Wetenschappelijk onderzoek in Medisch Spectrum Twente

2016

Inhoudsopgave

Voorwoord

Voor u ligt de achtste editie van het jaarlijkse overzicht van het wetenschappelijk overzicht wat door medewerkers van Medisch Spectrum Twente in 2016 is gepubliceerd. 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 2016 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2016 zijn 228 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is flink minder dan in ons topjaar 2015 maar wel ruim meer dan in alle andere jaren. De gemiddelde impact score van alle artikelen is 4,70, wat minder dan een half punt minder is dan in 2015. Dit jaar hebben we ook weer goed gescoord in toptijdschriften: éénmaal in de New England Journal of Medicine en 6 artikelen in de Lancet en Lancet subjournals.

Qua promoties was 2016 iets minder dan 2015 met 6 promoties in MST.

In STZ-verband wordt ook een lijst van publicaties door de STZ ziekenhuizen bijgehouden. Daarin worden alleen publicaties opgenomen waarin “Medisch Spectrum Twente” als affiliatie gemeld staat. Vorig jaar had ik al een oproep gedaan om **bij elke publicatie Medisch Spectrum Twente te vermelden als affiliatie**, ook als je hier maar deeltijd werkt en het onderzoek misschien grotendeels elders is uitgevoerd. Iedereen met een contract in MST hoort bij MST! Helaas zijn er nog behoorlijk wat publicaties waar MST niet bij vermeld wordt. Dit is een gemiste kans!

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 1^{e}, 2^{e} of laatste auteur is.

Om de ontwikkeling te kunnen volgen zijn de ranglijsten van 2016 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
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Overzicht publicaties en de Top 3

	2009	2010	2011	2012	2013	2014	2015	2016
Aantal unieke publicaties	109	177	190	213	191	212	245	226
Gemiddelde impact factor	3,16	5,12	3,63	3,97	4,38	4,03	5,06	4,70

2013			2014			2015			2016		
Top 3: Aantal publicaties:											
1	Neurologie	34	1	Neurologie	39	1	Medical School	35	1	Neurologie	41
2	Reumatologie	32	2	Medical School	33	2	Neurologie	33	2	Cardiologie	39
3	Medical School	24	3	Cardiologie	25	3	Heelkunde	31	3	Medical School	33
Top 3: Totale impact factor score:											
1	Neurologie	276	1	Cardiologie	149	1	Neurologie	184	1	Cardiologie	251
2	Reumatologie	157	2	Neurologie	110	2	Heelkunde	178	2	Neurologie	170
3	Cardiologie	106	3	Reumatologie	107	3	Cardiologie	141	3	Medical School	135
Top 3: Gemiddelde impact factor score:											
1	Neurochirurgie	24	1	MDL	6.1	1	Gynaecologie	12.5	1	Gynaecologie	16.7
2	Klin. Chemie	10	2	Pathologie	6.0	2	MDL	11.8	2	Radiotherapie	8.2
3	Neurologie	8	3	Cardiologie	6.0	3	Klin. chemie	10.5	3	Klin. Chemie	6.9
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:											
1	Reumatologie	24	1	Neurologie	22	1	Neurologie	17	1	Cardiologie	18
2	Neurologie	19	2	Medical School	18	2	Medical School	16	2	Medical School	16
3	Cardiologie	16	3	Cardiologie	15	3	Cardiologie	15	3	Neurologie	14
				Reumatologie	15		Heelkunde	15			
Top 3: Totale impact factor score als 1e, 2e of laatste auteur:											
1	Reumatologie	83	1	Cardiologie	98	1	Cardiologie	65	1	Cardiologie	110
2	Neurologie	66	2	Neurologie	52	2	Neurologie	48	2	Longziekten	57
3	Cardiologie	55	3	Medical School	51	3	Reumatologie	46	3	Neurologie	47
Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:											
1	Kindergnkd	5	1	Cardiologie	6.5	1	Gynaecologie	6.0	1	Cardiologie	6.1
2	Radiotherapie	5	2	Intensive Care	6.1	2	Pathologie	5.6	2	Longziekten	5.1
3	Microbiologie	5	3	MDL	4.7	3	Intensive Care	5.4	3	Microbiologie	4.4

Overzicht aantal publicaties per vakgroep:

