A total of 380 (92.7%) were fully triaged: 275 (72.4%) were MLH1-hypermethylated MMRd-ECs; 36 (9.5%) LS MMRd-ECs, and 69 (18.2%) MMRd-ECs due to other causes. Limiting screening of EC patients to 60 years or younger or to 70 years or younger would have resulted in missing 18 (50.0%) and 6 (16.7%) LS diagnoses, respectively. Five-year recurrence-free survival was 91.7% (95% confidence interval [CI] = 83.1% to 100%; hazard ratio = 0.45, 95% CI = 0.16 to 1.24, P = .12) for LS, 95.5% (95% CI = 90.7% to 100%; hazard ratio = 0.17, 95% CI = 0.05 to 0.55, P = .003) for "other" vs 78.6% (95% CI = 73.8% to 83.7%) for MLH1-hypermethylated MMRd-EC. The probability of subsequent LS-associated cancer at 10 years was 11.6% (95% CI = 0.0% to 24.7%), 1.5% (95% CI = 0.0% to 4.3%), and 7.0% (95% CI = 3.0% to 10.9%) within the LS, "other," and MLH1-hypermethylated MMRd-EC groups, respectively.
Conclusions: The LS prevalence in the Post Operative Radiation Therapy in Endometrial Carcinoma trial population was 2.8% and among MMRd-ECs was 9.5%. Patients with LS-associated ECs showed a trend towards better recurrence-free survival and higher risk for second cancers compared with patients with MLH1-hypermethylated MMRd-EC.

Gepubliceerd: J Natl Cancer Inst. 2021;113(9):1212-20.
Impact factor: 13.506; Q1

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6. **Pathway for radiation therapists online advanced adapter training and credentialing**
Shepherd M, Graham S, Ward A, Zwart L, Cai B, Shelley C, Booth J.

Online adaptive radiotherapy (oART) is an emerging advanced treatment option for cancer patients worldwide. Current oART practices using magnetic resonance (MR) and cone beam computed tomography (CBCT) based imaging are resource intensive and require physician presence, which is a barrier to widespread implementation. Global evidence demonstrates Radiation Therapists (RTTs) can lead the oART workflow with decision support tools and on 'on-call' caveats in a 'clinician-lite' approach without significantly compromising on treatment accuracy, speed or patient outcomes. With careful consideration of jurisdictional regulations and guidance from the multi-disciplinary team, RTTs can elevate beyond traditional scopes of practice. By implementing robust and evidence-based credentialing activities, they enable service sustainability and expand the real-world gains of adaptive radiotherapy to a greater number of cancer patients worldwide. This work summarises the evidence for RTT-led oART treatments and proposes a pathway for training and credentialing.

Gepubliceerd: Tech Innov Patient Support Radiat Oncol. 2021;20:54-60.
Impact factor: 0; NVT

Totale impact factor: 42.302
Gemiddelde impact factor: 7.050

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 4.126
Gemiddelde impact factor: 4.126

Reumatologie

1. **Addressing Health Literacy Needs in Rheumatology: Which Patient Health Literacy Profiles Need the Attention of Health Professionals?**
Bakker MM, Putrik P, Rademakers J, van de Laar M, Vonkeman H, Kok MR, Voorneveld-Nieuwenhuis H, Ramiro S, de Wit M, Buchbinder R, Batterham R, Osborne RH, Boonen A.

Objective: To identify and describe health literacy profiles of patients with rheumatic diseases and explore whether the identified health literacy profiles can be generalized to a broader rheumatology context.
Methods: Patients with rheumatoid arthritis, spondyloarthritis, and gout from 3 hospitals in different regions in The Netherlands completed the Health Literacy Questionnaire (HLQ). Hierarchical cluster analysis was used to identify patients' health literacy profiles based on 9 HLQ domains. A multinomial regression model with the identified health literacy profiles as the dependent variable was fitted to assess whether patients with a given disease type or attending a given hospital were more likely to belong to a specific profile.
Results: Among 895 participating patients, the lowest mean HLQ domain scores (indicating most difficulty) were found for "critical appraisal," "navigating the health system," and "finding good health information." The 10 identified profiles revealed substantial diversity in combinations of strengths and weaknesses. While 42% of patients scored moderate to high on all 9 domains (profiles 1 and 3), another 42% of patients (profiles 2, 4, 5, and 6) clearly struggled with 1 or several aspects of health literacy. Notably, 16% (profiles 7-10) exhibited difficulty across a majority of health literacy domains. The probability of belonging to one of the profiles was independent of the hospital where the patient was treated or the type of rheumatic disease.
Conclusion: Ten distinct health literacy profiles were identified among patients with rheumatic diseases, independent of disease type and treating hospital. These profiles can be used to facilitate the development of health literacy interventions in rheumatology.

Gepubliceerd: Arthritis Care Res (Hoboken). 2021;73(1):100-9.
Impact factor: 4.794; Q2

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2. **Telemedicine for patients with rheumatic and musculoskeletal diseases during the COVID-19 pandemic; a positive experience in the Netherlands**
Bos WH, van Tubergen A, Vonkeman HE.

To describe the delivery of care for patients with rheumatic and musculoskeletal diseases (RMDs) from the perspective of rheumatologists in the Netherlands during the first months of the COVID-19 pandemic. A mixed methods design was used with quantitative and qualitative data from a cross-sectional survey sent to all members of the Dutch Rheumatology Society in May 2020. The survey contained questions on demographics, the current way of care delivery, and also on usage, acceptance, facilitators and barriers of telemedicine. Quantitative data were analyzed descriptively. The answers to the open questions were categorized into themes. Seventy-five respondents completed the survey. During the COVID-19 pandemic, continuity of care was guaranteed through telephone and video consultations by 99% and 9% of the

respondents, respectively. More than 80% of the total number of outpatient visits were performed exclusively via telephone with in-person visits only on indication. One-quarter of the respondents used patient reported outcomes to guide telephone consultations. The top three facilitators for telemedicine were less travel time for patients, ease of use of the system and shorter waiting period for patients. The top three barriers were impossibility to perform physical examination, difficulty estimating how the patient is doing and difficulty in reaching patients. During the COVID-19 epidemic, care for patients with RMDs in the Netherlands continued uninterrupted by the aid of telemedicine. On average, respondents were content with current solutions, although some felt insecure mainly because of the inability to perform physical examination and missing nonverbal communication with their patients.

Gepubliceerd: Rheumatol Int. 2021;41(3):565-73.
Impact factor: 2.631; Q4

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3. **The value of open-source clinical science in pandemic response: lessons from ISARIC**
ISARIC Clinical Characterisation Group includes Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, Piersma D, van der Palen J, van der Valk P, van Veen I, Vonkeman H.

Gepubliceerd: Lancet Infect Dis. 2021;21(12):1623-4.
Impact factor: 25.071; Q1

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4. **Patient perspectives on how to improve education on medication side effects: cross-sectional observational study at a rheumatology clinic in The Netherlands**
Hegeman MC, Schoemaker-Delsing JA, Luttikholt JTM, Vonkeman HE.

Rheumatoid arthritis (RA) patients often report lacking information on medication side effects. The aims of this study were to observe how rheumatology healthcare providers deliver medication information and to determine in which specific domains information is missing. First, 12 single-blinded structured observations were performed during regular RA patient consultations. The observers noted whether and how medication and medication side effects were discussed. Second, 100 RA patients were asked to fill out an adaptation of the Satisfaction with Information about Medicines Scale (SIMS). Medication was discussed during all observed consultations. With new medication, its purpose and mode of action were explained in all cases, but possible side effects in only 33%. Overall, medication side effects were discussed in 58% of consultations. Most information delivery was verbal (92%). Response rate to the questionnaire was 61%. Overall satisfaction with medication education was mean 7.3 (± 1.9) (NRS 0-10) with a comparable high SIMS total satisfaction sum score of mean 12.3 (± 4.4). At subscale score levels, 89% were satisfied with the amount of information on the action and usage of medication, but only 47% with the information on the potential problems of medication. RA patients express overall high satisfaction with their medication education but there is still an unmet need for information on potential risks and side effects. Using the SIMS questionnaire in daily clinical practice may help focus medication education to the needs of the individual patient.
Gepubliceerd: Rheumatol Int. 2021;41(5):973-9.

Impact factor: 2.631; Q4

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5. **Patients' perspectives on a drug safety monitoring system for immune-mediated inflammatory diseases based on patient-reported outcomes**
Kosse LJ, Weits G, Vonkeman HE, Tas SW, Hoentjen F, Van Doorn MB, Spuls PI, D'Haens GR, Nurmohamed MT, van Puijenbroek EP, Van Den Bemt BJ, Jessurun NT.

Background: Patient-reported outcomes (PROs) on adverse drug reactions (ADRs) are increasingly used in cohort event monitoring (CEM) to obtain a better understanding of patients' real-world experience with drugs. Despite the leading role for patients, little is known about their perspectives on CEM systems.
Research design and methods: In a cross-sectional open survey following the rationale of the Technology Acceptance Model, we aimed to obtain insight in patients' perspectives on the perceived usefulness, ease of use and attitude toward using a PRO-based drug safety monitoring system for ADRs attributed to biologics.
Results: Patients considered structural reporting of ADRs in web-based questionnaires as useful and not burdensome. It was preferred to link the questionnaire frequency to regular hospital consultations or the biologic administration schedule. Various respondents were interested in sharing questionnaires with their medical specialist (49.0%) or pharmacist (34.2%), and suggested to minimize the questionnaire frequency in case of an unaltered situation or absence of ADRs.
Conclusions: Patients' perspectives should be considered in the setup of PRO-based CEM studies, as this contributes to data quality and patient centeredness. Since incorporation of patients' perspectives in CEM studies is indispensable, a delicate balance should be found between user-friendliness and study aims.

Gepubliceerd: Expert Opin Drug Saf. 2021;20(12):1565-72.
Impact factor: 4.250; Q2

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6. **Common Functional Ability Score for Young People With Juvenile Idiopathic Arthritis**
Shoop-Worrall SJW, Oude Voshaar MAH, McDonagh JE, van de Laar M, Wulffraat N, Thomson W, Hyrich KL, Verstappen SMM.

Objective: As young people enter adulthood, the interchangeable use of child and adult outcome measures may inaccurately capture changes over time. This study aimed to use item response theory (IRT) to model a continuous score for functional ability that can be used no matter which questionnaire is completed.
Methods: Adolescents (ages 11-17 years) in the UK Childhood Arthritis Prospective Study (CAPS) self-completed an adolescent Childhood Health Assessment Questionnaire (CHAQ) and a Health Assessment Questionnaire (HAQ). Their parents answered the proxy-completed CHAQ. Those children with at least 2 simultaneously completed questionnaires at initial presentation or 1 year were included. Psychometric properties of item responses within each questionnaire were tested using Mokken analyses to assess the applicability of IRT modeling. A previously developed IRT model from the Pharmachild-NL registry from The Netherlands was validated in CAPS participants. Agreement and correlations between IRT-scaled functional ability scores were tested using intraclass correlations and Wilcoxon's signed rank tests.

Results: In 303 adolescents, the median age at diagnosis was 13 years, and 61% were female. CHAQ scores consistently exceeded HAQ scores. Mokken analyses demonstrated high scalability, monotonicity, and the fact that each questionnaire yielded reliable scores. There was little difference in item response characteristics between adolescents enrolled in CAPS and Pharmachild-NL (maximum item residual 0.08). Significant differences were no longer evident between IRT-scaled HAQ and CHAQ scores.
Conclusion: IRT modeling allows the direct comparison of function scores regardless of different questionnaires being completed by different people over time. IRT modeling facilitates the ongoing assessment of function as adolescents transfer from pediatric clinics to adult services.

Gepubliceerd: Arthritis Care Res (Hoboken). 2021;73(7):947-54.
Impact factor: 4.794; Q2

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7. **Co-Design of a Disease Activity Based Self-Management Approach for Patients with Rheumatoid Arthritis**
Spijk-de Jonge MJ, Manders SHM, Huis AMP, Elwyn G, van de Laar M, van Riel P, Hulscher M.

Objective: The systematic development of an intervention to improve disease activity-based management of rheumatoid arthritis (RA) in daily clinical practice that is based on patient-level barriers.
Methods: The self-management strategy was developed through a step-wise approach, in a process of co-design with all stakeholders and by addressing patient level barriers to RA management based on disease activity.
Results: The resulting DAS-pass strategy consists of decision supportive information and guidance by a specialised rheumatology nurse. It aims to increase patients' knowledge on DAS28, to empower patients to be involved in disease management, and to improve patients' medication beliefs. The decision supportive information includes an informational leaflet and a patient held record. The nurse individualises the information, stimulates patients to communicate about disease activity, and offers the opportunity for questions or additional support.
Conclusion: The DAS-pass strategy was found helpful by stakeholders. It can be used to improve RA daily clinical practice. Our systematic approach can be used to improve patient knowledge and self-management on other RA related topics. Also, it can be used to improve the management of other chronic conditions. We therefore provide a detailed description of our methodology to assist those interested in developing an evidence-based strategy for educating and empowering patients.

Gepubliceerd: Mediterr J Rheumatol. 2021;32(1):21-30.
Impact factor: 0; NVT

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8. **Common patient-reported outcomes across ICHOM Standard Sets: the potential contribution of PROMIS®**
Terwee CB, Zuidgeest M, Vonkeman HE, Cella D, Haverman L, Roorda LD.

Background: The International Consortium for Health Outcomes Measurement (ICHOM) develops condition-specific Standard Sets of outcomes to be measured in clinical practice for value-based healthcare evaluation. Standard Sets are developed by different working groups, which is inefficient and may lead to inconsistencies in selected PROs and PROMs. We aimed to identify common PROs across ICHOM Standard Sets and examined to what extend these PROs can be measured with a generic set of PROMs: the Patient-Reported Outcomes Measurement Information System (PROMIS®).
Methods: We extracted all PROs and recommended PROMs from 39 ICHOM Standard Sets. Similar PROs were categorized into unique PRO concepts. We examined which of these PRO concepts can be measured with PROMIS.
Results: A total of 307 PROs were identified in 39 ICHOM Standard Sets and 114 unique PROMs are recommended for measuring these PROs. The 307 PROs could be categorized into 22 unique PRO concepts. More than half (17/22) of these PRO concepts (covering about 75% of the PROs and 75% of the PROMs) can be measured with a PROMIS measure.
Conclusion: Considerable overlap was found in PROs across ICHOM Standard Sets, and large differences in terminology used and PROMs recommended, even for the same PROs. We recommend a more universal and standardized approach to the selection of PROs and PROMs. Such an approach, focusing on a set of core PROs for all patients, measured with a system like PROMIS, may provide more opportunities for patient-centered care and facilitate the uptake of Standard Sets in clinical practice.

Gepubliceerd: BMC Med Inform Decis Mak. 2021;21(1):259.
Impact factor: 2.796; Q3

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9. **Gastrointestinal Adverse Drug Reaction Profile of Etanercept: Real-world Data From Patients and Healthcare Professionals**
van Lint JA, Jessurun NT, Tas SW, van den Bemt BJF, Nurmohamed MT, van Doorn MBA, Spuls PI, van Tubergen AM, Ten Klooster PM, van Puijenbroek EP, Hoentjen F, Vonkeman HE.

