Wetenschappelijk onderzoek in Medisch Spectrum Twente

2018

Inhoudsopgave

Voorwoord

Voor u ligt de 10e editie van het jaarlijkse overzicht van de wetenschappelijke output van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2018. 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 2018 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2018 zijn 240 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is sinds 2009 het op één na hoogste aantal. De gemiddelde impact score van alle artikelen is 5,64. Dit is het hoogste ooit! Vooral de afdeling cardiologie heeft hier sterk aan bijgedragen. In de diverse top 3 klasseringen staat de afdeling cardiologie bijna overal bovenaan. Dit jaar hebben we 3 keer in het absolute toptijdschrift the Lancet gepubliceerd en ook nog vijf keer in Lancet subjournals. Daarnaast wordt nu per publicatie ook weergegeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categoriën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden in 55% in Q1, 31% in Q2, 13% in Q3 en 1% in Q4. Qua promoties was 2018 een prima jaar met 8 promoties in MST.

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 2018 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

Prof. dr. Job van der Palen
Coördinator Wetenschappelijk Onderzoek
Medical School Twente
Medisch Spectrum Twente
E-mail: j.vanderpalen@mst.nl

Overzicht publicaties en de Top 3

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Unieke publicaties	177	190	213	191	212	245	226	216	240
Impact factor	5,12	3,63	3,97	4,38	4,03	5,06	4,70	4,47	5,64

	2015		2016		2017		2018	
Top 3: Aantal publicaties:								
1	Medical School	35	Neurologie	41	Cardiologie	31	Cardiologie	40
2	Neurologie	33	Cardiologie	39	Heelkunde	30	Neurologie	30
3	Heelkunde	31	Medical School	33	Neurologie	28	Longziekten	28
Top 3: Totale impact factor score:								
1	Neurologie	184	Cardiologie	251	Cardiologie	181	Cardiologie	306
2	Heelkunde	178	Neurologie	170	Neurologie	136	Intensive care	197
3	Cardiologie	141	Medical School	135	Heelkunde	116	Longziekten	148
Top 3: Gemiddelde impact factor score:								
1	Gynaecologie	12.5	Gynaecologie	16.7	Klin. Chemie	6.9	MDL	16.6
2	MDL	11.8	Radiotherapie	8.2	Radiotherapie	6.7	Intensive care	14.2
3	Klin. chemie	10.5	Klin. chemie	6.9	Interne gnkd	6.1	Cardiologie	7.7
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:								
1	Neurologie	17	Cardiologie	18	Cardiologie	14	Cardiologie	20
2	Medical School	16	Medical School	16	Longziekten	14	Longziekten	17
3	Cardiologie	15	Neurologie	14	Heelkunde	11	Neurologie	13
	Heelkunde	15					Medical School	13
Top 3: Totale impact factor score als 1e, 2e of laatste auteur:								
1	Cardiologie	65	Cardiologie	110	Cardiologie	63	Cardiologie	178
2	Neurologie	48	Longziekten	57	Neurologie	39	Longziekten	99
3	Reumatologie	46	Neurologie	47	Longziekten	37	Medical School	44
Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:								
1	Gynaecologie	6.0	Cardiologie	6.1	Gynaecologie	4.6	Cardiologie	8.9
2	Pathologie	5.6	Longziekten	5.1	Cardiologie	4.6	Longziekten	5.8
3	Intensive Care	5.4	Microbiologie	4.4	Neurologie	3.9	Microbiologie	5.2

Overzicht aantal publicaties per vakgroep:

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Anesthesiologie	2	1	1	0	0	2	0	1	0
Cardiologie	14	23	33	21	25	28	39	31	40
Gynaecologie	15	7	5	5	7	6	4	13	7
Heelkunde	38	26	24	13	21	31	26	30	20
Intensive Care	2	12	16	11	13	14	13	20	15
Interne Geneeskunde	13	17	15	16	20	17	8	11	24
Kindergeneeskunde	4	7	6	5	3	11	6	6	8
Klinische Chemie	14	10	6	2	6	7	5	5	7
Klinische Farmacie	3	4	4	4	6	8	10	3	8
Klinische Fysica	1	0	0	0	0	2	0	2	1
Klinische Psychologie	0	1	4	3	4	1	0	1	2
KNO	1	1	0	0	1	1	1	0	0
Lab. voor Microbiologie	6	8	5	7	2	2	4	3	1
Longziekten	5	17	10	11	12	16	19	24	28
MDL	5	4	13	6	11	5	9	10	5
Medical School Twente	13	13	27	24	33	35	33	26	24
Mond- kaak-, aangez.chirurgie	1	0	1	3	0	0	1	0	1
Neurochirurgie	0	0	2	1	5	9	5	5	4
Neurologie	23	21	19	34	39	33	41	28	30
Nucleaire Geneeskunde	1	0	1	0	0	2	0	0	0
Oogheelkunde	0	0	0	0	0	0	0	0	1
Orthopedie	2	3	3	0	4	7	5	4	2
Pathologie	6	9	12	1	5	8	4	9	3
Plastische Chirurgie	1	1	0	2	0	2	4	4	13
Psychiatrie	0	0	0	0	0	1	0	4	0
Radiologie	11	6	7	6	11	14	10	4	11
Radiotherapie	4	5	10	3	5	12	10	4	5
Reumatologie	17	25	21	32	20	23	15	7	15
Revalidatiegeneeskunde	5	4	11	7	8	6	0	0	1
Thoraxchirurgie	2	5	3	4	3	2	4	5	4
Urologie	0	0	0	0	0	0	0	0	1

Promoties in MST in 2018
Cardiologie

Ventricular Tachycardia in Repaired Tetralogy of Fallot

Risk Stratification and Invasive Treatment

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdediging op woensdag 6 juni 2018
klokke 15:00 uur

door

Gijsbert Floris Lodewijk Kapel

geboren te Leiderdorp in 1986

Promotor:	Prof. dr. K. Zeppenfeld
Copromotor:	Dr. M.J.M. Jongbloed
Leden promotiecommissie:	Prof. dr. N.A. Blom
	Prof. dr. M.G. Hazekamp
	Prof. dr. B.J.M. Mulder
	Dr. J. Hebe
	Dr. M.F. Scholten

Samenvatting
In dit proefschrift worden de anatomische kenmerken, correctie en epidemiologie van tetralogie van Fallot (TOF) en de uitdagingen van niet-invasieve risico stratificatie en invasieve behandeling van ventrikel tachycardie (VT) in TOF beschreven. Klassieke TOF wordt gekenmerkt door een (sub)pulmonale stenose, ventrikel septum defect (VSD), overrijdende aorta en hieraan secundaire concentrische rechter ventrikel (RV) hypertrofie. De chirurgische correctie bestaat uit het sluiten van het VSD met een patch en het opheffen van de (sub) pulmonale stenose. In het verleden werd de correctie verricht middels een transventriculaire benadering binnen de eerste 10 jaar van het leven. De transventriculaire benadering houdt in dat de chirurgische correctie wordt uitgevoerd via een incisie in de RV. Tegenwoordig wordt de correctie verricht via een transatriale-transpulmonale benadering in het eerste levensjaar. De transatriale-transpulmonale benadering houdt in dat de chirurgische correctie wordt uitgevoerd via een incisie in het rechter atrium en de arteria pulmonalis. De goede chirurgische technieken hebben geresulteerd in een verbetering van de overleving, met verdubbeling van de prevalentie van volwassenen met TOF tussen 1980 en 2010, namelijk van 0.1 naar 0.2 per 1000 volwassenen. Er wordt verwacht dat de prevalentie van volwassen met TOF nog zelfs verder zal toenemen. Volwassenen met TOF hebben een 29 maal zo hoog risico om plots te overlijden ten op zichten van gezonde leeftijdsgenoten. De prevalentie van ventriculaire ritmestoornissen in TOF is met 15% behoorlijk hoog. Deze hoge prevalentie werd geobserveerd in een cohort van 556 volwassen TOF patiënten met een gemiddelde leeftijd van 37±12 jaar. Tachtig procent van deze ventriculaire ritmestoornissen zijn snelle monomorfe macro reentry ventrikel tachycardieën met een gemiddelde snelheid van 213 slagen per minuut en gerelateerd aan anatomische isthmuses. Een anatomische isthmus is een smal stukje hartspierweefsel dat aan beide kanten wordt begrensd door anatomische structuren. De anatomische isthmuses in TOF zijn inherent aan het congenitale defect of het gevolg van de chirurgische correctie en worden begrensd door klepringen, patch materiaal en/of RV incisies. Het voorspellend vermogen van niet-invasieve risicofactoren voor VT is beperkt. Een beperkt aantal cases en zeer kleine cohort studies hebben aangetoond dat radiofrequente katheter ablatie van VT in volwassenen met TOF een aantrekkelijk optie is, waarbij substraat mapping het mogelijk maakt om snelle en hemodynamische instabiele VT te ableren. Ableren houdt in dat een klein stukje hartspierweefsel wordt opgewarmd of wordt bevroren waardoor littekenweefsel ontstaat. Het geableerde hartspierweefsel kan vervolgens geen elektriciteit meer geleiden. In het geval van het ableren van een VT wordt het kritieke onderdeel van het VT circuit geableerd waardoor het VT circuit wordt onderbroken.

In **hoofdstuk 2** werden de eigenschappen van de anatomische isthmus (breedte, lengte en geleidingssnelheid) gemeten in 74 gecorrigeerde TOF patiënten, die risico lopen op VT, met het gebruik van elektro anatomische mapping tijdens sinus ritme. Elektro anatomische mapping houdt in dat de elektrische activatie op meerdere plekken in het hart wordt gemeten waarvan vervolgens een kaart, een map, wordt gemaakt. Een elektro anatomische map geeft vervolgens een duidelijk overzicht van de elektrische activatie van het hart. Alle TOF patiënten hadden ten minste 1 anatomische isthmus en 28 patiënten waren induceerbaar voor 41 VT. De anatomische isthmus van de 28 patiënten met VT ten op zichten van de 46 patiënten zonder VT waren smaller, langer en hadden een lagere geleidingssnelheid. Zevenendertig van de 41 VT waren gerelateerd aan een anatomische isthmus. Alle

VT gerelateerde anatomische isthmuses hadden een geleidingssnelheid van <0.5 m/s (gedefinieerd als een traag geleidende anatomische isthmus). Daarentegen, 87 van 89 anatomische isthmuses van de 46 patiënten zonder VT hadden een geleidingssnelheid van ≥0.5ms. Alle 62 patiënten zonder traag geleide anatomische isthmus, 44 patiënten bij de eerste beoordeling en 18 patiënten na ablatie, hadden geen VT tijdens een periode van 262 patiëntjaren (gemiddeld 5±2 jaar per patiënt). Eerdere studies in patiënten met vergelijkbare risicofactoren en een ICD (primaire en secundaire preventie) hebben een VT prevalentie van 8-10% per jaar aangetoond. Deze prevalentie was gelijk in ons cohort van TOF patiënten die ontslagen werden met een traag geleidende anatomische isthmus. Dit bevestigt de sterke associatie tussen traag geleidende anatomische isthmus en VT in TOF.

Hoofdstuk 3 beschrijft de directe en lange termijn uitkomst van radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT met behulp van substraat mapping in een grote groep van 34 patiënten met een gecorrigeerde aangeboren hart afwijking. Achtentwintig van de 34 patiënten hadden TOF. Deze 34 patiënten waren induceerbaar voor snelle VT met een mediane cyclus lengte van 295ms (inter kwartiel: 242 – 346). Acuut succes, gedefinieerd als bidirectionele blokkade van de anatomische isthmus die gerelateerd was aan de VT en niet-induceerbaarheid van VT na ablatie, werd behaald in 25 patiënten (74%). Alle 25 patiënten met acuut succes hadden geen VT tijdens follow-up (4±2 jaar), slechts 1 patiënt met hartfalen kreeg een ICD schok voor ventrikel fibrilleren. Daarentegen hadden 4 van 9 patiënten zonder acuut succes een VT recidief.

In het cohort van de 28 TOF patiënten, die radiofrequente katheter ablatie van anatomische isthmus gerelateerde VT ondergingen (**Hoofdstuk 3**), was VT ablatie in 11 patiënten niet succesvol na een rechtszijdige benadering. De VT was in 8 van de 11 patiënten gerelateerd aan een septale anatomische isthmus. Een septale anatomische isthmus is gelegen tussen beide ventrikels. Een linkszijdige benadering werd niet verricht in 4 patiënten vanwege procedure tijd, conditie van de patiënt en/of aortaklep pathologie. De overige 4 patiënten die wel een linkszijdige procedure ondergingen werden beschreven in **hoofdstuk 4**. Radiofrequente katheter ablatie in de aortawortel termineerde VT en resulteerde in acuut succes in 3 patiënten. In 1 patiënt met reeds een biventriculaire ICD werd diastolische activiteit gezien ter plaatse van de His-bundel waar ablatie resulteerde in acuut succes en zoals verwacht in totaal AV-blok. Rechtszijdige ablatie lukte in deze patiënten waarschijnlijk niet vanwege hypertrofie van het myocard, een overliggende pulmonalis homograft of VSD-patch. Alle vier patiënten met een linkszijdige procedure hadden geen VT tijdens follow-up (2±1 jaar).

Het **vijfde hoofdstuk** beschrijft de bijdrage van het VT substraat aan QRS duur in de afwezigheid en aanwezigheid van een rechter bundeltak blok (RBTB) in een cohort van 78 TOF patiënten die VT inductie en elektro anatomische mapping tijdens sinus ritme ondergingen. Vierentwintig patiënten waren induceerbaar voor VT, 22 van de 24 patiënten met VT hadden een traag geleidende anatomische isthmus. Een traag geleidende anatomische isthmus werd in slechts 2 van de 54 patiënten zonder VT geobserveerd. De geleidingssnelheid van de anatomische isthmus van patiënten met VT was, zoals verwacht, lager. Er was geen verschil in RV geleidingssnelheid en RV grootte tussen patiënten met en zonder VT. In de 11 patiënten met een smal QRS complex was er geen verschil in QRS duur tussen patiënten met en zonder VT.

Echter, de totale RV activatie tijd en de RV activatie na het einde van het QRS complex waren beide langer in patiënten met een smal QRS complex en VT. De RV activatie na het einde van het QRS complex was gelokaliseerd ter plaatse van de traag geleidende anatomische isthmus, derhalve droeg deze niet bij aan het oppervlakte ECG. In de 67 patiënten met RBTB waren zowel de totale RV activatie tijd als de QRS duur langer in RBTB patiënten met VT ten opzichte van RBTB patiënten zonder VT. RBTB patiënten met een QRS duur ≥150ms ten opzichte van <150ms hadden een 14 maal zo hoge kans op induceerbare VT.

Het laatste hoofdstuk (**Hoofdstuk 6**) beschrijft de invloed van de correctie zelf, methode van de correctie en moment van de correctie op de aanwezigheid en eigenschappen van de anatomische isthmus in een cohort van 142 post mortem TOF harten (84 gecorrigeerd, 58 ongecorrigeerd). Anatomische isthmus 1, de isthmus tussen de tricuspidalis annulus en een RVOT patch/RV incisie, en anatomische isthmus 3, de isthmus tussen de pulmonalis annulus en het VSD, waren de meest prevalente anatomische isthmus en aanwezig in 99% van de post mortem TOF harten. De huidige transatriale-transpulmonale methode ten opzichte van de transventriculaire methode zorgde ervoor dat anatomische isthmus 2, de isthmus tussen de pulmonalis annulus en een RVOT patch/RV incisie, niet meer aanwezig was en was geassocieerd met een dikkere isthmus 1. De transatriale-transpulmonale methode onder de leeftijd van 1 jaar ten opzichte van ≥1 jaar resulteerde in het gebruik van een kleinere RVOT-patch, die uiteindelijk zou kunnen resulteren in een bredere isthmus 1 op het moment dat het hart volgroeid is. De methode en het moment van correctie hadden geen invloed op de aanwezigheid en dimensies van isthmus 3. De spreiding van isthmus 3 dimensies (dikte en breedte) was groot op alle leeftijden in zowel gecorrigeerde als ongecorrigeerde post mortem TOF harten. De sterke associatie tussen de breedte en dikte van isthmus 3 en de bekende klinische associatie tussen een smalle anatomische isthmus en trage geleiding welke VT faciliteren, hebben belangrijke implicaties voor behandeling van huidige TOF patiënten. Een smalle isthmus 3 is mogelijk nog het enige substraat voor VT in TOF in het huidige chirurgische tijdsvlak.

Conclusies

De prevalentie van volwassenen met TOF is 0.2 per 1000 volwassenen en zal verder toenemen vanwege de goede chirurgische resultaten. Volwassenen met TOF hebben desalniettemin een 29 maal hoger risico om plotseling te overlijden ten opzichte van gezonde leeftijdsgenoten. De prevalentie van ventriculaire ritmestoornissen in volwassen TOF patiënten is hoog met 15%. Ventriculaire ritmestoornissen in TOF zijn een belangrijke oorzaak voor morbiditeit en mortaliteit bij volwassenen. Het merendeel van deze ventriculaire ritmestoornissen zijn monomorfe VTs. Het dominante substraat voor VT in TOF zijn traag geleidende anatomische isthmuses die geïdentificeerd kunnen worden met elektro anatomische mapping tijdens sinus ritme waardoor individuele risicostratificatie en preventieve ablatie mogelijk is. Radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT in corrigeerde aangeboren hartafwijkingen kan worden uitgevoerd met een hoog acuut succes, met name in TOF. In het geval dat rechtszijdige radiofrequente katheter ablatie van een septale anatomisch isthmus gerelateerde VT in TOF niet succesvol is, kan linkszijdige ablatie veilig en succesvol worden verricht. Op het moment dat bidirectioneel blok bereikt kan worden van de anatomische isthmus die de kritieke isthmus van de VT bevat, kan radiofrequente katheter ablatie van anatomisch

isthmus gerelateerde VT als curatief worden beschouwd en kan zelfs in patiënten met een behouden hartfunctie een ICD implantatie voorkomen. De traag geleidende anatomische isthmuses zijn een belangrijke link tussen de QRS duur en het risico op VT in TOF patiënten. De traag geleidende anatomische isthmus in TOF patiënten met RBTB verlengen namelijk de totale RV activatie tijd en QRS duur. Een smal QRS complex in TOF sluit echter VT en de aanwezigheid van een traag geleidende anatomische isthmus niet uit. De meest prevalente aritmogene isthmus in TOF is de isthmus tussen de pulmonalis annulus en het VSD, namelijk isthmus 3. Isthmus 3 wordt niet beïnvloed door de correctie zelf, niet door methode van correctie en niet door het moment van correctie. Het is daarom de verwachting dat anatomische isthmus 3 de meest aritmogene anatomische isthmus zal blijven in toekomstige TOF patiënten.

Toekomstperspectief

Het dominante substraat voor VT in TOF zijn traag geleidende anatomische isthmuses die geïdentificeerd kunnen worden met elektro anatomische mapping tijdens sinus ritme waardoor individuele risicostratificatie en preventieve ablatie mogelijk is. Een succesvolle radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT in TOF kan als curatief worden beschouwd en kan bij behouden hartfunctie zelfs ICD implantatie voorkomen. Op dit moment is het onbekend wat het beste moment is voor invasieve risicostratificatie en het is onbekend of één procedure voldoende is. Toekomstige studies zouden daarom gericht moeten worden op het ophelderen van het mechanisme achter het ontstaan van trage geleiding van de anatomische isthmus in TOF om op die manier het beste moment vast te stellen voor invasieve risicostratificatie en/of preventieve ablatie mogelijk tijdens her-operatie of zelfs tijdens de initiële correctie.

Cardiologie

Percutaneous Coronary Interventions
from Various Perspectives

Dissertation

to obtain
the degree of doctor at the University of Twente
on the authority of the rector magnificus,
Prof. dr. T.T.M. Palstra,
on account of the decision of the graduation committee,
to be publicly defended
on Thursday 13 December 2018 at 14.45

by

Marlies Melanie Kok

Born on 13 October 1988
In Zevenaar, the Netherlands

Supervisor: Prof. dr. C. van Birgelen
Co-supervisor: Dr. C.J.M. Doggen

Members:

Prof. dr. J.G. Grandjean
Prof. dr. R.H. Geelkerken
Prof. dr. R.J. de Winter
Prof. dr. J.C.A. Hoorntje
Prof. dr. A.H.E.M. Maas
Prof. dr. P.W. Serruys

Samenvatting
In de afgelopen 40 jaar heeft er in het vak interventie cardiologie een constante ontwikkeling plaatsgevonden. Het ontwerp van nieuwe medicijn-afgevende stents is voortdurend verbeterd om nadelige uitkomsten na dotterbehandelingen te beperken en om de veiligheid en effectiviteit van de behandeling te verbeteren. Bij de nieuwe generatie medicijn-afgevende stents werd het metalen stent platform steeds flexibeler gemaakt om het plaatsingsgemak te verbeteren en ervoor te zorgen dat de hechting van de stent aan de vaatwand werd geoptimaliseerd, zodat de stents ook veilig konden worden gebruikt in complexere afwijkingen in de kransslagvaten.

Nieuwe ontwikkelingen op stentniveau zijn constant in beweging, dit heeft ertoe geleid dat er een overdaad aan korte-termijn uitkomsten van klinische onderzoeken met nieuwe stents is, terwijl er een relatieve schaarste bestaat van de langere termijn veiligheid en effectiviteit van deze stents. Hoewel de medische wereld wellicht in staat is om deze ontwikkelingen in rap tempo op te volgen, blijft het belangrijk om klinisch onderzoek voort te zetten naar de langere termijn resultaten van deze stents en deze ook te rapporteren, aangezien de patient voor de rest van zijn of haar leven vast zit aan die ene stent die is geïmplanteerd ten tijde van zijn of haar interventie.

Dit proefschrift toont de impact van verschillende type stents aan op de klinische uitkomsten in een patiëntenpopulatie die de dagelijkse praktijk weerspiegelt, en richt zich in het bijzonder op subgroepen van patienten die vaak onderbelicht zijn in klinische studies.

Verder worden de nieuwe ontwikkelingen besproken van stents die deels biologisch afbreekbaar zijn doordat ze een polymeer laag bevatten welke in de loop van tijd oplost nadat het zijn medicijn heeft afgegeven, alsmede de nieuwe technologische ontwikkelingen van duale therapie in een stent.

Hoofdstuk 1 geeft een korte samenvatting van de ontwikkeling van medicijn afgevende stents en de impact van nieuwe generatie medicijn afgevende stents op klinische uitkomsten. Daarnaast wordt het belang toegelicht van het onderzoek in specifieke subgroepen patienten die een verhoogd risico lopen op het krijgen van een ongewenst event; patienten met (ontwikkelende) diabetes en vrouwen die tot dusver werden behandeld zoals hun mannelijke tegenpolen, maar die in feite zeer verschillend zijn.

Deel I: Klinische uitkomsten van nieuwe generatie medicijn-afgevende stents

Hoofdstuk 2 rapporteert de 3-jaars resultaten van twee nieuwe generatie medicijnafgevende stents met permanente aanwezige polymeren; de Resolute Integrity stent en de Promus Element stent. Deze studie werd verricht in een brede patiëntenpopulatie van 1,811 patiënten die deelnamen aan de DUTCH PEERS studie. De 3-jaars follow-up was beschikbaar in 1,807 (99.8%) patiënten. De incidentie van het gecombineerde primaire eindpunt target vessel failure was laag en vergelijkbaar voor beide stents (10.7% vs. 10.3%). De individuele componenten van dit eindpunt waren eveneens laag en vergelijkbaar voor beide groepen, bovendien bleek het optreden van een trombus in de stent zeer zeldzaam.

Hoofdstuk 3 rapporteert de 5-jaars bevindingen van de DUTCH PEERS studie waarin de Resolute Integrity stent werd vergeleken met de Promus Element stent. Het late optreden van een trombus in de geïmplanteerde stent was er laag en vergelijkbaar voor beide stents (definitieve stent trombose of waarschijnlijke stent trombose was slechts aanwezig bij 1.5% en 1.3% van de totale studie populatie). Dit hoofdstuk bevestigt de veiligheid en effectiviteit van beide stents met een permanente polymeer, in een brede patienten populatie, tot 5 jaar na de implantatie van de stent.

Hoofdstuk 4 toont de eerste uitkomsten van de 1-jaars follow-up van de BIO-RESORT studie. De BIO-RESORT studie is een grote, gerandomiseerde, onderzoeker geïnitieerde, multicenter studie die de veiligheid en effectiviteit onderzocht van twee nieuwe stents met een biologisch afbreekbare polymeer (de everolimus-afgevende Synergy stent en de sirolimus-afgevende Orsiro stent) versus een veelgebruikte nieuwe generatie stent met een permanente polymer de zotarolimus-afgevende Resolute Integrity stent. Na 1 jaar follow-up bleken beide stents met zeer dunne stent struts niet ondergeschikt te zijn aan de al langer bekende Resolute Integrity stent met een permanente polymeer.

Hoofdstuk 5 onderzocht de 2-jaars veiligheid van de twee stents met een biologisch afbreekbare polymeer in vergelijking met een permanent aanwezige polymeer. Ook op 2 jaar bleken deze stents niet ondergeschikt aan het referentie model. Bovendien bleek uit een de landmark analyse dat de behandeling met de biologische-polymeer bedekte sirolimus-afgevende Orsiro stent een relatief lager risico gaf op het opnieuw ondergaan van een revascularisatie na 1 jaar in vergelijking met het referentie model de Resolute Integrity met de permanente polymeer.

Hoofdstuk 6 introduceert de rationale en het ontwerp van de BIONYX studie. De BIONYX studie is een onderzoeker geïnitieerde, internationale, gerandomiseerde studie waarbij patiënten uit 7 studiecentra uit zowel Nederland, Belgie als Israël werden geïncludeerd. Randomisatie vond plaats na stratificatie voor geslacht en de aanwezigheid van diabetes waarna patiënten werden toegewezen tot de nieuwere generatie zotarolimus-afgevende Resolute Onyx stent met een permanente polymeer versus de sirolimus-afgevende Orsiro stent met de biologisch afbreekbare polymeer die ook werd gebruikt in de BIO-RESORT trial. Het doel van de BIONYX studie is te onderzoeken of de veiligheid en effectiviteit na 1 jaar vergelijkbaar is in een brede patiënten populatie.

Hoofdstuk 7 rapporteert de primaire uitkomst van de 1-jaars resultaten van de BIONYX studie. De nieuwe Resolute Onyx stent was niet ondergeschikt aan de Orsiro stent wat betreft veiligheid en effectiviteit op 1 jaar follow-up. BIONYX is de eerste gerandomiseerde studie die deze Resolute Onyx stent onderzoekt.

Hoofdstuk 8 beschrijft een propensity score gematchte analyse waarin de COMBO-stent met een gecombineerde populatie van patiënten werd vergeleken die waren behanded in de DUTCH PEERS studie met een Resolute Integrity en Promus Element stent. De COMBO-stent combineert een sirolimus-afgevende laag met een endotheel progenitorbevattende laag, wat als doel heft om het herstel van de vaatwand na stentplaatsing te bevorderen. Na propensity score matching werd een populatie van 771 patiënten die waren behandeld met de COMBO-stent vergeleken met 771 patiënten die waren behandeld met de Resolute Integrity of Promus Element

stent. Twee jaar follow-up toont geen significant verschil in *target leasie failure* tussen beide groepen. Dit hoofdstuk toont dus aan dat in een propensity gematcht cohort er geen significant verschil bestaat tussen patiënten die waren behandeld met de COMBO-stent versus patiënten behandeld met de Resolute Integrity of Promus Element stent.

Deel II: Impact van diabetes op klinische uitkomsten na coronair interventies

Hoofdstuk 9 beschrijft de BIO-RESORT *Silent Diabetes* studie; de eerste studie op grote schaal die in patiënten zonder bekende diabetes een orale glucosetolerantie test heeft afgenomen nadat zij een dotterbehandeling hadden ondergaan. De proportie van patiënten uit deze brede populatie met een gestoord glucose metabolisme in de vorm van stille diabetes of prediabetes, is erg hoog. Het screenen van deze patiënten creëert de kans om tijdig een risico stratificatie te maken, aangezien zij slechtere uitkomsten hebben na dotterbehandeling met medicijn-afgevende stents dan patiënten die geen gestoorde glucose metabolisme hebben.

Hoofdstuk 10 toont dat het routinematig bepalen van HbA1c en nuchtere glucoses in een brede patiëntenpopulatie die werd verwezen voor een dotterbehandeling met medicijn-afgevende stents kan helpen in het identificeren welke individuen een verhoogd risico hebben op het krijgen van een nadelige uitkomst na hun behandeling. Het strikt vervolgen van deze patiënten kan helpen om de verdere ontwikkeling naar diabetes te voorkomen en de daarmee gepaard gaande ontwikkeling van coronairlijden.

Deel III: Sexe verschillen bij patiënten met obstructief coronairlijden

Hoofdstuk 11 rapporteert de bevindingen van een gepoolde analyse op patiënten-niveau van de gerandomiseerde TWENTE en DUTCH PEERS studies waarin patiënten werden behandeld met nieuwere generatie medicijn-afgevende stents met een permanente polymeer. Vrouwen hadden een statistisch significant hogere prevalentie van klinisch relevante pijn op de borst, ondanks dat er geen verschil was tussen mannen en vrouwen in het krijgen van een cardiovasculair event. Het opnieuw optreden van pijn op de borst na een dotterbehandeling bij vrouwen, zonder dat er ook een toename wordt gezien van een nieuwe revascularisatie, suggereert dat dit deels wordt verklaard door mechanismen anders dan een obstructie van de grote coronairen, zoals bijvoorbeeld dysfunctie van de microvasculatuur.

Hoofdstuk 12 onderzoekt het voorkomen van herhaalde angiografie die werd verricht na opnieuw optreden van pijn op de borst klachten in vrouwen ten opzichte van mannen die warden behandeld met dunne strut medicijn-afgevende stents in de BIORESORT studie. Vrouwen ervaren meer pijn op de borst op zowel 1 jaar als 2 jaar followup, tevens bezochten zij significant vaker de Eerste Harthulp, en kregen vaker opnieuw een angiografie in het tweede jaar na hun stentplaatsing. Mannen hadden daarentegen significant vaker een *target vessel revascularisatie*, terwijl de (cardiovasculaire) mortaliteit onder vrouwen hoger was.

Deel IV: Patiënt preferenties in de interventie cardiologie

Hoofdstuk 13 beschrijft de resultaten van de PAPAYA studie die aantoonde dat de meerderheid van de patiënten die meedoet aan een klinische studie de voorkeur geeft aan het invullen van een vragenlijst die zij via de post hadden ontvangen, en suggereert dat een follow-up methode via email waarschijnlijk zinvoller is in een populatie waarvan de gemiddelde leeftijd lager is dan die van de cardiologie patiënten die voor een dotterbehandeling komen. Op het moment lijkt een geïndividualiseerde aanpak voor follow-up in klinische studies de meest efficiënte manier. Artsen en onderzoekers moeten ernaar streven om hun follow-up methoden aan te passen op de sociale achtergrond van hun patiënten, het opleidingsniveau en de logistiek, om ervoor te zorgen dat patiënten betrokken blijven in klinische follow-up programma's na medische interventies.

Hoofdstuk 14 toont de resultaten van de PREVAS studie waarin patiënten preferenties werden onderzocht voor de vaattoegang bij percutane interventies. Patiënten hadden een sterke voorkeur voor factoren zoals een laag bloedingsrisico en het snel ambulant zijn, factoren die in lijn zijn met de transradiale aanpak bij een dotterbehandeling. Eerdere ervaring met een bepaalde vasculaire toegang heeft een enorme invloed op de directe patiënten preferentie, maar wanneer patiënten ervaring hadden met zowel de transradiale als de transfemorale aanpak, leidde dit vaker tot een uitgesproken voorkeur voor de transradiale benadering.
De meeste patiënten stellen het maken van een gedeelde beslissing op prijs wanneer het gaat om vasculaire toegang bij de dotterbehandeling, waarbij de meerderheid van de patiënten vindt dat deze gedeelde verantwoordelijkheid evenredig verdeeld moet zijn tussen de patiënt en de cardioloog.

Hoofdstuk 15 beschrijft de PRECORE studie waarin patiënten perspectieven werden onderzocht over het gebruik van gecombineerde eindpunten in klinische studies, alsmede de utiliteit die patiënten geven aan de mogelijke nadelige uitkomsten van een behandeling. De studie toonde aan dat patiënten een groter belang hechten aan het voorkomen van een 'hard' cardiovasculair event zoals dood, een grootschalige beroerte met blijvende invaliditeit of een groot hartinfarct, dan op events zoals het opnieuw moeten ondergaan van een revascularisatie procedure. Meer dan de helft van de patiënten gaf aan dat het voorkomen van een invaliderende beroerte belangrijker voor ze was dan het voorkomen van overlijden, wat suggereert dat veel patiënten het verlies van mobiliteit en zelfstandigheid ernstiger vinden dan overlijden. De meerderheid van de patiënten in de studie gaf aan dat ze het niet eens zijn met de huidige aanpak van klinische studies waarin individuele componenten van een gecombineerd eindpunt allen even zwaar meewegen.

Conclusies
Nieuwe generatie medicijn-afgevende stents tonen uitstekende resultaten wat betreft veiligheid en effectiviteit in studies met brede patiënten populaties, die een goede afspiegeling zijn van de dagelijkse populatie uit de klinische praktijk. De verfijningen in de stent ontwerpen hebben ertoe geleid dat de klinische uitkomsten nog verder geoptimaliseerd werden en er nog maar weinig nadelige uitkomsten optreden na dotterbehandeling van afgesloten of vernauwde kransslagaders van het hart.

Aangezien deze nadelige uitkomsten steeds minder vaak voorkomen worden verschillen tussen stents lang niet altijd meer duidelijk in studies die slechts korte-termijn resultaten rapporteren, maar openbaren deze verschillen zich pas later na meerdere jaren, of in een andere vorm van de geanticipeerde uitkomstmaten. De lange termijn resultaten waarbij patiënten tot 5 jaar na de procedure werden gevolgd, laten zien dat meer dan de helft van de events plaats vindt na het eerste jaar. Dit onderstreept het belang om ook na het bereiken van de primaire uitkomstmaat op 1 jaar, de patiënten te volgen om nadelige cardiovasculaire uitkomsten aan te tonen die mogelijkerwijs toe te bedelen zijn aan de gebruikte stent.

Subgroepen zoals diabetespatiënten of patiënten met prediabetes verdienen speciale aandacht, aangezien het aandeel van deze groep in de populatie patiënten die een dotterbehandeling moeten ondergaan aanzienlijk is en in de toekomst alleen maar verder zal toenemen. Deze patiënten met een gestoord glucose metabolisme hadden een significant verhoogd risico op het ontwikkelen van nadelige uitkomsten na een dotterbehandeling zoals het risico op overlijden, het krijgen van een hartinfarct, of het opnieuw moeten ondergaan van een dotterbehandeling of operatie. Het screenen van een abnormaal glucose metabolisme onder dotterpatiënten die niet bekend zijn met diabetes wordt geadviseerd, zodat patiënten die een verhoogd risico lopen tijdig kunnen worden geidentificeerd. Er is daarmee een grote gezondheidswinst te behalen door te voorkomen dat patiënten diabetes mellitus gaan ontwikkelen.

Als de gemeenschap van interventiecardiologen een blijvende impact wil maken op de levens van patiënten met kransslagaderlijden is een gestructureerde aanpak nodig om de behandeling na de dotterprocedure te optimaliseren. Restklachten van pijn op de borst na de dotterbehandeling maken dat patiënten zich gehinderd voelen in het dagelijks leven, wat resulteert in het ervaren van een hogere ziektelast. Voornamelijk vrouwen geven aan meer pijn op de borst te ervaren en daarmee vaker een Eerste Harthulp te bezoeken, terwijl zij minder vaak opnieuw een dotterprocedure of operatie ondergaan dan mannen. Bewustwording van sekseverschillen neemt toe en is cruciaal om ervoor te zorgen dat we effectieve zorg kunnen leveren aan alle patiënten.

Om ervoor te zorgen dat patiënten betrokken zijn in de behandeling van hun ziekte, en in het onderzoek naar hun ziekte, moet meer aandacht worden besteed aan de voorkeuren van een patiënt, patiënt gerapporteerde uitkomsten in studies en aan het verschaffen van geïndividualiseerde zorg.

Interne Geneeskunde

Metformin
Pharmacogenetics and Metabolic Effects

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht
op gezag van de Rector Magnificus, prof.dr. R.M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op maandag 9 juli 2018 om 12.00 uur

door

Mattijs Out

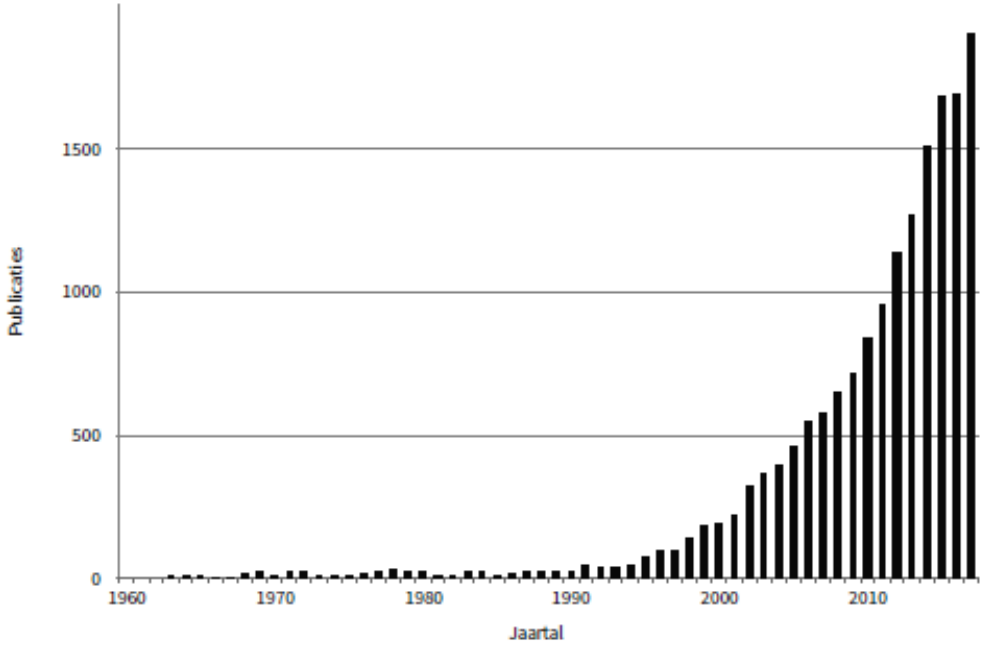
Geboren op 10 april 1976 te Krimpen aan den IJssel

Promotor:	prof.dr. C.D.A. Stehouwer
Copromotor:	dr. A. Kooy
Beoordelingscommissie:	prof.dr. N.C. Schaper
	dr. M.C.G.J. Brouwers
	prof.dr. H.J. Lambers Heerspink
	prof.dr. J.W.M. Muris
	dr. E. Serne

Samenvatting

Achtergrond en historisch perspectief

Zestig jaar nadat metformine voor het eerst werd voorgeschreven voor diabetes[1] en twintig jaar na de publicatie van de resultaten van de United Kingdom Prospective Diabetes Study (UKPDS)[2] is metformine de eerste keus voor medicamenteuze behandeling voor patiënten met diabetes mellitus type 2.[3] Metformine wordt jaarlijks meer dan honderd miljoen keer voorgeschreven. Zelfs na zestig jaar is er nog veel te ontdekken aan de effecten van metformine en de manier waarop metformine werkt. Het aantal jaarlijkse wetenschappelijke publicaties over metformine neemt nog altijd toe, tot bijna tweeduizend in 2017 (figuur 1).



Figuur 1. Aantal jaarlijkse publicaties over metformine (bron: PubMed).

De HOME studie

Het studieprotocol voor de Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME) studie werd eind jaren negentig geschreven. Destijds golden sulfonylureumderivaten nog als de eerste keus bij behandeling van diabetes mellitus type 2. In Nederland werd metformine in 1999 voor het eerst opgenomen als voorkeursbehandeling in de richtlijnen, maar alleen voor patiënten met een body mass index boven de 27 kg/m^2.[4] Pas in 2006 werd metformine in een herziening van de Nederlandse richtlijnen genoemd als eerste keuze voor medicamenteuze behandeling bij alle patiënten met diabetes mellitus type 2.[5] Het primaire doel van de HOME studie was om te onderzoeken of metformine beschermt tegen microvasculaire of macrovasculaire schade bij diabetes mellitus type 2. Dit is het derde proefschrift dat gebaseerd is op de resultaten van de HOME studie, met een vierde op komst. In 2004 publiceerde Michiel Wulffele de kortetermijnresultaten van metformine op glucoseregulatie, insulinebehoefte en vitamine B12.[6] In 2010 publiceerde Jolien de Jager haar proefschrift, waarin ze de langetermijneffecten van metformine beschreef op glucoseregulatie, microvasculaire en macrovasculaire eindpunten en vitamine B12-gehalte.[7] De HOME studie is wereldwijd nog altijd de

grootste lange termijn placebogecontroleerde studie met metformine bij diabetes mellitus type 2. Een recente meta-analyse noemde de studie als het onderzoek met het laagste risico op bias van de geincludeerde metformine onderzoeken.[8] Bovendien was de HOME studie het eerste gerandomiseerde langeter– mijnonderzoek naar de effecten van metformine op vitamine B12.[9]

Het Metformin Genetics Consortium (MetGen)
Gedurende het laatste decennium is de aandacht van het onderzoek met metformine verschoven van glucoseregulatie naar andere onderwerpen zoals de effecten van metformine in de darm,[10] de mogelijke rol van metformine bij preventie en behandeling van kanker[11] en zelfs veroudering.[12] Bovendien er is vooruitgang geboekt bij het ontrafelen van de werkingsmechanismen van metformine.[13] Niettemin is de aanzienlijke variabiliteit in reactie op metformine nog steeds niet volledig begrepen. Genetische variatie speelt een belangrijke rol. Zo kan 34% van de variatie in HbA1c-reductie verklaard worden door genetische verschillen.[14] De resultaten van studies naar polymorfismen zijn echter teleurstellend, omdat verschillende onderzoeken eerder gevonden associaties niet konden bevestigen, mede doordat deze studies vaak beperkt werden door kleine aantallen patiënten en varieteit in etniciteit. Daarom werd in 2013 tijdens een internationale workshop over de farmacogenetica van metformine een voorstel gedaan om een “metformine-consortium” in het leven te roepen, bestaande uit meerdere onderzoeksgroepen met inclusie van studies met patiënten van verschillende afkomst.[15] De eerste contacten werden gelegd tijdens een bijeenkomst op het jaarlijkse congres van de European Association for the Study of Diabetes (EASD) in 2013 in Barcelona, direct na een posterpresentatie van de resultaten van de farmacogenetische analyse van de HOME-studie.[16] Een maand later werd het MetGen Consortium opgericht. MetGen wordt geleid door prof.dr. Ewan Pearson van de universiteit van Dundee en prof. dr. Kathy Giacomini van de universiteit van Californie, San Francisco. Op het moment van schrijven bestaat het consortium uit een verzameling van talrijke cohorten met meer dan 10.000 personen, een aantal dat nog altijd toeneemt.[17]

Huidige bevindingen
Metformine verlaagt niet alleen het vitamine B12-gehalte, maar verhoogt ook de serumspiegels van methylmalonzuur (MMA) (HOME-studie)
Eerdere analyse van de HOME studie toonde aan dat metformine geassocieerd is met een verlaging van serum B12, progressief in de tijd en vergezeld gaand met een toename van het serum homocysteine, wat suggestief is voor B12-tekort op weefselniveau. De huidige studie toonde aan dat metformine na 52 maanden niet alleen het serum-B12 verlaagde, maar ook het MMA verhoogde: metformine verhoogde het MMA aan het einde van de studie in vergelijking met placebo met een gemiddeld verschil van 0,039 µmol/l (95% betrouwbaarheidsinterval 0,019 tot 0,055). Uitgedrukt in gramjaren metformine nam het MMA toe met 0,006 µmol/l per gram jaar (summary mean; 95% betrouwbaarheidsinterval 0,003 tot 0,009, in vergelijking met placebo).

De toename van MMA bij metforminegebruikers gaat gepaard met een significante verslechtering van een gevalideerde score voor klinische neuropathie (HOME-studie)
Gedurende 4,3 jaar leidde metformine in vergelijking met placebo niet tot meer neuropathie. Echter, mediation-analyse toonde aan dat dit nuleffect van metformine op de neuropathie kan worden verklaard door een gunstig effect op neuropathie door

verlaging van het HbA1c (een afname van de neuropathiescore van 0,04 x 0,50 = 0,020 per metformine gram jaar) en een nadelig effect door het verhogen van MMA (een toename van de neuropathiescore van 0,04 x 1,06 = 0,042 per metformine gramjaar). Dit betekent dat de schadelijke effecten van een dalend B12-gehalte wordt geneutraliseerd door de beschermende effecten van metformine door verbetering van de glucoseregulatie.

Metformine heeft geen effect op vitamine D-spiegels (HOME-onderzoek)
Metformine had in vergelijking met placebo geen effect op de 25(OH)D-spiegels, gecorrigeerd voor seizoenseffecten gedurende 16 maanden (coefficient: 1,002 per maand, multiplicatief model, 95% betrouwbaarheidsinterval: 0,998 tot 1,006). Metformine was geassocieerd met een kleine toename van 25(OH)D2 (coefficient: 1,012 per maand, 95% betrouwbaarheidsinterval1,003 tot 1,021). 25(OH)D2 besloeg echter slechts een zeer kleine fractie (3%) van het totaal 25(OH)D. Seizoensvariatie had de grootste impact op 25(OH)D-spiegels.

Het gebruik van metformine vermindert de energie-inname niet (HOME-studie)
In de HOME-studie werd de voedingsinname beoordeeld bij aanvang van de studie, na 1 jaar en na 4,3 jaar volgens de diet history methode. Analyse toonde aan dat metformine de energie-inname niet verminderde (–31,0 kcal/d; 95% betrouwbaarheidsinterval –107,4 tot 45,4). Bovendien toonden lineair mixed model analyses geen significant effect van energieinname als verklaring voor het verschil in gewichtstoename tussen de groepen. Daarom kan het voorkomen van gewichtstoename door metformine niet worden verklaard door een vermindering van de energie-inname.

Ongeveer een derde van het verschil in gewichtstoename tussen metformine en placeboontvangers kan worden verklaard door de vermindering van de insulinebehoefte door gebruik van metformine (HOME-studie)
Mediation-analyse toonde aan dat aan het einde van het onderzoek een patiënt die de actuele gemiddelde dosis metformine (2050 mg) ontving 3,2 +/- 0,5 kg minder gewichtstoename had, in vergelijking met placebo, waarvan ongeveer een derde (1,2 +/- 0,0 kg) kan worden verklaard door een verlaging van de insuline-inname door het gebruik van metformine.

De ATM SNP rs11212617 heeft niet alleen invloed op het effect van metformine op HbA1c en insulinebehoeften, maar ook op metformine plasmaconcentraties (HOME-studie)
We analyseerden de invloed van de polymorfismen rs12208357 en rs622342 in het gen dat codeert voor organic cation transporter 1 (OCT1), rs2289669 in het gen dat codeert voor multidrug and toxin extrusion transporter 1 (MATE1) en rs11212617 in het ataxia telangiectasia mutated gene (ATM), op de effecten van metformine op HbA1c en insulinebehoefte (dagelijkse dosis insuline, DDI). Uitkomstmaat was een gecombineerde HbA1c + DDI Z-score. Het minor allel van rs11212617 (ATM) was geassocieerd met een verbeterde Z-score (een afname per allel van 0,11, 95% betrouwbaarheidsinterval 0,01 tot 0,20) en een lagere plasmaconcentratie van metformine (–0,42 mg/ml per minor allel, 95% betrouwbaarheidsinterval: –0,81 tot –0,03). Het major allel van rs2289669 (MATE1) was ook geassocieerd met een verbeterde Z-score (–0,35, 95% betrouwbaarheidsinterval –0,09 tot –0,60). De plasmaconcentratie van metformine was ook geassocieerd met een verlaging van de

Z-score. De dagelijkse dosis metformine was echter de beste voorspeller voor de respons op metformine.

Het C-allel van rs8192675 in het intron van SLC2A2, dat codeert voor de glucosetransporter GLUT2, is geassocieerd met het glucoseverlagende effect van metformine bij diabetes mellitus type 2, vooral bij obese personen (MetGen-analyse)
Een drie-fasen genomewide associatiestudie (GWAS) met meer dan 13.000 deelnemers toonde aan dat het C-allel van rs8192675 in het intron van *SLC2A2*, coderend voor de glucosetransporter GLUT2, was geassocieerd met een 0,17% sterkere verlaging van het HbA1c door metformine. Bij obese personen met twee C-allelen was daalde het HbA1c met gemiddeld 0,33% meer dan bij personen met homozygotie voor het T-allel.

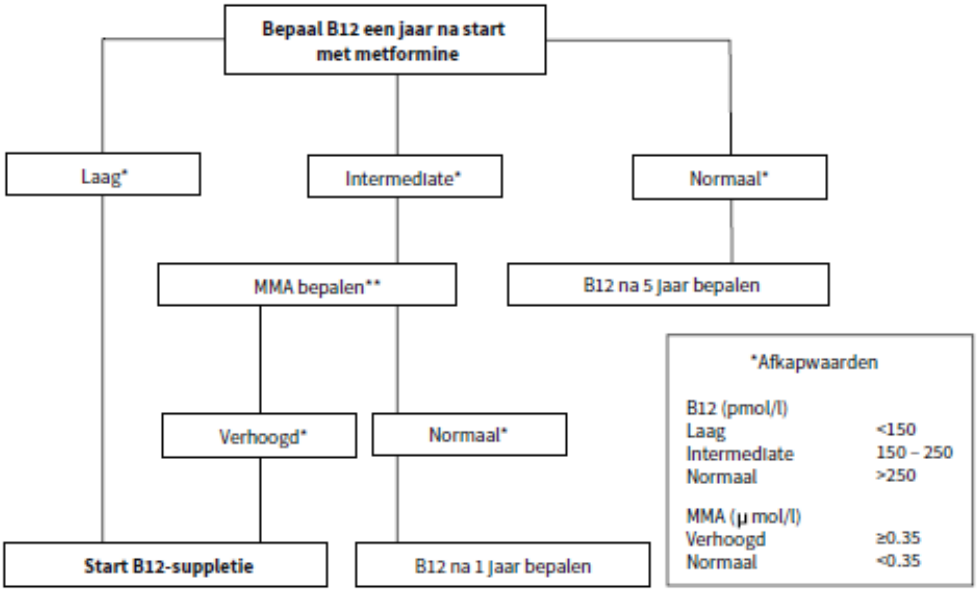
Variatie van transportergenen draagt weinig bij aan de variabiliteit in glycemische respons op metformine bij diabetes mellitus type 2 (MetGen-analyse)
Een meta-analyse werd uitgevoerd in de cohorten van het MetGen Consortium. Negen kandidaat-polymorfismen in vijf transportergenen (OCT1, OCT2, MATE1, MATE2-K en OCTN1) werden in bijna 8000 individuen geanalyseerd. Geen van de varianten toonde een significant effect op de respons van metformine in de primaire analyse of in de orienterende secundaire analyses.

Samenvatting, praktische implicaties en toekomstperspectief
In het eerste deel van dit proefschrift beschrijven we drie studies over mogelijke bijwerkingen van metformine. Ten eerste tonen we aan dat langdurige behandeling met metformine, in vergelijking met placebo, geassocieerd is met een toename van serum-MMA bij patiënten met diabetes mellitus type 2 behandeld met insuline. Dit effect van metformine neemt in de loop van de tijd toe en is afhankelijk van de cumulatieve dosis metformine. De resultaten zijn in lijn met eerdere bevindingen uit de HOME-studie die een progressieve afname van de serumconcentraties van B12 bij patiënten behandeld met metformine aantonen. Bovendien was de toename in serum-MMA door het gebruik van metformine geassocieerd met een kleine toename van een gevalideerde klinische neuropathie score. Deze uitkomsten suggereren dat de afname van B12 door metformine na verloop van tijd kan leiden tot weefselschade. Ten tweede toonden we aan dat metformine niet geassocieerd is met een verlaging van serum vitamine D-spiegels. Ten derde hebben we laten zien dat een gunstig neveneffect van metformine, het voorkomen van gewichtstoename, niet kan worden verklaard door verminderde voedselinname, aangezien onze analyse toonde dat metformine de calorieinname niet beinvloedt. Wel kan ongeveer een derde van het verschil in gewichtstoename tussen metformine en placebo-ontvangers verklaard worden door de vermindering van de insulinebehoefte bij gebruik van metformine.
In het tweede deel van het proefschrift beschrijven we drie studies naar de invloed van farmacogenetische variatie op de effecten van metformine. In de eerste farmacogenetische analyse repliceerden we een associatie tussen het minor allel van het ATM-polymorfisme rs11212617 en het effect van metformine. De meest interessante bevinding was dat dit minor allel niet alleen geassocieerd was met een verbeterde behandeluitkomst, maar ook met lagere plasmaconcentraties van metformine. Een verklaring zou kunnen zijn dat rs11212617 de intracellulaire opname van metformine verhoogt, waardoor de werkzaamheid toeneemt. Het target-gen van rs11212617 is nog niet bekend. Het ATM-gen wordt gesuggereerd als de meest

waarschijnlijke kandidaat, omdat ATM mogelijk betrokken is bij de acties van metformine.[18] De bevinding dat het minor allel geassocieerd was met lagere plasmaconcentraties, maakt het echter minder waarschijnlijk dat ATM het target-gen is, omdat van ATM niet bekend is dat het betrokken is bij de farmacokinetiek van metformine. Daarom zouden onze bevindingen de theorie kunnen ondersteunen dat rs11212617 de expressie beinvloedt van transporters die betrokken zijn bij de cellulaire opname van metformine in de lever of de darm. Daarnaast vonden we associaties tussen het MATE1-polymorfisme rs2289669 en de respons op metformine. De dagelijkse dosis metformine was echter de beste voorspeller van het behandelresultaat. De tweede en derde farmacogenetische studies zijn publicaties van het MetGen Consortium. Een GWAS met patiënten uit de MetGen-cohorten vond dat het C-allel van rs8192675 in het intron van *SLC2A2*, coderend voor de glucosetransporter GLUT2, was geassocieerd met een verbeterde respons op metformine, in het bijzonder bij obese patiënten. Ten slotte vond een meta-analyse van het MetGen Consortium bij geen van de negen geanalyseerde transportergenvarianten een significant effect op de respons van metformine.

Praktische implicaties

Internationale richtlijnen erkennen het risico op B12-deficientie als een nadeel van metformine. 3 Ze adviseren echter om te overwegen B12-waarden te meten, zonder krachtige aanbevelingen te doen. De meest recente versie van de Nederlandse richtlijnen voor de behandeling van diabetes type 2 beveelt screening op B12-deficientie tekort bij metformingebruikers niet aan.[19] De herziening van de richtlijn die inmiddels in conceptvorm verschenen is heeft vooral de adviezen over combinatietherapie aangepast.[20] Echter, we hebben begrepen dat de rubriek met aanbevelingen over bijwerkingen van metformine ongewijzigd zal blijven tot de volgende herziening (persoonlijke communicatie per e-mail met de Nederlandse richtlijncommissie, 18 december 2017). Onze bevindingen zijn echter een belangrijke aanwijzing dat metformine-gerelateerde B12-deficientie klinisch relevant is. Monitoring van B12 bij langdurig gebruik van metformine moet worden overwogen, vooral bij patiënten met neuropathie of macrocytaire anemie. Ik stel een stroomdiagram voor om te screenen op B12-tekort bij gebruikers van metformine (figuur 2) en adviseer om de B12-waarden een jaar na het begin van het gebruik van metformine te meten.Daarnaast adviseer ik om het MMA te testen wanneer B12-waarden alleen onvoldoende duidelijkheid geven. Afhankelijk van de uitkomst kan men besluiten om te beginnen met B12-suppletie of om de B12-meting na een of vijf jaar te herhalen. Ik heb een voorstel opgenomen voor afkapwaarden van B12- en MMA-niveaus.[21–23] Aangezien er echter nog geen consensus is over afkapwaarden voor B12 en MMA is het ook optioneel om lokale afkapwaarden te gebruiken. [21–23] Idealiter vergt dit voorstel nader onderzoek ter bevestiging.



Figuur 2. Stroomdiagram voor screening op B12-deficientie bij metforminegebruikers
* Aangezien er nog geen consensus is over afkapwaarden voor B12 en MMA, is het ook optioneel om lokale afkapwaarden te gebruiken. ** Vooral bij patiënten met neuropathie of anemie.

Toekomstperspectief

Zestig jaar na het eerste klinische gebruik is er nog veel te ontdekken over metformine. Tegenwoordig is metformine goed ingeslepen als de eerste keuze voor orale behandeling van type 2 diabetes. Afgezien van vergelijkingen met sulfonylureumderivaten en insuline zijn er geen lange-termijn data die metformine als eerste keus behandeling vergelijken met nieuwere glucoseverlagende middelen zoals SGLT2-remmers en GLP-1 receptoragonisten. Daarnaast blijft er onzekerheid bestaan over de vraag of metformine het risico op cardiovasculaire aandoeningen bij patiënten met diabetes type 2 vermindert, vooral als gevolg van een gebrek aan gerandomiseerde langetermijnonderzoeken. Aangezien metformine uit patent is en als voorkeursbehandeling 'ethisch bijna onvermijdelijk' bij de behandeling van diabetes type 2,[3] zijn nieuwe grote placebogecontroleerde onderzoeken met metformine moeilijk uit te voeren. Er zijn echter verschillende studies op komst voor mensen zonder diabetes type 2. Het Bethesda Diabetes Research Center met dr. Adriaan Kooy als hoofdonderzoeker staat op het punt te beginnen met de *Pregnancy Outcomes: Effects of Metformin* (POEM) studie, een multicenter gerandomiseerde driefase studie met metformine in zwangerschapsdiabetes. Daarnaast lopen er diverse in vitro en in vivo studies naar de mogelijke effecten van metformine op voorkomen en behandelen van kanker.[11] Bovendien staan drie grote studies naar effecten van metformine op veroudering op het punt om te beginnen met inclusie.[12] Het zal interessant zijn om te zien of deze onderzoeken zullen leiden tot nieuwe indicaties voor het gebruik van metformine. De tijd zal leren of metformine de eerstekeusbehandeling zal blijven of dat de nieuwe glucoseverlagende middelen de plaats van metformine bij behandeling van type 2 diabetes over zullen nemen. Ten slotte zal het fascinerend zijn om te volgen welke richting het onderzoek in de farmacogenetica zal uitgaan. Bevindingen zoals beschreven in dit proefschrift over de

invloed van genetische variatie op effecten van medicatie suggereren dat in de toekomst gestratificeerde geneeskunde op basis van genetische profielen een reele mogelijkheid kan zijn. Wereldwijde samenwerkingsverbanden zoals het MetGen Consortium zijn nodig om nieuwe farmacogenetische associaties te vinden en te repliceren. Deze mogelijkheden vereisen verdere studie, doorzettingsvermogen en misschien wel het belangrijkste, verbeeldingskracht.

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Longgeneeskunde

Adherence to Inhaled Medication in Copd:
Predictors and Outcomes

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
Prof.dr. T.T.M. Palstra,
volgens het besluit van het College voor Promoties
in het openbaar te verdedigen op
vrijdag 1 juni 2018 om 14.45 uur

door

Kirsten Koehorst-ter Huurne

geboren op 9 maart 1977,
te Haaksbergen

Promotor:	Prof. dr. J.A.M. van der Palen
Copromotoren:	Dr. M.G.J. Brusse-Keizer
	Dr. K.L.L. Movig
Leden:	Prof. dr. M.M.R. Vollenbroek
	Dr. C. Bode
	Prof. dr. H.A.M. Kerstjens
	Prof. dr. R. Dekhuijzen
	Prof. dr. M.L. Bouvy

Samenvatting

Chronic obstructive pulmonary disease (COPD) is op dit moment de vierde meest voorkomende doodsoorzaak in de wereld en een grote bron van ziektelast en sterfte. Farmacotherapie met inhalatiemedicatie kan de kans op vroegtijdige sterfte, symptomen en de frequentie en zwaarte van exacerbaties verminderen. Het kan daarnaast de gezondheidstoestand en de inspanningscapaciteit verbeteren. De effectiviteit van inhalatiemedicatie wordt sterk beïnvloed door de therapietrouw van de patiënt. Dit proefschrift beschrijft de therapietrouw bij COPD en is gebaseerd op data van de “Cohort of Mortality and Inflammation in COPD” (COMIC) studie. De COMIC studie is een single centre prospectieve cohort studie in Medisch Spectrum Twente ziekenhuis te Enschede in het oosten van Nederland. Er werden 795 patiënten geïncludeerd van december 2005 tot april 2010, met een follow-up periode van drie jaar. Therapieontrouw heeft verschillende verschijningsvormen en kan zowel bewust als onbewust optreden. Om differentiatie in therapietrouw aan te kunnen brengen hebben we in dit proefschrift vier therapetrouw-categorieën geïntroduceerd. We hebben gekozen voor twee afkapwaarden voor verminderde therapietrouw, 50- <75% voor suboptimaal en <50% voor ondergebruik en een maximum voor optimaal gebruik (75-125%) om tevens overgebruik (>125%) in kaart te brengen.

In **hoofdstuk 2** worden de therapietrouwverschillen beschreven van de gangbare inhalatiemedicatie bij COPD, waaronder langwerkende muscarine agonisten (LAMA), inhalatiecorticosteroiden (ICS), langwerkende beta-2-agonisten (LABA) en ICS/LABA combinatiepreparaten. Het percentage patiënten met optimale therapietrouw was hoog ten opzichte van de literatuur, variërend van 43,2 tot 75,8%. Het lijkt ook vooral hoog omdat in deze observationele studie de COPD patiënten zich niet bewust waren van het feit dat de apotheekgegevens gebruikt zouden worden voor het bepalen van therapietrouw. De beschreven resultaten komen overeen met een Nederlandse observationele studie waaruit bleek dat in de regio Twente, in het oosten van Nederland, sprake was van betere therapietrouw niveaus ten opzichte van andere regio’s. Ondergebruik was geassocieerd met een betere longfunctie aan het begin van de studie vergeleken met patiënten met optimaal gebruik, terwijl overgebruik was geassocieerd met een lagere longfunctie aan het begin, ook weer vergeleken met patiënten met optimaal gebruik. We zagen het hoogste percentage patiënten met optimale therapietrouw (75,8 en 68,2% respectievelijk) bij inhalatiemedicatie met een eenmaaldaagse dosering, tiotropium en ciclesonide. Het concept om therapietrouw te verbeteren door twee middelen in één inhalator te combineren (ICS/LABA combinatie fluticason/salmeterol) kon in dit proefschrift niet worden bevestigd. Dit kan mogelijk veroorzaakt worden door een vorm van selectiebias waarbij de voorschrijver kiest voor een combinatiepreparaat voor een patiënt bij wie een verminderde therapietrouw verwacht wordt.

In **hoofdstuk 3** wordt de invloed van het type inhalator op therapietrouw van de medicatie, beschreven in *hoofstuk 2*, bestudeerd. Therapietrouw van inhalatiemedicatie is gerelateerd aan de inhalator. Het hoogste percentage patiënten met optimale therapietrouw werd beschreven voor de Handihaler, namelijk 78%. Maar dit resultaat kan niet alleen worden toegeschreven aan de inhalator. Er dient rekening gehouden te worden met het feit dat de Handihaler gebruikt wordt voor het inhaleren van tiotropium, een geneesmiddel dat benauwdheidsklachten verminderd en slechts eenmaal daags gebruikt hoeft te worden. Overgebruik werd het meest geregistreerd voor de Turbuhaler (27%) en de dosisaerosol (14%). Overgebruik kan

het gevolg zijn van zowel verspilling als overdoseren. De mogelijkheid van een inhalator om een dosis af te geven zonder daadwerkelijk te inhaleren, vergroot het risico op overgebruik, zoals geregistreerd met behulp van apotheekgegevens. Daarnaast hebben veel dosisaerosolen geen teller om aan te geven hoeveel doseringen het nog bevat; het is mogelijk dat patiënten een 'test puf' gebruiken om te kijken of er nog medicatie in de inhalator zit. Bovendien heeft de medicatie in de Turbuhaler geen smaak, wat een patiënt onzeker kan maken of de medicatie daadwerkelijk genomen is, resulterend in een extra inhalatie om zeker te zijn. Daarom lijkt het ontwerp van een inhalator gerelateerd aan onder- en overgebruik van inhalatiemedicatie.

In **hoofdstuk 4** is een studie uitgevoerd om ziekte-specifieke en kwaliteit van leven-specifieke factoren te identificeren die voorspellend zijn voor therapietrouw van ICS en tiotropium in COPD patiënten. Longfunctie bleek een onafhankelijke voorspeller te zijn voor therapietrouw met zowel ICS als tiotropium. Patiënten met een betere longfunctie en >=1 ziekenhuisopname in het jaar vóór inclusie hadden een verhoogd risico op suboptimaal gebruik van ICS ten opzichte van patiënten met optimaal gebruik. Daarnaast voorspelde een betere longfunctie een verhoogd risico op ondergebruik. Voorspellers voor een verhoogde kans op overgebruik waren een lagere longfunctie, hogere scores op de Clinical COPD Questionnaire-vraag 3 (angst voor toename benauwdheid) en roken.

Wat betreft de therapietrouw van tioptropium waren voorspellers voor suboptimaal gebruik eveneens een betere longfunctie en het onvermogen om dagelijkse activiteiten uit te voeren zoals uitgevraagd met de EuroQol-5D vragenlijst. Opnieuw was een betere longfunctie een voorspeller voor ondergebruik vergeleken met patiënten met optimaal gebruik. Ook nam hier het risico op overgebruik toe bij hogere scores op de Clinical COPD Questionnaire-vraag 3, (angst voor de toename van benauwdheidsklachten).
Hoewel meerdere ziektefactoren en kwaliteit van leven factoren samen hingen met therapietrouw van ICS en tiotropium is het nog niet mogelijk een duidelijk profiel van een patiënt met slechte therapietrouw op te stellen.

In **hoofdstuk 5** worden de resultaten uit de voorgaande hoofdstukken met behulp van diepte-interviews aangevuld vanuit de optiek van de COPD-patiënt. De interviews gingen over therapietrouw en percepties en overtuigingen betreffende de ziekte COPD en de gebruikte medicatie. De gegevens uit de interviews lieten zien dat de patiënten met therapieontrouw over weinig kennis van de ziekte COPD beschikten en over hoe ze hun ziekte in goede banen konden leiden. Daarnaast was er sprake van een gebrek aan kennis op het gebied van de werkingsmechanismen van de verschillende geneesmiddelen en wanneer welk specifiek geneesmiddel gebruikt zou moeten worden. Bovendien gaven veel patiënten aan dat ze niet konden accepteren dat ze de ziekte COPD hadden. Onder- en overgebruikers vertoonden een ander patroon wat betreft percepties en overtuigingen over inhalatiemedicatie. Overgebruikers rapporteerden bijvoorbeeld meer verdriet over het niet meer mee kunnen doen met dagelijkse activiteiten en waren in het algemeen meer gefrustreerd. De belangrijkste bevindingen over de percepties en overtuigingen rond inhalatiemedicatie waren dat ondergebruikers aangaven minder medicatie te gebruiken omdat ze zich goed voelden, omdat ze niet te veel medicatie wilden gebruiken en dat inhalatoren te lang werden doorgebruikt nadat de inhalator al leeg

was. Overgebruikers rapporteerden meer “afhankelijkheid” van inhalatiemedicatie, spraken over “in paniek raken” als de medicatie niet voor handen was en over het vervroegd weggooien van inhalatoren omdat men bang was dat er geen medicatie meer vrij kwam bij inhalatie. De hierboven beschreven verschillen zowel in instelling als in praktisch gebruik, geven mogelijke verklaringen voor het geregistreerde over- en ondergebruik in de apotheekdata. Wanneer over- en/of ondergebruik worden gesignaleerd, bijvoorbeeld in de apotheek, is het belangrijk om op zoek te gaan naar de onderliggende redenen. Wordt het onder- of overgebruik veroorzaakt door (gebrekkige) kennis over de inhalatiemedicatie en/of de inhalator of is er sprake van overtuigingen en/of angst betreffende de ziekte COPD of de medicatie. Als we therapietrouw willen verbeteren is het van belang om aan alle hierboven benoemde zaken aandacht te besteden.

Hoofdstuk 6 beschrijft de associatie tussen therapietrouw met ICS en tiotropium en morbiteit en mortaliteit. Er kon geen associatie worden aangetoond tussen therapietrouw met ICS en het risico op een COPD exacerbatie waarvoor een ziekenhuisopname noodzakelijk was. Een therapieontrouw met tiotropium was wel geassocieerd met een verhoogd risico hierop. Therapietrouw met ICS was niet geassocieerd met tijd tot eerste pneumonie, terwijl supoptimaal en overgebruik van tiotropium wel geassocieerd waren met een verhoogd risico ten opzichte van optimaal gebruik.
Suboptimaal en ondergebruik van zowel ICS als tiotropium waren geassocieerd met een substantieel verhoogd sterfterisico vergeleken met optimaal gebruik. Dit risico lijkt zelfs toe te nemen als de therapietrouw afneemt, met hogere risico’s bij ondergebruik dan suboptimaal gebruik. Het is mogelijk dat dit veroorzaakt wordt doordat de patiënt het beschermende effect van de medicatie mist. Als een patiënt zich goed voelt kan dat een reden zijn minder medicatie te gebruiken omdat de patiënt geen behoefte voelt en/of het nut van de medicatie niet inziet. Een lagere longfunctie op aan het begin van de studie hing samen met een hoger risico op een ziekenhuisopname voor een ernstige exacerbatie, een hoger risico op een pneumonie en een hoger sterfterisico. Bovendien was een hogere dyspneu mMRC score (dit betekent dat een patiënt meer beperkt wordt door zijn kortademigheid) aan het begin van de studie geassocieerd met een hoger risico op een ziekenhuisopname voor een ernstige exacerbatie en met een hoger sterfterisico voor zowel ICS als tiotropiumgebruikers. Of de associatie tussen het overgebruik van tiotropium en het verhoogde risico op een exacerbatie met ziekenhuisopname en pneumonie veroorzaakt werd door de medicatie of de onderliggende ziekte kan niet aangetoond worden door het observationele karakter van de data, hoewel er wel gecorrigeerd werd voor longfunctie en mMRC. Overgebruik lijkt samen te hangen met de ernst van COPD aangezien overgebruik was geassocieerd met een lagere longfunctie en een hogere mMRC-score op baseline. Dit kan een verklaring zijn voor ahet verhoogde risico. Overgebruik kan het gevolg zijn van een slechte gezondheidstoestand die resulteert in een drang om meer medicatie te gebruiken.

In **hoofdstuk 7** worden de bevindingen samengevat en in een ruimere context geplaatst. Dit hoofdstuk wordt afgesloten met aanbevelingen voor zorgverleners in de dagelijkse praktijk en voor toekomstig onderzoek.
Inhalatietherapie voor de behandeling van COPD lijkt te complex en de bijsluiters die bij de geneesmiddelen meegeleverd worden bieden geen garantie voor een adequaat gebruik van de inhalatiemedicatie. Toekomstig onderzoek is nodig om te bepalen of

bijvoorbeeld het gebruik van pictogrammen therapietrouw bij COPD kan verbeteren. Toen de verschillende klasses inhalatiemedicatie op de markt gebracht werden, gebruikten de fabrikanten een kleurcodering voor de verschillende therapieopties om de patiënt te ondersteunen. De huidige generieke fabrikanten hebben echter een hele range van nieuwe kleuren geïntroduceerd die het herkennen van de verschillende middelen bemoeilijkt. Het gebruik van een kleurcodering zou een patiënt kunnen ondersteunen bij het onthouden welke medicatie wat doet. Daarnaast zou een inhalator zo ontworpen moeten worden dat een patiënt de inhalator kan laden met een zo beperkt mogelijk aantal handelingen, de inhalator zou feedback op een inhalatie moeten geven en fabrikanten moeten verplicht worden om een teller in de inhalator op te nemen. Het maken van een profiel of instrument voor het herkennen van een patiënt met therapieontrouw is geen gemakkelijke taak. Wanneer therapieontrouw opgemerkt wordt is het van belang om naar verschillende aspecten te kijken.

1. Is er sprake van bewuste therapieontrouw, ingegeven door de ernst van de ziekte? Bij ondergebruik; kiest de patiënt er voor om minder medicatie te gebruiken omdat hij zich goed voelt of omdat hij niet te veel medicatie wil gebruiken? Of in het geval van overgebruik; gebruikt de patiënt meer medicatie dan voorgeschreven omdat er sprake is van angst voor benauwdheid?
2. Wordt de therapieontrouw veroorzaakt door problemen met de inhalator of de inhalatie techniek?
3. Heeft de patiënt last van bijwerkingen van de inhalatiemedicatie? Dit kan een trigger zijn voor ondergebruik maar kan daarnaast ook een negatief effect hebben op kwaliteit van leven.
4. Hoe is het gesteld met de kennis van de patiënt op het gebied van de medicatie en de inhalator?
5. Wanneer een patiënt verschillende types inhalatiemedicatie gebruikt moet er rekening gehouden worden met het feit dat er sprake kan zijn van verschillende therapietrouw patronen voor de verschillende middelen.

Bij de behandeling van een patiënt is er sprake van een samenwerking tussen de patiënt en verschillende zorgverleners. Iedere patiënt zou advies en interventies op maat moeten ontvangen die ontworpen zijn om therapietrouw te verbeteren. Lokale apothekers kunnen een belangrijke rol spelen bij geïntegreerde COPD zorg. Apothekers kunnen een patiënt begeleiden met advies en scholing op het gebied van dosering, inhalatietechniek, verwachtingen omtrent de therapie, het belang van therapietrouw en daarnaast ondersteunen bij zelfmanagement. Bovendien kan de apotheker een belangrijke rol spelen bij het volgen van therapietrouw en inhalatietechniek van COPD patiënten.