	2009	2010	2011	2012	2013	2014	2015	2016
Anesthesiologie	1	2	1	1	0	0	2	0
Automatisering	0	0	0	0	0	0	1	0
Cardiologie	14	14	23	33	21	25	28	39
Gynaecologie	2	15	7	5	5	7	6	4
Heelkunde	16	38	26	24	13	21	31	26
Intensive Care	1	2	12	16	11	13	14	13
Interne Geneeskunde	12	13	17	15	16	20	17	8
Kindergeneeskunde	5	4	7	6	5	3	11	6
Klinische Chemie	4	14	10	6	2	6	7	5
Klinische Farmacie	4	3	4	4	4	6	8	10
Medische Techniek	0	1	0	0	0	0	2	0
Klinische Psychologie	0	0	1	4	3	4	1	0
KNO	0	1	1	0	0	1	1	1
Lab. voor Microbiologie	4	6	8	5	7	2	2	4
Longziekten	8	5	17	10	11	12	16	19
MDL	4	5	4	13	6	11	5	9
Medical School Twente	12	13	13	27	24	33	35	33
Mond- kaak-, aangez.chirurgie	0	1	0	1	3	0	0	1
Neurochirurgie	3	0	0	2	1	5	9	5
Neurologie	11	23	21	19	34	39	33	41
Nucleaire Geneeskunde	1	1	0	1	0	0	2	0
Orthopedie	1	2	3	3	0	4	7	5
Pathologie	1	6	9	12	1	5	8	4
Plastische Chirurgie	4	1	1	0	2	0	2	4
Psychiatrie	1	0	0	0	0	0	1	0
Radiologie	2	11	6	7	6	11	14	10
Radiotherapie	2	4	5	10	3	5	12	10
Reumatologie	14	17	25	21	32	20	23	15
Revalidatiegeneeskunde	2	5	4	11	7	8	6	0
Spoedeisende Hulp	0	2	1	0	0	0	0	0
Tandheelkunde	0	0	1	0	0	0	0	0
Thoraxchirurgie	4	2	5	3	4	3	2	4

Promoties in MST in 2016

Cardiologie

Deformation imaging and three-dimensional echocardiography:

Implications on clinical management of patients with ischemic heart disease

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 verdedigen op dinsdag 26 januari 2016
klokke 13.45 uur

door

Georgette Elise Hoogslag

geboren te Voorburg in 1988

Promotores: Prof. dr. J.J. Bax
Prof. dr. M.J. Schalij
Co-promotor: Dr. V. Delgado

Leden promotiecommissie:
Prof. dr. R.J. Klautz
Prof. dr. H.J. Wellens, Maastricht UMC, Maastricht
Prof. dr. J.W. Jukema
Prof. dr. D.E. Atsma
Dr. N. Ajmone Marsan
Dr. A.J. Scholte
Dr. P.M.J. Verhorst, Medisch Spectrum Twente, Enschede

Samenvatting

De algemene introductie (**Hoofdstuk 1**) van dit proefschrift geeft een overzicht van de huidige epidemiologie van coronairlijden met speciale aandacht voor ST-segment elevatie acuut myocardinfarct (STEMI). Verbeteringen in de behandeling van STEMI, inclusief het uitgebreide gebruik van evidence-based therapie en primaire percutane coronaire interventie, resulterende in een verbeterde kortetermijnoverleving, heeft geleid tot een groeiend aantal patiënten met linker ventrikel (LV) disfunctie en remodeling gedurende follow-up. Als een gevolg heeft deze populatie een verhoogd risico op hartfalen, re-infarct en (plotse hart-) dood. Conventionele 2-dimensionele echocardiografie is de beeldvormingstechniek van eerste keus om deze patiënten te evalueren, inclusief de beoordeling van LV volumes en ejectiefractie, diastolische functie, functionele mitralisklepinsufficiëntie (mitralisklepregurgitatie, MR) en rechter ventrikel (RV) dimensies en functie. Bovendien is de rol van geavanceerde echocardiografische beeldvormingstechnieken geïntroduceerd, waaronder 2-dimensionele speckle-tracking beeldvorming en 3-dimensionele echocardiografie. Het huidige proefschrift heeft als doel de rol van conventionele en geavanceerde echocardiografie te onderzoeken in de risicostratificatie van patiënten met ischemisch hartlijden, direct na STEMI en in de chronische fase, wanneer hartfalen zich mogelijk heeft ontwikkeld.

Deel I: Echocardiografie in ischemisch hartlijden

In het eerste deel worden conventionele en geavanceerde echocardiografische technieken gebruikt gericht op de risicostratificatie van patiënten met ischemisch hartlijden, voornamelijk in STEMI-patiënten, vanaf de acute fase tot 12 maanden na het myocardinfarct.