Objective: We aimed to describe the nature and frequency of gastrointestinal adverse drug reactions (GI-ADRs) of etanercept (ETN) using patient-reported and healthcare professional (HCP)-registered data and compared this frequency with the GI-ADR frequency of the widely used tumor necrosis factor-α inhibitor adalimumab (ADA).
Methods: Reported GI-ADRs of ETN for rheumatic diseases were collected from the Dutch Biologic Monitor and DREAM registries. We described the clinical course of GI-ADRs and compared the frequency with ADA in both data sources using Fisher exact test.
Results: Out of 416 patients using ETN for inflammatory rheumatic diseases in the Dutch Biologic Monitor, 25 (6%) patients reported 36 GI-ADRs. In the DREAM registries 11 GI-ADRs were registered for 9 patients (2.3%), out of 399 patients using ETN, with an incidence of 7.1 per 1000 patient-years. Most GI-ADRs consisted of diarrhea, nausea, and abdominal pain. GI-ADRs led to ETN discontinuation in 1 patient (4%) and dose adjustment in 4 (16%) in the Dutch Biologic Monitor. Eight GI-ADRs (73%) led to ETN discontinuation in the DREAM registries. The frequency of GI-ADRs of ETN did not significantly differ from GI-ADRs of ADA in both data sources (Dutch Biologic

Monitor: ETN 8.7% vs ADA 5.3%, P = 0.07; DREAM: ETN 2.8% vs ADA 4.7%, P = 0.16).
Conclusion: Most GI-ADRs associated with ETN concerned gastrointestinal symptoms. These ADRs may lead to dose adjustment or ETN discontinuation. The frequency of ETN-associated GI-ADRs was comparable to the frequency of ADA-associated GI-ADRs. Knowledge about these previously unknown ADRs can facilitate early recognition and improve patient communication.

Gepubliceerd: J Rheumatol. 2021;48(9):1388-94.
Impact factor: 4.666; Q2

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10. **Ranking facilitators and barriers of medication adherence by patients with inflammatory arthritis: a maximum difference scaling exercise**
Voshaar MJH, Vriezekolk JE, van Dulmen AM, van den Bemt BJF, van de Laar M.

Introduction: Facilitators and barriers of adherence to disease-modifying anti-rheumatic drugs (DMARDs) have been identified by patients with inflammatory arthritis earlier. However, the relative importance from the patients' perspective of these factors is unknown. Knowledge on this ranking might guide the development of interventions and may facilitate targeted communication on adherence. This study aims to examine 1) the relative importance patients attach to facilitators and barriers for DMARDs adherence, and 2) the relationship between patient characteristics and ranking of these factors.
Methods: One hundred twenty-eight outpatients with inflammatory arthritis; (60% female, mean age 62 years (SD = 12), median disease duration 15 years, IQR (7, 23) participated in a Maximum Difference scaling exercise and ranked 35 items based upon previously identified facilitators and barriers to medication adherence. Hierarchical Bayes estimation was used to compute mean Rescaled Probability Scores (RPS; 0-100) (i.e. relative importance score). Kendall's coefficient of concordance was used to examine a possible association between patients' characteristics (i.e. age, sex and educational level) and ranking of the items.
Results: The three most important items ranked by patients were: Reduction of symptoms formulated as "Arthritis medications help to reduce my symptoms" (RPS = 7.30, CI 7.17-7.44), maintaining independence formulated as "I can maintain my independence as much as possible" (RPS = 6.76, CI 6.54-6.97) and Shared decision making formulated as "I can decide -together with my physician- about my arthritis medications" (RPS = 6.48, CI 6.24-6.72). No associations between patient characteristics and ranking of factors were found.
Conclusions: Reducing symptoms, maintaining independency and shared decision making are patients' most important factors for DMARDs adherence. This knowledge might guide the development of interventions and may facilitate communication between health professionals and their patients on medication adherence.

Gepubliceerd: BMC Musculoskelet Disord. 2021;22(1):21.
Impact factor: 2.355; Q3

Totale impact factor: 53.988
Gemiddelde impact factor: 5.399

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 12.283
Gemiddelde impact factor: 3.071

Thoraxcentrum

1. **Update and, internal and temporal-validation of the FRANCE-2 and ACC-TAVI early-mortality prediction models for Transcatheter Aortic Valve Implantation (TAVI) using data from the Netherlands heart registration (NHR)**
Al-Farra H, de Mol B, Ravelli ACJ, Ter Burg W, Houterman S, Henriques JPS, Abu-Hanna A, Vis MM, Vos J, Timmers L, Tonino WAL, Schotborgh CE, Roolvink V, Porta F, Stoel MG, Kats S, Amoroso G, van der Werf HW, Stella PR, de Jaegere P.

Background: The predictive performance of the models FRANCE-2 and ACC-TAVI for early-mortality after Transcatheter Aortic Valve Implantation (TAVI) can decline over time and can be enhanced by updating them on new populations. We aim to update and internally and temporally validate these models using a recent TAVI-cohort from the Netherlands Heart Registration (NHR).
Methods: We used data of TAVI-patients treated in 2013-2017. For each original-model, the best update-method (model-intercept, model-recalibration, or model-revision) was selected by a closed-testing procedure. We internally validated both updated models with 1000 bootstrap samples. We also updated the models on the 2013-2016 dataset and temporally validated them on the 2017-dataset. Performance measures were the Area-Under ROC-curve (AU-ROC), Brier-score, and calibration graphs.
Results: We included 6177 TAVI-patients, with 4.5% observed early-mortality. The selected update-method for FRANCE-2 was model-intercept-update. Internal validation showed an AU-ROC of 0.63 (95%CI 0.62-0.66) and Brier-score of 0.04 (0.04-0.05). Calibration graphs show that it overestimates early-mortality. In temporal-validation, the AU-ROC was 0.61 (0.53-0.67).The selected update-method for ACC-TAVI was model-revision. In internal-validation, the AU-ROC was 0.63 (0.63-0.66) and Brier-score was 0.04 (0.04-0.05). The updated ACC-TAVI calibrates well up to a probability of 20%, and subsequently underestimates early-mortality. In temporal-validation the AU-ROC was 0.65 (0.58-0.72).
Conclusion: Internal-validation of the updated models FRANCE-2 and ACC-TAVI with data from the NHR demonstrated improved performance, which was better than in external-validation studies and comparable to the original studies. In temporal-validation, ACC-TAVI outperformed FRANCE-2 because it suffered less from changes over time.

Gepubliceerd: Int J Cardiol Heart Vasc. 2021;32:100716.
Impact factor: 0; NVT

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2. **Quantitative Flow Ratio to Predict Nontarget Vessel-Related Events at 5 Years in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Angiography-Guided Revascularization**
Bär S, Kavaliauskaite R, Ueki Y, Otsuka T, Kelbæk H, Engstrøm T, Baumbach A, Roffi M, von Birgelen C, Ostojic M, Pedrazzini G, Kornowski R, Tüller D, Vukcevic V, Magro M, Losdat S, Windecker S, Räber L.

Background: In ST-segment-elevation myocardial infarction, angiography-based complete revascularization is superior to culprit-lesion-only percutaneous coronary intervention. Quantitative flow ratio (QFR) is a novel, noninvasive, vasodilator-free

method used to assess the hemodynamic significance of coronary stenoses. We aimed to investigate the incremental value of QFR over angiography in nonculprit lesions in patients with ST-segment-elevation myocardial infarction undergoing angiography-guided complete revascularization.
Methods and Results: This was a retrospective post hoc QFR analysis of untreated nontarget vessels (any degree of diameter stenosis [DS]) from the randomized multicenter COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial by assessors blinded for clinical outcomes. The primary end point was cardiac death, spontaneous nontarget vessel myocardial infarction, and clinically indicated nontarget vessel revascularization (ie, ≥70% DS by 2-dimensional quantitative coronary angiography or ≥50% DS and ischemia) at 5 years. Of 1161 patients with ST-segment-elevation myocardial infarction, 946 vessels in 617 patients were analyzable by QFR. At 5 years, the rate of the primary end point was significantly higher in patients with QFR ≤0.80 (n=35 patients, n=36 vessels) versus QFR >0.80 (n=582 patients, n=910 vessels) (62.9% versus 12.5%, respectively; hazard ratio [HR], 7.33 [95% CI, 4.54-11.83], P<0.001), driven by higher rates of nontarget vessel myocardial infarction (12.8% versus 3.1%, respectively; HR, 4.38 [95% CI, 1.47-13.02], P=0.008) and nontarget vessel revascularization (58.6% versus 7.7%, respectively; HR, 10.99 [95% CI, 6.39-18.91], P<0.001) with no significant differences for cardiac death. Multivariable analysis identified QFR ≤0.80 but not ≥50% DS by 3-dimensional quantitative coronary angiography as an independent predictor of the primary end point. Results were consistent, including only >30% DS by 3-dimensional quantitative coronary angiography.
Conclusions: Our study suggests incremental value of QFR over angiography-guided percutaneous coronary intervention for nonculprit lesions among patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Gepubliceerd: J Am Heart Assoc. 2021;10(9):e019052.
Impact factor: 5.501; Q1

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3. **Interleukin 6 and Cardiovascular Outcomes in Patients With Chronic Kidney Disease and Chronic Coronary Syndrome**
Batra G, Ghukasyan Lakic T, Lindbäck J, Held C, White HD, Stewart RAH, Koenig W, Cannon CP, Budaj A, Hagström E, Siegbahn A, Wallentin L, STABILITY Investigators – includes von Birgelen C.

Importance: Inflammation promotes cardiovascular disease and anti-inflammatory treatment reduces cardiovascular events in patients with chronic coronary syndrome. Chronic kidney disease (CKD) is a risk factor for cardiovascular disease. It is unclear how inflammation mediated by interleukin 6 (IL-6) in patients with CKD is linked to cardiovascular disease.
Objective: To investigate associations between IL-6 and cardiovascular outcomes in patients with chronic coronary syndrome in association with kidney function.
Design, setting, and participants: This multicenter cohort study included patients enrolled at 663 centers in 39 countries with chronic coronary syndrome who were included in the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial. Patients were enrolled between December 2008 and April

2010 and were followed up for a median length of 3.7 years. Analysis in this substudy began September 2020. EXPOSURES: Exposures were IL-6 and creatinine estimated glomerular filtration rates (eGFR), which were collected at baseline. Associations between continuous and categorical levels (<2.0 ng/L vs ≥2.0 ng/L) of IL-6 and cardiovascular outcomes were tested in association with eGFR cutoffs (normal eGFR level [≥90 mL/min/1.73 m2], mildly decreased eGFR level [60-90 mL/min/1.73 m2], and moderately to severely decreased eGFR level [<60 mL/min/1.73 m2]).
Main outcomes and measures: Main outcome was major adverse cardiovascular events (MACE), a composite of cardiovascular death, myocardial infarction, and stroke.
Results: This substudy of the STABILITY trial included 14 611 patients with available IL-6 levels at baseline. The median (interquartile range) age was 65 (59-71) years, and 2700 (18.5%) were female. During follow-up, MACE occurred in 1459 individuals (10.0%). Higher levels of IL-6 were in continuous models independently associated with risk of MACE (P < .001) in all CKD strata. Using predefined strata, elevated IL-6 level (≥2.0 vs <2.0 ng/L) was associated with increased risk of MACE at normal kidney function (2.9% vs 1.9% events/y [hazard ratio, 1.35; 95% CI, 1.02-1.78]), mild CKD (3.3% vs 1.9% [hazard ratio, 1.57; 95% CI, 1.35-1.83]), and moderate to severe CKD (5.0% vs 2.9% [hazard ratio, 1.60; 95% CI, 1.28-1.99]).
Conclusions and relevance: In patients with chronic coronary syndrome, elevated levels of IL-6 were associated with risk of MACE in all CKD strata. Thus, IL-6 and CKD stage may help when identifying patients with chronic coronary syndrome for anti-inflammatory treatment.

Gepubliceerd: JAMA Cardiol. 2021;6(12):1440-5.
Impact factor: 14.676; Q1

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4. **Coronary bifurcations treated with thin-strut drug-eluting stents: a prespecified analysis of the randomized BIO-RESORT trial**
Buiten RA, Warta S, Ploumen EH, Doggen CJM, van der Heijden LC, Hartmann M, Danse PW, Schotborgh CE, Scholte M, Linssen GCM, Zocca P, von Birgelen C.

Background: Treatment of a coronary bifurcation lesion is often required in routine clinical practice, but data on the performance of very thin-strut biodegradable polymer drug-eluting stents are scarce.
Methods: Comparison of biodegradable polymer and durable polymer drug-eluting stents in an all comers population (BIO-RESORT) is a prospective, multicenter randomized clinical trial that included 3514 all-comer patients, who were randomized to very thin-strut biodegradable polymer-coated sirolimus- or everolimus-eluting stents, versus thin-strut durable polymer-coated zotarolimus-eluting stents. The approach of bifurcation stenting was left at the operator's discretion, and provisional stenting was generally preferred. This prespecified analysis assessed 3-year clinical outcome of all patients in whom treatment involved at least one bifurcation with a side-branch diameter ≥1.5 mm.
Results: Of all BIO-RESORT trial participants, 1236 patients were treated in bifurcation lesions and analyzed. Single- and two-stent techniques were used in 85.8% and 14.2%, respectively. 'True' bifurcation lesions (main vessel and side-branch obstructed) were treated in 31.1%. Three-year follow-up was available in 1200/1236 (97.1%) patients. The main endpoint target vessel failure (composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization) occurred in sirolimus-

eluting stents in 42/412 (10.3%) and in zotarolimus-eluting stents in 49/409 (12.1%) patients (P-logrank = 0.40). In everolimus-eluting stents, target vessel failure occurred in 40/415 (9.8%) patients (vs. zotarolimus-eluting stents: P-logrank = 0.26). There was no between-stent difference in individual components of target vessel failure. Findings were consistent in patients with single-vessel treatment and patients treated with a single-stent technique.
Conclusions: Three years after stenting all-comers with bifurcation lesions, clinical outcome was similar with the sirolimus-eluting and everolimus-eluting stents versus the zotarolimus-eluting stent.

Gepubliceerd: Coron Artery Dis. 2021;32(1):51-7.
Impact factor: 1.439; Q4

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5. **Prognostically relevant periprocedural myocardial injury and infarction associated with percutaneous coronary interventions: a Consensus Document of the ESC Working Group on Cellular Biology of the Heart and European Association of Percutaneous Cardiovascular Interventions (EAPCI)**
Bulluck H, Paradies V, Barbato E, Baumbach A, Bøtker HE, Capodanno D, De Caterina R, Cavallini C, Davidson SM, Feldman DN, Ferdinandy P, Gili S, Gyöngyösi M, Kunadian V, Ooi SY, Madonna R, Marber M, Mehran R, Ndrepepa G, Perrino C, Schüpke S, Silvain J, Sluijter JPG, Tarantini G, Toth GG, Van Laake LW, von Birgelen C, Zeitouni M, Jaffe AS, Thygesen K, Hausenloy DJ.

A substantial number of chronic coronary syndrome (CCS) patients undergoing percutaneous coronary intervention (PCI) experience periprocedural myocardial injury or infarction. Accurate diagnosis of these PCI-related complications is required to guide further management given that their occurrence may be associated with increased risk of major adverse cardiac events (MACE). Due to lack of scientific data, the cut-off thresholds of post-PCI cardiac troponin (cTn) elevation used for defining periprocedural myocardial injury and infarction, have been selected based on expert consensus opinions, and their prognostic relevance remains unclear. In this Consensus Document from the ESC Working Group on Cellular Biology of the Heart and European Association of Percutaneous Cardiovascular Interventions (EAPCI), we recommend, whenever possible, the measurement of baseline (pre-PCI) cTn and post-PCI cTn values in all CCS patients undergoing PCI. We confirm the prognostic relevance of the post-PCI cTn elevation >5× 99th percentile URL threshold used to define type 4a myocardial infarction (MI). In the absence of periprocedural angiographic flow-limiting complications or electrocardiogram (ECG) and imaging evidence of new myocardial ischaemia, we propose the same post-PCI cTn cut-off threshold (>5× 99th percentile URL) be used to define prognostically relevant 'major' periprocedural myocardial injury. As both type 4a MI and major periprocedural myocardial injury are strong independent predictors of all-cause mortality at 1 year post-PCI, they may be used as quality metrics and surrogate endpoints for clinical trials. Further research is needed to evaluate treatment strategies for reducing the risk of major periprocedural myocardial injury, type 4a MI, and MACE in CCS patients undergoing PCI.