Neurologie

TMS-EEG:
First Steps towards a Clinical Application in Epilepsy

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Twente,
op gezag van Rector Magnificus
Prof. dr. T.T.M. Palstra
volgens besluit van het College voor Promoties.
in het openbaar te verdedigen
op woensdag 6 juni 2018 om 12:45 uur

door

Esther Maria ter Braack

geboren op 4 juni 1984

te Enschede

Promotor:	Prof. dr. ir. M.J.A.M. van Putten
Leden:	Prof. dr. K. Vonck Prof. dr. ir. D.F. Stegeman Dr. H.J. Schelhaas Prof. dr. S.A. van gils Dr. E.H.F. van Asseldonk

Samenvatting
Epilepsie, veroorzaakt door een disbalans tussen activatie en renuning van hersenactiviteit, wordt gekemnerkt door het optreden van insulten. Een patiënt wordt gediagnosticeerd met epilepsie als er twee of meer insulten zijn geweest, als er aanwijzingen zijn voor een specifiek epilepsie syndroom, of als er één insult is geweest met een verhoogde kans op meer insulten. Een verhoogde kans op insulten is aanwezig als het electroencefalogram (EEG, hersenfilmpje) epileptiforme afwijkingen laat zien, of als er structurele hersenafwijkingen te zien zijn opeen MRJ scan. In patiënten die slechts één insult hebben doorgemaakt, en waarbij er geen verhoogd risico op meer insulten wordt gevonden, is de verwachting onzeker. Momenteel is de enige optie om af te wachten of er een tweede insult plaatsvindt voordat er zekerheid is over de diagnose epilepsie. De normale behandeling bij epilepsie bestaat uit het starten met anti-epileptica (AEDs) om verdere insulten te voorkomen. De effectiviteit van deze behandeling wordt bepaald door het wel of niet opnieuw optreden van insulten. Het zoeken naar een effectieve dosering van een AED (of combinatie van AEDs), of het concluderen dat een patiënt niet voldoende reagee11 op medicatie, kan meerdere maanden in beslag nemen.
Twee belangrijke uitdagingen bij epilepsie zijn om de diagnostiek te verbeteren in patiënten bij wie slechts één insult heeft opgetreden, en om de tijd te verkorten die nodig is om het succes van de behandeling met AEDs te evalueren. We vertrouwen hierbij nu vooral op de herhaling van insulten, maar omdat insulten heftig zijn om door te maken en ook mogelijk schadelijke effecten hebben, is er een behoefte aan een nieuwe biomarker om de ziekte te beoordelen.
Met Transcraniële Magnetische Stimulatie (TMS) worden korte magnetische pulsen op de hersenschors gegeven. De sterkte van de reactie van de geactiveerde hersencellen op deze stimulus kan gebruikt worden als een maat voor de balans tussen activatie en remming. TMS zou een bruikbare nieuwe tool kunnen zijn om (veranderingen in) deze balans te bestuderen, en is daarom interessant bij epilepsie. In deze thesis leggen we de focus op de TMS evoked potential (TEP): de EEG reactie na TMS die wordt verkregen na het middelen over meerdere TMS pulsen. Omdat epilepsie geassocieerd is met een hogere prikkelbaarheid, zou de TEP anders kunnen zijn bij epilepsie patiënten. Als dat zo is, dan zou de TEP een mogelijke biomarker kunnen zijn voor epilepsie diagnostiek, en als een monito1ing tool om het succes van de behandeling te evalueren.
Twee artefacten met een grote amplitude maken de beoordeling van de TEP lastig. Het kortdurende TMS puls aitefact geeft filterproblemen, en het langdurende spier activatie artefact ligt over de eerste componenten van de TEP heen. Bij Principiële Component Analyse (PCA), uitgevoerd op individuele TMS-EEG signalen, wordt een verdeling gevonden van de aitefacten met een grote ainplitude in de eerste principiële componenten en de activiteit van hersencellen met een lage ainplitude in latere principiële componenten. Na het één voor één verwijderen van de principiële componenten van de TMS-EEG data kan de afname in artefact amplitude en TEP amplitude beoordeeld worden. Met PCA kunnen beide artefacten venninderd worden, waarbij de eerste TEP componenten zichtbaar worden en verdere TEP analyse mogelijk is (**hoofdstuk 2**).
Het geven van TMS pulsen gaat gepaard met een klikkend geluid, waarmee een auditore evoked potential (AEP) wordt veroorzaakt die boven op de TEP ligt. Deze AEP kan verminderd worden door een koptelefoon te gebruiken waardoor ruis wordt afgespeeld en met een laag schuim tussen de spoel en het hoofd (**hoofdstuk 3**).
Toepassing van TMS-EEG bij een doof persoon bewijst dat de TEP zeker niet alleen

door geluid wordt veroorzaakt. De contributie van de somatosensorische evoked potential (SSEP) moet echter nog worden uitgezocht.
De variatie van de TEP is erg belangrijk voor een mogelijke klinische applicatie van TMS-EEG. Het lijkt erop dat de variatie tussen proefpersonen groot is, waardoor het onderscheiden van gezond en ziek lastig zou kunnen worden. De variatie binnen een proefpersoon lijkt kleiner te zijn, dus vervolgmetingen voor het evalueren van de behandeling zijn wellicht wel mogelijk. De motor drempel en motor evoked potential vairiëren niet gedurende de dag, en de TEP is erg reproduceerbaar tussen verschillende TMS-EEG sessies gedurende de dag (**hoofdstuk 4**).
Een studie in veertien epilepsie patiënten liet zien dat ze in vergelijking met gezonden een hogere motor drempel en een hogere amplitude van de TEP hadden (**hoofdstuk 5**). Een deel van deze verschillen zou wellicht verklaard kunnen worden door het gebruik van AEDs. Daarom moet toekomstig onderzoek naar de mogelijke diagnostische toepassing van de TEP zich focussen op het uitvoeren van TMS-EEG studies in patiënten met een eerste insult en in patiënten met epilepsie die geen AEDs gebruiken. Daai·naast zou TMS-EEG toegepast moeten worden voor en na het staiten van AEDs om te bekijken of de TEP bruikbaar is voor individuele vervolgmetingen.

Neurologie

Electrographic Signatures of
Postanoxic Brain Injury

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof.dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 14 september 2018 om 14:45 uur

door

Barry Johannes Ruijter

geboren op 19 september 1985
te Anna Paulowna

Promotor:	prof. dr. ir. M.J.A.M. van Putten
Copromotor:	dr. J. Hofmeijer
Overige leden:	prof. dr. R.J.A. van Wezel
	prof. dr. ir. N.J.J. Verdonschot
	prof. dr. Y.B.W.E.M. Roos
	dr. J. Horn
	prof. dr. J.G van Dijk
	dr. M.B. Westover

Samenvatting
Na een geslaagde reanimatie blijven het merendeel van de patiënten comateus ten gevolge van postanoxische encefalopathie. Bij meer dan de helft herstelt het bewustzijn nooit en behandelopties om de uitkomst te verbeteren zijn beperkt. Het onderzoek in dit proefschrift heeft als doel om de waarde van continue elektro-encefalografie (EEG) bij de prognosebepaling en behandeling van postanoxisch coma te valideren en te verbeteren.

In **hoofdstuk 2** bevestigen we dat het EEG een sensitief en betrouwbaar hulpmiddel is bij de uitkomstvoorspelling van comateuze patiënten na een hartstilstand. In een prospectief cohort van 850 patiënten, verzameld in vijf centra, tonen we aan dat de prognostische waarde het hoogst is binnen de eerste 24 uur na de hartstilstand. Op 12 uur na de hartstilstand voorspelde een gunstig EEG-patroon (continue of bijna continue achtergrondactiviteit met amplitudes ≥20 µV en afwezige periodieke activiteit) een goede uitkomst (Cerebral Performance Category 1-2) met sensitiviteit van 0.50 (95% betrouwbaarheidsinterval (BI): 0.46-0.55) en een specificiteit van 0.91 (95%-BI: 0.88- 0.93). Op latere tijdstippen nam de sensitiviteit toe, maar ten koste van de specificiteit. Een ongunstig EEG-patroon (gegeneraliseerde suppressie (alle activiteit <10 µV) of synchrone patronen met ten minste 50% suppressie) voorspelde betrouwbaar een slechte uitkomst (Cerebral Performance Category 3-5), op ieder tijdstip tussen 12 uur en 5 dagen na de hartstilstand. Op 12 uur was de sensitiviteit voor voorspelling van slechte uitkomst 0.47 (95%-BI: 0.42-0.51), bij een specificiteit van 1.00 (95%-BI: 0.99-1.00). Op latere tijdstippen daalde de sensitiviteit voor slechte uitkomst geleidelijk. De betrouwbaarheid van uitkomstvoorspellingen was gelijk voor alle centra, ondanks verschillen in behandeling.

In **hoofdstukken 3** en **4** introduceren we eenvoudige kwantitatieve EEG-maten, gebaseerd op aspecten die worden gebruikt bij visuele beoordeling van het EEG voor de uitkomstvoorspelling van postanoxisch coma. In **hoofdstuk 3** ligt de nadruk op kenmerken van het grondpatroon. We definieerden de *background continuity index* (BCI) als fractie van het signaal dat niet werd geclassificeerd als 'suppressie' (alle activiteit <10 µV gedurende ≥0.5 s), en de *burst-suppression amplitude ratio* (BSAR) als de gemiddelde amplitudeverhouding tussen 'bursts' en suppressies. Op 24 uur na de hartstilstand voorspelde een combinatie van BCI en BSAR een goede uitkomst met een sensitiviteit van 0.57 (95%-BI: 0.48-0.67), bij een specificiteit van 0.90 (95%-BI: 0.86-0.95). Een BCI <0.014 of een BSAR ≥6.12, vastgesteld op 10 uur na de hartstilstand of later, voorspelde betrouwbaar een slechte uitkomst. Op 12 uur voorspelde een combinatie van BCI en BSAR een slechte uitkomst met een sensitiviteit van 0.50 (95%-BI: 0.42- 0.57), bij een specificiteit van 1.00 (95%-BI: 0.99-1.00).

In **hoofdstuk 4** richten we ons op de subgroep van patiënten met epileptiforme EEG-patronen. We toonden aan dat een goede uitkomst slechts mogelijk was indien de epileptiforme activiteit ontstond na herstel van continuïteit van het grondpatroon. Een goede uitkomst was verder geassocieerd met een hogere ontladingsfrequentie, een lage relatieve amplitude en een minder sterke periodiciteit van ontladingen.

In **hoofdstuk 5** kwantificeren we de effecten van propofol op het postanoxische EEG en analyseren we of deze de betrouwbaarheid van uitkomstvoorspellingen beïnvloeden. Na het staken van propofol, op een mediaan van 41 uur na de

hartstilstand, nam de specificiteit van een gunstig EEG-patroon voor goede uitkomst af, terwijl de waarde van een ongunstig EEG-patroon voor de voorspelling van een slechte uitkomst gelijk bleef. Bij kwantitatieve EEG-analyse was propofol geassocieerd met een afname van amplitude, BCI, en alfa-delta-ratio, en een toename van de BSAR. Met een multivariabel model werd vastgesteld dat, ondanks de effecten van propofol op kwantitatief EEG, propofol de kans op een ongunstig EEG-patroon bij visuele beoordeling niet verhoogt (geadjusteerde odds ratio (aOR) 0.92 per toename van 2 mg/kg/uur, 95%-BI: 0.81-1.11) en de kans op een gunstig EEG-patroon niet verlaagt (aOR 0.98, 95%-BI: 0.81-1.09).

De mechanismen die verantwoordelijk zijn voor de specifieke EEG-patronen waargenomen bij postanoxische encefalopathie zijn grotendeels onbekend. In **hoofdstuk 6** presenteren we een biofysisch model waarin twee mogelijke mechanismen op het niveau van de synaps zijn opgenomen. In dit zogenaamde *mean field model* hebben we anoxische schade gemodelleerd als een versterkte korte-termijndepressie van synaptische activiteit, met een geleidelijk herstel over vele uren. Daarnaast werd exciterende neurotransmissie versterkt, in een mate die schaalde met de ernst van de postanoxische encefalopathie. De gesimuleerde EEG-patronen kwamen goed overeen met zes veelvoorkomende patronen bij postanoxisch coma, inclusief de kenmerkende overgangen tussen patronen die optreden wanneer tijd verstrijkt. Plausibele resultaten werden alleen verkregen indien de korte-termijndepressie van synaptische activiteit sterker was aangedaan bij exciterende synapsen dan bij inhiberende synapsen. De toevoeging van propofol in het model kon de gesimuleerde pathologische EEG-patronen laten verdwijnen. Echter, om deze patronen voorgoed te laten verdwijnen was het nodig om een mechanisme toe te voegen voor normalisatie van de synaptische excitatie-inhibitieratio op de lange termijn.

In **hoofdstuk 7** presenteren we het studieprotocol van TELSTAR, een multicentrische gerandomiseerde klinische trial naar de behandeling van elektrografische status epilepticus na reanimatie. In dit lopende onderzoek beogen we 172 patiënten te includeren, die worden gerandomiseerd voor ofwel agressieve behandeling ofwel geen medicamenteuze behandeling van status epilepticus. Iedere uitkomst van dit onderzoek zal leiden tot aanpassing van internationale richtlijnen, omdat beide behandelstrategieën momenteel worden beschouwd als standaardbehandeling. TELSTAR is gestart in 2014, en de inclusie zal naar verwachting in de tweede helft van 2019 worden afgerond.

Orthopedie

Prognostics of Outcome of Total Knee Replacement on Patient Selection and Intraoperative Issues

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit van Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 4 juli 2018
klokke 16:15 uur

door

Wiebe Christiaan Verra

geboren te Leiden
in 1984

Promotor:	Prof. Dr. R.G.H.H. Nelissen
Copromotor:	Dr. J.A. van Hilten
Leden promotiecommissie:	Prof. Dr. G. Kloppenburg
	Prof. Dr. J.G. van der Bom
	Prof. Dr. J.A.N. Verhaar
	Prof. Dr. C. Perka

Samenvatting

Het aantal Totale Knie Protheses (TKP's) dat per jaar wereldwijd geplaatst wordt groeit nog altijd. De TKP wordt gezien als het eindstadium in de behandeling van gonartrose; artrose van de knie. Van oudsher worden prestaties van orthopedische implantaten gemeten in overlevingsstatistieken. Het doel hiervan is om te zien hoe lang het duurt voordat de TKP gereviseerd moet worden. De overleving van TKP's is in het algemeen goed, daarom is er de laatste jaren steeds meer aandacht voor patiënt gerelateerde uitkomsten zoals patiënttevredenheid of kwaliteit van leven na de operatie.

In **hoofdstuk 2** wordt een studie beschreven naar de patiënttevredenheid en de kwaliteit van leven lange tijd na een TKP of totale heup prothese (THP) operatie; dat wil zeggen meer dan tien jaar na deze operatie. Hieruit blijkt dat zowel patiënten na TKP als na THP zeer tevreden zijn en hoge kwaliteit van leven scores laten zien. Het lijkt er echter ook op dat de mensen na een heupprothese iets meer tevreden zijn dan na een knieprothese.

De indicatiestelling (het selecteren van de juiste patiënten voor de behandeling) voor het overgaan tot het plaatsen van een TKP is in het algemeen belangrijk, maar zou ook een rol hebben kunnen spelen bij het eerder genoemde verschil in tevredenheid. Op dit moment bestaan er geen harde richtlijnen wanneer een TKP te plaatsen. Om een idee te krijgen wanneer in de praktijk in Nederland een orthopedisch chirurg overgaat tot het plaatsen van een TKP werd een onderzoek gedaan onder alle Nederlandse orthopedisch chirurgen. Zij kregen drie casus beschrijvingen toegestuurd met de vraag of ze een TKP zouden plaatsen of niet. De casus waren helemaal identiek op één onderdeel na en de orthopedisch chirurgen kregen willekeurig één van de twee versies voor zich (**hoofdstuk 3**). Het lijkt erop dat in de praktijk de graad van radiologische artrose en het hebben van oudere leeftijd belangrijke factoren waren om over te gaan tot het aanbevelen van een TKP. De mate van pijn leek minder belangrijk bij het stellen van de indicatie, hoewel uit de literatuur voortkomt dat het hebben van voldoende pijn de belangrijkste indicatie zou moeten zijn.

In **hoofdstuk 4** wordt vervolgens de indicatiestelling voor TKP vergeleken tussen Nederlandse orthopedisch chirurgen met die uit verschillende andere landen. Gebruikmakend van gegevens van meer dan 1.900 patiënten uit negen landen lijkt het erop dat Nederlandse orthopedisch chirurgen het meest terughoudend zijn in het aanbevelen van een TKP. Uit ditzelfde onderzoek blijkt dat Nederlandse patiënten ten tijde van de indicatiestelling de hoogste kwaliteit van leven scores hadden.

In **hoofdstuk 5** worden uitkomsten van de Leiden 85+ studie besproken. Het gaat hier om uitkomsten op het gebied van functionele prestaties van de oudste ouderen, namelijk die van 85 jaar en ouder, met TKP of THP en die prestaties bij oudste ouderen zonder een dergelijke prothese. De oudste ouderen met prothese presteerden functioneel net zo goed als de oudste ouderen zonder prothese. Ook het gezondheidsniveau was vergelijkbaar tussen de twee groepen.
TKP wordt gezien als een succesvolle behandeling van gonartrose en wordt wereldwijd door vele orthopedisch chirurgen ingezet. Er blijven rondom de TKP behandeling een aantal zaken punt van discussie. Zo wordt er gesteld dat het aanbrengen van een fibrinelijm in de knie tijdens de operatie een gunstig effect zou

hebben op het hemoglobine verlies of op het aantal bloedtransfusies rondom de operatie.

In **hoofdstuk 6** worden de resultaten beschreven van een grote gerandomiseerde klinische studie in meerder ziekenhuizen naar het effect van een fibrinelijm bij TKP operaties. De huidige zorgpaden bij TKP zijn zeer terughoudend met het toedienen van bloedtransfusies en het routinematig controleren van hemoglobine gehalte in het bloed. Vandaar dat in de studie met fibrinelijm gekozen is voor een functionele uitkomstmaat, namelijk de extensie ('het strekken') van de knie. Uit eerder onderzoek weten we dat er na TKP operaties zo'n 650-700 mL bloedverlies is wat onder andere in de knie kan blijven en kan zorgen voor een extensiebeperking (strekbeperking) van de knie met als gevolg een mogelijk moeizamere revalidatie van de operatie. Er werd geen verschil gevonden in knie extensie tussen patiënten die met of zonder fibrinelijm geopereerd waren. Ook wanneer het gebruik van drains meegenomen werd in de analyse werd er geen verschil gevonden.
Een andere voortdurende discussie onder kniechirurgen is het al dan niet offeren van de achterste kruisband.

Hoofdstuk 7 rapporteert de resultaten van een systematische review en meta-analyse binnen het kader van Cochrane waarvan de resultaten zowel als artikel in de Acta Orthopaedica zijn gepubliceerd als in de *Cochrane Library for Systematic Reviews*. Er konden 2.347 knieën geanalyseerd worden in de meta-analyse waardoor er uitkwam dat TKP's waarbij de achterste kruisband geofferd was 2.1 graden meer konden buigen. Dit was statistisch significant maar klinisch niet relevant. Uit dit onderzoek kan geconcludeerd worden dat er geen functionele, klinische of radiologische verschillen gevonden werden tussen TKP met of zonder opofferen van de achterste kruisband.
Na TKP of THP kan een prothese infectie ontstaan. Dit is één van de meest gevreesde complicaties van de behandeling en er wordt veel moeite gedaan om het risico op een infectie tot een minimum te beperken. Hypothermie (waarbij de temperatuur van patiënten tussen de 34 en 36 ^{o}C is) kan ontstaan tijdens de operatie en kan het risico op infectie doen toenemen. Hierom worden patiënten tijdens de operatie verwarmd. De meest gebruikte deken hiervoor maakt gebruikt van warme lucht. Deze warme lucht kan de luchtstroom op de operatiekamer dusdanig verstoren dat het risico op infectie van het operatiegebied weer toeneemt.

In **hoofdstuk 8** beschrijven we een onderzoek waarbij we onderzocht hebben of de warme lucht deken en een deken die uit zichzelf warm is en daarbij de luchtstroom niet verstoord beiden in staat zijn om hypothermie te voorkomen. Met het idee dat wanneer de deken die de luchtstroom niet verstoord even effectief is als de ander dat deze wellicht de voorkeur zou moeten genieten. We vonden een verschil van 0.2 ^{o}C ten nadele van de deken die zelf verwarmd. Dit verschil beschouwen we als niet relevant. In beide groepen werden ook geen verschillen in complicaties gevonden.

Reumatologie

Effectiveness of Treating to the Target of Remission Strategies
In Patients With Early Rheumatoid Arthritis

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Twente, op
gezag van Rector Magnificus
prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties in
het openbaar te verdedigen
op vrijdag 21 december om 10:45 uur

door

Laura Margaretha Maria Steunebrink

geboren op 18 november 1985
te Oldenzaal

Promotor:	Prof. dr. M.A.F.J. van de Laar
Copromotor:	Dr. H.E. Vonkeman
	Dr. P.M. ten Klooster
Leden:	Prof. Dr. J.A.M. van der Palen
	Prof. Dr. A.H.M. van der Helm - van Mil
	Prof. Dr. J.M. van Laar
	Prof. Dr. D. van Schaardenburg
	Dr. C. Bode
	Dr. H.H. Kuper

Samenvatting

Reumatoïde artritis (RA) is een ontstekingsziekte van het bindweefsel in het lichaam, met name de synoviale gewrichten. Aanhoudende ontsteking kan leiden tot beschadiging van de gewrichtscapsule en het gewrichtskraakbeen. Verschillende interventiestudies en onderzoeken in de dagelijkse klinische praktijk hebben aangetoond dat vroege, agressieve onderdrukking van ontstekingen tot aanhoudende remissie of op z'n minst een lage ziekteactiviteit kan leiden en gewrichtsschade en bijbehorende invaliditeit kan minimaliseren of zelfs voorkomen. De huidige behandelrichtlijnen pleiten voor treat-to-target (T2T) als de optimale behandelstrategie [1]. Binnen dit behandelingsparadigma worden opeenvolgende medicatieaanpassingen gemaakt totdat een vooraf bepaald doel van de mate van ziekteactiviteit (meestal remissie of lage ziekteactiviteit) wordt bereikt. De literatuur suggereert dat een T2T behandelstrategie leidt tot betere klinische uitkomsten dan alternatieve behandelstrategieën, maar het is nog steeds onduidelijk welke medicatiestrategie binnen T2T de beste resultaten oplevert. Het hoofddoel van dit proefschrift is om de effecten van twee T2T strategieën gericht op remissie in vroege RA, een step-up DMARD-monotherapie versus een initiële DMARD-combinatietherapie te vergelijken en te onderzoeken. De DREAM samenwerking startte de twee T2T remissie inductie cohorten over de tijd op, beide met een verschillend medicatieprotocol, waarvan de resultaten in dit proefschrift worden gepresenteerd.

Samenvatting en bevindingen

Hoofdstuk 3

Dit hoofdstuk presenteert de remissie percentages en voorspellers van remissie in het meest recente real-life T2T cohort (initiële DMARD-combinatie therapie) van opeenvolgende patiënten met een recente klinische diagnose van RA. In bijna 80% van de recent gediagnosticeerde RA-patiënten werd remissie snel bereikt tijdens het eerste jaar van hun ziekte. Onder een breed scala. van mogelijke prognostische factoren voor het bereiken van remissie, konden geen nauwkeurige voorspellers worden geïdentificeerd. Deze bevinding levert aanvullend bewijs dat een T2T-strategie gericht op remissie universeel gunstig lijkt voor recent gediagnosticeerde RA-patiënten in de klinische praktijk en daarom op grote schaal kan worden geïmplementeerd. De overgrote meerderheid van de patiënten in de huidige studie bereikte het behandeldoel alleen met conventionele synthetische disease modfying antirheumatic drugs (ziekteverloop beïnvloedende geneesmiddelen tegen reuma) (csDMARDs) en slechts 10% van de patiënten had binnen de eerste 12 maanden van de behandeling een biologische DMARD (bDMARD) nodig. Deze studie bevestigt dat remissie een realistisch doel is in de dagelijkse klinische praktijk Bovendien lijkt de huidige T2T strategie breed toepasbaar te zijn voor patiënten met recent gediagnosticeerde RA. Samen met de afwezigheid van duidelijke baseline voorspellers, suggereert dit dat artsen die zich richten op remissie in de dagelijkse klinische praktijk zich alleen op de uitkomsten zoals ziekteactiviteit, kunnen richten, zonder rekening te hoeven houden met andere patiëntkarakteristieken.

Hoofdstuk 4

Dit hoofdstuk vergelijkt de effectiviteit van twee T2T strategieën bij vroege RA patiënten. Voor dit doel werd een step-up DMARD monotherapie, beginnend met methotrexaat (MTX) monotherapie (strategie I) vergeleken met de initiële DMARD combinatiestrategie (strategie II). De resultaten van deze studie suggereren dat de

eerder gerapporteerde resultaten, die werden bereikt door implementatie van T2T met initiële MTX monotherapie in de dagelijkse klinische praktijk, kunnen worden gereproduceerd en zelfs verbeterd kunnen worden met behulp van initiële DMARD combinatietherapie. Initiële DMARD combinatietherapie resulteerde in vergelijkbare remissie percentages na 1 jaar, maar een significant kortere mediane tijd tot remissie. Op 6 maanden waren de gemiddelde ziekteactiviteit scores lager in patiënten met initiële DMARD combinatietherapie, dan bij de patiënten die behandeld werden met step-up DMARD monotherapie. Op 12 maanden bleken er geen significante verschillen in gemiddelde ziekteactiviteit scores of het aantal patiënten in remissie. Concluderend leidt T2T met initiële combinatietherapie tot een significant kortere tijd tot het bereiken van een eerste remissie.

Hoofdstuk 5
Dit hoofdstuk vergelijkt de radiografische uitkomsten van de step-up DMARD monotherapie (strategie I) versus de initiële DMARD combinatietherapie (strategie II). Deze studie toonde aan dat patiënten met een initiële DMARD monotherapie na 1 jaar significant meer en vaker klinische relevante radiografische progressie vertoonden. Een aanzienlijk groter aantal patiënten binnen strategie II vertoonde helemaal geen radiografische progressie en slechts een klein deel van de patiënten vertoonde klinische relevante progressie. Minder gevoelige gewrichten en hogere bezinking op baseline waren significant geassocieerd met het bereiken van klinische relevante progressie in de totale patiëntengroep.

Hoofdstuk 6
Dit hoofdstuk onderzoekt de associatie tussen het bereiken van gunstige klinische uitkomsten en de waargenomen verandering van patiënten zelf in de algehele gezondheidstoestand na 12 maanden behandeling met T2T bij patiënten met vroege RA en heeft als doel om determinanten van subjectieve verbetering te identificeren. De resultaten toonden aan dat meer dan een derde van de patiënten (35%) niet van mening was dat hun algehele gezondheid was verbeterd ondanks dat ze gunstige klinische resultaten hadden bereikt. Relatieve verbeteringen ten opzichte van baseline pijn en baseline vermoeidheid waren onafhankelijk geassocieerd met een onverbeterde algehele gezondheidsstatus. Deze studie toont aan dat klinische verbetering niet per definitie gelijk staat aan een verbeterde subjectieve gezondheid voor alle patiënten. Verbetering in klinische signalen en symptomen alleen is niet genoeg om gunstige gezondheid uitkomsten te bereiken voor alle vroege RA patiënten. De voorspellende waarde van verandering in pijn en vermoeidheid suggereert daarom dat het de moeite waard kan zijn om pijn en vermoeidheid te monitoren en te meten naast het reguliere meten van ziekteactiviteit in vroege RA.

Hoofdstuk 7
Dit hoofdstuk onderzoekt de longitudinale relatie tussen ziekteactiviteit en radiografische progressie bij patiënten met RA met een intensieve T2T strategie in de dagelijkse klinische praktijk. Op groepsniveau werd er geen significante correlatie waargenomen tussen tijd-geïntegreerde ziekteactiviteit en radiografische progressie na 6 maanden en 2 jaar follow-up. Op 1-jaar en 3-jaar follow-up was er slechts een zeer zwakke positieve correlatie. Een brede interindividuele variatie tussen ziekteactiviteit en radiografische progressie was ook duidelijk te zien in de individuele trajecten van patiënten. De hellingen van de individuele lijnen bevestigen daarentegen in elk tijdsinterval een redelijk proportioneel verband tussen

ziekteactiviteit en radiografische progressie. Vooral de hellingen in de eerste 6 maanden waren matig tot sterk geassocieerd met de hellingen op de latere tijdstippen. Zo'n 12 - 30% van de patiënten die over de tijd in remissie waren, liepen toch relevante radiografische schade op (SHS >= 3). Deze bevindingen suggereren dat, in het tijdperk van T2T behandeling, radiografische schade niet langer wordt veroorzaakt door alleen (consistente) hoge ziekteactiviteit, maar in plaats daarvan vooral een individueel bepaald ziekte proces is.

PubMed publicaties per vakgroep
Cardiologie

1. Effect of Guideline-Based Therapy on Left Ventricular Systolic Function Recovery After ST-Segment Elevation Myocardial Infarction
Abou R, Leung M, Goedemans L, Hoogslag GE, Schalij MJ, Marsan NA, Bax JJ, Delgado V

Little is known about the proportion of ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention, who have reduced left ventricular ejection fraction (LVEF) within 48 hours (baseline) of admission and exhibit LVEF recovery under optimal guideline-based medical treatment. Therefore, the present study evaluates the evolution of LVEF in patients after STEMI and under guideline-based medical therapy. In 2,853 STEMI patients treated with primary percutaneous coronary intervention, echocardiography was performed at baseline and at 6 months follow-up. Patients with previous myocardial infarction, reinfarction, coronary artery bypass grafting or incomplete echocardiographic data at 6 months follow-up were excluded. Reduced LVEF at baseline was defined as <40%. LVEF recovery was defined as LVEF >50% at 6 months follow-up. The prevalence of LVEF <40% at baseline was 13% (n=371 patients; mean age 60 [range 33 to 88] years; 76% men). At follow-up, 31% of patients remained with a LVEF <40%, 30% showed a LVEF between 41% and 49% and in 39% of patients LVEF improved to >50%. There were no differences in usage of guideline-based medications at discharge across groups. On multivariable analysis, peak troponin T levels (odds ratio [OR] 0.895; p < 0.001), baseline LVEF (OR 1.069; p=0.023) and absence of significant mitral regurgitation (OR 0.376; p=0.018) were independently associated with LV recovery at follow-up. In conclusion, the prevalence of LVEF <40% is low. With optimal medical therapy, LVEF normalizes in 39% of patients. Smaller enzymatic infarct size, baseline LVEF and absence of mitral regurgitation were independently associated with LVEF recovery at follow-up.

Gepubliceerd: Am J Cardiol 2018 Nov 15;122(10):1591-7
Impact factor: 3.171; Q2

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2. Functional comparison between the BuMA Supreme biodegradable polymer sirolimus-eluting stent and a durable polymer zotarolimus-eluting coronary stent using quantitative flow ratio: PIONEER QFR substudy
Asano T, Katagiri Y, Collet C, Tenekecioglu E, Miyazaki Y, Sotomi Y, Amoroso G, Aminian A, Brugaletta S, Vrolix M, Hernandez-Antolin R, van de Harst P, Iniguez-Romo A, Janssens L, Smits PC, Wykrzykowska JJ, Ribeiro VG, Pereira H, da Silva PC, Piek JJ, Reiber JHC, von Birgelen C, Sabate M, Onuma Y, Serruys PW

Aims: Quantitative flow ratio (QFR) based on three-dimensional quantitative coronary angiography (3D-QCA) is a novel method to assess physiological functionality after treatment with stents. The current study aimed to evaluate the difference in physiological functionality nine months after implantation of a bioresorbable polymer-based sirolimus-eluting stent with an electrografting base layer (BuMA Supreme: B-SES) versus a durable polymer-based zotarolimus-eluting stent (Resolute: R-ZES).

Methods and results: The current post hoc analysis was performed in the PIONEER randomised trial (1:1 randomisation to B-SES [83 patients/95 lesions] and R-ZES [87 patients/101 lesions]). QFR was measured in stented vessels in both arms at preprocedural, post-procedural and nine-month angiography without pharmacologically induced hyperaemia (contrast QFR). At nine months, both the values of QFR distal to the stent (B-SES: 0.89+/-0.10 vs. R-ZES: 0.89+/-0.11, p=0.97) and the number of vessels with QFR </=0.8 were not significantly different between the two groups (11.0% vs. 12.8%, p=0.72), while the in-stent binary restenosis rate was also comparable (3.7% vs. 3.5%, p=1.00). QFR gradient across the device (QFR) at nine months was also similar between the groups (B-SES: 0.03+/-0.04 vs. R-ZES: 0.03+/-0.07, p=0.95).
Conclusions: Quantitative flow assessment nine months after stenting did not differ between B-SES and R-ZES, despite a significant difference in in-stent late lumen loss.

Gepubliceerd: EuroIntervention 2018 Aug 3;14(5):e570-e579
Impact factor: 4.417; Q2

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3. Inferior acute myocardial infarction with anterior ST-segment elevations
Bouhuijzen LJ, Stoel MG

Gepubliceerd: Neth Heart J 2018 Oct;26(10):515-6
Impact factor: 1.476; Q3

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4. Cardiovascular and Noncardiovascular Death After Percutaneous Coronary Intervention: Insights From 32 882 Patients Enrolled in 21 Randomized Trials
Brener SJ, Tarantini G, Leon MB, Serruys PW, Smits PC, von Birgelen C, Crowley A, Ben-Yehuda O, Stone GW

Background: Despite advances in technology and technique, a substantial proportion of patients still die within several years after percutaneous coronary intervention (PCI). The relative rates of cardiovascular and noncardiovascular death after PCI remain uncertain.
Methods and results: We pooled individual patient-level data from 21 randomized clinical trials of PCI performed in 32 882 patients. All studies had independent adjudication of clinical events. We calculated the relative ratio of cardiovascular to noncardiovascular death in each trial up to 5 years and identified predictors of all-cause, cardiovascular, and noncardiovascular death. At the end of the follow-up period, 1980 patients had died (Kaplan-Meier estimated mortality rate, 9.19%). The rates of cardiovascular and noncardiovascular mortality at 5 years were 4.23% (945) and 5.17% (1035), respectively. The rate of cardiovascular death was higher than noncardiovascular death in the first 30 days after PCI (relative ratio, 6.99; 95% confidence interval, 3.16-15.42; P<0.001), similar between 30 days and 1 year, and lower between 1 and 5 years (relative ratio, 0.70; 95% confidence interval, 0.58-0.84; P=0.0005). Any adverse cardiac event (definite stent thrombosis, spontaneous myocardial infarction, or repeat revascularization) preceded cardiovascular and noncardiovascular mortality in 292 (30.9%) and 151 (14.6%) patients, respectively. In a multivariable model with adverse events entered as time-adjusted covariates,

myocardial infarction and definite ST were associated with early and late all-cause and cardiovascular mortality but not noncardiovascular mortality.
Conclusions: In this large-scale study of patients undergoing PCI, the 5-year rates of cardiovascular and noncardiovascular mortality were similar, but their relative timing was different.

Gepubliceerd: Circ Cardiovasc Interv 2018 Jul;11(7):e006488
Impact factor: 6.504; Q1

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5. Noninvasive Identification of Ventricular Tachycardia-Related Anatomical Isthmuses in Repaired Tetralogy of Fallot: What Is the Role of the 12-Lead Ventricular Tachycardia Electrocardiogram
Brouwer C, Kapel GFL, Jongbloed MRM, Schalij MJ, de Riva Silva M, Zeppenfeld K

Objectives: This study sought to evaluate the relation between 12-lead ventricular tachycardia (VT) electrocardiography (ECG) and VT-related anatomical isthmuses (AIs) in repaired tetralogy of Fallot (rTOF).
Background: Slow-conducting AIs are the dominant VT substrate in rTOF. Whether an AI is considered critical relies on pace mapping (PM) guided by the VT ECG.
Methods: VT ECGs, electroanatomical mapping data and PM results were analyzed in 25 rTOF patients (group 1) (age 57 +/- 13 years). Selection of PM and ablation sites was guided by VT ECG. In 7 patients (group 2) (age 33 +/- 14 years), PM was systematically performed within all AIs, irrespective of the VT ECG.
Results: In group 1, all 35 induced VTs (median VT cycle length 270 [interquartile range: 240 to 310] ms) were AI related. All 11 right bundle branch block (RBBB) VTs were related to AI3 (right ventricular septum if positive concordant [7 of 7]), coronary cusp if V2 transition break [3 of 4]). Left bundle branch block (LBBB) VTs with transition <V5 were mapped to AI3 (8 of 10) or AI2 (2 of 10) and LBBB VTs with transition >/=V5 to AI1 (8 of 14), AI3 (5 of 14), and AI4 (1 of 14). In group 2, all 8 induced VTs (median VT cycle length 240 [interquartile range: 230 to 268] ms) were AI related. All RBBB VTs were related to AI3 (right ventricular septum). For LBBB VTs, paced matches were obtained in AI3 and AI1. Activation mapping and/or ablation success confirmed AI3 to be critical for all 8 VTs.
Conclusions: In rTOF with only AI1 and AI3, RBBB VTs are due to clockwise and LBBB VTs to counterclockwise activation of AI3. Involvement of both AIs in the VT circuit limits the role of the 12-lead VT ECG and PM. AI3 can always be targeted irrespective of the 12-lead VT ECG.

Gepubliceerd: JACC Clin Electrophysiol 2018 Oct;4(10):1308-18
Impact factor: 0; nvt

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6. Effect of Increasing Stent Length on 3-Year Clinical Outcomes in Women Undergoing Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents: Patient-Level Pooled Analysis of Randomized Trials From the WIN-DES Initiative
Chandrasekhar J, Baber U, Sartori S, Stefanini GG, Sarin M, Vogel B, Farhan S, Camenzind E, Leon MB, Stone GW, Serruys PW, Wijns W, Steg PG, Weisz G, Chieffo A, Kastrati A, Windecker S, Morice MC, Smits PC, von Birgelen C, Mikhail

GW, Itchhaporia D, Mehta L, Kim HS, Valgimigli M, Jeger RV, Kimura T, Galatius S, Kandzari D, Dangas G, Mehran R

Objectives: The aim of this study was to examine whether stent length per patient and stent length per lesion are negative markers for 3-year outcomes in women following percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (DES).
Background: In the era of advanced stent technologies, whether stent length remains a correlate of adverse outcomes is unclear.
Methods: Women treated with new-generation DES in 14 randomized trials from the WIN-DES (Women in Innovation and Drug-Eluting Stents) pooled database were evaluated. Total stent length per patient, which was available in 5,403 women (quartile 1, 8 to 18 mm; quartile 2, 18 to 24 mm; quartile 3, 24 to 36 mm; quartile 4, >/=36 mm), and stent length per lesion, which was available in 5,232 women (quartile 1, 8 to 18 mm; quartile 2, 18 to 20 mm; quartile 3, 20 to 27 mm; quartile 4, >/=27 mm) were analyzed in quartiles. The primary endpoint was 3-year major adverse cardiovascular events (MACE), defined as a composite of all-cause death, myocardial infarction, or target lesion revascularization.
Results: In the per-patient analysis, a stepwise increase was observed with increasing stent length in the adjusted risk for 3-year MACE (p for trend <0.0001), myocardial infarction (p for trend <0.001), cardiac death (p for trend = 0.038), and target lesion revascularization (p for trend = 0.011) but not definite or probable stent thrombosis (p for trend = 0.673). In the per-lesion analysis, an increase was observed in the adjusted risk for 3-year MACE (p for trend = 0.002) and myocardial infarction (p for trend <0.0001) but not other individual endpoints. On landmark analysis for late event rates between 1 and 3 years, stent length per patient demonstrated weak associations with target lesion revascularization (p = 0.0131) and MACE (p = 0.0499), whereas stent length per lesion was not associated with higher risk for any late events, suggesting that risk was established early within the first year after PCI.
Conclusions: In this pooled analysis of women undergoing PCI with new-generation DES, increasing stent length per patient and per lesion were independent predictors of 3-year MACE but were not associated with definite or probable stent thrombosis.

Gepubliceerd: JACC Cardiovasc Interv 2018 Jan 8;11(1):53-65
Impact factor: 9.881; Q1

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7. Quantification of disturbed coronary flow by disturbed vorticity index and relation with fractional flow reserve
Chu M, von Birgelen C, Li Y, Westra J, Yang J, Holm NR, Reiber JHC, Wijns W, Tu S

Background and aims: The relation between FFR and local coronary flow patterns is incompletely understood. We aimed at developing a novel hemodynamic index to quantify disturbed coronary flow, and to investigate its relationship with lesion-associated pressure-drop, and fractional flow reserve (FFR).
Methods: Three-dimensional angiographic reconstruction and computational fluid dynamics were applied to simulate pulsatile coronary flow. Disturbed vorticity index (DVI) was derived to quantify the stenosis-induced flow disturbance. The relation between DVI and pressure-drop was assessed in 9 virtual obstruction models.

Furthermore, we evaluated the correlation between DVI, FFR, hyperemic flow velocity, and anatomic parameters in 84 intermediate lesions from 73 patients.
Results: In virtual models, DVI increased with increasing flow rate, stenosis severity, and lesion complexity. The correlation between DVI and pressure-drop across all models was excellent (determination coefficient R(2)=0.85, p<0.001). In vivo, DVI showed a correlation with FFR (rho (rho)=-0.74, p<0.001) that was stronger than the relations of FFR with hyperemic flow velocity (rho=-0.27, p=0.015), lesion length (rho=-0.36, p=0.001) and percent diameter stenosis (rho=-0.40, p<0.001).
Conclusions: DVI, a novel index to quantify disturbed flow, was related to pressure-drop in virtual obstruction models and showed a strong inverse relation with FFR in intermediate lesions in vivo. It supports the prognostic value of FFR and may provide additional information about sources of energy loss when measuring FFR.

Gepubliceerd: Atherosclerosis 2018 Jun;273:136-44
Impact factor: 4.467; Q2

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8. Hepatocellular Carcinoma After Fontan Operation
Egbe AC, Poterucha JT, Warnes CA, Connolly HM, Baskar S, Ginde S, Clift P, Kogon B, Book WM, Walker N, Wagenaar L, Moe T, Oechslin E, Kay WA, Norris M, Gordon-Walker T, Dillman JR, Trout A, Anwar N, Hoskoppal A, Veldtman GR

Gepubliceerd: Circulation 2018 Aug 14;138(7):746-8
Impact factor: 18.881; Q1

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9. Effects of Body Mass Index on Clinical Outcomes in Female Patients Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents: Results From a Patient-Level Pooled Analysis of Randomized Controlled Trials
Faggioni M, Baber U, Afshar AE, Giustino G, Sartori S, Sorrentino S, Steg PG, Stefanini GG, Windecker S, Leon MB, Stone GW, Wijns W, Serruys PW, Valgimigli M, Camenzind E, Weisz G, Smits PC, Kandzari DE, Galatius S, von Birgelen C, Jeger RV, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Dangas GD, Morice MC, Mehran R

Objectives: This study sought to investigate the effect of different body mass index (BMI) categories on clinical outcomes in female patients treated with percutaneous coronary intervention (PCI) and drug-eluting stents.
Background: Patients with higher BMI might, paradoxically, have better long-term clinical outcomes after acute coronary syndrome treated with PCI.
Methods: We pooled patient-level data for female participants from 26 randomized trials on PCI with drug-eluting stents. Patients were stratified into underweight (BMI, <18.5), normoweight (BMI, 18.5 to 24.9), overweight (BMI, 25 to 29.9), obese (BMI, 30 to 34.9), or morbidly obese (BMI, >/=35). The primary endpoint was major adverse cardiac events, a composite of death, myocardial infarction, or target lesion revascularization at 3 years.
Results: Among 11,557 female patients included in the pooled database, 9,420 were treated with a drug-eluting stent and had BMI data available. Patients with higher BMI were significantly younger and with more cardiovascular risk factors. Only 139 patients were underweight and had significantly higher adjusted rates of cardiac

mortality and all-cause mortality than the rest of the population (hazard ratio: 2.20 [1.31 to 3.71] compared with normoweight). There was a significantly lower frequency of unadjusted 3-year all-cause mortality in overweight, obese, and severely obese patients compared with normoweight. However, following multivariable analysis, a trend toward increased risk of death in severely obese patients was observed, describing an inverse "J"-shaped relation between BMI and 3-year mortality. Conversely, the relationship between BMI and other outcomes, such as major adverse cardiac events, was flat for normoweight and higher BMI.
Conclusions: The risk of 3-year adjusted cardiac events did not differ across BMI groups, whereas the risk of all-cause mortality compared with normoweight was significantly higher in underweight patients and lower in overweight patients with a trend toward increased risk in the severely obese population.

Gepubliceerd: JACC Cardiovasc Interv 2018;11(1):68-76
Impact factor: 9.881; Q1

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10. In vivo serial invasive imaging of the second-generation drug-eluting absorbable metal scaffold (Magmaris - DREAMS 2G) in de novo coronary lesions: Insights from the BIOSOLVE-II First-In-Man Trial
Garcia-Garcia HM, Haude M, Kuku K, Hideo-Kajita A, Ince H, Abizaid A, Tolg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Escaned J, Dijkstra J, Waksman R

Rationale: Bioresorbable scaffolds may confer clinical benefit in long-term studies; early mechanistic studies using intravascular imaging have provided insightful information about the immediate and mid-term local serial effects of BRS on the coronary vessel wall.
Objectives: We assessed baseline, 6- and 12-month imaging data of the drug-eluting absorbable metal scaffold (DREAMS 2G).
Methods and results: The international, first-in-man BIOSOLVE-II trial enrolled 123 patients with up to 2 de novo lesions (in vessels of 2.2 to 3.7mm). Angiographic based vasomotion, curvature and angulation were assessed; intravascular ultrasound (IVUS) derived radiofrequency (RF) data analysis and echogenicity were evaluated; optical coherence tomography (OCT) attenuation and backscattering analysis were also performed. There was hardly any difference in curvature between pre-procedure and 12months (-0.0019; p=0.48). The change in angulation from pre- to 12months was negligible (-3.58 degrees ; 95% CI [-5.97, -1.20]), but statistically significant. At 6months, the change in QCA based minimum lumen diameter in response to high dose of acetylcholine and IVUS-RF necrotic core percentage showed an inverse relationship (estimate of -0.489; p=0.055) and with fibrous volume a positive relationship (estimate of 0.53, p=0.035). Bioresorption analysis by OCT showed that the maximum attenuation values decreased significantly from post-procedure at 6months (Delta 6months vs. post-proc. is -13.5 [95% CI -14.6, -12.4]) and at 12months (Delta 12months vs. post-proc. is -14.0 [95% CI -15.4, -12.6]). By radiofrequency data, the percentage of dense calcium decreased significantly from post-procedure at 6months and at 12months. Likewise, by echogenicity, hyperechogenic structures decreased significantly from post-procedure at 6months; thereafter, they remained unchanged.

Conclusion: Following implantation of DREAMS 2G, restoration of the vessel geometry, vasomotion and bioresorption signs were observed at up to 12months; importantly, these changes occurred with preservation of the lumen size between 6 and 12months. NCT01960504.

Gepubliceerd: Int J Cardiol 2018;255(22):28
Impact factor: 4.034; Q2

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11. Safety and clinical performance of a drug eluting absorbable metal scaffold in the treatment of subjects with de novo lesions in native coronary arteries: Pooled 12-month outcomes of BIOSOLVE-II and BIOSOLVE-III
Haude M, Ince H, Kische S, Abizaid A, Tolg R, Alves LP, Van Mieghem NM, Verheye S, von Birgelen C, Christiansen EH, Barbato E, Garcia-Garcia HM, Waksman R

Objectives: Based on outcomes of the BIOSOLVE-II study, a novel second generation drug-eluting absorbable metal scaffold gained CE-mark in 2016. The BIOSOLVE-III study aimed to confirm these outcomes and to obtain additional 12-month angiographic data.
Background: Bioresorbable scaffolds are intended to overcome possible long-term effects of permanent stents such as chronic vessel wall inflammation, stent crushing, and fractures.
Methods: The prospective, multicenter BIOSOLVE-II and BIOSOLVE-III studies enrolled 184 patients with 189 lesions (123 patients in BIOSOLVE-II and 61 patients in BIOSOLVE-III). Primary endpoints were in-segment late lumen loss at 6 months (BIOSOLVE-II) and procedural success (BIOSOLVE-III).
Results: Mean patient age was 65.5 +/- 10.8 years and mean lesion reference diameter was 2.70 +/- 0.43 mm. In BIOSOLVE-III, there were significantly more type B2/C lesions than in BIOSOLVE-II (80.3% versus 43.4%, P < 0.0001) and significantly more moderate-to-severe calcifications (24.2% versus 10.7%, P = 0.014). At 12 months, there was no difference in late lumen loss between the two studies; in the overall population, it was 0.25 +/- 0.31 mm in-segment and 0.39 +/- 0.34 mm in-scaffold. Target lesion failure occurred in six patients (3.3%) and included two cardiac deaths, one target-vessel myocardial infarction, and three clinically driven target lesion revascularizations. No definite or probable scaffold thrombosis was observed.
Conclusion: The pooled outcomes of BIOSOLVE-II and BIOSOLVE-III provide further evidence on the safety and performance of a novel drug-eluting absorbable metal scaffold with constant clinical and angiographic performance parameters at 12 months and no definite or probable scaffold thrombosis.

Gepubliceerd: Catheter Cardiovasc Interv 2018 Aug 5;92(7):E502-E511
Impact factor: 2.602; Q2

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12. Serial assessment of endothelial function 1, 6, and 12 months after ST-elevation myocardial infarction
Kandhai-Ragunath JJ, Doggen CJM, van der Heijden LC, Kok MM, Zocca P, de Wagenaar B, Doelman C, Jorstad HT, Peters RJG, von Birgelen C

Knowledge about the changes in endothelial function after ST-elevation myocardial infarction (STEMI) is of substantial interest, but serial data are scarce. The aim of the present study was to noninvasively evaluate whether endothelial function, as assessed shortly after primary percutaneous coronary intervention (PPCI) for STEMI, may improve until 12-month follow-up. This prospective observational cohort study was performed in patients in the RESPONSE randomized trial who participated in a substudy and underwent noninvasive assessment of endothelial function at 1 (baseline), 6, and 12-month follow-up after treatment of a STEMI by PPCI. The reactive hyperemia peripheral artery tonometry (RH-PAT) method was used to assess endothelial function (higher RH-PAT index signifies better function). Of the 70 study participants, who were 57.4 +/- 9.7 years of age, 55 (78.6%) were male and 9 (13%) had diabetes. The endothelial function deteriorated significantly during follow-up: the RH-PAT index at baseline, 6, and 12-month follow-up was 1.90 +/- 0.58, 1.81 +/- 0.57, and 1.69 +/- 0.49, respectively (p = 0.04). Although patients were carefully treated in outpatient clinics and adequate pharmacological therapy was prescribed, we noted an increase in total cholesterol (p = 0.001), LDL cholesterol (p = 0.002), HbA1C (p = 0.054), and diastolic blood pressure (p = 0.047) However, multivariate analysis revealed that this increase in cardiovascular risk factors could not explain the observed deterioration in endothelial function. In patients with STEMI, we observed a significant deterioration in endothelial function during 12 months after PPCI that could not be explained by changes in the traditional cardiovascular risk profile.

Gepubliceerd: Heart Vessels 2018 Sep;33(9):978-85
Impact factor: 2.185; Q3

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13. Impact of surgery on presence and dimensions of anatomical isthmuses in tetralogy of Fallot

Kapel GFL, Laranjo S, Blom NA, Hazekamp MG, Schalij MJ, Bartelings MM, Jongbloed MRM, Zeppenfeld K

Objective: In tetralogy of Fallot (TOF), the dominant ventricular tachycardia substrates are slow-conducting anatomical isthmuses. Surgical correction has evolved, which might have influenced isthmus presence and dimensions.
Methods: One hundred and forty-two postmortem TOF specimens (84/58 corrected/uncorrected) were studied for isthmus presence. Isthmus 1 is located between the tricuspid annulus and right ventricular (RV) outflow tract (RVOT) patch/RV incision, isthmus 2 between RVOT patch/RV incision and pulmonary valve, isthmus 3 between pulmonary valve and ventricular septal defect (patch), isthmus 4 between ventricular septal defect (patch) and tricuspid annulus. Isthmus width and thickness were measured.
Results: Of 84 corrected postmortem TOF specimens (death: 6.6 years (4.0-11.5)), 83 demonstrated isthmus 1 (99%, width=25+/-10 mm, thickness=5+/-2 mm), 35 isthmus 2 (42%, width=10+/-9 mm, thickness=3+/-2 mm), 83 isthmus 3 (99%, width=10+/-6 mm, thickness=5+/-2 mm), and 5 isthmus 4 (6%, width=4+/-2 mm, thickness=2+/-1 mm). Transatrial-transpulmonary correction (n=49) as compared with transventricular correction (n=35) prevented isthmus 2 (0% vs 100%, P<0.001). Transatrial-transpulmonary correction at age <1 year (n=7) as compared with >/=1 year (n=42) required a smaller transannular RVOT patch (28+/-15 vs 45+/-14 mm, P<0.001). Mode and timing of correction did not influence presence and dimensions

of isthmus 3. In corrected and uncorrected TOF specimens (death 1.8 years (0.5-6.6)), the range of isthmus 3 dimensions was broad (width: min=2 mm, max=32 mm; thickness: min=1, max 13 mm) across all ages. Isthmus 3 width and thickness were strongly correlated (r=0.65, P<0.001).
Conclusions: In TOF, the current routine use of transatrial-transpulmonary correction prevents isthmus 2. Correction <1 year reduces transannular patch size, which may influence isthmus 1 width later in life. Mode and timing of correction did not change prevalence and dimensions of isthmus 3, in which dimensions varied widely in uncorrected and corrected TOF.

Gepubliceerd: Heart 2018 Jan 5;104(14):1200-7
Impact factor: 5.420; Q1

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14. Slow Conducting Electroanatomic Isthmuses: An Important Link Between QRS Duration and Ventricular Tachycardia in Tetralogy of Fallot
Kapel GFL, Brouwer C, Jalal Z, Sacher F, Venlet J, Schalij MJ, Thambo JB, Jongbloed MRM, Blom NA, de Riva M, Zeppenfeld K

Objectives: This study sought to evaluate the influence of slow conducting anatomic isthmuses (SCAI) as dominant ventricular tachycardia (VT) substrate on QRS duration.
Background: QRS prolongation has been associated with VT in repaired tetralogy of Fallot.
Methods: Seventy-eight repaired tetralogy of Fallot patients (age 37 +/- 15 years, 52 male, QRS duration 153 +/- 29 ms, 67 right bundle branch blocks [RBBB]) underwent programmed stimulation and electroanatomic activation mapping during sinus rhythm. Right ventricular (RV) surface, RV activation pattern, RV activation time, conduction velocity at AI, and remote RV sites were determined.
Results: Twenty-four patients were inducible for VT (VT+); SCAI was present in 22 of 24 VT+ but only in 2 of 54 patients without inducible VT (VT-). Conduction velocity through AI was slower in VT+ patients (median of 0.3 [0.3 to 0.4] vs. 0.7 [0.6 to 0.9] m/s; p < 0.01) but conduction velocity in the remote RV did not differ between groups. In non-RBBB, QRS duration was similar in VT+ patients (n = 6) and VT- patients (n = 5), but RV activation within SCAI exceeded QRS offset in VT+ patients (37 +/- 20 ms vs. -5 +/- 9 ms, p < 0.01). In RBBB, both QRS duration and RV activation time were longer in VT+ patients (n = 18, 17 of 18 QRS > 150 ms) compared with VT- patients (n = 49, 27 of 49 QRS > 150 ms) (173 +/- 22 ms vs. 156 +/- 20 ms; p < 0.01; 141 +/- 22 ms vs. 129 +/- 21 ms; p = 0.04). In VT+ patients, QRS prolongation >150 ms (n = 17) was due to SCAI or blocked isthmus in 15 patients (88%) and 1 (6%). In contrast, in VT- patients, QRS prolongation >150 ms (n = 27) was due to enlarged RV or blocked isthmus in 10 patients (37%) and 8 (30%), but due to SCAI in only 1 (4%). After exclusion of a severely enlarged RV, a QRS duration >150 ms was highly predictive for SCAI/blocked AI (OR: 17; 95% CI: 3.3 to 84; p < 0.01).
Conclusions: A narrow QRS interval does not exclude VT-related SCAI. In the presence of RBBB, SCAI further prolongs QRS duration. QRS duration >150 ms is highly suspicious for SCAI or isthmus block distinguishable by electroanatomic mapping.

Gepubliceerd: JACC Clin Electrophysiol 2018 Jun;4(6):781-93

Impact factor: 0; nvt

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15. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial
Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, Zurakowski A, Schotborgh CE, Hoorntje JCA, Eek CH, Cook S, Togni M, Meuwissen M, van Royen N, van Vliet R, Wedel H, Delewi R, Zijlstra F

Objective: To show that limiting dual antiplatelet therapy (DAPT) to six months in patients with event-free ST-elevation myocardial infarction (STEMI) results in a non-inferior clinical outcome versus DAPT for 12 months.
Design: Prospective, randomised, multicentre, non-inferiority trial.
Setting: Patients with STEMI treated with primary percutaneous coronary intervention (PCI) and second generation zotarolimus-eluting stent.
Participants: Patients with STEMI aged 18 to 85 that underwent a primary PCI with the implantation of second generation drug-eluting stents were enrolled in the trial. Patients that were event-free at six months after primary PCI were randomised at this time point.
Interventions: Patients that were taking DAPT and were event-free at six months were randomised 1:1 to single antiplatelet therapy (SAPT) (ie, aspirin only) or to DAPT for an additional six months. All patients that were randomised were then followed for another 18 months (ie, 24 months after the primary PCI).
Main outcome measures: The primary endpoint was a composite of all cause mortality, any myocardial infarction, any revascularisation, stroke, and thrombolysis in myocardial infarction major bleeding at 18 months after randomisation.
Results: A total of 1100 patients were enrolled in the trial between 19 December 2011 and 30 June 2015. 870 were randomised: 432 to SAPT versus 438 to DAPT. The primary endpoint occurred in 4.8% of patients receiving SAPT versus 6.6% of patients receiving DAPT (hazard ratio 0.73, 95% confidence interval 0.41 to 1.27, P=0.26). Non-inferiority was met (P=0.004 for non-inferiority), as the upper 95% confidence interval of 1.27 was smaller than the prespecified non-inferiority margin of 1.66.
Conclusions: DAPT to six months was non-inferior to DAPT for 12 months in patients with event-free STEMI at six months after primary PCI with second generation drug-eluting stents.
Trial registration: Clinicaltrials.gov NCT01459627.

Gepubliceerd: BMJ 2018 Oct 2;363:k3793
Impact factor: 23.562; Q1

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16. Patient preference for radial versus femoral vascular access for elective coronary procedures: The PREVAS study
Kok MM, Weernink MGM, von Birgelen C, Fens A, van der Heijden LC, van Til JA

Objectives: To explore patient preference for vascular access site in percutaneous coronary procedures, the perceived importance of benefits and risks of transradial access (TRA) and transfemoral access (TFA) were assessed. In addition, direct

preference for vascular access and preference for shared decision making (SDM) were evaluated.
Background: TRA has gained significant ground on TFA during the last decades. Surveys on patient preference have mostly been performed in dedicated TRA trials.
Methods: In the PREVAS study (Clinicaltrials.gov: NCT02625493) a stated preference elicitation method best-worst scaling (BWS) was used to determine patient preference for six treatment attributes: bleeding, switch of access-site, postprocedural vessel quality, mobilization and comfort, and over-night stay. Based on software-generated treatment scenarios, 142 patients indicated which characteristics they perceived most and least important in treatment choice. Best-minus-Worst scores and attribute importance were calculated.
Results: Bleeding risk was considered most important (attribute importance 31.3%), followed by length of hospitalization (22.6%), and mobilization(20.2%). Most patients preferred the approach of their current procedure (85.9%); however, 71.1% of patients with experience with both access routes favored TRA ($P < 0.001$). Most patients (38.0%) appreciated SDM, balanced between patient and cardiologist.
Conclusions: Patients appreciate lower bleeding risk and early ambulation, factors favoring TRA. Previous experience with a single access route has a major impact on preference, while experience with both routes generally resulted in preference for TRA. Most patients prefer balanced SDM. (c) 2017 The Authors Catheterization and Cardiovascular Interventions Published by Wiley Periodicals, Inc.

Gepubliceerd: Catheter Cardiovasc Interv 2018;91(1):17-24
Impact factor: 2.602; Q2

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17. Prediabetes and its Impact on Clinical Outcome After Coronary Intervention in a Broad Patient Population
Kok MM, von Birgelen C, Sattar N, Zocca P, Lowik MM, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Kant GD, Doelman C, Tjon Joe Gin RM, Stoel MG, van Houwelingen G, Linssen GCM, IJzerman MJ, Doggen CJM, van der Heijden LC

Aims: It is unclear whether detection of prediabetes(Pre-DM) by routine assessment of glycated haemoglobin A1c(HbA1c) and fasting plasma glucose(FPG) among patients undergoing percutaneous coronary intervention(PCI) with contemporary drug-eluting stents(DES) may help identify subjects with increased event risk. We assessed the relation between glycaemia status and 1-year outcome after PCI.
Methods and results: Glycaemia status was determined in 2,362 non-diabetic BIO-RESORT participants, treated at all four study sites, to identify Pre-DM (HbA1c 42-47mmol/mol; FPG 6.1-6.9mmol/L) and unknown diabetes mellitus(DM) (HbA1c>/=48mmol/mol; FPG>/=7.0mmol/L). Another 624 patients had medically treated DM. The main composite endpoint consisted of death, myocardial infarction, or revascularisation. Glycaemic state was known in 2,986 participants: 324(11%) patients had Pre-DM, 793(27%) had DM(known or new), and 1,869(63%) patients had normoglycaemia. Pre-DM and DM patients differed from normoglycemic patients in cardiovascular risk factors. The composite endpoint occurred in 11.1% in Pre-DM, 10.5% in DM, and 5.7% in normoglyacemia($p<0.001$). Pre-DM was associated with a 2-times higher event risk compared to normoglycaemia(adj.HR 2.0, 95%CI:1.4-3.0).
Conclusions: Following PCI with contemporary DES, all-comers with Pre-DM had significantly higher event risks than normoglycemic patients. In non-DM patients

requiring PCI, routine assessment of HbA1c and FPG appears to be of value to identify subjects with increased event risk.

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Impact factor: 4.417; Q2

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18. Two-year clinical outcome of all-comers treated with three highly dissimilar contemporary coronary drug-eluting stents in the randomised BIO-RESORT trial
Kok MM, Zocca P, Buiten RA, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Stoel MG, van Houwelingen G, Linssen GCM, Doggen CJM, von Birgelen C

Aims: The aim of the study was to evaluate the two-year clinical outcome of all-comer trial participants who were treated with two very different thin-strut biodegradable polymer versus thin-strut durable polymer drug-eluting stents (DES). Prolonged clinical outcome after discontinuation of dual antiplatelet therapy is of particular interest, given the highly dissimilar polymer types, amount, distribution, and degradation speed of both biodegradable polymer DES.
Methods and results: The BIO-RESORT trial (NCT01674803) randomly assigned 3,514 patients to treatment with biodegradable polymer SYNERGY everolimus-eluting stents (EES) or Orsiro sirolimus-eluting stents (SES), or durable polymer Resolute Integrity zotarolimus-eluting stents (ZES). At two-year follow-up (available in 98.8%), the rate of the primary composite endpoint target vessel failure (TVF) was 8.3% in ZES versus 6.8% in EES (p=0.19) and 6.6% in SES (p=0.12). Landmark analyses at one year revealed differences between SES and ZES in the rates of target lesion revascularisation and target lesion failure (0.6% vs. 1.5%, p=0.04, and 1.1% vs. 2.4%, p=0.02, respectively) as well as other composite secondary endpoints that reached statistical significance.
Conclusions: At two-year follow-up, there was no significant between-DES difference in the rates of the primary endpoint. Landmark analyses provided a signal that the use of SES versus ZES might reduce the risk of repeat revascularisation after one-year follow-up.

Gepubliceerd: EuroIntervention 2018 Oct 20;14(8):915-23
Impact factor: 4.417; Q2

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19. Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study
Maass AH, Vernooy K, Wijers SC, van 't Sant J, Cramer MJ, Meine M, Allaart CP, De Lange FJ, Prinzen FW, Gerritse B, Erdtsieck E, Scheerder COS, Hill MRS, Scholten M, Kloosterman M, Ter Horst IAH, Voors AA, Vos MA, Rienstra M, Van Gelder IC

Aims: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in systolic heart failure patients with ventricular conduction delay. Variability of individual response to CRT warrants improved patient selection. The Markers and Response to CRT (MARC) study was designed to investigate markers related to response to CRT.

Methods and results: We prospectively studied the ability of 11 clinical, 11 electrocardiographic, 4 echocardiographic, and 16 blood biomarkers to predict CRT response in 240 patients. Response was measured by the reduction of indexed left ventricular end-systolic volume (LVESVi) at 6 months follow-up. Biomarkers were related to LVESVi change using log-linear regression on continuous scale. Covariates that were significant univariately were included in a multivariable model. The final model was utilized to compose a response score. Age was 67 +/- 10 years, 63% were male, 46% had ischaemic aetiology, LV ejection fraction was 26 +/- 8%, LVESVi was 75 +/- 31 mL/m2, and QRS was 178 +/- 23 ms. At 6 months LVESVi was reduced to 58 +/- 31 mL/m2 (relative reduction of 22 +/- 24%), 130 patients (61%) showed >/= 15% LVESVi reduction. In univariate analysis 17 parameters were significantly associated with LVESVi change. In the final model age, QRSAREA (using vectorcardiography) and two echocardiographic markers (interventricular mechanical delay and apical rocking) remained significantly associated with the amount of reverse ventricular remodelling. This CAVIAR (CRT-Age-Vectorcardiographic QRSAREA -Interventricular Mechanical delay-Apical Rocking) response score also predicted clinical outcome assessed by heart failure hospitalizations and all-cause mortality.
Conclusions: The CAVIAR response score predicts the amount of reverse remodelling after CRT and may be used to improve patient selection. Clinical Trials: NCT01519908.

Gepubliceerd: Europace 2018 Feb 1;20(2):e1-e10
Impact factor: 5.231; Q1

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20. Impact of Diabetes and Increasing Body Mass Index Category on Left Ventricular Systolic and Diastolic Function
Ng ACT, Prevedello F, Dolci G, Roos CJ, Djaberi R, Bertini M, Ewe SH, Allman C, Leung DY, Marsan NA, Delgado V, Bax JJ

Background: Diabetes and obesity are both worldwide growing epidemics, and both are independently associated with increased risk for heart failure and death. The aim of this study was to examine the additive detrimental effect of both diabetes and increasing body mass index (BMI) category on left ventricular (LV) myocardial systolic and diastolic function.
Methods: The present retrospective multicenter study included 653 patients (337 with type 2 diabetes and 316 without diabetes) of increasing BMI category. All patients had normal LV ejection fractions. LV myocardial systolic (peak systolic global longitudinal strain and peak systolic global longitudinal strain rate) and diastolic (average mitral annular e' velocity and early diastolic global longitudinal strain rate) function was quantified using echocardiography.
Results: Increasing BMI category was associated with progressively more impaired LV myocardial function in patients with diabetes ($P < .001$). Patients with diabetes had significantly more impaired LV myocardial function for all BMI categories compared with those without diabetes ($P < .001$). On multivariate analysis, both diabetes and obesity were independently associated with an additive detrimental effect on LV myocardial systolic and diastolic function. However, obesity was associated with greater LV myocardial dysfunction than diabetes.

Conclusion: Both diabetes and increasing BMI category had an additive detrimental effect on LV myocardial systolic and diastolic function. Furthermore, increasing BMI category was associated with greater LV myocardial dysfunction than diabetes. As they frequently coexist together, future studies on patients with diabetes should also focus on obesity.

Gepubliceerd: J Am Soc Echocardiogr 2018 Aug;31(8):916-25
Impact factor: 6.827; Q1

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21. Amiodarone Rifampicin Drug-Drug Interaction Management With Therapeutic Drug Monitoring
Oude Munnink TH, Demmer A, Slenter RHJ, Movig KLL

The authors present a case of a 69-year-old man with arrhythmogenic right ventricular cardiomyopathy controlled with amiodarone and an infected orthopedic prosthesis requiring treatment with rifampicin. This combination involves a pharmacokinetic drug-drug interaction leading to subtherapeutic drug concentrations of amiodarone and its active metabolite. The long half-life of amiodarone and its active metabolite in combination with the late onset and offset of cytochrome P4503A (CYP3A4) induction by rifampicin makes this a challenging drug-drug interaction to cope with in clinical practice. Before, during, and after rifampicin treatment, the serum concentrations of amiodarone and its active metabolite were measured and the amiodarone dose was adjusted accordingly. The amiodarone dose required to maintain effective concentrations was 450% of the initial dose. The drug-drug interaction between amiodarone and rifampicin is relevant, both clinically and pharmacokinetically, and can be managed by dose adjustments of amiodarone based on serum concentrations.

Gepubliceerd: Ther Drug Monit 2018 Apr;40(2):159-61
Impact factor: 2.092; Q2

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22. Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention: An Individual Patient Data Pooled Analysis of 21 Randomized Trials and 32,524 Patients
Palmerini T, Della RD, Biondi-Zoccai G, Leon MB, Serruys PW, Smits PC, von Birgelen C, Ben-Yehuda O, Genereux P, Bruno AG, Jenkins P, Stone GW

Objectives: This study sought to investigate the impact of nonemergent, uncomplicated target lesion revascularization (TLR) on the risk of long-term mortality after percutaneous coronary intervention (PCI).
Background: Restenosis requiring TLR after PCI is generally considered a benign event.
Methods: The study pooled patient-level data from 21 randomized trials. Subjects dying the same day as or the day after the TLR procedure as well as those with myocardial infarction (MI) the day before, the same day as or the day after TLR were excluded. The primary endpoint of the study was all-cause mortality.
Results: The dataset included 32,524 patients who were stratified according to whether repeat TLR was performed during follow-up. During a median follow-up of 37

months, 2,330 (7.2%) patients underwent a nonemergent, uncomplicated TLR procedure. After adjusting for potential confounders, TLR was an independent predictor of mortality (hazard ratio: 1.23, 95% confidence interval: 1.04 to 1.45; p = 0.02). Patients undergoing nonemergent, uncomplicated TLR had significantly higher rates of non-procedure-related MI compared with those without TVR. Among patients undergoing elective TLR, MI occurring after TLR was an independent predictor of mortality (hazard ratio: 3.82; 95% confidence interval: 2.44 to 5.99; p < 0.0001).
Conclusions: Nonemergent, uncomplicated TLR after PCI is an independent predictor of long-term mortality, an association in part explained by higher rates of MI occurring after TLR. Efforts aimed at reducing TLR risk may translate into prognostic benefits including reduced rates of MI and survival.

Gepubliceerd: JACC Cardiovasc Interv 2018 May 14;11(9):892-902
Impact factor: 9.881; Q1

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23. Comparison of complications and shocks in paediatric and young transvenous and subcutaneous implantable cardioverter-defibrillator patients
Quast ABE, Brouwer TF, Kooiman KM, van Dessel PFHM, Blom NA, Wilde AAM, Knops RE

Background: Young implantable cardioverter-defibrillator (ICD) patients are prone to complications and inappropriate shocks (IAS). The subcutaneous ICD (S-ICD) may avoid lead-related complications. This study aims to describe the incidence and nature of device-related complications in young transvenous ICD (TV-ICD) and SICD patients.
Methods: Single-chamber TV-ICD and SICD patients up to and including the age of 25 years implanted between 2002 and 2015 were retrospectively analysed. Complications were defined as device-related complications requiring surgical intervention. IAS were defined as shocks for anything other than ventricular tachycardia or ventricular fibrillation. Follow-up data were collected 5 years post-implantation. Kaplan-Meier estimates for complications at 5year follow-up were calculated with a corresponding 95% confidence interval.
Results: Eighty-one patients (46 TV-ICD, 35 S-ICD) were included (median age 19.0 (IQR 16.0-23.0) and 16.5 (IQR 13.0-20.2) years respectively). Median follow-up was 60 and 40 months respectively. All-cause complication rate was 34% in the TV-ICD group and 25% in the SICD group (p= 0.64). TV-ICD patients had more lead complications: 23% (10-36%) versus 0% (p= 0.02). The rate of infections did not differ between TV-ICD and SICD: 2% (0-6%) versus 10% (0-21%) (p= 0.15). No systemic infections occurred in the SICD patients. The rates of IAS were similar, TV-ICD 22% (9-35%) versus SICD 14% (0-30%) (p= 0.40), as were those for appropriate shocks: 25% (11-39%) versus 27% (6-48%) (p= 0.92).
Conclusion: The rates of all-cause complications in this cohort were equal, though the nature of the complications differed. SICD patients did not suffer lead failures or systemic infections. An era effect is present between the two groups.

Gepubliceerd: Neth Heart J 2018 Oct 30;26(12):612-9
Impact factor: 1.476; Q3

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24. Applicability and accuracy of pretest probability calculations implemented in the NICE clinical guideline for decision making about imaging in patients with chest pain of recent onset

Roehle R, Wieske V, Schuetz GM, Gueret P, Andreini D, Meijboom WB, Pontone G, Garcia M, Alkadhi H, Honoris L, Hausleiter J, Bettencourt N, Zimmermann E, Leschka S, Gerber B, Rochitte C, Schoepf UJ, Shabestari AA, Norgaard B, Sato A, Knuuti J, Meijs MFL, Brodoefel H, Jenkins SMM, Ovrehus KA, Diederichsen ACP, Hamdan A, Halvorsen BA, Mendoza Rodriguez V, Wan YL, Rixe J, Sheikh M, Langer C, Ghostine S, Martuscelli E, Niinuma H, Scholte A, Nikolaou K, Ulimoen G, Zhang Z, Mickley H, Nieman K, Kaufmann PA, Buechel RR, Herzog BA, Clouse M, Halon DA, Leipsic J, Bush D, Jakamy R, Sun K, Yang L, Johnson T, Laissy JP, Marcus R, Muraglia S, Tardif JC, Chow B, Paul N, Maintz D, Hoe J, de Roos A, Haase R, Laule M, Schlattmann P, Dewey M

Objectives: To analyse the implementation, applicability and accuracy of the pretest probability calculation provided by NICE clinical guideline 95 for decision making about imaging in patients with chest pain of recent onset.
Methods: The definitions for pretest probability calculation in the original Duke clinical score and the NICE guideline were compared. We also calculated the agreement and disagreement in pretest probability and the resulting imaging and management groups based on individual patient data from the Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT).
Results: 4,673 individual patient data from the CoMe-CCT Consortium were analysed. Major differences in definitions in the Duke clinical score and NICE guideline were found for the predictors age and number of risk factors. Pretest probability calculation using guideline criteria was only possible for 30.8 % (1,439/4,673) of patients despite availability of all required data due to ambiguity in guideline definitions for risk factors and age groups. Agreement regarding patient management groups was found in only 70 % (366/523) of patients in whom pretest probability calculation was possible according to both models.
Conclusions: Our results suggest that pretest probability calculation for clinical decision making about cardiac imaging as implemented in the NICE clinical guideline for patients has relevant limitations. Key points: * Duke clinical score is not implemented correctly in NICE guideline 95. * Pretest probability assessment in NICE guideline 95 is impossible for most patients. * Improved clinical decision making requires accurate pretest probability calculation. * These refinements are essential for appropriate use of cardiac CT.

Gepubliceerd: Eur Radiol 2018 Sep;28(9):4006-17
Impact factor: 4.027; Q1

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25. Is the proximal left anterior descending coronary artery segment justifiably considered as the last frontier for stenting?

Roguin A, Solomonica A, von Birgelen C

Gepubliceerd: EuroIntervention 2018 Sep 20;14(7):729-31
Impact factor: 4.417; Q2

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26. High bleeding risk patients with acute coronary syndromes treated with contemporary drug-eluting stents and Clopidogrel or Ticagrelor: Insights from CHANGE DAPT
Zocca P, Kok MM, van der Heijden LC, van Houwelingen KG, Hartmann M, de Man FHAF, Stoel MG, Louwerenburg JHW, Knottnerus IL, Linssen GCM, Doggen CJM, von Birgelen C

Background: The prospective observational CHANGE DAPT study compared clopidogrel versus ticagrelor-based dual antiplatelet (DAPT) regimens in consecutive patients with acute coronary syndrome (ACS), treated with percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES). During the ticagrelor period (TP, May 2014-August 2015) there were more major bleedings than during the clopidogrel period (CP, December 2012-April 2014).
Methods and results: To evaluate whether the excess of major bleedings during TP may be limited to high bleeding risk (HBR) patients, we performed an explorative analysis of all 2062 CHANGE DAPT participants, of whom 547(26.5%) were classified as HBR (CP, n=245; TP, n=302). In HBR and non-HBR patients, we assessed the impact of CP versus TP on propensity score-adjusted rates of major bleeding and a pre-defined ischemic endpoint (composite of cardiac death, myocardial infarction, or stroke) at 1-year follow-up. Among HBR patients, the rate of major bleeding was significantly higher during TP (1.7% vs. 5.0%; HRadjusted 3.70 [95% CI 1.18-11.67], p=0.03), while there was no significant difference in the ischemic endpoint (6.6% vs. 8.0%, HRadjusted 1.23 [95% CI 0.63-2.42], p=0.54). In non-HBR patients, the rates of major bleeding (1.1% vs. 1.7%; HRadjusted 2.13 [95% CI 0.84-5.43], p=0.11) and the ischemic endpoint (2.8% vs. 3.4%, HRadjusted 1.38 [95% CI 0.74-2.57], p=0.32) were similar between both periods.
Conclusions: Among consecutive ACS patients, the increased risk of major bleeding during ticagrelor-based DAPT was limited to HBR patients. In both HBR and non-HBR patients, ticagrelor-based DAPT did not reduce ischemic outcomes following treatment with contemporary DES implantation.