Na een STEMI lopen patiënten met een verminderde LV functie het risico op ventriculaire aritmieën, vooral vroeg na een myocardinfarct en lang na een myocardinfarct. Desalniettemin lieten de resultaten van gerandomiseerde trials die patiënten direct na een STEMI includeerden, geen voordeel zien van een implanteerbare cardioverter defibrillator (ICD) in deze populatie. LV ejectiefractie was een gestaafd criterium om patiënten te selecteren voor ICD-implantatie in die trials en is geïncludeerd in huidige richtlijnen. Echter, LV ejectiefractie heeft een beperkte nauwkeurigheid om patiënten te identificeren die baat zullen hebben van een ICD. Evaluatie van functionele myocardweefselheterogeniteit met nieuwe beeldvormingstechnieken, zoals speckle-tracking echocardiografie, van de peri-infarctzone 3 maanden na STEMI is geassocieerd met cardiale dood en terechte ICD-therapie en zou daarom STEMI-patiënten kunnen identificeren die risico lopen op ventriculaire arritmieën (**Hoofdstuk 2**).

Een andere ongunstige ontwikkeling na STEMI is cardiale remodeling in zowel de LV als RV. Cardiale remodeling doet zich voor in de vroege fases van een myocardinfarct als gevolg van littekenformatie, infarctexpansie en verhoging van vullingsdrukken. Gedurende follow-up kan ventriculaire dilatatie ontstaan door verdere remodeling van residueel levend myocard om zo het stroke volume te handhaven. RV dilatatie ontstaat vooral in de eerste maanden na STEMI. Bovendien zijn veranderingen in LV volumes en functie geassocieerd met RV dilatatie. Deze gegevens onderstrepen de interventriculaire afhankelijkheid en daarmee het belang van de beoordeling van zowel de LV als RV na STEMI. Ondanks RV remodeling

blijft de RV functie behouden tot 12 maanden follow-up in de overgrote meerderheid van de patiënten. De aanwezigheid van meervatslijden, hogere peak troponine T-waarden, het gebruik van angiotensine-converterend-enzymremmers/ angiotensine-receptorblokkers bij ontslag en lagere baseline LV en RV functie kunnen RV disfunctie na 6 maanden identificeren (**Hoofdstuk 3**) welke zelf geassocieerd is met slechte langetermijnuitkomsten.
Verder kan de routinematige beoordeling van de ernst van MR na STEMI ook de risicostratificatie van ischemisch hartlijden versterken en de selectie van patiënten ondersteunen die mogelijk een doelwit kunnen zijn voor strikte medische therapie of die eventueel andere behandelingsmogelijkheden kunnen ondergaan, zoals cardiale resynchronisatietherapie (CRT), percutane of chirurgische benaderingen van functionele MR. Hoewel de graad van MR verandert over tijd na STEMI is baseline significante MR alsnog geassocieerd met de aanwezigheid van significante MR na 12 maanden. Belangrijker, significante MR gedurende follow-up voorspelt een slechte prognose met hogere risico's op totale en cardiale mortaliteit (**Hoofdstuk 4**).
Het LV remodelingsproces na een STEMI kan verschillen tussen diverse subpopulaties. Na een STEMI hebben patiënten met diabetes een slechtere langetermijnprognose vergeleken met patiënten zonder diabetes ondanks overeenkomstige veranderingen in LV volumes en ejectiefractie. Speckle-tracking echocardiografie is een sensitiever hulpmiddel om subtiele verschillen in LV systolische functie te evalueren en laat meer gestoorde LV strainwaarden zien in diabetespatiënten na STEMI in vergelijking met niet-diabeten (**Hoofdstuk 5**).
Daarom kan de echocardiografische beoordeling van LV globale longitudinale strain meer klinische waarde hebben bij diabeten na STEMI dan die van LV ejectiefractie. Kwantitatieve 3-dimensionele echocardiografische metingen gedurende dobutamine stress echocardiografie zou behulpzaam kunnen zijn in de identificatie van coronairlijden. Een geschikte meting zou LV excursie kunnen zijn, gezien deze de longitudinale contractie van de LV reflecteert welke initieel aangedaan is gedurende ischemie. Gewichtiger, patiënten met belangrijk coronairlijden op angiografie tonen een verslechtering in LV excursie van rust tot piekstress, terwijl de LV excursie gelijk blijft in patiënten zonder belangrijk coronairlijden (**Hoofdstuk 6**).