Gepubliceerd: Eur Heart J. 2021;42(27):2630-42.
Impact factor: 29.983; Q1

6. **Pregnancy outcome in thoracic aortic disease data from the Registry Of Pregnancy And Cardiac disease**
Campens L, Baris L, Scott NS, Broberg CS, Bondue A, Jondeau G, Grewal J, Johnson MR, Hall R, De Backer J, Roos-Hesselink JW, ROPAC investigators group – includes Wagenaar LJ.

Background: Cardiovascular disease is the leading cause of death during pregnancy with thoracic aortic dissection being one of the main causes. Thoracic aortic disease is commonly related to hereditary disorders and congenital heart malformations such as bicuspid aortic valve (BAV). Pregnancy is considered a high risk period in women with underlying aortopathy.
Methods: The ESC EORP Registry Of Pregnancy And Cardiac disease (ROPAC) is a prospective global registry that enrolled 5739 women with pre-existing cardiac disease. With this analysis, we aim to study the maternal and fetal outcome of pregnancy in women with thoracic aortic disease.
Results: Thoracic aortic disease was reported in 189 women (3.3%). Half of them were patients with Marfan syndrome (MFS), 26% had a BAV, 8% Turner syndrome, 2% vascular Ehlers-Danlos syndrome and 11% had no underlying genetic defect or associated congenital heart defect. Aortic dilatation was reported in 58% of patients and 6% had a history of aortic dissection. Four patients, of whom three were patients with MFS, had an acute aortic dissection (three type A and one type B aortic dissection) without maternal or fetal mortality. No complications occurred in women with a history of aortic dissection. There was no significant difference in median fetal birth weight if treated with a beta-blocker or not (2960 g (2358-3390 g) vs 3270 g (2750-3570 g), p value 0.25).
Conclusion: This ancillary analysis provides the largest prospective data review on pregnancy risk for patients with thoracic aortic disease. Overall pregnancy outcomes in women with thoracic aortic disease followed according to current guidelines are good.

Gepubliceerd: Heart. 2021;107(21):1704-9.
Impact factor: 5.994; Q1

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7. **Case-control study on the interplay between immunoparalysis and delirium after cardiac surgery**
Cheheili Sobbi S, Peters van Ton AM, Wesselink EM, Looije MF, Gerretsen J, Morshuis WJ, Slooter AJC, Abdo WF, Pickkers P, van den Boogaard M.

Background: Delirium occurs frequently following cardiothoracic surgery, and infectious disease is an important risk factor for delirium. Surgery and cardiopulmonary bypass induce suppression of the immune response known as immunoparalysis. We aimed to investigate whether delirious patients had more pronounced immunoparalysis following cardiothoracic surgery than patients without delirium, to explain this delirium-infection association.
Methods: A prospective matched case-control study was performed in two university hospitals. Cytokine production (tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8 and IL-10) of ex vivo lipopolysaccharide (LPS)-stimulated whole blood was analyzed in on-pump cardiothoracic surgery patients preoperatively, and at 5 timepoints up to 3 days after cardiothoracic surgery. Delirium was assessed by trained staff using two validated delirium scales and chart review.

Results: A total of 89 patients were screened of whom 14 delirious and 52 non-delirious patients were included. Ex vivo-stimulated production of TNF-α, IL-6, IL-8, and IL-10 was severely suppressed following cardiothoracic surgery compared to pre-surgery. Postoperative release of cytokines in non-delirious patients was attenuated by 84% [IQR: 13-93] for TNF-α, 95% [IQR: 78-98] for IL-6, and 69% [IQR: 55-81] for IL-10. The attenuation in ex vivo-stimulated production of these cytokines was not significantly different in patients with delirium compared to non-delirious patients ($p > 0.10$ for all cytokines).
Conclusions: The post-operative attenuation of ex vivo-stimulated production of pro- and anti-inflammatory cytokines was comparable between patients that developed delirium and those who remained delirium-free after on-pump cardiothoracic surgery. This finding suggests that immunoparalysis is not more common in cardiothoracic surgery patients with delirium compared to those without.

Gepubliceerd: J Cardiothorac Surg. 2021;16(1):239.
Impact factor: 1.637; Q4

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8. **Clopidogrel in noncarriers of CYP2C19 loss-of-function alleles versus ticagrelor in elderly patients with acute coronary syndrome: A pre-specified sub analysis from the POPular Genetics and POPular Age trials CYP2C19 alleles in elderly patients**
Claassens DMF, Gimbel ME, Bergmeijer TO, Vos GJA, Hermanides RS, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, de Vrey EA, Heestermans T, Jukema JW, von Birgelen C, Waalewijn RA, Hofma SH, den Hartog FR, Voskuil M, Van't Hof AWJ, Asselbergs FW, Mosterd A, Herrman JR, Dewilde W, Mahmoodi BK, Deneer VHM, Ten Berg JM.

Background: Patients with acute coronary syndrome (ACS) who are carrying CYP2C19 loss-of-function alleles derive less benefit from clopidogrel treatment. Despite this, in elderly patients, clopidogrel might be preferred over more potent P2Y(12) inhibitors due to a lower bleeding risk. Whether CYP2C19 genotype-guided antiplatelet treatment in the elderly could be of benefit has not been studied specifically.
Methods: Patients aged 70 years and older with known CYP2C19*2 and *3 genotype were identified from the POPular Genetics and POPular Age trials. Noncarriers of loss-of-function alleles treated with clopidogrel were compared to patients, irrespective of CYP2C19 genotype, treated with ticagrelor and to clopidogrel treated carriers of loss-of-function alleles. We assessed net clinical benefit (all-cause death, myocardial infarction, stroke and Platelet Inhibition and Patient Outcomes (PLATO) major bleeding), atherothrombotic outcomes (cardiovascular death, myocardial infarction, stroke) and bleeding outcomes (PLATO major and minor bleeding).
Results: A total of 991 patients were assessed. There was no significant difference in net clinical benefit (17.2% vs. 15.1%, adjusted hazard ratio (adjHR) 1.05, 95% confidence interval (CI) 0.77-1.44), atherothrombotic outcomes (9.7% vs. 9.2%, adjHR 1.00, 95%CI 0.66-1.50), and bleeding outcomes (17.7% vs. 19.8%, adjHR 0.80, 95%CI 0.62-1.12) between clopidogrel in noncarriers of loss-of-function alleles and ticagrelor respectively.
Conclusion: In ACS patients aged 70 years and older, there was no significant difference in net clinical benefit and atherothrombotic outcomes between noncarriers of a loss-of-function allele treated with clopidogrel and patients treated with ticagrelor.

The bleeding rate was numerically; though not statistically significant, lower in patients using clopidogrel.

Gepubliceerd: Int J Cardiol. 2021;334:10-7.
Impact factor: 4.164; Q2

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9. **Rationale and Design of the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure Study**
Dauw J, Lelonek M, Zegri-Reiriz I, Paredes-Paucar CP, Zara C, George V, Cobo-Marcos M, Knappe D, Shchekochikhin D, Lekhakul A, Klincheva M, Frea S, Miró Ò, Barker D, Borbély A, Nasr S, Doghmi N, de la Espriella R, Singh JS, Bovolo V, Fialho I, Ross NT, van den Heuvel M, Benkouar R, Findeisen H, Alhaddad IA, Al Balbissi K, Barge-Caballero G, Ghazi AM, Bruckers L, Martens P, Mullens W.

Aims: Although acute heart failure (AHF) with volume overload is treated with loop diuretics, their dosing and type of administration are mainly based upon expert opinion. A recent position paper from the Heart Failure Association (HFA) proposed a step-wise pharmacologic diuretic strategy to increase the diuretic response and to achieve rapid decongestion. However, no study has evaluated this protocol prospectively.
Methods and results: The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) study is an international, multicentre, non-randomized, open-label, pragmatic study in AHF patients on chronic loop diuretic therapy, admitted to the hospital for intravenous loop diuretic therapy, aiming to enrol 500 patients. Inclusion criteria are as follows: at least one sign of volume overload (oedema, ascites, or pleural effusion), use ≥ 40 mg of furosemide or equivalent for >1 month, and a BNP > 250 ng/L or an N-terminal pro-B-type natriuretic peptide > 1000 pg/L. The study is designed in two sequential phases. During Phase 1, all centres will treat consecutive patients according to the local standard of care. In the Phase 2 of the study, all centres will implement a standardized diuretic protocol in the next cohort of consecutive patients. The protocol is based upon the recently published HFA algorithm on diuretic use and starts with intravenous administration of two times the oral home dose. It includes early assessment of diuretic response with a spot urinary sodium measurement after 2 h and urine output after 6 h. Diuretics will be tailored further based upon these measurements. The study is powered for its primary endpoint of natriuresis after 1 day and will be able to detect a 15% difference with 80% power. Secondary endpoints are natriuresis and diuresis after 2 days, change in congestion score, change in weight, in-hospital mortality, and length of hospitalization.
Conclusions: The ENACT-HF study will investigate whether a step-wise diuretic approach, based upon early assessment of urinary sodium and urine output as proposed by the HFA, is feasible and able to improve decongestion in AHF with volume overload.

Gepubliceerd: ESC Heart Fail. 2021;8(6):4685-92.
Impact factor: 4.411; Q2

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10. **Myocardial Infarction and resuscitation of an adolescent: consequences of an unexplained disease**
de Jong JJD, Slenter RHJ, van Lierop P, Wagenaar LJ.

Background: Morbus Kawasaki is defined by unexplained fever combined with at least 4 out of 5 classic symptoms: bilateral conjunctivitis, polymorphic exanthema, strawberry tongue and red swollen lips, extremity changes and cervical lymphadenopathy. However, these symptoms do not always occur completely or simultaneously.
Case description: An 18-year old man was admitted after an out of hospital cardiac arrest caused by an occluded aneurysmatic LAD, which was treated with a percutanious coronary intervention. Coronary angiogram however also revealed coronary aneurysms of all coronaries, identifying an episode of unexplained fever and vasculitis 4 years prior as Morbus Kawasaki.
Conclusion: Echocardiogram, CTA and MRA can reveal coronary malformations and thus identify M. Kawasaki when there is an incomplete M. Kawasaki. An early diagnosis and treatment with high dose aspirin and intravenous immunoglobulines is essential to reduce the risk of cardiovascular complications later in life.

Gepubliceerd: Ned Tijdschr Geneeskd. 2021;165.
Impact factor: 0; NVT

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11. **Coronary crossing**
de Jong JJD, Tent H.

Gepubliceerd: Neth Heart J. 2021;29(3):172.
Impact factor: 2.380; Q3

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12. **Impact of renin-angiotensin system inhibitors on mortality during the COVID Pandemic among STEMI patients undergoing mechanical reperfusion: Insight from an international STEMI registry**
De Luca G, Cercek M, Okkels Jensen L, Bushljetikj O, Calmac L, Johnson T, Gracida Blancas M, Ganyukov V, Wojakowski W, von Birgelen C, A IJ, Tuccillo B, Versaci F, Ten Berg J, Laine M, Berkout T, Casella G, Kala P, López Ledesma B, Becerra V, Padalino R, Santucci A, Carrillo X, Scoccia A, Amoroso G, Lux A, Kovarnik T, Davlouros P, Gabrielli G, Flores Rios X, Bakraceski N, Levesque S, Guiducci V, Kidawa M, Marinucci L, Zilio F, Galasso G, Fabris E, Menichelli M, Manzo S, Caiazzo G, Moreu J, Sanchis Forés J, Donazzan L, Vignali L, Teles R, Agostoni P, Bosa Ojeda F, Lehtola H, Camacho-Freiere S, Kraaijeveld A, Antti Y, Visconti G, Lozano Martínez-Luengas I, Scheller B, Alexopulos D, Moreno R, Kedhi E, Uccello G, Faurie B, Gutierrez Barrios A, Scotto Di Uccio F, Wilbert B, Cortese G, Dirksen MT, Parodi G, Verdoia M.

Background: Concerns have been raised on a potential interaction between renin-angiotensin system inhibitors (RASI) and the susceptibility to coronavirus disease 2019 (COVID-19). No data have been so far reported on the prognostic impact of RASI in patients suffering from ST-elevation myocardial infarction (STEMI) during COVID-19 pandemic, which was the aim of the present study.
Methods: STEMI patients treated with primary percutaneous coronary intervention (PPCI) and enrolled in the ISACS-STEMI COVID-19 registry were included in the present sub-analysis and divided according to RASI therapy at admission.

Results: Our population is represented by 6095 patients, of whom 3654 admitted in 2019 and 2441 in 2020. No difference in the prevalence of SARSCoV2 infection was observed according to RASI therapy at admission (2.5% vs 2.1%, p = 0.5), which was associated with a significantly lower mortality (adjusted OR [95% CI]=0.68 [0.51-0.90], P = 0.006), confirmed in the analysis restricted to 2020 (adjusted OR [95% CI]=0.5[0.33-0.74], P = 0.001). Among the 5388 patients in whom data on in-hospital medication were available, in-hospital RASI therapy was associated with a significantly lower mortality (2.1% vs 16.7%, OR [95% CI]=0.11 [0.084-0.14], p < 0.0001), confirmed after adjustment in both periods. Among the 62 SARSCoV-2 positive patients, RASI therapy, both at admission or in-hospital, showed no prognostic effect.
Conclusions: This is the first study to investigate the impact of RASI therapy on the prognosis and SARSCoV2 infection of STEMI patients undergoing PPCI during the COVID-19 pandemic. Both pre-admission and in-hospital RASI were associated with lower mortality. Among SARSCoV2-positive patients, both chronic and in-hospital RASI therapy showed no impact on survival.

Gepubliceerd: Biomed Pharmacother. 2021;138:111469.
Impact factor: 6.530; Q1

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13. **Impact of SARS-CoV-2 positivity on clinical outcome among STEMI patients undergoing mechanical reperfusion: Insights from the ISACS STEMI COVID 19 registry**
De Luca G, Debel N, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, Ferrer GR, Ganyukov V, Wojakowski W, Kinnaird T, von Birgelen C, Cottin Y, A IJ, Tuccillo B, Versaci F, Royaards KJ, Berg JT, Laine M, Dirksen M, Siviglia M, Casella G, Kala P, Díez Gil JL, Banning A, Becerra V, De Simone C, Santucci A, Carrillo X, Scoccia A, Amoroso G, Van't Hof AW, Kovarnik T, Tsigkas G, Mehilli J, Gabrielli G, Rios XF, Bakraceski N, Levesque S, Cirrincione G, Guiducci V, Kidawa M, Spedicato L, Marinucci L, Ludman P, Zilio F, Galasso G, Fabris E, Menichelli M, Garcia-Touchard A, Manzo S, Caiazzo G, Moreu J, Forés JS, Donazzan L, Vignali L, Teles R, Benit E, Agostoni P, Ojeda FB, Lehtola H, Camacho-Freiere S, Kraaijeveld A, Antti Y, Boccalatte M, Deharo P, Martínez-Luengas IL, Scheller B, Varytimiadi E, Moreno R, Uccello G, Faurie B, Gutierrez Barrios A, Milewski M, Bruwiere E, Smits P, Wilbert B, Di Uccio FS, Parodi G, Kedhi E, Verdoia M.

Background and aims: SARS-Cov-2 predisposes patients to thrombotic complications, due to excessive inflammation, endothelial dysfunction, platelet activation, and coagulation/fibrinolysis disturbances. The aim of the present study was to evaluate clinical characteristics and prognostic impact of SARS-CoV-2 positivity among STEMI patients undergoing primary percutaneous coronary intervention (PPCI).
Methods: We selected SARS-CoV-2 positive patients included in the ISACS-STEMI COVID-19, a retrospective multicenter European registry including 6609 STEMI patients treated with PPCI from March 1st until April 30th, in 2019 and 2020. As a reference group, we randomly sampled 5 SARS-Cov-2 negative patients per each SARS-CoV-2 positive patient, individually matched for age, sex, and hospital/geographic area. Study endpoints were in-hospital mortality, definite stent thrombosis, heart failure.