Gepubliceerd: Int J Cardiol 2018 Oct 1;268:11-7
Impact factor: 4.034; Q2

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27. Are component endpoints equal? A preference study into the practice of composite endpoints in clinical trials
Vaanholt MCW, Kok MM, von Birgelen C, Weernink MGM, van Til JA

Objectives: To examine patients' perspectives regarding composite endpoints and the utility patients put on possible adverse outcomes of revascularization procedures.
Design: In the PRECORE study, a stated preference elicitation method Best-Worst Scaling (BWS) was used to determine patient preference for 8 component endpoints (CEs): need for redo percutaneous coronary intervention (PCI) within 1 year, minor stroke with symptoms <24 hours, minor myocardial infarction (MI) with symptoms <3 months, recurrent angina pectoris, need for redo coronary artery bypass grafting (CABG) within 1 year, major MI causing permanent disability, major stroke causing permanent disability and death within 24 hours.
Setting: A tertiary PCI/CABG centre.

Participants: One hundred and sixty patients with coronary artery disease who underwent PCI or CABG.
Main outcome measures: Importance weights (IWs).
Results: Patients considered need for redo PCI within 1 year (IW: 0.008), minor stroke with symptoms <24 hours (IW: 0.017), minor MI with symptoms <3 months (IW: 0.027), need for redo CABG within 1 year (IW: 0.119), recurrent angina pectoris (IW: 0.300) and major MI causing permanent disability (IW: 0.726) less severe than death within 24 hours (IW: 1.000). Major stroke causing permanent disability was considered worse than death within 24 hours (IW: 1.209). Ranking of CEs and the relative values attributed to the CEs differed among subgroups based on gender, age and educational level.
Conclusion: Patients attribute different weight to individual CEs. This has significant implications for the interpretation of clinical trial data.

Gepubliceerd: Health Expect 2018 Aug 14;21(6):1046-55
Impact factor: 2.173; Q2

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28. Perceived advantages and disadvantages of oral anticoagulants, and the trade-offs patients make in choosing anticoagulant therapy and adhering to their drug regimen
Vaanholt MCW, Weernink MGM, von Birgelen C, Groothuis-Oudshoorn CGM, IJzerman MJ, van Til JA

Objective: The objective of this study was to explore the perceived advantages and disadvantages of oral anticoagulant therapies (OAT), and the trade-offs patients make in choosing therapy and adhering to their drug regimen.
Methods: Five focus group sessions were conducted across Europe among patients with atrial fibrillation to identify the most important factors impacting OAT's value and adherence.
Results: The most frequently identified barriers to OAT were lack of knowledge; poor patient-physician relationships; distraction due to employment or social environment; prior bleeding event(s) or the fear of bleeding; and changes in routine. Factors identified as promoting adherence included patients' personality, motivation, attitudes, and medication-taking habits and routines, as well as good quality health services. Inconvenient aspects of vitamin-K antagonists, such as regular blood monitoring and diet restrictions, were not reported to influence adherence, but may trigger patients to switch to direct oral anticoagulants.
Conclusion: Most patients reported that a mixture of modifiable and non-modifiable factors helps them to take their drugs as prescribed. Individual patients' particular needs and preferences regarding OAT vary. PRACTICE IMPLICATIONS: OAT adherence can be promoted if therapies are tailored to patients' needs and preferences. Patients should be supported to share their preferences with their clinician.

Gepubliceerd: Patient Educ Couns 2018 Nov;101(11):1982-9
Impact factor: 2.785; Q2

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29. Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents (BIONYX): Rationale and design of the randomized TWENTE IV multicenter trial
van der Heijden LC, Kok MM, Zocca P, Jessurun GAJ, Schotborgh CE, Roguin A, Benit E, Aminian A, Danse PW, Lowik MM, Linssen GCM, van der Palen J, Doggen CJM, von Birgelen C

Aim: The aim was to compare in a noninferiority trial the efficacy and safety of 2 contemporary drug-eluting stents (DESs): a novel, durable polymer-coated stent versus an established bioabsorbable polymer-coated stent.
Methods and results: The BIONYX trial (ClinicalTrials.gov-no.NCT02508714) is an investigator-initiated, prospective, randomized, patient- and assessor-blinded, international, multicenter study in all-comer patients with all types of clinical syndromes and lesions who require percutaneous coronary interventions with DES. Patients at 7 study sites in the Netherlands, Belgium, and Israel were randomly assigned (1:1, stratified for gender and diabetes mellitus) to treatment with the novel, zotarolimus-eluting, durable polymer-coated Resolute Onyx stent that has a radiopaque, thin-strut, CoreWire stent platform versus the sirolimus-eluting, bioresorbable polymer-coated Orsiro stent (reference device) that has a very thin-strut, cobalt-chromium stent backbone. The primary end point is the 1-year incidence of the composite clinical end point target vessel failure consisting of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. A power calculation, assuming a target vessel failure rate of 6.0% (noninferiority margin 2.5%), revealed that 2,470 study patients would give the study 80% power (alpha level 5%), allowing for up to 3% loss to follow-up. The first patient was enrolled on October 7, 2015; on December 23, 2016, the last patient entered the study.
Conclusions: BIONYX is a large-scale, prospective, randomized, international, multicenter trial comparing a novel DES with durable coating versus a reference DES with biodegradable coating in all-comers. The study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States.

Gepubliceerd: Am Heart J 2018 Apr;198:25-32
Impact factor: 4.171; Q2

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30. Long-Term Outcome of Consecutive Patients With Previous Coronary Bypass Surgery, Treated With Newer-Generation Drug-Eluting Stents
van der Heijden LC, Kok MM, Zocca P, Sen H, Lowik MM, Mariani S, de Man FHAF, Hartmann M, Stoel MG, van Houwelingen KG, Louwerenburg JHW, Linssen GCM, Doggen CJM, Grandjean JG, von Birgelen C

Background: Percutaneous coronary intervention (PCI) in patients with previous coronary artery bypass grafting (CABG) is associated with adverse clinical events. Although newer generation drug-eluting stents showed favorable short-term safety profiles, there is a lack of long-term outcome data. We evaluated the impact of previous CABG on 5-year clinical outcomes of patients treated with PCI using newer-generation drug-eluting stents.

Methods and results: In this patient-level pooled analysis of the prospective TWENTE (The Real-World Endeavor Resolute versus Xience V Drug-Eluting Stent Study in Twente) trial and nonenrolled TWENTE registry, we assessed a consecutive series of patients who underwent PCI with newer-generation drug-eluting stents for non-ST-segment-elevation acute coronary syndromes or stable angina. Of all 1709 patients, 202 (11.8%) had a history of CABG. Patients with previous CABG had significantly higher 5-year rates of cardiac death (10.4% versus 4.3%; P<0.001) and target vessel revascularization (25.0% versus 8.1%; P<0.001). These differences remained statistically significant after adjustment for differences in baseline characteristics. Landmark analysis revealed that from 1- to 5-year follow-up, the rates of cardiac death (8.1% versus 3.2%; P<0.001) and target vessel revascularization (17.1% versus 5.9%; P<0.001) were significantly higher in patients with previous CABG. Among patients with a history of CABG, PCI of an obstructed vein graft was associated with a higher rate of 5-year target vessel revascularization (P=0.003).
Conclusions: At 5-year follow-up after PCI with newer-generation drug-eluting stents, the risk of cardiac death and target vessel revascularization was significantly higher in patients with previous CABG. The target vessel revascularization rate was highest in patients who underwent PCI of obstructed vein grafts.

Gepubliceerd: J Am Heart Assoc 2018 Jan 30;7(3)
Impact factor: 4.450; Q2

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31. Collateral Quality Decay Several Days After Primary Percutaneous Coronary Intervention: A Unique Observation From the EXPLORE Trial
van Dongen IM, Elias J, van Houwelingen G, Agostoni P, Hoebers LP, Ouweneel DM, Delewi R, Claessen BEPM, van der Schaaf RJ, Henriques JPS

Gepubliceerd: JACC Cardiovasc Interv 2018 Mar 12;11(5):511-2
Impact factor: 9.881; Q1

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32. Impact of collateralisation to a concomitant chronic total occlusion in patients with ST-elevation myocardial infarction: a subanalysis of the EXPLORE randomised controlled trial
van Dongen IM, Elias J, van Houwelingen KG, Agostoni P, Claessen BEPM, Hoebers LP, Ouweneel DM, Scheunhage EM, Delewi R, Piek JJ, Ramunddal T, Laanmets P, Eriksen E, Bax M, Suttorp MJ, van der Schaaf RJ, Tijssen JGP, Henriques JPS

Objective: The impact on cardiac function of collaterals towards a concomitant chronic total coronary occlusion (CTO) in patients with ST-elevation myocardial infarction (STEMI) has not been investigated yet. Therefore, we have evaluated the impact of well-developed collaterals compared with poorly developed collaterals to a concomitant CTO in STEMI.
Methods and results: In the EXPLORE trial, patients with STEMI and a concomitant CTO were randomised to either CTO percutaneous coronary intervention (PCI) or no-CTO PCI. Collateral grades were scored angiographically using the Rentrop grade classification. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV) at 4 months were measured using cardiac magnetic resonance imaging. Well-developed collaterals (Rentrop grades 2-3) to the CTO were present in

162 (54%) patients; these patients had a significantly higher LVEF at 4 months (46.2+/-11.4% vs 42.1+/-12.7%, p=0.004) as well as a trend for a lower LVEDV (208.2+/-55.7 mL vs 222.6+/-68.5 mL, p=0.054) when compared with patients with poorly developed collaterals to the CTO. There was no significant difference in the total amount of scar in the two groups. Event rates were statistically comparable between patients with well-developed collaterals and poorly developed collaterals to the CTO at long-term follow-up.
Conclusions: In patients with STEMI and a concomitant CTO, the presence of well-developed collaterals to a concomitant CTO is associated with a better LVEF at 4 months. However, this effect on LVEF did not translate into improvement in clinical outcome. Therefore, the presence of well-developed collaterals is important, but should not solely guide in the clinical decision-making process regarding any additional revascularisation of a concomitant CTO in patients with STEMI. Clinical trial registration: NTR1108.

Gepubliceerd: Open Heart 2018;5(2):e000810
Impact factor: 0; nvt

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33. "Silent" Diabetes and Clinical Outcome After Treatment With Contemporary Drug-Eluting Stents: The BIO-RESORT Silent Diabetes Study
von Birgelen C, Kok MM, Sattar N, Zocca P, Doelman C, Kant GD, Lowik MM, van der Heijden LC, Sen H, van Houwelingen KG, Stoel MG, Louwerenburg JHW, Hartmann M, de Man FHAF, Linssen GCM, Doggen CJM, Tandjung K

Objectives: This study sought to assess the prevalence and clinical impact of silent diabetes and pre-diabetes in "nondiabetic" percutaneous coronary intervention (PCI) all-comers.
Background: Patients with undetected and thus untreated (silent) diabetes may have higher event risks after PCI with contemporary drug-eluting stents (DES).
Methods: The BIO-RESORT Silent Diabetes study, performed at Thoraxcentrum Twente, is a substudy of the randomized multicenter BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) trial (NCT01674803). Patients underwent oral glucose tolerance testing (OGTT), and assessment of glycosylated hemoglobin with fasting plasma glucose. Primary endpoint was a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.
Results: Of the 988 participants, OGTT detected silent diabetes in 68 (6.9%), pre-diabetes in 133 (13.3%), and normal glucose metabolism in 788 (79.8%). Patients with silent diabetes had higher primary endpoint rates (13.2% vs. 7.6% vs. 4.8%; $p < 0.001$; silent diabetes vs. normal: hazard ratio: 4.2; 95% confidence interval: 1.9 to 9.2). Differences were driven by myocardial infarction ($p < 0.001$) which occurred mostly <48 h. Based on glycosylated hemoglobin and fasting plasma glucose, silent diabetes was found in 33 (3.3%) patients, pre-diabetes in 217 (22.0%) patients, and normal glucose metabolism in 738 (74.7%) patients; primary endpoint rates were similar to OGTT-based analyses (12.1% vs. 5.5% vs. 3.1%; $p = 0.01$). Multivariate analyses demonstrated that abnormal glucose metabolism by either diagnostic approach, present in 330 (33.4%) patients, independently predicted adverse event risk (hazard ratio: 2.2; 95% confidence interval: 1.2 to 4.2).

Conclusions: Abnormal glucose metabolism was detected in 1 of 3 "nondiabetic" PCI patients and was independently associated with up to 4-fold higher event risks. Future intervention trials should determine whether meaningful benefits accrue from routine glycemia testing in such patients.

Gepubliceerd: JACC Cardiovasc Interv 2018 Mar 12;11(5):448-59
Impact factor: 9.881; Q1

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34. First-in-man randomized comparison of BuMA Supreme biodegradable polymer sirolimus-eluting versus durable polymer zotarolimus-eluting coronary stents: The PIONEER trial
von Birgelen C, Asano T, Amoroso G, Aminian A, Brugaletta S, Vrolix M, Hernandez-Antolin R, van de Harst P, Iniguez A, Janssens L, Smits PC, Wykrzykowska JJ, Ribeiro VG, Periera H, Canas da SP, Piek JJ, Onuma Y, Serruys PW, Sabate M

Aims: A second iteration of a sirolimus-eluting stent (SES) that has a biodegradable PLGA-polymer coating with electrografting base layer on a thin-strut (80microm) cobalt-chromium platform (BuMA Supreme; SINOMED, Tianjin, China) has been developed. This first-in-man trial assessed the efficacy and safety of the novel device.
Methods and results: This randomized, multi-center, single-blinded, non-inferiority trial compared BuMA Supreme SES versus contemporary durable polymer zotarolimus-eluting stents (ZES) in terms of angiographic in-stent late lumen loss (LLL) at 9-months follow-up as the primary endpoint. A total of 170 patients were randomly allocated to treatment with SES (n=83) or ZES (n=87). At 9-month angiographic follow-up, in-stent LLL was 0.29+/-0.33mm in SES and 0.14+/-0.37mm in ZES (Pnon-inferiority=0.45). The in-stent percent diameter stenosis and the binary restenosis rate of the two treatment arms were similar (19.2+/-12.0% vs. 16.1+/-12.6%, p=0.09, and 3.3% vs. 4.4%, P=1.00, respectively). At 12-month clinical follow-up, there was no difference between treatment arms with regard to a device-oriented composite clinical endpoint (4.9% vs. 5.7%; p=0.72).
Conclusions: The PIONEER trial did not meet its primary endpoint in terms of in-stent LLL at 9-month follow-up. However, this result did not translate into any increase in restenosis rate or impairment in 12-month clinical outcomes.

Gepubliceerd: EuroIntervention 2017 Sep 19;13(17):2026-35
Impact factor: 4.417; Q2

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35. Late clinical outcome of stent trials: a matter of life or death?
von Birgelen C, Zocca P

Gepubliceerd: Lancet 2018 Sep 1;392(10149):713-4
Impact factor: 53.254; Q1

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36. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt-chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): an international, single-blind, randomised non-inferiority trial

von Birgelen C, Zocca P, Buiten RA, Jessurun GAJ, Schotborgh CE, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Anthonio RL, Stoel MG, Somi S, Hartmann M, Linssen GCM, Doggen CJM, Kok MM

Background: During the past decade, many patients had zotarolimus-eluting stents implanted, which had circular shape cobalt-chromium struts with limited radiographic visibility. The Resolute Onyx stent was developed to improve visibility while reducing strut thickness, which was achieved by using a novel composite wire with a dense platinum-iridium core and an outer cobalt-chromium layer. We did the first randomised clinical trial to assess the safety and efficacy of this often-used stent compared with the Orsiro stent, which consists of ultrathin cobalt-chromium struts.
Methods: We did an investigator-initiated, assessor-blinded and patient-blinded, randomised non-inferiority trial in an allcomers population at seven independently monitored centres in Belgium, Israel, and the Netherlands. Eligible participants were aged 18 years or older and required percutaneous coronary intervention with drug-eluting stents. After guide wire passage with or without predilation, members of the catheterisation laboratory team used web-based computer-generated allocation sequences to randomly assign patients (1:1) to either the Resolute Onyx or the Orsiro stent. Randomisation was stratified by sex and diabetes status. Patients and assessors were masked to allocated stents, but treating clinicians were not. The primary endpoint was target vessel failure at 1 year, a composite of cardiac death, target-vessel-related myocardial infarction, and target vessel revascularisation, and was assessed by intention to treat (non-inferiority margin 2.5%) on the basis of outcomes adjudicated by an independent event committee. This trial is registered with ClinicalTrials.gov, number NCT02508714.
Findings: Between Oct 7, 2015, and Dec 23, 2016, 2516 patients were enrolled, 2488 of whom were included in the intention-to-treat analysis (28 withdrawals or screening failures). 1243 participants were assigned to the Resolute Onyx group, and 1245 to the Orsiro group. Overall, 1765 (70.9%) participants presented with acute coronary syndromes and 1275 (51.2%) had myocardial infarctions. 1-year follow-up was available for 2478 (99.6%) patients. The primary endpoint was met by 55 (4.5%) patients in the Resolute Onyx group and 58 (4.7%) in the Orsiro group. Non-inferiority of Resolute Onyx to Orsiro was thus established (absolute risk difference -0.2% [95% CI -1.9 to 1.4]; upper limit of the one-sided 95% CI 1.1%; pnon-inferiority=0.0005). Definite or probable stent thrombosis occurred in one (0.1%) participant in the Resolute Onyx group and nine (0.7%) in the Orsiro group (hazard ratio 0.11 [95% CI 0.01-0.87]; p=0.0112).
Interpretation: The Resolute Onyx stent was non-inferior to Orsiro for a combined safety and efficacy endpoint at 1-year follow-up in allcomers. The low event rate in both groups suggests that both stents are safe, and the very low rate of stent thrombosis in the Resolute Onyx group warrants further clinical investigation.
Funding: Biotronik and Medtronic.

Gepubliceerd: Lancet 2018 Oct 6;392(10154):1235-45
Impact factor: 53.254; Q1

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37. Patients' Priorities for Oral Anticoagulation Therapy in Non-valvular Atrial Fibrillation: a Multi-criteria Decision Analysis

Weernink MGM, Vaanholt MCW, Groothuis-Oudshoorn CGM, von Birgelen C, IJzerman MJ, van Til JA

Introduction: Effectiveness of oral anticoagulants (OACs) is critically dependent on patients' adherence to intake regimens. We studied the relative impact of attributes related to effectiveness, safety, convenience, and costs on the value of OAC therapy from the perspective of patients with non-valvular atrial fibrillation.
Methods: Four attributes were identified by literature review and expert interviews: effectiveness (risk of ischemic stroke), safety (risk of major bleeding, minor bleeding, gastrointestinal complaints), convenience (intake frequency, diet restrictions, international normalized ratio [INR] blood monitoring, pill type/intake instructions), and out-of-pocket costs. Focus groups were held in Spain, Germany, France, Italy and the United Kingdom (N = 48) to elicit patients' preferences through the use of the analytical hierarchy process method.
Results: Effectiveness (60%) and side effects (27%) have a higher impact on the perceived value of OACs than drug convenience (7%) and out-of-pocket costs (6%). As for convenience, eliminating monthly INR monitoring was given the highest priority (40%), followed by reducing diet restrictions (27%), reducing intake frequency (17%) and improving the pill type/intake instructions (15%). The most important side effect was major bleeding (75%), followed by minor bleeding (15%) and gastrointestinal complaints (10%). Furthermore, 71% of patients preferred once-daily intake to twice-daily intake.
Discussion: Although the relative impact of convenience on therapy value is small, patients have different preferences for options within convenience criteria. Besides considerations on safety and effectiveness, physicians should also discuss attributes of convenience with patients, as it can be assumed that alignment to patient preferences in drug prescription and better patient education could result in higher adherence.

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Impact factor: 2.741; Q2

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38. Assessment of superficial coronary vessel wall deformation and stress: validation of in silico models and human coronary arteries in vivo
Wu X, von Birgelen C, Li Z, Zhang S, Huang J, Liang F, Li Y, Wijns W, Tu S

Cyclic biomechanical stress at the lumen-intima interface plays a crucial role in the rupture of coronary plaque. We performed a comprehensive assessment of a novel angiography-based method for four-dimensional (4D) dynamic assessment of superficial wall stress (SWS) and deformation with a total of 32 analyses in virtual stenosis models with equal lumen dimensions and 16 analyses in human coronary arteries in vivo. The in silico model analyses demonstrated that the SWS, derived by the proposed global displacement method without knowledge of plaque components or blood pressure, was comparable with the result calculated by traditional finite element method. Cardiac contraction-induced vessel deformation increased SWS. Softer plaque and positive arterial remodeling, associated with a greater plaque burden, showed more variation in mean lumen diameter within the cardiac cycle and resulted in higher SWS. In vivo patient analyses confirmed the accuracy of computed superficial wall deformation. The centerlines predicted by our method at random

selected time instant matched well with the actual one in angiograms by Procrustes analysis (scaling: 0.995 +/- 0.018; dissimilarity: 0.007 +/- 0.014). Over 50% of the maximum SWS occurred at proximal plaque shoulders. This novel 4D approach could be successfully to predict superficial wall deformation of coronary artery in vivo. The dynamic SWS might be more realistic to evaluate the risk of plaque rupture.

Gepubliceerd: Int J Cardiovasc Imaging 2018 Jun;34(6):849-61
Impact factor: 1.737; Q3

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39. 5-Year Outcome Following Randomized Treatment of All-Comers With Zotarolimus-Eluting Resolute Integrity and Everolimus-Eluting PROMUS Element Coronary Stents: Final Report of the DUTCH PEERS (TWENTE II) Trial
Zocca P, Kok MM, Tandjung K, Danse PW, Jessurun GAJ, Hautvast RWM, van Houwelingen KG, Stoel MG, Schramm AR, Tjon Joe Gin RM, de Man FHAF, Hartmann M, Louwerenburg JHW, Linssen GCM, Lowik MM, Doggen CJM, von Birgelen C

Objectives: The study sought to evaluate for the first time the 5-year outcomes after treating an all-comers population with newer-generation cobalt chromium-based Resolute Integrity zotarolimus-eluting stents (ZES) (Medtronic, Santa Rosa, California) versus platinum chromium-based PROMUS Element everolimus eluting stents (EES) (Boston Scientific, Natick, Massachusetts).
Background: The DUTCH PEERS (TWENTE II) (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity: TWENTE II) trial is a randomized, multicenter, single-blinded, investigator-initiated all-comers trial that found at its main analysis similar 1-year safety and efficacy for both drug-eluting stents. It is the first randomized trial ever to investigate the Resolute Integrity ZES and the first trial to compare both devices.
Methods: In total, 1,811 patients were 1:1 randomized to ZES versus EES. We performed a pre-specified assessment of the 5-year clinical outcomes in terms of safety and efficacy. The main endpoint target vessel failure (TVF) is a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization. Secondary endpoints included the individual components of TVF, and stent thrombosis. The study was independently monitored, and adverse clinical events were independently adjudicated.
Results: Five-year clinical follow-up data was available in 1,798 (99.3%) patients. The ZES and EES groups showed favorable outcomes, with similar 5-year incidence of TVF (13.2% vs. 14.2%; plog-rank = 0.62) and its individual components: cardiac death (4.5% vs. 4.9%; plog-rank = 0.69), target vessel-related myocardial infarction (3.1% vs. 2.6%; plog-rank = 0.47), and target vessel revascularization (7.6% vs. 8.6%; plog-rank = 0.46). The 5-year incidence of definite or probable stent thrombosis was similar (1.5% vs. 1.3%; plog-rank = 0.83).
Conclusions: At 5-year follow-up, the Resolute Integrity ZES and PROMUS Element EES showed similar and sustained results in terms of safety and efficacy for treating a broad population of all-comers.

Gepubliceerd: JACC Cardiovasc Interv 2018 Mar 12;11(5):462-9
Impact factor: 9.881; Q1

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40. High Bleeding Risk Patients Treated with Very Thin-Strut Biodegradable Polymer or Thin-Strut Durable Polymer Drug-Eluting Stents in the BIO-RESORT Trial

Zocca P, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Linssen GCM, Doggen CJM, von Birgelen C

Purpose: Patients with high bleeding risk (HBR) who undergo percutaneous coronary intervention also have an increased risk of ischemic events and represent an overall high-risk population. The coating of durable polymer drug-eluting stents (DP-DES) may induce inflammation and delay arterial healing, which might be reduced by novel biodegradable polymer DES (BP-DES). We aimed to evaluate the safety and efficacy of treating HBR patients with very thin-strut BP-DES versus thin-strut DP-DES.
Methods: Participants in BIO-RESORT (NCT01674803), an investigator-initiated multicenter, randomized all-comers trial, were treated with very thin-strut BP-DES (Synergy or Orsiro) or thin-strut DP-DES (Resolute Integrity). For the present analysis, patients were classified following HBR criteria based on previous trials. The primary endpoint was target vessel failure: a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.
Results: Of all 3514 patients, 1009 (28.7%) had HBR. HBR patients were older ($p < 0.001$) and had more co-morbidities than non-HBR patients ($p < 0.001$). At 1-year follow-up, HBR patients had significantly higher rates of target vessel failure (6.7 vs. 4.2%, $p = 0.003$), cardiac death (1.9 vs. 0.4%, $p < 0.001$), and major bleeding (3.3 vs. 1.5%, $p = 0.001$). Of all 1009 HBR patients, 673 (66.7%) received BP-DES and 336 (33.3%) had DP-DES. The primary endpoint was met by 43/673 (6.5%) patients treated with BP-DES and 24/336 (7.3%) treated with DP-DES (HR 0.88 [95%CI 0.54-1.46], $p = 0.63$). There were no significant between-group differences in the most global patient-oriented clinical endpoint (9.7 vs. 10.5%, HR 0.92 [95%CI 0.61-1.39], $p = 0.69$) and other secondary endpoints.
Conclusions: At 1-year follow-up, very thin-strut BP-DES showed similar safety and efficacy for treating HBR patients as thin-strut DP-DES.

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Impact factor: 2.771; Q2

Totale impact factor: 306.298
Gemiddelde impact factor: 7.657

Aantal artikelen 1e, 2e of laatste auteur: 20
Totale impact factor: 178.424
Gemiddelde impact factor: 8.921

Gynaecologie

1. Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial
Danhof NA, van Wely M, Repping S, Koks C, Verhoeve HR, de Bruin JP, Verberg MFG, van Hooff MHA, Cohlen BJ, van Heteren CF, Fleischer K, Gianotten J, van Disseldorp J, Visser J, Broekmans FJM, Mol BWJ, van der Veen F, Mochtar MH

Study question: Is FSH or clomiphene citrate (CC) the most effective stimulation regimen in terms of ongoing pregnancies in couples with unexplained subfertility undergoing IUI with adherence to strict cancellation criteria as a measure to reduce the number of multiple pregnancies?
Summary answer: In IUI with adherence to strict cancellation criteria, ovarian stimulation with FSH is not superior to CC in terms of the cumulative ongoing pregnancy rate, and yields a similar, low multiple pregnancy rate.
What is already known: FSH has been shown to result in higher pregnancy rates compared to CC, but at the cost of high multiple pregnancy rates. To reduce the risk of multiple pregnancy, new ovarian stimulation regimens have been suggested, these include strict cancellation criteria to limit the number of dominant follicles per cycle i.e. withholding insemination when more than three dominant follicles develop. With such a strategy, it is unclear whether the ovarian stimulation should be done with FSH or with CC.
Study design, size, duration: We performed an open-label multicenter randomized superiority controlled trial in the Netherlands (NTR 4057).
Participants/materials, setting, Methods: We randomized couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation with 75 IU FSH or 100 mg CC. Cycles were cancelled when more then three dominant follicles developed. The primary outcome was cumulative ongoing pregnancy rate. Multiple pregnancy was a secondary outcome. We analysed the data on intention to treat basis. We calculated relative risks and absolute risk difference with 95% CI.
Main results and the role of chance: Between July 2013 and March 2016, we allocated 369 women to ovarian stimulation with FSH and 369 women to ovarian stimulation with CC. A total of 113 women (31%) had an ongoing pregnancy following ovarian stimulation with FSH and 97 women (26%) had an ongoing pregnancy following ovarian stimulation with CC (RR = 1.16, 95% CI: 0.93-1.47, ARD = 0.04, 95% CI: -0.02 to 0.11). Five women (1.4%) had a multiple pregnancy following ovarian stimulation with FSH and eight women (2.2%) had a multiple pregnancy following ovarian stimulation with CC (RR = 0.63, 95% CI: 0.21-1.89, ARD = -0.01, 95% CI: -0.03 to 0.01).
Limitations, reasons for caution: We were not able to blind this study due to the nature of the interventions. We consider it unlikely that this has introduced performance bias, since pregnancy outcomes are objective outcome measures.
Wider implications of the findings: We revealed that adherence to strict cancellation criteria is a successful solution to reduce the number of multiple pregnancies in IUI. To decide whether ovarian stimulation with FSH or with CC should be the regimen of choice, costs and patients' preferences should be taken into account.
Study funding/competing interest(s): This trial received funding from the Dutch Organization for Health Research and Development (ZonMw). Prof. Dr B.W.J. Mol is

supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for Merck, ObsEva and Guerbet. The other authors declare that they have no competing interests.
Trial registration number: Nederlands Trial Register NTR4057.
Trial registration date: 1 July 2013.
Date of first patient's enrolment: The first patient was randomized at 27 August 2013.

Gepubliceerd: Hum Reprod 2018 Oct 1;33(10):1866-74
Impact factor: 4.990; Q1

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2. Influence of endometrial thickness on pregnancy rates in modified natural cycle frozen-thawed embryo transfer
Groenewoud ER, Cohlen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJM, de Bruin JP, van Dool G, Fleisher K, Friederich J, Goddijn M, Hoek A, Hoozemans DA, Kaaijk EM, Koks CAM, Laven JSE, van der Linden PJQ, Manger AP, van Rumste M, Spinder T, Macklon NS

Introduction: Pregnancy after frozen-thawed embryo transfer (FET) is a multifactorial process. Although embryo quality is a key factor in determining pregnancy, other factors, including maternal determinants, are also considered to be predictive. Even though an association between endometrial thickness measured by transvaginal ultrasound and pregnancy rates has been reported in patients undergoing various assisted reproductive technology treatments, whether endometrial thickness predicts achieving pregnancy after natural cycle FET (NC-FET) remains unclear.
Material and methods: In this cohort study, 463 patients allocated to the modified NC-FET (mNC-FET) arm of a previously published randomized controlled trial were included. Monitoring in mNC-FET cycles consisted of regular ultrasound scans, measuring both dominant follicle and endometrial thickness. When the dominant follicle reached a size of 16-20 mm, an injection of human chorionic gonadotrophin was administered and embryo thawing and transfer planned. No minimal endometrial thickness was defined below which transfer was to be deferred. The primary endpoint was ongoing pregnancy rate.
Results: Overall, the ongoing pregnancy rate per started FET cycle was 12.5%. Multivariate regression analyses showed that embryo quality was the only significant predictor for ongoing pregnancy. Mean endometrial thickness did not differ between patients achieving ongoing pregnancy and those who did not (9.0 vs. 8.8 mm, p = 0.4). Comparable results were obtained with regard to clinical pregnancy, live birth and miscarriage rates. The area under the receiver operator curve was 0.5, indicating little discriminatory value of endometrial thickness.
Conclusions: Given that endometrial thickness was not found to be predictive of pregnancy after mNC-FET, cancellation based on endometrial thickness alone may not be justified.

Gepubliceerd: Acta Obstet Gynecol Scand 2018 Jul;97(7):808-15
Impact factor: 2.694; Q2

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3. Surgical volume and conversion rate in laparoscopic hysterectomy: does volume matter? A multicenter retrospective cohort study
Keurentjes JHM, Briet JM, de Bock GH, Mourits MJE

Background: A multicenter, retrospective, cohort study was conducted in the Netherlands. The aim was to evaluate whether surgical volume of laparoscopic hysterectomies (LHs) performed by proven skilled gynecologists had an impact on the conversion rate from laparoscopy to laparotomy.
Methods: In 14 hospitals, all LHs performed by 19 proven skilled gynecologists between 2007 and 2010 were included in the analysis. Surgical volume, conversion rate and type of conversion (reactive or strategic) were retrospectively assessed. To estimate the impact of surgical volume on the conversion rate, logistic regressions were performed. These regressions were adjusted for patient's age, Body Mass Index (BMI), ASA classification, previous abdominal surgery and the indication (malignant versus benign) for the LH.
Results: During the study period, 19 proven skilled gynecologists performed a total of 1051 LHs. Forty percent of the gynecologists performed over 20 LHs per year (median 17.3, range 5.4-49.5). Conversion to laparotomy occurred in 5.0% of all LHs (53 of 1051); 38 (3.6%) were strategic and 15 (1.4%) were reactive conversions. Performing over 20 LHs per year was significantly associated with a lower overall conversion rate (ORadjusted 0.43, 95% CI 0.24-0.77), a lower strategic conversion rate (ORadjusted 0.32, 95% CI 0.16-0.65), but not with a lower reactive conversion rate (ORadjusted 0.96, 95% CI 0.33-2.79).
Conclusion: A higher annual surgical volume of LHs by proven skilled gynecologists is inversely related to the conversion rate to laparotomy, and results in a lower strategic conversion rate.

Gepubliceerd: Surg Endosc 2018;32(2):1021-6
Impact factor: 3.177; Q1

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4. Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment?
Prins JR, Eskandar S, Eggen BJL, Scherjon SA

Disturbances in fetal neurodevelopment have extensively been related to neurodevelopmental disorders in early and later life. Fetal neurodevelopment is dependent on adequate functioning of the fetal immune system. During pregnancy, the maternal immune system is challenged to both tolerate the semi-allogenic fetus and to protect the mother and fetus from microbes. The fetal immune system is influenced by maternal immune disturbances; therefore, perturbations in maternal immunity likely do not only alter pregnancy outcome but also alter fetal neurodevelopment. A possible common pathway could be modulating the functioning of tissue macrophages in the placenta and brain. Maternal immune tolerance towards the fetus involves several complex adaptations. In this active maternal immune state, the fetus develops its own immunity. As cytokines and other players of the immune system -which can pass the placenta- are involved in neurodevelopment, disruptions in immune balance influence fetal neurodevelopment. Several studies reported an association between maternal immune activation, complications of pregnancy as

preeclampsia, and altered neonatal neurodevelopment. A possible pathway involves dysfunctioning of microglia cells, the immune cells of the brain. Functionality of microglia cells during normal pregnancy is, however, poorly understood. The recent outbreak of ZIKA virus (ZKV), but also the literature on virus infections in general and its consequences on microglial cell function and fetal neurodevelopment show the devastating effects a virus infection during pregnancy can have.

Gepubliceerd: J Reprod Immunol 2018 Apr;126:18-22
Impact factor: 2.322; Q3

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5. Comparing induction of labour with oral misoprostol or Foley catheter at term: cost-effectiveness analysis of a randomised controlled multi-centre non-inferiority trial
Ten Eikelder M, van Baaren GJ, Oude Rengerink K, Jozwiak M, de Leeuw JW, Kleiverda G, Evers I, de Boer K, Brons J, Bloemenkamp K, Mol BW

Objective: To assess the costs of labour induction with oral misoprostol versus Foley catheter.
Design: Economic evaluation alongside a randomised controlled trial.
Setting: Obstetric departments of six tertiary and 23 secondary care hospitals in the Netherlands. POPULATION: Women with a viable term singleton pregnancy in cephalic presentation, intact membranes, an unfavourable cervix (Bishop score <6) without a previous caesarean section, were randomised for labour induction with oral misoprostol (n = 924) or Foley catheter (n = 921).
Methods: We performed economic analysis from a hospital perspective. We estimated direct medical costs associated with healthcare utilisation from randomisation until discharge. The robustness of our findings was evaluated in sensitivity analyses.
Main outcome measures: Mean costs and differences were calculated per women induced with oral misoprostol or Foley catheter.
Results: Mean costs per woman in the oral misoprostol group and Foley catheter group were euro4470 versus euro4158, respectively [mean difference euro312, 95% confidence interval (CI) -euro508 to euro1063]. Multiple sensitivity analyses did not change these conclusions. However, if cervical ripening for low-risk pregnancies in the Foley catheter group was carried out in an outpatient setting, with admittance to labour ward only at start of active labour, the difference would be euro4470 versus euro3489, respectively (mean difference euro981, 95% CI euro225-1817).
Conclusions: Oral misoprostol and Foley catheter generate comparable costs. Cervical ripening outside labour ward with a Foley catheter could potentially save almost euro1000 per woman.
Tweetable abstract: Oral misoprostol or Foley catheter for induction of labour generates comparable costs.

Gepubliceerd: BJOG 2018 Feb;125(3):375-83
Impact factor: 4.876; Q1

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6. The prognostic capacity of transvaginal hydrolaparoscopy to predict non-IVF conception

van Kessel M, Tros R, Oosterhuis J, Kuchenbecker WH, Vernooij EM, Bongers MY, Mol BWJ, Koks CA

Transvaginal hydrolaparoscopy (THL) is performed to investigate tubal pathology in subfertile women. This retrospective multicentre cohort study investigated the results of THL and subsequent pregnancy rates. Between 2000 and 2011, 1033 subfertile women participated in the study. The primary outcome measure was intrauterine pregnancy, either after natural conception or after treatment with intrauterine insemination or ovulation induction. Cumulative intrauterine pregnancy rates were calculated using Kaplan-Meier analysis and fecundity rate ratios (FRR) were established. THL showed bilateral patent tubes in 83%, one-sided tubal occlusion in 12.4% and bilateral tubal occlusion in 4.6% of women. Cumulative intrauterine pregnancy rates after 36 months were 52% for women with bilateral patent tubes, 44% for one-sided tubal occlusion (FRR 1.04; 95% confidence interval [CI], 0.78 to 1.39) and 7% for bilateral tubal occlusion (FRR 0.13; 95% CI, 0.04 to 0.43). Endometriosis was diagnosed in 6.4%, and adhesions in 9.1%, while 3.9% of women had both. Corresponding FRR were 0.73 (95% CI, 0.49 to 1.09), 0.68 (95% CI, 0.46 to 1.02) and 0.42 (95% CI, 0.20 to 0.84). In conclusion, women with bilateral tubal occlusion or a combination of endometriosis and adhesions found on THL significantly reduced chances of natural conception.

Gepubliceerd: Reprod Biomed Online 2018 May;36(5):552-9
Impact factor: 2.967; Q1

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7. Hysteroscopic resection of a uterine caesarean scar defect (niche) in women with postmenstrual spotting: a randomised controlled trial
Vervoort A, van der Voet LF, Hehenkamp W, Thurkow AL, van Kesteren P, Quartero H, Kuchenbecker W, Bongers M, Geomini P, de Vleeschouwer L, van Hooff M, van Vliet H, Veersema S, Renes WB, Oude Rengerink K, Zwolsman SE, Brolmann H, Mol B, Huirne J

Objective: To compare the effectiveness of a hysteroscopic niche resection versus no treatment in women with postmenstrual spotting and a uterine caesarean scar defect.
Design: Multicentre randomised controlled trial.
Setting: Eleven hospitals collaborating in a consortium for women's health research in the Netherlands. POPULATION: Women reporting postmenstrual spotting after a caesarean section who had a niche with a residual myometrium of >/=3 mm, measured during sonohysterography.
Methods: Women were randomly allocated to hysteroscopic niche resection or expectant management for 6 months.
Main outcome measures: The primary outcome was the number of days of postmenstrual spotting 6 months after randomisation. Secondary outcomes were spotting at the end of menstruation, intermenstrual spotting, dysuria, sonographic niche measurements, surgical parameters, quality of life, women's satisfaction, sexual function, and additional therapy. Outcomes were measured at 3 months and, except for niche measurements, also at 6 months after randomisation.
Results: We randomised 52 women to hysteroscopic niche resection and 51 women to expectant management. The median number of days of postmenstrual spotting at

baseline was 8 days in both groups. At 6 months after randomisation, the median number of days of postmenstrual spotting was 4 days (interquartile range, IQR 2-7 days) in the intervention group and 7 days (IQR 3-10 days) in the control group (P = 0.04); on a scale of 0-10, discomfort as a result of spotting had a median score of 2 (IQR 0-7) in the intervention group, compared with 7 (IQR 0-8) in the control group (P = 0.02).
Conclusions: In women with a niche with a residual myometrium of >/=3 mm, hysteroscopic niche resection reduced postmenstrual spotting and spotting-related discomfort.
Tweetable abstract: A hysteroscopic niche resection is an effective treatment to reduce niche-related spotting.

Gepubliceerd: BJOG 2018 Feb;125(3):326-34
Impact factor: 4.876; Q1

Totale impact factor: 25.797
Gemiddelde impact factor: 3.685

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 8.406
Gemiddelde impact factor: 2.802

Heelkunde

1. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer
Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU

Background/aims: To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer.
Methods: This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient's preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg.m-2 combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the -Clavien-Dindo classification.
Results: Twenty-five patients (25.3%) developed a grade 3-5 complication. Lower radiation attenuation was independently associated with overall ($p = 0.003$) and grade 3-5 complications ($p = 0.002$). Sarcopenic obesity was associated with overall complications (all $p < 0.05$). Skeletal muscle measurements and survival were not significantly related.
Conclusion: Radiation attenuation was associated with overall and grade 3-5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications.

Gepubliceerd: Dig Surg 2018 Jun 13;1-8
Impact factor: 2.031; Q2

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2. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial
Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM

Gepubliceerd: BMC Gastroenterol 2018 Feb 21;18(1):29
Impact factor: 2.731; Q3

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3. Snapshot Study on the Value of Omentoplasty in Abdominoperineal Resection with Primary Perineal Closure for Rectal Cancer

Blok RD, Musters GD, Borstlap WAA, Buskens CJ, Bemelman WA, Tanis PJ, Dutch Snapshot Research Group,includes Lips DJ

Background: Perineal wound complications are often encountered following abdominoperineal resection (APR). Filling of the pelvic space by omentoplasty (OP) might prevent these complications, but there is scant evidence to support its routine application.
Objective: The aim of this study was to evaluate the impact of OP on perineal wound complications.
Methods: All patients undergoing APR with primary perineal closure (PPC) for non-locally advanced rectal cancer in 71 Dutch centers in 2011 were selected from a cross-sectional snapshot study. Outcomes were compared between PPC with or without OP, which was based on variability in practice among surgeons.
Results: Of 639 patients who underwent APR for rectal cancer, 477 had a non-locally advanced tumor and PPC was performed. Of those, 172 (36%) underwent OP. Patients with OP statistically more often underwent an extralevator approach (32% vs. 14%). Median follow-up was 41 months (interquartile range 22-47). There were no significant differences with or without OP in terms of non-healing of the perineal wound at 30 days (47% vs. 48%), non-healing at the end of follow-up (9% vs. 5%), pelvic abscess (12% vs. 13%) or re-intervention for ileus (5% vs. 3%). Perineal hernia developed significantly more often after OP (13% vs. 7%), also by multivariable analysis (odds ratio 2.61, 95% confidence interval 1.271-5.364; p = 0.009).
Conclusions: In contrast to previous assumptions, OP after APR with PPC appeared not to improve perineal wound healing and seemed to increase the occurrence of perineal hernia. These findings question the routine use of OP for primary filling of the pelvic space.

Gepubliceerd: Ann Surg Oncol 2018 Mar;25(3):729-36
Impact factor: 3.857; Q1

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4. Watchful Waiting Versus Surgery of Mildly Symptomatic or Asymptomatic Inguinal Hernia in Men Aged 50 Years and Older: A Randomized Controlled Trial

de Goede B, Wijsmuller AR, van Ramshorst GH, van Kempen BJ, Hop WC, Klitsie PJ, Scheltinga MR, de Haan J, Mastboom WJ, van der Harst E, Simons MP, Kleinrensink GJ, Jeekel J, Lange JF, INCA Trialists' Collaboration

Objective: To compare if watchful waiting is noninferior to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia.
Background: The role of watchful waiting in older male patients with mildly symptomatic or asymptomatic inguinal hernia is still not well-established.
Methods: In this noninferiority trial, we randomly assigned men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia to either elective inguinal hernia repair or watchful waiting. Primary endpoint was the mean difference in a 4-point pain/discomfort score at 24 months of follow-up. Using a 0.20-point difference as a clinically relevant margin, it was hypothesized that watchful waiting was noninferior to elective repair. Secondary endpoints included quality of life, event-free survival, and crossover rates.

Results: Between January 2006 and August 2012, 528 patients were enrolled, of whom 496 met the inclusion criteria: 234 were assigned to elective repair and 262 to watchful waiting. The mean pain/discomfort score at 24 months was 0.35 [95% confidence interval (CI) 0.28-0.41)] in the elective repair group and 0.58 (95% CI 0.52-0.64) in the watchful waiting group. The difference of these means (MD) was -0.23 (95% CI -0.32 to -0.14). In the watchful waiting group, 93 patients (35.4%) eventually underwent elective surgery and 6 patients (2.3%) received emergent surgery for strangulation/incarceration. Postoperative complication rates and recurrence rates in these 99 operated individuals were comparable with individuals originally assigned to the elective repair group (8.1% vs 15.0%; P = 0.106, 7.1% vs 8.9%; P = 0.668, respectively).
Conclusions: Our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint. Nevertheless, in view of all other findings, we feel that our results justify watchful waiting as a reasonable alternative compared with surgery in men aged 50 years and older.

Gepubliceerd: Ann Surg 2018;267(1):42-9
Impact factor: 9.203; Q1

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5. Signet Ring Cell Carcinoma of the Ampulla of Vater: A Rare Histopathological Variant
de Klein GW, van Baarlen J, Mekenkamp LJ, Liem MSL, Klaase JM

Signet ring cell carcinoma (SRCC) of the ampulla of Vater is an extremely rare tumor. Our case describes a 45-year-old female presenting with jaundice and pruritus. Computed tomography, endoscopy, and endoscopic retrograde cholangiopancreatography showed a tumor of the ampulla of Vater without distant metastasis. Histological biopsy confirmed a malignant tumor with SRCC characteristics and immunohistochemical staining revealed a mixed type profile (both intestinal and pancreatobiliary characteristics). A pylorus-preserving pancreatoduodenectomy was performed and the patient recovered without complications. Pathology results concluded a pT2N0 ampullary SRCC. SRCC of the ampulla of Vater is known to be highly malignant. After 13 months of follow-up, our patient showed no signs of recurrence.

Gepubliceerd: Case Rep Gastroenterol 2018 Jan;12(1):194-201
Impact factor: 0; nvt

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6. Minimally invasive versus open pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial
de Rooij T, van Hilst J, Bosscha K, Dijkgraaf MG, Gerhards MF, Groot Koerkamp B, Hagendoorn J, de Hingh IH, Karsten TM, Lips DJ, Luyer MD, Molenaar IQ, van Santvoort HC, Tran TCK, Busch OR, Festen S, Besselink MG

Background: Data from observational studies suggest that minimally invasive pancreatoduodenectomy (MIPD) is superior to open pancreatoduodenectomy regarding intraoperative blood loss, postoperative morbidity, and length of hospital stay, without increasing total costs. However, several case-matched studies failed to

demonstrate superiority of MIPD, and large registry studies from the USA even suggested increased mortality for MIPDs performed in low-volume (<10 MIPDs annually) centers. Randomized controlled multicenter trials are lacking but clearly required. We hypothesize that time to functional recovery is shorter after MIPD compared with open pancreatoduodenectomy, even in an enhanced recovery setting.
Methods/design: LEOPARD-2 is a randomized controlled, parallel-group, patient-blinded, multicenter, phase 2/3, superiority trial in centers that completed the Dutch Pancreatic Cancer Group LAELAPS-2 training program for laparoscopic pancreatoduodenectomy or LAELAPS-3 training program for robot-assisted pancreatoduodenectomy and have performed >/= 20 MIPDs. A total of 136 patients with symptomatic benign, premalignant, or malignant disease will be randomly assigned to undergo minimally invasive or open pancreatoduodenectomy in an enhanced recovery setting. After the first 40 patients (phase 2), the data safety monitoring board will assess safety outcomes (not blinded for treatment allocation) and decide on continuation to phase 3. Patients from phase 2 will then be included in phase 3. The primary outcome measure is time (days) to functional recovery. All patients will be blinded for the surgical approach, at least until postoperative day 5, but preferably until functional recovery has been attained. Secondary outcome measures are operative and postoperative outcomes, including clinically relevant complications, mortality, quality of life, and costs.
Discussion: The LEOPARD-2 trial is designed to assess whether MIPD reduces time to functional recovery, as compared with open pancreatoduodenectomy in an enhanced recovery setting.
Trial registration: Netherlands Trial Register, NTR5689 . Registered on 2 March 2016.

Gepubliceerd: Trials 2018 Jan 3;19(1):1
Impact factor: 2.067; Q3

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7. Complications after hip fracture surgery: are they preventable?
Flikweert ER, Wendt KW, Diercks RL, Izaks GJ, Landsheer D, Stevens M, Reininga IHF

Purpose: Surgery for hip fractures is frequently followed by complications that hinder the rehabilitation of patients. The aim of this study was to describe the incidence rate and type of complications, including mortality, after hip fracture surgery, and to identify the risk factors of these complications that may be amenable to prevention.
Methods: Prospective cohort study of all consecutive patients aged >/=60 treated for a hip fracture at University Medical Center Groningen between July 2009 and June 2013. All patients were treated in a comprehensive multidisciplinary care pathway. Logistic regression analyses were used to investigate which variables were significant risk factors for the occurrence of complications. Additional analyses were conducted to investigate whether the independent variables were significant risk factors for several specific complications and mortality.
Results: The study population consisted of 479 patients with a mean age of 78.4 (SD 9.5) years; 33% were men. The overall complication rate was 75%. Delirium was the complication seen most frequently (19%); the incidence of surgical complications was 9%. Most risk factors for complications were not preventable (high comorbidity rate, high age and dependent living situation). However, general anesthesia (OR 1.51;

95% CI 0.97-2.35) and delay in surgery (OR 3.16; 95% CI 1.43-6.97) may be risk factors that can potentially be prevented. Overall, the mortality risk was not higher in patients with a complication, but delirium and pneumonia were risk factors for mortality.
Conclusion: The overall complication rate after hip fracture surgery was high. Only few complications were potentially preventable.

Gepubliceerd: Eur J Trauma Emerg Surg 2017 Aug 9;44(4):573-80
Impact factor: 1.704; Q2

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8. Wound swab and wound biopsy yield similar culture results
Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Klont R, Guebitz G, Heinzle A, van der Palen J

The question remains whether wound swabs yield similar culture results to the traditional gold standard, biopsies. Swabs are not invasive and easy to perform. However, they are believed to capture microorganisms from the surface rather than microorganisms that have invaded tissue. Several studies compared swabs and biopsies using different populations and sampling methods, complicating the ability to draw conclusions for clinical practice. This study aimed to compare swab and biopsy in clinical practice, by including a variety of wounds and using standard sampling and culture procedures. Swabs (Levine technique) and biopsies were taken for microbiological culture in a standardized manner from the same location of one wound for each patient. Statistical analyses were performed to determine overall agreement, and observed agreement and kappa for specific microorganisms. A variety of wounds of 180 patients from different healthcare facilities in The Netherlands were included. Skin flora was more frequently cultured from swabs, resulting in similar recovery rates when excluding skin flora (1.34 vs 1.35). Swabs were able to identify all microorganisms cultured from biopsies in 131 wounds (72.8%) wounds. Most frequently identified organisms were Staphylococcus aureus, Pseudomonas aeruginosa, and beta-haemolytic streptococci species. Observed agreement and kappa for these organisms varied between 87.2 and 97.8% and 0.73 and 0.85, respectively. This study demonstrates that swabs and biopsies tend to yield the same culture results when taken from the same location. For frequently occurring microorganisms, agreement between the two methods was even higher. Therefore, there seems to be no direct need for invasive biopsy in clinical practice.

Gepubliceerd: Wound Repair Regen 2018 Mar;26(2):192-9
Impact factor: 2.952; Q1

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9. Limited Adherence to Peripheral Arterial Disease Guidelines and Suboptimal Ankle Brachial Index Reliability in Dutch Primary Care
Hageman D, Pesser N, Gommans LNM, Willigendael EM, van Sambeek MRHM, Huijbers E, Snoeijen A, Scheltinga MRM, Teijink JAW

Objective/background: The Dutch College of General Practitioners' guideline on peripheral arterial disease (PAD) provides clear recommendations on the management of PAD. An ankle brachial index (ABI) measurement, prescription of

antiplatelet drugs and statins, and supervised exercise therapy (SET) for intermittent claudication (IC) are advised. The aims of this study were to determine the adherence of general practitioners (GPs) to their own guideline on PAD and to evaluate the reliability of primary care ABI measurements.
Methods: This was a cross-sectional study. All patients suspected of having symptomatic PAD who were referred by GPs to a large hospital in 2015 were evaluated regarding three of the guideline criteria: (i) ABI measurement; (ii) prescription of secondary prevention; (iii) initiation of SET. ABI values obtained in primary care and the hospital's vascular laboratory were compared using correlation coefficients and regression analysis. An abnormal ABI was defined as a value <.9 (normal ABI >/=.9).
Results: Of 308 potential patients with new onset PAD, 58% (n = 178) had undergone ABI measurement prior to referral. A modest correlation between ABI values obtained in primary care and the vascular laboratory was found (r = .63, p < .001). Furthermore, a moderate reliability was calculated (intraclass correlation coefficient 0.60, 95% confidence interval 0.49-0.69, p < .001). Of the new patients with an abnormal ABI, 59% used antiplatelet drugs and 55% used statins. A referral for SET was initiated by a GP in 10% of new PAD patients with IC symptoms.
Conclusions: Adherence by Dutch GPs to their own society's PAD guideline has room for improvement. The reliability of ABI measurements is suboptimal, whereas rates of prescription of secondary prevention and initiation of SET as primary treatment for IC need upgrading.

Gepubliceerd: Eur J Vasc Endovasc Surg 2018 Jun;55(6):867-73
Impact factor: 3.877; Q1

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10. Displaced femoral neck fractures in patients 60 years of age or younger: results of internal fixation with the dynamic locking blade plate
Kalsbeek JH, van Walsum ADP, Vroemen JPAM, Janzing HMJ, Winkelhorst JT, Bertelink BP, Roerdink WH

Aims: The objective of this study was to investigate bone healing after internal fixation of displaced femoral neck fractures (FNFs) with the Dynamic Locking Blade Plate (DLBP) in a young patient population treated by various orthopaedic (trauma) surgeons.
Patients and methods: We present a multicentre prospective case series with a follow-up of one year. All patients aged </= 60 years with a displaced FNF treated with the DLBP between 1st August 2010 and December 2014 were included. Patients with pathological fractures, concomitant fractures of the lower limb, symptomatic arthritis, local infection or inflammation, inadequate local tissue coverage, or any mental or neuromuscular disorder were excluded. Primary outcome measure was failure in fracture healing due to nonunion, avascular necrosis, or implant failure requiring revision surgery.
Results: In total, 106 consecutive patients (mean age 52 years, range 23 to 60; 46% (49/106) female) were included. The failure rate was 14 of 106 patients (13.2%, 95% confidence interval (CI) 7.1 to 19.9). Avascular necrosis occurred in 11 patients (10.4%), nonunion in six (5.6%), and loss of fixation in two (1.9%).
Conclusion: The rate of fracture healing after DLBP fixation of displaced femoral neck fracture in young patients is promising and warrants further investigation by a

randomized trial to compare the performance against other contemporary methods of fixation.

Gepubliceerd: Bone Joint J 2018 Apr 1;100-B(4):443-9
Impact factor: 3.581; Q1

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11. The Dutch Audit of Carotid Interventions: Transparency in Quality of Carotid Endarterectomy in Symptomatic Patients in the Netherlands
Karthaus EG, Vahl A, Kuhrij LS, Elsman BHP, Geelkerken RH, Wouters MWJM, Hamming JF, de Borst GJ, includes Beuk R.J, Meerwaldt R, Willigendael EM

Background: The Dutch Audit for Carotid Interventions (DACI) registers all patients undergoing interventions for carotid artery stenosis in the Netherlands. This study describes the design of the DACI and results of patients with a symptomatic stenosis undergoing carotid endarterectomy (CEA). It aimed to evaluate variation between hospitals in process of care and (adjusted) outcomes, as well as predictors of major stroke/death after CEA.
Methods: All patients with a symptomatic stenosis, who underwent CEA and were registered in the DACI between 2014 and 2016 were included in this cohort. Descriptive analyses of patient characteristics, process of care, and outcomes were performed. Casemix adjusted hospital procedural outcomes as (30 day/in hospital) mortality, stroke/death, and major stroke/death, were compared with the national mean. A multivariable logistic regression model (backward elimination at $p > 0.10$) was used to identify predictors of major stroke/death.
Results: A total of 6459 patients, registered by 52 hospitals, were included. The majority (4,832, 75%) were treated <2 weeks after their first hospital consultation, varying from 40% to 93% between hospitals. Mortality, stroke/death, and major stroke/death were, respectively, 1.1%, 3.6%, and 1.8%. Adjusted major stroke/death rates for hospital comparison varied between 0 and 6.5%. Nine hospitals performed significantly better, none performed significantly worse. Predictors of major stroke/death were sex, age, pulmonary disease, presenting neurological symptoms, and peri-operative shunt.
Conclusion: CEA in The Netherlands is associated with an overall low mortality and (major) stroke/death rate. Whereas the indicator time to intervention varied between hospitals, mortality and (major) stroke/death were not significantly distinctive enough to identify worse practices and therefore were unsuitable for hospital comparison in the Dutch setting. Additionally, predictors of major stroke/death at population level could be identified.

Gepubliceerd: Eur J Vasc Endovasc Surg 2018 Oct;56(4):476-85
Impact factor: 3.877; Q1

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12. Evolution of the Proximal Sealing Rings of the Anaconda Stent-Graft After Endovascular Aneurysm Repair
Koenrades MA, Klein A, Leferink AM, Slump CH, Geelkerken RH

Purpose: To provide insight into the evolution of the saddle-shaped proximal sealing rings of the Anaconda stent-graft after endovascular aneurysm repair (EVAR).

Methods: Eighteen abdominal aortic aneurysm patients were consecutively enrolled in a single-center, prospective, observational cohort study (LSPEAS; Trialregister.nl identifier NTR4276). The patients were treated electively using an Anaconda stent-graft with a mean 31% oversizing (range 17-47). According to protocol, participants were to be followed for 2 years, during which 5 noncontrast electrocardiogram-gated computed tomography scans would be conducted. Three patients were eliminated within 30 days (1 withdrew, 1 died, and a third was converted before stent-graft deployment), leaving 15 patients (mean age 72.8+/-3.7 years; 14 men) for this analysis. Evolution in size and shape (symmetry) of both proximal infrarenal sealing rings were assessed from discharge to 24 months using dedicated postprocessing algorithms.
Results: At 24 months, the mean diameters of the first and second ring stents had increased significantly (first ring: 2.2+/-1.0 mm, p<0.001; second ring: 2.7+/-1.1 mm, p<0.001). At 6 months, the first and second rings had expanded to a mean 96.6%+/-2.1% and 94.8%+/-2.7%, respectively, of their nominal diameter, after which the rings expanded slowly; ring diameters stabilized to near nominal size (first ring, 98.3%+/-1.1%; second ring, 97.2%+/-1.4%) at 24 months irrespective of initial oversizing. No type I or III endoleaks or aneurysm-, device-, or procedure-related adverse events were noted in follow-up. The difference in the diametric distances between the peaks and valleys of the saddle-shaped rings was marked at discharge but became smaller after 24 months for both rings (first ring: median 2.0 vs 1.2 mm, p=0.191; second ring: median 2.8 vs 0.8 mm; p=0.013).
Conclusion: Irrespective of initial oversizing, the Anaconda proximal sealing rings radially expanded to near nominal size within 6 months after EVAR. Initial oval-shaped rings conformed symmetrically and became nearly circular through 24 months. These findings should be taken into account in planning and follow-up.

Gepubliceerd: J Endovasc Ther 2018 Aug;25(4):480-91
Impact factor: 2.732; Q2

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13. Risk-Assessment of Esophageal Surgery: Diagnosis and Treatment of Celiac Trunk Stenosis
Lammerts RGM, van Det MJ, Geelkerken RH, Kouwenhoven EA

Anastomotic leakage of the gastric conduit following surgical treatment of esophageal cancer is a life-threatening complication. An important risk factor associated with anastomotic leakage is calcification of the supplying arteries of the gastric conduit. The patency of calcified splanchnic arteries cannot be assessed on routine computed tomography (CT) scans for esophageal cancer and, as such, in selected patients with known or assumed mesenteric artery disease, additional CT angiography of the abdominal arteries with 1 mm slices is strongly encouraged. If the mesenteric perfusion is compromised in patients with resectable esophageal cancer, angioplasty procedures with stenting of the mesenteric arteries could be performed to prevent possible ischemia of the gastric conduit.

Gepubliceerd: Thorac Cardiovasc Surg Rep 2018 Jan;7(1):e21-e23
Impact factor: 0; nvt

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14. Failure to Rescue - a Closer Look at Mortality Rates Has No Added Value for Hospital Comparisons but Is Useful for Team Quality Assessment in Abdominal Aortic Aneurysm Surgery in The Netherlands
Lijftogt N, Karthaus EG, Vahl A, van Zwet EW, van der Willik EM, Tollenaar RAEM, Hamming JF, Wouters MWJM, includes Geelkerken RH, Beuk R.J, Meerwaldt R, Willigendael EM

Objectives: Failure to rescue (FTR) is a composite quality indicator, defined as the proportion of deceased patients following major complications. The aims of this study were to compare FTR with mortality for hospital comparisons in abdominal aortic aneurysm (AAA) surgery in The Netherlands and investigate hospital volume and associated factors.
Methods: Patients prospectively registered between 2013 and 2015 in the Dutch Surgical Aneurysm Audit (DSAA) were analysed. FTR was analysed for AAA patients and subgroups elective (EAAA) and acute (AAAA; symptomatic or ruptured) aneurysms. Variables and hospital volume were analysed by uni- and multivariable regression analysis. Adjusted hospital comparisons for mortality, major complications, and FTR were presented in funnel plots. Isomortality lines were constructed when presenting FTR and major complication rates.
Results: A total of 9258 patients were analysed in 61 hospitals: 7149 EAAA patients (77.2%) and 2109 AAAA patients (22.8%). There were 2785 (30.1%) patients with complications (unadjusted range 5-65% per hospital): 2161 (77.6%) with major and 624 (28.4%) patients with minor complications. Overall mortality was 6.6% (adjusted range 0-16% per hospital) and FTR was 28.4% (n = 613) (adjusted range 0-60% per hospital). Glasgow Coma Scale, age, pulse, creatinine, electrocardiography, and operative setting were independently associated with FTR. Hospital volume was not associated with FTR. In AAAA patients hospital volume was significantly associated with a lower adjusted major complication and mortality rate (OR 0.62, 95% CI 0.49-0.78; and 0.64, 95% CI 0.48-0.87). Four hospitals had a significant lower adjusted FTR with different major complication rates on different isomortality lines.
Conclusions: There was more variation in FTR than in mortality between hospitals. FTR identified the same best performing hospitals as for mortality and therefore was of limited additional value in measuring quality of care for AAA surgery. FTR can be used for internal quality improvement with major complications in funnel plots and diagrams with isomortality lines.

Gepubliceerd: Eur J Vasc Endovasc Surg 2018 Nov;56(5):652-61
Impact factor: 3.877; Q1

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15. Interactive online learning on perioperative management of elderly patients
Ozturk E, van Iersel M, van Loon K, den Rooijen C, van Dongen E, van Wijngaarden RL, Klaase J, van Goor H

Introduction: Surgical specialists and residents lack knowledge to adequately manage frail older patients. This study aims to evaluate the effects of an interactive online course regarding attitude, self-confidence and knowledge in perioperative management of the elderly patient.
Methods: The six-weeks course consisted of expert videos, literature readings, quizzes and forum discussions. Surgical consultants with geriatric expertise and

geriatricians moderated online discussions and stimulated interaction. Knowledge, self-confidence and attitude of course participants were compared at the beginning and end of the course.
Results: 206 medical practitioners started the course. Knowledge scores improved significantly from 49% to 65% ($p<0.005$). Participants felt more secure ($p<0.005$) in the treatment of the older patient at the end of the course. A better attitude correlated with a higher total knowledge score in surgeons and surgical residents ($p=0.02$).
Conclusion: A six-week interactive online course on perioperative management of elderly patients increases relevant geriatric knowledge and improves self-confidence of residents and faculty.

Gepubliceerd: Am J Surg 2018 Sep;216(3):624-9
Impact factor: 2.141; Q2

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16. The Dutch Pancreas Biobank Within the Parelsnoer Institute: A Nationwide Biobank of Pancreatic and Periampullary Diseases
Strijker M, Gerritsen A, van Hilst J, Bijlsma MF, Bonsing BA, Brosens LA, Bruno MJ, van Dam RM, Dijk F, van Eijck CH, Farina Sarasqueta A, Fockens P, Gerhards MF, Groot Koerkamp B, van der Harst E, de Hingh IH, van Hooft JE, Huysentruyt CJ, Kazemier G, Klaase JM, van Laarhoven CJ, van Laarhoven HW, Liem MS, de Meijer VE, van Rijssen LB, van Santvoort HC, Suker M, Verhagen JH, Verheij J, Verspaget HW, Wennink RA, Wilmink JW, Molenaar IQ, Boermeester MA, Busch OR, Besselink MG

Objectives: Large biobanks with uniform collection of biomaterials and associated clinical data are essential for translational research. The Netherlands has traditionally been well organized in multicenter clinical research on pancreatic diseases, including the nationwide multidisciplinary Dutch Pancreatic Cancer Group and Dutch Pancreatitis Study Group. To enable high-quality translational research on pancreatic and periampullary diseases, these groups established the Dutch Pancreas Biobank.
Methods: The Dutch Pancreas Biobank is part of the Parelsnoer Institute and involves all 8 Dutch university medical centers and 5 nonacademic hospitals. Adult patients undergoing pancreatic surgery (all indications) are eligible for inclusion. Preoperative blood samples, tumor tissue from resected specimens, pancreatic cyst fluid, and follow-up blood samples are collected. Clinical parameters are collected in conjunction with the mandatory Dutch Pancreatic Cancer Audit.
Results: Between January 2015 and May 2017, 488 patients were included in the first 5 participating centers: 4 university medical centers and 1 nonacademic hospital. Over 2500 samples were collected: 1308 preoperative blood samples, 864 tissue samples, and 366 follow-up blood samples.
Conclusions: Prospective collection of biomaterials and associated clinical data has started in the Dutch Pancreas Biobank. Subsequent translational research will aim to improve treatment decisions based on disease characteristics.

Gepubliceerd: Pancreas 2018 Apr;47(4):495-501
Impact factor: 2.958; Q3

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17. Two versus five days of antibiotics after appendectomy for complex acute appendicitis (APPIC): study protocol for a randomized controlled trial
van den Boom AL, de Wijkerslooth EML, van Rosmalen J, Beverdam FH, Boerma EG, Boermeester MA, Bosmans JWAM, Burghgraef TA, Consten ECJ, Dawson I, Dekker JWT, Emous M, van Geloven AAW, Go PMNY, Heijnen LA, Huisman SA, Jean Pierre D, de Jonge J, Kloeze JH, Koopmanschap MA, Langeveld HR, Luyer MDP, Melles DC, Mouton JW, van der Ploeg APT, Poelmann FB, Ponten JEH, van Rossem CC, Schreurs WH, Shapiro J, Steenvoorde P, Toorenvliet BR, Verhelst J, Versteegh HP, Wijnen RMH, Wijnhoven BPL

Background: Acute appendicitis is one of the most common indications for emergency surgery. In patients with a complex appendicitis, prolonged antibiotic prophylaxis is recommended after appendectomy. There is no consensus regarding the optimum duration of antibiotics. Guidelines propose 3 to 7 days of treatment, but shorter courses may be as effective in the prevention of infectious complications. At the same time, the global issue of increasing antimicrobial resistance urges for optimization of antibiotic strategies. The aim of this study is to determine whether a short course (48 h) of postoperative antibiotics is non-inferior to current standard practice of 5 days.
Methods: Patients of 8 years and older undergoing appendectomy for acute complex appendicitis - defined as a gangrenous and/or perforated appendicitis or appendicitis in presence of an abscess - are eligible for inclusion. Immunocompromised or pregnant patients are excluded, as well as patients with a contraindication to the study antibiotics. In total, 1066 patients will be randomly allocated in a 1:1 ratio to the experimental treatment arm (48 h of postoperative intravenously administered (IV) antibiotics) or the control arm (5 days of postoperative IV antibiotics). After discharge from the hospital, patients participate in a productivity-cost-questionnaire at 4 weeks and a standardized telephone follow-up at 90 days after appendectomy. The primary outcome is a composite endpoint of infectious complications, including intra-abdominal abscess (IAA) and surgical site infection (SSI), and mortality within 90 days after appendectomy. Secondary outcomes include IAA, SSI, restart of antibiotics, length of hospital stay (LOS), reoperation, percutaneous drainage, readmission rate, and cost-effectiveness. The non-inferiority margin for the difference in the primary endpoint rate is set at 7.5% (one-sided test at a 0.025). Both per-protocol and intention-to-treat analyses will be performed.
Discussion: This trial will provide evidence on whether 48 h of postoperative antibiotics is non-inferior to a standard course of 5 days of antibiotics. If non-inferiority is established, longer intravenous administration following appendectomy for complex appendicitis can be abandoned, and guidelines need to be adjusted accordingly.
Trial registration: Dutch Trial Register, NTR6128 . Registered on 20 December 2016.

Gepubliceerd: Trials 2018 May 2;19(1):263
Impact factor: 2.067; Q3

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18. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit
van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, Bosscha K, van Dam RM, van Eijck CH, Gerhards MF, Gerritsen JJ, van der Harst E, de Hingh IH, de

Jong KP, Kazemier G, Klaase J, van der Kolk BM, van Laarhoven CJ, Luyer MD, Molenaar IQ, Patijn GA, Rupert CG, Scheepers JJ, van der Schelling GP, Vahrmeijer AL, Busch ORC, van Santvoort HC, Groot KB, Besselink MG

Background: In the mandatory nationwide Dutch Pancreatic Cancer Audit, rates of major complications and Failure to Rescue (FTR) after pancreatoduodenectomy between low- and high-mortality hospitals are compared, and independent predictors for FTR investigated.
Methods: Patients undergoing pancreatoduodenectomy in 2014 and 2015 in The Netherlands were included. Hospitals were divided into quartiles based on mortality rates. The rate of major complications (Clavien-Dindo >/=3) and death after a major complication (FTR) were compared between these quartiles. Independent predictors for FTR were identified by multivariable logistic regression analysis.
Results: Out of 1.342 patients, 391 (29%) developed a major complication and in-hospital mortality was 4.2%. FTR occurred in 56 (14.3%) patients. Mortality was 0.9% in the first hospital quartile (4 hospitals, 327 patients) and 8.1% in the fourth quartile (5 hospitals, 310 patients). The rate of major complications increased by 40% (25.7% vs 35.2%) between the first and fourth hospital quartile, whereas the FTR rate increased by 560% (3.6% vs 22.9%). Independent predictors of FTR were male sex (OR = 2.1, 95%CI 1.2-3.9), age >75 years (OR = 4.3, 1.8-10.2), BMI >/=30 (OR = 2.9, 1.3-6.6), histopathological diagnosis of periampullary cancer (OR = 2.0, 1.1-3.7), and hospital volume <30 (OR = 3.9, 1.6-9.6).
Conclusions: Variations in mortality between hospitals after pancreatoduodenectomy were explained mainly by differences in FTR, rather than the incidence of major complications.

Gepubliceerd: HPB (Oxford) 2018 Aug;20(8):759-67
Impact factor: 3.131; Q1

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19. A phantom study for the comparison of different brands of computed tomography scanners and software packages for endovascular aneurysm repair sizing and planning
Velu JF, Groot Jebbink E, de Vries JP, van der Palen J, Slump CH, Geelkerken RH
Objectives: Correct sizing of endoprostheses used for the treatment of abdominal aortic aneurysms is important to prevent endoleaks and migration. Sizing requires several steps and each step introduces a possible sizing error. The goal of this study was to investigate the magnitude of these errors compared to the golden standard: a vessel phantom. This study focuses on the errors in sizing with three different brands of computed tomography angiography scanners in combination with three reconstruction software packages.
Methods: Three phantoms with a different diameter, altitude and azimuth were scanned with three computed tomography scanners: Toshiba Aquilion 64-slice, Philips Brilliance iCT 256-slice and Siemens Somatom Sensation 64-slice. The phantom diameters were determined in the stretched view after central lumen line reconstruction by three observers using Simbionix PROcedure Rehearsal Studio, 3mensio and TeraRecon planning software. The observers, all novices in sizing endoprostheses using planning software, measured 108 slices each. Two senior vascular surgeons set the tolerated error margin of sizing on +/-1.0 mm.

Results: In total, 11.3% of the measurements (73/648) were outside the set margins of +/-1.0 mm from the phantom diameter, with significant differences between the scanner types (14.8%, 12.1%, 6.9% for the Siemens scanner, Philips scanner and Toshiba scanner, respectively, p-value = 0.032), but not between the software packages (8.3%, 11.1%, 14.4%, p-value = 0.141) or the observers (10.6%, 9.7%, 13.4%, p-value = 0.448).
Conclusions: It can be concluded that the errors in sizing were independent of the used software packages, but the phantoms scanned with Siemens scanner were significantly more measured incorrectly than the phantoms scanned with the Toshiba scanner. Consequently, awareness on the type of computed tomography scanner and computed tomography scanner setting is necessary, especially in complex abdominal aortic aneurysms sizing for fenestrated or branched endovascular aneurysm repair if appropriate the sizing is of upmost importance.

Gepubliceerd: Vascular 2018 Apr;26(2):198-202
Impact factor: 1.089; Q4

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20. Chronic wounds: Innovations in diagnostics and therapeutics
Haalboom M

One of the major global health issues is the existence of chronic wounds. Chronic wounds are wounds that show a delayed, or even failed, healing process. The healing process often stagnates in the inflammatory phase or proliferative phase. Since traditional treatment methods have shown to be of limited effectiveness in chronic wound care, the focus has shifted to increase the knowledge of the wound healing process and the deficiencies encountered in chronic wounds. This increased knowledge has provided the opportunity for development of new diagnostics and therapeutics in chronic wound care that detect and treat specific deficiencies instead of one common treatment for all chronic wounds. This mini review aims to provide an overview of the current knowledge about the wound healing process and its deficiencies in chronic wound care. In addition, some promising diagnostic and therapeutic innovations will be highlighted.

Gepubliceerd: Curr Med Chem 2018;25(41):5772-81
Impact factor: 3.469; Q2

Totale impact factor: 56.711
Gemiddelde impact factor: 2.836

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 22.442
Gemiddelde impact factor: 2.494

Intensive Care

1. Correction to: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017
Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto MG, Olsen KM, Rodgers S, Russell JA, Van den Berghe G

To update the 2008 consensus statements for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adult and pediatric patients.

Gepubliceerd: Intensive Care Med 2018 Mar;44(3):401-2
Impact factor: 15.008; Q1

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2. Proenkephalin A 119-159 (Penkid) Is an Early Biomarker of Septic Acute Kidney Injury: The Kidney in Sepsis and Septic Shock (Kid-SSS) Study
Hollinger A, Wittebole X, Francois B, Pickkers P, Antonelli M, Gayat E, Chousterman BG, Lascarrou JB, Dugernier T, Di Somma S, Struck J, Bergmann A, Beishuizen A, Constatin JM, Damoisel C, Deye N, Gaudry S, Huberlant V, Marx G, Mercier E, Oueslati H, Hartmann O, Sonneville R, Laterre PF, Mebazaa A, Legrand M

Introduction: Sepsis is the leading cause of acute kidney injury (AKI) in critically ill patients. The Kidney in Sepsis and Septic Shock (Kid-SSS) study evaluated the value of proenkephalin A 119-159 (penkid)-a sensitive biomarker of glomerular function, drawn within 24 hours upon intensive care unit (ICU) admission and analyzed using a chemiluminescence immunoassay-for kidney events in sepsis and septic shock.
Methods: The Kid-SSS study was a substudy of Adrenomedullin and Outcome in Severe Sepsis and Septic Shock (AdrenOSS) (NCT02393781), a prospective, observational, multinational study including 583 patients admitted to the intensive care unit with sepsis or septic shock and a validation cohort of 525 patients from the French and euRopean Outcome reGistry in Intensive Care Units (FROG-ICU) study. The primary endpoint was major adverse kidney events (MAKEs) at day 7, composite of death, renal replacement therapy, and persistent renal dysfunction. The secondary endpoints included AKI, transient AKI, worsening renal function (WRF), and 28-day mortality.
Results: Median age was 66 years (interquartile range 55-75), and 28-day mortality was 22% (95% confidence interval [CI] 19%-25%). Of the patients, 293 (50.3%) were in shock upon ICU admission. Penkid was significantly elevated in patients with MAKEs, persistent AKI, and WRF (median = 65 [IQR = 45-106] vs. 179 [114-242]; 53 [39-70] vs. 133 [79-196] pmol/l; and 70 [47-121] vs. 174 [93-242] pmol/l, all $P < 0.0001$), also after adjustment for confounding factors (adjusted odds ratio = 3.3 [95% CI = 1.8-6.0], 3.9 [95% CI = 2.1-7.2], and 3.4 [95% CI = 1.9-6.2], all $P < 0.0001$). Penkid increase preceded elevation of serum creatinine with WRF and was low in renal recovery.