Deel II: Echocardiografie in chronisch hartfalen
Het tweede deel beschrijft de rol van conventionele en geavanceerde echocardiografie in de klinische besluitvorming bij patiënten met ischemisch hartlijden die chronisch hartfalen hebben ontwikkeld.
De gouden standaard voor de behandeling van hartfalen is harttransplantatie na het falen van medische therapie, chirurgie en/of CRT. CRT heeft aangetoond een effectieve behandelingsoptie te zijn in geselecteerde hartfalenpatiënten door het vertragen of omkeren van het LV remodelingsproces evenals door het verbeteren van de klinische symptomen en langetermijnuitkomst. Desalniettemin reageert 20% tot 40% van de patiënten niet op CRT volgens de huidige definities van CRT-respons gebaseerd op klinische of echocardiografische eindpunten. Door verlaging in de waarden van de biomarker N-terminal pro-brain natriuretisch peptide toe te voegen aan de echocardiografisch gemeten omgekeerde LV remodeling, daarmee een nieuwe definitie van CRT-respons creëerend, kan meer accuraat de groep van patiënten geselecteerd worden die werkelijk reageert op CRT (**Hoofdstuk 7**).

Tot slot hebben patiënten met ischemisch hartlijden een verhoogd risico op ventriculaire aritmieën. Verschillen in het aritmogene substraat kunnen de wisselende werkzaamheid van ICDs over de tijd om plotse hartdood te voorkomen, verklaren. Speckle-tracking echocardiografie zou nuttig kunnen zijn in dit verband, aangezien deze de temporele heterogeniteit van segmentele myocarddeformatie toelaat te beoordelen, welke de elektromechanische heterogeniteit van myocardweefsel kan reflecteren. Deze zogenaamde mechanische dispersie is geassocieerd met het optreden van ventriculaire tachycardie in patiënten na STEMI (**Hoofdstuk 8**). Daarom kan het in details meten van echocardiografische karakteristieken van patiënten met ischemisch hartlijden met behulp van LV mechanische dispersie bijdragen aan de risicostratificatie van ventriculaire aritmieën.

Conclusies en toekomstperspectieven

Evaluatie van patiënten met ischemisch hartlijden middels echocardiografie is onontbeerlijk. Zowel in de acute fase van een STEMI, gedurende follow-up en in de chronische fase wanneer mogelijk hartfalen heeft ontwikkeld, is de echocardiografische beoordeling een essentieel onderdeel van de dagelijkse klinische praktijk.

Direct na STEMI moet het risico op een mogelijke toekomstige nadelige uitkomst, zoals cardiale remodeling, LV en RV disfunctie, ventriculaire aritmieën en totale en cardiale mortaliteit, geschat worden met behulp van een combinatie van klinische en echocardiografische karakteristieken. Verder kan gedurende de follow-up de boordeling van dezelfde echocardiografische parameters nog betere prognostische informatie verschaffen. Met deze strategie kunnen patiënten mogelijk eerder geïdentificeerd worden bij wie strikte medische therapie tot doel gesteld moet worden en aanvullende behandelingsopties kunnen worden overwogen. Bij patiënten met chronisch hartfalen kan echocardiografie een additionele waarde hebben om patiënten te identificeren die baat zullen hebben van een van de vele hartfalenbehandelingsmodaliteiten. Tevens zou het therapeutische effect van deze modaliteiten moeten worden geëvalueerd met echocardiografie.

Heelkunde

Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van Rector Magnificus
prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 3 februari 2016 om 14.30 uur

door

Charlotte Julia Verberne

geboren op 19 juni 1983
te Zierikzee

Promotor: Prof. dr. T. Wiggers
Prof. dr. G.H. de Bock

Beoordelingscommissie:
Prof. dr. R.J. Porte
Prof. dr. E. Buskens
Prof. dr. J. Stoker

Samenvatting

In Nederland krijgen jaarlijks ongeveer 13000 patiënten de diagnose “kanker aan de dikke darm of endeldarm” ofwel colorectale kanker. De behandeling is gericht op operatieve verwijdering van de kwaadaardigheid zodat er geen kanker meer aanwezig is; dit wordt curatie genoemd. Na curatieve chirurgie voor colorectale kanker blijven patiënten onder controle bij de arts. Deze controle wordt follow-up genoemd. Het belangrijkste doel van de follow-up is de vroegtijdige opsporing van terugkerende (recidiverende) ziekte; dit kan gaan om zowel locaal recidief (in de darm) of uitzaaiingen elders in het lichaam. Zo’n 20–25% van alle patiënten wordt geconfronteerd met recidiverende ziekte.