Results: Our population is represented by 62 positive SARS-CoV-2 positive patients who were compared with a matched population of 310 STEMI patients. No significant difference was observed in baseline characteristics or the modality of access to the PCI center. In the SARS-CoV-2 positive patients, the culprit lesion was more often located in the RCA ($p < 0.001$). Despite similar pre and postprocedural TIMI flow, we observed a trend in higher use of GP IIb-IIIa inhibitors and a significantly higher use of thrombectomy in the SARS-CoV-2 positive patients. SARS-CoV-2 positivity was associated with a remarkably higher in hospital mortality (29% vs 5.5%, $p < 0.001$), definite in-stent thrombosis (8.1% vs 1.6%, $p = 0.004$) and heart failure (22.6% vs 10.6%, $p = 0.001$) that was confirmed after adjustment for confounding factors.
Conclusions: Our study showed that among STEMI patients, SARS-CoV-2 positivity is associated with larger thrombus burden, a remarkably higher mortality but also higher rates of in-stent thrombosis and heart failure.

Gepubliceerd: Atherosclerosis. 2021;332:48-54.
Impact factor: 5.162; Q1

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14. **Renin-angiotensin system inhibitors and mortality among diabetic patients with STEMI undergoing mechanical reperfusion during the COVID-19 pandemic**
De Luca G, Nardin M, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, Roura Ferrer G, Quadros A, Milewski M, Scotto di Uccio F, von Birgelen C, Versaci F, Ten Berg J, Casella G, Lung AWS, Kala P, Díez Gil JL, Carrillo X, Dirksen M, Becerra-Munoz VM, Lee MK, Juzar DA, de Moura Joaquim R, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld A, Galasso G, Lux A, Marinucci L, Guiducci V, Menichelli M, Scoccia A, Yamac AH, Mert KU, Flores Rios X, Kovarnik T, Kidawa M, Moreu J, Flavien V, Fabris E, Martínez-Luengas IL, Boccalatte M, Bosa Ojeda F, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Sanchis Forés J, Vignali L, Pereira H, Manzo S, Ordoñez S, Arat Özkan A, Scheller B, Lehtola H, Teles R, Mantis C, Antti Y, Brum Silveira JA, Zoni R, Bessonov I, Savonitto S, Kochiadakis G, Alexopulos D, Uribe CE, Kanakakis J, Faurie B, Gabrielli G, Gutierrez Barrios A, Bachini JP, Rocha A, Tam FC, Rodriguez A, Lukito AA, Saint-Joy V, Pessah G, Tuccillo A, Cortese G, Parodi G, Bouraghda MA, Kedhi E, Lamelas P, Suryapranata H, Verdoia M.

Background: During the coronavirus disease 2019 (COVID-19) pandemic, concerns have been arisen on the use of renin-angiotensin system inhibitors (RASI) due to the potentially increased expression of Angiotensin-converting-enzyme (ACE)2 and patient's susceptibility to SARS-CoV2 infection. Diabetes mellitus have been recognized favoring the coronavirus infection with consequent increase mortality in COVID-19. No data have been so far reported in diabetic patients suffering from ST-elevation myocardial infarction (STEMI), a very high-risk population deserving of RASI treatment.
Methods: The ISACS-STEMI COVID-19 registry retrospectively assessed STEMI patients treated with primary percutaneous coronary intervention (PPCI) in March/June 2019 and 2020 in 109 European high-volume primary PCI centers. This subanalysis assessed the prognostic impact of chronic RASI therapy at admission on mortality and SARS-CoV2 infection among diabetic patients.
Results: Our population is represented by 3812 diabetic STEMI patients undergoing mechanical reperfusion, 2038 in 2019 and 1774 in 2020. Among 3761 patients with

available data on chronic RASI therapy, between those ones with and without treatment there were several differences in baseline characteristics, (similar in both periods) but no difference in the prevalence of SARS-CoV2 infection (1.6% vs 1.3%, respectively, p = 0.786). Considering in-hospital medication, RASI therapy was overall associated with a significantly lower in-hospital mortality (3.3% vs 15.8%, p < 0.0001), consistently both in 2019 and in 2010.
Conclusions: This is first study to investigate the impact of RASI therapy on prognosis and SARS-CoV2 infection of diabetic patients experiencing STEMI and undergoing PPCI during the COVID-19 pandemic. Both pre-admission chronic RASI therapy and in-hospital RASI did not negatively affected patients' survival during the hospitalization, neither increased the risk of SARS-CoV2 infection.
Trial registration number: NCT04412655.

Gepubliceerd: Diabet Epidemiol Manag. 2021;4:100022.
Impact factor: 0; NVT

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15. **Daylight saving time does not seem to be associated with number of percutaneous coronary interventions for acute myocardial infarction in the Netherlands**
Derks L, Houterman S, Geuzebroek GSC, van der Harst P, Smits PC, PCI Registration Committee of the Netherlands Heart Registration – includes Stoel MG.

Background: In multiple studies, the potential relationship between daylight saving time (DST) and the occurrence of acute myocardial infarction (MI) has been investigated, with mixed results. Using the Dutch Percutaneous Coronary Intervention (PCI) registry facilitated by the Netherlands Heart Registration, we investigated whether the transitions to and from DST interact with the incidence rate of PCI for acute MI.
Methods: We assessed changes in hospital admissions for patients with ST-elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) undergoing PCI between 1 January 2015 and 31 December 2018. We compared the incidence rate of PCI procedures during the first 3 or 7 days after the transition with that during a control period (2 weeks before transition plus second week after transition). Incidence rate ratio (IRR) was calculated using Poisson regression. Potential gender differences were also investigated.
Results: A total of 80,970 PCI procedures for STEMI or NSTEMI were performed. No difference in incidence rate a week after the transition to DST in spring was observed for STEMI (IRR 0.95, 95% confidence interval (CI) 0.87-1.03) or NSTEMI (IRR 1.04, 95% CI 0.96-1.12). After the transition from DST in autumn, the IRR was also comparable with the control period (STEMI: 1.03, 95% CI 0.95-1.12, and NSTEMI: 0.98, 95% CI 0.91-1.06). Observing the first 3 days after each transition yielded similar results. Gender-specific results were comparable.
Conclusion: Based on data from a large, nationwide registry, there was no correlation between the transition to or from DST and a change in the incidence rate of PCI for acute MI.

Gepubliceerd: Neth Heart J. 2021;29(9):427-32.
Impact factor: 2.380; Q3

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16. **Contemporary management of patients with atrial fibrillation in the Netherlands and Belgium: a report from the EORP-AF long-term general registry**
Erkuner O, van Eck M, Xhaet O, Verheij H, Neefs J, Duygun A, Nijmeijer R, Said SAM, Uiterwaal H, Hagens V, Bhagwandien R, Szili-Torok T, Bijsterveld N, Tjeerdsma G, Vijgen J, Friart A, Hoffer E, Evrard P, Srynger M, Meeder J, de Groot JR, van Opstal J, Gevers R, Lip GYH, Boriani G, Crijns H, Luermans J, Mairesse GH.

Background: Contemporary data regarding the characteristics, treatment and outcomes of patients with atrial fibrillation (AF) are needed. We aimed to assess these data and guideline adherence in the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) long-term general registry.
Methods: We analysed 967 patients from the EORP-AF long-term general registry included in the Netherlands and Belgium from 2013 to 2016. Baseline and 1year follow-up data were gathered.
Results: At baseline, 887 patients (92%) received anticoagulant treatment. In 88 (10%) of these patients, no indication for chronic anticoagulant treatment was present. A rhythm intervention was performed or planned in 52 of these patients, meaning that the remaining 36 (41%) were anticoagulated without indication. Forty patients were not anticoagulated, even though they had an indication for chronic anticoagulation. Additionally, 63 of the 371 patients (17%) treated with a non-vitamin K antagonist oral anticoagulant (NOAC) were incorrectly dosed. In total, 50 patients (5%) were overtreated and 89 patients (9%) were undertreated. However, the occurrence of major adverse cardiac and cerebrovascular events (MACCE) was still low with 4.2% (37 patients).
Conclusions: Overtreatment and undertreatment with anticoagulants are still observable in 14% of this contemporary, West-European AF population. Still, MACCE occurred in only 4% of the patients after 1 year of follow-up.

Gepubliceerd: Neth Heart J. 2021;29(11):584-94.
Impact factor: 2.380; Q3

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17. **Reappraisal of Atrial fibrillation: interaction between hyperCoagulability, Electrical remodelling and Vascular destabilisation in the progression of AF (RACE V) Tissue Bank Project: study design**
Gilbers MD, Bidar E, Maesen B, Zeemering S, Isaacs A, Crijns H, van Gelder I, Rienstra M, Verheule S, Maessen J, Stoll M, Schotten U.

Background: The development of atrial fibrillation (AF) is a complex multifactorial process. Over the past few decades, much has been learned about the pathophysiological processes that can lead to AF from a variety of specific disease models in animals. However, our ability to recognise these disease processes in AF patients is still limited, which has contributed to the limited progress in improving rhythm control in AF.
Aims/objectives: We believe that a better understanding and detection of the individual pathophysiological mechanisms underlying AF is a prerequisite for developing patient-tailored therapies. The RACE V Tissue Bank Project will contribute to the unravelling of the main molecular mechanisms of AF by studying histology and genome-wide RNA expression profiles and combining this information with detailed phenotyping of patients undergoing cardiac surgery.

Methods: As more and more evidence suggests that AF may occur not only during the first days but also during the months and years after surgery, we will systematically study the incidence of AF during the first years after cardiac surgery in patients with or without a history of AF. Both the overall AF burden as well as the pattern of AF episodes will be studied. Lastly, we will study the association between the major molecular mechanisms and the clinical presentation of the patients, including the incidence and pattern of AF during the follow-up period.
Conclusion: The RACE V Tissue Bank Project combines deep phenotyping of patients undergoing cardiac surgery, including rhythm follow-up, analysis of molecular mechanisms, histological analysis and genome-wide RNA sequencing. This approach will provide detailed insights into the main pathological alterations associated with AF in atrial tissue and thereby contribute to the development of individualised, mechanistically informed patient-tailored treatment for AF.

Gepubliceerd: Neth Heart J. 2021;29(5):280-7.
Impact factor: 2.380; Q3

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18. **Downsizing Is Not Enough: Minimal Invasive Extracorporeal Circulation Is More Than Just a Circuit: Reply**
Halfwerk FR, Mariani S, Grandjean JG.

Gepubliceerd: Ann Thorac Surg. 2021;112(1):345-6.
Impact factor: 4.330; Q2

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19. **Objective Quantification of In-Hospital Patient Mobilization after Cardiac Surgery Using Accelerometers: Selection, Use, and Analysis**
Halfwerk FR, van Haaren JHL, Klaassen R, van Delden RW, Veltink PH, Grandjean JG.

Cardiac surgery patients infrequently mobilize during their hospital stay. It is unclear for patients why mobilization is important, and exact progress of mobilization activities is not available. The aim of this study was to select and evaluate accelerometers for objective qualification of in-hospital mobilization after cardiac surgery. Six static and dynamic patient activities were defined to measure patient mobilization during the postoperative hospital stay. Device requirements were formulated, and the available devices reviewed. A triaxial accelerometer (AX3, Axivity) was selected for a clinical pilot in a heart surgery ward and placed on both the upper arm and upper leg. An artificial neural network algorithm was applied to classify lying in bed, sitting in a chair, standing, walking, cycling on an exercise bike, and walking the stairs. The primary endpoint was the daily amount of each activity performed between 7 a.m. and 11 p.m. The secondary endpoints were length of intensive care unit stay and surgical ward stay. A subgroup analysis for male and female patients was planned. In total, 29 patients were classified after cardiac surgery with an intensive care unit stay of 1 (1 to 2) night and surgical ward stay of 5 (3 to 6) nights. Patients spent 41 (20 to 62) min less time in bed for each consecutive hospital day, as determined by a mixed-model analysis ($p < 0.001$). Standing, walking, and walking the stairs increased during the hospital stay. No differences between men (n = 22) and women (n = 7) were observed for all endpoints

in this study. The approach presented in this study is applicable for measuring all six activities and for monitoring postoperative recovery of cardiac surgery patients. A next step is to provide feedback to patients and healthcare professionals, to speed up recovery.

Gepubliceerd: Sensors (Basel). 2021;21(6).
Impact factor: 3.576; Q2

20**. Age dependency of plasma vitamin B12 status markers in Dutch children and adolescents**
Heiner-Fokkema MR, Riphagen IJ, Wiersema NS, van Zanden JJ, Kootstra-Ros JE, Pinxterhuis TH, Hooimeijer HL, van Spronsen FJ, Muller Kobold AC, de Jong WHA.

Background: Vitamin B12 deficiency in children may be associated with (severe) neurological manifestations, therefore recognition is important. Diagnosing vitamin B12 deficiency in children is challenging. This study aimed to investigate plasma methylmalonic acid, holotranscobalamin, and total cobalamin in children 0-18 years of age and to estimate age-dependent reference intervals.
Methods: Plasma vitamin B12 markers were measured in collected plasma samples of 170 children 0-18 years visiting a local primary care laboratory. All had within-reference hemoglobin and MCV values. Pediatric plasma vitamin B12 biomarkers were measured and reference values were derived thereof.
Results: Plasma methylmalonic acid was higher in young children, in particular between 1 and 6 months of age; total cobalamin and holotranscobalamin were highest from 0.5 to 4 years and decreased till 10 years of age. Plasma holotranscobalamin was highly correlated with plasma total cobalamin; their ratio was independent of age. Plasma methylmalonic acid was slightly more related to total cobalamin than to holotranscobalamin. A large proportion of mainly young children would be misclassified when adult references are applied.
Conclusions: Pediatric reference values for cobalamin markers are necessary to allow for early recognition and monitoring of children suspect of (clinical) cobalamin deficiency. IMPACT: We analyzed three plasma vitamin B12 status markers, i.e., total cobalamin, holotranscobalamin, and methylmalonic acid, in the plasma of 170 children 0-18 years of age and were able to derive reference intervals thereof. Recognition of vitamin B12 deficiency in children is important but challenging as pediatric reference intervals for plasma vitamin B12 status markers, particularly plasma holotranscobalamin, are not well described. We think that our results may help early recognition and monitoring of children suspect of (clinical) vitamin B12 deficiency.

Gepubliceerd: Pediatr Res. 2021;90(5):1058-64.
Impact factor: 3.756; Q1

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21. **Transient ST-elevation myocardial infarction versus persistent ST-elevation myocardial infarction. An appraisal of patient characteristics and functional outcome**
Janssens GN, Lemkes JS, van der Hoeven NW, van Leeuwen MAH, Everaars H, van de Ven PM, Brinckman SL, Timmer JR, Meuwissen M, Meijers JCM, van der Weerdt

AP, Ten Cate TJF, Piek JJ, von Birgelen C, Diletti R, Escaned J, van Rossum AC, Nijveldt R, van Royen N.

Background: Up to 24% of patients presenting with ST-elevation myocardial infarction (STEMI) show resolution of ST-elevation and symptoms before revascularization. The mechanisms of spontaneous reperfusion are unclear. Given the more favorable outcome of transient STEMI, it is important to obtain further insights in differential aspects.
Methods: We compared 251 patients who presented with transient STEMI (n = 141) or persistent STEMI (n = 110). Clinical angiographic and laboratory data were collected at admission and in subset of patients additional index hemostatic data and at steady-state follow-up. Cardiac magnetic resonance imaging (CMR) was performed at 2-8 days to assess myocardial injury.
Results: Transient STEMI patients had more cardiovascular risk factors than STEMI patients, including more arterial disease and higher cholesterol values. Transient STEMI patients showed angiographically more often no intracoronary thrombus (41.1% vs. 2.7%, P < 0.001) and less often a high thrombus burden (9.2% vs. 40.0%, P < 0.001). CMR revealed microvascular obstruction less frequently (4.2% vs. 34.6%, P < 0.001) and smaller infarct size [1.4%; interquartile range (IQR), 0.0-3.7% vs. 8.8%; IQR, 3.9-17.1% of the left ventricle, P < 0.001] with a better preserved left ventricular ejection fraction (57.8 ± 6.7% vs. 52.5 ± 7.6%, P < 0.001). At steady state, fibrinolysis was higher in transient STEMI, as demonstrated with a reduced clot lysis time (89 ± 20% vs. 99 ± 25%, P = 0.03).
Conclusions: Transient STEMI is a syndrome with less angiographic thrombus burden and spontaneous infarct artery reperfusion, resulting in less myocardial injury than STEMI. The presence of a more effective fibrinolysis in transient STEMI patients may explain these differences and might provide clues for future treatment of STEMI.