Conclusion: Admission penkid concentration was associated with MAKEs, AKI, and WRF in a timely manner in septic patients.

Gepubliceerd: Kidney Int Rep 2018 Nov;3(6):1424-33
Impact factor: 3.357; Q1

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3. Cost-effectiveness of procalcitonin testing to guide antibiotic treatment duration in critically ill patients: results from a randomised controlled multicentre trial in the Netherlands
Kip MMA, van Oers JA, Shajiei A, Beishuizen A, Berghuis AMS, Girbes AR, de Jong E, de Lange DW, Nijsten MWN, IJzerman MJ, Koffijberg H, Kusters R

Background: Procalcitonin (PCT) testing can help in safely reducing antibiotic treatment duration in intensive care patients with sepsis. However, the cost-effectiveness of such PCT guidance is not yet known.
Methods: A trial-based analysis was performed to estimate the cost-effectiveness of PCT guidance compared with standard of care (without PCT guidance). Patient-level data were used from the SAPS trial in which 1546 patients were randomised. This trial was performed in the Netherlands, which is a country with, on average, low antibiotic use and a short duration of hospital stay. As quality of life among sepsis survivors was not measured during the SAPS, this was derived from a Dutch follow-up study. Outcome measures were (1) incremental direct hospital cost and (2) incremental cost per quality-adjusted life year (QALY) gained from a healthcare perspective over a one-year time horizon. Uncertainty in outcomes was assessed with bootstrapping.
Results: Mean in-hospital costs were €46,081/patient in the PCT group compared with €46,146/patient with standard of care (i.e. - €65 (95% CI - €6314 to €6107); - 0.1%). The duration of the first course of antibiotic treatment was lower in the PCT group with 6.9 vs. 8.2 days (i.e. - 1.2 days (95% CI - 1.9 to - 0.4), - 14.8%). This was accompanied by lower in-hospital mortality of 21.8% vs. 29.8% (absolute decrease 7.9% (95% CI - 13.9% to - 1.8%), relative decrease 26.6%), resulting in an increase in mean QALYs/patient from 0.47 to 0.52 (i.e. + 0.05 (95% CI 0.00 to 0.10); + 10.1%). However, owing to high costs among sepsis survivors, healthcare costs over a one-year time horizon were €73,665/patient in the PCT group compared with €70,961/patient with standard of care (i.e. + €2704 (95% CI - €4495 to €10,005), + 3.8%), resulting in an incremental cost-effectiveness ratio of €57,402/QALY gained. Within this time frame, the probability of PCT guidance being cost-effective was 64% at a willingness-to-pay threshold of €80,000/QALY.
Conclusions: Although the impact of PCT guidance on total healthcare-related costs during the initial hospitalisation episode is likely negligible, the lower in-hospital mortality may lead to a non-significant increase in costs over a one-year time horizon. However, since uncertainty remains, it is recommended to investigate the long-term cost-effectiveness of PCT guidance, from a societal perspective, in different countries and settings.

Gepubliceerd: Crit Care 2018 Nov 13;22(1):293
Impact factor: 6.425; Q1

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4. Positive End-Expiratory Pressure Ventilation Induces Longitudinal Atrophy in Diaphragm Fibers
Lindqvist J, van den Berg M, van der Pijl R, Hooijman PE, Beishuizen A, Elshof J, de Waard M, Girbes A, Spoelstra-de Man A, Shi ZH, van den Brom C, Bogaards S, Shen S, Strom J, Granzier H, Kole J, Musters RJP, Paul MA, Heunks LMA, Ottenheijm CAC

Rationale: Diaphragm weakness in critically ill patients prolongs ventilator dependency and duration of hospital stay and increases mortality and healthcare costs. The mechanisms underlying diaphragm weakness include cross-sectional fiber atrophy and contractile protein dysfunction, but whether additional mechanisms are at play is unknown.
Objectives: To test the hypothesis that mechanical ventilation with positive end-expiratory pressure (PEEP) induces longitudinal atrophy by displacing the diaphragm in the caudal direction and reducing the length of fibers.
Methods: We studied structure and function of diaphragm fibers of mechanically ventilated critically ill patients and mechanically ventilated rats with normal and increased titin compliance.
Measurements and main results: PEEP causes a caudal movement of the diaphragm, both in critically ill patients and in rats, and this caudal movement reduces fiber length. Diaphragm fibers of 18-hour mechanically ventilated rats (PEEP of 2.5 cm H2O) adapt to the reduced length by absorbing serially linked sarcomeres, the smallest contractile units in muscle (i.e., longitudinal atrophy). Increasing the compliance of titin molecules reduces longitudinal atrophy.
Conclusions: Mechanical ventilation with PEEP results in longitudinal atrophy of diaphragm fibers, a response that is modulated by the elasticity of the giant sarcomeric protein titin. We postulate that longitudinal atrophy, in concert with the aforementioned cross-sectional atrophy, hampers spontaneous breathing trials in critically ill patients: during these efforts, end-expiratory lung volume is reduced, and the shortened diaphragm fibers are stretched to excessive sarcomere lengths. At these lengths, muscle fibers generate less force, and diaphragm weakness ensues.

Gepubliceerd: Am J Respir Crit Care Med 2018 Aug 15;198(4):472-85
Impact factor: 15.239; Q1

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5. Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock-1 (AdrenOSS-1) study
Mebazaa A, Geven C, Hollinger A, Wittebole X, Chousterman BG, Blet A, Gayat E, Hartmann O, Scigalla P, Struck J, Bergmann A, Antonelli M, Beishuizen A, Constantin JM, Damoisel C, Deye N, Di SS, Dugernier T, Francois B, Gaudry S, Huberlant V, Lascarrou JB, Marx G, Mercier E, Oueslati H, Pickkers P, Sonneville R, Legrand M, Laterre PF

Background: Adrenomedullin (ADM) regulates vascular tone and endothelial permeability during sepsis. Levels of circulating biologically active ADM (bio-ADM) show an inverse relationship with blood pressure and a direct relationship with vasopressor requirement. In the present prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock 1 (, AdrenOSS-1) study,

we assessed relationships between circulating bio-ADM during the initial intensive care unit (ICU) stay and short-term outcome in order to eventually design a biomarker-guided randomized controlled trial.
Methods: AdrenOSS-1 was a prospective observational multinational study. The primary outcome was 28-day mortality. Secondary outcomes included organ failure as defined by Sequential Organ Failure Assessment (SOFA) score, organ support with focus on vasopressor/inotropic use, and need for renal replacement therapy. AdrenOSS-1 included 583 patients admitted to the ICU with sepsis or septic shock.
Results: Circulating bio-ADM levels were measured upon admission and at day 2. Median bio-ADM concentration upon admission was 80.5 pg/ml [IQR 41.5-148.1 pg/ml]. Initial SOFA score was 7 [IQR 5-10], and 28-day mortality was 22%. We found marked associations between bio-ADM upon admission and 28-day mortality (unadjusted standardized HR 2.3 [CI 1.9-2.9]; adjusted HR 1.6 [CI 1.1-2.5]) and between bio-ADM levels and SOFA score ($p < 0.0001$). Need of vasopressor/inotrope, renal replacement therapy, and positive fluid balance were more prevalent in patients with a bio-ADM > 70 pg/ml upon admission than in those with bio-ADM </= 70 pg/ml. In patients with bio-ADM > 70 pg/ml upon admission, decrease in bio-ADM below 70 pg/ml at day 2 was associated with recovery of organ function at day 7 and better 28-day outcome (9.5% mortality). By contrast, persistently elevated bio-ADM at day 2 was associated with prolonged organ dysfunction and high 28-day mortality (38.1% mortality, HR 4.9, 95% CI 2.5-9.8).
Conclusions: AdrenOSS-1 shows that early levels and rapid changes in bio-ADM estimate short-term outcome in sepsis and septic shock. These data are the backbone of the design of the biomarker-guided AdrenOSS-2 trial.
Trial registration: ClinicalTrials.gov, NCT02393781 . Registered on March 19, 2015.

Gepubliceerd: Crit Care 2018 Dec 21;22(1):354
Impact factor: 6.425; Q1

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6. Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial
Pickkers P, Mehta RL, Murray PT, Joannidis M, Molitoris BA, Kellum JA, Bachler M, Hoste EAJ, Hoiting O, Krell K, Ostermann M, Rozendaal W, Valkonen M, Brealey D, Beishuizen A, Meziani F, Murugan R, de Goede AA, Payen D, van den Berg E, Arend J

Importance: Sepsis-associated acute kidney injury (AKI) adversely affects long-term kidney outcomes and survival. Administration of the detoxifying enzyme alkaline phosphatase may improve kidney function and survival.
Objective: To determine the optimal therapeutic dose, effect on kidney function, and adverse effects of a human recombinant alkaline phosphatase in patients who are critically ill with sepsis-associated AKI.
Design, setting, and participants: The STOP-AKI trial was an international (53 recruiting sites), randomized, double-blind, placebo-controlled, dose-finding, adaptive phase 2a/2b study in 301 adult patients admitted to the intensive care unit with a diagnosis of sepsis and AKI. Patients were enrolled between December 2014 and May 2017, and follow-up was conducted for 90 days. The final date of follow-up was August 14, 2017. Interventions: In the intention-to-treat analysis, in part 1 of the trial,

patients were randomized to receive recombinant alkaline phosphatase in a dosage of 0.4 mg/kg (n = 31), 0.8 mg/kg (n = 32), or 1.6 mg/kg (n = 29) or placebo (n = 30), once daily for 3 days, to establish the optimal dose. The optimal dose was identified as 1.6 mg/kg based on modeling approaches and adverse events. In part 2, 1.6 mg/kg (n = 82) was compared with placebo (n = 86). Main Outcomes and Measures: The primary end point was the time-corrected area under the curve of the endogenous creatinine clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC1-7 ECC). Incidence of fatal and nonfatal (serious) adverse events ([S]AEs) was also determined.
Results: Overall, 301 patients were enrolled (men, 70.7%; median age, 67 years [interquartile range 59-73]). From day 1 to day 7, median ECC increased from 26.0 mL/min (IQR, 8.8 to 59.5) to 65.4 mL/min (IQR, 26.7 to 115.4) in the recombinant alkaline phosphatase 1.6-mg/kg group vs from 35.9 mL/min (IQR, 12.2 to 82.9) to 61.9 mL/min (IQR, 22.7 to 115.2) in the placebo group (absolute difference, 9.5 mL/min [95% CI, -23.9 to 25.5]; P = .47). Fatal adverse events occurred in 26.3% of patients in the 0.4-mg/kg recombinant alkaline phosphatase group; 17.1% in the 0.8-mg/kg group, 17.4% in the 1.6-mg/kg group, and 29.5% in the placebo group. Rates of nonfatal SAEs were 21.0% for the 0.4-mg/kg recombinant alkaline phosphatase group, 14.3% for the 0.8-mg/kg group, 25.7% for the 1.6-mg/kg group, and 20.5% for the placebo group.
Conclusion and relevance: Among patients who were critically ill with sepsis-associated acute kidney injury, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. Further research is necessary to assess other clinical outcomes.
Trial registration: ClinicalTrials.gov Identifier: NCT02182440.

Gepubliceerd: JAMA 2018 Nov 20;320(19):1998-2009
Impact factor: 47.661; Q1

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7. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis
Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsey AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maravic-Stojkovic V, Verduri A, Beghe B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B

Background: In February, 2017, the US Food and Drug Administration approved the blood infection marker procalcitonin for guiding antibiotic therapy in patients with acute respiratory infections. This meta-analysis of patient data from 26 randomised controlled trials was designed to assess safety of procalcitonin-guided treatment in patients with acute respiratory infections from different clinical settings.
Methods: Based on a prespecified Cochrane protocol, we did a systematic literature search on the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase, and pooled individual patient data from trials in which patients with respiratory infections were randomly assigned to receive antibiotics based on procalcitonin concentrations (procalcitonin-guided group) or control. The coprimary

endpoints were 30-day mortality and setting-specific treatment failure. Secondary endpoints were antibiotic use, length of stay, and antibiotic side-effects.
Findings: We identified 990 records from the literature search, of which 71 articles were assessed for eligibility after exclusion of 919 records. We collected data on 6708 patients from 26 eligible trials in 12 countries. Mortality at 30 days was significantly lower in procalcitonin-guided patients than in control patients (286 [9%] deaths in 3336 procalcitonin-guided patients vs 336 [10%] in 3372 controls; adjusted odds ratio [OR] 0.83 [95% CI 0.70 to 0.99], p=0.037). This mortality benefit was similar across subgroups by setting and type of infection (pinteractions>0.05), although mortality was very low in primary care and in patients with acute bronchitis. Procalcitonin guidance was also associated with a 2.4-day reduction in antibiotic exposure (5.7 vs 8.1 days [95% CI -2.71 to -2.15], p<0.0001) and a reduction in antibiotic-related side-effects (16% vs 22%, adjusted OR 0.68 [95% CI 0.57 to 0.82], p<0.0001).
Interpretation: Use of procalcitonin to guide antibiotic treatment in patients with acute respiratory infections reduces antibiotic exposure and side-effects, and improves survival. Widespread implementation of procalcitonin protocols in patients with acute respiratory infections thus has the potential to improve antibiotic management with positive effects on clinical outcomes and on the current threat of increasing antibiotic multiresistance.
Funding: National Institute for Health Research.

Gepubliceerd: Lancet Infect Dis 2018;18(1):95-107
Impact factor: 25.148; Q1

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8. Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials
Schuetz P, Bolliger R, Merker M, Christ-Crain M, Stolz D, Tamm M, Luyt CE, Wolff M, Schroeder S, Nobre V, Reinhart K, Branche A, Damas P, Nijsten M, Deliberato RO, Verduri A, Beghe B, Cao B, Shehabi Y, Jensen JS, Beishuizen A, de Jong E, Briel M, Welte T, Mueller B

Introduction: Although evidence indicates that use of procalcitonin to guide antibiotic decisions for the treatment of acute respiratory infections (ARI) decreases antibiotic consumption and improves clinical outcomes, algorithms used within studies had differences in PCT cut-off points and frequency of testing. We therefore analyzed studies evaluating procalcitonin-guided antibiotic therapy and propose consensus algorithms for different respiratory infection types.
Areas covered: We systematically searched randomized-controlled trials (search strategy updated on February 2018) on procalcitonin-guided antibiotic therapy of ARI in adults using a pre-specified Cochrane protocol and analyzed algorithms from 32 trials that included 10,285 patients treated in primary care settings, emergency departments (ED), and intensive care units (ICU). We derived consensus algorithms for use of procalcitonin by the type of ARI including community-acquired pneumonia, bronchitis, chronic obstructive pulmonary disease or asthma exacerbation, sepsis, and post-operative sepsis due to respiratory infection. Consensus algorithm recommendations differ with regard to timing of treatment (i.e. timing of initiation in low-risk patients or discontinuation in high-risk patients) and procalcitonin cut-off points for the recommendation/strong recommendation to discontinue antibiotics (</=

0.25/</= 0.1 microg/L in ED and inpatients, </= 0.5/</= 0.25 microg/L in ICU patients, and reduction by >/= 80% from peak levels in sepsis patients).
Expert commentary: Our proposed algorithms may facilitate safe and efficient implementation of procalcitonin-guided antibiotic protocols in diverse healthcare settings. Still, the decision about initiation and cessation of antibiotic treatment remains a clinical decision based on the patient assessment and the severity of illness and use of procalcitonin should not delay empirical treatment in high risk situations.

Gepubliceerd: Expert Rev Anti Infect Ther 2018 Jul;16(7):555-64
Impact factor: 3.141; Q2

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9. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study
Sonder P, Janssens GN, Beishuizen A, Henry CL, Rittenberger JC, Callaway CW, Dezfulian C, Polderman KH

Background: Mild therapeutic hypothermia (32-36 degrees C) is associated with improved outcomes in patients with brain injury after cardiac arrest (CA). Various devices are available to induce and maintain hypothermia, but few studies have compared the performance of these devices. We performed a prospective study to compare four frequently used cooling systems in inducing and maintaining hypothermia followed by controlled rewarming.
Methods: We performed a prospective multi-centered study in ten ICU's in three hospitals within the UPMC health system. Four different cooling technologies (seven cooling methods in total) were studied: two external water-circulating cooling blankets (Meditherm(R) and Blanketrol(R)), gel-coated adhesive cooling pads (Arctic Sun(R)), and endovascular cooling catheters with balloons circulating ice-cold saline (Thermogard(R)). For the latter system we studied three different types of catheter with two, three or four water-circulating balloons, respectively. In contrast to previous studies, we not only studied the cooling rate (i.e., time to target temperature) in the induction phase, but also the percentage of the time during the maintenance phase that temperature was on target +/-0.5 degrees C, and the efficacy of devices to control rewarming. We believe that these are more important indicators of device performance than induction speed alone.
Results: 129 consecutive patients admitted after CA and treated with hypothermia were screened, and 120 were enrolled in the study. Two researchers dedicated fulltime to this study monitored TH treatment in all patients, including antishivering measures, additional cooling measures used (e.g. icepacks and cold fluid infusion), and all other issues related to temperature management. Baseline characteristics were similar for all groups. Cooling rates were 2.06+/-1.12 degrees C/h for endovascular cooling, 1.49+/-0.82 for Arctic sun, 0.61+/-0.36 for Meditherm and 1.22+/-1.12 for Blanketrol. Time within target range +/-0.5 degrees C was 97.3+/-6.0% for Thermogard, 81.8+/-25.2% for Arctic Sun, 57.4+/-29.3% for Meditherm, and 64.5+/-20.1% for Blanketrol. The following differences were significant: Thermogard vs. Meditherm ($p<0.01$), Thermogard vs. Blanketrol ($p<0.01$), and Arctic Sun vs. Meditherm ($p<0.02$). No major complications occurred with any device.
Conclusions: Endovascular cooling and gel-adhesive pads provide more rapid hypothermia induction and more effective temperature maintenance compared to

water-circulating cooling blankets. This applied to induction speed, but (more importantly) also to time within target range during maintenance.

Gepubliceerd: Resuscitation 2018 Mar;124:14-20
Impact factor: 5.863; Q1

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10. Fluid balance-adjusted creatinine at initiation of continuous venovenous hemofiltration and mortality. A post-hoc analysis of a multicenter randomized controlled trial
Stads S, Schilder L, Nurmohamed SA, Bosch FH, Purmer IM, den Boer SS, Kleppe CG, Vervloet MG, Beishuizen A, Girbes ARJ, Ter Wee PM, Gommers D, Groeneveld ABJ, Oudemans-van Straaten HM

Introduction: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high mortality. The creatinine-based stage of AKI is considered when deciding to start or delay RRT. However, creatinine is not only determined by renal function (excretion), but also by dilution (fluid balance) and creatinine generation (muscle mass). The aim of this study was to explore whether fluid balance-adjusted creatinine at initiation of RRT is related to 28-day mortality independent of other markers of AKI, surrogates of muscle mass and severity of disease.
Methods: We performed a post-hoc analysis on data from the multicentre CASH trial comparing citrate to heparin anticoagulation during continuous venovenous hemofiltration (CVVH). To determine whether fluid balance-adjusted creatinine was associated with 28-day mortality, we performed a logistic regression analysis adjusting for confounders of creatinine generation (age, gender, body weight), other markers of AKI (creatinine, urine output) and severity of disease.
Results: Of the 139 patients, 32 patients were excluded. Of the 107 included patients, 36 died at 28 days (34%). Non-survivors were older, had higher APACHE II and inclusion SOFA scores, lower pH and bicarbonate, lower creatinine and fluid balance-adjusted creatinine at CVVH initiation. In multivariate analysis lower fluid balance-adjusted creatinine (OR 0.996, 95% CI 0.993-0.999, p = 0.019), but not unadjusted creatinine, remained associated with 28-day mortality together with bicarbonate (OR 0.869, 95% CI 0.769-0.982, P = 0.024), while the APACHE II score non-significantly contributed to the model.
Conclusion: In this post-hoc analysis of a multicentre trial, low fluid balance-adjusted creatinine at CVVH initiation was associated with 28-day mortality, independent of other markers of AKI, organ failure, and surrogates of muscle mass, while unadjusted creatinine was not. More tools are needed for better understanding of the complex determinants of "AKI classification", "CVVH initiation" and their relation with mortality, fluid balance is only one.

Gepubliceerd: PLoS One 2018;13(6):e0197301
Impact factor: 2.766; Q1

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11. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial
van den Boogaard M, Slooter AJC, Bruggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, Simons KS, Dennesen PJW, Van der Voort

PHJ, Houterman S, van der Hoeven JG, Pickkers P, van der Woude MCE, Besselink A, Hofstra LS, Spronk PE, van den Bergh W, Donker DW, Fuchs M, Karakus A, Koeman M, van Duijnhoven M, Hannink G

Importance: Results of studies on use of prophylactic haloperidol in critically ill adults are inconclusive, especially in patients at high risk of delirium.
Objective: To determine whether prophylactic use of haloperidol improves survival among critically ill adults at high risk of delirium, which was defined as an anticipated intensive care unit (ICU) stay of at least 2 days. Design, Setting, and Participants: Randomized, double-blind, placebo-controlled investigator-driven study involving 1789 critically ill adults treated at 21 ICUs, at which nonpharmacological interventions for delirium prevention are routinely used in the Netherlands. Patients without delirium whose expected ICU stay was at least a day were included. Recruitment was from July 2013 to December 2016 and follow-up was conducted at 90 days with the final follow-up on March 1, 2017. Interventions: Patients received prophylactic treatment 3 times daily intravenously either 1 mg (n = 350) or 2 mg (n = 732) of haloperidol or placebo (n = 707), consisting of 0.9% sodium chloride. Main Outcome and Measures: The primary outcome was the number of days that patients survived in 28 days. There were 15 secondary outcomes, including delirium incidence, 28-day delirium-free and coma-free days, duration of mechanical ventilation, and ICU and hospital length of stay.
Results: All 1789 randomized patients (mean, age 66.6 years [SD, 12.6]; 1099 men [61.4%]) completed the study. The 1-mg haloperidol group was prematurely stopped because of futility. There was no difference in the median days patients survived in 28 days, 28 days in the 2-mg haloperidol group vs 28 days in the placebo group, for a difference of 0 days (95% CI, 0-0; P = .93) and a hazard ratio of 1.003 (95% CI, 0.78-1.30, P=.82). All of the 15 secondary outcomes were not statistically different. These included delirium incidence (mean difference, 1.5%, 95% CI, -3.6% to 6.7%), delirium-free and coma-free days (mean difference, 0 days, 95% CI, 0-0 days), and duration of mechanical ventilation, ICU, and hospital length of stay (mean difference, 0 days, 95% CI, 0-0 days for all 3 measures). The number of reported adverse effects did not differ between groups (2 [0.3%] for the 2-mg haloperidol group vs 1 [0.1%] for the placebo group).
Conclusion and relevance: Among critically ill adults at high risk of delirium, the use of prophylactic haloperidol compared with placebo did not improve survival at 28 days. These findings do not support the use of prophylactic haloperidol for reducing mortality in critically ill adults.
Trial registration: clinicaltrials.gov Identifier: NCT01785290.

Gepubliceerd: JAMA 2018 Feb 20;319(7):680-90
Impact factor: 47.661; Q1

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12. Postmortem histopathology of electroencephalography and evoked potentials in postanoxic coma
van Putten MJAM, Jansen C, Tjepkema-Cloostermans MC, Beernink TMJ, Koot R, Bosch F, Beishuizen A, Hofmeijer J

Early EEG patterns and SSEP responses are associated with neurological recovery of comatose patients with postanoxic encephalopathy after cardiac arrest. However,

the nature and distribution of brain damage underlying the characteristic EEG and SSEP patterns are unknown. We relate EEG and SSEP findings with results from histological analyses of the brains of eleven non-survivors. With restoration towards continuous rhythms within 24h after cardiac arrest, no signs of structural neuronal damage were observed. Absent SSEP responses were always accompanied by thalamic damage. Pathological burst suppression patterns were associated with a variable degree of neuronal damage to cortex, cerebellum and hippocampus. In patients with additional thalamic involvement, burst-suppression with identical bursts was observed, a characteristic EEG pattern presumably reflecting residual activity from a relatively isolated and severely compromised cortex.

Gepubliceerd: Resuscitation 2018 Dec 15;134:26-32
Impact factor: 5.863; Q1

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13. Delirium prediction in the intensive care unit: comparison of two delirium prediction models
Wassenaar A, Schoonhoven L, Devlin JW, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, Simons KS, Egerod I, Burry LD, Beishuizen A, Matos J, Donders ART, Pickkers P, van den Boogaard M

Background: Accurate prediction of delirium in the intensive care unit (ICU) may facilitate efficient use of early preventive strategies and stratification of ICU patients by delirium risk in clinical research, but the optimal delirium prediction model to use is unclear. We compared the predictive performance and user convenience of the prediction model for delirium (PRE-DELIRIC) and early prediction model for delirium (E-PRE-DELIRIC) in ICU patients and determined the value of a two-stage calculation.
Methods: This 7-country, 11-hospital, prospective cohort study evaluated consecutive adults admitted to the ICU who could be reliably assessed for delirium using the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist. The predictive performance of the models was measured using the area under the receiver operating characteristic curve. Calibration was assessed graphically. A physician questionnaire evaluated user convenience. For the two-stage calculation we used E-PRE-DELIRIC immediately after ICU admission and updated the prediction using PRE-DELIRIC after 24 h.
Results: In total 2178 patients were included. The area under the receiver operating characteristic curve was significantly greater for PRE-DELIRIC (0.74 (95% confidence interval 0.71-0.76)) compared to E-PRE-DELIRIC (0.68 (95% confidence interval 0.66-0.71)) (z score of - 2.73 ($p < 0.01$)). Both models were well-calibrated. The sensitivity improved when using the two-stage calculation in low-risk patients. Compared to PRE-DELIRIC, ICU physicians (n = 68) rated the E-PRE-DELIRIC model more feasible.
Conclusions: While both ICU delirium prediction models have moderate-to-good performance, the PRE-DELIRIC model predicts delirium better. However, ICU physicians rated the user convenience of E-PRE-DELIRIC superior to PRE-DELIRIC. In low-risk patients the delirium prediction further improves after an update with the PRE-DELIRIC model after 24 h.
Trial registration: ClinicalTrials.gov, NCT02518646 . Registered on 21 July 2015.

Gepubliceerd: Crit Care 2018 May 5;22(1):114
Impact factor: 6.425; Q1

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14. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials
Wirz Y, Meier MA, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Schroeder S, Nobre V, Annane D, Reinhart K, Damas P, Nijsten M, Shajiei A, deLange DW, Deliberato RO, Oliveira CF, Shehabi Y, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Mueller B, Schuetz P

Background: The clinical utility of serum procalcitonin levels in guiding antibiotic treatment decisions in patients with sepsis remains unclear. This patient-level meta-analysis based on 11 randomized trials investigates the impact of procalcitonin-guided antibiotic therapy on mortality in intensive care unit (ICU) patients with infection, both overall and stratified according to sepsis definition, severity, and type of infection.
Methods: For this meta-analysis focusing on procalcitonin-guided antibiotic management in critically ill patients with sepsis of any type, in February 2018 we updated the database of a previous individual patient data meta-analysis which was limited to patients with respiratory infections only. We used individual patient data from 11 trials that randomly assigned patients to receive antibiotics based on procalcitonin levels (the "procalcitonin-guided" group) or the current standard of care (the "controls"). The primary endpoint was mortality within 30 days. Secondary endpoints were duration of antibiotic treatment and length of stay.
Results: Mortality in the 2252 procalcitonin-guided patients was significantly lower compared with the 2230 control group patients (21.1% vs 23.7%; adjusted odds ratio 0.89, 95% confidence interval (CI) 0.8 to 0.99; p = 0.03). These effects on mortality persisted in a subgroup of patients meeting the sepsis 3 definition and based on the severity of sepsis (assessed on the basis of the Sequential Organ Failure Assessment (SOFA) score, occurrence of septic shock or renal failure, and need for vasopressor or ventilatory support) and on the type of infection (respiratory, urinary tract, abdominal, skin, or central nervous system), with interaction for each analysis being > 0.05. Procalcitonin guidance also facilitated earlier discontinuation of antibiotics, with a reduction in treatment duration (9.3 vs 10.4 days; adjusted coefficient -1.19 days, 95% CI -1.73 to -0.66; p < 0.001).
Conclusion: Procalcitonin-guided antibiotic treatment in ICU patients with infection and sepsis patients results in improved survival and lower antibiotic treatment duration.

Gepubliceerd: Crit Care 2018 Aug 15;22(1):191
Impact factor: 6.425; Q1

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15. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study
Guerin C, Beuret P, Constantin JM, Bellani G, Garcia-Olivares P, Roca O, Meertens JH, Maia PA, Becher T, Peterson J, Larsson A, Gurjar M, Hajjej Z, Kovari F, Assiri

AH, Mainas E, Hasan MS, Morocho-Tutillo DR, Baboi L, Chretien JM, Francois G, Ayzac L, Chen L, Brochard L, Mercat A, includes Vermeijden W, Beishuizen A, Trof R

Introduction: While prone positioning (PP) has been shown to improve patient survival in moderate to severe acute respiratory distress syndrome (ARDS) patients, the rate of application of PP in clinical practice still appears low. Aim: This study aimed to determine the prevalence of use of PP in ARDS patients (primary endpoint), the physiological effects of PP, and the reasons for not using it (secondary endpoints).
Methods: The APRONET study was a prospective international 1-day prevalence study performed four times in April, July, and October 2016 and January 2017. On each study day, investigators in each ICU had to screen every patient. For patients with ARDS, use of PP, gas exchange, ventilator settings and plateau pressure (Pplat) were recorded before and at the end of the PP session. Complications of PP and reasons for not using PP were also documented. Values are presented as median (1st-3rd quartiles).
Results: Over the study period, 6723 patients were screened in 141 ICUs from 20 countries (77% of the ICUs were European), of whom 735 had ARDS and were analyzed. Overall 101 ARDS patients had at least one session of PP (13.7%), with no differences among the 4 study days. The rate of PP use was 5.9% (11/187), 10.3% (41/399) and 32.9% (49/149) in mild, moderate and severe ARDS, respectively (P = 0.0001). The duration of the first PP session was 18 (16-23) hours. Measured with the patient in the supine position before and at the end of the first PP session, PaO2/FIO2 increased from 101 (76-136) to 171 (118-220) mmHg (P = 0.0001) driving pressure decreased from 14 [11-17] to 13 [10-16] cmH2O (P = 0.001), and Pplat decreased from 26 [23-29] to 25 [23-28] cmH2O (P = 0.04). The most prevalent reason for not using PP (64.3%) was that hypoxemia was not considered sufficiently severe. Complications were reported in 12 patients (11.9%) in whom PP was used (pressure sores in five, hypoxemia in two, endotracheal tube-related in two ocular in two, and a transient increase in intracranial pressure in one).
Conclusions: In conclusion, this prospective international prevalence study found that PP was used in 32.9% of patients with severe ARDS, and was associated with low complication rates, significant increase in oxygenation and a significant decrease in driving pressure.

Gepubliceerd: Intensive Care Med 2018 Jan;44(1):22-37
Impact factor: 15.008; Q1

Totale impact factor: 212.415
Gemiddelde impact factor: 14.161

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

Interne Geneeskunde

1. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial
Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM

Gepubliceerd: BMC Gastroenterol 2018 Feb 21;18(1):29
Impact factor: 2.731; Q3

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2. Declining HCV incidence in Dutch HIV positive men who have sex with men after unrestricted access to HCV therapy
Boerekamps A, Van den Berk GE, Fanny LN, Leyten EM, Van Kasteren ME, van Eeden A, Posthouwer D, Claassen MA, Dofferhoff AS, Verhagen DWM, Bierman WF, Lettinga KD, Kroon FP, Delsing CE, Groeneveld PH, Soetekouw R, Peters EJ, Hullegie SJ, Popping S, Van de Vijver DAMC, Boucher CA, Arends JE, Rijnders BJ

Background: Direct acting antivirals (DAA) cure 95% of patients infected with hepatitis C (HCV). Modeling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections but real-life data are lacking. The incidence of HCV among Dutch HIV-positive men who have sex with men (MSM) has been high for >10 years. In 2015 DAA became available to all Dutch HCV patients and resulted in a rapid treatment uptake in HIV-positive MSM. We assessed whether this uptake was followed by a decrease in the incidence of HCV infections.
Methods: Two prospective acute HCV treatment studies enrolled patients in 17 Dutch HIV centers, having 76% of the total HIV-positive MSM population in care in the Netherlands. Patients were recruited in 2014 and 2016, the year preceding and following unrestricted DAA availability. We compared the HCV incidence in both years.
Results: The acute HCV incidence decreased from 93 infections during 8290 person years of follow up in 2014 (11.2/1000 PYFU, 95% CI 9.1-13.7) to 49 during 8961 PYFU in 2016 (5.5/1000, 95% CI 4.1-7.2). The incidence rate ratio of 2016 compared with 2014 was 0.49 (95% C.I. 0.35-0.69). Simultaneously, a significant increase in the percentage positive syphilis (+2.2%) and gonorrhea (+2.8%) tests in HIV-positive MSM was observed at sexual health clinics across the Netherlands and contradicts a decrease in risk behavior as an alternative explanation.
Conclusions: Unrestricted DAA availability in the Netherlands was followed by a 51% decrease in acute HCV infections among HIV-positive MSM.

Gepubliceerd: Clin Infect Dis 2018;66(9):1360-5
Impact factor: 9.117; Q1

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3. High Treatment Uptake in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients After Unrestricted Access to Direct-Acting Antivirals in the Netherlands
Boerekamps A, Newsum AM, Smit C, Arends JE, Richter C, Reiss P, Rijnders BJA, Brinkman K, van der Valk M, NVHB-SHM Hepatitis Working Group and the Netherlands ATHENA HIV Observational Cohort,includes Delsing CE, Kootstra GJ

Background: The Netherlands has provided unrestricted access to direct-acting antivirals (DAAs) since November 2015. We analyzed the nationwide hepatitis C virus (HCV) treatment uptake among patients coinfected with human immunodeficiency virus (HIV) and HCV.
Methods: Data were obtained from the ATHENA HIV observational cohort in which >98% of HIV-infected patients ever registered since 1998 are included. Patients were included if they ever had 1 positive HCV RNA result, did not have spontaneous clearance, and were known to still be in care. Treatment uptake and outcome were assessed. When patients were treated more than once, data were included from only the most recent treatment episode. Data were updated until February 2017. In addition, each treatment center was queried in April 2017 for a data update on DAA treatment and achieved sustained virological response.
Results: Of 23574 HIV-infected patients ever linked to care, 1471 HCV-coinfected patients (69% men who have sex with men, 15% persons who [formerly] injected drugs, and 15% with another HIV transmission route) fulfilled the inclusion criteria. Of these, 87% (1284 of 1471) had ever initiated HCV treatment between 2000 and 2017, 76% (1124 of 1471) had their HCV infection cured; DAA treatment results were pending in 6% (92 of 1471). Among men who have sex with men, 83% (844 of 1022) had their HCV infection cured, and DAA treatment results were pending in 6% (66 of 1022). Overall, 187 patients had never initiated treatment, DAAs had failed in 14, and a pegylated interferon-alfa-based regimen had failed in 54.
Conclusions: Fifteen months after unrestricted DAA availability the majority of HIV/HCV-coinfected patients in the Netherlands have their HCV infection cured (76%) or are awaiting DAA treatment results (6%). This rapid treatment scale-up may contribute to future HCV elimination among these patients.

Gepubliceerd: Clin Infect Dis 2018 Apr 17;66(9):1352-9
Impact factor: 9.117; Q1

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4. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury
Booij HA, Gaykema WDC, Kuijpers KAJ, Pouwels MJM, den Hertog HM

Background: Poststroke fatigue (PSF) is a highly prevalent and debilitating condition. However, the etiology remains incompletely understood. Literature suggests the co-prevalence of pituitary dysfunction (PD) with stroke, and the question raises whether this could be a contributing factor to the development of PSF. This study reviews the prevalence of PD after stroke and other acquired brain injuries and its association with fatigue.
Summary: We performed a bibliographic literature search of MEDLINE and EMBASE databases for English language studies on PD in adult patients with stroke, traumatic brain injury (TBI) or aneurysmatic subarachnoid hemorrhage (aSAH). Forty-two

articles were selected for review. Up to 82% of patients were found to have any degree of PD after stroke. Growth hormone deficiency was most commonly found. In aSAH and TBI, prevalences up to 49.3% were reported. However, data differed widely between studies, mostly due to methodological differences including the diagnostic methods used to define PD and the focus on the acute or chronic phase. Data on PD and outcome after stroke, aSAH and TBI are conflicting. No studies were found investigating the association between PD and PSF. Data on the association between PD and fatigue after aSAH and TBI were scarce and conflicting, and fatigue is rarely been investigated as a primary end point.
Key messages: Data according to the prevalence of PD after stroke and other acquired brain injury suggest a high prevalence of PD after these conditions. However, the clinical relevance and especially the association with fatigue need to be established.

Gepubliceerd: Endocr Connect 2018 Jun;7(6):R223-R237
Impact factor: 3.041; Q3

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5. Dystrophy of the fingernails: a diagnostic clue
de Blok CJM, van Rooijen CR

Gepubliceerd: Neth J Med 2018 Apr;76(3):132
Impact factor: 1.156;Q3

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6. Signet Ring Cell Carcinoma of the Ampulla of Vater: A Rare Histopathological Variant
de Klein GW, van Baarlen J, Mekenkamp LJ, Liem MSL, Klaase JM

Signet ring cell carcinoma (SRCC) of the ampulla of Vater is an extremely rare tumor. Our case describes a 45-year-old female presenting with jaundice and pruritus. Computed tomography, endoscopy, and endoscopic retrograde cholangiopancreatography showed a tumor of the ampulla of Vater without distant metastasis. Histological biopsy confirmed a malignant tumor with SRCC characteristics and immunohistochemical staining revealed a mixed type profile (both intestinal and pancreatobiliary characteristics). A pylorus-preserving pancreatoduodenectomy was performed and the patient recovered without complications. Pathology results concluded a pT2N0 ampullary SRCC. SRCC of the ampulla of Vater is known to be highly malignant. After 13 months of follow-up, our patient showed no signs of recurrence.

Gepubliceerd: Case Rep Gastroenterol 2018 Jan;12(1):194-201
Impact factor: 0; nvt

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7. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in The Netherlands
Franken MG, Leeneman B, Jochems A, Schouwenburg MG, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, van den Eertwegh AJM, de Groot JWB, van der Hoeven KJM, Hospers GAP, Kapiteijn E, Koornstra R, Kruit WHJ, Louwman MWJ,

Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, Vreugdenhil G, Wouters MWJM, van Zeijl M, Haanen JBAG, Uyl-de Groot CA

There is limited evidence on the costs associated with ipilimumab. We investigated healthcare costs of all Dutch patients with advanced cutaneous melanoma who were treated with ipilimumab. Data were retrieved from the nation-wide Dutch Melanoma Treatment Registry. Costs were determined by applying unit costs to individual patient resource use. A total of 807 patients who were diagnosed between July 2012 and July 2015 received ipilimumab in Dutch practice. The mean (median) episode duration was 6.27 (4.61) months (computed from the start of ipilimumab until the start of a next treatment, death, or the last date of follow-up). The average total healthcare costs amounted to &OV0556;81 484, but varied widely (range: &OV0556;18 131-&OV0556;160 002). Ipilimumab was by far the most important cost driver (&OV0556;73 739). Other costs were related to hospital admissions (&OV0556;3323), hospital visits (&OV0556;1791), diagnostics and imaging (&OV0556;1505), radiotherapy (&OV0556;828), and surgery (&OV0556;297). Monthly costs for resource use other than ipilimumab were &OV0556;1997 (SD: &OV0556;2629). Treatment-naive patients (n=344) had higher total costs compared with previously-treated patients (n=463; &OV0556;85 081 vs. &OV0556;78 811). Although patients with colitis (n=106) had higher costs for resource use other than ipilimumab (&OV0556;11 426) compared with patients with other types of immune-related adverse events (n=90; &OV0556;9850) and patients with no immune-related adverse event (n=611; &OV0556;6796), they had lower total costs (&OV0556;76 075 vs. &OV0556;87 882 and &OV0556;81 480, respectively). In conclusion, this nation-wide study provides valuable insights into the healthcare costs of advanced cutaneous melanoma patients who were treated with ipilimumab in clinical practice. Most of the costs were attributable to ipilimumab, but the costs and its distribution varied considerably across subgroups.

Gepubliceerd: Anticancer Drugs 2018 Jul;29(6):579-88
Impact factor: 1.869; Q3

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8. Cost-Effectiveness Analysis of the DiagnOSAS Screening Tool Compared With Polysomnography Diagnosis in Dutch Primary Care
Geessinck FAJ, Pleijhuis RG, Mentink RJ, van der Palen J, Koffijberg H

Study objectives: The growing recognition of obstructive sleep apnea (OSA) as a serious health condition, increasing waiting lists for sleep tests, and a high proportion of unnecessary referrals from general practice highlight the need for alternative diagnostic strategies for OSA. This study's objective was to investigate the cost-effectiveness of DiagnOSAS, a screening tool that strives to facilitate fast and well-informed referral to hospitals and sleep clinics for diagnosis, in The Netherlands. **Methods:** A Markov model was constructed to assess cost-effectiveness in men aged 50 years. The diagnostic process of OSA was simulated with and without DiagnOSAS, taking into account the occurrence of hazardous OSA effects: car accidents, myocardial infarction, and stroke. The cost-effectiveness of "DiagnOSAS Strategy" and a "Rapid Diagnosis Scenario," in which time to diagnosis was halved, was assessed.

Results: Base case results show that, within a 10-year time period, DiagnOSAS saves €226 per patient at a negligible decrease (< 0.01) in quality-adjusted life-years (QALYs), resulting in an incremental cost-effectiveness ratio of €56,997/QALY. The "Rapid Diagnosis Scenario" dominates usual care (ie, is both cheaper and more effective). For a willingness-to-pay threshold of €20,000/QALY the probability that the "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" are cost-effective equals 91.7% and 99.3%, respectively.
Conclusions: DiagnOSAS appears to be a cost-saving alternative for the usual OSA diagnostic strategy in The Netherlands. When DiagnOSAS succeeds in decreasing time to diagnosis, it could substantially improve health outcomes as well.

Gepubliceerd: J Clin Sleep Med 2018 Jun 15;14(6):1005-15
Impact factor: 3.396; Q2

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9. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial
Goldschmidt H, Lokhorst HM, Mai EK, van der Holt B, Blau IW, Zweegman S, Weisel KC, Vellenga E, Pfreundschuh M, Kersten MJ, Scheid C, Croockewit S, Raymakers R, Hose D, Potamianou A, Jauch A, Hillengass J, Stevens-Kroef M, Raab MS, Broijl A, Lindemann HW, Bos GMJ, Brossart P, van Marwijk Kooy M, Ypma P, Duehrsen U, Schaafsma MR, Bertsch U, Hielscher T, Jarari L, Salwender HJ, Sonneveld P

The Dutch-Belgian Cooperative Trial Group for Hematology Oncology Group-65/German-speaking Myeloma Multicenter Group-HD4 (HOVON-65/GMMG-HD4) phase III trial compared bortezomib (BTZ) before and after high-dose melphalan and autologous stem cell transplantation (HDM, PAD arm) compared with classical cytotoxic agents prior and thalidomide after HDM (VAD arm) in multiple myeloma (MM) patients aged 18-65 years. Here, the long-term follow-up and data on second primary malignancies (SPM) are presented. After a median follow-up of 96 months, progression-free survival (censored at allogeneic transplantation, PFS) remained significantly prolonged in the PAD versus VAD arm (hazard ratio (HR)=0.76, 95% confidence interval (95% CI) of 0.65-0.89, P=0.001). Overall survival (OS) was similar in the PAD versus VAD arm (HR=0.89, 95% CI: 0.74-1.08, P=0.24). The incidence of SPM were similar between the two arms (7% each, P=0.73). The negative prognostic effects of the cytogenetic aberration deletion 17p13 (clone size 10%) and renal impairment at baseline (serum creatinine >2 mg dl-1) on PFS and OS remained abrogated in the PAD but not VAD arm. OS from first relapse/progression was similar between the study arms (HR=1.02, P=0.85). In conclusion, the survival benefit with BTZ induction/maintenance compared with classical cytotoxic agents and thalidomide maintenance is maintained without an increased risk of SPM.Leukemia advance online publication, 1 August 2017; doi:10.1038/leu.2017.211.

Gepubliceerd: Leukemia 2018;32(2):383-90
Impact factor: 10.023; Q1

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10. Gender differences in the use of cardiovascular interventions in HIV-positive persons; the D:A:D Study

Hatleberg CI, Ryom L, El-Sadr W, Mocroft A, Reiss P, De Wit S, Dabis F, Pradier C, d'Arminio Monforte A, Kovari H, Law M, Lundgren JD, Sabin CA, Data Collection of Adverse Events of Anti-HIV drugs (D:A:D) Study group,includes Kootstra GJ, Delsing CE

Introduction: There is paucity of data related to potential gender differences in the use of interventions to prevent and treat cardiovascular disease (CVD) among HIV-positive individuals. We investigated whether such differences exist in the observational D:A:D cohort study.
Methods: Participants were followed from study enrolment until the earliest of death, six months after last visit or February 1, 2015. Initiation of CVD interventions [lipid-lowering drugs (LLDs), angiotensin-converting enzyme inhibitors (ACEIs), anti-hypertensives, invasive cardiovascular procedures (ICPs) were investigated and Poisson regression models calculated whether rates were lower among women than men, adjusting for potential confounders.
Results: Women (n = 12,955) were generally at lower CVD risk than men (n = 36,094). Overall, initiation rates of CVD interventions were lower in women than men; LLDs: incidence rate 1.28 [1.21, 1.35] vs. 2.40 [2.34, 2.46]; ACEIs: 0.88 [0.82, 0.93] vs. 1.43 [1.39, 1.48]; anti-hypertensives: 1.40 [1.33, 1.47] vs. 1.72 [1.68, 1.77] and ICPs: 0.08 [0.06, 0.10] vs. 0.30 [0.28, 0.32], and this was also true for most CVD interventions when exclusively considering periods of follow-up for which individuals were at high CVD risk. In fully adjusted models, women were less likely to receive CVD interventions than men (LLDs: relative rate 0.83 [0.78, 0.88]; ACEIs: 0.93 [0.86, 1.01]; ICPs: 0.54 [0.43, 0.68]), except for the receipt of anti-hypertensives (1.17 [1.10, 1.25]).
Conclusion: The use of most CVD interventions was lower among women than men. Interventions are needed to ensure that all HIV-positive persons, particularly women, are appropriately monitored for CVD and, if required, receive appropriate CVD interventions.

Gepubliceerd: J Int AIDS Soc 2018 Mar;21(3)
Impact factor: 5.135; Q1

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11. Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands
Jochems A, Leeneman B, Franken MG, Schouwenburg MG, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, van den Eertwegh AJM, Groenewegen G, de Groot JWB, Haanen JBAG, Hospers GAP, Kapiteijn E, Koornstra RH, Kruit WHJ, Louwman MWJ, Piersma D, van Rijn RS, Ten Tije AJ, Vreugdenhil G, Wouters MWJM, Uyl-de Groot CA, van der Hoeven KJM

Phase III trials with ipilimumab showed an improved survival in patients with metastatic melanoma. We evaluated the use and safety of ipilimumab, and the survival of all patients with metastatic cutaneous melanoma (N=807) receiving ipilimumab in real-world clinical practice in The Netherlands using data from the Dutch Melanoma Treatment Registry. Patients who were registered between July 2012 and July 2015 were included and analyzed according to their treatment status: treatment-naive (N=344) versus previously-treated (N=463). Overall, 70% of treatment-naive patients and 62% of previously-treated patients received all four

planned doses of ipilimumab. Grade 3 and 4 immune-related adverse events occurred in 29% of treatment-naive patients and 21% of previously-treated patients. No treatment-related deaths occurred. Median time to first event was 5.4 months [95% confidence interval (CI): 4.7-6.5 months] in treatment-naive patients and 4.4 months (95% CI: 4.0-4.7 months) in previously-treated patients. Median overall survival was 14.3 months (95% CI: 11.6-16.7 months) in treatment-naive patients and 8.7 months (95% CI: 7.6-9.6 months) in previously-treated patients. In both patient groups, an elevated lactate dehydrogenase level (hazard ratio: 2.25 and 1.70 in treatment-naive and previously-treated patients, respectively) and American Joint Committee on Cancer M1c-stage disease (hazard ratio: 1.81 and 1.83, respectively) were negatively associated with overall survival. These real-world outcomes of ipilimumab slightly differed from outcomes in phase III trials. Although phase III trials are crucial for establishing efficacy, real-world data are of great added value enhancing the generalizability of outcomes of ipilimumab in clinical practice.

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Impact factor: 1.869; Q3

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12. Prediabetes and its Impact on Clinical Outcome After Coronary Intervention in a Broad Patient Population

Kok MM, von Birgelen C, Sattar N, Zocca P, Lowik MM, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Kant GD, Doelman C, Tjon Joe Gin RM, Stoel MG, van Houwelingen G, Linssen GCM, IJzerman MJ, Doggen CJM, van der Heijden LC

Aims: It is unclear whether detection of prediabetes(Pre-DM) by routine assessment of glycated haemoglobin A1c(HbA1c) and fasting plasma glucose(FPG) among patients undergoing percutaneous coronary intervention(PCI) with contemporary drug-eluting stents(DES) may help identify subjects with increased event risk. We assessed the relation between glycaemia status and 1-year outcome after PCI.
Methods and results: Glycaemia status was determined in 2,362 non-diabetic BIO-RESORT participants, treated at all four study sites, to identify Pre-DM (HbA1c 42-47mmol/mol; FPG 6.1-6.9mmol/L) and unknown diabetes mellitus(DM) (HbA1c>/=48mmol/mol; FPG>/=7.0mmol/L). Another 624 patients had medically treated DM. The main composite endpoint consisted of death, myocardial infarction, or revascularisation. Glycaemic state was known in 2,986 participants: 324(11%) patients had Pre-DM, 793(27%) had DM(known or new), and 1,869(63%) patients had normoglycaemia. Pre-DM and DM patients differed from normoglycemic patients in cardiovascular risk factors. The composite endpoint occurred in 11.1% in Pre-DM, 10.5% in DM, and 5.7% in normoglyacemia($p<0.001$). Pre-DM was associated with a 2-times higher event risk compared to normoglycaemia(adj.HR 2.0, 95%CI:1.4-3.0).
Conclusions: Following PCI with contemporary DES, all-comers with Pre-DM had significantly higher event risks than normoglycemic patients. In non-DM patients requiring PCI, routine assessment of HbA1c and FPG appears to be of value to identify subjects with increased event risk.

Gepubliceerd: EuroIntervention 2018 Jan 9;14(9):e1049-e1056
Impact factor: 4.417; Q2

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13. Caregivers of patients receiving long-term treatment with a tyrosine kinase inhibitor (TKI) for gastrointestinal stromal tumour (GIST): a cross-sectional assessment of their distress and burden
Langenberg SMCH, Reyners AKL, Wymenga ANM, Sieling GCM, Veldhoven CMM, van Herpen CML, Prins JB, van der Graaf WTA

Background: TKIs are a long-term treatment for GIST, and may have an impact on caregivers.
Material and methods: For this cross-sectional study, patients and caregivers were both included when patients had been treated with TKIs for at least six months. Caregivers completed questionnaires including demographics, distress (Hospital Anxiety and Depression scale), burden (Self-Perceived Pressure from Informal Care) general health (RAND-36), comorbidity (Self-administered Comorbidity Questionnaire), social support (Social Support List - Discrepancies) and marital satisfaction (Maudsley Marital Questionnaire). Patients completed similar questionnaires, without 'burden'. We conducted analyses to explore differences between caregivers with low/moderate versus high levels of burden and low versus high levels of distress.
Results: Sixty-one out of seventy-one eligible couples (84%) were included in the analysis. The median age of the caregivers was 60 years; 66% were female and 78% were the patients' spouse. The median age of the patients was 66 years; 43% were female. Caregivers experienced high levels of burden and distress in 10% and 23%, respectively. Caregivers with high levels of burden perceived significantly lower mental health, less vitality, lower general health and high levels of distress. Significantly higher levels of burden were found in non-spouses, caregivers of patients with more treatment-related side-effects, caregivers who spent more hours caring, and those caring for more than one person. For distress, caregivers with high levels of distress perceived significantly more burden, lower social functioning, more role physical and emotional problems, lower mental health, less vitality and lower general health. Furthermore, high levels of distress were found in caregivers of more dependent patients and those caring for more than one person.
Conclusions: Caregivers of the patients with GIST treated with TKI are managing well. There is a small, vulnerable group of caregivers with high levels of burden and/or distress, show more health-related problems, both physical and mental, and require adequate support.

Gepubliceerd: Acta Oncol 2018 Oct 3;1-9
Impact factor: 3.473; Q2

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14. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis
Meijerink MR, Puijk RS, van Tilborg AAJM, Henningsen KH, Fernandez LG, Neyt M, Heymans J, Frankema JS, de Jong KP, Richel DJ, Prevoo W, Vlayen J

Purpose: To assess safety and outcome of radiofrequency ablation (RFA) and microwave ablation (MWA) as compared to systemic chemotherapy and partial hepatectomy (PH) in the treatment of colorectal liver metastases (CRLM).

Methods: MEDLINE, Embase and the Cochrane Library were searched. Randomized trials and comparative observational studies with multivariate analysis and/or matching were included. Guidelines from National Guideline Clearinghouse and Guidelines International Network were assessed using the AGREE II instrument.
Results: The search revealed 3530 records; 328 were selected for full-text review; 48 were included: 8 systematic reviews, 2 randomized studies, 26 comparative observational studies, 2 guideline-articles and 10 case series; in addition 13 guidelines were evaluated. Literature to assess the effectiveness of ablation was limited. RFA + systemic chemotherapy was superior to chemotherapy alone. PH was superior to RFA alone but not to RFA + PH or to MWA. Compared to PH, RFA showed fewer complications, MWA did not. Outcomes were subject to residual confounding since ablation was only employed for unresectable disease.
Conclusion: The results from the EORTC-CLOCC trial, the comparable survival for ablation + PH versus PH alone, the potential to induce long-term disease control and the low complication rate argue in favour of ablation over chemotherapy alone. Further randomized comparisons of ablation to current-day chemotherapy alone should therefore be considered unethical. Hence, the highest achievable level of evidence for unresectable CRLM seems reached. The apparent selection bias from previous studies and the superior safety profile mandate the setup of randomized controlled trials comparing ablation to surgery.

Gepubliceerd: Cardiovasc Intervent Radiol 2018 Aug;41(8):1189-204
Impact factor: 2.210; Q2

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15. A gene variant near ATM affects the response to metformin and metformin plasma levels: a post hoc analysis of an RCT
Out M, Becker ML, van Schaik RH, Lehert P, Stehouwer CD, Kooy A

Aim: To determine the influence of polymorphisms on the effects of metformin on HbA1c, daily dose of insulin and metformin plasma concentration.
Methods: In a post hoc analysis of a 4.3 year placebo-controlled randomized trial with 390 patients with Type 2 diabetes already on insulin, we analyzed the influence of polymorphisms in genes coding for ATM and the transporters OCT1 and MATE1. Outcome measures were a combined HbA1c + daily dose of insulin Z score and metformin plasma concentrations.
Results: rs11212617 (ATM) was associated with an improved Z score and a lower metformin plasma concentration. In addition, the major allele of rs2289669 (MATE1) was also associated with an improved Z score.
Conclusion: The ATM SNP rs11212617 significantly affected the effect of metformin and metformin plasma concentration. Further research is needed to determine the clinical importance of these findings, in particular the effects on metformin plasma concentration.

Gepubliceerd: Pharmacogenomics 2018 Jun 1;19(8):715-26
Impact factor: 2.302; Q3

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16. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: Post hoc analysis of a randomized controlled 4.3year trial

Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CDA

Aims: Metformin treatment is associated with a decrease of serum vitamin B12, but whether this reflects tissue B12 deficiency is controversial. We studied the effects of metformin on serum levels of methylmalonic acid (MMA), a biomarker for tissue B12 deficiency, and on onset or progression of neuropathy.
Methods: In the HOME trial, 390 insulin-treated patients with type 2 diabetes were treated with metformin or placebo for 52months. In a post hoc analysis, we analyzed the association between metformin, MMA and a validated Neuropathy Score (NPS).
Results: Metformin vs placebo increased MMA at the end of the study (95%CI: 0.019 to 0.055, p=0.001). Mediation analysis showed that the effect of metformin on the NPS consisted of a beneficial effect through lowering HbA1c (-0.020 per gram year) and an adverse effect through increasing MMA (0.042 per gram year), resulting in a non-significant net effect (0.032 per gram year, 95% CI: -0.121 to 0.182, p=0.34).
Conclusion: Metformin not only reduces serum levels of B12, but also progressively increases serum MMA. The increase of MMA in metformin users was associated with significant worsening of the NPS. These results provide further support that metformin-related B12 deficiency is clinically relevant. Monitoring of B12 in users of metformin should be considered.

Gepubliceerd: J Diabetes Complications 2018 Feb;32(2):171-8
Impact factor: 2.792; Q3

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17. Long-term treatment with metformin in type 2 diabetes and vitamin D levels: A post-hoc analysis of a randomized placebo-controlled trial
Out M, Top WMC, Lehert P, Schalkwijk CA, Stehouwer CDA, Kooy A

Aims: To study the effects of metformin, as compared to placebo, on serum levels of vitamin D (25-hydroxyvitamin D [25(OH)D]) in patients with advanced type 2 diabetes. MATERIALS AND
Methods: In the HOME trial, a randomized placebo-controlled trial, 390 insulin-treated patients with type 2 diabetes were treated with 850 mg metformin or placebo thrice daily for 52 months. In a post-hoc analysis, we examined changes in the combined levels of 25(OH)D2 and 25(OH)D3 at 4 and 16 months during the study.
Results: Mean combined 25(OH)D at baseline was 68.2 nmoL/L (95% confidence interval [CI]: 65.5-71.1). In mixed model analysis, metformin, as compared to placebo, had no effect on 25(OH)D levels during 16 months (coefficient: 1.002 per month, multiplicative model; 95% CI: 0.998-1.006, P = .30). Metformin was associated with a small increase of 25(OH)D2 (coefficient: 1.012 per month; 95% CI: 1.003-1.021, P = .008). However, 25(OH)D2 is only a very small fraction (3%) of 25(OH)D. Seasonal variation had the biggest impact on 25(OH)D levels. Vitamin B12 levels were not associated with the levels of 25(OH)D.
Conclusion: Metformin had no effect on serum 25(OH)D during 16 months in the setting of a clinical randomized controlled trial in patients with type 2 diabetes. Our results show that metformin doesn't lead to vitamin D deficiency.

Gepubliceerd: Diabetes Obes Metab 2018 Aug;20(8):1951-6
Impact factor: 5.980; Q1

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18. Metformin-associated prevention of weight gain in insulin-treated type 2 diabetic patients cannot be explained by decreased energy intake: A post hoc analysis of a randomized placebo-controlled 4.3-year trial
Out M, Miedema I, Jager-Wittenaar H, van der Schans C, Krijnen W, Lehert P, Stehouwer C, Kooy A

Metformin prevents weight gain in patients with type 2 diabetes (T2D). However, the mechanisms involved are still unknown. In this post hoc analysis of the HOME trial, we aimed to determine whether metformin affects energy intake. Patients with T2D were treated with 850 mg metformin or received placebo added to insulin (1-3 times daily) for 4.3 years. Dietary intake was assessed at baseline, after 1 year and after 4.3 years, according to the dietary history method. Among the 310 included participants, 179 (93 placebo, 86 metformin) completed all 3 dietary assessments. We found no significant difference in energy intake after 4.3 years between the groups (metformin vs placebo: -31.0 kcal/d; 95% CI, -107.4 to 45.4; F-value, 1.3; df = 415; P = .27). Body weight in placebo users increased significantly more than in metformin-users during 4.3 years (4.9 +/- 4.9 vs 1.1 +/- 5.2 kg; t test: P </= .001). Linear mixed models did not show a significant effect of energy intake as explanation for the difference in weight gain between the groups (F-value, 0.1; df = 1; P = .82). In conclusion, the prevention of weight gain by metformin cannot be explained by reduced energy intake.

Gepubliceerd: Diabetes Obes Metab 2018 Jan;20(1):219-23
Impact factor: 5.980; Q1

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19. Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: prognostic factors associated with clinical outcomes
Schouwenburg MG, Jochems A, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, van Zeijl MCT, Aarts MJ, van Akkooi ACJ, van den Berkmortel FWPJ, Blokx WAM, de Groot JWB, Hospers GAP, Kapiteijn E, Koornstra RH, Kruit WH, Louwman MWJ, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, Vreugdenhil G, Wouters MWJM, van der Hoeven JJM

The aim of this population-based study was to identify the factors associated with clinical outcomes in vemurafenib-treated patients and to evaluate outcomes across subgroups of patients with different risk profiles. Data were retrieved from the Dutch Melanoma Treatment Registry. Time to next treatment (TTNT) and overall survival (OS) of all metastatic melanoma patients who received vemurafenib between 2012 and 2015 were assessed using Kaplan-Meier estimates. A risk score was developed on the basis of all prognostic factors associated with TTNT and OS derived from multivariable Cox regression analyses. Patients were stratified according to the presence of prognostic risk factors by counting the number of factors, ranging from 0 to 6. A total of 626 patients received vemurafenib with a median follow-up of 35.8 months. The median TTNT and OS were 4.7 months [95% confidence intervals (CI): 4.4-5.1] and 7.3 months (95% CI: 6.6-8.0). The strongest prognostic factors were serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance score, number of organ sites involved and brain metastases. Patients with a favourable risk profile (no risk factors) had a median TTNT and OS of 7.1 (95%

CI: 5.8-8.5) and 15.4 months (95% CI: 10.0-20.9). The median OS more than halved for patients with greater than or equal to 2 risk factors compared with patients with no risk factors. The clinical outcomes of vemurafenib in metastatic melanoma patients with a favourable risk profile are comparable with the results of the trials. Combining prognostic factors into a risk score could be valuable to stratify patients into favourable and poor-prognosis groups.

Gepubliceerd: Melanoma Res 2018 Aug;28(4):326-32
Impact factor: 3.135; Q1

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20. Management of drug interactions with direct-acting antivirals in Dutch HIV/hepatitis C virus-coinfected patients: adequate but not perfect
Smolders EJ, Smit C, de KC, Dofferhoff A, Arends JE, Brinkman K, Rijnders B, van der Valk M, Reiss P, Burger DM, Data Collection of Adverse Events of Anti-HIV drugs (D:A:D) Study group,includes Kootstra GJ, Delsing CE

Objectives: Direct-acting antivirals (DAAs) for treatment of chronic hepatitis C virus (HCV) infection can cause drug-drug interactions (DDIs) with combination antiretroviral therapy (cART) and non-cART co-medication. We mapped how physicians manage DDIs between DAAs and co-medication and analysed treatment outcomes.
Methods: Data were prospectively collected as part of the ATHENA HIV observational cohort and retrospectively analysed. Dutch patients with HIV/HCV coinfection who initiated treatment with DAAs between January 2015 and May 2016 were included. Co-medication 3 months prior to and during DAA therapy was identified. Potential DDIs with the DAAs were checked using http://hep-druginteractions.org. DDIs were categorized as: (1) no interaction expected; (2) potential interaction; (3) contra-indication; (4) no recommendation. These categories were used to determine which patients switched or had a DDI during DAA therapy with co-medication.
Results: A total of 423 patients were treated with DAAs, of whom 418 (99%) used cART and 251 (59%) used non-cART co-medication. Before commencing DAA treatment, in 17 of 84 (20%) patients the non-cART co-medication which could result in a category 2/3 DDI was discontinued before DAA initiation, including two of six (33%) prescriptions of category 3 drugs. A total of 196 of 418 (47%) patients had a category 2/3 DDI between their DAA regimen and cART. Category 2/3 DDIs were prevented by switching cART in 78 of 147 (53%) and 47 of 49 (98%) patients. Overall, 367 of 423 (87%) patients have achieved a sustained virological response (33 in follow-up).
Conclusions: Prescription patterns suggest that physicians are aware of potential DDIs between co-medication and DAAs, in particular potential DDIs with cART. Greater awareness is needed concerning category 3 interactions between non-cART co-medication and DAAs.

Gepubliceerd: HIV Med 2018 Mar;19(3):216-26
Impact factor: 2.932; Q2

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21. Short-term efficacy and safety of antithymocyte globulin treatment in elderly patients with acquired aplastic anaemia
Tjon JM, de Groot MR, Sypkens Smit SMA, de Wreede LC, Snijders TJF, Koene HR, Meijer E, Raaijmakers MHG, Schaap M, Raymakers R, Zeerleder SS, Halkes CJM

Gepubliceerd: Br J Haematol 2018 Feb;180(3):459-62
Impact factor: 5.128; Q1

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22. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial
van de Donk NW, van der Holt B, Minnema MC, Vellenga E, Croockewit S, Kersten MJ, von dem Borne PA, Ypma P, Schaafsma R, de Weerdt O, Klein SK, Delforge M, Levin MD, Bos GM, Jie KG, Sinnige H, Coenen JL, de Waal EG, Zweegman S, Sonneveld P, Lokhorst HM

Background: In patients with recently diagnosed multiple myeloma, the HOVON-50 phase 3 trial showed improved event-free survival for thalidomide-containing induction and maintenance regimens (in conjunction with high-dose melphalan and autologous stem cell transplantation [auto-SCT]) after a median of 52 months of follow-up, by comparison with regimens containing classical cytotoxic drugs. In this follow-up analysis, we aimed to determine the long-term effects of thalidomide in induction and maintenance therapy in multiple myeloma.
Methods: In this open-label, phase 3 randomised controlled trial, patients with recently diagnosed multiple myeloma were recruited from 44 Dutch and Belgian hospitals. Participants had been diagnosed with multiple myeloma of Durie-Salmon stage II or III and were aged 18-65 years. Patients were randomly assigned (1:1) either to receive three 28-day cycles of vincristine (0.4 mg, intravenous rapid infusion on days 1-4), doxorubicin (9 mg/m(2), intravenous rapid infusion on days 1-4) and dexamethasone (40 mg, orally on days 1-4, 9-12, and 17-20; control group); or to receive the same regimen, but with thalidomide (200-400 mg, orally on days 1-28) instead of vincristine (thalidomide group). No masking after assignment to intervention was used. Patients were randomly assigned to groups, stratified by centre and treatment policy (one vs two courses of high-dose melphalan and auto-SCT). After stem cell harvest, patients received one or two courses of 200 mg/m(2) melphalan intravenously with auto-SCT. Patients with at least a partial response to high-dose melphalan and auto-SCT were eligible for maintenance therapy, starting 2-3 months after high-dose melphalan. Patients in the control group received maintenance therapy with interferon alfa (3 x 10(6) international units, subcutaneously, three times weekly). Patients in the thalidomide group received thalidomide as maintenance therapy (50 mg, orally, daily). Maintenance therapy was given until relapse, progression, or the occurrence of adverse events. The primary endpoint of the study was event-free survival (EFSc; censored at allogeneic stem cell transplantation), analysed by intention to treat. The study is closed for enrolment and this Article represents the final analysis. This trial was registered with the Netherlands Trial Register, number NTR238.
Findings: Between Nov 27, 2001 and May 31, 2005, 556 patients were enrolled in the study, of whom 536 (96%) were eligible for evaluation and were randomly allocated (268 [50%] to the control group and 268 [50%] to the thalidomide group).

These 536 patients were assessed for the primary endpoint of EFSc. At an extended median follow-up of 129 months (IQR 123-136), EFSc was significantly longer in the thalidomide group compared with the control group (multivariate analysis hazard ratio [HR] 0.62, 95% CI 0.50-0.77; p<0.0001). Thalidomide maintenance was stopped because of toxicity in 65 (42%) of 155 patients in the thalidomide group (neuropathy in 49 [75%] patients, skin reactions in four [6%] patients, fatigue in two [3%] patients, and as other symptoms [such as abdominal pain, pancreatitis, and dyspnoea] in ten [15%] patients). 24 (27%) of 90 patients in the control group discontinued protocol treatment during maintenance therapy with interferon alfa because of toxicity (five [21%] patients with psychiatric side-effects, five [21%] patients with flu-like symptoms, four [17%] patients with haematological toxicity [thrombocytopenia and leucocytopenia], three [13%] patients with skin reactions, and seven [29%] patients with other symptoms [such as infections, cardiomyopathy, and headache]). The frequency of second primary malignancies was similar in both groups. There were 23 second primary malignancies in 17 patients in the control group and 29 second primary malignancies in 24 patients in the thalidomide group. There were 19 treatment-related deaths in the control group, and 16 treatment-related deaths in the thalidomide group.
Interpretation: Our data indicate that thalidomide-based treatment could be a treatment option for patients with multiple myeloma who are eligible for auto-SCT who live in countries without access to proteasome inhibitors or lenalidomide. However, careful follow-up and timely dose adjustments are important to prevent the development of thalidomide-induced neurotoxicity.
Funding: The Dutch Cancer Foundation.

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Impact factor: 10.698; Q1

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23. Recent treatment results for metastatic melanoma: data from the Dutch Melanoma Treatment Registry
van Zeijl MCT, van den Eertwegh AJM, Wouters MWJM, Jochems A, Schouwenburg MG, Haanen JBAG, Aarts MJ, van den Berkmortel FWPJ, de Groot JWB, Hospers GAP, Kapiteijn E, Koornstra RH, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van der Hoeven KJM

Objective: To evaluate treatment strategies and survival of patients with unresectable stage IIIc or IV melanoma since the 2012 introduction of new drugs in the Netherlands.
Design: Prospective cohort study. Method: We analysed data from the Dutch Melanoma Treatment Registry (DMTR) regarding patients diagnosed with unresectable stage IIIc or IV melanoma in the period of 1 July 2012 to 31 December 2015. We estimated survival times using the Kaplan-Meier method. The relationship between year of diagnosis and survival was estimated using Cox regression analysis, adjusted for age, WHO performance status, lactate dehydrogenase values, stage, brain metastases and distant metastases.
Results: Out of 2,768 registered patients, approximately three-quarters received systemic therapy. This treatment was subject to change every year. Median survival was 10.7 months (95% CI: 9.6-13.2) in 2012 and 13.8 months (95% CI: 11.8-15.6) in 2015. Median survival for patients receiving systemic therapy was 17.1 months in

2015. 2-year survival in this period increased from 23% to 40%. Patients diagnosed in 2015 had better survival than patients of 2014 (hazard ratio (HR) 0.82; 95% CI: 0.73-0.93). This was also true for patients receiving systemic therapy (HR: 0.79; 95% CI: 0.69-0.91).
Conclusion: Fast availability of new drugs, initiated by the then minister of VWS (health, welfare and sport) and the professional organisation, has thoroughly changed treatment of unresectable stage IIIc and IV melanoma. Data from the DMTR indicate safe use of these new drugs in daily practice and improved survival of advanced-melanoma patients in recent years.

Gepubliceerd: Ned Tijdschr Geneeskd 2018 Jun 15;162:D2420
Impact factor: 0; nvt

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24. "Silent" Diabetes and Clinical Outcome After Treatment With Contemporary Drug-Eluting Stents: The BIO-RESORT Silent Diabetes Study
von Birgelen C, Kok MM, Sattar N, Zocca P, Doelman C, Kant GD, Lowik MM, van der Heijden LC, Sen H, van Houwelingen KG, Stoel MG, Louwerenburg JHW, Hartmann M, de Man FHAF, Linssen GCM, Doggen CJM, Tandjung K

Objectives: This study sought to assess the prevalence and clinical impact of silent diabetes and pre-diabetes in "nondiabetic" percutaneous coronary intervention (PCI) all-comers.
Background: Patients with undetected and thus untreated (silent) diabetes may have higher event risks after PCI with contemporary drug-eluting stents (DES).
Methods: The BIO-RESORT Silent Diabetes study, performed at Thoraxcentrum Twente, is a substudy of the randomized multicenter BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) trial (NCT01674803). Patients underwent oral glucose tolerance testing (OGTT), and assessment of glycosylated hemoglobin with fasting plasma glucose. Primary endpoint was a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.
Results: Of the 988 participants, OGTT detected silent diabetes in 68 (6.9%), pre-diabetes in 133 (13.3%), and normal glucose metabolism in 788 (79.8%). Patients with silent diabetes had higher primary endpoint rates (13.2% vs. 7.6% vs. 4.8%; $p < 0.001$; silent diabetes vs. normal: hazard ratio: 4.2; 95% confidence interval: 1.9 to 9.2). Differences were driven by myocardial infarction ($p < 0.001$) which occurred mostly <48 h. Based on glycosylated hemoglobin and fasting plasma glucose, silent diabetes was found in 33 (3.3%) patients, pre-diabetes in 217 (22.0%) patients, and normal glucose metabolism in 738 (74.7%) patients; primary endpoint rates were similar to OGTT-based analyses (12.1% vs. 5.5% vs. 3.1%; $p = 0.01$). Multivariate analyses demonstrated that abnormal glucose metabolism by either diagnostic approach, present in 330 (33.4%) patients, independently predicted adverse event risk (hazard ratio: 2.2; 95% confidence interval: 1.2 to 4.2).
Conclusions: Abnormal glucose metabolism was detected in 1 of 3 "nondiabetic" PCI patients and was independently associated with up to 4-fold higher event risks. Future intervention trials should determine whether meaningful benefits accrue from routine glycemia testing in such patients.