Gepubliceerd: Int J Cardiol. 2021;336:22-8.
Impact factor: 4.164; Q2

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22. **Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial**
Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, AJJ I, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Al Nooryani A, Rivero F, Malinowski K, De Luca G, Garcia Garcia H, Granada JF, Wojakowski W.

Aims: The aim of this study was to understand the impact of optical coherence tomography (OCT)-detected thin-cap fibroatheroma (TCFA) on clinical outcomes of diabetes mellitus (DM) patients with fractional flow reserve (FFR)-negative lesions.
Methods and results: COMBINE OCT-FFR study was a prospective, double-blind, international, natural history study. After FFR assessment, and revascularization of FFR-positive lesions, patients with >/=1 FFR-negative lesions (target lesions) were classified in two groups based on the presence or absence of >/=1 TCFA lesion. The primary endpoint compared FFR-negative TCFA-positive patients with FFR-negative TCFA-negative patients for a composite of cardiac mortality, target vessel myocardial infarction, clinically driven target lesion revascularization or unstable angina requiring hospitalization at 18 months. Among 550 patients enrolled, 390 (81%) patients had

>/=1 FFR-negative lesions. Among FFR-negative patients, 98 (25%) were TCFA positive and 292 (75%) were TCFA negative. The incidence of the primary endpoint was 13.3% and 3.1% in TCFA-positive vs. TCFA-negative groups, respectively (hazard ratio 4.65; 95% confidence interval, 1.99-10.89; P < 0.001). The Cox regression multivariable analysis identified TCFA as the strongest predictor of major adverse clinical events (MACE) (hazard ratio 5.12; 95% confidence interval 2.12-12.34; P < 0.001).
Conclusions: Among DM patients with >/=1 FFR-negative lesions, TCFA-positive patients represented 25% of this population and were associated with a five-fold higher rate of MACE despite the absence of ischaemia. This discrepancy between the impact of vulnerable plaque and ischaemia on future adverse events may represent a paradigm shift for coronary artery disease risk stratification in DM patients.

Gepubliceerd: Eur Heart J. 2021;42(45):4671-9.
Impact factor: 29.983; Q1

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23. **A randomized prospective multicenter trial for stroke prevention by prophylactic surgical closure of the left atrial appendage in patients undergoing bioprosthetic aortic valve surgery--LAA-CLOSURE trial protocol**
Kiviniemi T, Bustamante-Munguira J, Olsson C, Jeppsson A, Halfwerk FR, Hartikainen J, Suwalski P, Zindovic I, Copa GR, van Schaagen FRN, Hanke T, Cebotari S, Malmberg M, Fernandez-Gutierrez M, Bjurbom M, Schersten H, Speekenbrink R, Riekkinen T, Ek D, Vasankari T, Lip GYH, Airaksinen KEJ, van Putte B.

Patients undergoing surgical aortic valve replacement (SAVR) are at high risk for atrial fibrillation (AF) and stroke after surgery. There is an unmet clinical need to improve stroke prevention in this patient population. The LAA-CLOSURE trial aims to assess the efficacy and safety of prophylactic surgical closure of the left atrial appendage for stroke and cardiovascular death prevention in patients undergoing bioprosthetic SAVR. This randomized, open-label, prospective multicenter trial will enroll 1,040 patients at 13 European sites. The primary endpoint is a composite of cardiovascular mortality, stroke and systemic embolism at 5 years. Secondary endpoints include cardiovascular mortality, stroke, systemic embolism, bleed fulfilling academic research consortium (BARC) criteria, hospitalization for decompensated heart failure and health economic evaluation. Sample size is based on 30% risk reduction in time to event analysis of primary endpoint. Prespecified reports include 30-day safety analysis focusing on AF occurrence and short-term outcomes and interim analyses at 1 and 3 years for primary and secondary outcomes. Additionally, substudies will be performed on the completeness of the closure using transesophageal echocardiography/cardiac computed tomography and long-term ECG recording at one year after the operation.

Gepubliceerd: Am Heart J. 2021;237:127-34.
Impact factor: 4.749; Q1

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24. **Predictors and outcomes of procedural failure of percutaneous coronary intervention of a chronic total occlusion-A subanalysis of the EXPLORE trial**

Kolk MZH, van Veelen A, Agostoni P, van Houwelingen GK, Ouweneel DM, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, Suttorp MJ, Claessen B, van der Schaaf RJ, Elias J, van Dongen IM, Henriques JPS.

Objective: To evaluate predictors of procedural success of percutaneous coronary intervention (PCI) of chronic total coronary occlusions (CTOs) in a non-infarct-related artery following ST-segment elevation myocardial infarction (STEMI), and demonstrate the effect on left ventricular functionality (LVF), infarct size (IS), and pro-arrhythmic electrocardiogram (ECG) parameters.
Background: Predictors of unsuccessful revascularization of a CTO are numerous, although following STEMI, these are lacking. Besides, effects of failed CTO PCI (FPCI) on the myocardium are unknown.
Methods: This is a subanalysis of the EXPLORE trial, in which 302 STEMI patients with a concurrent CTO were randomized to CTO PCI (n = 147) or no-CTO PCI (NPCI, n = 154). For the purpose of this subanalysis, we divided patients into successful CTO PCI (SPCI, n = 106), FPCI (n = 41), and NPCI (n = 154) groups. Cardiac magnetic resonance imaging and angiographic data were derived from the EXPLORE database, combined with ECG parameters. To gain more insight, all outcomes were compared with patients that did not undergo CTO PCI.
Results: In multivariate regression, only CTO lesion length >20 mm was an independent predictor of procedural failure (OR 3.31 [1.49-7.39]). No significant differences in median left ventricular ejection fraction, left ventricular end-diastolic volume, IS, and the pro-arrhythmic ECG parameters such as QT-dispersion, QTc-time, and TpTe-intervals were seen between the SPCI and FPCI groups at 4 months follow-up.
Conclusion: This subanalysis of the EXPLORE trial has demonstrated that a CTO lesion length >20 mm is an independent predictor of CTO PCI failure, whereas procedural failure did not lead to any adverse effects on LVF nor pro-arrhythmic ECG parameters.

Gepubliceerd: Catheter Cardiovasc Interv. 2021;97(6):1176-83.
Impact factor: 2.692; Q3

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25. **The first multicentre study on coronary anomalies in the Netherlands: MuSCAT**
Koppel CJ, Driesen BW, de Winter RJ, van den Bosch AE, van Kimmenade R, Wagenaar LJ, Jukema JW, Hazekamp MG, van der Kley F, Jongbloed MRM, Kiès P, Egorova AD, Verheijen DBH, Damman P, Schoof PH, Wilschut J, Stoel M, Speekenbrink RGH, Voskuil M, Vliegen HW.

Background: Current guidelines on coronary anomalies are primarily based on expert consensus and a limited number of trials. A gold standard for diagnosis and a consensus on the treatment strategy in this patient group are lacking, especially for patients with an anomalous origin of a coronary artery from the opposite sinus of Valsalva (ACAOS) with an interarterial course. AIM: To provide evidence-substantiated recommendations for diagnostic work-up, treatment and follow-up of patients with anomalous coronary arteries.
Methods: A clinical care pathway for patients with ACAOS was established by six Dutch centres. Prospectively included patients undergo work-up according to protocol

using computed tomography (CT) angiography, ischaemia detection, echocardiography and coronary angiography with intracoronary measurements to assess anatomical and physiological characteristics of the ACAOS. Surgical and functional follow-up results are evaluated by CT angiography, ischaemia detection and a quality-of-life questionnaire. Patient inclusion for the first multicentre study on coronary anomalies in the Netherlands started in 2020 and will continue for at least 3 years with a minimum of 2 years of follow-up. For patients with a right or left coronary artery originating from the pulmonary artery and coronary arteriovenous fistulas a registry is maintained.
Results: Primary outcomes are: (cardiac) death, myocardial ischaemia attributable to the ACAOS, re-intervention after surgery and intervention after initially conservative treatment. The influence of work-up examinations on treatment choice is also evaluated.
Conclusions: Structural evidence for the appropriate management of patients with coronary anomalies, especially (interarterial) ACAOS, is lacking. By means of a structured care pathway in a multicentre setting, we aim to provide an evidence-based strategy for the diagnostic evaluation and treatment of this patient group.

Gepubliceerd: Neth Heart J. 2021;29(6):311-7.
Impact factor: 2.380; Q3

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26. **A Completely Endovascular Solution for Transcatheter Aortic Valve Implantation Embolisation and Inversion into the Aortic Arch**
Leeuwerke SJG, Menting TP, Stoel MG, Geelkerken RH.

Introduction: Transcatheter aortic valve implantation (TAVI) has evolved into the preferred alternative to surgical valve replacement for severe aortic valve stenosis with high surgical risk. With expanding indications, life threatening complications including transcatheter aortic valve embolisation and inversion (TAVEI), in which the valve dislodges, inverts, and migrates caudally, may increase concomitantly.
Report: An 80 year old male with severe aortic valve stenosis underwent balloon expandable transcatheter aortic valve implantation (TAVI). Valve embolisation into the aortic arch inverted the bioprothesis, excluding the option of fixation in the descending aorta. Through-valve thoracic endovascular aortic repair (TEVAR) was performed after bifemoral snaring using a through-and-through wire technique and pulling the valve into the descending aorta.
Discussion: TAVI is emerging as the preferred treatment for severe aortic valve stenosis and comes with unique procedural complications, such as life threatening transcatheter aortic valve embolisation and inversion (TAVEI). Although some authors prefer treating embolisation of a non-inverted balloon expandable valve into the aorta by using the valvuloplasty balloon to pull the valve distally and fixing it in the descending aorta, this risks further expansion of the valve and consequently fixing it in an undesirable position and is not possible if the valve inverts. Downstream placement of the valve by snaring with a guiding catheter covering/protecting a through-and-through wire technique, combined with through-valve TEVAR, provides a new bail out strategy for this serious complication and may reduce TAVEI associated mortality and morbidity.

Gepubliceerd: EJVES Vasc Forum. 2021;52:13-6.
Impact factor: 0; NVT

27. **Complications in pulmonary vein isolation in the Netherlands Heart Registration differ with sex and ablation technique**
Mol D, Houterman S, Balt JC, Bhagwandien RE, Blaauw Y, Delnoy PH, van Driel VJ, Driessen AH, Folkeringa RJ, Hassink RJ, van Huysduynen BH, Luermans JG, Ouss AJ, Stevenhagen YJ, van Veghel D, Westra SW, de Jong JS, de Groot JR.

Aims: Pulmonary vein isolation (PVI) has become a cornerstone of the invasive treatment of atrial fibrillation. Severe complications are reported in 1-3% of patients. This study aims to compare complications and follow-up outcome of PVI in patients with atrial fibrillation.
Methods and results: The data were extracted from the Netherlands Heart Registration. Procedural and follow-up outcomes in patients treated with conventional radiofrequency (C-RF), multielectrode phased RF (Ph-RF), or cryoballoon (CB) ablation from 2012 to 2017 were compared. Subgroup analysis was performed to identify variables associated with complications and repeat ablations. In total, 13 823 patients (69% male) were included. The reported complication incidence was 3.6%. Patients treated with C-RF developed more cardiac tamponades (C-RF 0.8% vs. Ph-RF 0.3% vs. CB 0.3%, P ≤ 0.001) and vascular complications (C-RF 1.7% vs. Ph-RF 1.2% vs. CB 1.3%, P ≤ 0.001). Ph-RF was associated with fewer bleeding complications (C-RF: 1.0% vs. Ph-RF: 0.4% vs. CB: 0.7%, P = 0.020). Phrenic nerve palsy mainly occurred in patients treated with CB (C-RF: 0.1% vs. Ph-RF: 0.2% vs. CB: 1.5%, P ≤ 0.001). In total, 18.4% of patients were referred for repeat ablation within 1 year. Female sex, age, and CHA2DS2-VASc were independent risk factors for cardiac tamponade and bleeding complications, with an adjusted OR for female patients of 2.97 (95% CI 1.98-4.45) and 2.02 (95% CI 1.03-4.00) respectively.
Conclusion: The reported complication rate during PVI was low. Patients treated with C-RF ablation were more likely to develop cardiac tamponades and vascular complications. Female sex was associated with more cardiac tamponade and bleeding complications.

Gepubliceerd: Europace. 2021;23(2):216-25.
Impact factor: 5.214; Q2

28. **Impact of Endothelial Shear Stress on Absorption Process of Resorbable Magnesium Scaffold: A BIOSOLVE-II Substudy**
Ozaki Y, Kuku KO, Sakellarios A, Haude M, Hideo-Kajita A, Desale S, Siogkas P, Sioros S, Ince H, Abizaid A, Tölg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Escaned J, Michalis L, Fotiadis DI, Djikstra J, Waksman R, Garcia-Garcia HM.

Background/purpose: Local hemodynamic forces such as endothelial shear stress (ESS) may have an influence on appropriate neointimal healing, vessel remodeling, and struts' absorption process following second-generation drug-eluting resorbable magnesium scaffold (RMS, Magmaris, Biotronik AG, Buelach, Switzerland) placement. The aim of this study was to investigate the impact of ESS assessed by optical coherence tomography (OCT)-based computational fluid dynamic (CFD) simulations on absorption process and coronary lumen dimension after Magmaris implantation.

Methods and results: A total of 22 patients who were enrolled in the BIOSOLVE-II trial and underwent serial OCT assessment immediately after Magmaris implantation and at 6- and 12-month follow-up were included. We evaluated qualitative OCT findings frame by frame, and CFD simulations were performed to calculate the ESS at 3-dimensional (3D) reconstructed arteries. For quantitative calculation, the average ESS within each 1-mm section was classified into three groups: low (<1.0 Pa), intermediate (1.0-2.5 Pa), or high (>2.5 Pa). A significant difference of percentage remnants of scaffold was observed among the 3 groups at 12-month follow-up (P = 0.001) but not at 6-month follow-up. Low-ESS segment at baseline resulted in a greater lumen change of -1.857 ± 1.902 mm(2) at 1 year compared to -1.277 ± 1.562 mm(2) in the intermediate-ESS segment (P = 0.017) and - 0.709 ± 1.213 mm(2) in the high-ESS segment (P = 0.001).
Conclusion: After Magmaris implantation, the presence of higher ESS might be associated with slower strut absorption process but less luminal loss.

Gepubliceerd: Cardiovasc Revasc Med. 2021;29:9-15.
Impact factor: 0; NVT

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29. **Treating diabetic all-comers with contemporary drug-eluting stents: Prespecified comparisons from the BIO-RESORT and the BIONYX randomized trials**
Ploumen EH, Buiten RA, Kok MM, Doggen CJM, Roguin A, Jessurun GAJ, Schotborgh CE, Danse PW, Benit E, Aminian A, van Houwelingen KG, Stoel MG, Scholte M, Hartmann M, Linssen GCM, Zocca P, von Birgelen C.