Gepubliceerd: JACC Cardiovasc Interv 2018 Mar 12;11(5):448-59

Impact factor: 9.881; Q1

Totale impact factor: 106.382
Gemiddelde impact factor: 4.433

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 26.734
Gemiddelde impact factor: 3.342

Kindergeneeskunde

1. Implementing paediatric early warning scores systems in the Netherlands: future implications
de Groot JF, Damen N, de Loos E, van de Steeg L, Koopmans L, Rosias P, Bruijn M, Goorhuis J, Wagner C

Background: Paediatric Early Warning Scores (PEWS) are increasingly being used for early identification and management of clinical deterioration in paediatric patients. A PEWS system includes scores, cut-off points and appropriate early intervention. In 2011, The Dutch Ministry of Health advised hospitals to implement a PEWS system in order to improve patient safety in paediatric wards. The objective of this study was to examine the results of implementation of PEWS systems and to gain insight into the attitudes of professionals towards using a PEWS system in Dutch non-university hospitals.
Methods: Quantitative data were gathered at start, midway and at the end of the implementation period through retrospective patient record review (n = 554). Semi-structured interviews with professionals (n = 8) were used to gain insight in the implementation process and experiences. The interviews were transcribed and analysed using an inductive approach.
Results: Looking at PEWS systems of the five participating hospitals, different parameters and policies were found. While all hospitals included heart rate and respiratory rate, other variables differed among hospitals. At baseline, none of the hospitals used a PEWS system. After 1 year, PEWS were recorded in 69.2% of the patient records and elevated PEWS resulted in appropriate action in 49.1%. Three themes emerged from the interviews: 1) while the importance of using a PEWS system was acknowledged, professionals voiced some doubts about the effectiveness and validity of their PEWS system 2) registering PEWS required little extra effort and was facilitated by PEWS being integrated into the electronic patient record 3) Without a national PEWS system or guidelines, hospitals found it difficult to identify a suitable PEWS system for their setting. Existing systems were not always considered applicable in a non-university setting.
Conclusions: After 1 year, hospitals showed improvements in the use of their PEWS system, although some were decidedly more successful than others. Doubts among staff about validity, effectiveness and communication with other hospitals during transfer to higher level care hospital might hinder sustainable implementation. For these purposes the development of a national PEWS system is recommended, consisting of a "core set" of PEWS, cut-off points and associated early intervention

Gepubliceerd: BMC Pediatr 2018 Apr 6;18(1):128
Impact factor: 2.042; Q2

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2. Predicting inflammatory bowel disease in children with abdominal pain and diarrhoea: calgranulin-C versus calprotectin stool tests
Heida A, van de Vijver E, van Ravenzwaaij D, Van Biervliet S, Hummel TZ, Yuksel Z, Gonera-de Jong G, Schulenberg R, Muller Kobold A, van Rheenen PF

Objective: Calgranulin-C (S100A12) is a new faecal marker of inflammation that is potentially more specific for inflammatory bowel disease (IBD) than calprotectin, since it is only released by activated granulocytes. We compared calgranulin-C and calprotectin to see which of the two tests best predicted IBD in children with chronic abdominal pain and diarrhoea.
Design: Delayed-type cross-sectional diagnostic study.
Setting and patients: Previously undiagnosed patients aged 6-17 years, who were seen in paediatric clinics in the Netherlands and Belgium, sent in a stool sample for analysis. Patients with a high likelihood of IBD underwent upper and lower endoscopy (ie, preferred reference test), while those with a low likelihood were followed for 6 months for latent IBD to become visible (ie, alternative reference test). We used Bayesian modelling to correct for differential verification bias.
Main outcome measures: Primary outcome was the specificity for IBD using predefined test thresholds (calgranulin-C: 0.75 microg/g, calprotectin: 50 microg/g). Secondary outcome was the test accuracy with thresholds based on receiver operating characteristics (ROC) analysis.
Results: IBD was diagnosed in 93 of 337 patients. Calgranulin-C had significantly better specificity than calprotectin when predefined thresholds were used (97% (95% credible interval (CI) 94% to 99%) vs 71% (95% CI 63% to 79%), respectively). When ROC-based thresholds were used (calgranulin-C: 0.75 microg/g, calprotectin: 400 microg/g), both tests performed equally well (specificity: 97% (95% CI 94% to 99%) vs 98% (95% CI 95% to 100%)).
Conclusions: Both calgranulin-C and calprotectin have excellent test characteristics to predict IBD and justify endoscopy.
Trial registration number: NCT02197780

Gepubliceerd: Arch Dis Child 2018 Jun;103(6):565-71
Impact factor: 3.258; Q1

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3. The efficacy of home telemonitoring versus conventional follow-up: a randomised controlled trial among teenagers with inflammatory bowel disease
Heida A, Dijkstra A, Muller Kobold A, Rossen J, Kindermann A, Kokke F, de Meij T, Norbruis O, Weersma R, Wessels M, Hummel T, Escher H, van WeringH., Hendriks D, Mearin L, Groen H, Verkade H, van Rheenen P

Background and aims: Conventional follow-up of teenagers with inflammatory bowel diseases (IBD) is done during scheduled outpatient visits regardless of how well the patient feels. We designed a telemonitoring strategy for early recognition of flares and compared its efficacy with conventional follow-up.
Methods: Multicentre randomised trial in patients aged 10-19 years with IBD in clinical remission at baseline. Participants assigned to telemonitoring received automated alerts to complete a symptom score and send a stool sample for calprotectin measurement. This resulted in an individual prediction for flare with associated treatment advice and test interval. In conventional follow-up the health check interval was left to the physician's discretion. Primary endpoint was cumulative incidence of disease flares. Secondary endpoints were percentage of participants with a positive change in quality-of-life and cost-effectiveness of the intervention.
Results: We included 170 participants (84 telemonitoring; 86 conventional follow-up). At 52 weeks the mean number of face-to-face visits was significantly lower in the

telemonitoring group compared to conventional follow-up (3.6 versus 4.3, P<0.001). The incidence of flares (33 versus 34%, P= 0.93) and the proportion of participants reporting positive change in quality-of-life (54% versus 44%, P=0.27) were similar. Mean annual cost-saving was €89 and increased to €360 in those compliant to the protocol.
Conclusions: Telemonitoring is as safe as conventional follow-up, reduces outpatient visits and societal costs. The positive impact on quality-of-life was similar in both groups. This strategy is attractive for teenagers and families, and health professionals may be interested in using it to keep teenagers who are well out of hospital and ease pressure on overstretched outpatient services.
Trial registration: NTR3759 (Netherlands Trial Registry)

Gepubliceerd: J Crohns Colitis 2018;12(4):432-41
Impact factor: 6.637; Q1

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4. Are serum ferritin and transferrin saturation risk markers for restless legs syndrome in young adults? Longitudinal and cross-sectional data from the Western Australian Pregnancy Cohort (Raine) Study
Lammers N, Curry-Hyde A, Smith AJ, Eastwood PR, Straker LM, Champion D, McArdle N

Restless legs syndrome has been associated with serum iron deficiency in clinical studies. However, studies investigating this relationship have had inconsistent results and there are no studies in young adults. Therefore, we investigated the relationship between serum measures of iron stores and restless legs syndrome in young adults in the community. Participants in the Western Australian Pregnancy Cohort (Raine) Study answered questions on restless legs syndrome (n = 1,100, 54% female) at age 22 years, and provided serum measures of iron stores (ferritin and transferrin saturation) at ages 17 and 22 years. Restless legs syndrome was diagnosed when four International RLS Study Group criteria were met (urge to move, dysaesthesia, relief by movement, worsening during evening/night) and these symptoms occurred >/=5 times per month. Logistic regression was used to assess associations between serum iron stores and restless legs syndrome, adjusting for potential confounders. The prevalence of restless legs syndrome at age 22 years was 3.0% (n = 33, 70% female). Among those who provided restless legs syndrome and iron data at age 22 years (n = 865), the median (interquartile range) ferritin was not different between the restless legs syndrome (55 [29.5-103.5] microg L(-1)) and the non-restless legs syndrome group (65.0 [35.0-103.3] microg L(-1) , p = 0.2), nor were there differences in iron deficiency prevalence (p = 0.36). There was no association between restless legs syndrome (22 years) and iron stores (17, 22 years) before or after adjustment for potential confounders. There was no association between restless legs syndrome at 22 years and iron stores at 17 or 22 years in this cohort. Serum iron stores may not be a useful indicator of restless legs syndrome risk in young adults in the community

Gepubliceerd: J Sleep Res 2018 Jul 31;e12741
Impact factor: 3.433; Q2

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5. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study
Martinon-Torres F, Salas A, Rivero-Calle I, Cebey-Lopez M, Pardo-Seco J, Herberg JA, Boeddha NP, Klobassa DS, Secka F, Paulus S, de GR, Schlapbach LJ, Driessen GJ, Anderson ST, Emonts M, Zenz W, Carrol ED, van der Flier M, Levin M, EUCLIDS Consortium includes Thio B

Background: Sepsis and severe focal infections represent a substantial disease burden in children admitted to hospital. We aimed to understand the burden of disease and outcomes in children with life-threatening bacterial infections in Europe.
Methods: The European Union Childhood Life-threatening Infectious Disease Study (EUCLIDS) was a prospective, multicentre, cohort study done in six countries in Europe. Patients aged 1 month to 18 years with sepsis (or suspected sepsis) or severe focal infections, admitted to 98 participating hospitals in the UK, Austria, Germany, Lithuania, Spain, and the Netherlands were prospectively recruited between July 1, 2012, and Dec 31, 2015. To assess disease burden and outcomes, we collected demographic and clinical data using a secured web-based platform and obtained microbiological data using locally available clinical diagnostic procedures.
Findings: 2844 patients were recruited and included in the analysis. 1512 (53.2%) of 2841 patients were male and median age was 39.1 months (IQR 12.4-93.9). 1229 (43.2%) patients had sepsis and 1615 (56.8%) had severe focal infections. Patients diagnosed with sepsis had a median age of 27.6 months (IQR 9.0-80.2), whereas those diagnosed with severe focal infections had a median age of 46.5 months (15.8-100.4; p<0.0001). Of 2844 patients in the entire cohort, the main clinical syndromes were pneumonia (511 [18.0%] patients), CNS infection (469 [16.5%]), and skin and soft tissue infection (247 [8.7%]). The causal microorganism was identified in 1359 (47.8%) children, with the most prevalent ones being Neisseria meningitidis (in 259 [9.1%] patients), followed by Staphylococcus aureus (in 222 [7.8%]), Streptococcus pneumoniae (in 219 [7.7%]), and group A streptococcus (in 162 [5.7%]). 1070 (37.6%) patients required admission to a paediatric intensive care unit. Of 2469 patients with outcome data, 57 (2.2%) deaths occurred: seven were in patients with severe focal infections and 50 in those with sepsis.
Interpretation: Mortality in children admitted to hospital for sepsis or severe focal infections is low in Europe. The disease burden is mainly in children younger than 5 years and is largely due to vaccine-preventable meningococcal and pneumococcal infections. Despite the availability and application of clinical procedures for microbiological diagnosis, the causative organism remained unidentified in approximately 50% of patients. Funding: European Union's Seventh Framework programme

Gepubliceerd: Lancet Child Adolesc Health 2018 Jun;2(6):404-14
Impact factor: 0; nvt

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6. Barriers and Facilitators When Implementing Web-Based Disease Monitoring and Management as a Substitution for Regular Outpatient Care in Pediatric Asthma: Qualitative Survey Study
van den Wijngaart LS, Geense WW, Boehmer AL, Brouwer ML, Hugen CA, van Ewijk BE, Koenen-Jacobs MJ, Landstra AM, Niers LE, van Onzenoort-Bokken L, Ottink MD, Rikkers-Mutsaerts ER, Groothuis I, Vaessen-Verberne AA, Roukema J, Merkus PJ

Background: Despite their potential benefits, many electronic health (eHealth) innovations evaluated in major studies fail to integrate into organizational routines, and the implementation of these innovations remains problematic.
Objective: The purpose of this study was to describe health care professionals' self-identified perceived barriers and facilitators for the implementation of a Web-based portal to monitor asthmatic children as a substitution for routine outpatient care. Also, we assessed patients' (or their parents) satisfaction with this eHealth innovation.
Methods: Between April and November 2015, we recruited 76 health care professionals (from 14 hospitals). During a period of 6 months, participants received 3 questionnaires to identify factors that facilitated or impeded the use of this eHealth innovation. Questionnaires for patients (or parents) were completed after the 6-month virtual asthma clinic (VAC) implementation period.
Results: Major perceived barriers included concerns about the lack of structural financial reimbursement for Web-based monitoring, lack of integration of this eHealth innovation with electronic medical records, the burden of Web-based portal use on clinician workload, and altered patient-professional relationship (due to fewer face-to-face contacts). Major perceived facilitators included enthusiastic and active initiators, a positive attitude of professionals toward eHealth, the possibility to tailor care to individual patients ("personalized eHealth"), easily deliverable care according to current guidelines using the VAC, and long-term profit and efficiency.
Conclusions: The implementation of Web-based disease monitoring and management in children is complex and dynamic and is influenced by multiple factors at the levels of the innovation itself, individual professionals, patients, social context, organizational context, and economic and political context. Understanding and defining the barriers and facilitators that influence the context is crucial for the successful implementation and sustainability of eHealth innovations

Gepubliceerd: J Med Internet Res 2018 Oct 30;20(10):e284
Impact factor: 4.671; Q1

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7. Perinatal Outcomes in Vertically Infected Neonates During a Chikungunya Outbreak on the Island of Curacao

van Enter BJD, Huibers MHW, van Rooij L, Steingrover R, van Hensbroek MB, Voigt RR, Hol J

Recent outbreaks of Chikungunya virus (CHIKV) infection confirm the vulnerability of neonates after vertical transmission. In 2014, CHIKV was reported for the first time in the Americas, including the island of Curacao. We describe the outcomes of symptomatic neonates with vertically transmitted CHIKV infection during the CHIKV epidemic, who were admitted in the Saint Elisabeth Hospital, Willemstad, Curacao. There were three symptomatic neonates with serologically confirmed infection. Two neonates developed neurological complications, including convulsions and intracerebral bleeding. One newborn, in whom maternal infection occurred 7 weeks before delivery, had a fatal outcome after birth. Maternal-fetal transmission of CHIKV may cause severe neonatal complications. There is a need to share experiences and to implement protocols toward the management of perinatal CHIKV infection

Gepubliceerd: Am J Trop Med Hyg 2018 Oct 15;99(6):1415-8

Impact factor: 2.564; Q2

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8. Chikungunya Virus Infections Among Infants-Who Classification Not Applicable
van Keulen V, Huibers M, Manshande M, van Hensbroek MB, van Rooij L

Chikungunya virus caused an epidemic on Curacao in 2014-2015. Infants are highly at risk for clinical syndromes as sepsis-like illness and central nervous system disease. Clinical recognition is important if laboratory test, polymerase chain reaction and enzyme-linked immunosorbent assay are not available. The World Health Organization created criteria for identification of probable Chikungunya virus. None of the studied infants met these criteria. We believe the criteria suggested by World Health Organization should be modified for infants.

Gepubliceerd: Pediatr Infect Dis J 2018 Mar;37(3):e83-e86
Impact factor: 2.305; Q2

Totale impact factor: 24.910
Gemiddelde impact factor: 3.114

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.738
Gemiddelde impact factor: 2.869

Klinische chemie

1. Impact of the Choice of IGF-I Assay and Normative Dataset on the Diagnosis and Treatment of Growth Hormone Deficiency in Children
Broeren MAC, Krabbe JG, Boesten LS, Hokken-Koelega ACS, de Rijke YB

Background: The analysis of insulin-like growth factor I (IGF-I) is an important tool for pediatricians in the diagnosis and treatment of growth hormone deficiency in children. However, significant differences exist in IGF-I assays and normative datasets, which can have important clinical consequences.
Methods: IGF-I analyses were performed using the IDS-iSYS platform on 1,897 samples from pediatric patients (0.5-18 years old). Z-scores were calculated based on normative IGF-I data from Bidlingmaier et al. (SD-BM) [J Clin Endocrinol Metab. 2014 May; 99(5): 1712-21] and normative IGF-I data from the IGF-I harmonization program in the Netherlands (SD-NL). The differences in Z-scores were analyzed at relevant clinical decision points (-2 SD, +2 SD). These normative datasets were also compared to normative data reported by Elmlinger et al. [Clin Chem Lab Med. 2004; 42(6): 654-64].
Results: The difference in Z-score between SD-BM and SD-NL was highest in males between 0 and 3 years old, exceeding 2 SD. Clinically relevant discordance between both Z-scores at -2 and +2 SD was found in 12.7% of all samples. The IGF-I levels at -2 and +2 SD reported in the normative dataset of Elmlinger et al. were up to 100% higher than the IGF-I levels reported by Bidlingmaier et al. or the Dutch harmonization program.
Conclusion: Pediatricians and laboratory specialists should be aware of relevant differences that can exist between IGF-I assays and normative data. Well-defined pediatric reference ranges for the IDS-iSYS platform are highly desirable

Gepubliceerd: Horm Res Paediatr 2018;90(3):181-9
Impact factor: 2.013; Q2

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2. Association between fluid management and dilutional coagulopathy in severe postpartum haemorrhage: a nationwide retrospective cohort study
Gillissen A, van den Akker T, Caram-Deelder C, Henriquez DDCA, Bloemenkamp KWM, van Roosmalen JJM, Eikenboom J, van der Bom JG, TeMpOH-1 study group includes Slomp J

Background: The view that 2 l of crystalloid and 1.5 l of colloid can be infused while awaiting compatible blood for patients with major postpartum haemorrhage is based on expert opinion documents. We describe real-world changes in levels of coagulation parameters after the administration of different volumes of clear fluids to women suffering from major postpartum haemorrhage.
Methods: We performed a nationwide retrospective cohort study in the Netherlands among 1038 women experiencing severe postpartum haemorrhage who had received at least four units of red cells or fresh frozen plasma or platelets in addition to red cells. The volume of clear fluids administered before the time of blood sampling was classified into three fluid administration strategies, based on the RCOG guideline: < 2

L, 2-3.5 L and > 3.5 L. Outcomes included haemoglobin, haematocrit, platelet count, fibrinogen, aPTT and PT levels.
Results: Haemoglobin, haematocrit, platelet count, fibrinogen and aPTT were associated with volumes of clear fluids, which was most pronounced early during the course of postpartum haemorrhage. During the earliest phases of postpartum haemorrhage median haemoglobin level was 10.1 g/dl (IQR 8.5-11.6) among the women who received < 2 L clear fluids and 8.1 g/dl (IQR 7.1-8.4) among women who received > 3.5 L of clear fluids; similarly median platelet counts were 181 x 10(9)/litre (IQR 131-239) and 89 x 10(9)/litre (IQR 84-135), aPTT 29 s (IQR 27-33) and 38 s (IQR 35-55) and fibrinogen 3.9 g/L (IQR 2.5-5.2) and 1.6 g/L (IQR 1.3-2.1).
Conclusions: In this large cohort of women with severe postpartum haemorrhage, administration of larger volumes of clear fluids was associated with more severe deterioration of coagulation parameters corresponding to dilution. Our findings provide thus far the best available evidence to support expert opinion-based guidelines recommending restrictive fluid resuscitation in women experiencing postpartum haemorrhage.
Trial registration: Netherlands Trial Register (NTR4079), registration date July 17, 2013

Gepubliceerd: BMC Pregnancy Childbirth 2018 Oct 11;18(1):398
Impact factor: 2.331: Q2

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3. Serial assessment of endothelial function 1, 6, and 12 months after ST-elevation myocardial infarction
Kandhai-Ragunath JJ, Doggen CJM, van der Heijden LC, Kok MM, Zocca P, de Wagenaar B, Doelman C, Jorstad HT, Peters RJG, von Birgelen C

Knowledge about the changes in endothelial function after ST-elevation myocardial infarction (STEMI) is of substantial interest, but serial data are scarce. The aim of the present study was to noninvasively evaluate whether endothelial function, as assessed shortly after primary percutaneous coronary intervention (PPCI) for STEMI, may improve until 12-month follow-up. This prospective observational cohort study was performed in patients in the RESPONSE randomized trial who participated in a substudy and underwent noninvasive assessment of endothelial function at 1 (baseline), 6, and 12-month follow-up after treatment of a STEMI by PPCI. The reactive hyperemia peripheral artery tonometry (RH-PAT) method was used to assess endothelial function (higher RH-PAT index signifies better function). Of the 70 study participants, who were 57.4 +/- 9.7 years of age, 55 (78.6%) were male and 9 (13%) had diabetes. The endothelial function deteriorated significantly during follow-up: the RH-PAT index at baseline, 6, and 12-month follow-up was 1.90 +/- 0.58, 1.81 +/- 0.57, and 1.69 +/- 0.49, respectively (p = 0.04). Although patients were carefully treated in outpatient clinics and adequate pharmacological therapy was prescribed, we noted an increase in total cholesterol (p = 0.001), LDL cholesterol (p = 0.002), HbA1C (p = 0.054), and diastolic blood pressure (p = 0.047) However, multivariate analysis revealed that this increase in cardiovascular risk factors could not explain the observed deterioration in endothelial function. In patients with STEMI, we observed a significant deterioration in endothelial function during 12 months after PPCI that could not be explained by changes in the traditional cardiovascular risk profile

Gepubliceerd: Heart Vessels 2018 Sep;33(9):978-85
Impact factor: 2.185; Q3

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4. Prediabetes and its Impact on Clinical Outcome After Coronary Intervention in a Broad Patient Population
Kok MM, von Birgelen C, Sattar N, Zocca P, Lowik MM, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Kant GD, Doelman C, Tjon Joe Gin RM, Stoel MG, van Houwelingen G, Linssen GCM, IJzerman MJ, Doggen CJM, van der Heijden LC

Aims: It is unclear whether detection of prediabetes(Pre-DM) by routine assessment of glycated haemoglobin A1c(HbA1c) and fasting plasma glucose(FPG) among patients undergoing percutaneous coronary intervention(PCI) with contemporary drug-eluting stents(DES) may help identify subjects with increased event risk. We assessed the relation between glycaemia status and 1-year outcome after PCI. **Methods and results:** Glycaemia status was determined in 2,362 non-diabetic BIO-RESORT participants, treated at all four study sites, to identify Pre-DM (HbA1c 42-47mmol/mol; FPG 6.1-6.9mmol/L) and unknown diabetes mellitus(DM) (HbA1c>/=48mmol/mol; FPG>/=7.0mmol/L). Another 624 patients had medically treated DM. The main composite endpoint consisted of death, myocardial infarction, or revascularisation. Glycaemic state was known in 2,986 participants: 324(11%) patients had Pre-DM, 793(27%) had DM(known or new), and 1,869(63%) patients had normoglycaemia. Pre-DM and DM patients differed from normoglycemic patients in cardiovascular risk factors. The composite endpoint occurred in 11.1% in Pre-DM, 10.5% in DM, and 5.7% in normoglyacemia(p<0.001). Pre-DM was associated with a 2-times higher event risk compared to normoglycaemia(adj.HR 2.0, 95%CI:1.4-3.0). **Conclusions:** Following PCI with contemporary DES, all-comers with Pre-DM had significantly higher event risks than normoglycemic patients. In non-DM patients requiring PCI, routine assessment of HbA1c and FPG appears to be of value to identify subjects with increased event risk

Gepubliceerd: EuroIntervention 2018 Jan 9;14(9):e1049-e1056
Impact factor: 4.417; Q2

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5. Impact of interactions between drugs and laboratory test results on diagnostic test interpretation - a systematic review
van Balveren JA, Verboeket-van de Venne WPHG, Erdem-Eraslan L, de Graaf AJ, Loot AE, Musson REA, Oosterhuis WP, Schuijt MP, van der Sijs H, Verheul RJ, de Wolf HK, Kusters R, Hoedemakers RMJ

Intake of drugs may influence the interpretation of laboratory test results. Knowledge and correct interpretation of possible drug-laboratory test interactions (DLTIs) is important for physicians, pharmacists and laboratory specialists. Laboratory results may be affected by analytical or physiological effects of medication. Failure to take into account the possible unintended influence of drug use on a laboratory test result may lead to incorrect diagnosis, incorrect treatment and unnecessary follow-up. The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support systems on laboratory test interpretation. Particular interactions were reported in a large number of articles, but they were

fragmentarily described and some papers even reported contradictory findings. To provide an overview of information that clinicians and laboratory staff need to interpret test results, DLTI databases have been made by several groups. In a literature search, only four relevant studies have been found on DLTI decision support applications for laboratory test interpretation in clinical practice. These studies show a potential benefit of automated DLTI messages to physicians for the correct interpretation of laboratory test results. Physicians reported 30-100% usefulness of DLTI messages. In one study 74% of physicians sometimes even refrained from further additional examination. The benefit of decision support increases when a refined set of clinical rules is determined in cooperation with health care professionals. The prevalence of DLTIs is high in a broad range of combinations of laboratory tests and drugs and these frequently remain unrecognized

Gepubliceerd: Clin Chem Lab Med 2018 Nov 27;56(12):2004-9
Impact factor: 3.556; Q1

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6. "Silent" Diabetes and Clinical Outcome After Treatment With Contemporary Drug-Eluting Stents: The BIO-RESORT Silent Diabetes Study
von Birgelen C, Kok MM, Sattar N, Zocca P, Doelman C, Kant GD, Lowik MM, van der Heijden LC, Sen H, van Houwelingen KG, Stoel MG, Louwerenburg JHW, Hartmann M, de Man FHAF, Linssen GCM, Doggen CJM, Tandjung K

Objectives: This study sought to assess the prevalence and clinical impact of silent diabetes and pre-diabetes in "nondiabetic" percutaneous coronary intervention (PCI) all-comers.
Background: Patients with undetected and thus untreated (silent) diabetes may have higher event risks after PCI with contemporary drug-eluting stents (DES).
Methods: The BIO-RESORT Silent Diabetes study, performed at Thoraxcentrum Twente, is a substudy of the randomized multicenter BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) trial (NCT01674803). Patients underwent oral glucose tolerance testing (OGTT), and assessment of glycosylated hemoglobin with fasting plasma glucose. Primary endpoint was a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.
Results: Of the 988 participants, OGTT detected silent diabetes in 68 (6.9%), pre-diabetes in 133 (13.3%), and normal glucose metabolism in 788 (79.8%). Patients with silent diabetes had higher primary endpoint rates (13.2% vs. 7.6% vs. 4.8%; $p < 0.001$; silent diabetes vs. normal: hazard ratio: 4.2; 95% confidence interval: 1.9 to 9.2). Differences were driven by myocardial infarction ($p < 0.001$) which occurred mostly <48 h. Based on glycosylated hemoglobin and fasting plasma glucose, silent diabetes was found in 33 (3.3%) patients, pre-diabetes in 217 (22.0%) patients, and normal glucose metabolism in 738 (74.7%) patients; primary endpoint rates were similar to OGTT-based analyses (12.1% vs. 5.5% vs. 3.1%; $p = 0.01$). Multivariate analyses demonstrated that abnormal glucose metabolism by either diagnostic approach, present in 330 (33.4%) patients, independently predicted adverse event risk (hazard ratio: 2.2; 95% confidence interval: 1.2 to 4.2).
Conclusions: Abnormal glucose metabolism was detected in 1 of 3 "nondiabetic" PCI patients and was independently associated with up to 4-fold higher event risks.

Future intervention trials should determine whether meaningful benefits accrue from routine glycemia testing in such patients

Gepubliceerd: JACC Cardiovasc Interv 2018 Mar 12;11(5):448-59
Impact factor: 9.881; Q1

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7. Falsely positive anti-glomerular basement membrane antibodies in a patient with hantavirus induced acute kidney injury - a case report
Zijlstra HW, Mulder AHL, Geeraedts F, Visser F

Background: Hantavirus infection is an uncommon cause of acute renal failure with massive proteinuria. Serology tests to support a presumptive diagnosis usually take a few days. During the initial work-up, autoimmune causes including anti-glomerular basement membrane (GBM) glomerulonephritis need to be excluded, because these require urgent therapy. In this case the delay in serological testing caused a dilemma in treatment initiation.
Case presentation: An 18-year-old patient was admitted to the hospital with acute renal failure, erythrocyturia and massive proteinuria. Routine blood analysis showed leucocytosis (40,5 x 109/l) and a serum creatinine of 233 mumol/l. Infectious causes, e.g. leptospirosis or hantavirus infection, or an autoimmune disease, e.g., AAV or anti-GBM glomerulonephritis was the most feasible underlying diagnosis. Before hantavirus serology results were known, anti-GBM antibodies were positive. Treatment for anti-GBM glomerulonephritis was withheld, because of the absence of other signs and symptoms of the disease and slight improvement of renal function. The diagnosis of acute hantavirus infection was later on confirmed, by seroconversion of a follow-up serum sample. Without further intervention renal function recovered and anti-GBM antibodies disappeared.
Conclusion: Hantavirus infection may induce anti-GBM antibodies, falsely suggestive of anti-GBM glomerulonephritis. Anti-GBM antibodies are supposed to be 100% specific. No earlier reports of false positive anti-GBM titers were reported. Nevertheless, the anti-GBM antibodies in this case were seen as an innocent bystander effect. Considering the need of urgent initiation of plasmapheresis and administration of immunosuppressants it may lead to diagnostic dilemmas with crucial therapeutic consequences. Knowledge of this anomaly when diagnosing acute renal failure, is very important

Gepubliceerd: BMC Nephrol 2018 Oct 22;19(1):286
Impact factor: 2.395: Q2

Totale impact factor: 26.868
Gemiddelde impact factor: 3.838

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 4.498
Gemiddelde impact factor: 2.249

Klinische farmacie

1. Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD
Koehorst-Ter Huurne K, Groothuis-Oudshoorn CG, van der Valk PD, Movig KL, van der Palen J, Brusse-Keizer M

Aim: The aim of this study was to analyze the association between therapy adherence to inhaled corticosteroids (ICSs) and tiotropium on the one hand and morbidity and mortality in COPD on the other hand.
Methods: Therapy adherence to ICSs and tiotropium over a 3-year period of, respectively, 635 and 505 patients was collected from pharmacy records. It was expressed as percentage and deemed optimal at >/=75-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). The association between adherence and time to first hospital admission for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), community acquired pneumonia (CAP), and mortality was analyzed, with optimal use as the reference category.
Results: Suboptimal use and underuse of ICSs and tiotropium were associated with a substantial increase in mortality risk: hazard ratio (HR) of ICSs was 2.9 (95% CI 1.7-5.1) and 5.3 (95% CI 3.3-8.5) and HR of tiotropium was 3.9 (95% CI 2.1-7.5) and 6.4 (95% CI 3.8-10.8) for suboptimal use and underuse, respectively. Suboptimal use and overuse of tiotropium were also associated with an increased risk of CAP, HR 2.2 (95% CI 1.2-4.0) and HR 2.3 (95% CI 1.2-4.7), respectively. Nonadherence to tiotropium was also associated with an increased risk of severe AECOPD: suboptimal use HR 3.0 (95% CI 2.01-4.5), underuse HR 1.9 (95% CI 1.2-3.1), and overuse HR 1.84 (95% CI 1.1-3.1). Nonadherence to ICSs was not related to time to first AECOPD or first CAP.
Conclusion: Poor adherence to ICSs and tiotropium was associated with a higher mortality risk. Furthermore, nonadherence to tiotropium was associated with a higher morbidity. The question remains whether improving adherence can reduce morbidity and mortality

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2018;13:1683-90
Impact factor: 2.917; Q2

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2. Patients with underuse or overuse of inhaled corticosteroids have different perceptions and beliefs regarding COPD and inhaled medication
Koehorst-Ter Huurne K, Brusse-Keizer M, van der Valk PD, Movig K, van der Palen J, Bode C

Background: Therapy adherence in COPD is crucial for treating symptoms, preventing exacerbations, and related complications. To achieve optimal adherence, it is important to recognize and understand a nonadherent patient. Objective: To study perceptions and beliefs regarding COPD and inhaled medication in COPD patients with poor adherence.
Methods: Twenty patients (10 underuse, 10 overuse) were interviewed in semistructured in-depth interviews, about mental and physical health, illness

perceptions, knowledge regarding COPD, and experience with, knowledge of, and acceptance of COPD medication and inhalation devices.
Results: A majority of patients did not fully accept their disease, showed little disease knowledge, and many revealed signs of depressive mood and severe fatigue. Overusers reported more grief about decreased participation in daily life and were more frustrated in general. Underusers claimed using less medication because they felt well, did not want to use too much medication, and used their inhalation devices too long. Overusers reported medication "dependency"; they tended to catastrophize when being without medication and discarded inhalation devices too early because they feared running out of medication.
Conclusion: Overusers and underusers showed a different pattern in perceptions and beliefs regarding inhaled medication and COPD. Practical implications: It is important to understand the reasons for under- and overuse. Is it related to practical issues regarding knowledge or is it influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed for improving adherence

Gepubliceerd: Patient Prefer Adherence 2018;12:1777-83
Impact factor: 1.733; Q2

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3. Patient-reported outcome measures in a pharmacokinetic study with sunitinib, a prospective cohort study
Koldenhof JJ, Lankheet NAG, Steeghs N, Teunissen SCCM, Witteveen PO

Purpose: During treatment with tyrosine kinase inhibitors, such as sunitinib, patients experience treatment and/or disease-related symptoms. Although application of patient-reported outcome measures (PROMs) enhances early recognition of symptoms, early clinical trials are focused on symptom severity objectified by the Common Terminology Criteria for Adverse Events (CTCAE) in order to evaluate drug safety and to determine a personalized and/or safe dosage range. To gain insight into patient-reported symptoms in addition to healthcare professional-reported adverse events (AEs), a substudy was conducted in an ongoing pharmacokinetic-guided sunitinib dosing study.
Methods: In patients for whom sunitinib was considered standard therapy or patients with advanced/metastatic tumors for whom no standard therapy was available, patient-reported symptoms and well-being besides healthcare professional-reported AEs were assessed.
Results: Twenty-nine patients were included for analysis. Over 50% of them experienced a decreased well-being, caused by symptoms of mild and moderate intensity. Compared to healthcare professionals, all measured symptoms, with the exception of fatigue and vomiting, were reported statistically significantly more often by patients.
Conclusions: Application of PROMs in early clinical trials on personalized or individualized oral targeted anticancer agents is feasible and enhances early recognition of symptom burden due to multiple CTCAE grade 1-2 AEs, just as pro-active symptom management and effect evaluation of interventions performed. Application of PROMs in these trials might be clinically relevant in obtaining dose-limiting toxicities

Gepubliceerd: Support Care Cancer 2018 Aug;26(8):2641-50

Impact factor: 2.676; Q2

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4. Drug-drug interactions with aprepitant in antiemetic prophylaxis for chemotherapy
Schoffelen R, Lankheet AG, van Herpen CML, van der Hoeven JJM, Desar IME, Kramers C

In the current guidelines to prevent hemotherapyinduced nausea and vomiting, multiple antiemetic drugs are administered simultaneously. In patients who receive highly emetogenic chemotherapy, aprepitant, an NK1-receptor antagonist, is combined with ondansetron and dexamethasone. Aprepitant can influence the pharmacokinetics of other drugs, as it is an inhibitor and inducer of CYP3A4. Some anticancer drugs and other co-medication frequently used in cancer patients are CYP3A4 or CYP29C substrates. We give an overview of the metabolism and current data on clinically relevant drug-drug interactions with aprepitant during chemotherapy. Physicians should be aware of the potential risk of drug-drug interactions with aprepitant, especially in regimens with curative intent. More research should be performed on drug-drug interactions with aprepitant and their clinical consequences to make evidence-based recommendations

Gepubliceerd: Neth J Med 2018 Apr;76(3):109-14
Impact factor: 1.156;Q3

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5. Molecular Imaging of Radiolabeled Bispecific T-Cell Engager (89)Zr-AMG211 Targeting CEA-Positive Tumors
Waaijer SJH, Warnders FJ, Stienen S, Friedrich M, Sternjak A, Cheung HK, van Scheltinga AGTT, Schroder CP, de Vries EGE, Lub-de Hooge MN

Purpose: AMG 211, a bispecific T-cell engager (BiTE) antibody construct, targets carcinoembryonic antigen (CEA) and the CD3 epsilon subunit of the human T-cell receptor. AMG 211 was labeled with zirconium-89 ((89)Zr) or fluorescent dye to evaluate the tumor-targeting properties.Experimental
Design: (89)Zr-AMG211 was administered to mice bearing CEA-positive xenograft tumors of LS174T colorectal adenocarcinoma or BT474 breast cancer cells, as well as CEA-negative HL-60 promyelocytic leukemia xenografts. Biodistribution studies with 2- to 10-mug (89)Zr-AMG211 supplemented with unlabeled AMG 211 up to 500-mug protein dose were performed. A BiTE that does not bind CEA, (89)Zr-Mec14, served as a negative control. (89)Zr-AMG211 integrity was determined in tumor lysates ex vivo Intratumoral distribution was studied with IRDye800CW-AMG211. Moreover, (89)Zr-AMG211 was manufactured according to Good Manufacturing Practice (GMP) guidelines for clinical trial NCT02760199
Results: (89)Zr-AMG211 demonstrated dose-dependent tumor uptake at 6 hours. The highest tumor uptake was observed with a 2-mug dose, and the lowest tumor uptake was observed with a 500-mug dose. After 24 hours, higher uptake of 10-mug (89)Zr-AMG211 occurred in CEA-positive xenografts, compared with CEA-negative xenografts. Although the blood half-life of (89)Zr-AMG211 was approximately 1 hour, tumor retention persisted for at least 24 hours. (89)Zr-Mec14 showed no tumor accumulation beyond background level. Ex vivo autoradiography revealed time-

dependent disintegration of (89)Zr-AMG211. 800CW-AMG211 was specifically localized in CEA-expressing viable tumor tissue. GMP-manufactured (89)Zr-AMG211 fulfilled release specifications.
Conclusions: (89)Zr-AMG211 showed dose-dependent CEA-specific tumor targeting and localization in viable tumor tissue. Our data enabled its use to clinically evaluate AMG 211 in vivo behavior.

Gepubliceerd: Clin Cancer Res 2018 Oct 15;24(20):4988-96
Impact factor: 10.199; Q1

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6. Influence of protein properties and protein modification on biodistribution and tumor uptake of anticancer antibodies, antibody derivatives, and non-Ig scaffolds
Warnders FJ, Lub-de Hooge MN, de Vries EGE, Kosterink JGW

Newly developed protein drugs that target tumor-associated antigens are often modified in order to increase their therapeutic effect, tumor exposure, and safety profile. During the development of protein drugs, molecular imaging is increasingly used to provide additional information on their in vivo behavior. As a result, there are increasing numbers of studies that demonstrate the effect of protein modification on whole body distribution and tumor uptake of protein drugs. However, much still remains unclear about how to interpret obtained biodistribution data correctly. Consequently, there is a need for more insight in the correct way of interpreting preclinical and clinical imaging data. Summarizing the knowledge gained to date may facilitate this interpretation. This review therefore provides an overview of specific protein properties and modifications that can affect biodistribution and tumor uptake of anticancer antibodies, antibody fragments, and nonimmunoglobulin scaffolds. Protein properties that are discussed in this review are molecular size, target interaction, FcRn binding, and charge. Protein modifications that are discussed are radiolabeling, fluorescent labeling drug conjugation, glycosylation, humanization, albumin binding, and polyethylene glycolation

Gepubliceerd: Med Res Rev 2018 Sep;38(6):1837-73
Impact factor: 8.290; Q1

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7. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol
Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA

Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients.

Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal carers' QoL and cost-effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven, this could further promote the implementation of pharmaceutical care in a primary care setting

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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8. Amiodarone Rifampicin Drug-Drug Interaction Management With Therapeutic Drug Monitoring
Oude Munnink TH, Demmer A, Slenter RHJ, Movig KLL

The authors present a case of a 69-year-old man with arrhythmogenic right ventricular cardiomyopathy controlled with amiodarone and an infected orthopedic prosthesis requiring treatment with rifampicin. This combination involves a pharmacokinetic drug-drug interaction leading to subtherapeutic drug concentrations of amiodarone and its active metabolite. The long half-life of amiodarone and its active metabolite in combination with the late onset and offset of cytochrome P4503A (CYP3A4) induction by rifampicin makes this a challenging drug-drug interaction to cope with in clinical practice. Before, during, and after rifampicin treatment, the serum concentrations of amiodarone and its active metabolite were measured and the amiodarone dose was adjusted accordingly. The amiodarone dose required to maintain effective concentrations was 450% of the initial dose. The drug-drug interaction between amiodarone and rifampicin is relevant, both clinically and pharmacokinetically, and can be managed by dose adjustments of amiodarone based on serum concentrations.

Gepubliceerd: Ther Drug Monit 2018 Apr;40(2):159-61
Impact factor: 2.092; Q2

Totale impact factor: 29.063
Gemiddelde impact factor: 3.633

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 22.321
Gemiddelde impact factor: 4.464

Klinische fysica

1. Comparing dual energy CT and subtraction CT on a phantom: which one provides the best contrast in iodine maps for sub-centimetre details?
Baerends E, Oostveen LJ, Smit CT, Das M, Sechopoulos I, Brink M, de Lange F, Prokop M

Objectives: To compare contrast-to-noise ratios (CNRs) and iodine discrimination thresholds on iodine maps derived from dual energy CT (DECT) and subtraction CT (SCT).
Methods: A contrast-detail phantom experiment was performed with 2 to 15 mm diameter tubes containing water or iodinated contrast concentrations ranging from 0.5 mg/mL to 20 mg/mL. DECT scans were acquired at 100 kVp and at 140 kVp+Sn filtration. SCT scans were acquired at 100 kVp. Iodine maps were created by material decomposition (DECT) or by subtraction of water scans from iodine scans (SCT). Matched exposure levels varied from 8 to 15 mGy. Iodine discrimination thresholds (Cr) and response times were determined by eight observers.
Results: The adjusted mean CNR was 1.9 times higher for SCT than for DECT. Exposure level had no effect on CNR. All observers discriminated all details >/=10 mm at 12 and 15 mGy. For sub-centimetre details, the lowest calculated Cr was </= 0.50 mg/mL for SCT and 0.64 mg/mL for DECT. The smallest detail was discriminated at >/=4.4 mg/mL with SCT and at >/=7.4 mg/mL with DECT. Response times were lower for SCT than DECT.
Conclusions: SCT results in higher CNR and reduced iodine discrimination thresholds compared to DECT for sub-centimetre details.
Key points: * Subtraction CT iodine maps exhibit higher CNR than dual-energy iodine maps * Lower iodine concentrations can be discriminated for sub-cm details with SCT * Response times are lower using SCT compared to dual-energy CT

Gepubliceerd: Eur Radiol 2018 Dec;28(12):5051-9
Impact factor: 4.027; Q1

Totale impact factor: 4.027
Gemiddelde impact factor: 4.027

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

Klinische psychologie

1. Reduced Cancer Incidence in Huntington's Disease: Analysis in the Registry Study
McNulty P, Pilcher R, Ramesh R, Necuiniate R, Hughes A, Farewell D, Holmans P, Jones L, REGISTRY Investigators of the European Huntington's Disease Network, includes van Hout MSE, van Vugt JPP

Background: People with Huntington's disease (HD) have been observed to have lower rates of cancers.
Objective: To investigate the relationship between age of onset of HD, CAG repeat length, and cancer diagnosis.
Methods: Data were obtained from the European Huntington's disease network REGISTRY study for 6540 subjects. Population cancer incidence was ascertained from the GLOBOCAN database to obtain standardised incidence ratios of cancers in the REGISTRY subjects.
Results: 173/6528 HD REGISTRY subjects had had a cancer diagnosis. The age-standardised incidence rate of all cancers in the REGISTRY HD population was 0.26 (CI 0.22-0.30). Individual cancers showed a lower age-standardised incidence rate compared with the control population with prostate and colorectal cancers showing the lowest rates. There was no effect of CAG length on the likelihood of cancer, but a cancer diagnosis within the last year was associated with a greatly increased rate of HD onset (Hazard Ratio 18.94, $p < 0.001$).
Conclusions: Cancer is less common than expected in the HD population, confirming previous reports. However, this does not appear to be related to CAG length in HTT. A recent diagnosis of cancer increases the risk of HD onset at any age, likely due to increased investigation following a cancer diagnosis.

Gepubliceerd: J Huntingtons Dis 2018;7(3):209-22
Impact factor: 0; nvt

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2. Chronic solvent-induced encephalopathy: course and prognostic factors of neuropsychological functioning
van Valen E, Wekking E, van Hout M, van der Laan G, Hageman G, van Dijk F, de Boer A, Sprangers M

Purpose: Working in conditions with daily exposure to organic solvents for many years can result in a disease known as chronic solvent-induced encephalopathy (CSE). The aims for this study were to describe the neuropsychological course of CSE after first diagnosis and to detect prognostic factors for neuropsychological impairment after diagnosis.
Methods: This prospective study follows a Dutch cohort of CSE patients who were first diagnosed between 2001 and 2011 and underwent a second neuropsychological assessment 1.5-2 years later. Cognitive subdomains were assessed and an overall cognitive impairment score was calculated. Paired t tests and multivariate linear regression analyses were performed to describe the neuropsychological course and to obtain prognostic factors for the neuropsychological functioning at follow-up.

Results: There was a significant improvement on neuropsychological subdomains at follow-up, with effect sizes between small and medium (Cohen's d 0.27-0.54) and a significant overall improvement of neuropsychological impairment with a medium effect size (Cohen's d 0.56). Prognostic variables for more neuropsychological impairment at follow-up were a higher level of neuropsychological impairment at diagnosis and having a comorbid diagnosis of a psychiatric disorder at diagnosis. **Conclusions:** Results are in line with previous research on the course of CSE, stating that CSE is a non-progressive disease after cessation of exposure. However, during follow-up the percentage patients with permanent work disability pension increased from 14 to 37%. Preventive action is needed in countries where exposure to organic solvents is still high to prevent new cases of CSE.

Gepubliceerd: Int Arch Occup Environ Health 2018 Oct;91(7):843-58
Impact factor: 2.148; Q2

Totale impact factor: 2.148
Gemiddelde impact factor: 1.074

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

Longziekten

1. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial
Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM

Gepubliceerd: BMC Gastroenterol 2018 Feb 21;18(1):29
Impact factor: 2.731; Q3

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2. Stable-State Midrange Proadrenomedullin Is Associated With Severe Exacerbations in COPD
Citgez E, Zuur-Telgen M, van der Palen J, van der Valk PD, Stolz D, Brusse-Keizer M

Background: Elevated levels of midrange proadrenomedullin (MR-proADM) are associated with worse outcome in different diseases, including COPD. The association of stable-state MR-proADM with severe acute exacerbations of COPD (AECOPDs) requiring hospitalization, or with community-acquired pneumonia (CAP) in patients with COPD, has not been studied yet. The aim of this study was to evaluate the association of stable-state MR-proADM with severe AECOPD and CAP in patients with COPD.
Methods: This study pooled data of 1,285 patients from the Cohort of Mortality and Inflammation in COPD (COMIC) and PRedicting Outcome using systemic Markers In Severe Exacerbations of Chronic Obstructive Pulmonary Disease (PROMISE-COPD) cohort studies. Time until first severe AECOPD was compared between patients with high (>/= 0.87 nmol/L) or low (< 0.87 nmol/L) levels of plasma MR-proADM in stable state as previously defined. For time until first CAP, only COMIC data (n = 795) were available.
Results: Patients with COPD with high-level stable-state MR-proADM have a significantly higher risk for severe AECOPD compared with those with low-level MR-proADM with a corrected hazard ratio (HR) of 1.30 (95% CI, 1.01-1.68). Patients with high-level stable-state MR-proADM had a significantly higher risk for CAP compared with patients with COPD with low-level MR-proADM in univariate analysis (HR, 1.93; 95% CI, 1.24-3.01), but after correction for age, lung function, and previous AECOPD, the association was no longer significant (corrected HR, 1.10; 95% CI, 0.68-1.80).
Conclusions: Stable-state high-level MR-proADM in patients with COPD is associated with severe AECOPD but not with CAP

Gepubliceerd: Chest 2018 Jul;154(1):51-7
Impact factor: 7.652; Q1

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3. Clinical and inflammatory phenotyping by breathomics in chronic airway diseases irrespective of the diagnostic label

de Vries R, Dagelet YWF, Spoor P, Snoey E, Jak PMC, Brinkman P, Dijkers E, Bootsma SK, Elskamp F, de Jongh FHC, Haarman EG, In 't Veen JCCM, Maitland-van der Zee AH, Sterk PJ

Asthma and chronic obstructive pulmonary disease (COPD) are complex and overlapping diseases that include inflammatory phenotypes. Novel anti-eosinophilic/anti-neutrophilic strategies demand rapid inflammatory phenotyping, which might be accessible from exhaled breath.Our objective was to capture clinical/inflammatory phenotypes in patients with chronic airway disease using an electronic nose (eNose) in a training and validation set.This was a multicentre cross-sectional study in which exhaled breath from asthma and COPD patients (n=435; training n=321 and validation n=114) was analysed using eNose technology. Data analysis involved signal processing and statistics based on principal component analysis followed by unsupervised cluster analysis and supervised linear regression.Clustering based on eNose resulted in five significant combined asthma and COPD clusters that differed regarding ethnicity (p=0.01), systemic eosinophilia (p=0.02) and neutrophilia (p=0.03), body mass index (p=0.04), exhaled nitric oxide fraction (p<0.01), atopy (p<0.01) and exacerbation rate (p<0.01). Significant regression models were found for the prediction of eosinophilic (R(2)=0.581) and neutrophilic (R(2)=0.409) blood counts based on eNose. Similar clusters and regression results were obtained in the validation set.Phenotyping a combined sample of asthma and COPD patients using eNose provides validated clusters that are not determined by diagnosis, but rather by clinical/inflammatory characteristics. eNose identified systemic neutrophilia and/or eosinophilia in a dose-dependent manner

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Impact factor: 12.244; Q1

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4. Doxapram Treatment and Diaphragmatic Activity in Preterm Infants
de Waal CG, Hutten GJ, Kraaijenga JV, de Jongh FH, van Kaam AH

Background: Doxapram is a treatment option for severe apnea of prematurity (AOP). However, the effect of doxapram on the diaphragm, the main respiratory muscle, is not known.
Objectives: To investigate the effect of doxapram on diaphragmatic activity measured with transcutaneous electromyography of the diaphragm (dEMG).
Methods: A pilot study was conducted in a tertiary neonatal intensive care unit. Diaphragmatic activity was measured from 30 min before up to 3 h after the start of doxapram treatment. dEMG parameters were compared to baseline (5 min before doxapram treatment) and at 15, 60, 120 and 180 min after the start of doxapram infusion.
Results: Eleven preterm infants were included with a mean gestational age of 25.5 +/- 1.2 weeks and birth weight of 831 +/- 129 g. The amplitudedEMG, peakdEMG and tonicdEMG values did not change in the 3 h after the start of doxapram infusion compared to baseline. Clinically, the number of apnea episodes in the 24 h after doxapram treatment decreased significantly.

Conclusion: Doxapram infusion does not alter diaphragmatic activity measured with transcutaneous dEMG in preterm infants with AOP, indicating that its working mechanism is primarily on respiratory drive and not on respiratory muscle activity

Gepubliceerd: Neonatology 2018 Oct 23;115(1):85-8
Impact factor: 2.688; Q1

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5. The Effect of Minimally Invasive Surfactant Therapy on Diaphragmatic Activity
de Waal CG, Hutten GJ, de Jongh FH, van Kaam AH

Background: Minimally invasive surfactant therapy (MIST) is increasingly used to treat preterm infants with respiratory distress syndrome (RDS). However, the effect of MIST on breathing effort is poorly studied.
Objectives: To describe the effect of MIST on neural breathing effort assessed with transcutaneous electromyography of the diaphragm (dEMG) in preterm infants with RDS.
Methods: Preterm infants with a gestational age < 37 weeks treated with MIST for RDS were included. dEMG measurements were done from 15 min before to 1 h after MIST. The percentage change in dEMG activity after MIST and the clinical response were analyzed.
Results: Twenty preterm infants (mean gestational age 29.3 [SD 2.1] weeks; mean birth weight 1,230 [SD 391] g) were included. Seventeen infants did complete the 1-h measurement. Eleven (65%) infants had a decrease in their peakdEMG activity (median change -11.8% [IQR -26.8 to 5.8, p = 0.08]) 1 h after MIST. TonicdEMG activity decreased in 12 (71%) infants, with a median reduction of 6.3% (IQR -29.2 to 9.0, p = 0.07). FiO2 showed a rapid decrease following MIST (before, 0.47 [IQR 0.38-0.84]; 1 h after, 0.25 [IQR 0.21-0.30], p < 0.001).
Conclusion: In addition to improved oxygenation, MIST results in a decrease in neural breathing effort measured by dEMG activity in the majority of preterm infants with RDS

Gepubliceerd: Neonatology 2018;114(1):76-81
Impact factor: 2.688; Q1

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6. Retrospective validation of a new volumetric capnography parameter for the exclusion of pulmonary embolism at the emergency department
Fabius TM, Eijsvogel MMM, Brusse-Keizer MGJ, Sanchez OM, Verschuren F, de Jongh FHC

Volumetric capnography might be used to exclude pulmonary embolism (PE) without the need for computed tomography pulmonary angiography. In a pilot study, a new parameter (CapNoPE) combining the amount of carbon dioxide exhaled per breath (carbon dioxide production (V CO2)), the slope of phase 3 of the volumetric capnogram (slope 3) and respiratory rate (RR) showed promising diagnostic accuracy (where CapNoPE=(V CO2 xslope 3)/RR). To retrospectively validate CapNoPE for the exclusion of PE, the volumetric capnograms of 205 subjects (68 with PE) were analysed, based on a large multicentre dataset of volumetric capnograms from

subjects with suspected PE at the emergency department. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve and diagnostic accuracy of the in-pilot established threshold (1.90 Pa.min) were calculated. CapNoPE was 1.56+/-0.97 Pa.min in subjects with PE versus 2.51+/-1.67 Pa.min in those without PE (p<0.001). The AUC of the ROC curve was 0.714 (95% CI 0.64-0.79). For the cut-off of >/=1.90 Pa.min, sensitivity was 64.7%, specificity was 59.9%, the negative predictive value was 77.4% and the positive predictive value was 44.4%. The CapNoPE parameter is decreased in patients with PE but its diagnostic accuracy seems too low to use in clinical practice

Gepubliceerd: ERJ Open Res 2018 Oct;4(4)
Impact factor: 0; nvt

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7. Low-dose CT for lung cancer screening - Authors' reply
Field JK, Heuvelmans MA, Devaraj A, Heussel CP, Baldwin DR, Vliegenthart R, Duffy SW, Oudkerk M

Gepubliceerd: Lancet Oncol 2018 Mar;19(3):e135-e136
Impact factor: 36.421; Q1

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8. A humidifier in the invasive mode during noninvasive respiratory support could increase condensation and thereby impair airway patency
Flink RC, van Kaam AH, de Jongh FH

Aim: Humidifying noninvasively ventilated preterm infants is critical to prevent dehydration of respiratory mucosa, but over-humidification can result in impaired airway patency and lung mechanics. This neonatal bench study investigated the humidity delivered using invasive and noninvasive humidification modes during nasal continuous positive airway pressure.
Methods: The study was conducted at the neonatal intensive care unit of Emma Children's Hospital, the Netherlands, in March 2014. A mannequin was connected to a CareFusion Infant Flow SiPAP system, combined with a Fisher & Paykel MR850 humidifier and a Carefusion Infant Flow LP Generator. We measured the temperature, relative humidity and absolute humidity at the humidification chamber's expiratory port and at the patient's mask.
Results: The absolute humidity at the mask was 35-40 mg H2 O/L at 38-39 degrees C (relative humidity 74-80%) for the invasive mode of the humidifier and 23-27 mg H2 O/L at 34-35 degrees C (relative humidity 63-70%) for the noninvasive mode. The absolute humidities exceeded the recommended values for the invasive mode of the humidifier, but not the noninvasive mode, and could be associated with increased condensation.
Conclusion: The absolute humidity delivered by the humidifier in invasive mode could be associated with increased condensation, which has been associated with airway impairment

Gepubliceerd: Acta Paediatr 2018 Nov;107(11):1888-92
Impact factor: 2.580; Q1

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9. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing
Hallstrand TS, Leuppi JD, Joos G, Hall GL, Carlsen KH, Kaminsky DA, Coates AL, Cockcroft DW, Culver BH, Diamant Z, Gauvreau GM, Horvath I, de Jongh FHC, Laube BL, Sterk PJ, Wanger J

Recently, this international task force reported the general considerations for bronchial challenge testing and the performance of the methacholine challenge test, a "direct" airway challenge test. Here, the task force provides an updated description of the pathophysiology and the methods to conduct indirect challenge tests. Because indirect challenge tests trigger airway narrowing through the activation of endogenous pathways that are involved in asthma, indirect challenge tests tend to be specific for asthma and reveal much about the biology of asthma, but may be less sensitive than direct tests for the detection of airway hyperresponsiveness. We provide recommendations for the conduct and interpretation of hyperpnoea challenge tests such as dry air exercise challenge and eucapnic voluntary hyperpnoea that provide a single strong stimulus for airway narrowing. This technical standard expands the recommendations to additional indirect tests such as hypertonic saline, mannitol and adenosine challenge that are incremental tests, but still retain characteristics of other indirect challenges. Assessment of airway hyperresponsiveness, with direct and indirect tests, are valuable tools to understand and to monitor airway function and to characterise the underlying asthma phenotype to guide therapy. The tests should be interpreted within the context of the clinical features of asthma

Gepubliceerd: Eur Respir J 2018 Nov;52(5):1801033
Impact factor: 12.244; Q1

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10. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening
Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, de Jonge GJ, Walter JE, van Ooijen PMA, de Koning HJ, Oudkerk M

Objective: To evaluate the influence of nodule margin on inter- and intrareader variability in manual diameter measurements and semi-automatic volume measurements of solid nodules detected in low-dose CT lung cancer screening.
Methods: 25 nodules of each morphological category (smooth, lobulated, spiculated and irregular) were randomly selected from 93 participants of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON). Semi-automatic volume measurements were performed using Syngo LungCARE(R) software (Version Somaris/5 VB10A-W, Siemens, Forchheim, Germany). Three radiologists independently measured mean diameters manually. Impact of nodule margin on interreader variability was evaluated based on systematic error and 95% limits of agreement. Interreader variability was compared with the nodule growth cut-off as used in Lung CT Screening Reporting and Data System (LungRADS; +1.5-mm diameter) and the Dutch-Belgian Randomized Lung Cancer Screening Trial(acronym: NELSON) /British Thoracic Society (+25% volume).
Results: For manual diameter measurements, a significant systematic error (up to 1.2 mm) between readers was found in all morphological categories. For semi-

automatic volume measurements, no statistically significant systematic error was found. The interreader variability in mean diameter measurements exceeded the 1.5-mm cut-off for nodule growth for all morphological categories [smooth: +/-1.9 mm (+27%), lobulated: +/-2.0 mm (+33%), spiculated: +/-3.5 mm (+133%), irregular: +/-4.5 mm (+200%)]. The 25% vol growth cut-off was exceeded slightly for spiculated [28% (+12%)] and irregular [27% (+8%)] nodules.
Conclusion:: Lung nodule sizing based on manual diameter measurement is affected by nodule margin. Interreader variability increases especially for nodules with spiculated and irregular margins, and causes substantial misclassification of nodule growth. This effect is almost neglectable for semi-automated volume measurements. Semi-automatic volume measurements are superior for both size and growth determination of pulmonary nodules.
Advances in knowledge: Nodule assessment based on manual diameter measurements is susceptible to nodule margin. This effect is almost neglectable for semi-automated volume measurements. The larger interreader variability for manual diameter measurement results in inaccurate lung nodule growth detection and size classification

Gepubliceerd: Br J Radiol 2018 Oct;91(1090):20170405
Impact factor: 1.814; Q3

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11. Appropriate screening intervals in low-dose CT lung cancer screening
Heuvelmans MA, Oudkerk M

Lung cancer screening by low-dose chest CT (LDCT) is now being implemented in the United States, and in Europe it was recently recommended to start planning for implementation. Current lung cancer screening programmes include up to 25 annual LDCTs, plus shorter-term follow-up LDCTs when indicated. However, the choice of a yearly CT scan has not been based on biological mechanisms, and it is questionable whether all persons eligible for lung cancer screening require annual screening. A tailored approach in screening programs to balance potential harms and benefits from screening becomes more and more important when lung cancer screening is performed more widespread. If lung cancer screening participants can be identified at mid-high lung cancer risk that can be followed safely by prolonged screening intervals, reduction of possible physiological harms, radiation exposure and costs can be expected. Different randomized controlled lung cancer screening studies have shown that the baseline screen result can be used to identify a subset of participants with a low 2-year lung cancer probability. These participants may be safely followed after a prolonged screening interval with the optimal screening interval probably between 1 and 2 years until their risk profile changes. In case a new pulmonary nodule appears at subsequent screening, or a small baseline nodule starts growing, participants should always return to annual LDCT screening after the appropriate workup

Gepubliceerd: Transl Lung Cancer Res 2018 Jun;7(3):281-7
Impact factor: 0; nvt

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12. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening
Heuvelmans MA, Walter JE, Vliegenthart R, van Ooijen PMA, de Bock GH, de Koning HJ, Oudkerk M

We studied 2240 indeterminate solid nodules (volume 50-500mm(3)) to determine the correlation of diameter and semi-automated volume measurements for pulmonary nodule size estimation. Intra-nodular diameter variation, defined as maximum minus minimum diameter through the nodule's center, varied by 2.8 mm (median, IQR:2.2-3.7 mm), so above the 1.5 mm cutoff for nodule growth used in Lung CT Screening Reporting and Data System (Lung-RADS). Using mean or maximum axial diameter to assess nodule volume led to a substantial mean overestimation of nodule volume of 47.2% and 85.1%, respectively, compared to semi-automated volume. Thus, size of indeterminate nodules is poorly represented by diameter. Trial registration number: Pre-results, ISRCTN63545820

Gepubliceerd: Thorax 2018 Aug;73(8):779-81
Impact factor: 9.655; Q1

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13. Management of baseline and new sub-solid nodules in CT lung cancer screening
Heuvelmans MA, Walter JE, Oudkerk M

Gepubliceerd: Expert Rev Respir Med 2018 Jan;12(1):1-3
Impact factor: 2.607; Q2

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14. Pulmonary nodules measurements in CT lung cancer screening
Heuvelmans MA, Oudkerk M

Gepubliceerd: J Thorac Dis 2018 Jun;10(Suppl 17):S2100-S2102
Impact factor: 1.804; Q4

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15. Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD
Koehorst-Ter Huurne K, Groothuis-Oudshoorn CG, van der Valk PD, Movig KL, van der Palen J, Brusse-Keizer M

Aim: The aim of this study was to analyze the association between therapy adherence to inhaled corticosteroids (ICSs) and tiotropium on the one hand and morbidity and mortality in COPD on the other hand.
Methods: Therapy adherence to ICSs and tiotropium over a 3-year period of, respectively, 635 and 505 patients was collected from pharmacy records. It was expressed as percentage and deemed optimal at >/=75-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). The association between adherence and time to first hospital admission for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), community acquired pneumonia (CAP), and mortality was analyzed, with optimal use as the reference category.

Results: Suboptimal use and underuse of ICSs and tiotropium were associated with a substantial increase in mortality risk: hazard ratio (HR) of ICSs was 2.9 (95% CI 1.7-5.1) and 5.3 (95% CI 3.3-8.5) and HR of tiotropium was 3.9 (95% CI 2.1-7.5) and 6.4 (95% CI 3.8-10.8) for suboptimal use and underuse, respectively. Suboptimal use and overuse of tiotropium were also associated with an increased risk of CAP, HR 2.2 (95% CI 1.2-4.0) and HR 2.3 (95% CI 1.2-4.7), respectively. Nonadherence to tiotropium was also associated with an increased risk of severe AECOPD: suboptimal use HR 3.0 (95% CI 2.01-4.5), underuse HR 1.9 (95% CI 1.2-3.1), and overuse HR 1.84 (95% CI 1.1-3.1). Nonadherence to ICSs was not related to time to first AECOPD or first CAP.
Conclusion: Poor adherence to ICSs and tiotropium was associated with a higher mortality risk. Furthermore, nonadherence to tiotropium was associated with a higher morbidity. The question remains whether improving adherence can reduce morbidity and mortality

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2018;13:1683-90
Impact factor: 2.917; Q2

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16. Patients with underuse or overuse of inhaled corticosteroids have different perceptions and beliefs regarding COPD and inhaled medication
Koehorst-Ter Huurne K, Brusse-Keizer M, van der Valk PD, Movig K, van der Palen J, Bode C

Background: Therapy adherence in COPD is crucial for treating symptoms, preventing exacerbations, and related complications. To achieve optimal adherence, it is important to recognize and understand a nonadherent patient. Objective: To study perceptions and beliefs regarding COPD and inhaled medication in COPD patients with poor adherence.
Methods: Twenty patients (10 underuse, 10 overuse) were interviewed in semistructured in-depth interviews, about mental and physical health, illness perceptions, knowledge regarding COPD, and experience with, knowledge of, and acceptance of COPD medication and inhalation devices.
Results: A majority of patients did not fully accept their disease, showed little disease knowledge, and many revealed signs of depressive mood and severe fatigue. Overusers reported more grief about decreased participation in daily life and were more frustrated in general. Underusers claimed using less medication because they felt well, did not want to use too much medication, and used their inhalation devices too long. Overusers reported medication "dependency"; they tended to catastrophize when being without medication and discarded inhalation devices too early because they feared running out of medication.
Conclusion: Overusers and underusers showed a different pattern in perceptions and beliefs regarding inhaled medication and COPD. Practical implications: It is important to understand the reasons for under- and overuse. Is it related to practical issues regarding knowledge or is it influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed for improving adherence

Gepubliceerd: Patient Prefer Adherence 2018;12:1777-83
Impact factor: 1.733; Q2

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17. Transcutaneous electromyographic respiratory muscle recordings to quantify patient-ventilator interaction in mechanically ventilated children
Koopman AA, Blokpoel RGT, van Eykern LA, de Jongh FHC, Burgerhof JGM, Kneyber MCJ

Background: To explore the feasibility of transcutaneous electromyographic respiratory muscle recordings to automatically quantify the synchronicity of patient-ventilator interaction in the pediatric intensive care unit.
Methods: Prospective observational study in a tertiary paediatric intensive care unit in an university hospital. Spontaneous breathing mechanically ventilated children < 18 years of age were eligible for inclusion. Patients underwent a 5-min continuous recording of ventilator pressure waveforms and transcutaneous electromyographic signal of the diaphragm. To evaluate patient-ventilator interaction, the obtained neural inspiration and ventilator pressurization timings were used to calculate trigger and cycle-off errors of each breath. Calculated errors were displayed in the dEMG-phase scale.
Results: Data of 23 patients were used for analysis. Based on the dEMG-phase scale, the median rates of synchronous, dyssynchronous and asynchronous breaths as classified by the automated analysis were 12.2% (1.9-33.8), 47.5% (36.3-63.1), and 28.9% (6.6-49.0).
Conclusions: The dEMG-phase scale quantifying patient-ventilator breath synchronicity was demonstrated to be feasible and a reliable scale for mechanically ventilated children, reflected by high intra-class correlation coefficients. As this non-invasive tool is not restricted to a type of ventilator, it could easily be clinical implemented in the ventilated pediatric population. However; correlation studies between the EMG signal measured by surface EMG and esophageal catheters have to be performed

Gepubliceerd: Ann Intensive Care 2018 Jan 24;8(1):12
Impact factor: 3.771; Q2

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18. Multi-centre prospective study on diagnosing subtypes of lung cancer by exhaled-breath analysis
Kort S, Tiggeloven MM, Brusse-Keizer M, Gerritsen JW, Schouwink JH, Citgez E, de Jongh FHC, Samii S, van der Maten J, van den Bogart M, van der Palen J

Objectives: Lung cancer is a leading cause of mortality. Exhaled-breath analysis of volatile organic compounds (VOC's) might detect lung cancer early in the course of the disease, which may improve outcomes. Subtyping lung cancers could be helpful in further clinical decisions. MATERIALS AND
Methods: In a prospective, multi-centre study, using 10 electronic nose devices, 144 subjects diagnosed with NSCLC and 146 healthy subjects, including subjects considered negative for NSCLC after investigation, breathed into the Aeonose (The eNose Company, Zutphen, Netherlands). Also, analyses into subtypes of NSCLC, such as adenocarcinoma (AC) and squamous cell carcinoma (SCC), and analyses of patients with small cell lung cancer (SCLC) were performed.
Results: Choosing a cut-off point to predominantly rule out cancer resulted for NSCLC in a sensitivity of 94.4%, a specificity of 32.9%, a positive predictive value of

58.1%, a negative predictive value (NPV) of 85.7%, and an area under the curve (AUC) of 0.76. For AC sensitivity, PPV, NPV, and AUC were 81.5%, 56.4%, 79.5%, and 0.74, respectively, while for SCC these numbers were 80.8%, 45.7%, 93.0%, and 0.77, respectively. SCLC could be ruled out with a sensitivity of 88.9% and an NPV of 96.8% with an AUC of 0.86.
Conclusion: Electronic nose technology with the Aeonose can play an important role in rapidly excluding lung cancer due to the high negative predictive value for various, but not all types of lung cancer. Patients showing positive breath tests should still be subjected to further diagnostic testing

Gepubliceerd: Lung Cancer 2018 Nov;125:223-9
Impact factor: 4.486; Q1

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19. Classifying Apnea of Prematurity by Transcutaneous Electromyography of the Diaphragm
Kraaijenga JV, Hutten GJ, de Waal CG, de Jongh FH, Onland W, van Kaam AH

Background: Treatment of apnea is highly dependent on the type of apnea. Chest impedance (CI) has inaccuracies in monitoring respiration, which compromises accurate apnea classification. Electrical activity of the diaphragm measured by transcutaneous electromyography (EMG) is feasible in preterm infants and might improve the accuracy of apnea classification.
Objectives: To compare the accuracy of apnea classification based on diaphragmatic EMG (dEMG) and CI tracings in preterm infants.
Methods: Fifteen cases of central apnea, 5 of obstructive apnea, and 10 of mixed apnea were selected from recordings containing synchronized continuous tracings of respiratory inductive plethysmography (RIP), airway flow, heart rate (HR), oxygen saturation (SpO2), and breathing activity measured by dEMG and CI. Twenty-two assessors (neonatologists, pediatricians-in-training, and nurses) classified each apnea twice; once based on dEMG, HR, and SpO2 tracings, and once based on CI, HR, and SpO2. The assessors were blinded to the type of respiratory tracing (dEMG or CI) and to the RIP and flow tracings.
Results: In total 1,320 assessments were performed, and in 71.1% the apnea was classified correctly. Subgroup analysis based on respiratory tracing showed that 74.8% of the dEMG tracings were classified correctly compared to 67.3% of the CI tracings ($p < 0.001$). This improved apnea classification based on dEMG was present for central (86.7 vs. 80.3%, $p < 0.02$) and obstructive (56.4 vs. 32.7%, $p < 0.001$) apnea. The improved apnea classification based on dEMG tracing was independent of the type of assessor.
Conclusion: Transcutaneous dEMG improves the accuracy of apnea classification when compared to CI in preterm infants, making this technique a promising candidate for future monitoring systems

Gepubliceerd: Neonatology 2018;113(2):140-5
Impact factor: 2.688; Q1

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20. The role of social support in improving chronic obstructive pulmonary disease self-management

Lenferink A, van der Palen J, Effing T

Gepubliceerd: Expert Rev Respir Med 2018 Aug;12(8):623-6
Impact factor: 2.607; Q2

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21. Improving physical activity, sedentary behaviour and sleep in COPD: perspectives of people with COPD and experts via a Delphi approach
Lewthwaite H, Effing TW, Lenferink A, Olds T, Williams MT

Background: Little is known about how to achieve enduring improvements in physical activity (PA), sedentary behaviour (SB) and sleep for people with chronic obstructive pulmonary disease (COPD). This study aimed to: (1) identify what people with COPD from South Australia and the Netherlands, and experts from COPD- and non-COPD-specific backgrounds considered important to improve behaviours; and (2) identify areas of dissonance between these different participant groups.
Methods: A four-round Delphi study was conducted, analysed separately for each group. Free-text responses (Round 1) were collated into items within themes and rated for importance on a 9-point Likert scale (Rounds 2-3). Items meeting *a priori* criteria from each group were retained for rating by all groups in Round 4. Items and themes achieving a median Likert score of ≥7 and an interquartile range of ≤2 across all groups at Round 4 were judged important. Analysis of variance with Tukey's post-hoc tested for statistical differences between groups for importance ratings.
Results: Seventy-three participants consented to participate in this study, of which 62 (85%) completed Round 4. In Round 4, 81 items (PA *n* = 54; SB *n* = 24; sleep *n* = 3) and 18 themes (PA *n* = 9; SB *n* = 7; sleep *n* = 2) were considered important across all groups concerning: (1) symptom/disease management, (2) targeting behavioural factors, and (3) less commonly, adapting the social/physical environments. There were few areas of dissonance between groups.
Conclusion: Our Delphi participants considered a multifactorial approach to be important to improve PA, SB and sleep. Recognising and addressing factors considered important to recipients and providers of health care may provide a basis for developing behaviour-specific interventions leading to long-term behaviour change in people with COPD.