Background: Patients with diabetes have more extensive coronary disease, resulting in higher risks of adverse clinical events following stenting. In all-comer patients, contemporary DES have shown excellent safety and efficacy, but data on diabetic patients are scarce. Separately for the BIO-RESORT and BIONYX trials, we assessed the 2-year clinical outcomes of diabetic patients, treated with various contemporary drug-eluting stents (DES).
Methods: We performed two prespecified secondary analyses of two randomized DES trials, which both stratified for diabetes. The main endpoint was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization. Follow-up was finished before the COVID-19 pandemic.
Results: In BIO-RESORT, 624/3514 (17.8%) had diabetes: 211 received Orsiro sirolimus-eluting stents (SES), 203 Synergy everolimus-eluting stents (EES), and 210 Resolute Integrity zotarolimus-eluting stents (RI-ZES). TVF did not differ between SES (10.2%) and EES (10.0%) versus RI-ZES (12.7%) (SES vs. RI-ZES HR:0.78, 95%-CI [0.44-1.40]; p = 0.40, EES vs. RI-ZES HR:0.79, 95%-CI [0.44-1.40]; p = 0.42). In BIONYX, 510/2488 (20.5%) patients had diabetes: 250 received SES and 260 Resolute Onyx zotarolimus-eluting stents (RO-ZES). There was no difference in TVF between SES (10.7%) versus RO-ZES (12.2%) (HR:0.88, 95%-CI [0.52-1.48]; p = 0.63).
Conclusions: There was no difference in 2-year clinical outcome among patients with diabetes, who were treated with SES, or EES, versus RI-ZES. In addition there was no difference in clinical outcome in diabetic patients, who were treated with SES versus RO-ZES. These findings may be considered as a signal of safety and efficacy of the studied DES in patients with diabetes.

Gepubliceerd: Int J Cardiol. 2021;325:37-44.
Impact factor: 4.164; Q2

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30. **First Report of 3-Year Clinical Outcome After Treatment With Novel Resolute Onyx Stents in the Randomized BIONYX Trial**
Ploumen EH, Buiten RA, Zocca P, Doggen CJ, Aminian A, Schotborgh CE, Jessurun GA, Roguin A, Danse PW, Benit E, von Birgelen C.

Background: At 1 year, the international randomized BIONYX trial (ClinicalTrials.gov:NCT02508714) established non-inferiority regarding safety and efficacy of the novel Resolute Onyx zotarolimus-eluting stent (RO-ZES) vs. the Orsiro sirolimus-eluting stent (O-SES). Although the RO-ZES is used in daily practice, no clinical results have been published beyond 2 years.
Methods and Results: We assessed 3-year clinical outcomes of 2,488 all-comers after percutaneous coronary intervention (PCI) with RO-ZES vs. O-SES. The main endpoint was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction (MI), or target vessel revascularization. Time-to-endpoints was assessed by Kaplan-Meier methods and between-group comparisons by log-rank tests. Follow-up was available in 2,433/2,488 (97.8%) patients. There was no significant between-stent difference in TVF (RO-ZES 112/1,243 [9.2%] vs. O-SES 109/1,245 [8.9%], hazard ratio [HR]: 1.03, 95% confidence interval [CI] 0.79-1.34; Plog-rank=0.85) and its individual components. The all-cause mortality was significantly lower after PCI with RO-ZES (3.7% vs.5.4%, HR: 0.67, 95% CI 0.46-0.97; Plog-rank=0.034), but cardiac mortality did not differ significantly (1.1% vs.1.9%, HR: 0.56, 95% CI 0.28-1.11; Plog-rank=0.09). Definite-or-probable stent thrombosis rates were low for both groups (0.6% vs.1.2%, HR: 0.46, 95% CI 0.19-1.14; Plog-rank=0.09).
Conclusions: This first 3-year randomized assessment of the RO-ZES showed a favorable rate of TVF that matched the outcomes of patients treated with O-SES. We observed a lower rate of all-cause death in the RO-ZES group, but long-term clinical follow-up is of interest.

Gepubliceerd: Circ J. 2021;85(11):1983-90.
Impact factor: 2.993; Q3

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31. **Acute myocardial infarction treated with novel Resolute Onyx and Orsiro stents in the randomized BIONYX trial**
Ploumen EH, Buiten RA, Zocca P, Doggen CJM, Jessurun GAJ, Schotborgh CE, Roguin A, Danse PW, Benit E, Aminian A, Anthonio RL, Somi S, Linssen GCM, Hartmann M, Kok MM, von Birgelen C.

Objectives: To compare 2-year outcome following treatment with drug-eluting stents (DES) for acute myocardial infarction (MI) versus non-MI clinical syndromes. In acute MI patients, a stent-level comparison was performed, comparing Resolute Onyx versus Orsiro stents.
Background: In patients presenting with acute MI, higher adverse event rates have been reported. So far, no clinical results >1 year have been published of acute MI patients treated with Resolute Onyx.

Methods: This post-hoc analysis of the randomized BIONYX trial(NCT02508714) assessed the main outcome target vessel failure (TVF: cardiac death, target vessel MI, or target vessel revascularization) with Kaplan-Meier methods.
Results: Of all 2,488 trial participants, acute MI patients (n = 1,275[51.2%]) were significantly younger and had less comorbidities than non-MI patients (n = 1,213[48.8%]). TVF rates were lower in acute MI patients (77/1,275[6.1%] vs. 103/1,213[8.6%], HR:0.70, 95%-CI 0.52-0.94; p(log-rank) = 0.02), mainly driven by target vessel revascularization (4.1 vs. 6.1%, p(log-rank) = 0.03). Multivariate analysis showed no independent association of clinical syndrome with TVF (adjusted-HR: 0.81, 95%-CI 0.60-1.10; p = .17). In MI patients treated with Resolute Onyx (n = 626) versus Orsiro (n = 649), there was no difference in TVF (6.2 vs. 6.1%; p(log-rank) = 0.97) and its components. There was only 1(0.2%) definite-or-probable stent thrombosis in RO-ZES and 8(1.2%) in O-SES (p = .053).
Conclusions: Two years after treatment with thin-strut DES in this randomized trial, patients treated for acute MI had lower adverse event rates than non-MI patients. Yet, these findings were mainly attributable to between-group differences in patient and lesion characteristics. In patients who underwent PCI for acute MI, both Resolute Onyx and Orsiro showed favorable and similar 2-year outcomes.

Gepubliceerd: Catheter Cardiovasc Interv. 2021;98(2):E188-e96.
Impact factor: 2.692; Q3

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32. **Impact of prediabetes and diabetes on 3-year outcome of patients treated with new-generation drug-eluting stents in two large-scale randomized clinical trials**
Ploumen EH, Pinxterhuis TH, Zocca P, Roguin A, Anthonio RL, Schotborgh CE, Benit E, Aminian A, Danse PW, Doggen CJM, von Birgelen C, Kok MM.

Background: Diabetes is associated with adverse outcomes after percutaneous coronary intervention with drug-eluting stents (DES), but for prediabetes this association has not been definitely established. Furthermore, in patients with prediabetes treated with contemporary stents, bleeding data are lacking. We assessed 3-year ischemic and bleeding outcomes following treatment with new-generation DES in patients with prediabetes and diabetes as compared to normoglycemia.
Methods: For this post-hoc analysis, we pooled patient-level data of the BIO-RESORT and BIONYX stent trials which both stratified for diabetes at randomization. Both trials were multicenter studies performed in tertiary cardiac centers. Study participants were patients of whom glycemic state was known based on hemoglobin A1c, fasting plasma glucose, or medically treated diabetes. Three-year follow-up was available in 4212/4330 (97.3 %) patients. The main endpoint was target vessel failure, a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization.
Results: Baseline cardiovascular risk profiles were progressively abnormal in patients with normoglycemia, prediabetes, and diabetes. The main endpoint occurred in 54/489 patients with prediabetes (11.2 %) and 197/1488 with diabetes (13.7 %), as compared to 142/2,353 with normoglycemia (6.1 %) (HR: 1.89, 95 %-CI 1.38-2.58, p < 0.001, and HR: 2.30, 95 %-CI 1.85-2.86, p < 0.001, respectively). In patients with prediabetes, cardiac death and target vessel revascularization rates were significantly higher (HR: 2.81, 95 %-CI 1.49-5.30, p = 0.001, and HR: 1.92, 95 %-CI 1.29-2.87, p = 0.001), and in patients with diabetes all individual components of the main endpoint were significantly higher than in patients with normoglycemia (all p ≤ 0.001). Results were

consistent after adjustment for confounders. Major bleeding rates were significantly higher in patients with prediabetes and diabetes, as compared to normoglycemia (3.9 % and 4.1 % vs. 2.3 %; HR:1.73, 95 %-CI 1.03-2.92, p = 0.040, and HR:1.78, 95 %-CI 1.23-2.57, p = 0.002). However, after adjustment for confounders, differences were no longer significant.
Conclusions: Not only patients with diabetes but also patients with prediabetes represent a high-risk population. After treatment with new-generation DES, both patient groups had higher risks of ischemic and bleeding events. Differences in major bleeding were mainly attributable to dissimilarities in baseline characteristics. Routine assessment of glycemic state may help to identify patients with prediabetes for intensified management of cardiovascular risk factors.
Trial registrattion: BIO-RESORT ClinicalTrials.gov: NCT01674803, registered 29-08-2012; BIONYX ClinicalTrials.gov: NCT02508714, registered 27-7-2015.

Gepubliceerd: Cardiovasc Diabetol. 2021;20(1):217.
Impact factor: 9.951; Q1

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33. **Novel DES Aims at Full Thromboresistance: Another Promising Player on the Field?**
Ploumen EH, von Birgelen C.

Gepubliceerd: Cardiovasc Revasc Med. 2021;32:25-6.
Impact factor: 0; NVT

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34. **Hepatocellular carcinoma and the Fontan circulation: Clinical presentation and outcomes**
Possner M, Gordon-Walker T, Egbe AC, Poterucha JT, Warnes CA, Connolly HM, Ginde S, Clift P, Kogon B, Book WM, Walker N, Wagenaar LJ, Moe T, Oechslin E, Kay WA, Norris M, Dillman JR, Trout AT, Anwar N, Hoskoppal A, Broering DC, Bzeizi K, Veldtman G.

Background: Fontan-associated liver disease (FALD) is universal in patients with a Fontan circulation. Hepatocellular carcinoma (HCC) is one of its severe expressions, and, though rare, frequently fatal. The purpose of this study was to describe the clinical presentation, risk factors, and outcomes of HCC in patients with a Fontan circulation.
Methods: A multicenter case series of Fontan patients with a diagnosis of HCC formed the basis of this study. The case series was extended by published cases and case reports. Clinical presentation, tumor characteristics, laboratory and hemodynamic findings as well as treatment types and outcomes, were described.
Results: Fifty-four Fontan patients (50% female) with a diagnosis of HCC were included. Mean age at HCC diagnosis was 30 ± 9.4 years and mean duration from Fontan surgery to HCC diagnosis was 21.6 ± 7.4 years. Median HCC size at the time of diagnosis was 4 cm with a range of 1 to 22 cm. The tumor was located in the right hepatic lobe in 65% of the patients. Fifty-one percent had liver cirrhosis at the time of HCC diagnosis. Fifty percent of the patients had no symptoms related to HCC and alpha-fetoprotein was normal in 26% of the cases. Twenty-six patients (48%) died during a median follow-up duration of 10.6 (range 1-50) months.

Conclusions: HCC in Fontan patients occurs at a young age with a 1-year survival rate of only 50%. Meticulous liver surveillance is crucial to detect small tumors in the early stage.

Gepubliceerd: Int J Cardiol. 2021;322:142-8.
Impact factor: 4.164; Q2

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35. **Procedural myocardial injury, infarction and mortality in patients undergoing elective PCI: a pooled analysis of patient-level data**
Silvain J, Zeitouni M, Paradies V, Zheng HL, Ndrepepa G, Cavallini C, Feldman DN, Sharma SK, Mehilli J, Gili S, Barbato E, Tarantini G, Ooi SY, von Birgelen C, Jaffe AS, Thygesen K, Montalescot G, Bulluck H, Hausenloy DJ.

Aims: The prognostic importance of cardiac procedural myocardial injury and myocardial infarction (MI) in chronic coronary syndrome (CCS) patients undergoing elective percutaneous coronary intervention (PCI) is still debated.
Methods and results: We analysed individual data of 9081 patients undergoing elective PCI with normal pre-PCI baseline cardiac troponin (cTn) levels. Multivariate models evaluated the association between post-PCI elevations in cTn and 1-year mortality, while an interval analysis evaluated the impact of the size of the myocardial injury on mortality. Our analysis was performed in the overall population and also according to the type of cTn used [52.0% had high-sensitivity cTn (hs-cTn)]. Procedural myocardial injury, as defined by the Fourth Universal Definition of MI (UDMI) [post-PCI cTn elevation ≥1 × 99th percentile upper reference limit (URL)], occurred in 52.8% of patients and was not associated with 1-year mortality [adj odds ratio (OR), 1.35, 95% confidence interval (CI) (0.84-1.77), P = 0.21]. The association between post-PCI cTn elevation and 1-year mortality was significant starting ≥3 × 99th percentile URL. Major myocardial injury defined by post-PCI ≥5 × 99th percentile URL occurred in 18.2% of patients and was associated with a two-fold increase in the adjusted odds of 1-year mortality [2.29, 95% CI (1.32-3.97), P = 0.004]. In the subset of patients for whom periprocedural evidence of ischaemia was collected (n = 2316), Type 4a MI defined by the Fourth UDMI occurred in 12.7% of patients and was strongly associated with 1-year mortality [adj OR 3.21, 95% CI (1.42-7.27), P = 0.005]. We also present our results according to the type of troponin used (hs-cTn or conventional troponin).
Conclusion: Our analysis has demonstrated that in CCS patients with normal baseline cTn levels, the post-PCI cTn elevation of ≥5 × 99th percentile URL used to define Type 4a MI is associated with 1-year mortality and could be used to detect 'major' procedural myocardial injury in the absence of procedural complications or evidence of new myocardial ischaemia.

Gepubliceerd: Eur Heart J. 2021;42(4):323-34.
Impact factor: 29.983; Q1

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36. **Risk, Clinical Course, and Outcome of Ischemic Stroke in Patients Hospitalized With COVID-19: A Multicenter Cohort Study**
Sluis WM, Linschoten M, Buijs JE, Biesbroek JM, den Hertog HM, Ribbers T, Nieuwkamp DJ, van Houwelingen RC, Dias A, van Uden IWM, Kerklaan JP, Bienfait HP, Vermeer SE, de Jong SW, Ali M, Wermer MJH, de Graaf MT, Brouwers P,

Asselbergs FW, Kappelle LJ, van der Worp HB, Algra AM, CAPACITY-COVID Collaborative Consortium – includes Meijs MFL.

Background and Purpose: The frequency of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) varies in the current literature, and risk factors are unknown. We assessed the incidence, risk factors, and outcomes of acute ischemic stroke in hospitalized patients with COVID-19.
Methods: We included patients with a laboratory-confirmed SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) infection admitted in 16 Dutch hospitals participating in the international CAPACITY-COVID registry between March 1 and August 1, 2020. Patients were screened for the occurrence of acute ischemic stroke. We calculated the cumulative incidence of ischemic stroke and compared risk factors, cardiovascular complications, and in-hospital mortality in patients with and without ischemic stroke.
Results: We included 2147 patients with COVID-19, of whom 586 (27.3%) needed treatment at an intensive care unit. Thirty-eight patients (1.8%) had an ischemic stroke. Patients with stroke were older but did not differ in sex or cardiovascular risk factors. Median time between the onset of COVID-19 symptoms and diagnosis of stroke was 2 weeks. The incidence of ischemic stroke was higher among patients who were treated at an intensive care unit (16/586; 2.7% versus nonintensive care unit, 22/1561; 1.4%; P=0.039). Pulmonary embolism was more common in patients with (8/38; 21.1%) than in those without stroke (160/2109; 7.6%; adjusted risk ratio, 2.08 [95% CI, 1.52-2.84]). Twenty-seven patients with ischemic stroke (71.1%) died during admission or were functionally dependent at discharge. Patients with ischemic stroke were at a higher risk of in-hospital mortality (adjusted risk ratio, 1.56 [95% CI, 1.13-2.15]) than patients without stroke.
Conclusions: In this multicenter cohort study, the cumulative incidence of acute ischemic stroke in hospitalized patients with COVID-19 was ≈2%, with a higher risk in patients treated at an intensive care unit. The majority of stroke patients had a poor outcome. The association between ischemic stroke and pulmonary embolism warrants further investigation.