Gepubliceerd: PeerJ 2018;6:e4604
Impact factor: 2.118; Q2

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22. Reproducibility of hypercapnic ventilatory response measurements with steady-state and rebreathing methods
Mannee DC, Fabius TM, Wagenaar M, Eijsvogel MMM, de Jongh FHC

In this study, the hypercapnic ventilatory response (HCVR) was measured, defined as the ventilation response to carbon dioxide tension (PCO2). We investigated which method, rebreathing or steady-state, is most suitable for measurement of the HCVR in healthy subjects, primarily based on reproducibility. Secondary outcome parameters were subject experience and duration. 20 healthy adults performed a rebreathing and steady-state HCVR measurement on two separate days. Subject experience was assessed using numeric rating scales (NRS). The intraclass

correlation coefficient (ICCs) of the sensitivity to carbon dioxide above the ventilatory recruitment threshold and the projected apnoea threshold were calculated to determine the reproducibility of both methods. The ICCs of sensitivity were 0.89 (rebreathing) and 0.56 (steady-state). The ICCs of the projected apnoea threshold were 0.84 (rebreathing) and 0.25 (steady-state). The steady-state measurement was preferred by 16 out of 20 subjects; the differences in NRS scores were small. The hypercapnic ventilatory response measured using the rebreathing setup provided reproducible results, while the steady-state method did not. This may be explained by high variability in end-tidal PCO2 . Differences in subject experience between the methods are small

Gepubliceerd: ERJ Open Res 2018 Jan;4(1):00141-2017
Impact factor: 0; nvt

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23. The Mozart study: a relation between dynamic hyperinflation and physical activity in patients with chronic obstructive pulmonary disease?
van Leuteren RW, Dijkhuis S, de Jongh FH, van der Valk PD, Tabak M, Brusse-Keizer MG

Background: Many patients with chronic obstructive pulmonary disease (COPD) experience dyspnoea during exercise, resulting in a reduction of physical activity (PA). Dynamic hyperinflation (DH) is seen as a major cause of dyspnoea in COPD.
Objective: The objective of the current study was to investigate the relationship between DH, in terms of the amount of DH and the development and recovery rate of DH in patients with COPD, and PA.
Methods: Thirty-five patients with stable COPD were included from an outpatient clinic (14 GOLD II and 21 GOLD III, median age 65). PA was assessed using an accelerometer. Subjects underwent metronome-paced tachypnoea (MPT) to induce DH. To quantify the amount of DH during MPT, a decrease in inspiratory capacity (IC) or a change in IC as percentage of total lung capacity was used.
Results: No significant correlations were found between the parameters describing DH and PA. Secondary correlation analyses showed a negative correlation between static hyperinflation (SH) and PA (r = -0.39; P = 0.02). The pattern of breathing during MPT and the test itself showed high interpatient variability.
Conclusions: The absence of a significant correlation between DH and PA is contrary to previous studies. SH did show a correlation with PA. The variety in results and the technical difficulties in execution of the measurements ask for a new, more reliable, method to detect DH and investigate its relation with PA in patients with COPD

Gepubliceerd: Clin Physiol Funct Imaging 2018;38(3):409-15
Impact factor: 2.600; Q2

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24. Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: the NELSON study
Walter JE, Heuvelmans MA, Bock GH, Yousaf-Khan U, Groen HJM, Aalst CMV, Nackaerts K, Ooijen PMAV, Koning HJ, Vliegenthart R, Oudkerk M

Purpose: New nodules after baseline are regularly found in low-dose CT lung cancer screening and have a high lung cancer probability. It is unknown whether morphological and location characteristics can improve new nodule risk stratification by size.
Methods: Solid non-calcified nodules detected during incidence screening rounds of the randomised controlled Dutch-Belgian lung cancer screening (NELSON) trial and registered as new or previously below detection limit (15 mm(3)) were included. A multivariate logistic regression analysis with lung cancer as outcome was performed, including previously established volume cut-offs (<30 mm(3), 30-<200 mm(3) and >/=200 mm(3)) and nodule characteristics (location, distribution, shape, margin and visibility <15 mm(3) in retrospect).
Results: Overall, 1280 new nodules were included with 73 (6%) being lung cancer. Of nodules >/=30 mm(3) at detection and visible <15 mm(3) in retrospect, 22% (6/27) were lung cancer. Discrimination based on volume cut-offs (area under the receiver operating characteristic curve (AUC): 0.80, 95% CI 0.75 to 0.84) and continuous volume (AUC: 0.82, 95% CI 0.77 to 0.87) was similar. After adjustment for volume cut-offs, only location in the right upper lobe (OR 2.0, P=0.012), central distribution (OR 2.4, P=0.001) and visibility <15 mm(3) in retrospect (OR 4.7, P=0.003) remained significant predictors for lung cancer. The Hosmer-Lemeshow test (P=0.75) and assessment of bootstrap calibration curves indicated adequate model fit. Discrimination based on the continuous model probability (AUC: 0.85, 95% CI 0.81 to 0.89) was superior to volume cut-offs alone, but when stratified into three risk groups (AUC: 0.82, 95% CI 0.78 to 0.86), discrimination was similar.
Conclusion: Contrary to morphological nodule characteristics, growth-independent characteristics may further improve volume-based new nodule lung cancer prediction, but in a three-category stratification approach, this is limited.
Trial registration number: ISRCTN63545820; pre-results

Gepubliceerd: Thorax 2018 Aug;73(8):741-7
Impact factor: 9.655; Q1

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25. New Subsolid Pulmonary Nodules in Lung Cancer Screening: The NELSON Trial
Walter JE, Heuvelmans MA, Yousaf-Khan U, Dorrius MD, Thunnissen E, Schermann A, Groen HJM, van der Aalst CM, Nackaerts K, Vliegenthart R, de Koning HJ, Oudkerk M

Introduction: Low-dose computed tomography (LDCT) lung cancer screening is recommended in the United States. While new solid nodules after baseline screening have a high lung cancer probability at small size and require lower size cutoff values than baseline nodules, there only is limited evidence on management of new subsolid nodules.
Methods: Within the Dutch-Belgian randomized controlled LDCT lung cancer screening trial (NELSON), 7557 participants underwent baseline screening between April 2004 and December 2006. Participants with new subsolid nodules detected after the baseline screening round were included.
Results: In the three incidence screening rounds, 60 new subsolid nodules (43 [72%] part-solid, 17 [28%] nonsolid) not visible in retrospect were detected in 51 participants, representing 0.7% (51 of 7295) of participants with at least one incidence

screening. Eventually, 6% (3 of 51) of participants with a new subsolid nodule were diagnosed with (pre-)malignancy in such a nodule. All (pre-)malignancies were adenocarcinoma (in situ) and diagnostic workup (referral 950, 364, and 366 days after first detection, respectively) showed favorable staging (stage I). Overall, 67% (33 of 49) of subsolid nodules with an additional follow-up screening were resolving.
Conclusions: Less than 1% of participants in LDCT lung cancer screening presents with a new subsolid nodule after baseline. Contrary to new solid nodules, data suggest that new subsolid nodules may not require a more aggressive follow-up

Gepubliceerd: J Thorac Oncol 2018 Sep;13(9):1410-4
Impact factor: 10.340; Q1

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26. Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: The NELSON study
Walter JE, Heuvelmans MA, de Bock GH, Yousaf-Khan U, Groen HJM, van der Aalst CM, Nackaerts K, van Ooijen PMA, de Koning HJ, Vliegenthart R, Oudkerk M

Background: New nodules are regularly found after the baseline round of low-dose computed tomography (LDCT) lung cancer screening. The relationship between a participant's number of new nodules and lung cancer probability is unknown.
Methods: Participants of the ongoing Dutch-Belgian Randomized Lung Cancer Screening (NELSON) Trial with (sub)solid nodules detected after baseline and registered as new by the NELSON radiologists were included. The correlation between a participant's new nodule count and the largest new nodule size was assessed using Spearman's rank correlation. To evaluate the new nodule count as predictor for new nodule lung cancer together with largest new nodule size, a multivariable logistic regression analysis was performed.
Results: In total, 705 participants with 964 new nodules were included. In 48% (336/705) of participants no nodule had been found previously during baseline screening and in 22% (154/705) of participants >1 new nodule was detected (range 1-12 new nodules). Eventually, 9% (65/705) of the participants had lung cancer in a new nodule. In 100% (65/65) of participants with new nodule lung cancer, the lung cancer was the largest or only new nodule at initial detection. The new nodule lung cancer probability did not differ significantly between participants with 1 (10% [56/551], 95%CI 8-13%) or >1 new nodule (6% [9/154], 95%CI 3-11%, P=.116). An increased number of new nodules positively correlated with a participant's largest nodule size (P<0.001, Spearman's rho 0.177). When adjusted for largest new nodule size, the new nodule count had a significant negative association with lung cancer (odds ratio 0.59, 0.37-0.95, P=.03).
Conclusion: A participant's new nodule count alone only has limited association with lung cancer. However, a higher new nodule count correlates with an increased largest new nodule size, while the lung cancer probability remains equivalent, and may improve lung cancer risk prediction by size only

Gepubliceerd: Lung Cancer 2018 Nov;125:103-8
Impact factor: 4.486; Q1

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27. Changes in quantitative CT image features of ground-glass nodules in differentiating invasive pulmonary adenocarcinoma from benign and in situ lesions: histopathological comparisons
Zhang YP, Heuvelmans MA, Zhang H, Oudkerk M, Zhang GX, Xie XQ

Aim: To evaluate progressive changes in quantitative CT features of the non-solid component of ground-glass nodules (GGNs) from baseline to follow-up to differentiate invasive (minimally invasive adenocarcinoma [MIA] and invasive adenocarcinoma [IA]) GGNs from benign or pre-invasive (adenocarcinoma in situ [AIS]) lesions.
MATERIALS AND
Methods: Patients with a GGN detected at baseline and follow-up computed tomography (CT), examined by tissue sampling were included in the study. The diameter and mean, maximum, minimum CT density and density deviation from the non-solid component of whole GGNs were measured. Progression of these features over time was analysed by linear regression analysis. Multivariate receiver operating characteristics analyses of combined measures created by a logistic regression model were performed to evaluate diagnostic performance for invasive GGNs.
Results: Sixty-one patients (24 males) with 70 GGNs were included. Fifteen GGNs were benign, six AIS, 38 MIA, and 11 IA. The mean diameter of all histological subtypes increased from baseline to follow-up, the largest increase was found in the MIA group ($p<0.001$). For MIA and IA, the mean, maximum, minimum density, and density deviation had a positive correlation over time, whilst benign and pre-invasive GGNs showed a negative correlation for these features. A diagnostic model based on three GGN features (increasing in diameter, mean density, and density deviation) identified invasive GGNs with a sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (AUC) of 83.7%, 61.9%, and 0.786, respectively ($p<0.001$).
Conclusion: In GGN follow-up, the diameter of benign and AIS, and invasive GGNs significantly increased. Additional analysis of mean density and density deviation in the non-solid component may help to identify invasive GGNs

Gepubliceerd: Clin Radiol 2018 May;73(5):504
Impact factor: 2.282: Q2

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28. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD
van der Palen J, Moeskops-van Beurden W, Dawson CM, James WY, Preece A, Midwinter D, Barnes N, Sharma R

Background: Administering maintenance COPD therapy with a combination of multiple inhalers may increase inhaler errors. This study evaluated the potential benefits of using a single Ellipta dry powder inhaler (DPI) compared with two combinations of DPIs commonly used to deliver triple maintenance therapy.
Methods: Patients receiving inhaled COPD medication were enrolled in this multicenter, randomized, open-label, placebo-device, crossover study with a 2x2 complete block design (NCT0298218), which comprised two substudies: Ellipta vs Diskus + HandiHaler (substudy 1) or Turbuhaler + HandiHaler (substudy 2). Patients demonstrated inhaler use after reading the relevant patient information leaflet (PIL). A

trained investigator assessed user errors (critical errors [errors likely to result in no or significantly reduced medication being inhaled] and overall errors). The primary endpoint was the proportion of patients making >/=1 critical error after reading the PIL. The secondary endpoints included error rates during </=2 reassessments following investigator instruction (if required), instruction time, and patient preference.
Results: After reading the PIL, significantly fewer patients made critical errors with Ellipta compared with Diskus + HandiHaler (9% [7/80] vs 75% [60/80], respectively; P<0.001) or Turbuhaler + HandiHaler (9% [7/79] vs 73% [58/79], respectively; P<0.001). The number of patients making overall errors was also lower with Ellipta vs tested inhaler combinations (P<0.001 for each substudy). The median instruction time needed for error-free use was shorter with Ellipta in substudies 1 and 2 (2.7 and 2.6 minutes, respectively) vs either combination (10.6 [Diskus + HandiHaler] and 11.3 minutes [Turbuhaler + HandiHaler], respectively). Significantly more patients preferred Ellipta over Diskus + HandiHaler or Turbuhaler + HandiHaler overall for taking their COPD medication (81% vs 9% and 84% vs 4%, respectively) and per the number of steps for taking their COPD medication (89% vs 8% and 91% vs 5%, respectively).
Conclusion: Fewer patients with COPD made critical errors with the single DPI, and patients required less instruction time, compared with each dual DPI combination

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2018;13:2515-23
Impact factor: 2.917; Q2

Totale impact factor: 147.730
Gemiddelde impact factor: 5.276

Aantal artikelen 1e, 2e of laatste auteur: 17
Totale impact factor: 99.306
Gemiddelde impact factor: 5.842

MDL

1. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial

Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM

Gepubliceerd: BMC Gastroenterol 2018 Feb 21;18(1):29
Impact factor: 2.731; Q3

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2. No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies

Engel C, Vasen HF, Seppala T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, Bucksch K, Buttner R, Holinski-Feder E, Holzapfel S, Huneburg R, Jacobs MAJM, Jarvinen H, Kloor M, von Knebel DM, Koornstra JJ, van Kouwen M, Langers AM, van de Meeberg PC, Morak M, Moslein G, Nagengast FM, Pylvanainen K, Rahner N, Renkonen-Sinisalo L, Sanduleanu S, Schackert HK, Schmiegel W, Schulmann K, Steinke-Lange V, Strassburg CP, Vecht J, Verhulst ML, de Vos Tot Nederveen Cappel W, Zachariae S, Mecklin JP, Loeffler M

Background & aims: Patients with Lynch syndrome are at high risk for developing colorectal cancer (CRC). Regular colonoscopic surveillance is recommended, but there is no international consensus on the appropriate interval. We investigated whether shorter intervals are associated with lower CRC incidence and detection at earlier stages by comparing the surveillance policies in Germany, which evaluates patients by colonoscopy annually, in the Netherlands (patients evaluated at 1-2-year intervals), and Finland (patients evaluated at 2-3-year intervals).
Methods: We collected data from 16,327 colonoscopic examinations (conducted from 1984 through 2015) of 2747 patients with Lynch syndrome (pathogenic variants in the MLH1, MSH2, or MSH6 genes) from the German HNPCC Consortium, the Dutch Lynch Syndrome Registry, and the Finnish Lynch Syndrome Registry. Our analysis included 23,309 person-years of cumulative observation time. Time from the index colonoscopy to incident CRC or adenoma was analyzed using the Kaplan-Meier method; groups were compared using the log-rank test. We performed multivariable Cox regression analyses to identify factors associated with CRC risk (diagnosis of CRC before the index colonoscopy, sex, mutation, age, and presence of adenoma at the index colonoscopy).
Results: The 10-year cumulative CRC incidence ranged from 4.1% to 18.4% in patients with low- and high-risk profiles, respectively, and varied with age, sex, mutation, and prior detection of CRC or adenoma. Observed colonoscopy intervals were largely in accordance with the country-specific recommendations. We found no significant differences in cumulative CRC incidence or CRC stage at detection among countries. There was no significant association between CRC stage and time since last colonoscopy.

Conclusions: We did not find a significant reduction in CRC incidence or stage of detection in Germany (annual colonoscopic surveillance) than in countries with longer surveillance intervals (the Netherlands, with 1-2-year intervals, and Finland, with 2-3-year intervals). Overall, we did not find a significant association of the interval with CRC risk, although age, sex, mutation, and prior neoplasia were used to individually modify colonoscopy intervals. Studies are needed to develop and validate risk-adapted surveillance strategies and to identify patients who benefit from shorter surveillance intervals

Gepubliceerd: Gastroenterology 2018 Nov;155(5):1400-9
Impact factor: 20.773; Q1

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3. Risk Factors and Clinical Outcomes of Head and Neck Cancer in Inflammatory Bowel Disease: A Nationwide Cohort Study
Nissen LHC, Derikx LAAP, Jacobs AME, van Herpen CM, Kievit W, Verhoeven R, van den Broek E, Bekers E, van den Heuvel T, Pierik M, Rahamat-Langendoen J, Takes RP, Melchers WJG, Nagtegaal ID, Hoentjen F, Dutch Head and Neck Society Pg, IBD/HNC group includes Russel M

Background: Immunosuppressed inflammatory bowel disease (IBD) patients are at increased risk to develop extra-intestinal malignancies. Immunosuppressed transplant patients show increased incidence of head and neck cancer with impaired survival. This study aims to identify risk factors for oral cavity (OCC) and pharyngeal carcinoma (PC) development in IBD, to compare clinical characteristics in IBD with the general population, and to assess the influence of immunosuppressive medication on survival.
Methods: We retrospectively searched the Dutch Pathology Database to identify all IBD patients with OCC and PC between 1993 and 2011. Two case-control studies were performed: We compared cases with the general IBD population to identify risk factors, and we compared cases with non-IBD cancer patients for outcome analyses.
Results: We included 66 IBD patients and 2141 controls with OCC, 31 IBD patients and 1552 controls with PC, and 1800 IBD controls. Age at IBD diagnosis was a risk factor for OCC development, Crohn's disease (CD; odds ratio [OR], 1.04; 95% confidence interval [CI], 1.02-1.07), and ulcerative colitis (UC; OR, 1.03; 95% CI, 1.01-1.06). For PC, this applied to UC (OR, 1.05; 95% CI, 1.01-1.06). IBD OCC cases showed impaired survival (P = 0.018); in PC, survival was similar. There was no effect of immunosuppression on survival. Human papillomavirus (HPV) testing of IBD cases revealed 52.2% (12/23) HPV-positive oropharyngeal carcinomas (OPCs).
Conclusion: This study shows that IBD is associated with impaired OCC survival. Higher age at IBD diagnosis is a risk factor for OCC development. We found no influence of immunosuppression on survival; 52.2% of OPC in IBD contained HPV

Gepubliceerd: Inflamm Bowel Dis 2018 Aug 16;24(9):2015-26
Impact factor: 4.347; Q1

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4. Fluid hydration to prevent post-ERCP pancreatitis in average- to high-risk patients receiving prophylactic rectal NSAIDs (FLUYT trial): study protocol for a randomized controlled trial

Smeets XJNM, da Costa DW, Fockens P, Mulder CJJ, Timmer R, Kievit W, Zegers M, Bruno MJ, Besselink MGH, Vleggaar FP, van der Hulst RWM, Poen AC, Heine GDN, Venneman NG, Kolkman JJ, Baak LC, Romkens TEH, van Dijk SM, Hallensleben NDL, van de Vrie W, Seerden TCJ, Tan ACIT, Voorburg AMCJ, Poley JW, Witteman BJ, Bhalla A, Hadithi M, Thijs WJ, Schwartz MP, Vrolijk JM, Verdonk RC, van Delft F, Keulemans Y, van Goor H, Drenth JPH, van Geenen EJM

Background: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most common complication of ERCP and may run a severe course. Evidence suggests that vigorous periprocedural hydration can prevent PEP, but studies to date have significant methodological drawbacks. Importantly, evidence for its added value in patients already receiving prophylactic rectal non-steroidal anti-inflammatory drugs (NSAIDs) is lacking and the cost-effectiveness of the approach has not been investigated. We hypothesize that combination therapy of rectal NSAIDs and periprocedural hydration would significantly lower the incidence of post-ERCP pancreatitis compared to rectal NSAIDs alone in moderate- to high-risk patients undergoing ERCP.
Methods: The FLUYT trial is a multicenter, parallel group, open label, superiority randomized controlled trial. A total of 826 moderate- to high-risk patients undergoing ERCP that receive prophylactic rectal NSAIDs will be randomized to a control group (no fluids or normal saline with a maximum of 1.5 mL/kg/h and 3 L/24 h) or intervention group (lactated Ringer's solution with 20 mL/kg over 60 min at start of ERCP, followed by 3 mL/kg/h for 8 h thereafter). The primary endpoint is the incidence of post-ERCP pancreatitis. Secondary endpoints include PEP severity, hydration-related complications, and cost-effectiveness.
Discussion: The FLUYT trial design, including hydration schedule, fluid type, and sample size, maximize its power of identifying a potential difference in post-ERCP pancreatitis incidence in patients receiving prophylactic rectal NSAIDs.
Trial registration: EudraCT: 2015-000829-37 . Registered on 18 February 2015. ISRCTN: 13659155 . Registered on 18 May 2015

Gepubliceerd: Trials 2018 Apr 2;19(1):207
Impact factor: 2.067; Q3

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5. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial

van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, Cappendijk VC, Consten EC, Dejong CH, van Eijck CH, Erkelens WG, van Goor H, van Grevenstein WMU, Haveman JW, Hofker SH, Jansen JM, Lameris JS, van Lienden KP, Meijssen MA, Mulder CJ, Nieuwenhuijs VB, Poley JW, Quispel R, de Ridder RJ, Romkens TE, Scheepers JJ, Schepers NJ, Schwartz MP, Seerden T, Spanier BWM, Straathof JWA, Strijker M, Timmer R, Venneman NG, Vleggaar FP, Voermans RP, Witteman BJ, Gooszen HG, Dijkgraaf MG, Fockens P

Background: Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared

both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up approach in terms of clinical and economic outcomes.
Methods: In this multicentre, randomised, superiority trial, we recruited adult patients with infected necrotising pancreatitis and an indication for invasive intervention from 19 hospitals in the Netherlands. Patients were randomly assigned to either the endoscopic or the surgical step-up approach. The endoscopic approach consisted of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. The primary endpoint was a composite of major complications or death during 6-month follow-up. Analyses were by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN09186711.
Findings: Between Sept 20, 2011, and Jan 29, 2015, we screened 418 patients with pancreatic or extrapancreatic necrosis, of which 98 patients were enrolled and randomly assigned to the endoscopic step-up approach (n=51) or the surgical step-up approach (n=47). The primary endpoint occurred in 22 (43%) of 51 patients in the endoscopy group and in 21 (45%) of 47 patients in the surgery group (risk ratio [RR] 0.97, 95% CI 0.62-1.51; p=0.88). Mortality did not differ between groups (nine [18%] patients in the endoscopy group vs six [13%] patients in the surgery group; RR 1.38, 95% CI 0.53-3.59, p=0.50), nor did any of the major complications included in the primary endpoint.
Interpretation: In patients with infected necrotising pancreatitis, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The outcome of this trial will probably result in a shift to the endoscopic step-up approach as treatment preference.
Funding: The Dutch Digestive Disease Foundation, Fonds NutsOhra, and the Netherlands Organization for Health Research and Development

Gepubliceerd: Lancet 2018;391(10115):51-8
Impact factor: 53.254; Q1

Totale impact factor: 83.172
Gemiddelde impact factor: 16.634

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

Medical School Twente

1. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer
Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU

Background/aims: To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer.
Methods: This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient's preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg.m-2 combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the -Clavien-Dindo classification.
Results: Twenty-five patients (25.3%) developed a grade 3-5 complication. Lower radiation attenuation was independently associated with overall ($p = 0.003$) and grade 3-5 complications ($p = 0.002$). Sarcopenic obesity was associated with overall complications (all $p < 0.05$). Skeletal muscle measurements and survival were not significantly related.
Conclusion: Radiation attenuation was associated with overall and grade 3-5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications

Gepubliceerd: Dig Surg 2018 Jun 13;1-8
Impact factor: 2.031; Q2

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2. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial
Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM

Gepubliceerd: BMC Gastroenterol 2018 Feb 21;18(1):29
Impact factor: 2.731; Q3

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3. Development and validation of a diagnostic prediction model distinguishing complicated from uncomplicated diverticulitis

Bolkenstein HE, van de Wall BJ, Consten EC, van der Palen J, Broeders IA, Draaisma WA

Objectives: Most diverticulitis patients (80%) who are referred to secondary care have uncomplicated diverticulitis (UD) which is a self-limiting disease and can be treated at home. The aim of this study is to develop a diagnostic model that can safely rule out complicated diverticulitis (CD) based on clinical and laboratory parameters to reduce unnecessary referrals.
Methods: A retrospective cross-sectional study was performed including all patients who presented at the emergency department with CT-proven diverticulitis. Patient characteristics, clinical signs and laboratory parameters were collected. CD was defined as > Hinchey 1A. Multivariable logistic regression analyses were used to quantify which (combination of) variables were independently related to the presence or absence of CD. A diagnostic prediction model was developed and validated to rule out CD.
Results: A total of 943 patients were included of whom 172 (18%) had CD. The dataset was randomly split into a derivation and validation set. The derivation dataset contained 475 patients of whom 82 (18%) patients had CD. Age, vomiting, generalized abdominal pain, change in bowel habit, abdominal guarding, C-reactive protein and leucocytosis were univariably related to CD. The final validated diagnostic model included abdominal guarding, C-reactive protein and leucocytosis (AUC 0.79 (95% CI 0.73-0.84)). At a CD risk threshold of </=7.5% this model had a negative predictive value of 96%.
Conclusion: This proposed prediction model can safely rule out complicated diverticulitis. Clinical practitioners could cautiously use this model to aid them in the decision whether or not to subject patients to further secondary care diagnostics or treatment

Gepubliceerd: Scand J Gastroenterol 2018 Nov 5;53(10-11):1291-7
Impact factor: 2.629; Q3

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4. Identification of Users for a Smoking Cessation Mobile App: Quantitative Study
Chevalking SKL, Ben Allouch S, Brusse-Keizer M, Postel MG, Pieterse ME

Background: The number of mobile apps that support smoking cessation is growing, indicating the potential of the mobile phone as a means to support cessation. Knowledge about the potential end users for cessation apps results in suggestions to target potential user groups in a dissemination strategy, leading to a possible increase in the satisfaction and adherence of cessation apps.
Objective: This study aimed to characterize potential end users for a specific mobile health (mHealth) smoking cessation app.
Methods: A quantitative study was conducted among 955 Dutch smokers and ex-smokers. The respondents were primarily recruited from addiction care facilities and hospitals through Web-based media via websites and forums. The respondents were surveyed on their demographics, smoking behavior, and personal innovativeness. The intention to use and the attitude toward a cessation app were determined on a 5-point Likert scale. To study the association between the characteristics and intention

to use and attitude, univariate and multivariate ordinal logistic regression analyses were performed.
Results: The multivariate ordinal logistic regression showed that the number of previous quit attempts (odds ratio [OR] 4.1, 95% CI 2.4-7.0, and OR 3.5, 95% CI 2.0-5.9) and the score on the Fagerstrom Test of Nicotine Dependence (OR 0.8, 95% CI 0.8-0.9, and OR 0.8, 95% CI 0.8-0.9) positively correlates with the intention to use a cessation app and the attitude toward cessation apps, respectively. Personal innovativeness also positively correlates with the intention to use (OR 0.3, 95% CI 0.2-0.4) and the attitude towards (OR 0.2, 95% CI 0.1-0.4) a cessation app. No associations between demographics and the intention to use or the attitude toward using a cessation app were observed.
Conclusions: This study is among the first to show that demographic characteristics such as age and level of education are not associated with the intention to use and the attitude toward using a cessation app when characteristics related specifically to the app, such as nicotine dependency and the number of quit attempts, are present in a multivariate regression model. This study shows that the use of mHealth apps depends on characteristics related to the content of the app rather than general user characteristics

Gepubliceerd: J Med Internet Res 2018 Apr 9;20(4):e118
Impact factor: 4.671; Q1

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5. Stable-State Midrange Proadrenomedullin Is Associated With Severe Exacerbations in COPD
Citgez E, Zuur-Telgen M, van der Palen J, van der Valk PD, Stolz D, Brusse-Keizer M

Background: Elevated levels of midrange proadrenomedullin (MR-proADM) are associated with worse outcome in different diseases, including COPD. The association of stable-state MR-proADM with severe acute exacerbations of COPD (AECOPDs) requiring hospitalization, or with community-acquired pneumonia (CAP) in patients with COPD, has not been studied yet. The aim of this study was to evaluate the association of stable-state MR-proADM with severe AECOPD and CAP in patients with COPD.
Methods: This study pooled data of 1,285 patients from the Cohort of Mortality and Inflammation in COPD (COMIC) and PRedicting Outcome using systemic Markers In Severe Exacerbations of Chronic Obstructive Pulmonary Disease (PROMISE-COPD) cohort studies. Time until first severe AECOPD was compared between patients with high (>/= 0.87 nmol/L) or low (< 0.87 nmol/L) levels of plasma MR-proADM in stable state as previously defined. For time until first CAP, only COMIC data (n = 795) were available.
Results: Patients with COPD with high-level stable-state MR-proADM have a significantly higher risk for severe AECOPD compared with those with low-level MR-proADM with a corrected hazard ratio (HR) of 1.30 (95% CI, 1.01-1.68). Patients with high-level stable-state MR-proADM had a significantly higher risk for CAP compared with patients with COPD with low-level MR-proADM in univariate analysis (HR, 1.93; 95% CI, 1.24-3.01), but after correction for age, lung function, and previous AECOPD, the association was no longer significant (corrected HR, 1.10; 95% CI, 0.68-1.80).
Conclusions: Stable-state high-level MR-proADM in patients with COPD is associated with severe AECOPD but not with CAP

Gepubliceerd: Chest 2018 Jul;154(1):51-7
Impact factor: 7.652; Q1

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6. Retrospective validation of a new volumetric capnography parameter for the exclusion of pulmonary embolism at the emergency department
Fabius TM, Eijsvogel MMM, Brusse-Keizer MGJ, Sanchez OM, Verschuren F, de Jongh FHC

Volumetric capnography might be used to exclude pulmonary embolism (PE) without the need for computed tomography pulmonary angiography. In a pilot study, a new parameter (CapNoPE) combining the amount of carbon dioxide exhaled per breath (carbon dioxide production (V CO2)), the slope of phase 3 of the volumetric capnogram (slope 3) and respiratory rate (RR) showed promising diagnostic accuracy (where CapNoPE=(V CO2 xslope 3)/RR). To retrospectively validate CapNoPE for the exclusion of PE, the volumetric capnograms of 205 subjects (68 with PE) were analysed, based on a large multicentre dataset of volumetric capnograms from subjects with suspected PE at the emergency department. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve and diagnostic accuracy of the in-pilot established threshold (1.90 Pa.min) were calculated. CapNoPE was 1.56+/-0.97 Pa.min in subjects with PE versus 2.51+/-1.67 Pa.min in those without PE (p<0.001). The AUC of the ROC curve was 0.714 (95% CI 0.64-0.79). For the cut-off of >/=1.90 Pa.min, sensitivity was 64.7%, specificity was 59.9%, the negative predictive value was 77.4% and the positive predictive value was 44.4%. The CapNoPE parameter is decreased in patients with PE but its diagnostic accuracy seems too low to use in clinical practice

Gepubliceerd: ERJ Open Res 2018 Oct;4(4)
Impact factor: 0; nvt

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7. Cost-Effectiveness Analysis of the DiagnOSAS Screening Tool Compared With Polysomnography Diagnosis in Dutch Primary Care
Geessinck FAJ, Pleijhuis RG, Mentink RJ, van der Palen J, Koffijberg H

Study objectives: The growing recognition of obstructive sleep apnea (OSA) as a serious health condition, increasing waiting lists for sleep tests, and a high proportion of unnecessary referrals from general practice highlight the need for alternative diagnostic strategies for OSA. This study's objective was to investigate the cost-effectiveness of DiagnOSAS, a screening tool that strives to facilitate fast and well-informed referral to hospitals and sleep clinics for diagnosis, in The Netherlands.
Methods: A Markov model was constructed to assess cost-effectiveness in men aged 50 years. The diagnostic process of OSA was simulated with and without DiagnOSAS, taking into account the occurrence of hazardous OSA effects: car accidents, myocardial infarction, and stroke. The cost-effectiveness of "DiagnOSAS Strategy" and a "Rapid Diagnosis Scenario," in which time to diagnosis was halved, was assessed.
Results: Base case results show that, within a 10-year time period, DiagnOSAS saves €226 per patient at a negligible decrease (< 0.01) in quality-adjusted life-years

(QALYs), resulting in an incremental cost-effectiveness ratio of €56,997/QALY. The "Rapid Diagnosis Scenario" dominates usual care (ie, is both cheaper and more effective). For a willingness-to-pay threshold of €20,000/QALY the probability that the "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" are cost-effective equals 91.7% and 99.3%, respectively.
Conclusions: DiagnOSAS appears to be a cost-saving alternative for the usual OSA diagnostic strategy in The Netherlands. When DiagnOSAS succeeds in decreasing time to diagnosis, it could substantially improve health outcomes as well

Gepubliceerd: J Clin Sleep Med 2018 Jun 15;14(6):1005-15
Impact factor: 3.396; Q2

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8. Wound swab and wound biopsy yield similar culture results
Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Klont R, Guebitz G, Heinzle A, van der Palen J

The question remains whether wound swabs yield similar culture results to the traditional gold standard, biopsies. Swabs are not invasive and easy to perform. However, they are believed to capture microorganisms from the surface rather than microorganisms that have invaded tissue. Several studies compared swabs and biopsies using different populations and sampling methods, complicating the ability to draw conclusions for clinical practice. This study aimed to compare swab and biopsy in clinical practice, by including a variety of wounds and using standard sampling and culture procedures. Swabs (Levine technique) and biopsies were taken for microbiological culture in a standardized manner from the same location of one wound for each patient. Statistical analyses were performed to determine overall agreement, and observed agreement and kappa for specific microorganisms. A variety of wounds of 180 patients from different healthcare facilities in The Netherlands were included. Skin flora was more frequently cultured from swabs, resulting in similar recovery rates when excluding skin flora (1.34 vs 1.35). Swabs were able to identify all microorganisms cultured from biopsies in 131 wounds (72.8%) wounds. Most frequently identified organisms were Staphylococcus aureus, Pseudomonas aeruginosa, and beta-haemolytic streptococci species. Observed agreement and kappa for these organisms varied between 87.2 and 97.8% and 0.73 and 0.85, respectively. This study demonstrates that swabs and biopsies tend to yield the same culture results when taken from the same location. For frequently occurring microorganisms, agreement between the two methods was even higher. Therefore, there seems to be no direct need for invasive biopsy in clinical practice

Gepubliceerd: Wound Repair Regen 2018 Mar;26(2):192-9
Impact factor: 2.952; Q1

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9. Breast-conserving therapy for primary Ductal Carcinoma in Situ in The Netherlands: A multi-center study and population-based analysis
Jobsen JJ, Scheijmans LJEE, Smit WGJM, Stenfert Kroese MC, Struikmans H, van der Palen J

Objective: The aim of this study was to analyse the efficacy of breast-conserving therapy (BCT) for women with primary DCIS in a population-based setting.
Methods: Data were used from five Radiotherapy centres in The Netherlands from 2000 to 2010, all treated with BCT. Of all the cases, 59.2% received a boost of radiotherapy after their whole breast irradiation (WBI), irrespective of margin status.
Results: A total of 1248 cases with primary DCIS were analysed. The 10-years LRFS was 92.9%. Age </=50 years and a positive margin were significantly related to local relapse free survival (LRFS). Having a boost had no impact on LRFS, showing a nearly equal recurrence pattern in patients with and without a boost. Separate analyses were done on patients who had received and not received a boost of radiotherapy after WBI. We noted 9.1% contra-lateral breast tumours. The 10-years disease specific survival (DSS) rate was 99.0%.
Conclusions: DCIS of the breast and treated with BCT results in excellent LRFS and DSS. Primary surgical lumpectomy with negative margins followed by WBI seems to be the treatment of choice in DCIS treated with BCS with respect to IBTR

Gepubliceerd: Breast 2018 Jul 18;42:3-9
Impact factor: 2.951; Q1

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10. Systematic review of association between critical errors in inhalation and health outcomes in asthma and COPD
Kocks JWH, Chrystyn H, van der Palen J, Thomas M, Yates L, Landis SH, Driessen MT, Gokhale M, Sharma R, Molimard M

Inhaled medications are the cornerstone of treatment and management of asthma and COPD. However, inhaler device errors are common among patients and have been linked with reduced symptom control, an increased risk of exacerbations, and increased healthcare utilisation. These observations have prompted GINA (Global INitiative for Asthma) and GOLD (Global initiative for chronic Obstructive Lung Disease) to recommend regular assessment of inhaler technique in a bid to improve therapeutic outcomes. To better define the relationship between device errors and health outcomes (clinical outcomes, quality of life, and healthcare utilisation) in asthma and COPD, we conducted a systematic review of the literature, with a particular focus on the methods used to assess the relationship between device errors and outcomes. Sixteen studies were identified (12 in patients with asthma, one in patients with COPD, and three in both asthma and COPD) with varying study designs, endpoints, and patient populations. Most of the studies reported that inhalation errors were associated with worse disease outcomes in patients with asthma or COPD. Patients who had a reduction in errors over time had improved outcomes. These findings suggest that time invested by healthcare professionals is vital to improving inhalation technique in asthma and COPD patients to improve health outcomes

Gepubliceerd: NPJ Prim Care Respir Med 2018 Nov 16;28(1):43
Impact factor: Q1

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11. Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD

Koehorst-Ter Huurne K, Groothuis-Oudshoorn CG, van der Valk PD, Movig KL, van der Palen J, Brusse-Keizer M

Aim: The aim of this study was to analyze the association between therapy adherence to inhaled corticosteroids (ICSs) and tiotropium on the one hand and morbidity and mortality in COPD on the other hand.
Methods: Therapy adherence to ICSs and tiotropium over a 3-year period of, respectively, 635 and 505 patients was collected from pharmacy records. It was expressed as percentage and deemed optimal at >/=75-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). The association between adherence and time to first hospital admission for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), community acquired pneumonia (CAP), and mortality was analyzed, with optimal use as the reference category.
Results: Suboptimal use and underuse of ICSs and tiotropium were associated with a substantial increase in mortality risk: hazard ratio (HR) of ICSs was 2.9 (95% CI 1.7-5.1) and 5.3 (95% CI 3.3-8.5) and HR of tiotropium was 3.9 (95% CI 2.1-7.5) and 6.4 (95% CI 3.8-10.8) for suboptimal use and underuse, respectively. Suboptimal use and overuse of tiotropium were also associated with an increased risk of CAP, HR 2.2 (95% CI 1.2-4.0) and HR 2.3 (95% CI 1.2-4.7), respectively. Nonadherence to tiotropium was also associated with an increased risk of severe AECOPD: suboptimal use HR 3.0 (95% CI 2.01-4.5), underuse HR 1.9 (95% CI 1.2-3.1), and overuse HR 1.84 (95% CI 1.1-3.1). Nonadherence to ICSs was not related to time to first AECOPD or first CAP.
Conclusion: Poor adherence to ICSs and tiotropium was associated with a higher mortality risk. Furthermore, nonadherence to tiotropium was associated with a higher morbidity. The question remains whether improving adherence can reduce morbidity and mortality

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2018;13:1683-90
Impact factor: 2.917; Q2

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12. Patients with underuse or overuse of inhaled corticosteroids have different perceptions and beliefs regarding COPD and inhaled medication
Koehorst-Ter Huurne K, Brusse-Keizer M, van der Valk PD, Movig K, van der Palen J, Bode C

Background: Therapy adherence in COPD is crucial for treating symptoms, preventing exacerbations, and related complications. To achieve optimal adherence, it is important to recognize and understand a nonadherent patient.
Objective: To study perceptions and beliefs regarding COPD and inhaled medication in COPD patients with poor adherence.
Methods: Twenty patients (10 underuse, 10 overuse) were interviewed in semistructured in-depth interviews, about mental and physical health, illness perceptions, knowledge regarding COPD, and experience with, knowledge of, and acceptance of COPD medication and inhalation devices.
Results: A majority of patients did not fully accept their disease, showed little disease knowledge, and many revealed signs of depressive mood and severe fatigue. Overusers reported more grief about decreased participation in daily life and were more frustrated in general. Underusers claimed using less medication because they

felt well, did not want to use too much medication, and used their inhalation devices too long. Overusers reported medication "dependency"; they tended to catastrophize when being without medication and discarded inhalation devices too early because they feared running out of medication.
Conclusion: Overusers and underusers showed a different pattern in perceptions and beliefs regarding inhaled medication and COPD. Practical implications: It is important to understand the reasons for under- and overuse. Is it related to practical issues regarding knowledge or is it influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed for improving adherence

Gepubliceerd: Patient Prefer Adherence 2018;12:1777-83
Impact factor: 1.733; Q2

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13. Multi-centre prospective study on diagnosing subtypes of lung cancer by exhaled-breath analysis
Kort S, Tiggeloven MM, Brusse-Keizer M, Gerritsen JW, Schouwink JH, Citgez E, de Jongh FHC, Samii S, van der Maten J, van den Bogart M, van der Palen J

Objectives: Lung cancer is a leading cause of mortality. Exhaled-breath analysis of volatile organic compounds (VOC's) might detect lung cancer early in the course of the disease, which may improve outcomes. Subtyping lung cancers could be helpful in further clinical decisions.
Materials and methods: In a prospective, multi-centre study, using 10 electronic nose devices, 144 subjects diagnosed with NSCLC and 146 healthy subjects, including subjects considered negative for NSCLC after investigation, breathed into the Aeonose (The eNose Company, Zutphen, Netherlands). Also, analyses into subtypes of NSCLC, such as adenocarcinoma (AC) and squamous cell carcinoma (SCC), and analyses of patients with small cell lung cancer (SCLC) were performed.
Results: Choosing a cut-off point to predominantly rule out cancer resulted for NSCLC in a sensitivity of 94.4%, a specificity of 32.9%, a positive predictive value of 58.1%, a negative predictive value (NPV) of 85.7%, and an area under the curve (AUC) of 0.76. For AC sensitivity, PPV, NPV, and AUC were 81.5%, 56.4%, 79.5%, and 0.74, respectively, while for SCC these numbers were 80.8%, 45.7%, 93.0%, and 0.77, respectively. SCLC could be ruled out with a sensitivity of 88.9% and an NPV of 96.8% with an AUC of 0.86.
Conclusion: Electronic nose technology with the Aeonose can play an important role in rapidly excluding lung cancer due to the high negative predictive value for various, but not all types of lung cancer. Patients showing positive breath tests should still be subjected to further diagnostic testing

Gepubliceerd: Lung Cancer 2018 Nov;125:223-9
Impact factor: 4.486; Q1

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14. COPD-related fatigue: Impact on daily life and treatment opportunities from the patient's perspective
Kouijzer M, Brusse-Keizer M, Bode C

Background: Fatigue is a highly prevalent, challenging and understudied symptom of COPD, which influences the quality of life of patients. This study addresses the patient's perspective on the impact of fatigue on their daily lives and explores possible treatment options to tackle the burden of fatigue.
Methods: Twenty semi-structured interviews were conducted with ten patients hospitalised for a COPD exacerbation and ten outpatients with COPD. Data were transcribed verbatim and coded in an iterative (deductive and inductive) coding process.
Findings: Patients perceived severe negative impact of fatigue on their daily lives and emphasized that they were limited in physical, emotional, cognitive and social functioning. These limitations caused a high mental burden which challenged patients' coping resources and making fatigue a symptom difficult to accept. The majority of patients mentioned that they had, to some degree, lost the joy in life or in some cases, even lost the will to live. Patients reported the need for effective treatment and recommended a multidisciplinary approach and blended care, in which an online treatment to improve fatigue management is combined with face-to-face contact with a healthcare professional to increase social support.
Discussion: These findings indicate that patients perceive the impact of fatigue on their daily lives to be a key factor in decreasing their quality of life. To increase awareness of fatigue in healthcare professionals and patients and to facilitate early fatigue self-management, a pro-active approach by healthcare professionals might be the best way to realize effective tailored treatment

Gepubliceerd: Respir Med 2018 Aug;141:47-51
Impact factor: 3.230; Q2

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15. The role of social support in improving chronic obstructive pulmonary disease self-management
Lenferink A, van der Palen J, Effing T

Gepubliceerd: Expert Rev Respir Med 2018 Aug;12(8):623-6
Impact factor: 2.607; Q2

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16. The influence of early or delayed provision of ankle-foot orthoses on pelvis, hip and knee kinematics in patients with sub-acute stroke: A randomized controlled trial
Nikamp CDM, van der Palen J, Hermens HJ, Rietman JS, Buurke JH

Background: Compensatory pelvis, hip- and knee movements are reported after stroke to overcome insufficient foot-clearance. Ankle-foot orthoses (AFOs) are often used to improve foot-clearance, but the optimal timing of AFO-provision post-stroke is unknown. Early AFO-provision to prevent foot-drop might decrease the development of compensatory movements, but it is unknown whether timing of AFO-provision affects post-stroke kinematics.
Research questions: 1) To compare the effect of AFO-provision at two different points in time (early versus delayed) on frontal pelvis and hip, and sagittal hip and knee kinematics in patients with sub-acute stroke. Effects were assessed after 26

weeks; 2) To study whether possible changes in kinematics or walking speed during the 26-weeks follow-up period differed between both groups.
Method: An explorative randomized controlled trial was performed, including unilateral hemiparetic patients maximal six weeks post-stroke with indication for AFO-use. Subjects were randomly assigned to AFO-provision early (at inclusion) or delayed (eight weeks later). 3D gait-analysis with and without AFO was performed in randomized order. Measurements were performed in study-week 1, 9, 17 and 26.
Results: Twenty-six subjects (15 early, 11 delayed) were analyzed. After 26 weeks, no differences in kinematics were found between both groups for any of the joint angles, both for the without and with AFO-condition. Changes in kinematics during the 26-weeks follow-up period did not differ between both groups for any of the joint angles during walking without AFO. Significant differences in changes in walking speed during the 26-weeks follow-up were found (p=0.034), corresponding to the first eight weeks after AFO-provision.
Significance: Results indicate that early or delayed AFO-use post-stroke does not influence pelvis, hip and knee movements after 26 weeks, despite that AFO-use properly corrected drop-foot. AFOs should be provided to improve drop-foot post-stroke, but not with the intention to influence development of compensatory patterns around pelvis and hip

Gepubliceerd: Gait Posture 2018 Jun;63:260-7
Impact factor: 2.273; Q2

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17. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol
Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA

Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients. Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal carers' QoL and cost-effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven,

this could further promote the implementation of pharmaceutical care in a primary care setting

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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18. Measuring Patient-Reported Outcomes Adaptively: Multidimensionality Matters!
Paap MCS, Kroeze KA, Glas CAW, Terwee CB, van der Palen J, Veldkamp BP

As there is currently a marked increase in the use of both unidimensional (UCAT) and multidimensional computerized adaptive testing (MCAT) in psychological and health measurement, the main aim of the present study is to assess the incremental value of using MCAT rather than separate UCATs for each dimension. Simulations are based on empirical data that could be considered typical for health measurement: a large number of dimensions (4), strong correlations among dimensions (.77-.87), and polytomously scored response data. Both variable- (SE < .316, SE < .387) and fixed-length conditions (total test length of 12, 20, or 32 items) are studied. The item parameters and variance-covariance matrix Phi are estimated with the multidimensional graded response model (GRM). Outcome variables include computerized adaptive test (CAT) length, root mean square error (RMSE), and bias. Both simulated and empirical latent trait distributions are used to sample vectors of true scores. MCATs were generally more efficient (in terms of test length) and more accurate (in terms of RMSE) than their UCAT counterparts. Absolute average bias was highest for variable-length UCATs with termination rule SE < .387. Test length of variable-length MCATs was on average 20% to 25% shorter than test length across separate UCATs. This study showed that there are clear advantages of using MCAT rather than UCAT in a setting typical for health measurement

Gepubliceerd: Appl Psychol Meas 2018 Jul;42(5):327-42
Impact factor: 0.923; Q3

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19. Blended Smoking Cessation Treatment: Exploring Measurement, Levels, and Predictors of Adherence
Siemer L, Brusse-Keizer MG, Postel MG, Ben Allouch S, Patrinopoulos Bougioukas A, Sanderman R, Pieterse ME

Background: Blended face-to-face and Web-based treatment is a promising way to deliver cognitive behavioral therapy. Since adherence has been shown to be a measure for treatment's acceptability and a determinant for treatment's effectiveness, in this study, we explored adherence to a new blended smoking cessation treatment (BSCT).
Objective: The objective of our study was to (1) develop an adequate method to measure adherence to BSCT; (2) define an adequate degree of adherence to be used as a threshold for being adherent; (3) estimate adherence to BSCT; and (4) explore the possible predictors of adherence to BSCT.
Methods: The data of patients (N=75) were analyzed to trace adherence to BSCT delivered at an outpatient smoking cessation clinic. In total, 18 patient activities (eg,

using a Web-based smoking diary tool or responding to counselors' messages) were selected to measure adherence; the degree of adherence per patient was compared with quitting success. The minimum degree of adherence of patients who reported abstinence was examined to define a threshold for the detection of adherent patients. The number of adherent patients was calculated for each of the 18 selected activities; the degree of adherence over the course of the treatment was displayed; and the number of patients who were adherent was analyzed. The relationship between adherence and 33 person-, smoking-, and health-related characteristics was examined.
Results: The method for measuring adherence was found to be adequate as adherence to BSCT correlated with self-reported abstinence (P=.03). Patients reporting abstinence adhered to at least 61% of BSCT. Adherence declined over the course of the treatment; the percentage of adherent patients per treatment activity ranged from 82% at the start of the treatment to 11%-19% at the final-third of BSCT; applying a 61% threshold, 18% of the patients were classified as adherent. Marital status and social modeling were the best independent predictors of adherence. Patients having a partner had 11-times higher odds of being adherent (OR [odds ratio]=11.3; CI: 1.33-98.99; P=.03). For social modeling, graded from 0 (=partner and friends are not smoking) to 8 (=both partner and nearly all friends are smoking), each unit increase was associated with 28% lower odds of being adherent (OR=0.72; CI: 0.55-0.94; P=.02).
Conclusions: The current study is the first to explore adherence to a blended face-to-face and Web-based treatment (BSCT) based on a substantial group of patients. It revealed a rather low adherence rate to BSCT. The method for measuring adherence to BSCT could be considered adequate because the expected dose-response relationship between adherence and quitting could be verified. Furthermore, this study revealed that marital status and social modeling were independent predictors of adherence.
Trial registration: Netherlands Trial Registry NTR5113;

Gepubliceerd: J Med Internet Res 2018 Aug 1;20(8):e246
Impact factor: 4.671; Q1

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20. Can we predict a delirium after cardiac surgery? A validation study of a delirium risk checklist
Ten Broeke M, Koster S, Konings T, Hensens AG, van der Palen J

Background: Delirium is a common temporary mental disorder that often occurs in patients who undergo cardiac surgery. It is important to prevent the negative side effects of delirium by identifying high-risk patients before surgery. Koster and colleagues designed a risk model to identify patients with an increased risk of postoperative delirium after cardiac surgery. Aim: The aim of this study was to validate the risk model for delirium and further improve the risk model.
Methods: A delirium risk checklist containing predictors associated with postoperative delirium was used during the preoperative outpatient screening in 329 patients. The delirium observation screening scale was used preoperatively and postoperatively to assess delirium.
Results: Compared with the model of Koster and colleagues age greater than 70 years and a history of delirium were confirmed as statistically significant predictors of

postoperative delirium, while cognitive impairment and alcohol abuse were almost significant factors. The European system for cardiac operative risk evaluation (EuroSCORE), comorbidity and type of surgery could not predict a postoperative delirium again. The area under the curve of this model was 0.79 (95% confidence interval (CI) 0.73-0.86; P<0.001). Based on the data of this study the model was improved with the following independent predictors of postoperative delirium: age, more than one comorbidity, history of delirium and a lower standardised mini mental state examination score as with an area under the curve of 0.79 (95% CI 0.73-0.85; P<0.001).
Conclusion: The risk model could not be fully validated. It is difficult to validate a risk model over time; there are different circumstances such as the increased focus on the prevention of delirium

Gepubliceerd: Eur J Cardiovasc Nurs 2018;17(3):255-61
Impact factor: 2.651; Q1

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21. Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents (BIONYX): Rationale and design of the randomized TWENTE IV multicenter trial
van der Heijden LC, Kok MM, Zocca P, Jessurun GAJ, Schotborgh CE, Roguin A, Benit E, Aminian A, Danse PW, Lowik MM, Linssen GCM, van der Palen J, Doggen CJM, von Birgelen C

Aim: The aim was to compare in a noninferiority trial the efficacy and safety of 2 contemporary drug-eluting stents (DESs): a novel, durable polymer-coated stent versus an established bioabsorbable polymer-coated stent.
Methods and results: The BIONYX trial (ClinicalTrials.gov-no.NCT02508714) is an investigator-initiated, prospective, randomized, patient- and assessor-blinded, international, multicenter study in all-comer patients with all types of clinical syndromes and lesions who require percutaneous coronary interventions with DES. Patients at 7 study sites in the Netherlands, Belgium, and Israel were randomly assigned (1:1, stratified for gender and diabetes mellitus) to treatment with the novel, zotarolimus-eluting, durable polymer-coated Resolute Onyx stent that has a radiopaque, thin-strut, CoreWire stent platform versus the sirolimus-eluting, bioresorbable polymer-coated Orsiro stent (reference device) that has a very thin-strut, cobalt-chromium stent backbone. The primary end point is the 1-year incidence of the composite clinical end point target vessel failure consisting of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. A power calculation, assuming a target vessel failure rate of 6.0% (noninferiority margin 2.5%), revealed that 2,470 study patients would give the study 80% power (alpha level 5%), allowing for up to 3% loss to follow-up. The first patient was enrolled on October 7, 2015; on December 23, 2016, the last patient entered the study.
Conclusions: BIONYX is a large-scale, prospective, randomized, international, multicenter trial comparing a novel DES with durable coating versus a reference DES with biodegradable coating in all-comers. The study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States

Gepubliceerd: Am Heart J 2018 Apr;198:25-32
Impact factor: 4.171; Q2

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22. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD
van der Palen J, Moeskops-van Beurden W, Dawson CM, James WY, Preece A, Midwinter D, Barnes N, Sharma R

Background: Administering maintenance COPD therapy with a combination of multiple inhalers may increase inhaler errors. This study evaluated the potential benefits of using a single Ellipta dry powder inhaler (DPI) compared with two combinations of DPIs commonly used to deliver triple maintenance therapy.
Methods: Patients receiving inhaled COPD medication were enrolled in this multicenter, randomized, open-label, placebo-device, crossover study with a 2x2 complete block design (NCT0298218), which comprised two substudies: Ellipta vs Diskus + HandiHaler (substudy 1) or Turbuhaler + HandiHaler (substudy 2). Patients demonstrated inhaler use after reading the relevant patient information leaflet (PIL). A trained investigator assessed user errors (critical errors [errors likely to result in no or significantly reduced medication being inhaled] and overall errors). The primary endpoint was the proportion of patients making >/=1 critical error after reading the PIL. The secondary endpoints included error rates during </=2 reassessments following investigator instruction (if required), instruction time, and patient preference.
Results: After reading the PIL, significantly fewer patients made critical errors with Ellipta compared with Diskus + HandiHaler (9% [7/80] vs 75% [60/80], respectively; P<0.001) or Turbuhaler + HandiHaler (9% [7/79] vs 73% [58/79], respectively; P<0.001). The number of patients making overall errors was also lower with Ellipta vs tested inhaler combinations (P<0.001 for each substudy). The median instruction time needed for error-free use was shorter with Ellipta in substudies 1 and 2 (2.7 and 2.6 minutes, respectively) vs either combination (10.6 [Diskus + HandiHaler] and 11.3 minutes [Turbuhaler + HandiHaler], respectively). Significantly more patients preferred Ellipta over Diskus + HandiHaler or Turbuhaler + HandiHaler overall for taking their COPD medication (81% vs 9% and 84% vs 4%, respectively) and per the number of steps for taking their COPD medication (89% vs 8% and 91% vs 5%, respectively).
Conclusion: Fewer patients with COPD made critical errors with the single DPI, and patients required less instruction time, compared with each dual DPI combination

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2018;13:2515-23
Impact factor: 2.917; Q2

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23. The Mozart study: a relation between dynamic hyperinflation and physical activity in patients with chronic obstructive pulmonary disease?
van Leuteren RW, Dijkhuis S, de Jongh FH, van der Valk PD, Tabak M, Brusse-Keizer MG

Background: Many patients with chronic obstructive pulmonary disease (COPD) experience dyspnoea during exercise, resulting in a reduction of physical activity (PA). Dynamic hyperinflation (DH) is seen as a major cause of dyspnoea in COPD.
Objective: The objective of the current study was to investigate the relationship between DH, in terms of the amount of DH and the development and recovery rate of DH in patients with COPD, and PA.
Methods: Thirty-five patients with stable COPD were included from an outpatient clinic (14 GOLD II and 21 GOLD III, median age 65). PA was assessed using an accelerometer. Subjects underwent metronome-paced tachypnoea (MPT) to induce DH. To quantify the amount of DH during MPT, a decrease in inspiratory capacity (IC) or a change in IC as percentage of total lung capacity was used.
Results: No significant correlations were found between the parameters describing DH and PA. Secondary correlation analyses showed a negative correlation between static hyperinflation (SH) and PA (r = -0.39; P = 0.02). The pattern of breathing during MPT and the test itself showed high interpatient variability.
Conclusions: The absence of a significant correlation between DH and PA is contrary to previous studies. SH did show a correlation with PA. The variety in results and the technical difficulties in execution of the measurements ask for a new, more reliable, method to detect DH and investigate its relation with PA in patients with COPD

Gepubliceerd: Clin Physiol Funct Imaging 2018;38(3):409-15
Impact factor: 2.600; Q2

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24. A phantom study for the comparison of different brands of computed tomography scanners and software packages for endovascular aneurysm repair sizing and planning
Velu JF, Groot Jebbink E, de Vries JP, van der Palen J, Slump CH, Geelkerken RH

Objectives: Correct sizing of endoprostheses used for the treatment of abdominal aortic aneurysms is important to prevent endoleaks and migration. Sizing requires several steps and each step introduces a possible sizing error. The goal of this study was to investigate the magnitude of these errors compared to the golden standard: a vessel phantom. This study focuses on the errors in sizing with three different brands of computed tomography angiography scanners in combination with three reconstruction software packages.
Methods: Three phantoms with a different diameter, altitude and azimuth were scanned with three computed tomography scanners: Toshiba Aquilion 64-slice, Philips Brilliance iCT 256-slice and Siemens Somatom Sensation 64-slice. The phantom diameters were determined in the stretched view after central lumen line reconstruction by three observers using Simbionix PROcedure Rehearsal Studio, 3mensio and TeraRecon planning software. The observers, all novices in sizing endoprostheses using planning software, measured 108 slices each. Two senior vascular surgeons set the tolerated error margin of sizing on +/-1.0 mm.
Results: In total, 11.3% of the measurements (73/648) were outside the set margins of +/-1.0 mm from the phantom diameter, with significant differences between the scanner types (14.8%, 12.1%, 6.9% for the Siemens scanner, Philips scanner and Toshiba scanner, respectively, p-value = 0.032), but not between the software

packages (8.3%, 11.1%, 14.4%, p-value = 0.141) or the observers (10.6%, 9.7%, 13.4%, p-value = 0.448).
Conclusions: It can be concluded that the errors in sizing were independent of the used software packages, but the phantoms scanned with Siemens scanner were significantly more measured incorrectly than the phantoms scanned with the Toshiba scanner. Consequently, awareness on the type of computed tomography scanner and computed tomography scanner setting is necessary, especially in complex abdominal aortic aneurysms sizing for fenestrated or branched endovascular aneurysm repair if appropriate the sizing is of upmost importance

Gepubliceerd: Vascular 2018 Apr;26(2):198-202
Impact factor: 1.089; Q4

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25. Characteristics of older cyclists (65+) and factors associated with self-reported cycling accidents in the Netherlands
Engbers C, Dubbeldam R, Brusse-Keizer MGJ, Buurke JH, de Waard D, Rietman JS

Cycling supports the mobility, health and independency of the ageing population. However, older cyclists have an increased injury risk. On average, the risk of older people to sustain an injury in a cycling accident is three times higher per cycling kilometre than for middle-aged people and the injury risk increases with age. In comparison with middle-aged cyclists (<65 years), the risk of hospitalization is more than four times as high for older cyclists (=65 years). The aim of this study was to reveal characteristics of older cyclists in general and to explore which of these characteristics are associated with self-reported cycling accidents from age 59. More than eight hundred older cyclists (>65 years) filled out a questionnaire, which included questions on demographics, bicycle specifications and personal characteristics. By means of a logistic regression, the relationship between personal factors and self-reported bicycle falls were studied. The univariate models showed that age, physical and mental impairments, bicycle model, living environment, feelings of uncertainty of the cyclist and changed cycling behaviour (such as more patience, lower speed) were related to falling off a bicycle. From the multivariate model we can conclude that several factors are associated with falling off a bicycle in the older population: (1) every year the cyclists becomes one year older (from the age of 65), the chance they have fallen increases with 7.3%, (2) If cyclists have mental impairments, the chance they have fallen increases with a factor 2.5, (3) if cyclists were less than completely confident the chance they have fallen increases with factor 1.8, (4) if cyclists live in a rural environment compared to an urban environment the chance they have fallen increases with a factor 2.1. In conclusion, demographic, cycling and personal factors can be related to increased self-reported fall risk. It is advised to take these factors into account when implementing new cycling related safety measures.

Gepubliceerd: Transportation Research Part F-Traffic Psychology and Behaviour 2018;56:522-30
Impact factor: 1.935; Q2

Totale impact factor: 69.674
Gemiddelde impact factor: 2.787

Aantal artikelen 1e, 2e of laatste auteur: 13
Totale impact factor: 43.640
Gemiddelde impact factor: 3.357

Microbiologie

1. Susceptibility of ESBL Escherichia coli and Klebsiella pneumoniae to fosfomycin in the Netherlands and comparison of several testing methods including Etest, MIC test strip, Vitek2, Phoenix and disc diffusion
van den Bijllaardt W, Schijffelen MJ, Bosboom RW, Cohen SJ, Diederen B, Kampinga G, Le TN, Overdevest I, Stals F, Voorn P, Waar K, Mouton JW, Muller AE

Objectives: Fosfomycin susceptibility testing is complicated and prone to error. Before using fosfomycin widely in patients with serious infections, acquisition of WT distribution data and reliable susceptibility testing methods are crucial. In this study, the performance of five methods for fosfomycin testing in the routine laboratory against the reference method was evaluated.
Methods: Ten laboratories collected up to 100 ESBL-producing isolates each (80 Escherichia coli and 20 Klebsiella pneumoniae). Isolates were tested using Etest, MIC test strip (MTS), Vitek2, Phoenix and disc diffusion. Agar dilution was performed as the reference method in a central laboratory. Epidemiological cut-off values (ECOFFs) were determined for each species and susceptibility and error rates were calculated.
Results: In total, 775 E. coli and 201 K. pneumoniae isolates were tested by agar dilution. The ECOFF was 2 mg/L for E. coli and 64 mg/L for K. pneumoniae. Susceptibility rates based on the EUCAST breakpoint of </=32 mg/L were 95.9% for E. coli and 87.6% for K. pneumoniae. Despite high categorical agreement rates for all methods, notably in E. coli, none of the alternative antimicrobial susceptibility testing methods performed satisfactorily. Due to poor detection of resistant isolates, very high error rates of 23.3% (Etest), 18.5% (MTS), 18.8% (Vitek2), 12.5% (Phoenix) and 12.9% (disc diffusion) for E. coli and 22.7% (Etest and MTS), 16.0% (Vitek2) and 12% (Phoenix) for K. pneumoniae were found. None of the methods adequately differentiated between WT and non-WT populations.
Conclusions: Overall, it was concluded that none of the test methods is suitable as an alternative to agar dilution in the routine laboratory.

Gepubliceerd: J Antimicrob Chemother 2018 Sep 1;73(9):2380-7
Impact factor: 5.217; Q1

Totale impact factor: 5.217
Gemiddelde impact factor: 5.217

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 5.217
Gemiddelde impact factor: 5.217

Mond- kaak en aangezichtschirurgie

1. Variation in Integrated Head and Neck Cancer Care: Impact of Patient and Hospital Characteristics
van Overveld LFJ, Takes RP, Braspenning JCC, Baatenburg de Jong RJ, de Boer JP, Brouns JJA, Bun RJ, Dik EA, van Dijk BAC, van Es RJJ, Hoebers FJP, Kolenaar B, Kropveld A, Langeveld TPM, Verschuur HP, de Visscher JGAM, van Weert S, Witjes MJH, Smeele LE, Merkx MAW, Hermens RPMG

Background: Monitoring and effectively improving oncologic integrated care requires dashboard information based on quality registrations. The dashboard includes evidence-based quality indicators (QIs) that measure quality of care. This study aimed to assess the quality of current integrated head and neck cancer care with QIs, the variation between Dutch hospitals, and the influence of patient and hospital characteristics.
Methods: Previously, 39 QIs were developed with input from medical specialists, allied health professionals, and patients' perspectives. QI scores were calculated with data from 1,667 curatively treated patients in 8 hospitals. QIs with a sample size of >400 patients were included to calculate reliable QI scores. We used multilevel analysis to explain the variation.
Results: Current care varied from 29% for the QI about a case manager being present to discuss the treatment plan to 100% for the QI about the availability of a treatment plan. Variation between hospitals was small for the QI about patients discussed in multidisciplinary team meetings (adherence: 95%, range 88%-98%), but large for the QI about malnutrition screening (adherence: 50%, range 2%-100%). Higher QI scores were associated with lower performance status, advanced tumor stage, and tumor in the oral cavity or oropharynx at the patient level, and with more curatively treated patients (volume) at hospital level.
Conclusions: Although the quality registration was only recently launched, it already visualizes hospital variation in current care. Four determinants were found to be influential: tumor stage, performance status, tumor site, and volume. More data are needed to assure stable results for use in quality improvement.

Gepubliceerd: J Natl Compr Canc Netw 2018 Dec;16(12):1491-8
Impact factor: 6.471; Q1

Totale impact factor: 6.471
Gemiddelde impact factor: 6.471

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

Neurochirurgie

1. Skin Augmentation as a Last-Resort Operative Technique During Decompressive Craniectomy
Goedemans T, van der Veer O, Verbaan D, Bot M, Lequin MB, Coert BA, van Furth WR, Bouma GJ, Vandertop WP, Buis DR, van den Munckhof P

Objective: Since 2009, we have performed skin augmentation using a Gore-Tex patch as a last-resort measure to reduce intracranial pressure (ICP) in uncontrollable brain swelling during decompressive craniectomy (DC). Here, we report our experience and outcome in a consecutive series of patients undergoing DC with skin augmentation (DC+S).
Methods: In 2009-2015, a prospective database was created registering all patients who underwent DC+S when ICP increased >25 mm Hg while approximating the skin edges after DC (or when closing the skin was impossible because of uncontrollable brain swelling in patients without an ICP monitoring catheter). Patients' baseline characteristics and 1-year outcome were compared with patients undergoing DC without the need of skin augmentation in the same time frame. Outcome according to the Glasgow Outcome Scale (GOS) was dichotomized into favorable (GOS score 4-5) and unfavorable (GOS 1-3).
Results: Of a total of 180 consecutive patients with DC, 20 (11%) underwent DC+S. Four (20%) survived favorably, 2 (10%) unfavorably, and 14 (70%) died (compared with 36%, 22%, and 42%, respectively, in patients with standard DC). Four of 7 patients in whom DC+S was performed >/=24 hours after injury or at second surgery survived favorably, versus none of the 13 patients in whom DC+S was performed <24 hours after injury and at first surgery. Two of 10 patients surviving the first week after DC+S had a skinplasty-related infection.
Conclusions: Decompressive craniectomy with skin augmentation may be used as a last-resort measure in cases of severe brain swelling despite DC.

Gepubliceerd: World Neurosurg 2018 Nov;119:e417-e428
Impact factor: 1.924; Q2

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2. Pathophysiology and Nonsurgical Treatment of Chronic Subdural Hematoma: From Past to Present to Future
Holl DC, Volovici V, Dirven CMF, Peul WC, van Kooten F, Jellema K, van der Gaag NA, Miah IP, Kho KH, den Hertog HM, Lingsma HF, Dammers R

Background: Chronic subdural hematoma (CSDH) is one of the more frequent pathologic entities in daily neurosurgical practice. Historically, CSDH was considered progressive recurrent bleeding with a traumatic cause. However, recent evidence has suggested a complex intertwined pathway of inflammation, angiogenesis, local coagulopathy, recurrent microbleeds, and exudates. The aim of the present review is to collect existing data on pathophysiology of CSDH to direct further research questions aiming to optimize treatment for the individual patient.
Methods: We performed a thorough literature search in PubMed, Ovid, EMBASE, CINAHL, and Google scholar, focusing on any aspect of the pathophysiology and nonsurgical treatment of CSDH.

Results: After a (minor) traumatic event, the dural border cell layer tears, which leads to the extravasation of cerebrospinal fluid and blood in the subdural space. A cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis is set in motion. The most commonly used treatment is surgical drainage. However, because of the pathophysiologic mechanisms, the mortality and high morbidity associated with surgical drainage, drug therapy (dexamethasone, atorvastatin, tranexamic acid, or angiotensin-converting enzyme inhibitors) might be a beneficial alternative in many patients with CSDH.
Conclusions: Based on pathophysiologic mechanisms, animal experiments, and small patient studies, medical treatment may play a role in the treatment of CSDH. There is a lack of level I evidence in the nonsurgical treatment of CSDH. Therefore, randomized controlled trials, currently lacking, are needed to assess which treatment is most effective in each individual patient.

Gepubliceerd: World Neurosurg 2018 Aug;116:402-11
Impact factor: 1.924; Q2

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3. Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial
Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, Koot RW, Volovici V, Dirven CMF, van Kooten F, Kho KH, den Hertog HM, van der Naalt J, Jacobs B, Groen RJM, Lingsma HF, Dammers R, Jellema K, van der Gaag NA

Background: Chronic subdural haematoma (CSDH) is a common neurological disease with a rapidly rising incidence due to increasing age and widespread use of anticoagulants. Surgical intervention by burr-hole craniotomy (BHC) is the current standard practice for symptomatic patients, but associated with complications, a recurrence rate of up to 30% and increased mortality. Dexamethasone (DXM) therapy is, therefore, used as a non-surgical alternative but considered to achieve a lower success rate. Furthermore, the benefit of DXM therapy appears much more deliberate than the immediate relief from BHC. Lack of evidence and clinical equipoise among caregivers prompts the need for a head-to-head randomised controlled trial. The objective of this study is to compare the effect of primary DXM therapy versus primary BHC on functional outcome and cost-effectiveness in symptomatic patients with CSDH.
Methods/design: This study is a prospective, multicentre, randomised controlled trial (RCT). Consecutive patients with a CSDH with a Markwalder Grading Scale (MGS) grade 1 to 3 will be randomised to treatment with DXM or BHC. The DXM treatment scheme will be 16 mg DXM per day (8 mg twice daily, days 1 to 4) which is then halved every 3 days until a dosage of 0.5 mg a day on day 19 and stopped on day 20. If the treatment response is insufficient (i.e. persistent or progressive symptomatology due to insufficient haematoma resolution), additional surgery can be performed. The primary outcomes are the functional outcome by means of the modified Rankin Scale (mRS) score at 3 months and cost-effectiveness at 12 months. Secondary outcomes are quality of life at 3 and 12 months using the Short Form Health Survey (SF-36) and Quality of Life after Brain Injury Overall Scale (QOLIBRI), haematoma thickness after 2 weeks on follow-up computed tomography (CT), haematoma recurrence during the first 12 months, complications and drug-related adverse events, failure of therapy within 12 months after randomisation and requiring intervention, mortality during the

first 3 and 12 months, duration of hospital stay and overall healthcare and productivity costs. To test non-inferiority of DXM therapy compared to BHC, 210 patients in each treatment arm are required (assumed adjusted common odds ratio DXM compared to BHC 1.15, limit for inferiority < 0.9). The aim is to include a total of 420 patients in 3 years with an enrolment rate of 60%. Discussion: The present study should demonstrate whether treatment with DXM is as effective as BHC on functional outcome, at lower costs.
Trial registration: EUCTR 2015-001563-39 . Date of registration: 29 March 2015.

Gepubliceerd: Trials 2018 Oct 20;19(1):575
Impact factor: 2.067; Q3

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4. Vascular risk factors in older patients with depression: outcome of electroconvulsive therapy versus medication
Spaans HP, Kok RM, Bouckaert F, Van Den Berg JF, Tunney OC, Sienaert P, Verwijk E, Kho KH, Stek ML

Objective: Research suggests that in depression, vascular burden predicts a lower efficacy for medication (MED) and a more favourable outcome for electroconvulsive therapy (ECT). Therefore, we investigated the influence of the following vascular risk factors (VRF): hypercholesterolemia, hypertension, smoking, diabetes mellitus, cardiovascular disease, and cerebral vascular accident/transient ischemic attack, on remission from major depression after ECT versus MED.
Methods: The study sample consisted of 81 inpatients with a DSM-IV unipolar major depression diagnosis (mean age 72.2 years, SD = 7.6, mean Montgomery-Asberg Depression Rating Scale score 32.9, SD = 6.2) participating in a randomized controlled trial comparing nortriptyline versus venlafaxine and 43 inpatients (mean age 73.7 years, SD = 7.5, mean Montgomery-Asberg Depression Rating Scale score 30.6, SD = 7.1) from an randomized controlled trial comparing brief pulse versus ultrabrief pulse ECT. The presence of VRF was established from the medical records. The remission rate of patients with VRF was compared with those of patients without VRF.
Results: The remission rate was 58% (19/33) in the ECT group with >/=1 VRF and 32% (23/73) in the MED group with >/=1 VRF (chi2 = 6.456, p = 0.011). Comparing patients with no VRF versus >/=1 VRF, the remission rate decreased from 80 to 58% (chi2 = 1.652, p = 0.276) in ECT patients and from 38 to 32% (chi2 = 0.119, p = 0.707) in MED patients. Applying different cut-offs for the number of VRFs yielded the same trends. Logistic regression revealed no interaction between VRF and treatment condition. **Conclusion:** The superior efficacy of ECT over pharmacotherapy in major depression in older age was independent of the presence of VRF. Copyright (c) 2017 John Wiley & Sons, Ltd.

Gepubliceerd: Int J Geriatr Psychiatry 2018;33(2):371-8
Impact factor: 2.940; Q2

Totale impact factor: 8.855
Gemiddelde impact factor: 2.214

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.924
Gemiddelde impact factor: 1.924

Neurologie

1. Early Predictors for Long-Term Functional Outcome After Mild Traumatic Brain Injury in Frail Elderly Patients
Abdulle AE, de Koning ME, van der Horn HJ, Scheenen ME, Roks G, Hageman G, Spikman JM, van der Naalt J

Objective: To identify the effect of frailty and early postinjury measures on the long-term outcome after mild traumatic brain injury in elderly patients.
Setting: Patients admitted to 3 Dutch hospitals designated as level 1 trauma centers.
Participants: The elderly (>/=60 years) with mild traumatic brain injury (N = 161).
Design: A prospective observational cohort study.
Main measures: Posttraumatic complaints and the Hospital Anxiety and Depression Scale determined 2 weeks postinjury; the Glasgow Outcome Scale Extended and Groningen frailty indicator determined 1 to 3 years postinjury.
Results: A total of 102 nonfrail (63%) and 59 frail elderly (37%) patients, mean age of 70.8 (6.3) years were included. Most patients (54%; 72% nonfrail and 24% frail) recovered completely 1 to 3 years postinjury. Two weeks postinjury, 81% had posttraumatic complaints (83% frail and 80% nonfrail elderly), and 30% showed emotional distress (50% frail and 20% nonfrail). Frailty (odds ratio, 2.1; 95% confidence interval, 1.59-2.77) and presence of early complaints (odds ratio, 1.13; 95% confidence interval, 1.01-1.27) (Nagelkerke R = 46%) were found to predict long-term outcome, whereas age was not a significant predictor.
Conclusion: The frail elderly had worse long-term outcome, and early complaints were found to be a stronger predictor of unfavorable outcome than age. Understanding the implications of frailty on outcome could help clinicians recognize patients at risk of a poor outcome and allocate care more efficiently.

Gepubliceerd: J Head Trauma Rehabil 2018 Nov;33(6):E59-E67
Impact factor: 3.406; Q1

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2. Detection of small traumatic hemorrhages using a computer-generated average human brain CT
Afzali-Hashemi L, Hazewinkel M, Tjepkema-Cloostermans MC, van Putten MJAM, Slump CH

Computed tomography is a standard diagnostic imaging technique for patients with traumatic brain injury (TBI). A limitation is the poor-to-moderate sensitivity for small traumatic hemorrhages. A pilot study using an automatic method to detect hemorrhages [Formula: see text] in diameter in patients with TBI is presented. We have created an average image from 30 normal noncontrast CT scans that were automatically aligned using deformable image registration as implemented in Elastix software. Subsequently, the average image was aligned to the scans of TBI patients, and the hemorrhages were detected by a voxelwise subtraction of the average image from the CT scans of nine TBI patients. An experienced neuroradiologist and a radiologist in training assessed the presence of hemorrhages in the final images and determined the false positives and false negatives. The 9 CT scans contained 67 small haemorrhages, of which 97% was correctly detected by our system. The

neuroradiologist detected three false positives, and the radiologist in training found two false positives. For one patient, our method showed a hemorrhagic contusion that was originally missed. Comparing individual CT scans with a computed average may assist the physicians in detecting small traumatic hemorrhages in patients with TBI.

Gepubliceerd: J Med Imaging (Bellingham) 2018 Apr;5(2):024004
Impact factor: 0; nvt

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3. Long-interval intracortical inhibition as biomarker for epilepsy: a transcranial magnetic stimulation study
Bauer PR, de Goede AA, Stern WM, Pawley AD, Chowdhury FA, Helling RM, Bouet R, Kalitzin SN, Visser GH, Sisodiya SM, Rothwell JC, Richardson MP, van Putten MJAM, Sander JW

Cortical excitability, as measured by transcranial magnetic stimulation combined with electromyography, is a potential biomarker for the diagnosis and follow-up of epilepsy. We report on long-interval intracortical inhibition data measured in four different centres in healthy controls (n = 95), subjects with refractory genetic generalized epilepsy (n = 40) and with refractory focal epilepsy (n = 69). Long-interval intracortical inhibition was measured by applying two supra-threshold stimuli with an interstimulus interval of 50, 100, 150, 200 and 250 ms and calculating the ratio between the response to the second (test stimulus) and to the first (conditioning stimulus). In all subjects, the median response ratio showed inhibition at all interstimulus intervals. Using a mixed linear-effects model, we compared the long-interval intracortical inhibition response ratios between the different subject types. We conducted two analyses; one including data from the four centres and one excluding data from Centre 2, as the methods in this centre differed from the others. In the first analysis, we found no differences in long-interval intracortical inhibition between the different subject types. In all subjects, the response ratios at interstimulus intervals 100 and 150 ms showed significantly more inhibition than the response ratios at 50, 200 and 250 ms. Our second analysis showed a significant interaction between interstimulus interval and subject type (P = 0.0003). Post hoc testing showed significant differences between controls and refractory focal epilepsy at interstimulus intervals of 100 ms (P = 0.02) and 200 ms (P = 0.04). There were no significant differences between controls and refractory generalized epilepsy groups or between the refractory generalized and focal epilepsy groups. Our results do not support the body of previous work that suggests that long-interval intracortical inhibition is significantly reduced in refractory focal and genetic generalized epilepsy. Results from the second analysis are even in sharper contrast with previous work, showing inhibition in refractory focal epilepsy at 200 ms instead of facilitation previously reported. Methodological differences, especially shorter intervals between the pulse pairs, may have contributed to our inability to reproduce previous findings. Based on our results, we suggest that long-interval intracortical inhibition as measured by transcranial magnetic stimulation and electromyography is unlikely to have clinical use as a biomarker of epilepsy.

Gepubliceerd: Brain 2018 Feb 1;141(2):409-21
Impact factor: 10.848; Q1

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4. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury
Booij HA, Gaykema WDC, Kuijpers KAJ, Pouwels MJM, den Hertog HM

Background: Poststroke fatigue (PSF) is a highly prevalent and debilitating condition. However, the etiology remains incompletely understood. Literature suggests the co-prevalence of pituitary dysfunction (PD) with stroke, and the question raises whether this could be a contributing factor to the development of PSF. This study reviews the prevalence of PD after stroke and other acquired brain injuries and its association with fatigue.
Summary: We performed a bibliographic literature search of MEDLINE and EMBASE databases for English language studies on PD in adult patients with stroke, traumatic brain injury (TBI) or aneurysmatic subarachnoid hemorrhage (aSAH). Forty-two articles were selected for review. Up to 82% of patients were found to have any degree of PD after stroke. Growth hormone deficiency was most commonly found. In aSAH and TBI, prevalences up to 49.3% were reported. However, data differed widely between studies, mostly due to methodological differences including the diagnostic methods used to define PD and the focus on the acute or chronic phase. Data on PD and outcome after stroke, aSAH and TBI are conflicting. No studies were found investigating the association between PD and PSF. Data on the association between PD and fatigue after aSAH and TBI were scarce and conflicting, and fatigue is rarely been investigated as a primary end point.
Key messages: Data according to the prevalence of PD after stroke and other acquired brain injury suggest a high prevalence of PD after these conditions. However, the clinical relevance and especially the association with fatigue need to be established.