Gepubliceerd: Stroke. 2021;52(12):3978-86.
Impact factor: 7.914; Q1

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37. **Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on Acute Admissions at the Emergency and Cardiology Departments Across Europe**
Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, Braunschweig F, Caldeira D, Cuculi F, D'Elia E, Edes IF, Garus M, Greenwood JP, Halfwerk FR, Hindricks G, Knuuti J, Kristensen SD, Landmesser U, Lund LH, Lyon A, Mebazaa A, Merkely B, Nawrocka-Millward S, Pinto FJ, Ruschitzka F, Semedo E, Senni M, Sepehri Shamloo A, Sorensen J, Stengaard C, Thiele H, Toggweiler S, Tukiendorf A, Verhorst PM, Wright DJ, Zamorano P, Zuber M, Narula J, Bax JJ, Ponikowski P.

Purpose: We evaluated whether the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic was associated with changes in the pattern of acute cardiovascular admissions across European centers.
Methods: We set-up a multicenter, multinational, pan-European observational registry in 15 centers from 12 countries. All consecutive acute admissions to emergency

departments and cardiology departments throughout a 1-month period during the COVID-19 outbreak were compared with an equivalent 1-month period in 2019. The acute admissions to cardiology departments were classified into 5 major categories: acute coronary syndrome, acute heart failure, arrhythmia, pulmonary embolism, and other.
Results: Data from 54,331 patients were collected and analyzed. Nine centers provided data on acute admissions to emergency departments comprising 50,384 patients: 20,226 in 2020 compared with 30,158 in 2019 (incidence rate ratio [IRR] with 95% confidence interval [95%CI]: 0.66 [0.58-0.76]). The risk of death at the emergency departments was higher in 2020 compared to 2019 (odds ratio [OR] with 95% CI: 4.1 [3.0-5.8], P < 0.0001). All 15 centers provided data on acute cardiology departments admissions: 3007 patients in 2020 and 4452 in 2019; IRR (95% CI): 0.68 (0.64-0.71). In 2020, there were fewer admissions with IRR (95% CI): acute coronary syndrome: 0.68 (0.63-0.73); acute heart failure: 0.65 (0.58-0.74); arrhythmia: 0.66 (0.60-0.72); and other: 0.68(0.62-0.76). We found a relatively higher percentage of pulmonary embolism admissions in 2020: odds ratio (95% CI): 1.5 (1.1-2.1), P = 0.02. Among patients with acute coronary syndrome, there were fewer admissions with unstable angina: 0.79 (0.66-0.94); non-ST segment elevation myocardial infarction: 0.56 (0.50-0.64); and ST-segment elevation myocardial infarction: 0.78 (0.68-0.89).
Conclusion: In the European centers during the COVID-19 outbreak, there were fewer acute cardiovascular admissions. Also, fewer patients were admitted to the emergency departments with 4 times higher death risk at the emergency departments.

Gepubliceerd: Am J Med. 2021;134(4):482-9.
Impact factor: 4.965; Q1

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38. **Dutch Outcome in Implantable Cardioverter-Defibrillator Therapy: Implantable Cardioverter-Defibrillator-Related Complications in a Contemporary Primary Prevention Cohort**
van Barreveld M, Verstraelen TE, van Dessel P, Boersma LVA, Delnoy P, Tuinenburg AE, Theuns D, van der Voort PH, Kimman GJ, Buskens E, Zwinderman AH, Wilde AAM, Dijkgraaf MGW.

Background: One third of primary prevention implantable cardioverter-defibrillator patients receive appropriate therapy, but all remain at risk of defibrillator complications. Information on these complications in contemporary cohorts is limited. This study assessed complications and their risk factors after defibrillator implantation in a Dutch nationwide prospective registry cohort and forecasts the potential reduction in complications under distinct scenarios of updated indication criteria.
Methods and Results: Complications in a prospective multicenter registry cohort of 1442 primary implantable cardioverter-defibrillator implant patients were classified as major or minor. The potential for reducing complications was derived from a newly developed prediction model of appropriate therapy to identify patients with a low probability of benefitting from the implantable cardioverter-defibrillator. During a follow-up of 2.2 years (interquartile range, 2.0-2.6 years), 228 complications occurred in 195 patients (13.6%), with 113 patients (7.8%) experiencing at least one major complication. Most common ones were lead related (n=93) and infection (n=18). Minor complications occurred in 6.8% of patients, with lead-related (n=47) and pocket-related (n=40) complications as the most prevailing ones. A surgical reintervention or additional

hospitalization was required in 53% or 61% of complications, respectively. Complications were strongly associated with device type. Application of stricter implant indication results in a comparable proportional reduction of (major) complications.
Conclusions: One in 13 patients experiences at least one major implantable cardioverter-defibrillator-related complication, and many patients undergo a surgical reintervention. Complications are related to defibrillator implantations, and these should be discussed with the patient. Stricter implant indication criteria and careful selection of device type implanted may have significant clinical and financial benefits.

Gepubliceerd: J Am Heart Assoc. 2021;10(7):e018063.
Impact factor: 5.501; Q1

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39. **Cardiac imaging in ischemic stroke or transient ischemic attack of undetermined cause: Systematic review & meta-analysis**
van der Maten G, Dijkstra S, Meijs MFL, von Birgelen C, van der Palen J, den Hertog HM.

Background: Patients with ischemic stroke or transient ischemic attack (TIA) of undetermined cause often undergo cardiac imaging in search of a cardioembolic source. As the choice of the most appropriate imaging approach is controversial and therapeutic implications have changed over time, we aimed to identify in patients with "cryptogenic stroke or TIA" the yield of transthoracic or transesophageal echocardiography (TTE or TEE) and cardiac computed tomography (CT).
Methods and results: We performed a systematic review and meta-analysis according to the PRISMA guidelines. Included were studies that assessed consecutive patients with ischemic stroke or TIA of undetermined cause to evaluate the yield of TTE, TEE, or cardiac CT for detecting cardioembolic sources. For each type of cardioembolic source the pooled prevalence was calculated. Only six out of 1458 studies fulfilled the inclusion criteria (1022 patients). One study reported the yield of TTE, four of TEE, and one of both TTE and TEE; no study assessed cardiac CT. Mean patient age ranged from 44.3-71.2 years, 49.2-59.7% were male. TTE detected 43 cardioembolic sources in 316 patients (4 (1.3%) major, 39 (12.3%) minor), and TEE 248 in 937 patients (55 (5.9%) major, 193 (20.6%) minor). The most prevalent major cardioembolic source was left atrial appendage thrombus, yet results were heterogeneous among studies.
Conclusions: TTE and TEE infrequently detect major cardioembolic sources that require a change of therapy. Findings should be interpreted with caution due to the limited number of studies. A large-sized prospective clinical trial is warranted to support evidence-based decision-making.

Gepubliceerd: Int J Cardiol. 2021;339:211-8.
Impact factor: 4.164; Q2

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40. **Detection of Major Cardioembolic Sources in Real-World Patients with Ischemic Stroke or Transient Ischemic Attack of Undetermined Cause**
van der Maten G, Reimer JMB, Meijs MFL, von Birgelen C, Brusse-Keizer MGJ, den Hertog HM.

Background/Aim: Current guidelines recommend transthoracic echocardiography (TTE) and ambulatory rhythm monitoring following ischemic stroke or transient ischemic attack (TIA) of undetermined cause for identifying cardioembolic sources (CES). Due to ongoing controversies about this routine strategy, we evaluated its yield in a real-world setting.
Methods: In a tertiary medical center, we retrospectively evaluated consecutive patients with ischemic stroke or TIA of undetermined cause, who (after standard work-up) underwent TTE, ambulatory rhythm monitoring, or both. CES were classified as major if probably related to ischemic events and warranting a change of therapy.
Results: Between January 2014 and December 2017, 674 patients had ischemic stroke or TIA of undetermined cause. Of all 484 patients (71.8%) who underwent TTE, 9 (1.9%) had a major CES. However, 7 of them had already been identified for cardiac evaluation due to new major electrocardiographic abnormalities or cardiac symptoms. Thus, only 2 patients (0.4%) truly benefitted from unselected TTE screening. Ambulatory rhythm monitoring was performed in 411 patients (61.0%) and revealed AF in 10 patients (2.4%).
Conclusion: Detecting a major CES is essential because appropriate treatment lowers the risk of recurrent stroke. Nonetheless, in this real-world study that aimed at routine use of TTE and ambulatory rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause, the prevalence of major CES was low. Most patients with major CES on TTE already had an indication for referral to a cardiologist, suggesting that major CES might also have been identified with a much more selective use of TTE.

Gepubliceerd: Cerebrovasc Dis Extra. 2021;11(1):22-8.
Impact factor: 0; NVT

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41. **Reply to the letter of Groenveld et al.: 'Routine measurement of oesophageal temperature during cryoballoon pulmonary vein isolation'**
van Opstal JM, Stevenhagen YJ, van Dessel P, Scholten MF.

Gepubliceerd: Neth Heart J. 2021;29(4):239-40.
Impact factor: 2.380; Q3

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42. **Development and external validation of prediction models to predict implantable cardioverter-defibrillator efficacy in primary prevention of sudden cardiac death**
Verstraelen TE, van Barreveld M, van Dessel P, Boersma LVA, Delnoy P, Tuinenburg AE, Theuns D, van der Voort PH, Kimman GP, Buskens E, Hulleman M, Allaart CP, Strikwerda S, Scholten MF, Meine M, Abels R, Maass AH, Firouzi M, Widdershoven J, Elders J, van Gent MWF, Khan M, Vernooy K, Grauss RW, Tukkie R, van Erven L, Spierenburg HAM, Brouwer MA, Bartels GL, Bijsterveld NR, Borger van der Burg AE, Vet MW, Derksen R, Knops RE, Bracke F, Harden M, Sticherling C, Willems R, Friede T, Zabel M, Dijkgraaf MGW, Zwinderman AH, Wilde AAM.
Aims: This study was performed to develop and externally validate prediction models for appropriate implantable cardioverter-defibrillator (ICD) shock and mortality to identify subgroups with insufficient benefit from ICD implantation.
Methods and results: We recruited patients scheduled for primary prevention ICD implantation and reduced left ventricular function. Bootstrapping-based Cox

proportional hazards and Fine and Gray competing risk models with likely candidate predictors were developed for all-cause mortality and appropriate ICD shock, respectively. Between 2014 and 2018, we included 1441 consecutive patients in the development and 1450 patients in the validation cohort. During a median follow-up of 2.4 (IQR 2.1-2.8) years, 109 (7.6%) patients received appropriate ICD shock and 193 (13.4%) died in the development cohort. During a median follow-up of 2.7 (IQR 2.0-3.4) years, 105 (7.2%) received appropriate ICD shock and 223 (15.4%) died in the validation cohort. Selected predictors of appropriate ICD shock were gender, NSVT, ACE/ARB use, atrial fibrillation history, Aldosterone-antagonist use, Digoxin use, eGFR, (N)OAC use, and peripheral vascular disease. Selected predictors of all-cause mortality were age, diuretic use, sodium, NT-pro-BNP, and ACE/ARB use. C-statistic was 0.61 and 0.60 at respectively internal and external validation for appropriate ICD shock and 0.74 at both internal and external validation for mortality.
Conclusion: Although this cohort study was specifically designed to develop prediction models, risk stratification still remains challenging and no large group with insufficient benefit of ICD implantation was found. However, the prediction models have some clinical utility as we present several scenarios where ICD implantation might be postponed.

Gepubliceerd: Europace. 2021;23(6):887-97.
Impact factor: 5.214; Q2

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43. **Similar long-term outcome of dissimilar drug-eluting stents: is it time to change the assessment?**
von Birgelen C, Ploumen EH.

Gepubliceerd: EuroIntervention. 2021;16(18):e1468-e9.
Impact factor: 6.534; Q1

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44. **Early career perspectives of young Dutch cardiologists**
Vorselaars VMM, van der Heijden AC, Joustra R, Berger WR, van Hout GPJ, Kapel GFL, Nuis RJ, Woudstra P, Piers SRD.

Background: There are nationwide concerns about the unemployment rate among young Dutch cardiologists and the increase in temporary positions. Therefore, the aim of this study was to investigate the unemployment rate in this subgroup as well as the length of time between the end of their training and the acquisition of a permanent position.
Methods: All cardiologists who completed their training between January 2015 and December 2018 were invited to fill in an online questionnaire about their demographic characteristics, professional profile and employment status. The unemployment rate was calculated and Kaplan-Meier curves were used to determine the time between the end of training and the first permanent contract.
Results: In total, 174 participants were included (mean age 35 ± 3 years, 64% male, median follow-up 2.3 years (interquartile range 1.4-3.2 years)). The unemployment rate was 0.6% (n = 1). Only 12 participants (7%) started their career with a permanent position. The percentage of cardiologists with a temporary position was 82%, 61% and 33% at 1, 2 and 3 years, respectively. The percentage of cardiologists with a temporary

position did not differ with regard to age, gender, holding a PhD degree or type of teaching institution attended (academic vs non-academic). Forty-four per cent of participants perceived the current job market to be problematic.
Conclusions: The unemployment rate among young cardiologists in the Netherlands was low between 2015 and 2018. The vast majority of cardiologists start their career on a temporary contract. Three years later, 33% still hold temporary positions. Due to the resultant job insecurity, many young cardiologists describe the job market as problematic.

Gepubliceerd: Neth Heart J. 2021;29(9):433-40.
Impact factor: 2.380; Q3

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45. **Angiography-Based 4-Dimensional Superficial Wall Strain and Stress: A New Diagnostic Tool in the Catheterization Laboratory**
Wu X, Ono M, Kawashima H, Poon EKW, Torii R, Shahzad A, Gao C, Wang R, Barlis P, von Birgelen C, Reiber JHC, Bourantas CV, Tu S, Wijns W, Serruys PW, Onuma Y.

A novel method for four-dimensional superficial wall strain and stress (4D-SWS) is derived from the arterial motion as pictured by invasive coronary angiography. Compared with the conventional finite element analysis of cardiovascular biomechanics using the estimated pulsatile pressure, the 4D-SWS approach can calculate the dynamic mechanical state of the superficial wall in vivo, which could be directly linked with plaque rupture or stent fracture. The validation of this approach using in silico models showed that the distribution and maximum values of superficial wall stress were similar to those calculated by conventional finite element analysis. The in vivo deformation was validated on 16 coronary arteries, from the comparison of centerlines predicted by the 4D-SWS approach against the actual centerlines reconstructed from angiograms at a randomly selected time-point, which demonstrated a good agreement of the centerline morphology between both approaches (scaling: 0.995 ± 0.018 and dissimilarity: 0.007 ± 0.014). The in silico vessel models with softer plaque and larger plaque burden presented more variation in mean lumen diameter and resulted in higher superficial wall stress. In more than half of the patients (n = 16), the maximum superficial wall stress was found at the proximal lesion shoulder. Additionally, in three patients who later suffered from acute coronary syndrome, the culprit plaque rupture sites co-localized with the site of highest superficial wall stress on their baseline angiography. These representative cases suggest that angiography-based superficial wall dynamics have the potential to identify coronary segments at high-risk of plaque rupture and fracture sites of implanted stents. Ongoing studies are focusing on identifying weak spots in coronary bypass grafts, and on exploring the biomechanical mechanisms of coronary arterial remodeling and aneurysm formation. Future developments involve integration of fast computational techniques to allow online availability of superficial wall strain and stress in the catheterization laboratory.