Gepubliceerd: Endocr Connect 2018 Jun;7(6):R223-R237
Impact factor: 3.041; Q3

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5. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis
de Bruijn MAAM, Aarsen FK, van Oosterhout MP, van der Knoop MM, Catsman-Berrevoets CE, Schreurs MWJ, Bastiaansen DEM, Sillevis Smitt PAE, Neuteboom RF, Titulaer MJ, CHANCE Study Group includes Portier RP

Objective: To provide detailed long-term outcome data of children and adolescents following pediatric anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis, to identify neuropsychological impairments, and to evaluate the influence of these factors on quality of life (QoL).
Methods: All Dutch children diagnosed with anti-NMDAR encephalitis were identified. Patients currently aged 4 years or older were included in the follow-up study, consisting of a visit to our clinic for a detailed interview and a standardized neuropsychological assessment. The following domains were included: attention, memory, language, executive functioning, QoL, and fatigue. Primary outcome measures were z scores on sustained attention, long-term verbal memory, QoL, fatigue, and working memory.

Results: Twenty-eight patients were included. Median Pediatric Cerebral Performance Category at last visit was 1 (interquartile range 1-2, range 1-4), and 64% (18/28) of patients returned consistently to their previous school level. Twenty-two patients were included in the cross-sectional part of the long-term follow-up study. Median follow-up time was 31 months (interquartile range 15-49, range 5-91). There were problems with sustained attention ($z = -2.10$, 95% confidence interval = -2.71 to -1.46, $p < 0.0001$) and fatigue ($z = -0.96$, 95% confidence interval = -1.64 to -0.28, $p = 0.008$). Cognitive deficits were not correlated with QoL, while fatigue was strongly correlated with QoL ($r = 0.82$, $p < 0.0001$).
Conclusions: Although follow-up is often reported as "good" following pediatric anti-NMDAR encephalitis, many patients have cognitive problems and fatigue, even up until adolescence, resulting in academic achievement problems and lower QoL. For physicians, it is essential to be aware of these problems, to provide valuable advice to patients and caregivers in the acute and follow-up phase, and to consider early neuropsychological counseling.

Gepubliceerd: Neurology 2018 May 29;90(22):e1997-e2005
Impact factor: 8.055; Q1

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6. Accurate Coil Positioning is Important for Single and Paired Pulse TMS on the Subject Level
de Goede AA, Ter Braack EM, van Putten MJAM

Function-guided navigation is commonly used when assessing cortical excitability using transcranial magnetic stimulation (TMS). However, the required accuracy, stability and the effect of a change in coil positioning are not entirely known. This study investigates the accuracy of function-guided navigation for determining the hotspot. Furthermore, it evaluates the effect of a change in coil location on the single and paired pulse excitability measures: motor evoked potential (MEP) amplitude, TMS evoked potential (TEP) and long intracortical inhibition (LICI), and of a change in coil orientation on LICI. Eight healthy subjects participated in the single pulse study, and ten in the paired pulse study. A robot-guided navigation system was used to ensure accurate and stable coil positioning at the motor hotspot as determined using function-guided navigation. In addition, we targeted four locations at 2 mm and four at 5 mm distance around the initially defined hotspot, and we increased and decreased the coil orientation by 10 degrees . In none of the subjects, the largest MEP amplitudes were evoked at the originally determined hotspot, resulting in a poor accuracy of function-guided navigation. At the group level, a change in coil location had no significant effect on the MEP amplitude, TEP, or LICI, and a change in coil orientation did not significantly affected LICI. However, at the subject level significant effects on MEP amplitude, TEP, and LICI were found for changes in coil location or orientation, although absolute differences were relatively small and did not show a consistent pattern. This study indicates that a high accuracy in coil positioning is especially required to measure cortical excitability reliably in individual subjects using single or paired pulse TMS.

Gepubliceerd: Brain Topogr 2018 Nov;31(6):917-30
Impact factor: 2.703; Q2

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7. Incidence and outcome of acquired demyelinating syndromes in Dutch children: update of a nationwide and prospective study
de Mol CL, Wong YYM, van Pelt ED, Ketelslegers IA, Bakker DP, Boon M, Braun KPJ, van Dijk KGJ, Eikelenboom MJ, Engelen M, Geleijns K, Haaxma CA, Niermeijer JMF, Niks EH, Peeters EAJ, Peeters-Scholte CMPC, Poll-The BT, Portier RP, de Rijk-van Andel JF, Samijn JPA, Schippers HM, Snoeck IN, Stroink H, Vermeulen RJ, Verrips A, Visscher F, Vles JSH, Willemsen MAAP, Catsman-Berrevoets CE, Hintzen RQ, Neuteboom RF

Introduction: Acquired demyelinating syndromes (ADS) are immune-mediated demyelinating disorders of the central nervous system in children. A nationwide, multicentre and prospective cohort study was initiated in the Netherlands in 2006, with a reported ADS incidence of 0.66/100,000 per year and MS incidence of 0.15/100,000 per year in the period between 2007 and 2010. In this study, we provide an update on the incidence and the long-term follow-up of ADS in the Netherlands.
Methods: Children < 18 years with a first attack of demyelination were included consecutively from January 2006 to December 2016. Diagnoses were based on the International Paediatric MS study group consensus criteria. Outcome data were collected by neurological and neuropsychological assessments, and telephone call assessments.
Results: Between 2011 and 2016, 55/165 of the ADS patients were diagnosed with MS (33%). This resulted in an increased ADS and MS incidence of 0.80/100,000 per year and 0.26/100,000 per year, respectively. Since 2006 a total of 243 ADS patients have been included. During follow-up (median 55 months, IQR 28-84), 137 patients were diagnosed with monophasic disease (56%), 89 with MS (37%) and 17 with multiphasic disease other than MS (7%). At least one form of residual deficit including cognitive impairment was observed in 69% of all ADS patients, even in monophasic ADS. An Expanded Disability Status Scale score of >/= 5.5 was reached in 3/89 MS patients (3%).
Conclusion: The reported incidence of ADS in Dutch children has increased since 2010. Residual deficits are common in this group, even in monophasic patients. Therefore, long-term follow-up in ADS patients is warranted.

Gepubliceerd: J Neurol 2018 Jun;265(6):1310-9
Impact factor: 3.783; Q1

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8. Development and validation of the Dutch Stroke Score for predicting disability and functional outcome after ischemic stroke: A tool to support efficient discharge planning
de Ridder IR, Dijkland SA, Scheele M, den Hertog HM, Dirks M, Westendorp WF, Nederkoorn PJ, van de Beek D, Ribbers GM, Steyerberg EW, Lingsma HF, Dippel DW

Introduction: We aimed to develop and validate a prognostic score for disability at discharge and functional outcome at three months in patients with acute ischemic stroke based on clinical information available on admission. Patients and
Methods: The Dutch Stroke Score (DSS) was developed in 1227 patients with ischemic stroke included in the Paracetamol (Acetaminophen) In Stroke study.

Predictors for Barthel Index (BI) at discharge ('DSS-discharge') and modified Rankin Scale (mRS) at three months ('DSS-3 months') were identified in multivariable ordinal regression. The models were internally validated with bootstrapping techniques. The DSS-3 months was externally validated in the PRomoting ACute Thrombolysis in Ischemic StrokE study (1589 patients) and the Preventive Antibiotics in Stroke Study (2107 patients). Model performance was assessed in terms of discrimination, expressed by the area under the receiver operating characteristic curve (AUC), and calibration.
Results: At model development, the strongest predictors of Barthel Index at discharge were age per decade over 60 (odds ratio = 1.55, 95% confidence interval (CI) 1.41-1.68), National Institutes of Health Stroke Scale (odds ratio = 1.24 per point, 95% CI 1.22-1.26) and diabetes (odds ratio = 1.62, 95% CI 1.32-1.91). The internally validated AUC was 0.76 (95% CI 0.75-0.79). The DSS-3 months, additionally consisting of previous stroke and atrial fibrillation, performed similarly at internal (AUC 0.75, 95% CI 0.74-0.77) and external validation (AUC 0.74 in PRomoting ACute Thrombolysis in Ischemic StrokE (95% CI 0.72-0.76) and 0.69 in Preventive Antibiotics in Stroke Study (95% CI 0.69-0.72)). Observed outcome was slightly better than predicted.
Discussion: The DSS had satisfactory performance in predicting BI at discharge and mRS at three months in ischemic stroke patients. Conclusion: If further validated, the DSS may contribute to efficient stroke unit discharge planning alongside patients' contextual factors and therapeutic needs.

Gepubliceerd: Eur Stroke J 2018 Jun;3(2):165-73
Impact factor: 0; nvt

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9. A woman with spontaneous neck pain
Geerdes M, Smook SP, von Schukkmann TA

A 42-year-old woman presented with neck pain without previous trauma. On suspicion of spondylodiscitis, an MRI of the cervical spine was made. This MRI and an additional CT showed calcific tendinitis of the longus colli muscle, a self-limiting disorder.

Gepubliceerd: Ned Tijdschr Geneeskd 2018;162:D2042
Impact factor: 0; nvt

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10. Detecting Cortical Spreading Depolarization with Full Band Scalp Electroencephalography: An Illusion?
Hofmeijer J, van Kaam CR, van de Werff B, Vermeer SE, Tjepkema-Cloostermans MC, van Putten MJAM

Introduction: There is strong evidence suggesting detrimental effects of cortical spreading depolarization (CSD) in patients with acute ischemic stroke and severe traumatic brain injury. Previous studies implicated scalp electroencephalography (EEG) features to be correlates of CSD based on retrospective analysis of EEG epochs after having detected "CSD" in time aligned electrocorticography. We studied the feasibility of CSD detection in a prospective cohort study with continuous EEG in

18 patients with acute ischemic stroke and 18 with acute severe traumatic brain injury.
Methods: Full band EEG with 21 silver/silver chloride electrodes was started within 48 h since symptom onset. Five additional electrodes were used above the infarct. We visually analyzed all raw EEG data in epochs of 1 h. Inspection was directed at detection of the typical combination of CSD characteristics, i.e., (i) a large slow potential change (SPC) accompanied by a simultaneous amplitude depression of >1Hz activity, (ii) focal presentation, and (iii) spread reflected as appearance on neighboring electrodes with a delay.
Results: In 3,035 one-hour EEG epochs, infraslow activity (ISA) was present in half to three quarters of the registration time. Typically, activity was intermittent with amplitudes of 40-220 microV, approximately half was oscillatory. There was no specific spatial distribution. Relevant changes of ISA were always visible in multiple electrodes, and not focal, as expected in CSD. ISA appearing as "SPC" was mostly associated with an amplitude increase of faster activities, and never with suppression. In all patients, depressions of spontaneous brain activity occurred. However, these were not accompanied by simultaneous SPC, occurred simultaneously on all channels, and were not focal, let alone spread, as expected in CSD.
Conclusion: With full band scalp EEG in patients with cortical ischemic stroke or traumatic brain injury, we observed various ISA, probably modulating cortical excitability. However, we were unable to identify unambiguous characteristics of CSD.

Gepubliceerd: Front Neurol 2018;9:17
Impact factor: 3.508; Q2

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11. Pathophysiology and Nonsurgical Treatment of Chronic Subdural Hematoma: From Past to Present to Future
Holl DC, Volovici V, Dirven CMF, Peul WC, van Kooten F, Jellema K, van der Gaag NA, Miah IP, Kho KH, den Hertog HM, Lingsma HF, Dammers R

Background: Chronic subdural hematoma (CSDH) is one of the more frequent pathologic entities in daily neurosurgical practice. Historically, CSDH was considered progressive recurrent bleeding with a traumatic cause. However, recent evidence has suggested a complex intertwined pathway of inflammation, angiogenesis, local coagulopathy, recurrent microbleeds, and exudates. The aim of the present review is to collect existing data on pathophysiology of CSDH to direct further research questions aiming to optimize treatment for the individual patient.
Methods: We performed a thorough literature search in PubMed, Ovid, EMBASE, CINAHL, and Google scholar, focusing on any aspect of the pathophysiology and nonsurgical treatment of CSDH.
Results: After a (minor) traumatic event, the dural border cell layer tears, which leads to the extravasation of cerebrospinal fluid and blood in the subdural space. A cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis is set in motion. The most commonly used treatment is surgical drainage. However, because of the pathophysiologic mechanisms, the mortality and high morbidity associated with surgical drainage, drug therapy (dexamethasone, atorvastatin, tranexamic acid, or angiotensin-converting enzyme inhibitors) might be a beneficial alternative in many patients with CSDH.

Conclusions: Based on pathophysiologic mechanisms, animal experiments, and small patient studies, medical treatment may play a role in the treatment of CSDH. There is a lack of level I evidence in the nonsurgical treatment of CSDH. Therefore, randomized controlled trials, currently lacking, are needed to assess which treatment is most effective in each individual patient.

Gepubliceerd: World Neurosurg 2018 Aug;116:402-11
Impact factor: 1.924; Q2

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12. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry)
Jansen IGH, Mulder MJHL, Goldhoorn RB, MR CLEAN Registry Investigators includes den Hertog HM en Sturm EJC

Objective: To determine outcomes and safety of endovascular treatment for acute ischaemic stroke, due to proximal intracranial vessel occlusion in the anterior circulation, in routine clinical practice.
Design: Ongoing, prospective, observational cohort study.
Setting: 16 centres that perform endovascular treatment in the Netherlands.
Participants: 1488 patients included in the Multicentre Randomised Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) Registry who had received endovascular treatment, including stent retriever thrombectomy, aspiration, and all alternative methods for acute ischaemic stroke within 6.5 hours from onset of symptoms between March 2014 and June 2016.
Main outcome measures: The primary outcome was the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death) at 90 days after the onset of symptoms. Secondary outcomes were excellent functional outcome (mRS score 0-1), good functional outcome (mRS score 0-2), and favourable functional outcome (mRS score 0-3) at 90 days; score on the extended thrombolysis in cerebral infarction scale at the end of the intervention procedure; National Institutes of Health Stroke Scale score 24-48 hours after intervention; and complications that occurred during intervention, hospital admission, or three months' follow up period. Outcomes and safety variables in the MR CLEAN Registry were compared with the MR CLEAN trial intervention and control arms.
Results: A statistically significant shift was observed towards better functional outcome in patients in the MR CLEAN Registry compared with the MR CLEAN trial intervention arm (adjusted common odds ratio 1.30, 95% confidence interval 1.02 to 1.67) and the MR CLEAN trial control arm (1.85, 1.46 to 2.34). The reperfusion rate, with successful reperfusion defined as a score of 2B-3 on the extended thrombolysis in cerebral infarction score, was 58.7%, the same as for patients in the MR CLEAN trial. Duration from onset of stroke to start of endovascular treatment and from onset of stroke to successful reperfusion or last contrast bolus was one hour shorter for patients in the MR CLEAN Registry. Symptomatic intracranial haemorrhage occurred in 5.8% of patients in the MR CLEAN Registry compared with 7.7% in the MR CLEAN trial intervention arm and 6.4% in the MR CLEAN trial control arm.
Conclusion: In routine clinical practice, endovascular treatment for patients with acute ischaemic stroke is at least as effective and safe as in the setting of a randomised controlled trial.

Gepubliceerd: BMJ 2018 Mar 9;360:k949
Impact factor: 23.562; Q1

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13. Prediabetes and macrovascular disease: Review of the association, influence on outcome and effect of treatment
Kleinherenbrink W, Osei E, den Hertog HM, Zandbergen AAM

Gepubliceerd: Eur J Intern Med 2018 Sep;55:6-11
Impact factor: 3.282; Q1

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14. A Reduction in Time with Electronic Monitoring In Stroke (ARTEMIS): study protocol for a randomised multicentre trial
Koster GT, Nguyen TTM, Groot AED, Coutinho JM, Bosch J, den Hertog HM, van Walderveen MAA, Algra A, Wermer MJH, Roos YB, Kruyt ND

Introduction: Time is the most crucial factor limiting efficacy of intravenous thrombolysis (IVT) and intra-arterial thrombectomy (IAT). The delay between alarming the Emergency Medical Services (EMS) dispatch office and IVT/IAT initiation, that is, the 'total system delay' (TSD), depends on logistics and team effort. A promising method to reduce TSD is real-time audio-visual feedback to caregivers involved. With 'A Reduction in Time with Electronic Monitoring in Stroke' (ARTEMIS), we aim to investigate the effect of real-time audio-visual feedback on actual TSD to IVT/IAT to caregivers.
Methods and analysis: ARTEMIS is a multiregional, multicentre, randomised open end-point trial including patients >/=18 years considered IVT/IAT-eligible by the EMS dispatch office or on-site EMS personnel. Patients are electronically tracked and randomised for real-time audio-visual feedback on TSD to caregivers via premounted handhelds and tablets throughout the TSD trajectory. Primary outcome is TSD to IVT/IAT. Secondary outcomes comprise proportion of IVT/IAT-treated patients, symptomatic intracerebral haemorrhage, IVT/IAT-treated stroke mimics, clinical outcome after three months and cost-effectiveness. Separate analyses for IAT-patients with or without prior IVT, within or out of office hours and EMS region will be performed. With 75 IAT-patients and 225 IVT-patients in each arm, we will be able to demonstrate a 20 min difference in TSD to IAT and a 10 min difference in TSD to IVT (p=0.05 and power=0.8).
Ethics and dissemination: Study findings will be disseminated through peer-reviewed journals and (inter)national conference presentations.
Trial registration number: NCT02808806; Pre-results.

Gepubliceerd: BMJ Open 2018 Jun 27;8(6):e020844
Impact factor: 2.413; Q2

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15. Evolution of Excitation-Inhibition Ratio in Cortical Cultures Exposed to Hypoxia
le Feber J, Dummer A, Hassink GC, van Putten MJAM, Hofmeijer J

In the core of a brain infarct, neuronal death occurs within minutes after loss of perfusion. In the penumbra, a surrounding area with some residual perfusion, neurons initially remain structurally intact, but hypoxia-induced synaptic failure impedes neuronal activity. Penumbral activity may recover or further deteriorate, reflecting cell death. Mechanisms leading to either outcome remain ill-understood, but may involve changes in the excitation to inhibition (E/I) ratio. The E/I ratio is determined by structural (relative densities of excitatory and inhibitory synapses) and functional factors (synaptic strengths). Clinical studies demonstrated excitability alterations in regions surrounding the infarct core. These may be related to structural E/I changes, but the effects of hypoxia /ischemia on structural connectivity have not yet been investigated, and the role of structural connectivity changes in excitability alterations remains unclear. We investigated the evolution of the structural E/I ratio and associated network excitability in cortical cultures exposed to severe hypoxia of varying duration. 6-12 h of hypoxia reduced the total synaptic density. In particular, the inhibitory synaptic density dropped significantly, resulting in an elevated E/I ratio. Initially, this does not lead to increased excitability due to hypoxia-induced synaptic failure. Increased excitability becomes apparent upon reoxygenation after 6 or 12 h, but not after 24 h. After 24 h of hypoxia, structural patterns of vesicular glutamate stainings change. This possibly reflects disassembly of excitatory synapses, and may account for the irreversible reduction of activity and stimulus responses seen after 24 h.

Gepubliceerd: Front Cell Neurosci 2018;12:183
Impact factor: 4.300; Q1

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16. Reader response: Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion
LeCouffe NE, Treurniet KM, Majoie CBLM, Roos YBWE, Coutinho JM, MR CLEAN-NO IV Investigators includes Brouwers PJAM

Gepubliceerd: Neurology 2018 Dec 11;91(24):1115
Impact factor: 8.055; Q1

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17. Reduced Cancer Incidence in Huntington's Disease: Analysis in the Registry Study
McNulty P, Pilcher R, Ramesh R, Necuiniate R, Hughes A, Farewell D, Holmans P, Jones L, REGISTRY Investigators of the European Huntington's Disease Network icludes van Hout MSE, van Vugt JPP

Background: People with Huntington's disease (HD) have been observed to have lower rates of cancers.
Objective: To investigate the relationship between age of onset of HD, CAG repeat length, and cancer diagnosis.
Methods: Data were obtained from the European Huntington's disease network REGISTRY study for 6540 subjects. Population cancer incidence was ascertained from the GLOBOCAN database to obtain standardised incidence ratios of cancers in the REGISTRY subjects.

Results: 173/6528 HD REGISTRY subjects had had a cancer diagnosis. The age-standardised incidence rate of all cancers in the REGISTRY HD population was 0.26 (CI 0.22-0.30). Individual cancers showed a lower age-standardised incidence rate compared with the control population with prostate and colorectal cancers showing the lowest rates. There was no effect of CAG length on the likelihood of cancer, but a cancer diagnosis within the last year was associated with a greatly increased rate of HD onset (Hazard Ratio 18.94, $p < 0.001$).
Conclusions: Cancer is less common than expected in the HD population, confirming previous reports. However, this does not appear to be related to CAG length in HTT. A recent diagnosis of cancer increases the risk of HD onset at any age, likely due to increased investigation following a cancer diagnosis.

Gepubliceerd: J Huntingtons Dis 2018;7(3):209-22
Impact factor: 0; nvt

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18. Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial
Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, Koot RW, Volovici V, Dirven CMF, van Kooten F, Kho KH, den Hertog HM, van der Naalt J, Jacobs B, Groen RJM, Lingsma HF, Dammers R, Jellema K, van der Gaag NA

Background: Chronic subdural haematoma (CSDH) is a common neurological disease with a rapidly rising incidence due to increasing age and widespread use of anticoagulants. Surgical intervention by burr-hole craniotomy (BHC) is the current standard practice for symptomatic patients, but associated with complications, a recurrence rate of up to 30% and increased mortality. Dexamethasone (DXM) therapy is, therefore, used as a non-surgical alternative but considered to achieve a lower success rate. Furthermore, the benefit of DXM therapy appears much more deliberate than the immediate relief from BHC. Lack of evidence and clinical equipoise among caregivers prompts the need for a head-to-head randomised controlled trial. The objective of this study is to compare the effect of primary DXM therapy versus primary BHC on functional outcome and cost-effectiveness in symptomatic patients with CSDH.
Methods/design: This study is a prospective, multicentre, randomised controlled trial (RCT). Consecutive patients with a CSDH with a Markwalder Grading Scale (MGS) grade 1 to 3 will be randomised to treatment with DXM or BHC. The DXM treatment scheme will be 16 mg DXM per day (8 mg twice daily, days 1 to 4) which is then halved every 3 days until a dosage of 0.5 mg a day on day 19 and stopped on day 20. If the treatment response is insufficient (i.e. persistent or progressive symptomatology due to insufficient haematoma resolution), additional surgery can be performed. The primary outcomes are the functional outcome by means of the modified Rankin Scale (mRS) score at 3 months and cost-effectiveness at 12 months. Secondary outcomes are quality of life at 3 and 12 months using the Short Form Health Survey (SF-36) and Quality of Life after Brain Injury Overall Scale (QOLIBRI), haematoma thickness after 2 weeks on follow-up computed tomography (CT), haematoma recurrence during the first 12 months, complications and drug-related adverse events, failure of therapy within 12 months after randomisation and requiring intervention, mortality during the first 3 and 12 months, duration of hospital stay and overall healthcare and productivity costs. To test non-inferiority of DXM therapy compared to BHC, 210 patients in each

treatment arm are required (assumed adjusted common odds ratio DXM compared to BHC 1.15, limit for inferiority < 0.9). The aim is to include a total of 420 patients in 3 years with an enrolment rate of 60%.
Discussion: The present study should demonstrate whether treatment with DXM is as effective as BHC on functional outcome, at lower costs.
Trial registration: EUCTR 2015-001563-39 . Date of registration: 29 March 2015.

Gepubliceerd: Trials 2018 Oct 20;19(1):575
Impact factor: 2.067; Q3

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19. The revised Cerebral Recovery Index improves predictions of neurological outcome after cardiac arrest
Nagaraj SB, Tjepkema-Cloostermans MC, Ruijter BJ, Hofmeijer J, van Putten MJAM

Objective: Analysis of the electroencephalogram (EEG) background pattern helps predicting neurological outcome of comatose patients after cardiac arrest (CA). Visual analysis may not extract all discriminative information. We present predictive values of the revised Cerebral Recovery Index (rCRI), based on continuous extraction and combination of a large set of evolving quantitative EEG (qEEG) features and machine learning techniques.
Methods: We included 551 subsequent patients from a prospective cohort study on continuous EEG after CA in two hospitals. Outcome at six months was classified as good (Cerebral Performance Category (CPC) 1-2) or poor (CPC 3-5). Forty-four qEEG features (from time, frequency and entropy domain) were selected by the least absolute shrinkage and selection operator (LASSO) method and used in a Random Forests classification system. We trained and evaluated the system with 10-fold cross validation. For poor outcome prediction, the sensitivity at 100% specificity (Se100) and the area under the receiver operator curve (AUC) were used as performance of the prediction model. For good outcome, we used the sensitivity at 95% specificity (Se95).
Results: Two hundred fifty-six (47%) patients had a good outcome. The rCRI predicted poor outcome with AUC=0.94 (95% CI: 0.83-0.91), Se100 = 0.66 (0.65-0.78), and AUC=0.88 (0.78-0.93), Se100 = 0.60 (0.51-0.75) at 12 and 24 h after CA, respectively. The rCRI predicted good outcome with Se95=0.72 (0.61-0.85) and 0.40 (0.30-0.51) at 12 and 24 h after CA, respectively.
Conclusions: Resu*lts obtained in this study suggest that with machine learning algorithms and large set of qEEG features, it is possible to efficiently monitor patient outcome after CA. We also demonstrate the importance of selection of optimal performance metric to train a classifier model for outcome prediction. Significance: The rCRI is a sensitive, reliable predictor of neurological outcome of comatose patients after CA.

Gepubliceerd: Clin Neurophysiol 2018 Oct 27;129(12):2557-66
Impact factor: 3.614; Q2

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20. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol

Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA

Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients.
Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal carers' QoL and cost-effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven, this could further promote the implementation of pharmaceutical care in a primary care setting.

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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21. Impaired fasting glucose is associated with unfavorable outcome in ischemic stroke patients treated with intravenous alteplase
Osei E, Fonville S, Zandbergen AAM, Koudstaal PJ, Dippel DWJ, den Hertog HM

Objectives: Hyperglycemia on admission and diabetes mellitus type II are associated with unfavorable outcome in stroke patients. We studied whether impaired fasting glucose (IFG) is associated with unfavorable outcome in ischemic stroke patients treated with intravenous alteplase as well and if IFG is a stronger prognostic factor than hyperglycemia on admission.
Methods: We studied 220 consecutive patients with ischemic stroke treated with intravenous alteplase. In all nondiabetic patients, fasting glucose was determined on day 2-5. IFG was defined as fasting glucose level of >/= 5.6 mmol/L, hyperglycemia on admission as glucose levels >/= 7.9 mmol/L. The primary effect measure was the adjusted common odds ratio (acOR) for a shift in the direction of worse outcome on the modified Rankin Scale at 3 months, estimated with ordinal logistic regression, and adjusted for common prognostic factors.
Results: The fasting glucose levels were available in 194 and admission glucose levels in 215 patients. Sixty-three (32.5%) had IFG, 58 (27%) hyperglycemia on admission and 32 (14.6%) pre-existent diabetes. Patients with IFG showed a shift

towards worse functional outcome compared with patients with normal fasting glucose levels (acOR 2.77; 95% CI 1.54-4.97), which was stronger than hyperglycemia on admission (acOR 1.75; 95% CI 0.91-3.4).
Conclusions: IFG is associated with unfavorable outcome after treatment with intravenous alteplase for acute ischemic stroke. IFG predicts unfavorable outcome better than hyperglycemia on admission.

Gepubliceerd: J Neurol 2018 Jun;265(6):1426-31
Impact factor: 3.783; Q1

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22. Potential genetic modifiers of disease risk and age at onset in patients with frontotemporal lobar degeneration and GRN mutations: a genome-wide association study

Pottier C, Zhou X, Perkerson RB, III, Baker M, Jenkins GD, Serie DJ, Ghidoni R, Benussi L, Binetti G, Lopez de MA, Zulaica M, Moreno F, Le Ber I, Pasquier F, Hannequin D, Sanchez-Valle R, Antonell A, Llado A, Parsons TM, Finch NA, Finger EC, Lippa CF, Huey ED, Neumann M, Heutink P, Synofzik M, Wilke C, Rissman RA, Slawek J, Sitek E, Johannsen P, Nielsen JE, Ren Y, van Blitterswijk M, DeJesus-Hernandez M, Christopher E, Murray ME, Bieniek KF, Evers BM, Ferrari C, Rollinson S, Richardson A, Scarpini E, Fumagalli GG, Padovani A, Hardy J, Momeni P, Ferrari R, Frangipane F, Maletta R, Anfossi M, Gallo M, Petrucelli L, Suh E, Lopez OL, Wong TH, van Rooij JGJ, Seelaar H, Mead S, Caselli RJ, Reiman EM, Noel Sabbagh M, Kjolby M, Nykjaer A, Karydas AM, Boxer AL, Grinberg LT, Grafman J, Spina S, Oblak A, Mesulam MM, Weintraub S, Geula C, Hodges JR, Piguet O, Brooks WS, Irwin DJ, Trojanowski JQ, Lee EB, Josephs KA, Parisi JE, Ertekin-Taner N, Knopman DS, Nacmias B, Piaceri I, Bagnoli S, Sorbi S, Gearing M, Glass J, Beach TG, Black SE, Masellis M, Rogaeva E, Vonsattel JP, Honig LS, Kofler J, Bruni AC, Snowden J, Mann D, Pickering-Brown S, Diehl-Schmid J, Winkelmann J, Galimberti D, Graff C, Oijerstedt L, Troakes C, Al-Sarraj S, Cruchaga C, Cairns NJ, Rohrer JD, Halliday GM, Kwok JB, van Swieten JC, White CL, III, Ghetti B, Murell JR, Mackenzie IRA, Hsiung GR, Borroni B, Rossi G, Tagliavini F, Wszolek ZK, Petersen RC, Bigio EH, Grossman M, Van Deerlin VM, Seeley WW, Miller BL, Graff-Radford NR, Boeve BF, Dickson DW, Biernacka JM, Rademakers R

Background: Loss-of-function mutations in GRN cause frontotemporal lobar degeneration (FTLD). Patients with GRN mutations present with a uniform subtype of TAR DNA-binding protein 43 (TDP-43) pathology at autopsy (FTLD-TDP type A); however, age at onset and clinical presentation are variable, even within families. We aimed to identify potential genetic modifiers of disease onset and disease risk in GRN mutation carriers.
Methods: The study was done in three stages: a discovery stage, a replication stage, and a meta-analysis of the discovery and replication data. In the discovery stage, genome-wide logistic and linear regression analyses were done to test the association of genetic variants with disease risk (case or control status) and age at onset in patients with a GRN mutation and controls free of neurodegenerative disorders. Suggestive loci ($p<1 \times 10(-5)$) were genotyped in a replication cohort of patients and controls, followed by a meta-analysis. The effect of genome-wide significant variants at the GFRA2 locus on expression of GFRA2 was assessed using mRNA expression studies in cerebellar tissue samples from the Mayo Clinic brain

bank. The effect of the GFRA2 locus on progranulin concentrations was studied using previously generated ELISA-based expression data. Co-immunoprecipitation experiments in HEK293T cells were done to test for a direct interaction between GFRA2 and progranulin.
Findings: Individuals were enrolled in the current study between Sept 16, 2014, and Oct 5, 2017. After quality control measures, statistical analyses in the discovery stage included 382 unrelated symptomatic GRN mutation carriers and 1146 controls free of neurodegenerative disorders collected from 34 research centres located in the USA, Canada, Australia, and Europe. In the replication stage, 210 patients (67 symptomatic GRN mutation carriers and 143 patients with FTLD without GRN mutations pathologically confirmed as FTLD-TDP type A) and 1798 controls free of neurodegenerative diseases were recruited from 26 sites, 20 of which overlapped with the discovery stage. No genome-wide significant association with age at onset was identified in the discovery or replication stages, or in the meta-analysis. However, in the case-control analysis, we replicated the previously reported TMEM106B association (rs1990622 meta-analysis odds ratio [OR] 0.54, 95% CI 0.46-0.63; p=3.54 x 10(-16)), and identified a novel genome-wide significant locus at GFRA2 on chromosome 8p21.3 associated with disease risk (rs36196656 meta-analysis OR 1.49, 95% CI 1.30-1.71; p=1.58 x 10(-8)). Expression analyses showed that the risk-associated allele at rs36196656 decreased GFRA2 mRNA concentrations in cerebellar tissue (p=0.04). No effect of rs36196656 on plasma and CSF progranulin concentrations was detected by ELISA; however, co-immunoprecipitation experiments in HEK293T cells did suggest a direct binding of progranulin and GFRA2.
Interpretation: TMEM106B-related and GFRA2-related pathways might be future targets for treatments for FTLD, but the biological interaction between progranulin and these potential disease modifiers requires further study. TMEM106B and GFRA2 might also provide opportunities to select and stratify patients for future clinical trials and, when more is known about their potential effects, to inform genetic counselling, especially for asymptomatic individuals.
Funding: National Institute on Aging, National Institute of Neurological Disorders and Stroke, Canadian Institutes of Health Research, Italian Ministry of Health, UK National Institute for Health Research, National Health and Medical Research Council of Australia, and the French National Research Agency.

Gepubliceerd: Lancet Neurol 2018 Jun;17(6):548-58
Impact factor: 27.144; Q1

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23. ADARRI: a novel method to detect spurious R-peaks in the electrocardiogram for heart rate variability analysis in the intensive care unit
Rebergen DJ, Nagaraj SB, Rosenthal ES, Bianchi MT, van Putten MJ, Westover MB

We developed a simple and fully automated method for detecting artifacts in the R-R interval (RRI) time series of the ECG that is tailored to the intensive care unit (ICU) setting. From ECG recordings of 50 adult ICU-subjects we selected 60 epochs with valid R-peak detections and 60 epochs containing artifacts leading to missed or false positive R-peak detections. Next, we calculated the absolute value of the difference between two adjacent RRIs (adRRI), and obtained the empirical probability distributions of adRRI values for valid R-peaks and artifacts. From these, we

calculated an optimal threshold for separating adRRI values arising from artifact versus non-artefactual data. We compared the performance of our method with the methods of Berntson and Clifford on the same data. We identified 257,458 R-peak detections, of which 235,644 (91.5%) were true detections and 21,814 (8.5%) arose from artifacts. Our method showed superior performance for detecting artifacts with sensitivity 100%, specificity 99%, precision 99%, positive likelihood ratio of 100 and negative likelihood ratio <0.001 compared to Berntson's and Clifford's method with a sensitivity, specificity, precision and positive and negative likelihood ratio of 99%, 78%, 82%, 4.5, 0.013 for Berntson's method and 55%, 98%, 96%, 27.5, 0.460 for Clifford's method, respectively. A novel algorithm using a patient-independent threshold derived from the distribution of adRRI values in ICU ECG data identifies artifacts accurately, and outperforms two other methods in common use. Furthermore, the threshold was calculated based on real data from critically ill patients and the algorithm is easy to implement.

Gepubliceerd: J Clin Monit Comput 2018;32(1):53-61
Impact factor: 2.450; Q3

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24. The prognostic value of discontinuous EEG patterns in postanoxic coma
Ruijter BJ, Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJAM

Objective: To assess the value of background continuity and amplitude fluctuations of the EEG for the prediction of outcome of comatose patients after cardiac arrest. **Methods:** In a prospective cohort study, we analyzed EEGs recorded in the first 72h after cardiac arrest. We defined the background continuity index (BCI) as the fraction of EEG not spent in suppressions (amplitudes <10microV for >/=0.5s), and the burst-suppression amplitude ratio (BSAR) as the mean amplitude ratio between non-suppressed and suppressed segments. Outcome was assessed at 6months and categorized as "good" (Cerebral Performance Category 1-2) or "poor" (CPC 3-5). **Results:** Of the 559 patients included, 46% had a good outcome. Combinations of BCI and BSAR resulted in the highest prognostic accuracies. Good outcome could be predicted at 24h with 57% sensitivity (95% confidence interval (CI): 48-67) at 90% specificity (95%-CI: 86-95). Poor outcome could be predicted at 12h with 50% sensitivity (95%-CI: 42-56) at 100% specificity (95%-CI: 99-100). **Conclusions:** EEG background continuity and the amplitude ratio between bursts and suppressions reliably predict the outcome of postanoxic coma. Significance: The presented features provide an objective, rapid, and reliable tool to assist in EEG interpretation in the Intensive Care Unit.

Gepubliceerd: Clin Neurophysiol 2018 Aug;129(8):1534-43
Impact factor: 3.614; Q2

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25. Deep learning for detection of focal epileptiform discharges from scalp EEG recordings
Tjepkema-Cloostermans MC, de Carvalho RCV, van Putten MJAM

Objective: Visual assessment of the EEG still outperforms current computer algorithms in detecting epileptiform discharges. Deep learning is a promising novel

approach, being able to learn from large datasets. Here, we show pilot results of detecting epileptiform discharges using deep neural networks.
Methods: We selected 50 EEGs from focal epilepsy patients. All epileptiform discharges (n=1815) were annotated by an experienced neurophysiologist and extracted as 2s epochs. In addition, 50 normal EEGs were divided into 2s epochs. All epochs were divided into a training (n=41,381) and test (n=8775) set. We implemented several combinations of convolutional and recurrent neural networks, providing the probability for the presence of epileptiform discharges. The network with the largest area under the ROC curve (AUC) in the test set was validated on seven independent EEGs with focal epileptiform discharges and twelve normal EEGs.
Results: The final network had an AUC of 0.94 for the test set. Validation allowed detection of epileptiform discharges with 47.4% sensitivity and 98.0% specificity (FPR: 0.6/min). For the normal EEGs in the validation set, the specificity was 99.9% (FPR: 0.03/min).
Conclusions: Deep neural networks can accurately detect epileptiform discharges from scalp EEG recordings. Significance: Deep learning may result in a fundamental shift in clinical EEG analysis.

Gepubliceerd: Clin Neurophysiol 2018 Oct;129(10):2191-6
Impact factor: 3.614; Q2

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26. Contralesional Brain Activity in Acute Ischemic Stroke
Van Kaam RC, van Putten MJAM, Vermeer SE, Hofmeijer J

Background: The noninjured, contralateral hemisphere is increasingly acknowledged in the process of recovery from acute ischemic stroke. We estimated the value of conventional electroencephalography (EEG) recordings for identifying contralateral hemisphere involvement in relation to functional recovery.
Methods: We analyzed 2-min epochs from 21 electrode EEG registrations of 18 patients with acute hemispheric ischemic stroke and compared with 18 age-matched controls. Outcome was dichotomized as good (modified Rankin Scale [mRS] 0-2) or poor (mRS 3-5 or death) at 3 months. Effects of the infarct on the ipsi-and contralateral hemispheres were analyzed by the delta/alpha ratio (DAR) and 2 measures of functional connectivity (magnitude squared coherence [MSC] and weighted phase lag index [WPLI]).
Results: DAR was higher in patients than in controls, both in the ipsilateral and in the contralateral hemisphere (median 4.5 +/- 6.7 ipsilateral and 2.4 +/- 2.0 contralateral vs. 0.5 +/- 0.5 in the control group, $p < 0.001$), indicating robust EEG changes in both lesioned and non-lesioned hemisphere. MSC and WPLI in the alpha and beta frequency bands were lower in patients than in controls in both hemispheres, indicating clear disturbances of functional connectivity ($p < 0.05$). In the poor outcome group, contralateral MSC and WPLI were lower than in the good outcome group, although these differences did not reach statistical significance.
Conclusions: Short conventional EEG measurements show robust changes of brain activity and functional connectivity in both ipsilateral and contralateral hemispheres of patients with acute ischemic stroke. Changes of remote functional connectivity tend to interact with functional recovery. Future studies should estimate predictive values for individual patients and interactions with plasticity enhancing treatments.

Gepubliceerd: Cerebrovasc Dis 2018;45(1-2):85-92
Impact factor: 2.931; Q2

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27. Postmortem histopathology of electroencephalography and evoked potentials in postanoxic coma
van Putten MJAM, Jansen C, Tjepkema-Cloostermans MC, Beernink TMJ, Koot R, Bosch F, Beishuizen A, Hofmeijer J

Early EEG patterns and SSEP responses are associated with neurological recovery of comatose patients with postanoxic encephalopathy after cardiac arrest. However, the nature and distribution of brain damage underlying the characteristic EEG and SSEP patterns are unknown. We relate EEG and SSEP findings with results from histological analyses of the brains of eleven non-survivors. With restoration towards continuous rhythms within 24h after cardiac arrest, no signs of structural neuronal damage were observed. Absent SSEP responses were always accompanied by thalamic damage. Pathological burst suppression patterns were associated with a variable degree of neuronal damage to cortex, cerebellum and hippocampus. In patients with additional thalamic involvement, burst-suppression with identical bursts was observed, a characteristic EEG pattern presumably reflecting residual activity from a relatively isolated and severely compromised cortex.

Gepubliceerd: Resuscitation 2018 Dec 15;134:26-32
Impact factor: 5.863; Q1

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28. Predicting sex from brain rhythms with deep learning
van Putten MJAM, Olbrich S, Arns M

We have excellent skills to extract sex from visual assessment of human faces, but assessing sex from human brain rhythms seems impossible. Using deep convolutional neural networks, with unique potential to find subtle differences in apparent similar patterns, we explore if brain rhythms from either sex contain sex specific information. Here we show, in a ground truth scenario, that a deep neural net can predict sex from scalp electroencephalograms with an accuracy of >80% ($p < 10(-5)$), revealing that brain rhythms are sex specific. Further, we extracted sex-specific features from the deep net filter layers, showing that fast beta activity (20-25 Hz) and its spatial distribution is a main distinctive attribute. This demonstrates the ability of deep nets to detect features in spatiotemporal data unnoticed by visual assessment, and to assist in knowledge discovery. We anticipate that this approach may also be successfully applied to other specialties where spatiotemporal data is abundant, including neurology, cardiology and neuropsychology.

Gepubliceerd: Sci Rep 2018 Feb 15;8(1):3069
Impact factor: 4.122: Q1

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29. Chronic solvent-induced encephalopathy: course and prognostic factors of neuropsychological functioning

van Valen E, Wekking E, van Hout M, van der Laan G, Hageman G, van Dijk F, de Boer A, Sprangers M

Purpose: Working in conditions with daily exposure to organic solvents for many years can result in a disease known as chronic solvent-induced encephalopathy (CSE). The aims for this study were to describe the neuropsychological course of CSE after first diagnosis and to detect prognostic factors for neuropsychological impairment after diagnosis.
Methods: This prospective study follows a Dutch cohort of CSE patients who were first diagnosed between 2001 and 2011 and underwent a second neuropsychological assessment 1.5-2 years later. Cognitive subdomains were assessed and an overall cognitive impairment score was calculated. Paired t tests and multivariate linear regression analyses were performed to describe the neuropsychological course and to obtain prognostic factors for the neuropsychological functioning at follow-up.
Results: There was a significant improvement on neuropsychological subdomains at follow-up, with effect sizes between small and medium (Cohen's d 0.27-0.54) and a significant overall improvement of neuropsychological impairment with a medium effect size (Cohen's d 0.56). Prognostic variables for more neuropsychological impairment at follow-up were a higher level of neuropsychological impairment at diagnosis and having a comorbid diagnosis of a psychiatric disorder at diagnosis.
Conclusions: Results are in line with previous research on the course of CSE, stating that CSE is a non-progressive disease after cessation of exposure. However, during follow-up the percentage patients with permanent work disability pension increased from 14 to 37%. Preventive action is needed in countries where exposure to organic solvents is still high to prevent new cases of CSE.

Gepubliceerd: Int Arch Occup Environ Health 2018 Oct;91(7):843-58
Impact factor: 2.148; Q2

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30. Three VCP Mutations in Patients with Frontotemporal Dementia
Wong TH, Pottier C, Hondius DC, Meeter LHH, van Rooij JGJ, Melhem S, van Minkelen R, van Duijn CM, Rozemuller AJM, Seelaar H, Rademakers R, van Swieten JC

Valosin-containing protein (VCP) is involved in multiple cellular activities. Mutations in VCP lead to heterogeneous clinical presentations including inclusion body myopathy with Paget's disease of the bone, frontotemporal dementia and amyotrophic lateral sclerosis, even in patients carrying the same mutation. We screened a cohort of 48 patients with familial frontotemporal dementia (FTD) negative for MAPT, GRN, and C9orf72 mutations for other known FTD genes by using whole exome sequencing. In addition, we carried out targeted sequencing of a cohort of 37 patients with frontotemporal lobar degeneration with Transactive response DNA-binding protein 43 (TDP-43) subtype from the Netherlands Brain bank. Two novel (p.Thr262Ser and p.Arg159Ser) and one reported (p.Met158Val) VCP mutations in three patients with a clinical diagnosis of FTD were identified, and were absence in population-match controls. All three patients presented with behavioral changes, with additional semantic deficits in one. No signs of Paget or muscle disease were observed. Pathological examination of the patient with VCP p.Arg159Ser mutation showed numerous TDP-43 immunoreactive (IR) neuronal intranuclear inclusions (NII) and

dystrophic neurites (DN), while a lower number of NII and DN were observed in the patient with the VCP p.Thr262Ser mutation. Pathological findings of both patients were consistent with FTLD-TDP subtype D. Furthermore, only rare VCP-IR NII was observed in both cases. Our study expands the clinical heterogeneity of VCP mutations carriers, and indicates that other additional factors, such as genetic modifiers, may determine the clinical phenotype.

Gepubliceerd: J Alzheimers Dis 2018;65(4):1139-46
Impact factor: 3.476; Q2

Totale impact factor: 143.706
Gemiddelde impact factor: 4.790

Aantal artikelen 1e, 2e of laatste auteur: 13
Totale impact factor: 40.269
Gemiddelde impact factor: 3.098

Oogheelkunde

1. Effects of clinical parameters on patient-reported outcome in cataract patients: a multicentre study
Stolk-Vos AC, Visser MS, Klijn S, Timman R, Lansink P, Nuijts R, Tjia K, Zijlmans B, Kranenburg LW, Busschbach JV, Reus NJ

Purpose: Ophthalmologists tend to evaluate the results of cataract surgery by focusing on the clinical visual and refractive outcomes and the incidence of complications, where patients' main interest might be their ability to perform daily activities. Therefore, there appears to be a need for optimizing effective communication between patients and ophthalmologist about the outcome of cataract surgery. The aim of this multicentre study was to determine the effects of whether the surgery was performed in one or two eyes, ocular comorbidity and per- and postoperative complications on visual function experienced by patients measured with the Catquest-9SF.
Methods: To measure patient-reported outcomes, Catquest-9SF data were collected between 2014 and 2015 in five Dutch hospitals. Data from 870 pairs of questionnaires - completed before and after cataract surgery - were compared with clinical data. Clinical data, retrieved from patients' medical files, consisted of one or two eye surgery, ocular comorbidity and per- and postoperative complications.
Results: Quality of vision improved more in patients who had surgery in both eyes and had fewer postoperative complications (both $p < 0.001$). We found a nonsignificant trend that quality of vision was worse when ocular comorbidity was present. No significant effect of peroperative complications was observed.
Conclusion: Our results emphasize the added value of the Catquest-9SF as a tool for visual function experienced by patients; the additional information can complement clinical parameters to improve patient-centred approaches in clinical practice.

Gepubliceerd: Acta Ophthalmol 2018 Sep;96(6):586-91
Impact factor:

Totale impact factor: 3.324
Gemiddelde impact factor: 3.324

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

Orthopedie

1. Amiodarone Rifampicin Drug-Drug Interaction Management With Therapeutic Drug Monitoring
Oude Munnink TH, Demmer A, Slenter RHJ, Movig KLL

The authors present a case of a 69-year-old man with arrhythmogenic right ventricular cardiomyopathy controlled with amiodarone and an infected orthopedic prosthesis requiring treatment with rifampicin. This combination involves a pharmacokinetic drug-drug interaction leading to subtherapeutic drug concentrations of amiodarone and its active metabolite. The long half-life of amiodarone and its active metabolite in combination with the late onset and offset of cytochrome P4503A (CYP3A4) induction by rifampicin makes this a challenging drug-drug interaction to cope with in clinical practice. Before, during, and after rifampicin treatment, the serum concentrations of amiodarone and its active metabolite were measured and the amiodarone dose was adjusted accordingly. The amiodarone dose required to maintain effective concentrations was 450% of the initial dose. The drug-drug interaction between amiodarone and rifampicin is relevant, both clinically and pharmacokinetically, and can be managed by dose adjustments of amiodarone based on serum concentrations.

Gepubliceerd: Ther Drug Monit 2018 Apr;40(2):159-61
Impact factor: 2.092; Q2

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2. The effect of a fibrin sealant on knee function after total knee replacement surgery. Results from the FIRST trial. A multicenter randomized controlled trial
Verra WC, van Hilten JA, Honohan A, van Zwet EW, van der Bom JG, Nelissen RGHH

Background: Total knee replacement (TKR) is increasingly performed in short term hospital stay, making same day mobilization an important issue is after surgery. This implies little joint effusion by reducing intra-articular blood loss, which will enhance knee range of motion. The application of a topical fibrin sealant on the intraoperative bare bone and synovial tissue may contribute to better early full mobilization and thus improved functional outcomes. Since ambulation with a fully extended knee is less strenuous, we hypothesized that patients who received fibrin sealant would demonstrate improved early knee extension after six weeks compared to patients who received standard care.
Methods: A multicenter randomized controlled trial in a consecutive series of osteoarthritis patients scheduled for TKR surgery. Participants were randomized to receive fibrin sealant or not before closing the knee joint capsule. Primary outcome was change in knee extension angle(degrees) at short term (2 weeks) follow-up (cExt). Secondary outcomes were 6-week extension angle, knee flexion angle, hemoglobin loss, blood transfusion rates, complication rates, the Knee Society Score, and the KOOS and EQ5D questionnaires.
Results: When data on primary outcome became available from 250 patients, an interim analysis was performed by an independent Data Safety Monitoring Board for

safety and effectivity assessment. This analysis showed that sufficient patients were included to detect a cExt of 10 degrees between both groups. Inclusion was stopped however, all in the meantime included patients were treated according to their randomization. A total of 466 were available for analysis. Both groups were comparable in terms of baseline characteristics. The estimated mean cExt difference was 0.2 degrees (95%CI -0.5 to 0.9). No differences in secondary outcomes were found.
Conclusions: No beneficial effects or side effects were found of a topically applied fibrin sealant during TKR surgery. These results discourage the clinical use of a fibrin sealant in TKR.
Trial registration: Dutch Trial Register, NTR2500.

Gepubliceerd: PLoS One 2018;13(7):e0200804
Impact factor: 2.766; Q1

Totale impact factor: 4.858
Gemiddelde impact factor: 2.429

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 4.858
Gemiddelde impact factor: 2.429

Pathologie

1. Evaluating the benefits of digital pathology implementation: time savings in laboratory logistics
Baidoshvili A, Bucur A, van Leeuwen J, van der Laak J, Kluin P, van Diest PJ

Background: The benefits of digital pathology for workflow improvement and thereby cost savings in pathology, at least partly outweighing investment costs, are being increasingly recognised. Successful implementations in a variety of scenarios have started to demonstrate the cost benefits of digital pathology for both research and routine diagnosis, contributing to a sound business case encouraging further adoption. To further support new adopters, there is still a need for detailed assessment of the impact that this technology has on the relevant pathology workflows, with an emphasis on time-saving.
Aims: To assess the impact of digital pathology adoption on logistic laboratory tasks (i.e. not including pathologists' time for diagnosis-making) in the Laboratorium Pathologie Oost Nederland, a large regional pathology laboratory in The Netherlands.
Methods and results: To quantify the benefits of digitisation, we analysed the differences between the traditional analogue and new digital workflows, carried out detailed measurements of all relevant steps in key analogue and digital processes, and compared the time spent. We modelled and assessed the logistic savings in five workflows: (i) routine diagnosis; (ii) multidisciplinary meeting; (iii) external revision requests; (iv) extra stainings; and (v) external consultation. On average, >19 working hours were saved on a typical day by working digitally, with the highest savings in routine diagnosis and multidisciplinary meeting workflows.
Conclusions: By working digitally, a significant amount of time could be saved in a large regional pathology laboratory with a typical case mix. We also present the data in each workflow per task and concrete logistic steps to allow extrapolation to the context and case mix of other laboratories.

Gepubliceerd: Histopathology 2018 Nov;73(5):784-94
Impact factor: 3.267; Q1

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2. Validation of a whole-slide image-based teleconsultation network
Baidoshvili A, Stathonikos N, Freling G, Bart J, 't Hart N, van der Laak J, Doff J, van der Vegt B, Kluin PM, van Diest PJ

Aims: Most validation studies on digital pathology diagnostics have been performed in single institutes. Because rapid consultation on cases with extramural experts is one of the most important uses for digital pathology laboratory networks, the aim of this study was to validate a whole-slide image-based teleconsultation network between three independent laboratories.
Methods and results: Each laboratory contributed 30 biopsies and/or excisions, totalling 90 specimens (776 slides) of varying difficulty and covering a wide variety of organs and subspecialties. All slides were scanned centrally at x40 scanning magnification and uploaded, and subsequently assessed digitally by 16 pathologists using the same image management system and viewer. Each laboratory was excluded from digital assessment of their own cases. Concordance rates between the

two diagnostic modalities (light microscopic versus digital) were compared. Loading speed of the images, zooming latency and focus quality were scored. Leaving out eight minor discrepancies without any clinical significance, the concordance rate between remote digital and original microscopic diagnoses was 97.8%. The two cases with a major discordance (for which the light microscopic diagnoses were deemed to be the better ones) resulted from a different interpretation of diagnostic criteria in one case and an image quality issue in the other case. Average scores for loading speed of the images, zooming latency and focus quality were 2.37 (on a scale up to 3), 2.39 (scale up to 3) and 3.06 (scale up to 4), respectively.
Conclusions: This validation study demonstrates the suitability of a teleconsultation network for remote digital consultation using whole-slide images. Such networks may contribute to faster revision and consultation in pathology while maintaining diagnostic standards.

Gepubliceerd: Histopathology 2018 Nov;73(5):777-83
Impact factor: 3.267; Q1

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3. Signet Ring Cell Carcinoma of the Ampulla of Vater: A Rare Histopathological Variant
de Klein GW, van Baarlen J, Mekenkamp LJ, Liem MSL, Klaase JM

Signet ring cell carcinoma (SRCC) of the ampulla of Vater is an extremely rare tumor. Our case describes a 45-year-old female presenting with jaundice and pruritus. Computed tomography, endoscopy, and endoscopic retrograde cholangiopancreatography showed a tumor of the ampulla of Vater without distant metastasis. Histological biopsy confirmed a malignant tumor with SRCC characteristics and immunohistochemical staining revealed a mixed type profile (both intestinal and pancreatobiliary characteristics). A pylorus-preserving pancreatoduodenectomy was performed and the patient recovered without complications. Pathology results concluded a pT2N0 ampullary SRCC. SRCC of the ampulla of Vater is known to be highly malignant. After 13 months of follow-up, our patient showed no signs of recurrence.

Gepubliceerd: Case Rep Gastroenterol 2018 Jan;12(1):194-201
Impact factor: 0; nvt

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4. The Importance of eSlide Macro Images for Primary Diagnosis with Whole Slide Imaging
Fraggetta F, Yagi Y, Garcia-Rojo M, Evans AJ, Tuthill JM, Baidoshvili A, Hartman DJ, Fukuoka J, Pantanowitz L

Introduction: A whole slide image (WSI) is typically comprised of a macro image (low-power snapshot of the entire glass slide) and stacked tiles in a pyramid structure (with the lowest resolution thumbnail at the top). The macro image shows the label and all pieces of tissue on the slide. Many whole slide scanner vendors do not readily show the macro overview to pathologists. We demonstrate that failure to do so may result in a serious misdiagnosis. Materials and

Methods: Various examples of errors were accumulated that occurred during the digitization of glass slides where the virtual slide differed from the macro image of the original glass slide. Such examples were retrieved from pathology laboratories using different types of scanners in the USA, Canada, Europe, and Asia.
Results: The reasons for image errors were categorized into technical problems (e.g., automatic tissue finder failure, image mismatches, and poor scan coverage) and human operator mistakes (e.g., improper manual region of interest selection). These errors were all detected because they were highlighted in the macro image.
Conclusion: Our experience indicates that WSI can be subject to inadvertent errors related to glitches in scanning slides, corrupt images, or mistakes made by humans when scanning slides. Displaying the macro image that accompanies WSIs is critical from a quality control perspective in digital pathology practice as this can help detect these serious image-related problems and avoid compromised diagnoses.

Gepubliceerd: J Pathol Inform 2018;9:46
Impact factor: 0; nvt

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5. 1399 H&E-stained sentinel lymph node sections of breast cancer patients: the CAMELYON dataset
Litjens G, Bandi P, Ehteshami BB, Geessink O, Balkenhol M, Bult P, Halilovic A, Hermsen M, van de Loo R, Vogels R, Manson QF, Stathonikos N, Baidoshvili A, van Diest P, Wauters C, van Dijk M, van der Laak J

Background: The presence of lymph node metastases is one of the most important factors in breast cancer prognosis. The most common way to assess regional lymph node status is the sentinel lymph node procedure. The sentinel lymph node is the most likely lymph node to contain metastasized cancer cells and is excised, histopathologically processed, and examined by a pathologist. This tedious examination process is time-consuming and can lead to small metastases being missed. However, recent advances in whole-slide imaging and machine learning have opened an avenue for analysis of digitized lymph node sections with computer algorithms. For example, convolutional neural networks, a type of machine-learning algorithm, can be used to automatically detect cancer metastases in lymph nodes with high accuracy. To train machine-learning models, large, well-curated datasets are needed.
Results: We released a dataset of 1,399 annotated whole-slide images (WSIs) of lymph nodes, both with and without metastases, in 3 terabytes of data in the context of the CAMELYON16 and CAMELYON17 Grand Challenges. Slides were collected from five medical centers to cover a broad range of image appearance and staining variations. Each WSI has a slide-level label indicating whether it contains no metastases, macro-metastases, micro-metastases, or isolated tumor cells. Furthermore, for 209 WSIs, detailed hand-drawn contours for all metastases are provided. Last, open-source software tools to visualize and interact with the data have been made available.
Conclusions: A unique dataset of annotated, whole-slide digital histopathology images has been provided with high potential for re-use.

Gepubliceerd: Gigascience 2018 Jun 1;7(6)
Impact factor: 7.267; Q1

Totale impact factor: 13.801
Gemiddelde impact factor: 2.760

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 6.534
Gemiddelde impact factor: 2.178

Plastische Chirurgie

1. Risk factors for developing capsular contracture in women after breast implant surgery: A systematic review of the literature
Bachour Y, Bargon CA, de Blok CJM, Ket JCF, Ritt MJPF, Niessen FB

Background: Capsular contracture is the most frequent complication in breast augmentation or reconstruction with breast implants. The exact mechanism for this complication is not completely understood. Yet, it is most likely to be a multifactorial condition. Several patient-, surgery-, and implant-specific risk factors have been related to cause capsular contracture. This review aims to provide a clear overview of all risk factors for capsular contracture.
Methods: A systematic literature review was performed focusing on patient-, surgery, and/or implant-related factors related to capsular contracture in breast implants. PubMed, Embase, and Wiley/Cochrane Library databases were searched for relevant articles published from inception up to October 20, 2016. The included studies were assessed for the following main variables: study characteristics, patient characteristics, indication for surgery, type of surgery, implant characteristics, and other characteristics.
Results: Data on the risk factors for the development of capsular contracture were retrieved from 40 studies. A presumptive increased risk in the development of capsular contracture is shown for the following variables: longer duration of follow-up, breast reconstructive surgery in patients with a history of breast cancer, subglandular implant placement, postoperative hematoma, and a textured implant surface. There is little, weak, or no evidence for the association of other factors with capsular contracture. This review also shows a large heterogeneity between studies and within the definition of capsular contracture.
Conclusion: This review provides an overview of the relationship between patient-, surgery-, and implant-specific risk factors in the development of capsular contracture.

Gepubliceerd: J Plast Reconstr Aesthet Surg 2018 Sep;71(9):e29-e48
Impact factor: 2.158; Q2

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2. High risk device registries: Global value, costs, and sustainable funding
Becherer BE, Spronk PER, Mureau MAM, Mulgrew S, Perks AGB, Stark B, Pusic AL, Lumenta DB, Hopper I, Cooter RD, Rakhorst HA

Background: Well-designed implant registries have been shown to be a worthwhile investment, from both a health and economic perspective. However, many registries do not attain desirable capture rates or lack sufficient funding, potentially leading to premature termination. This study aims to provide information about rarely discussed, yet pivotal topics regarding the long-term survival of implant registries, focusing on costs, funding models, and the role of stakeholders.
Methods: Worldwide, relatively recently developed breast device (BD) registries were compared to long-standing, orthopaedic (OD) and cardiovascular device (CD) registries. A standardised questionnaire was sent to the registries' designated representatives with key positions, discussing start-up costs, costs of maintenance, value of investment, governance, stakeholders, funding, and sustainability.

Results: Thirteen registries were included, originating from nine countries (seven BD registries, five OD registries, one CD registry). In general, start-up costs were comparable, and younger registries were more expensive to maintain. Numerous stakeholders showed interest in registry outcomes. However, only 50% of the registries reported a sustainable funding structure.
Conclusion: This study provides a global perspective on implantable device registries. All registries provided important information, serving three unique purposes by evaluating the quality of healthcare provided, the quality of all registered devices, and processing recall information. Yet, only half of the registries were certain of sustainable funding, and thus their future existence. It is of utmost importance to bring this to the attention of all parties involved.

Gepubliceerd: J Plast Reconstr Aesthet Surg 2018 Sep;71(9):1362-80
Impact factor: 2.158; Q2

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3. The Prevalence of Triangular Fibrocartilage Complex Signal Abnormalities on Magnetic Resonance Imaging Relative to Clinical Suspicion of Pathology
Bendre HH, Oflazoglu K, van Leeuwen WF, Rakhorst H, Ring D, Chen NC

Purpose: To determine the prevalence of triangular fibrocartilage complex (TFCC) signal changes in patients undergoing magnetic resonance imaging (MRI) of the wrist and its relationship to a clinical suspicion of TFCC pathology. The secondary purpose was to study factors that are associated with TFCC signal changes.
Methods: In this retrospective study, we looked for any TFCC signal changes in the reports of MRI findings performed during a 3-year period in 1,134 patients. Demographic characteristics, the categorized indications for MRI, and symptoms at the time of the MRI were also retrieved from the medical records. Patients were divided into 6 groups, based on age, to calculate the proportions of TFCC signal changes in the entire cohort and as an incidental finding among patients without a clinical suspicion of TFCC pathology within each age group.
Results: A total of 321 patients (28%) had incidental TFCC signal changes. The prevalence among 18- to 30 year-olds was 19%, and increased to 64% in patients older than 70 years. Multivariable logistic regression analysis demonstrated that an increase in age is significantly associated with having TFCC signal changes on MRI in patients who have a low clinical suspicion of TFCC pathology. The rate of incidental TFCC signal changes steadily increases with age.
Conclusions: The TFCC signal abnormalities on MRI are more common with increasing age in patients with low clinical suspicion of TFCC pathology. At age 70, more than half of all patients will have TFCC signal changes, and more than 90% are present in patients with a low clinical suspicion of TFCC pathology.
Type of study/level of evidence: Diagnostic IV.

Gepubliceerd: J Hand Surg Am 2018 Sep;43(9):819-26
Impact factor: 1.776; Q3

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4. MR arthrography is slightly more accurate than conventional MRI in detecting TFCC lesions of the wrist

Boer BC, Vestering M, van Raak SM, van Kooten EO, Huis In 't Veld R, Vochteloo AJH

Introduction: In case of clinical suspicion of triangular fibrocartilage complex (TFCC) injury, different imaging techniques are used. The aim of this study was to determine whether MRA is superior to MRI and whether 3.0 T is better than 1.5 T (expresses in sensitivity, specificity and accuracy) in detecting TFCC injury, using arthroscopy as the gold standard.
Materials and methods: The arthroscopic and MR findings of 150 patients who underwent arthroscopy for ulnar-sided wrist pain between January 2009 and November 2016 were retrospectively reviewed.
Results: MRA was slightly more accurate compared to conventional MRI, and 1.5 T was slightly more accurate than 3.0 T. 1.5 T wrist MRA had a sensitivity of 80%, a specificity of 100% and accuracy of 90%; 3.0 T wrist MRA 73, 100 and 86%, resp. Conventional 1.5 T wrist MRI had a sensitivity of 71%, a specificity of 75% and accuracy of 73%. For 3.0 T conventional MRI, this was 73, 67 and 70%, resp.
Conclusions: MRA seems slightly superior to conventional MRI, but one could question whether this difference in diagnostic accuracy outweighs the burden and risks of an invasive procedure for patients with its additional costs. Furthermore, we could not confirm the superiority of 3 T compared to 1.5 T.

Gepubliceerd: Eur J Orthop Surg Traumatol 2018 Dec;28(8):1549-53
Impact factor: 0.181; Q4

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5. Dupuytren disease is highly prevalent in male field hockey players aged over 60 years
Broekstra DC, van den Heuvel ER, Lanting R, Harder T, Smits I, Werker PMN

Background/aim: Dupuytren disease is a fibroproliferative hand condition. The role of exposure to vibration as a risk factor has been studied with contradictory results. Since field hockey is expected to be a strong source of hand-arm vibration, we hypothesised that long-term exposure to field hockey is associated with Dupuytren disease.
Methods: In this cross-sectional cohort study, the hands of 169 male field hockey players (IQR: 65-71 years) and 156 male controls (IQR: 59-71 years) were examined for signs of Dupuytren disease. Details about their age, lifestyle factors, medical history, employment history and leisure activities were gathered. Prior to the analyses, the groups were balanced in risk factors using propensity score matching. The association between field hockey and Dupuytren disease was determined using a subject-specific generalised linear mixed model with a binomial distribution and logit link function (matched pairs analysis).
Results: Dupuytren disease was observed in 51.7% of the field hockey players, and in 13.8% of the controls. After propensity score matching, field hockey playing as dichotomous variable, was associated with Dupuytren disease (OR=9.42, 95% CI 3.01 to 29.53). A linear dose-response effect of field hockey (hours/week x years) within the field hockey players could not be demonstrated (OR=1.03, 95% CI 0.68 to 1.56).

Discussion: We found that field hockey playing has a strong association with the presence of Dupuytren disease. Clinicians in sports medicine should be alert to this less common diagnosis in this sport.

Gepubliceerd: Br J Sports Med 2018 Oct;52(20):1327-31
Impact factor: 7.867; Q1

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6. Crowdsourcing Public Perceptions of Plastic Surgeons: Is There a Gender Bias?
Bucknor A, Christensen J, Kamali P, Egeler S, van Veldhuisen C, Rakhorst H, Mathijssen I, Lin SJ, Furnas H

Background: Implicit gender bias may result in lower wages for women, fewer leadership positions, and lower perceived competence. Understanding public and patient gender preferences for plastic surgeons may enable opportunities to address public perceptions. This investigation evaluates public preferences for a plastic surgeon's gender or demeanor.
Methods: Members of the Amazon Mechanical Turk crowdsourcing platform read 1 of the 8 randomly assigned scenarios describing a hypothetical situation requiring a plastic surgeon to operate on their mother. The scenarios differed only by surgeon gender, surgeon demeanor ("agentic," traditionally more masculine versus "communal," traditionally more feminine), or type of surgery. Using a Likert scale, respondents indicated their agreement with 7 statements on surgeon competence, skills, leadership qualities, likeability, respect, trustworthiness, and, ultimately, preference as a surgeon. Independent t tests were used to compare scores. Lower scores indicated a more negative response.
Results: Overall, 341 responses were received: 55.7% were male and 45.5% white. There were no significant differences in any of the 7 characteristics assessed when examining by surgeon gender, only. However, female surgeons with a communal demeanor were perceived as less competent (4.32 versus 4.51, P = 0.018) and less skilled (4.36 versus 4.56, P = 0.019) than agentic female surgeons. Male respondents rated female surgeons lower than male surgeons in terms of competence (P = 0.018), skills (P = 0.034), likeability (P = 0.042), and preferred choice as a surgeon (P = 0.033).
Conclusions: Women plastic surgeons' demeanor and respondent gender affected perception of certain characteristics. Women plastic surgeons may consider ways to engage with the public to address possible gender role stereotypes.

Gepubliceerd: Plast Reconstr Surg Glob Open 2018 Apr;6(4):e1728
Impact factor: 0; nvt

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7. Gender Inequality for Women in Plastic Surgery: A Systematic Scoping Review
Bucknor A, Kamali P, Phillips N, Mathijssen I, Rakhorst H, Lin SJ, Furnas H

Background: Previous research has highlighted the gender-based disparities present throughout the field of surgery. This study aims to evaluate the breadth of the issues facing women in plastic surgery, worldwide.

Methods: A systematic scoping review was undertaken from October of 2016 to January of 2017, with no restrictions on date or language. A narrative synthesis of the literature according to themed issues was developed, together with a summary of relevant numeric data.
Results: From the 2247 articles identified, 55 articles were included in the analysis. The majority of articles were published from the United States. Eight themes were identified, as follows: (1) workforce figures; (2) gender bias and discrimination; (3) leadership and academia; (4) mentorship and role models; (5) pregnancy, parenting, and childcare; (6) relationships, work-life balance, and professional satisfaction; (7) patient/public preference; and (8) retirement and financial planning. Despite improvement in numbers over time, women plastic surgeons continue to be underrepresented in the United States, Canada, and Europe, with prevalence ranging from 14 to 25.7 percent. Academic plastic surgeons are less frequently female than male, and women academic plastic surgeons score less favorably when outcomes of academic success are evaluated. Finally, there has been a shift away from overt discrimination toward a more ingrained, implicit bias, and most published cases of bias and discrimination are in association with pregnancy.
Conclusions: The first step toward addressing the issues facing women plastic surgeons is recognition and articulation of the issues. Further research may focus on analyzing geographic variation in the issues and developing appropriate interventions.

Gepubliceerd: Plast Reconstr Surg 2018 Jun;141(6):1561-77
Impact factor: 3.621; Q1

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8. Establishing Priorities for the International Confederation of Plastic Surgery Societies
Cooter RD, Brightman LA, Clarke HM, Cruz NI, Evans GRD, Koh KS, Murphy RX, Jr., Perks GAB, Rakhorst HA

Background: The mission of the International Confederation of Plastic Surgery Societies (ICOPLAST) is to improve patient outcomes through collaboratively structured processes in education, advocacy and communication. This article explains how we approached the task of establishing priorities for this nascent confederation in an equitable and achievable manner.
Methods: In late 2016, an online survey was sent to the inaugural 62 ICOPLAST member national societies for dissemination to their respective plastic surgeon members. Functional domains and proposed initiatives were ranked according to their level of importance by individual plastic surgeons.
Results: The survey was completed by 572 plastic surgeons. As a functional domain, education was highly ranked by 75.3% of respondents, followed by patient safety (67.4%), communication (59.3%), humanitarian (46.6%), regulation (41.2%), and advocacy (41.1%). Respondents also ranked individual initiatives within each domain to produce a compilation list of the top 13 initiatives of importance.
Conclusion: This study has identified priorities of importance to ICOPLAST members, which will aid in building a strategic framework and enhancing outcomes for patients, plastic surgeons, and the field of plastic surgery more broadly.

Gepubliceerd: Plast Reconstr Surg Glob Open 2018 Sep;6(9):e1878
Impact factor: 0; nvt

9. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, Sernee A, Klazen CAH, Lobbes MBI, van der Hulst RRWJ, Rakhorst HA, de Jong D

Importance: Breast implants are among the most commonly used medical devices. Since 2008, the number of women with breast implants diagnosed with anaplastic large-cell lymphoma in the breast (breast-ALCL) has increased, and several reports have suggested an association between breast implants and risk of breast-ALCL. However, relative and absolute risks of breast-ALCL in women with implants are still unknown, precluding evidence-based counseling about implants.
Objective: To determine relative and absolute risks of breast-ALCL in women with breast implants.
Design, setting, and participants: Through the population-based nationwide Dutch pathology registry we identified all patients diagnosed with primary non-Hodgkin lymphoma in the breast between 1990 and 2016 and retrieved clinical data, including breast implant status, from the treating physicians. We estimated the odds ratio (OR) of ALCL associated with breast implants in a case-control design, comparing implant prevalence between women with breast-ALCL and women with other types of breast lymphoma. Cumulative risk of breast-ALCL was derived from the age-specific prevalence of breast implants in Dutch women, estimated from an examination of 3000 chest x-rays and time trends from implant sales. Main Outcomes and Measures: Relative and absolute risks of breast-ALCL in women with breast implants.
Results: Among 43 patients with breast-ALCL (median age, 59 years), 32 had ipsilateral breast implants, compared with 1 among 146 women with other primary breast lymphomas (OR, 421.8; 95% CI, 52.6-3385.2). Implants among breast-ALCL cases were more often macrotextured (23 macrotextured of 28 total implants of known type, 82%) than expected (49193 sold macrotextured implants of total sold 109449 between 2010 and 2015, 45%) based on sales data ($P < .001$). The estimated prevalence of breast implants in women aged 20 to 70 years was 3.3%. Cumulative risks of breast-ALCL in women with implants were 29 per million at 50 years and 82 per million at 70 years. The number of women with implants needed to cause 1 breast-ALCL case before age 75 years was 6920.
Conclusion and relevance: Breast implants are associated with increased risk of breast-ALCL, but the absolute risk remains small. Our results emphasize the need for increased awareness among the public, medical professionals, and regulatory bodies, promotion of alternative cosmetic procedures, and alertness to signs and symptoms of breast-ALCL in women with implants.

Gepubliceerd: JAMA Oncol 2018 Mar 1;4(3):335-41
Impact factor: 20.871; Q1

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10. Macrotextured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42,000 Implants

de Boer M, Hauptmann M, de Jong D, van Leeuwen FE, Rakhorst HA, van der Hulst RRWJ

Gepubliceerd: Plast Reconstr Surg 2018 Oct;142(4):590e-1e
Impact factor: 3.621; Q1

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11. Breast Implant Registries: A Call to Action
Hopper I, Ahern S, Nguyen TQ, Mulvany C, McNeil JJ, Deva AK, Klein H, Stark B, Rakhorst HA, Cooter RD

Gepubliceerd: Aesthet Surg J 2018 Jun 13;38(7):807-10
Impact factor: 2.824; Q1

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12. Immediate Breast Reconstruction among Patients with Medicare and Private Insurance: A Matched Cohort Analysis
Kamali P, Ricci JA, Curiel DA, Cohen JB, Chattha A, Rakhorst HA, Lee BT, Lin SJ

Background: By eliminating economic hurdles, the Women's Health and Cancer Rights Act of 1998 represented a paradigm shift in the availability of breast reconstruction. Yet, studies report disparities among Medicare-insured women. These studies do not account for the inherent differences in age and comorbidities between a younger privately insured and an older Medicare population. We examined immediate breast reconstruction (IBR) utilization between a matched pre- and post-Medicare population.
Methods: Using the Nationwide Inpatient Sample database (1992-2013), breast cancer patients undergoing IBR were identified. To minimize confounding medical variables, 64-year-old privately insured women were compared with 66-year-old Medicare-insured women. Demographic data, IBR rates, and complication rates were compared. Trend over time was plotted for both cohorts.
Result: A total of 21,402 64-year-old women and 25,568 66-year-old women were included. Both groups were well matched in terms of demographic type of reconstruction and complication rates. 72.3% of 64-year-old and 71.2 of % 66-year-old women opted for mastectomy. Of these, 25.5% (n = 3,941) of 64-year-old privately insured and 17.7% (n = 3,213) of 66-year-old Medicare-insured women underwent IBR (P < 0.01). During the study period, IBR rates increased significantly in both cohorts in a similar cohort.
Conclusion: This study demonstrates significant increasing IBR rates in both cohorts. Moreover, after an initial slower upward trend, after a decade, IBR in 66-year-old Medicare-insured women approached similar rates of breast reconstruction among those with private insurance. Trends in unilateral versus bilateral mastectomy are also seen.