Gepubliceerd: Front Cardiovasc Med. 2021;8:667310.
Impact factor: 6.050; Q1

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46. **Quality of life and healthcare utilisation improvements after atrial fibrillation ablation**
Gupta D, Vijgen J, de Potter T, Scherr D, van Herendael H, Knecht S, Kobza R, Berte B, Sandgaard N, Albenque JP, Széplaki G, Stevenhagen Y, Taghji P, Wright M, Duytschaever M.

Objective: Pulmonary vein isolation (PVI) guided by a standardised CLOSE (contiguous optimised lesions) protocol has been shown to increase clinical success after catheter ablation for paroxysmal atrial fibrillation (PAF). This study analysed healthcare utilisation and quality of life (QOL) outcomes from a large multicentre prospective study, measured association between QOL and atrial fibrillation (AF) burden and identified factors associated with lack of QOL improvement.
Methods: CLOSE-guided ablation was performed in 329 consecutive patients (age 61.4 years, 60.8% male) with drug-refractory PAF in 17 European centres. QOL was measured at baseline and 12 months post-ablation via Atrial Fibrillation Effect on QualiTy of Life Survey (AFEQT) and EuroQoL EQ-5D-5L questionnaires. All-cause and cardiovascular hospitalisations and cardioversions over 12 months pre-ablation and post-ablation were recorded. Rhythm monitoring included weekly and symptom-driven trans-telephonic monitoring, plus ECG and Holter monitoring at 3, 6 and 12 months. AF burden was defined as the percentage of postblanking tracings with an atrial tachyarrhythmia ≥30 s. Continuous measures across multiple time points were analysed using paired t-tests, and associations between various continuous measures were analysed using independent sample t-tests. Each statistical test used two-sided p values with a significance level of 0.05.
Results: Both QOL instruments showed significant 12-month improvements across all domains: AFEQT score increased 25.1-37.5 points and 33.3%-50.8% fewer patients reporting any problem across EuroQoL EQ-5D-5L domains. Overall, AFEQT improvement was highly associated with AF burden (p=0.009 for <10% vs ≥10% burden, p<0.001 for <20% vs ≥20% burden). Cardiovascular hospitalisations were significantly decreased after ablation (42%, p=0.001). Patients without substantial improvement in AFEQT (55/301, 18.2%) had higher AFEQT and CHA2DS2-VASc scores at baseline, and higher AF burden following PVI.
Conclusions: QOL improved and healthcare utilisation decreased significantly after ablation with a standardised CLOSE protocol. QOL improvement was significantly associated with impairment at baseline and AF burden after ablation.

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Impact factor: 5.994; Q1

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47. **Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk**
Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice MC, Chevalier B, Onuma Y, Windecker S, Tonino PAL, Roffi M, Lesiak M, Mahfoud F, Bartunek J, Hildick-Smith D, Colombo A, Stanković G, Iñiguez A, Schultz C, Kornowski R, Ong PJL, Alasnag M, Rodriguez AE, Moschovitis A, Laanmets P, Donahue M, Leonardi S, Smits PC, MASTER DAPT Investigators – includes von Birgelen C.

Background: The appropriate duration of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear.
Methods: One month after they had undergone implantation of a biodegradable-polymer sirolimus-eluting coronary stent, we randomly assigned patients at high bleeding risk to discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue it for at least 2 additional months (standard therapy). The three ranked primary outcomes were net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding; cumulative incidences were assessed at 335 days. The first two outcomes were assessed for noninferiority in the per-protocol population, and the third outcome for superiority in the intention-to-treat population.
Results: Among the 4434 patients in the per-protocol population, net adverse clinical events occurred in 165 patients (7.5%) in the abbreviated-therapy group and in 172 (7.7%) in the standard-therapy group (difference, -0.23 percentage points; 95% confidence interval [CI], -1.80 to 1.33; P<0.001 for noninferiority). A total of 133 patients (6.1%) in the abbreviated-therapy group and 132 patients (5.9%) in the standard-therapy group had a major adverse cardiac or cerebral event (difference, 0.11 percentage points; 95% CI, -1.29 to 1.51; P = 0.001 for noninferiority). Among the 4579 patients in the intention-to-treat population, major or clinically relevant nonmajor bleeding occurred in 148 patients (6.5%) in the abbreviated-therapy group and in 211 (9.4%) in the standard-therapy group (difference, -2.82 percentage points; 95% CI, -4.40 to -1.24; P<0.001 for superiority).
Conclusions: One month of dual antiplatelet therapy was noninferior to the continuation of therapy for at least 2 additional months with regard to the occurrence of net adverse clinical events and major adverse cardiac or cerebral events; abbreviated therapy also resulted in a lower incidence of major or clinically relevant nonmajor bleeding.

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Impact factor: 91.253; Q1

Totale impact factor: 346.184
Gemiddelde impact factor: 7.366

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 44.456
Gemiddelde impact factor: 3.175

Urologie

1. **Optimizing the risk threshold of lymph node involvement for performing extended pelvic lymph node dissection in prostate cancer patients: a cost-effectiveness analysis**

Hueting TA, Cornel EB, Korthorst RA, Pleijhuis RG, Somford DM, van Basten JA, van der Palen JAM, Koffijberg H.

Background: Extended pelvic lymph node dissection (ePLND) may be omitted in prostate cancer (CaP) patients with a low predicted risk of lymph node involvement (LNI). The aim of the current study was to quantify the cost-effectiveness of using different risk thresholds for predicted LNI in CaP patients to inform decision making on omitting ePLND.
Methods: Five different thresholds (2%, 5%, 10%, 20%, and 100%) used in practice for performing ePLND were compared using a decision analytic cohort model with the 100% threshold (i.e., no ePLND) as reference. Compared outcomes consisted of quality-adjusted life years (QALYs) and costs. Baseline characteristics for the hypothetical cohort were based on an actual Dutch patient cohort containing 925 patients who underwent ePLND with risks of LNI predicted by the Memorial Sloan Kettering Cancer Center web-calculator. The best strategy was selected based on the incremental cost effectiveness ratio when applying a willingness to pay (WTP) threshold of €20,000 per QALY gained. Probabilistic sensitivity analysis was performed with Monte Carlo simulation to assess the robustness of the results.
Results: Costs and health outcomes were lowest (€4,858 and 6.04 QALYs) for the 100% threshold, and highest (€10,939 and 6.21 QALYs) for the 2% threshold, respectively. The incremental cost effectiveness ratio for the 2%, 5%, 10%, and 20% threshold compared with the first threshold above (i.e., 5%, 10%, 20%, and 100%) were €189,222/QALY, €130,689/QALY, €51,920/QALY, and €23,187/QALY respectively. Applying a WTP threshold of €20.000 the probabilities for the 2%, 5%, 10%, 20%, and 100% threshold strategies being cost-effective were 0.0%, 0.3%, 4.9%, 30.3%, and 64.5% respectively.
Conclusion: Applying a WTP threshold of €20.000, completely omitting ePLND in CaP patients is cost-effective compared to other risk-based strategies. However, applying a 20% threshold for probable LNI to the Briganti 2012 nomogram or the Memorial Sloan Kettering Cancer Center web-calculator, may be a feasible alternative, in particular when higher WTP values are considered.

Gepubliceerd: Urol Oncol. 2021;39(1):72.e7-.e14.
Impact factor: 0; NVT

Totale impact factor: 0
Gemiddelde impact factor: 0

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

Waardegedreven zorg

1. **Opposite Incidence Trends for Differentiated and Medullary Thyroid Cancer in Young Dutch Patients over a 30-Year Time Span**
Lebbink CA, van den Broek MFM, Kwast ABG, Derikx JPM, Dierselhuis MP, Kruijff S, Links TP, van Trotsenburg ASP, Valk GD, Vriens MR, Verrijn Stuart AA, van Santen HM, Karim-Kos HE.

Thyroid cancer is the most common endocrine malignancy in children. A rising incidence has been reported worldwide. Possible explanations include the increased use of enhanced imaging (leading to incidentalomas) and an increased prevalence of risk factors. We aimed to evaluate the incidence and survival trends of thyroid cancer in Dutch children, adolescents, and young adults (0-24 years) between 1990 and 2019. The age-standardized incidence rates of differentiated thyroid cancer (DTC, including papillary and follicular thyroid cancer (PTC and FTC, respectively)) and medullary thyroid cancer (MTC), the average annual percentage changes (AAPC) in incidence rates, and 10-year overall survival (OS) were calculated based on data obtained from the nationwide cancer registry (Netherlands Cancer Registry). A total of 839 patients aged 0-24 years had been diagnosed with thyroid carcinoma (PTC: 594 (71%), FTC: 128 (15%), MTC: 114 (14%)) between 1990 and 2019. The incidence of PTC increased significantly over time (AAPC +3.6%; 95%CI +2.3 to +4.8), the incidence rate of FTC showed a stable trend ((AAPC -1.1%; 95%CI -3.4 to +1.1), while the incidence of MTC decreased significantly (AAPC: -4.4% (95%CI -7.3 to -1.5). The 10-year OS was 99.5% (1990-1999) and 98.6% (2000-2009) in patients with DTC and 92.4% (1990-1999) and 96.0% (2000-2009) in patients with MTC. In this nationwide study, a rising incidence of PTC and decreasing incidence of MTC were observed. For both groups, in spite of the high proportion of patients with lymph node involvement at diagnosis for DTC and the limited treatment options for MTC, 10-year OS was high.

Gepubliceerd: Cancers (Basel). 2021;13(20).
Impact factor: 6.639; Q1

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2. **Clinicopathologic predictors of early relapse in advanced epithelial ovarian cancer: development of prediction models using nationwide data**
Said SA, Bretveld RW, Koffijberg H, Sonke GS, Kruitwagen R, de Hullu JA, van Altena AM, Siesling S, van der Aa MA.

Objective: To identify clinicopathologic factors predictive of early relapse (platinum-free interval (PFI) of </=6 months) in advanced epithelial ovarian cancer (EOC) in first-line treatment, and to develop and internally validate risk prediction models for early relapse.
Methods: All consecutive patients diagnosed with advanced stage EOC between 01-01-2008 and 31-12-2015 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery and platinum-based chemotherapy as initial EOC treatment were selected. Two prediction models, i.e. pretreatment and postoperative, were developed. Candidate predictors of early relapse were fitted into multivariable logistic regression models. Model performance was assessed on calibration and discrimination. Internal validation was performed through bootstrapping to correct for model optimism.

Results: A total of 4,557 advanced EOC patients were identified, including 1,302 early relapsers and 3,171 late or non-relapsers. Early relapsers were more likely to have FIGO stage IV, mucinous or clear cell type EOC, ascites, >1 cm residual disease, and to have undergone NACT-ICS. The final pretreatment model demonstrated subpar model performance (AUC = 0.64 [95 %-CI 0.62-0.66]). The final postoperative model based on age, FIGO stage, pretreatment CA-125 level, histologic subtype, presence of ascites, treatment approach, and residual disease after debulking, demonstrated adequate model performance (AUC = 0.72 [95 %-CI 0.71-0.74]). Bootstrap validation revealed minimal optimism of the final postoperative model.
Conclusion: A (postoperative) discriminative model has been developed and presented online that predicts the risk of early relapse in advanced EOC patients. Although external validation is still required, this prediction model can support patient counselling in daily clinical practice.

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Impact factor: 2.984; Q2

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3. **Trends over time in the incidence and use of hormonal therapy in endometrial cancer: a population-based study in the Netherlands**
van Weelden WJ, Bretveld R, Romano A, van Erp S, Engels S, Lalisang R, Pijnenborg J, van der Aa M.

Introduction: According to current guidelines, hormonal therapy may be applied in endometrioid type endometrial cancer as an alternative to surgery for fertility preservation and in medically unfit patients. Since it is unknown how often hormonal therapy is applied, the objective of this study was to investigate trends over time in hormonal therapy use in the background of the overall incidence of endometrial cancer.
Methods: All patients with endometrial cancer (n=48 222) registered in the Netherlands Cancer Registry in the period 1989-2018 were included. European age-standardized incidence rates with corresponding estimated annual percentage change were calculated to describe trends in the incidence of endometrial cancer. The use of hormonal therapy was analyzed in the three periods 1989-1998, 1999-2008, and 2009-2018 for the following sub-groups: primary and adjuvant therapy, International Federation of Gynecology and Oncology (FIGO) stage I-II and III-IV, and by age group.
Results: The European age-standardized incidence rate of endometrioid endometrial cancer peaked in 2004 with a significant increase from 1989 to 2004 (annual percentage change 0.55; 95% CI 0.10 to 0.99, p=0.020) and a subsequent decrease from 2005 to 2018 (annual percentage change -1.79; 95% CI -2.28 to -1.31, p<0.001). The incidence rate of non-endometrioid type endometrial cancer increased significantly in the study period. Hormonal therapy was used in 1482 (3.5%) patients with endometrioid endometrial cancer. Among patients with FIGO stage I aged ≤40 years, hormonal therapy increased from 0% in 1989-1998 to 27% in 2009-2018. Primary hormonal treatment increased from 175 patients (5.5%) to 329 patients (7.8%) in those aged ≥75 years. Adjuvant hormonal treatment was mostly used in advanced stage endometrial cancer.
Conclusions: The use of primary hormonal therapy in endometrioid type endometrial cancer increased over time in patients aged ≤40 years and among elderly patients. The observed trends in the current use of hormonal therapy support the need to study the

effect of hormonal treatment in elderly patients and as adjuvant treatment in advanced stage endometrial cancer.

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Impact factor: 3.437; Q2

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4. **Reproducibility and responsiveness of the Frailty Index and Frailty Phenotype in older hospitalized patients**
Feenstra M, Oud FMM, Jansen CJ, Smidt N, van Munster BC, de Rooij SE.

Background: There is growing interest for interventions aiming at preventing frailty progression or even to reverse frailty in older people, yet it is still unclear which frailty instrument is most appropriate for measuring change scores over time to determine the effectiveness of interventions. The aim of this prospective cohort study was to determine reproducibility and responsiveness properties of the Frailty Index (FI) and Frailty Phenotype (FP) in acutely hospitalized medical patients aged 70 years and older.
Methods: Reproducibility was assessed by Intra-Class Correlation Coefficients (ICC), standard error of measurement (SEM) and smallest detectable change (SDC); Responsiveness was assessed by the standardized response mean (SRM), and area under the receiver operating characteristic curve (AUC).
Results: At baseline, 243 patients were included with a median age of 76 years (range 70-98). The analytic samples included 192 and 187 patients in the three and twelve months follow-up analyses, respectively. ICC of the FI were 0.85 (95 % confidence interval [CI]: 0.76; 0.91) and 0.84 (95% CI: 0.77; 0.90), and 0.65 (95% CI: 0.49; 0.77) and 0.77 (95% CI: 0.65; 0.84) for the FP. SEM ranged from 5 to 13 %; SDC from 13 to 37 %. SRMs were good in patients with unchanged frailty status (< 0.50), and doubtful to good for deteriorated and improved patients (0.43-1.00). AUC's over three months were 0.77 (95% CI: 0.69; 0.86) and 0.71 (95% CI: 0.62; 0.79) for the FI, and 0.68 (95% CI: 0.58; 0.77) and 0.65 (95% CI: 0.55; 0.74) for the FP. Over twelve months, AUCs were 0.78 (95% CI: 0.69; 0.87) and 0.82 (95% CI: 0.73; 0.90) for the FI, and 0.78 (95% CI: 0.69; 0.87) and 0.75 (95% CI: 0.67; 0.84) for the FP.
Conclusions: The Frailty Index showed better reproducibility and responsiveness properties compared to the Frailty Phenotype among acutely hospitalized older patients.

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Impact factor: 3.921; Q1

Totale impact factor: 16.981
Gemiddelde impact factor: 4.245

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 7.358
Gemiddelde impact factor: 3.679