Gepubliceerd: Plast Reconstr Surg Glob Open 2018 Jan;6(1):e1552
Impact factor: 0; nvt

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13. Postoncological lacrimal duct reconstruction: A practical classification system for reconstructive planning and short-term results of a case series
van Burink MV, Rakhorst HA, van Couwelaar GM, Schmidbauer U

Background: Surgical resection of skin tumors in the medial canthal area may damage the lacrimal duct and can result in chronic epiphora. Postoncologic reconstruction of the lacrimal duct has not been studied extensively. The current study discusses the anatomical and functional features of the lacrimal duct. It describes short-term functional outcomes after monocanalicular reconstruction of the lacrimal duct in a case series of 10 patients.
Methods: From February 2015 to October 2017, all patients with a postoncological lacrimal duct defect were analyzed to make an anatomical classification. The functional outcomes of patients after monocanalicular reconstruction were measured with the Munk scale up to 3 months after stent removal.
Results: Twelve patients had lacrimal duct defects after Mohs resection. Anatomical characteristics were used to create a clinical classification for lacrimal duct defects. This classification divides the upper (U) and lower (L) proximal lacrimal duct into two sections which can be damaged: the punctum and pars verticalis (1), the canaliculus horizontalis (2), or combined (3). The Common lacrimal duct (C) is the distal part of the lacrimal duct and can also be affected. Ten patients were analyzed after lacrimal duct reconstruction. Three months after stent removal, none of the patients suffered from epiphora.
Conclusions: This article proposes an anatomical classification for lacrimal duct defects in the proximal lacrimal drainage system. The classification can be applied in comparing cases and determining reconstructive strategies after oncologic skin tumor resection. Short-term results are promising for future efforts to reconstruct the lacrimal duct.

Gepubliceerd: J Plast Reconstr Aesthet Surg 2018 Dec;71(12):1796-803
Impact factor: 2.158; Q2

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14. A systematic review and meta-analysis of arthroscopic assisted techniques for thumb carpometacarpal joint osteoarthritis
Wilkens SC, Bargon CA, Mohamadi A, Chen NC, Coert JH

Arthroscopic management of thumb carpometacarpal (CMC) osteoarthrosis (OA) is an approach that has unclear results. We performed a systematic review encompassing three electronic databases up to May 2016 for studies describing arthroscopic-assisted techniques for thumb CMC OA. Meta-analyses of visual analogue scores (VAS) for pain, Disabilities of the Arm, Shoulder and Hand (DASH) scores, grip strength and pinch strength before and after arthroscopy were performed for ten included non-randomized cohort studies comprising 294 patients. Based on Hedges' g measure, we found a large effect on VAS and DASH scores, a small effect on grip strength and no effect on pinch strength. On average, VAS improved by 4.1 cm, DASH by 22 points and grip strength by 2.8 kg. Complications were reported in 4% of patients. The use of arthroscopic-assisted techniques for thumb CMC OA is still limited; however, it may be a reasonable option for patients with thumb CMC OA who do not respond to non-operative treatment.

Gepubliceerd: J Hand Surg Eur Vol 2018 Dec;43(10):1098-105
Impact factor: 2.648; Q1

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15. Hand Posturing Is a Nonverbal Indicator of Catastrophic Thinking for Finger, Hand, or Wrist Injury

Wilkens SC, Lans J, Bargon CA, Ring D, Chen NC

Background: Prior research documents that greater psychologic distress (anxiety/depression) and less effective coping strategies (catastrophic thinking, kinesophobia) are associated with greater pain intensity and greater limitations. Recognition and acknowledgment of verbal and nonverbal indicators of psychologic factors might raise opportunities for improved psychologic health. There is evidence that specific patient words and phrases indicate greater catastrophic thinking. This study tested proposed nonverbal indicators (such as flexion of the wrist during attempted finger flexion or extension of uninjured fingers as the stiff and painful finger is flexed) for their association with catastrophic thinking. QUESTIONS/PURPOSES: (1) Do patients with specific protective hand postures during physical examination have greater pain interference (limitation of activity in response to nociception), limitations, symptoms of depression, catastrophic thinking (protectiveness, preparation for the worst), and kinesophobia (fear of movement)? (2) Do greater numbers of protective hand postures correlate with worse scores on these measures?
Methods: Between October 2014 and September 2016, 156 adult patients with stiff or painful fingers within 2 months after sustaining a finger, hand, or wrist injury were invited to participate in this study. Six patients chose not to participate as a result of time constraints and one patient was excluded as a result of inconsistent scoring of a possible hand posture, leaving 149 patients for analysis. We asked all patients to complete a set of questionnaires and a sociodemographic survey. We used Patient Reported Outcomes Measurement Information System (PROMIS) Depression, Upper Extremity Physical Function, and Pain Interference computer adaptive test (CAT) questionnaires. We used the Abbreviated Pain Catastrophizing Scale (PCS-4) to measure catastrophic thinking in response to nociception. Finally, we used the Tampa Scale of Kinesophobia (TSK) to assess fear of movement. The occurrence of protective hand postures during the physical examination was noted by both the physician and researcher. For uncertainty or disagreement, a video of the physical examination was recorded and a group decision was made.
Results: Patients with one or more protective hand postures did not score higher on the PROMIS Pain Interference CAT (hand posture: 59 [56-64]; no posture: 59 [54-63]; difference of medians: 0; p = 0.273), Physical Function CAT (32 +/- 8 versus 34 +/- 8; mean difference: 2 [confidence interval {CI}, -0.5 to 5]; p = 0.107), nor the Depression CAT (48 [41-55] versus 48 [42-53]; difference of medians: 0; p = 0.662). However, having at least one hand posture was associated with a higher degree of catastrophic thinking (PCS scores: 13 [6-26] versus 10 [3-16]; difference of medians: 3; p = 0.0104) and a higher level of kinesophobia (TSK: 40 +/- 6 versus 38 +/- 6; mean difference: -2 [CI, -4 to -1]; p = 0.0420). Greater catastrophic thinking was associated with a greater number of protective hand postures on average (rho: 0.20, p = 0.0138).
Conclusions: Protective hand postures and (based on prior research) specific words and phrases are associated with catastrophic thinking and kinesophobia, less effective coping strategies that hinder recovery. Surgeons can learn to recognize these signs and begin to treat catastrophic thinking and kinesophobia starting with compassion, empathy, and patience and be prepared to add formal support (such as cognitive-behavioral therapy) to help facilitate recovery. LEVEL OF EVIDENCE: Level III, diagnostic study.

Gepubliceerd: Clin Orthop Relat Res 2018 Apr;476(4):706-13
Impact factor: 4.091; Q1

Totale impact factor: 53.974
Gemiddelde impact factor: 3.598

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 6.964
Gemiddelde impact factor: 1.741

Radiologie

1. Detection of small traumatic hemorrhages using a computer-generated average human brain CT
Afzali-Hashemi L, Hazewinkel M, Tjepkema-Cloostermans MC, van Putten MJAM, Slump CH

Computed tomography is a standard diagnostic imaging technique for patients with traumatic brain injury (TBI). A limitation is the poor-to-moderate sensitivity for small traumatic hemorrhages. A pilot study using an automatic method to detect hemorrhages [Formula: see text] in diameter in patients with TBI is presented. We have created an average image from 30 normal noncontrast CT scans that were automatically aligned using deformable image registration as implemented in Elastix software. Subsequently, the average image was aligned to the scans of TBI patients, and the hemorrhages were detected by a voxelwise subtraction of the average image from the CT scans of nine TBI patients. An experienced neuroradiologist and a radiologist in training assessed the presence of hemorrhages in the final images and determined the false positives and false negatives. The 9 CT scans contained 67 small haemorrhages, of which 97% was correctly detected by our system. The neuroradiologist detected three false positives, and the radiologist in training found two false positives. For one patient, our method showed a hemorrhagic contusion that was originally missed. Comparing individual CT scans with a computed average may assist the physicians in detecting small traumatic hemorrhages in patients with TBI.

Gepubliceerd: J Med Imaging (Bellingham) 2018 Apr;5(2):024004
Impact factor: 0; nvt

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2. MR arthrography is slightly more accurate than conventional MRI in detecting TFCC lesions of the wrist
Boer BC, Vestering M, van Raak SM, van Kooten EO, Huis In 't Veld R, Vochteloo AJH

Introduction: In case of clinical suspicion of triangular fibrocartilage complex (TFCC) injury, different imaging techniques are used. The aim of this study was to determine whether MRA is superior to MRI and whether 3.0 T is better than 1.5 T (expresses in sensitivity, specificity and accuracy) in detecting TFCC injury, using arthroscopy as the gold standard.
Materials and methods: The arthroscopic and MR findings of 150 patients who underwent arthroscopy for ulnar-sided wrist pain between January 2009 and November 2016 were retrospectively reviewed.
Results: MRA was slightly more accurate compared to conventional MRI, and 1.5 T was slightly more accurate than 3.0 T. 1.5 T wrist MRA had a sensitivity of 80%, a specificity of 100% and accuracy of 90%; 3.0 T wrist MRA 73, 100 and 86%, resp. Conventional 1.5 T wrist MRI had a sensitivity of 71%, a specificity of 75% and accuracy of 73%. For 3.0 T conventional MRI, this was 73, 67 and 70%, resp.
Conclusions: MRA seems slightly superior to conventional MRI, but one could question whether this difference in diagnostic accuracy outweighs the burden and

risks of an invasive procedure for patients with its additional costs. Furthermore, we could not confirm the superiority of 3 T compared to 1.5 T.

Gepubliceerd: Eur J Orthop Surg Traumatol 2018 Dec;28(8):1549-53
Impact factor: 0.181; Q4

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3. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast
de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, Sernee A, Klazen CAH, Lobbes MBI, van der Hulst RRWJ, Rakhorst HA, de Jong D

Importance: Breast implants are among the most commonly used medical devices. Since 2008, the number of women with breast implants diagnosed with anaplastic large-cell lymphoma in the breast (breast-ALCL) has increased, and several reports have suggested an association between breast implants and risk of breast-ALCL. However, relative and absolute risks of breast-ALCL in women with implants are still unknown, precluding evidence-based counseling about implants. Objective: To determine relative and absolute risks of breast-ALCL in women with breast implants.
Design, setting, and participants: Through the population-based nationwide Dutch pathology registry we identified all patients diagnosed with primary non-Hodgkin lymphoma in the breast between 1990 and 2016 and retrieved clinical data, including breast implant status, from the treating physicians. We estimated the odds ratio (OR) of ALCL associated with breast implants in a case-control design, comparing implant prevalence between women with breast-ALCL and women with other types of breast lymphoma. Cumulative risk of breast-ALCL was derived from the age-specific prevalence of breast implants in Dutch women, estimated from an examination of 3000 chest x-rays and time trends from implant sales.
Main outcomes and measures: Relative and absolute risks of breast-ALCL in women with breast implants.
Results: Among 43 patients with breast-ALCL (median age, 59 years), 32 had ipsilateral breast implants, compared with 1 among 146 women with other primary breast lymphomas (OR, 421.8; 95% CI, 52.6-3385.2). Implants among breast-ALCL cases were more often macrotextured (23 macrotextured of 28 total implants of known type, 82%) than expected (49193 sold macrotextured implants of total sold 109449 between 2010 and 2015, 45%) based on sales data ($P < .001$). The estimated prevalence of breast implants in women aged 20 to 70 years was 3.3%. Cumulative risks of breast-ALCL in women with implants were 29 per million at 50 years and 82 per million at 70 years. The number of women with implants needed to cause 1 breast-ALCL case before age 75 years was 6920.
Conclusion and relevance: Breast implants are associated with increased risk of breast-ALCL, but the absolute risk remains small. Our results emphasize the need for increased awareness among the public, medical professionals, and regulatory bodies, promotion of alternative cosmetic procedures, and alertness to signs and symptoms of breast-ALCL in women with implants.

Gepubliceerd: JAMA Oncol 2018 Mar 1;4(3):335-41
Impact factor: 20.871; Q1

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4. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial
Firanescu CE, de Vries J, Lodder P, Venmans A, Schoemaker MC, Smeet AJ, Donga E, Juttmann JR, Klazen CAH, Elgersma OEH, Jansen FH, Tielbeek AV, Boukrab I, Schonenberg K, van Rooij WJJ, Hirsch JA, Lohle PNM

Objective: To assess whether percutaneous vertebroplasty results in more pain relief than a sham procedure in patients with acute osteoporotic compression fractures of the vertebral body.
Design: Randomised, double blind, sham controlled clinical trial.
Setting: Four community hospitals in the Netherlands, 2011-15.
Participants: 180 participants requiring treatment for acute osteoporotic vertebral compression fractures were randomised to either vertebroplasty (n=91) or a sham procedure (n=89).
Interventions: Participants received local subcutaneous lidocaine (lignocaine) and bupivacaine at each pedicle. The vertebroplasty group also received cementation, which was simulated in the sham procedure group.
Main outcome measures: Main outcome measure was mean reduction in visual analogue scale (VAS) scores at one day, one week, and one, three, six, and 12 months. Clinically significant pain relief was defined as a decrease of 1.5 points in VAS scores from baseline. Secondary outcome measures were the differences between groups for changes in the quality of life for osteoporosis and Roland-Morris disability questionnaire scores during 12 months' follow-up.
Results: The mean reduction in VAS score was statistically significant in the vertebroplasty and sham procedure groups at all follow-up points after the procedure compared with baseline. The mean difference in VAS scores between groups was 0.20 (95% confidence interval -0.53 to 0.94) at baseline, -0.43 (-1.17 to 0.31) at one day, -0.11 (-0.85 to 0.63) at one week, 0.41 (-0.33 to 1.15) at one month, 0.21 (-0.54 to 0.96) at three months, 0.39 (-0.37 to 1.15) at six months, and 0.45 (-0.37 to 1.24) at 12 months. These changes in VAS scores did not, however, differ statistically significantly between the groups during 12 months' follow-up. The results for secondary outcomes were not statistically significant. Use of analgesics (non-opioids, weak opioids, strong opioids) decreased statistically significantly in both groups at all time points, with no statistically significant differences between groups. Two adverse events occurred in the vertebroplasty group: one respiratory insufficiency and one vasovagal reaction.
Conclusions: Percutaneous vertebroplasty did not result in statistically significantly greater pain relief than a sham procedure during 12 months' follow-up among patients with acute osteoporotic vertebral compression fractures.
Trial registration: ClinicalTrials.gov NCT01200277.

Gepubliceerd: BMJ 2018 May 9;361:k1551
Impact factor: 23.562; Q1

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5. [A woman with spontaneous neck pain]
Geerdes M, Smook SP, von Schukkmann TA

A 42-year-old woman presented with neck pain without previous trauma. On suspicion of spondylodiscitis, an MRI of the cervical spine was made. This MRI and an additional CT showed calcific tendinitis of the longus colli muscle, a self-limiting disorder.

Gepubliceerd: Ned Tijdschr Geneeskd 2018;162:D2042
Impact factor: 0; nvt

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6. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry)
Jansen IGH, Mulder MJHL, Goldhoorn RB, MR CLEAN Registry Investigators,includes HM den Hertog en EJC Sturm

Objective: To determine outcomes and safety of endovascular treatment for acute ischaemic stroke, due to proximal intracranial vessel occlusion in the anterior circulation, in routine clinical practice.
Design: Ongoing, prospective, observational cohort study.
Setting: 16 centres that perform endovascular treatment in the Netherlands.
Participants: 1488 patients included in the Multicentre Randomised Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) Registry who had received endovascular treatment, including stent retriever thrombectomy, aspiration, and all alternative methods for acute ischaemic stroke within 6.5 hours from onset of symptoms between March 2014 and June 2016.
Main outcome measures: The primary outcome was the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death) at 90 days after the onset of symptoms. Secondary outcomes were excellent functional outcome (mRS score 0-1), good functional outcome (mRS score 0-2), and favourable functional outcome (mRS score 0-3) at 90 days; score on the extended thrombolysis in cerebral infarction scale at the end of the intervention procedure; National Institutes of Health Stroke Scale score 24-48 hours after intervention; and complications that occurred during intervention, hospital admission, or three months' follow up period. Outcomes and safety variables in the MR CLEAN Registry were compared with the MR CLEAN trial intervention and control arms.
Results: A statistically significant shift was observed towards better functional outcome in patients in the MR CLEAN Registry compared with the MR CLEAN trial intervention arm (adjusted common odds ratio 1.30, 95% confidence interval 1.02 to 1.67) and the MR CLEAN trial control arm (1.85, 1.46 to 2.34). The reperfusion rate, with successful reperfusion defined as a score of 2B-3 on the extended thrombolysis in cerebral infarction score, was 58.7%, the same as for patients in the MR CLEAN trial. Duration from onset of stroke to start of endovascular treatment and from onset of stroke to successful reperfusion or last contrast bolus was one hour shorter for patients in the MR CLEAN Registry. Symptomatic intracranial haemorrhage occurred in 5.8% of patients in the MR CLEAN Registry compared with 7.7% in the MR CLEAN trial intervention arm and 6.4% in the MR CLEAN trial control arm.
Conclusion: In routine clinical practice, endovascular treatment for patients with acute ischaemic stroke is at least as effective and safe as in the setting of a randomised controlled trial.

Gepubliceerd: BMJ 2018 Mar 9;360:k949

Impact factor: 23.562; Q1

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7. Functional MRI for Treatment Evaluation in Patients with Head and Neck Squamous Cell Carcinoma: A Review of the Literature from a Radiologist Perspective
Nooij RP, Hof JJ, van Laar PJ, van der Hoorn A

Purpose of review: To show the role of functional MRI in patients treated for head and neck squamous cell carcinoma.
Recent findings: MRI is commonly used for treatment evaluation in patients with head and neck tumors. However, anatomical MRI has its limits in differentiating between post-treatment effects and tumor recurrence. Recent studies showed promising results of functional MRI for response evaluation.
Summary: This review analyzes possibilities and limitations of functional MRI sequences separately to obtain insight in the post-therapy setting. Diffusion, perfusion and spectroscopy show promise, especially when utilized complimentary to each other. These functional MRI sequences aid in the early detection which might improve survival by increasing effectiveness of salvage therapy. Future multicenter longitudinal prospective studies are needed to provide standardized guidelines for the use of functional MRI in daily clinical practice.

Gepubliceerd: Curr Radiol Rep 2018;6(1):2
Impact factor: 0; nvt

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8. Validation and update of a lymph node metastasis prediction model for breast cancer
Qiu SQ, Aarnink M, van Maaren MC, Dorrius MD, Bhattacharya A, Veltman J, Klazen CAH, Korte JH, Estourgie SH, Ott P, Kelder W, Zeng HC, Koffijberg H, Zhang GJ, van Dam GM, Siesling S

Purpose: This study aimed to validate and update a model for predicting the risk of axillary lymph node (ALN) metastasis for assisting clinical decision-making.
Methods: We included breast cancer patients diagnosed at six Dutch hospitals between 2011 and 2015 to validate the original model which includes six variables: clinical tumor size, tumor grade, estrogen receptor status, lymph node longest axis, cortical thickness and hilum status as detected by ultrasonography. Subsequently, we updated the original model using generalized linear model (GLM) tree analysis and by adjusting its intercept and slope. The area under the receiver operator characteristic curve (AUC) and calibration curve were used to assess the original and updated models. Clinical usefulness of the model was evaluated by false-negative rates (FNRs) at different cut-off points for the predictive probability.
Results: Data from 1416 patients were analyzed. The AUC for the original model was 0.774. Patients were classified into four risk groups by GLM analysis, for which four updated models were created. The AUC for the updated models was 0.812. The calibration curves showed that the updated model predictions were better in agreement with actual observations than the original model predictions. FNRs of the updated models were lower than the preset 10% at all cut-off points when the predictive probability was less than 12.0%.

Conclusions: The original model showed good performance in the Dutch validation population. The updated models resulted in more accurate ALN metastasis prediction and could be useful preoperative tools in selecting low-risk patients for omission of axillary surgery.

Gepubliceerd: Eur J Surg Oncol 2018 May;44(5):700-7
Impact factor: 3.184; Q1

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9. Mono, bi- and tri-exponential diffusion MRI modelling for renal solid masses and comparison with histopathological findings
van Baalen S, Froeling M, Asselman M, Klazen C, Jeltes C, van Dijk L, Vroling B, Dik P, Ten Haken B

Purpose: To compare diffusion tensor imaging (DTI), intravoxel incoherent motion (IVIM), and tri-exponential models of the diffusion magnetic resonance imaging (MRI) signal for the characterization of renal lesions in relationship to histopathological findings.
Methods: Sixteen patients planned to undergo nephrectomy for kidney tumour were scanned before surgery at 3 T magnetic resonance imaging (MRI), with T2-weighted imaging, DTI and diffusion weighted imaging (DWI) using ten b-values. DTI parameters (mean diffusivity [MD] and fractional anisotropy [FA]) were obtained by iterative weighted linear least squared fitting of the DTI data and bi-, and tri-exponential fit parameters (Dbi, fstar,and Dtri, ffast,finterm) using a nonlinear fit of the multiple b-value DWI data. Average parameters were calculated for regions of interest, selecting the lesions and healthy kidney tissue. Tumour type and specificities were determined after surgery by histological examination. Mean parameter values of healthy tissue and solid lesions were compared using a Wilcoxon-signed ranked test and MANOVA.
Results: Thirteen solid lesions (nine clear cell carcinomas, two papillary renal cell carcinoma, one haemangioma and one oncocytoma) and four cysts were included. The mean MD of solid lesions are significantly ($p < 0.05$) lower than healthy cortex and medulla, (1.94 +/- 0.32*10(- 3) mm(2)/s versus 2.16 +/- 0.12*10(- 3) mm(2)/s and 2.21 +/- 0.14*10(- 3) mm(2)/s, respectively) whereas ffast is significantly higher (7.30 +/- 3.29% versus 4.14 +/- 1.92% and 4.57 +/- 1.74%) and finterm is significantly lower (18.7 +/- 5.02% versus 28.8 +/- 5.09% and 26.4 +/- 6.65%). Diffusion coefficients were high (>/=2.0*10(- 3) mm(2)/s for MD, 1.90*10(- 3) mm(2)/s for Dbi and 1.6*10(- 3) mm(2)/s for Dtri) in cc-RCCs with cystic structures and/or haemorrhaging and low (</=1.80*10(- 3) mm(2)/s for MD, 1.40*10(- 3) mm(2)/s for Dbi and 1.05*10(- 3) mm(2)/s for Dtri) in tumours with necrosis or sarcomatoid differentiation.
Conclusion: Parameters derived from a two- or three-component fit of the diffusion signal are sensitive to histopathological features of kidney lesions.

Gepubliceerd: Cancer Imaging 2018 Nov 26;18(1):44
Impact factor: 3.016; Q2

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10. Proximal and Distal Occlusion of Complex Cerebral Aneurysms-Implications of Flow Modeling by Fluid-Structure Interaction Analysis
Helthuis JHG, Bhat S, van Doormaal TPC, Kumar RK, van der Zwan A

Background: In complex cerebral aneurysms, adequate treatment by complete occlusion is not always possible. Partial occlusion by either proximal or distal occlusion is an alternative. However, the hemodynamic consequences of these partial occlusion options are often not easily predictable.
Objective: To assess the feasibility of fluid-structure interaction (FSI) analysis to investigate the hemodynamic changes after partial occlusion in cerebral aneurysms.
Methods: Two patients were analyzed. One was treated by proximal occlusion and 1 by distal occlusion. In both, flow replacement bypass surgery was performed. Three-dimensional models were constructed from magnetic resonance angiography (MRA) scans and used for FSI analysis. A comparative study was done for pre- and postoperative conditions. Postoperative thrombosis was modeled and analyzed for the distal occlusion. FSI results were compared to postoperative angiograms and computed tomography (CT)-scans.
Results: Proximal occlusion resulted in reduction of velocity, wall shear stresses, and disappearance of helical flow patterns in the complete aneurysm. Distal occlusion showed a decrease of velocity and wall shear stress in the dome of the aneurysm. Results were validated against postoperative CT-scans and angiograms at 1-, 7-, and 9-mo follow-up. Addition of thrombus to the distal occlusion model showed no change in velocities and luminal pressure but resulted in decrease in wall tension.
Conclusion: This pilot study showed hemodynamic changes in 2 patients with proximal and distal occlusion of complex cerebral aneurysms. The FSI results were in line with the follow-up CT scans and angiograms and indicate the potential of FSI as a tool in patient-specific surgical interventions.

Gepubliceerd: Oper Neurosurg (Hagerstown) 2018 Aug 1;15(2):217-30
Impact factor: 1.670; Q3

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11. High resolution 7T and 9.4T-MRI of human cerebral arterial casts enables accurate estimations of the cerebrovascular morphometry
Helthuis JHG, van der Zwan A, van Doormaal TPC, Bleys RLAW, Harteveld AA, van der Toorn A, Brozici M, Hendrikse J, Zwanenburg JJM

Quantitative data on the morphology of the cerebral arterial tree could aid in modelling and understanding cerebrovascular diseases, but is scarce in the range between 200 micrometres and 1 mm diameter arteries. Traditional manual measurements are difficult and time consuming. 7T-MRI and 9.4T-MRI of human cerebral arterial plastic casts could proof feasible for acquiring detailed morphological data of the cerebral arterial tree in a time efficient method. One cast of the complete human cerebral arterial circulation embedded in gadolinium-containing gelatine gel was scanned at 7T-MRI (0.1 mm isotropic resolution). A small section of another cast was scanned at 9.4T-MRI (30 microm isotropic resolution). Subsequent 3D-reconstruction was performed using a semi-automatic approach. Validation of 7T-MRI was performed by comparing the radius calculated using MRI to manual measurements on the same cast. As manual measurement of the small section was not feasible, 9.4T-MRI was validated by scanning the small section both at 7T-MRI and 9.4T MRI and comparing the diameters of arterial segments. Linear regression slopes were 0.97 (R-squared 0.94) and 1.0 (R-squared 0.90) for 7T-MRI and 9.4T-MRI. This data shows that 7T-MRI and 9.4T-MRI and subsequent 3D reconstruction

of plastic casts is feasible, and allows for characterization of human cerebral arterial tree morphology.

Gepubliceerd: Sci Rep 2018 Sep 24;8(1):14235
Impact factor: 4.122; Q1

Totale impact factor: 80.168
Gemiddelde impact factor: 7.288

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 5.973
Gemiddelde impact factor: 0.996

Radiotherapie

1. Breast-conserving therapy for primary Ductal Carcinoma in Situ in The Netherlands: A multi-center study and population-based analysis
Jobsen JJ, Scheijmans LJEE, Smit WGJM, Stenfert Kroese MC, Struikmans H, van der Palen J

Objective: The aim of this study was to analyse the efficacy of breast-conserving therapy (BCT) for women with primary DCIS in a population-based setting.
Methods: Data were used from five Radiotherapy centres in The Netherlands from 2000 to 2010, all treated with BCT. Of all the cases, 59.2% received a boost of radiotherapy after their whole breast irradiation (WBI), irrespective of margin status.
Results: A total of 1248 cases with primary DCIS were analysed. The 10-years LRFS was 92.9%. Age </=50 years and a positive margin were significantly related to local relapse free survival (LRFS). Having a boost had no impact on LRFS, showing a nearly equal recurrence pattern in patients with and without a boost. Separate analyses were done on patients who had received and not received a boost of radiotherapy after WBI. We noted 9.1% contra-lateral breast tumours. The 10-years disease specific survival (DSS) rate was 99.0%.
Conclusions: DCIS of the breast and treated with BCT results in excellent LRFS and DSS. Primary surgical lumpectomy with negative margins followed by WBI seems to be the treatment of choice in DCIS treated with BCS with respect to IBTR.

Gepubliceerd: Breast 2018 Jul 18;42:3-9
Impact factor: 2.951; Q1

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2. Totally minimally invasive esophagectomy after neoadjuvant chemoradiotherapy: Long-term oncologic outcomes
Lubbers M, van Det MJ, Kreuger MJ, Hoekstra R, Hendriksen EM, Vermeer M, Kouwenhoven EA

Background and objectives: Minimally invasive esophagectomy is emerging with comparable short-term outcomes as open esophagectomies. Neoadjuvant chemoradiotherapy followed by surgery is considered standard of care in the Netherlands for patients with esophageal cancer. The aim of this study was to analyze the long-term oncologic outcome after neoadjuvant chemoradiotherapy followed by totally minimally invasive esophagectomy.
Methods: Neoadjuvant carboplatin and paclitaxel based chemotherapy was concomitantly given with 41.4 Gy radiotherapy. Six weeks after neoadjuvant treatment, totally minimally invasive esophagectomy was performed.
Results: From December 2010 until December 2015 161 patients received this combination of treatment. In 128 male and 33 female patients with median age of 65 years (58-71), 88 minimally invasive esophagectomies with intrathoracic anastomosis and 73 minimally invasive esophagectomies with cervical anastomosis were carried out. Radical (R0) resection was confirmed in 156 patients (97%). In hospital mortality occurred in 6 patients (3.7%). Overall survival was 79% and 51% at 1 and 5 years, respectively, with a median follow-up of 24.5 months (13-38). Disease-free survival was, respectively, 76% and 55%.

Conclusions: Totally minimally invasive esophagectomy after neoadjuvant chemoradiotherapy for esophageal cancer is a safe treatment with low postoperative mortality rates and favorable overall and disease-free survival.

Gepubliceerd: J Surg Oncol 2018 Mar;117(4):651-8
Impact factor: 2.886; Q1

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3. Interobserver variability in the delineation of the primary lung cancer and lymph nodes on different four-dimensional computed tomography reconstructions
Mercieca S, Belderbos JSA, De Jaeger K, Schinagl DAX, van der Voort Van Zijp N, Pomp J, Theuws J, Khalifa J, van de Vaart P, van Herk M

Purpose: The study compared interobserver variation in the delineation of the primary tumour (GTVp) and lymph nodes (GTVln) between three different 4DCT reconstruction types; Maximum Intensity Projection (MIP), Mid-Ventilation (Mid-V) and Mid-Position (Mid-P).
Material and methods: Seven radiation oncologists delineated the GTVp and GTVln on the MIP, Mid-V and Mid-P 4DCT image reconstructions of 10 lung cancer patients. The volumes, the mean standard deviation (SD) and distribution of SD (SD/area) over the median surface contour were compared for different tumour regions.
Results: The overall mean delineated volume on the MIP was significantly larger ($p<0.001$) than the Mid-V and Mid-P. For the GTVp the Mid-P had the lowest interobserver variation (SD=0.261cm), followed by Mid-V (SD=0.314cm) and MIP (SD=0.330cm) For GTVln the Mid-V had the lowest interobserver variation (SD=0.425cm) followed by the MIP (SD=0.477cm) and Mid-P (SD=0.543cm). The SD/area distribution showed a statistically significant difference between the MIP versus Mid-P and Mid-P versus Mid-V for both GTVp and GTVln ($p<0.001$), with outliers indicating interpretation differences for GTVp located close to the mediastinum and GTVln.
Conclusion: The Mid-P reduced the interobserver variation for the GTVp. Delineation protocols must be improved to benefit from the improved image quality of Mid-P for the GTVln.

Gepubliceerd: Radiother Oncol 2018;126(2):325-32
Impact factor: 4.942; Q1

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4. Comparison of 36 Gy, 20 Gy, or No Radiation Therapy After 6 Cycles of EBVP Chemotherapy and Complete Remission in Early-Stage Hodgkin Lymphoma Without Risk Factors: Results of the EORT-GELA H9-F Intergroup Randomized Trial
Thomas J, Ferme C, Noordijk EM, Morschhauser F, Girinsky T, Gaillard I, Lugtenburg PJ, Andre M, Lybeert MLM, Stamatoullas A, Beijert M, Helias P, Eghbali H, Gabarre J, van der Maazen RWM, Jaubert J, Bouabdallah K, Boulat O, Roesink JM, Christian B, Ong F, Bordessoule D, Tertian G, Gonzalez H, Vranovsky A, Quittet P, Tirelli U, de Jong D, Audouin J, Aleman BMP, Henry-Amar M

Purpose: While patients with early-stage Hodgkin lymphoma (HL) have an excellent outcome with combined treatment, the radiation therapy (RT) dose and treatment with chemotherapy alone remain questionable. This noninferiority trial evaluates the feasibility of reducing the dose or omitting RT after chemotherapy.
Methods and materials: Patients with untreated supradiaphragmatic HL without risk factors (age >/= 50 years, 4 to 5 nodal areas involved, mediastinum-thoracic ratio >/= 0.35, and erythrocyte sedimentation rate >/= 50 mm in first hour without B symptoms or erythrocyte sedimentation rate >/= 30 mm in first hour with B symptoms) were eligible for the trial. Patients in complete remission after chemotherapy were randomized to no RT, low-dose RT (20 Gy in 10 fractions), or standard-dose involved-field RT (36 Gy in 18 fractions). The limit of noninferiority was 10% for the difference between 5-year relapse-free survival (RFS) estimates. From September 1998 to May 2004, 783 patients received 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone; 592 achieved complete remission or unconfirmed complete remission, of whom 578 were randomized to receive 36 Gy (n=239), 20 Gy of involved-field RT (n=209), or no RT (n=130).
Results: Randomization to the no-RT arm was prematurely stopped (>/=20% rate of inacceptable events: toxicity, treatment modification, early relapse, or death). Results in the 20-Gy arm (5-year RFS, 84.2%) were not inferior to those in the 36-Gy arm (5-year RFS, 88.6%) (difference, 4.4%; 90% confidence interval [CI] -1.2% to 9.9%). A difference of 16.5% (90% CI 8.0%-25.0%) in 5-year RFS estimates was observed between the no-RT arm (69.8%) and the 36-Gy arm (86.3%); the hazard ratio was 2.55 (95% CI 1.44-4.53; P<.001). The 5-year overall survival estimates ranged from 97% to 99%.
Conclusions: In adult patients with early-stage HL without risk factors in complete remission after epirubicin, bleomycin, vinblastine, and prednisone chemotherapy, the RT dose may be limited to 20 Gy without compromising disease control. Omitting RT in these patients may jeopardize the treatment outcome.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2017 Oct 27;100(5):1133-45
Impact factor: 5.554; Q1

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5. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy
Wortman BG, Creutzberg CL, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, van der Steen-Banasik EM, Mens JWM, Slot A, Kroese MCS, van Triest B, Nijman HW, Stelloo E, Bosse T, de Boer SM, van Putten WLJ, Smit VTHB, Nout RA

Background: PORTEC-2 was a randomised trial for women with high-intermediate risk (HIR) endometrial cancer, comparing pelvic external beam radiotherapy (EBRT) with vaginal brachytherapy (VBT). We evaluated long-term outcomes combined with the results of pathology review and molecular analysis.
Methods: 427 women with HIR endometrial cancer were randomised between 2002-2006 to VBT or EBRT. Primary endpoint was vaginal recurrence (VR). Pathology review was done in 97.4%, combined with molecular analysis.
Results: Median follow-up was 116 months; 10-year VR was 3.4% versus 2.4% for VBT vs. EBRT (p = 0.55). Ten-year pelvic recurrence (PR) was more frequent in the VBT group (6.3% vs. 0.9%, p = 0.004), mostly combined with distant metastases (DM). Ten-year isolated PR was 2.5% vs. 0.5%, p = 0.10, and DM 10.4 vs. 8.9% (p =

0.45). Overall survival for VBT vs. EBRT was 69.5% vs. 67.6% at 10 years (p = 0.72). L1CAM and p53-mutant expression and substantial lymph-vascular space invasion were risk factors for PR and DM. EBRT reduced PR in cases with these risk factors. **Conclusion:** Long-term results of the PORTEC-2 trial confirm VBT as standard adjuvant treatment for HIR endometrial cancer. Molecular risk assessment has the potential to guide adjuvant therapy. EBRT provided better pelvic control in patients with unfavourable risk factors.

Gepubliceerd: Br J Cancer 2018 Oct;119(9):1067-74
Impact factor: 5.922; Q1

Totale impact factor: 22.255
Gemiddelde impact factor: 4.451

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.951
Gemiddelde impact factor: 2.951

Reumatologie

1. A goal management intervention for patients with polyarthritis and elevated levels of depressive symptoms: a quasiexperimental study
Arends RY, Bode C, Taal E, van de Laar MAFJ

Purpose: Goal was to establish whether an intervention that aims to increase goal management competencies is effective in decreasing elevated levels of depressive symptoms and increasing well-being in patients with polyarthritis.
Materials and methods: Eighty-five persons with polyarthritis and elevated levels of depressive symptoms participated in the goal management intervention consisting of six group-based meetings. A quasiexperimental design with baseline measurement, follow-up at 6 months and a reference group of 151 patients from an observational study was applied. Primary outcome was depression; secondary outcomes were anxiety, purpose in life, positive affect, satisfaction with participation, goal management strategies, and arthritis self-efficacy. A linear mixed model procedure was applied to evaluate changes in outcomes.
Results: No improvement was found for depressive symptoms and no changes were found for the secondary outcomes, except for positive affect that improved in the intervention group. This increase was mediated by an increase in goal adjustment. Furthermore, goal maintenance decreased and self-efficacy for other symptoms increased in the intervention group.
Conclusion: This study indicates that interventions designed to aid patients with arthritis with goal management skills are potentially helpful for increasing positive affect, although further studies are needed. Implications for rehabilitation People with polyarthritis have to manage their disease in combination with possibly conflicting roles and personal goals, resulting in an ongoing process of finding equilibrium in a constantly changing situation. Based on a person-focused view, the program Right on Target focused on coping with threatened activities and life goals due to arthritis. The program consisted of six group-based meetings led by a trained nurse and a personal trajectory wherein participants were stimulated to try out various behavioral options related to an own threatened activity in concordance with their personal goals. The program seemed effective in increasing flexible goal adjustment and self-efficacy and participants experienced more positive affect directly after the program and at 6-month follow-up.

Gepubliceerd: Disabil Rehabil 2018 Nov 19;1-10
Impact factor: 2.042; Q1

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2. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis
Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel PLCM, Gabriel SE, Matteson EL, Kvien TK, Douglas K, Sandoo A, Arts E, Wallberg-Jonsson S, Innala L, Karpouzas G, Dessein PH, Tsang L, El-Gabalawy H, Hitchon C, Ramos VP, Yanez IC, Sfikakis PP, Zampeli E, Gonzalez-Gay MA, Corrales A, van de Laar MA, Vonkeman HE, Meek I, Semb AG

Objectives: Patients with rheumatoid arthritis (RA) have an excess risk of cardiovascular disease (CVD). We aimed to assess the impact of CVD risk factors, including potential sex differences, and RA-specific variables on CVD outcome in a large, international cohort of patients with RA.
Methods: In 13 rheumatology centres, data on CVD risk factors and RA characteristics were collected at baseline. CVD outcomes (myocardial infarction, angina, revascularisation, stroke, peripheral vascular disease and CVD death) were collected using standardised definitions.
Results: 5638 patients with RA and no prior CVD were included (mean age: 55.3 (SD: 14.0) years, 76% women). During mean follow-up of 5.8 (SD: 4.4) years, 148 men and 241 women developed a CVD event (10-year cumulative incidence 20.9% and 11.1%, respectively). Men had a higher burden of CVD risk factors, including increased blood pressure, higher total cholesterol and smoking prevalence than women (all $p<0.001$). Among the traditional CVD risk factors, smoking and hypertension had the highest population attributable risk (PAR) overall and among both sexes, followed by total cholesterol. The PAR for Disease Activity Score and for seropositivity were comparable in magnitude to the PAR for lipids. A total of 70% of CVD events were attributable to all CVD risk factors and RA characteristics combined (separately 49% CVD risk factors and 30% RA characteristics).
Conclusions: In a large, international cohort of patients with RA, 30% of CVD events were attributable to RA characteristics. This finding indicates that RA characteristics play an important role in efforts to reduce CVD risk among patients with RA.

Gepubliceerd: Ann Rheum Dis 2018;77(1):48-54
Impact factor: 12.350; Q1

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3. Development of an item bank to measure factual disease and treatment related knowledge of rheumatoid arthritis patients in the treat to target era
de Jonge MJ, Oude Voshaar MAH, Huis AMP, van de Laar MAFJ, Hulscher MEJL, van Riel PLCM

Objective: To develop a Disease and treatment associated Knowledge in RA item bank (DataK-RA) based on item response theory.
Methods: Initial items were developed from a systematic review. Rheumatology professionals identified relevant content trough a RAND modified Delphi scoring procedure and consensus meeting. RA patients provided additional content trough a focus group. Patients and professionals rated readability, feasibility and comprehensiveness of resulting items. Cross-sectional data were collected to evaluate psychometric properties of the items.
Results: Data of 473 patients were used for item reduction and calibration. Twenty items were discarded based on corrected item-total point biserial correlation <0.30. Confirmatory factor analysis with weighted least squares estimation on the polychoric correlation matrix suggested good fit for a unidimensional model for the remaining 42 items (CFI 0.97 TLI=0.97, RMSEA=0.02, WRMR=0.97), supporting the proposed scoring procedure. Scores were highly reliable and normally distributed with minimal ceiling (1.8%) and no floor effects. 75% of tested hypotheses about the association of DataK-RA scores with related constructs were supported, indicating good construct validity.

Conclusion: DataK-RA is a psychometrically sound item bank. PRACTICE IMPLICATIONS: DataK-RA provides health professionals and researchers with a tool to identify and target patients' information needs or to assess effects of educational efforts.

Gepubliceerd: Patient Educ Couns 2018;101(1):67-73
Impact factor: 2.785; Q2

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4. Tailored, Therapist-Guided Internet-Based Cognitive Behavioral Therapy Compared to Care as Usual for Patients With Rheumatoid Arthritis: Economic Evaluation of a Randomized Controlled Trial
Ferwerda M, van Beugen S, van Middendorp H, Visser H, Vonkeman H, Creemers M, van Riel P, Kievit W, Evers A

Background: Internet-based cognitive behavioral therapy can aid patients with rheumatoid arthritis with elevated levels of distress to enhance their quality of life. However, implementation is currently lacking and there is little evidence available on the (cost-) effectiveness of different treatment strategies.
Objective: Cost-benefit ratios are necessary for informing stakeholders and motivating them to implement effective treatment strategies for improving health-related quality of life (HRQoL) of patients with rheumatoid arthritis. A cost-effectiveness study from a societal perspective was conducted alongside a randomized controlled trial on a tailored, therapist-guided internet-based cognitive behavioral therapy (ICBT) intervention for patients with rheumatoid arthritis with elevated levels of distress as an addition to care as usual (CAU).
Methods: Data were collected at baseline or preintervention, 6 months or postintervention, and every 3 months thereafter during the 1-year follow-up. Effects were measured in terms of quality-adjusted life years (QALYs) and costs from a societal perspective, including health care sector costs (health care use, medication, and intervention costs), patient travel costs for health care use, and costs associated with loss of labor.
Results: The intervention improved the quality of life compared with only CAU (Delta QALYs=0.059), but at a higher cost (Delta=€4211). However, this increased cost substantially reduced when medication costs were left out of the equation (Delta=€1863). Of all, 93% (930/1000) of the simulated incremental cost-effectiveness ratios were in the north-east quadrant, indicating a high probability that the intervention was effective in improving HRQoL, but at a greater monetary cost for society compared with only CAU.
Conclusions: A tailored and guided ICBT intervention as an addition to CAU for patients with rheumatoid arthritis with elevated levels of distress was effective in improving quality of life. Consequently, implementation of ICBT into standard health care for patients with rheumatoid arthritis is recommended. However, further studies on cost reductions in this population are warranted.
Trial registration: Nederlands Trial Register NTR2100

Gepubliceerd: J Med Internet Res 2018 Oct 11;20(10):e260
Impact factor: 4.671; Q1

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5. Impact of Stopping Tumor Necrosis Factor Inhibitors on Rheumatoid Arthritis Patients' Burden of Disease
Ghiti Moghadam M, Ten Klooster PM, Vonkeman HE, Kneepkens EL, Klaasen R, Stolk JN, Tchetverikov I, Vreugdenhil SA, van Woerkom JM, Goekoop-Ruiterman YPM, Landewe RBM, van Riel PLCM, van de Laar MAFJ, Jansen TL

Objective: To determine the impact of stopping tumor necrosis factor inhibitor (TNFi) treatment on patient-reported outcomes (PROs) of physical and mental health status, health utility, pain, disability, and fatigue in patients with established rheumatoid arthritis (RA).
Methods: In the pragmatic, 12-month POET trial, 817 RA patients with >/=6 months of remission or stable low disease activity were randomized 2:1 to stopping or continuing TNFi. In case of flare, TNFi was restarted at the discretion of the rheumatologist. PROs were assessed every 3 months.
Results: TNFi was restarted within 12 months in 252 of 531 patients (47.5%) in the stop group. At 3 months, mean PRO scores were significantly worse in the stop group, and a larger proportion of patients experienced a minimum clinically important difference (MCID) on all PROs. Effect sizes (ES) were strongest for health utility (ES -0.24) and pain (ES -0.30). Mean scores improved again after this point, but disability scores remained significantly different at 12 months. After 12 months, the relative risk of experiencing an MCID ranged from 1.16 for mental health status to 1.58 for fatigue. Mean PRO scores for patients restarting TNFi within 6 months were no longer significantly different from those that did not restart TNFi at 12 months.
Conclusion: Stopping TNFi had a significant negative short-term impact on a broad range of PROs. Long-term negative consequences appeared to be limited, and outcomes in patients needing to restart TNFi within the first 6 months tended to be restored at 12 months.

Gepubliceerd: Arthritis Care Res (Hoboken) 2018 Apr;70(4):516-24
Impact factor: 4.149; Q1

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6. Multi-biomarker disease activity score as a predictor of disease relapse in patients with rheumatoid arthritis stopping TNF inhibitor treatment
Ghiti Moghadam M, Lamers-Karnebeek FBG, Vonkeman HE, Ten Klooster PM, Tekstra J, Schilder AM, Visser H, Sasso EH, Chernoff D, Lems WF, van Schaardenburg DJ, Landewe R, Bernelot Moens HJ, Radstake TRDJ, van Riel PLCM, van de Laar MAFJ, Jansen TL

Objective: Successfully stopping or reducing treatment for patients with rheumatoid arthritis (RA) in low disease activity (LDA) may improve cost-effectiveness of care. We evaluated the multi-biomarker disease activity (MBDA) score as a predictor of disease relapse after discontinuation of TNF inhibitor (TNFi) treatment.
Methods: 439 RA patients who were randomized to stop TNFi treatment in the POET study were analyzed post-hoc. Three indicators of disease relapse were assessed over 12 months: 1) restarting TNFi treatment, 2) escalation of any DMARD therapy and 3) physician-reported flare. MBDA score was assessed at baseline. Associations between MBDA score and disease relapse were examined using univariate analysis and multivariate logistic regression.

Results: At baseline, 50.1%, 35.3% and 14.6% of patients had low (<30), moderate (30-44) or high (>44) MBDA scores. Within 12 months, 49.9% of patients had restarted TNFi medication, 59.0% had escalation of any DMARD and 57.2% had >/=1 physician-reported flare. MBDA score was associated with each indicator of relapse. At least one indicator of relapse was observed in 59.5%, 68.4% and 81.3% of patients with low, moderate or high MBDA scores, respectively (P = 0.004). Adjusted for baseline DAS28-ESR, disease duration, BMI and erosions, high MBDA scores were associated with increased risk for restarting TNFi treatment (OR = 1.85, 95% CI 1.00-3.40), DMARD escalation (OR = 1.99, 95% CI 1.01-3.94) and physician-reported flare (OR = 2.00, 95% 1.06-3.77).
Conclusion: For RA patients with stable LDA who stopped TNFi, a high baseline MBDA score was independently predictive of disease relapse within 12 months. The MBDA score may be useful for identifying patients at risk of relapse after TNFi discontinuation.

Gepubliceerd: PLoS One 2018;13(5):e0192425
Impact factor: 2.766; Q1

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7. The revised Bristol Rheumatoid Arthritis Fatigue measures and the Rheumatoid Arthritis Impact of Disease scale: validation in six countries
Hewlett S, Kirwan J, Bode C, Cramp F, Carmona L, Dures E, Englbrecht M, Fransen J, Greenwood R, Hagel S, van de Laar M, Molto A, Nicklin J, Petersson IF, Redondo M, Schett G, Gossec L

Objective: To evaluate the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ), the revised Bristol Rheumatoid Arthritis Numerical Rating Scales (BRAF-NRS V2) and the Rheumatoid Arthritis Impact of Disease (RAID) scale in six countries.
Methods: We surveyed RA patients in France, Germany, The Netherlands, Spain, Sweden and the UK, including the HAQ, 36-item Short Form Health Survey (SF-36) and potential revisions of the BRAF-NRS coping and Spanish RAID coping items. Factor structure and internal consistency were examined by factor analysis and Cronbach's alpha and construct validity by Spearman's correlation.
Results: A total of 1276 patients participated (76% female, 25% with a disease duration <5 years, median HAQ 1.0). The original BRAF-MDQ four-factor structure and RAID single-factor structure were confirmed in every country with 66% of variation in items explained by each factor and all item factor loadings of 0.71-0.98. Internal consistency for the BRAF-MDQ total and subscales was a Cronbach's alpha of 0.75-0.96 and for RAID, 0.93-0.96. Fatigue construct validity was shown for the BRAF-MDQ and BRAF-NRS severity and effect scales, correlated internally with SF-36 vitality and with RAID fatigue (r = 0.63-0.93). Broader construct validity for the BRAFs and RAID was shown by correlation with each other, HAQ and SF-36 domains (r = 0.46-0.82), with similar patterns in individual countries. The revised BRAF-NRS V2 Coping item had stronger validity than the original in all analyses. The revised Spanish RAID coping item performed as well as the original.
Conclusion: Across six European countries, the BRAF-MDQ identifies the same four aspects of fatigue, and along with the RAID, shows strong factor structure and internal consistency and moderate-good construct validity. The revised BRAF-NRS V2 shows improved construct validity and replaces the original.

Gepubliceerd: Rheumatology (Oxford) 2018 Feb 1;57(2):300-8
Impact factor: 5.245; Q1

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8. The eumusc.net standards of care for rheumatoid arthritis: importance and current implementation according to patients and healthcare providers in the Netherlands
Hifinger M, Ramiro S, Putrik P, van Eijk-Hustings Y, Woolf A, Smolen JS, Stoffer-Marx M, Uhlig T, Moe RH, Saritas M, Janson M, van der Helm-van Mil, van de Laar M, Vonkeman H, de Wit M, Boonen A

Objectives: The eumusc.net standards of care (SOCs) for rheumatoid arthritis (RA) aimed to improve quality of care across Europe. This study investigated importance and implementation of each standard according to patients and health care professionals (HCPs) in the Netherlands and identified barriers towards implementation.
Methods: Dutch patients, rheumatologists and rheumatology nurses rated importance and implementation (0-10 numeric rating scale (NRS); 10=most important/best implemented) for each of the 20 SOCs. A care gap, adjusted for importance, was calculated: (100=highest gap). Statistical differences between a) patients and HCPs and b) subgroups of patients (demographics, health) were tested. Additionally, patients indicated agreement (0-10) with 6 implementation barriers.
Results: 386 patients and 91 HCPs were included. Both ranked adequate disease modifying anti-rheumatic drug treatment (9.3(SD1.2), 9.2(SD0.8)), access to care in emergencies (9.2(SD1.2), 9.2(SD1.0)) and regular re-appraisal when treatment fails (9.2(SD1.3), 9.0(SD1.0)) the most important SOCs, and these were among the best implemented (NRS>/=8.5) SOCs. After accounting for applicability, patients and HCP identified care gaps for early diagnosis (25.5(SD32.0), 22.3(SD16.3)), availability of a treatment plan (25.1(SD22.7), 25.7(SD18.5)) and patients also for a regular schedule of assessment of disease (28.6(SD25.5)).Patients with poorer health or higher education scored systematically lower on care received while sharing similar priorities. Patients and HCPs considered limited reimbursement of specific health services a main barrier for implementation and patients additionally identified limited time of physicians.
Conclusions: Dutch patients and HCPs overall agreed on priorities in care and found relevant SOCs well implemented. However, suggestions for improvement were raised especially by patients with poorer health and/or higher education.

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Impact factor: 3.201; Q2

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9. A retrospective analysis of medication prescription records for determining the levels of compliance and persistence to urate-lowering therapy for the treatment of gout and hyperuricemia in The Netherlands
Janssen CA, Oude Voshaar MAH, Vonkeman HE, Krol M, van de Laar MAFJ

Urate-lowering therapy (ULT) is a recommended life-long treatment for gout patients. However, despite these recommendations, recurrent gout attacks are commonly

observed in clinical practice. The purpose of this study was to assess the levels of compliance and persistence to ULT in The Netherlands, in order to reflect on the current gout care delivered by health professionals. Anonymous prescription records were obtained from IQVIA's Dutch retrospective longitudinal prescription database, containing ULT dispensing data for allopurinol, febuxostat, and benzbromarone from November 2013 to July 2017. Compliance to ULT was determined by calculating the proportion of days covered (PDC) over 12 months. Persistence over 12 months was evaluated by determining the time to discontinuation, without surpassing a refill gap of > 30 days. Association of PDC and persistence with age, gender, and first prescriber were examined using beta regression- and cox-regression models, respectively. There were 45,654 patients who met the inclusion criteria. Overall, 51.7% of the patients had a ULT coverage of >/= 80% of the days in 1 year (PDC >/= 0.80), and 42.7% of the patients were still persistent after 1 year. Men, older patients, and patients whose first prescriber was a rheumatologist were more persistent and had a higher PDC. Our results show that medication adherence to ULT after 1 year is suboptimal, considering that current guidelines recommend ULT as a life-long treatment. Future studies addressing the reasons for treatment cessation and improving treatment adherence seem warranted.

Gepubliceerd: Clin Rheumatol 2018 Aug;37(8):2291-6
Impact factor: 2.141; Q3

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10. Rasch measurement in rheumatoid arthritis: deriving psychometrically optimal measures from the Rasch Everyday Activity Limitation item bank
Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, van de Laar MAFJ

Objective: Recently we developed the Rasch Everyday Activity Limitations (REAL) generic item bank for measuring physical function. In this study we evaluate the REAL item bank in 209 RA patients and demonstrate how computerized adaptive testing (CAT) and Optimal Test Assembly methods can be used to derive measures from the REAL item bank with superior measurement performance compared with the HAQ Disability Index (HAQ-DI).
Methods: Structural validity of the item bank was assessed using confirmatory factor analysis. The validity of the REAL score metric in RA was evaluated by examining differential item functioning against the general population calibration sample. Besides the REAL-CAT, a 6-item short form (REAL-6) was developed using Optimal Test Assembly that was optimized with respect to common disability levels in RA, content and reading ease. Measurement precision of the different instruments was examined using item response theory methods. Construct validity was evaluated by testing hypothesized correlations with external measures.
Results: Good model-data fit was observed for a one-dimensional model and only two items showed differential item functioning of substantial magnitude. The REAL-CAT had superior measurement precision compared with HAQ-DI and REAL-6. REAL-6 outperformed HAQ-DI across all but the very lowest level of physical function. All three instruments demonstrated good construct validity (>75% of hypotheses affirmed) and only HAQ-DI had a ceiling effect (23.9%).
Conclusion: This study supports the validity of the REAL item bank and illustrates the potential of CAT and OTA applications based on the REAL item bank for assessing physical function in RA.

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Impact factor: 5.245; Q1

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11. Vasodilator function worsens after cessation of tumour necrosis factor inhibitor therapy in patients with rheumatoid arthritis only if a flare occurs
Rongen GA, van Ingen I, Kok M, Vonkeman H, Janssen M, Jansen TL

Vasodilator function is reported to be reduced in rheumatoid arthritis (RA), and is considered an early sign of vascular dysfunction, which is normalised by TNF inhibitors (TNFi). To optimise cost-effectiveness, tapering or interruption of TNFi therapy in established RA patients is advocated. We explored whether cessation of TNFi results in impaired vasodilator function and whether this relates to the development of a Disease Activity Score (DAS28)-based flare. Forty-one patients were assessed for eligibility as RA with at least 12 months of low disease activity (based on 28 joint counts); 35 enrolled into the randomised study: 8 were randomised to continue, 27 to stopping TNFi. Forearm vasodilation to acetylcholine (ACh) and sodium nitroprusside (SNP) was assessed before cessation of TNFi therapy (visit 1) and 6 months after (dis)continuation of TNFi or at flare (based on DAS28) whichever came first (visit 2). None of the patients who continued their TNFi therapy flared. Eight out of 22 patients who stopped TNFi therapy flared. The vasodilator response to ACh and SNP was reduced significantly in patients who experienced a flare of RA: In patients who did not experience a flare, the vasodilator response to ACh or SNP was not significantly affected. Vasodilator function is reduced after cessation of TNFi, but only when RA reactivates, indicating that early vasodilator dysfunction is a consequence rather than a cause of systemic inflammation in RA and not specifically related to inhibition of TNFalpha signalling. Without close monitoring, microvascular damage can occur after TNFi interruption with potential devastating implications for cardiovascular health.
Trial registration: NCT02130076.

Gepubliceerd: Clin Rheumatol 2018 Apr;37(4):909-16
Impact factor: 2.141; Q3

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12. Determinants of Perceived Health Nonimprovement in Early Rheumatoid Arthritis Patients With Favorable Treatment Outcomes
Steunebrink LMM, Oude Voshaar MAH, Taal E, Vonkeman HE, Zijlstra TR, van de Laar MAFJ

Objective: To explore the association between achieving favorable clinical outcomes and patients' perceived change in overall health status after 12 months of treat-to-target in patients with early rheumatoid arthritis (RA) and to identify determinants of subjective nonimprovement.
Methods: Baseline and 12-month data of patients included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study with at least a moderate response (by European League Against Rheumatism criteria) after 1 year were selected for analysis. Logistic regression analysis was used to identify factors associated with nonimproved perceived overall health status at 12 months.

Results: At 12 months, 75 of 210 patients (35%) did not consider their health to have improved despite having achieved favorable clinical outcomes. Relative change from baseline in pain (Wald = 20.20; P < 0.01) and fatigue (Wald = 5.58; P = 0.02) was independently associated with nonimproved perceived overall health status. The results were similar when only patients with </=1 swollen joint were analyzed. An improvement of 55% in pain measured on a visual analog scale was found to discriminate reasonably well between patients who considered their health to have improved versus patients who did not, with an area under the receiver operating characteristic curve of 0.70 (95% confidence interval 0.61-0.78).
Conclusion: These results demonstrate that clinical improvements do not equate with improved subjective health for all patients. The association of nonimprovement with changes in pain and fatigue suggest that it might be worthwhile to monitor and address pain and fatigue in addition to and independently of disease activity in early RA.

Gepubliceerd: Arthritis Care Res (Hoboken) 2018 Apr;70(4):510-5
Impact factor: 4.149; Q1

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13. An Economic Evaluation of Stopping Versus Continuing Tumor Necrosis Factor Inhibitor Treatment in Rheumatoid Arthritis Patients With Disease Remission or Low Disease Activity: Results From a Pragmatic Open-Label Trial
Tran-Duy A, Ghiti Moghadam M, Oude Voshaar MAH, Vonkeman HE, Boonen A, Clarke P, McColl G, Ten Klooster PM, Zijlstra TR, Lems WF, Riyazi N, Griep EN, Hazes JMW, Landewe R, Bernelot Moens HJ, van Riel PLCM, van de Laar MAFJ, Jansen TL

Objective: To evaluate, from a societal perspective, the incremental cost-effectiveness of withdrawing tumor necrosis factor inhibitor (TNFi) treatment compared to continuation of these drugs within a 1-year, randomized trial among rheumatoid arthritis patients with longstanding, stable disease activity or remission.
Methods: Data were collected from a pragmatic, open-label trial. Cost-utility analysis was performed using the nonparametric bootstrapping method, and a cost-effectiveness acceptability curve was constructed using the net-monetary benefit framework, where a willingness-to-accept threshold (WTA) was defined as the minimal cost saved that a patient accepted for each quality-adjusted life year (QALY) lost.
Results: A total of 531 patients were randomized to the stop group and 286 patients to the continuation group. Withdrawal of TNFi treatment resulted in a >60% reduction of the total drug cost, but led to an increase of approximately 30% in other health care expenditures. Compared to continuation, stopping TNFi resulted in a mean yearly cost saving of €7,133 (95% confidence interval [95% CI] €6,071, €8,234]) and was associated with a mean loss of QALYs of 0.02 (95% CI 0.002, 0.040). Mean saved cost per QALY lost and per extra flare incurred in the stop group compared to the continuation group was €368,269 (95% CI €155,132, €1,675,909) and €17,670 (95% CI €13,650, €22,721), respectively. At a WTA of €98,438 per QALY lost, the probability that stopping TNFi treatment is cost-effective was 100%.
Conclusion: Although an official WTA is not defined, the mean saved cost of €368,269 per QALY lost seems acceptable in The Netherlands, given existing data on willingness to pay.

Gepubliceerd: Arthritis Rheumatol 2018 Oct;70(10):1557-64
Impact factor: 7.873; Q1

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14. Long-term disease and patient-reported outcomes of a continuous treat-to-target approach in patients with early rheumatoid arthritis in daily clinical practice
Versteeg GA, Steunebrink LMM, Vonkeman HE, Ten Klooster PM, van der Bijl AE, van de Laar MAFJ

Patients in real life may differ from those in clinical trials. The aim of this study is to report 5-year outcomes of a continuous treat-to-target (T2T) approach in patients with rheumatoid arthritis (RA) in daily clinical practice. In the Dutch RhEumatoid Arthritis Monitoring cohort, all patients with a clinical diagnosis of RA were treated according to a protocolled T2T strategy, aimed at 28-joint Disease Activity Score (DAS28) < 2.6. Outcomes were percentages of patients in distinct levels of disease activity, mean course of DAS28 and prevalence of sustained (drug-free) remission. Also, data on functional disability (Health Assessment Questionnaire) and health-related quality of life (Short-Form 36) were examined. Mean DAS28 improved from 4.93 (95% CI 4.81-5.05) at baseline to 2.49 (95% CI 2.35-2.63) after 12 months and remained stable thereafter. Percentages of patients at 12 months with DAS28 < 2.6 (remission), DAS28 >/= 2.6 and </= 3.2 (low disease activity), DAS28 > 3.2 and </= 5.1 (moderate disease activity) and DAS28 > 5.1 (high disease activity) were 63, 16, 18 and 3%, respectively. Sustained remission (DAS28 < 2.6 during >/= 6 months) was observed at least once in 84% of the patients and drug-free remission (DAS28 < 2.6 during >/= 6 months after withdrawal of all disease-modifying anti-rheumatic drugs) in 36% of the patients. Functional disability and health-related quality of life significantly improved during the first 24 weeks. Continuous application of T2T in real-life RA patients leads to favourable disease- and patient-related outcomes.

Gepubliceerd: Clin Rheumatol 2018 May;37(5):1189-97
Impact factor: 2.141; Q3

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15. Employment and the role of personal factors among patients with ankylosing spondylitis: a Dutch cross-sectional case-control study
Webers C, Vanhoof L, van Genderen S, Heuft L, van de Laar M, Luime J, van der Heijde D, van Gaalen FA, Spoorenberg A, Boonen A

Objectives: To update the knowledge on employment and the role of mastery, a personal factor reflecting the level of control over life and disease, among Dutch patients with ankylosing spondylitis (AS) compared to general population subjects. **Methods:** Data of persons </=65 years participating in a Dutch cross-sectional multicentre study on social participation in AS were used. Being employed was the main outcome. Standardised employment ratios (SERs) were calculated using indirect standardisation after adjusting for age, gender and education and repeated after stratification by symptom duration tertiles. Modified Poisson regressions were performed to understand the role of mastery (Pearlin's scale) independent of sociodemographic and health-related factors.

Results: 214 patients and 470 controls (127 (59.3%) and 323 (68.7%) males; mean age 48.3 (SD 10.4) and 39.3 (SD 12.7) years, respectively) completed an online questionnaire. SER (95%CI) in patients was 0.83 (0.69-0.98); 0.84 (0.67-1.04) in males; 0.83 (0.59-1.07) in females. Adjusted absolute employment of patients compared to controls was 69% versus 84%; 73% versus 86% for males; 62% versus 78% for females. In multivariable analyses stratified for patients and controls, mastery was associated with being employed in patients, but only in those with low education. In controls, not mastery but higher education was associated with being employed. **Conclusion:** Our study reveals that patients suffering from AS compared to population controls are less likely to be employed. Mastery is an important personal factor associated with employment in patients but not in controls. Interventions aimed at improving employment of patients with AS should likely account for mastery.

Gepubliceerd: RMD Open 2018;4(1):e000680
Impact factor: 0; nvt

Totale impact factor: 60.899
Gemiddelde impact factor: 4.060

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 30.506
Gemiddelde impact factor: 3.813

Revalidatiegeneeskunde

1. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury
Booij HA, Gaykema WDC, Kuijpers KAJ, Pouwels MJM, den Hertog HM

Background: Poststroke fatigue (PSF) is a highly prevalent and debilitating condition. However, the etiology remains incompletely understood. Literature suggests the co-prevalence of pituitary dysfunction (PD) with stroke, and the question raises whether this could be a contributing factor to the development of PSF. This study reviews the prevalence of PD after stroke and other acquired brain injuries and its association with fatigue. Summary: We performed a bibliographic literature search of MEDLINE and EMBASE databases for English language studies on PD in adult patients with stroke, traumatic brain injury (TBI) or aneurysmatic subarachnoid hemorrhage (aSAH). Forty-two articles were selected for review. Up to 82% of patients were found to have any degree of PD after stroke. Growth hormone deficiency was most commonly found. In aSAH and TBI, prevalences up to 49.3% were reported. However, data differed widely between studies, mostly due to methodological differences including the diagnostic methods used to define PD and the focus on the acute or chronic phase. Data on PD and outcome after stroke, aSAH and TBI are conflicting. No studies were found investigating the association between PD and PSF. Data on the association between PD and fatigue after aSAH and TBI were scarce and conflicting, and fatigue is rarely been investigated as a primary end point. Key messages: Data according to the prevalence of PD after stroke and other acquired brain injury suggest a high prevalence of PD after these conditions. However, the clinical relevance and especially the association with fatigue need to be established.

Gepubliceerd: Endocr Connect 2018 Jun;7(6):R223-R237
Impact factor: 3.041; Q3

Totale impact factor: 3.041
Gemiddelde impact factor: 3.041

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

Thoraxchirurgie

1. Incidence of perioperative stroke in clampless aortic anastomosis during off-pump coronary artery bypass grafting
Formica F, Tata G, Singh G, Mariani S, D'Alessandro S, Messina LA, Sangalli F, Paolini G

This study aimed to assess if clampless off-pump coronary artery bypass grafting (OPCAB) decreases the incidence of perioperative stroke (POS) rate and in-hospital mortality. The secondary aim was to evaluate 12-year rates of overall mortality. Between January 2003 to December 2015, data of 645 consecutive patients undergoing isolated CABG were retrospectively collected. 363 underwent aortic no-touch OPCAB (No-touch group) and 282 underwent OPCAB with the Heartstring device (HS group). In-hospital mortality and perioperative stroke rate as primary endpoint, as well as long-term follow-up outcome were analysed. In-hospital mortality was lower into No-touch group compared with HS group but without significant statistical difference (1.7 vs. 3.2%, p = 0.19, respectively); the rate of postoperative stroke was higher in No-touch group compared with HS group, although this difference did not reach statistically significance. Delirium was reported with higher presentation rate in HS group (3.9 vs. 0.8%, p = 0.01). Blood transfusions rate was higher in HS subjects (23.4 vs. 16.1%, p = 0.01). Intubation time, ICU, and hospital length of stay were increased in the HS group (p = 0.008, p = 0.001 and p = 0.003, respectively). Over a 12-year follow-up period, survival probabilities at 1, 5, and 10 years were 93.6 +/- 1.3 vs. 93.2 +/- 1.5, 80.4 +/- 2.6 vs. 80.3 +/- 2.2, and 57.9 +/- 5 vs. 58.4 +/- 3.8% in the No-touch and HS group, respectively (p = 0.97). In this retrospective study, clampless off-pump CABG lowers perioperative stroke rate whose incidence is, however, not inferior compared with No-touch technique, and no statistically significance was detected. Delirium has a higher presentation rate in clampless off-pump CABG.

Gepubliceerd: Heart Vessels 2018 Jun;33(6):595-604
Impact factor: 2.185; Q3

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2. Supercritical carbon dioxide decellularised pericardium: Mechanical and structural characterisation for applications in cardio-thoracic surgery
Halfwerk FR, Rouwkema J, Gossen JA, Grandjean JG

Introduction: Many biomaterials are used in cardio-thoracic surgery with good short-term results. However, calcification, dehiscence, and formation of scar tissue are reported. The aim of this research is to characterise decellularised pericardium after supercritical carbon dioxide (scCO2) processing as an alternative biological material for uses in cardio-thoracic surgery.
Methods: Porcine and bovine pericardium were decellularised using scCO2. Mechanical properties such as tensile strength, elastic modulus, fracture toughness and suture retention strength were determined. Ultrastructure was visualised using Scanning Electron Microscopy. Water uptake and swelling was experimentally determined. Commercially available glutaraldehyde treated bovine pericardium was used as gold standard for comparison.

Results: scCO2 decellularised porcine (and bovine pericardium) maintained their tensile strength compared to untreated native pericardium (13.3 +/- 2.4MPa vs 14.0 +/- 4.1MPa, p = 0.73). Tensile strength of glutaraldehyde treated pericardium was significantly higher compared to untreated pericardium (19.4 +/- 7.3MPa vs 10.2 +/- 2.2MPa, p = 0.02). Suture retention strength of scCO2 treated pericardium was significantly higher than glutaraldehyde treated pericardium (p = 0.01). We found no anisotropy of scCO2 or glutaraldehyde treated pericardium based on a trouser tear test. Ultrastructure was uncompromised in scCO2 treated pericardium, while glutaraldehyde treated pericardium showed deterioration of extracellular matrix.
Conclusion: scCO2 processing preserves initial mechanical and structural properties of porcine and bovine pericardium, while glutaraldehyde processing damages the extracellular matrix of bovine pericardium. Decellularisation of tissue using scCO2 might give long-term solutions for cardio-thoracic surgery without compromising initial good mechanical properties.

Gepubliceerd: J Mech Behav Biomed Mater 2018 Jan;77:400-7
Impact factor: 3.239; Q1

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3. Can we predict a delirium after cardiac surgery? A validation study of a delirium risk checklist
Ten Broeke M, Koster S, Konings T, Hensens AG, van der Palen J

Background: Delirium is a common temporary mental disorder that often occurs in patients who undergo cardiac surgery. It is important to prevent the negative side effects of delirium by identifying high-risk patients before surgery. Koster and colleagues designed a risk model to identify patients with an increased risk of postoperative delirium after cardiac surgery. Aim: The aim of this study was to validate the risk model for delirium and further improve the risk model.
Methods: A delirium risk checklist containing predictors associated with postoperative delirium was used during the preoperative outpatient screening in 329 patients. The delirium observation screening scale was used preoperatively and postoperatively to assess delirium.
Results: Compared with the model of Koster and colleagues age greater than 70 years and a history of delirium were confirmed as statistically significant predictors of postoperative delirium, while cognitive impairment and alcohol abuse were almost significant factors. The European system for cardiac operative risk evaluation (EuroSCORE), comorbidity and type of surgery could not predict a postoperative delirium again. The area under the curve of this model was 0.79 (95% confidence interval (CI) 0.73-0.86; P<0.001). Based on the data of this study the model was improved with the following independent predictors of postoperative delirium: age, more than one comorbidity, history of delirium and a lower standardised mini mental state examination score as with an area under the curve of 0.79 (95% CI 0.73-0.85; P<0.001).
Conclusion: The risk model could not be fully validated. It is difficult to validate a risk model over time; there are different circumstances such as the increased focus on the prevention of delirium.

Gepubliceerd: Eur J Cardiovasc Nurs 2018;17(3):255-61
Impact factor: 2.651; Q1

4. Long-Term Outcome of Consecutive Patients With Previous Coronary Bypass Surgery, Treated With Newer-Generation Drug-Eluting Stents
van der Heijden LC, Kok MM, Zocca P, Sen H, Lowik MM, Mariani S, de Man FHAF, Hartmann M, Stoel MG, van Houwelingen KG, Louwerenburg JHW, Linssen GCM, Doggen CJM, Grandjean JG, von Birgelen C

Background: Percutaneous coronary intervention (PCI) in patients with previous coronary artery bypass grafting (CABG) is associated with adverse clinical events. Although newer generation drug-eluting stents showed favorable short-term safety profiles, there is a lack of long-term outcome data. We evaluated the impact of previous CABG on 5-year clinical outcomes of patients treated with PCI using newer-generation drug-eluting stents. METHODS AND
Results: In this patient-level pooled analysis of the prospective TWENTE (The Real-World Endeavor Resolute versus Xience V Drug-Eluting Stent Study in Twente) trial and nonenrolled TWENTE registry, we assessed a consecutive series of patients who underwent PCI with newer-generation drug-eluting stents for non-ST-segment-elevation acute coronary syndromes or stable angina. Of all 1709 patients, 202 (11.8%) had a history of CABG. Patients with previous CABG had significantly higher 5-year rates of cardiac death (10.4% versus 4.3%; P<0.001) and target vessel revascularization (25.0% versus 8.1%; P<0.001). These differences remained statistically significant after adjustment for differences in baseline characteristics. Landmark analysis revealed that from 1- to 5-year follow-up, the rates of cardiac death (8.1% versus 3.2%; P<0.001) and target vessel revascularization (17.1% versus 5.9%; P<0.001) were significantly higher in patients with previous CABG. Among patients with a history of CABG, PCI of an obstructed vein graft was associated with a higher rate of 5-year target vessel revascularization (P=0.003).
Conclusions: At 5-year follow-up after PCI with newer-generation drug-eluting stents, the risk of cardiac death and target vessel revascularization was significantly higher in patients with previous CABG. The target vessel revascularization rate was highest in patients who underwent PCI of obstructed vein grafts.

Gepubliceerd: J Am Heart Assoc 2018 Jan 30;7(3)
Impact factor: 4.450; Q2

Totale impact factor: 12.525
Gemiddelde impact factor: 3.131

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.890
Gemiddelde impact factor: 2.945

Urologie

1. Mono, bi- and tri-exponential diffusion MRI modelling for renal solid masses and comparison with histopathological findings
van Baalen S, Froeling M, Asselman M, Klazen C, Jeltes C, van Dijk L, Vroling B, Dik P, Ten Haken B

Purpose: To compare diffusion tensor imaging (DTI), intravoxel incoherent motion (IVIM), and tri-exponential models of the diffusion magnetic resonance imaging (MRI) signal for the characterization of renal lesions in relationship to histopathological findings.
Methods: Sixteen patients planned to undergo nephrectomy for kidney tumour were scanned before surgery at 3 T magnetic resonance imaging (MRI), with T2-weighted imaging, DTI and diffusion weighted imaging (DWI) using ten b-values. DTI parameters (mean diffusivity [MD] and fractional anisotropy [FA]) were obtained by iterative weighted linear least squared fitting of the DTI data and bi-, and tri-exponential fit parameters (Dbi, fstar,and Dtri, ffast,finterm) using a nonlinear fit of the multiple b-value DWI data. Average parameters were calculated for regions of interest, selecting the lesions and healthy kidney tissue. Tumour type and specificities were determined after surgery by histological examination. Mean parameter values of healthy tissue and solid lesions were compared using a Wilcoxon-signed ranked test and MANOVA.
Results: Thirteen solid lesions (nine clear cell carcinomas, two papillary renal cell carcinoma, one haemangioma and one oncocytoma) and four cysts were included. The mean MD of solid lesions are significantly ($p < 0.05$) lower than healthy cortex and medulla, (1.94 +/- 0.32*10(- 3) mm(2)/s versus 2.16 +/- 0.12*10(- 3) mm(2)/s and 2.21 +/- 0.14*10(- 3) mm(2)/s, respectively) whereas ffast is significantly higher (7.30 +/- 3.29% versus 4.14 +/- 1.92% and 4.57 +/- 1.74%) and finterm is significantly lower (18.7 +/- 5.02% versus 28.8 +/- 5.09% and 26.4 +/- 6.65%). Diffusion coefficients were high (>/=2.0*10(- 3) mm(2)/s for MD, 1.90*10(- 3) mm(2)/s for Dbi and 1.6*10(- 3) mm(2)/s for Dtri) in cc-RCCs with cystic structures and/or haemorrhaging and low (</=1.80*10(- 3) mm(2)/s for MD, 1.40*10(- 3) mm(2)/s for Dbi and 1.05*10(- 3) mm(2)/s for Dtri) in tumours with necrosis or sarcomatoid differentiation.
Conclusion: Parameters derived from a two- or three-component fit of the diffusion signal are sensitive to histopathological features of kidney lesions.

Gepubliceerd: Cancer Imaging 2018 Nov 26;18(1):44
Impact factor: 3.016; Q2

Totale impact factor: 3.016
Gemiddelde impact factor: 3.016

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