Follow-up na colorectale kanker is een uitdaging voor medische professionals. Verbeteringen in de detectie van de uitgebreidheid van de ziekte vóór de operatie (de preoperatieve stadiering) hebben geleid tot een ander patroon in de diagnose van recidieven ná de operatie. Daardoor is follow-up aan verandering onderhevig. Ook andere aspecten spelen een rol. Patiënten verwachten dat de dokter recidief ziekte in een vroeg stadium herkent; artsen moeten de juiste stappen weten te zetten indien een vermoeden op recidief ziekte ontstaat. Enerzijds heeft het verbeteren van chirurgische technieken geleid tot meer mogelijkheden voor het behandelen van recidieven; anderzijds vergrijst de patiëntenpopulatie zodat sommige opties een brug te ver zijn voor de oudere patiënt. Het medisch handelen wordt gebaseerd op rationele, liefst bewezen methoden, maar juist bij oncologische zorg spelen emoties en minder rationele argumenten vaak een rol in de medische besluitvorming.

Onderzoek doen naar follow-up is dus ook een uitdaging. Follow-up bestaat uit meerdere onderdelen zoals beeldvormend onderzoek en bloedonderzoek. Bij het doen van wetenschappelijk onderzoek moet de focus worden gelegd op specifieke aspecten van follow-up om het aandeel van elk aspect in de uitkomst (zoals het eerder vinden van een recidief) apart te kunnen onderzoeken. Dit proefschrift legt de nadruk op de rol van een reeds lang bekend en bijna ouderwets aspect: Carcinoembryonic Antigen (CEA).

CEA is een tumormarker. De CEA waarde kan worden bepaald in bloed van de patiënt en de waarde zal bij zo’n 80% van de patiënten stijgen op het moment dat er recidief ziekte is in het lichaam. De bepaling is goedkoop en in elk laboratorium beschikbaar. Dit maakt CEA tot een zeer waardevolle follow-up “tool”. Tot nu toe is het echter niet duidelijk wat de beste manier is om CEA in te zetten. De juiste frequentie en drempelwaarde van CEA alsmede het stijgingspatroon bij recidief ziekte en de relatie van CEA met beeldvormend onderzoek zijn nog niet goed bekend. Het onderzoek in dit proefschrift legt zich toe op de exacte rol voor CEA in follow-up van colorectale kanker.

Hoofdstuk 2 is een literatuurstudie met als vraag of voor het vaker curatief behandelen van recidiverende ziekte de CEA stijging meer van belang is dan de absolute CEA waarde. Deze hypothese werd jaren geleden geopperd en is gebaseerd op de relatie tussen tumorgroei en CEA. Het overzichtsartikel uit hoofdstuk 2 bevestigt dat er wel degelijk wetenschappelijk bewijs is dat CEA stijging een rol speelt in de verhoogde kans van curatie van recidieven, hoewel de gevonden literatuur belangrijke methodologische beperkingen kent. Deze bevindingen uit de literatuur zijn daarna getest in een fase-II studie. In deze studie,

OptCEA genaamd, kregen 241 patiënten follow-up met frequente CEA metingen en verder onderzoek in het geval van een (vooraf gedefinieerde) CEA stijging. Recidieven werden gevonden in 28 patiënten (12%, gemiddelde follow-up periode van 18 maanden). Van deze 28 patiënten kwamen er 12 (43%) in aanmerking voor een curatieve behandeling. De sensitiviteit van dit CEA schema voor het opsporen van recidieven was 79% en de specificiteit was 88%. De OptCEA studie heeft geleid tot de werkhypothese dat frequente CEA metingen en beeldvorming op basis van CEA stijging een hoog potentieel hebben om recidief ziekte vroegtijdig op te sporen, terwijl er minder controle bezoeken in het ziekenhuis nodig waren. Daarnaast kwam aan het licht dat de logistiek voor de frequente laboratoriumtests complex is; om hierin tegemoet te komen werd een ondersteunend softwareprogramma ontwikkeld.

In **hoofdstuk 3** wordt dat softwareprogramma getest. Voor patiënten die frequente CEA bepalingen ondergingen werden de CEA waarden automatisch vanuit het laboratorium in het programma ingevoerd, waarna het programma een brief met hierin de uitslag en een interpretatie van de laatste waarde genereerde. Deze patiëntengroep werd vergeleken met een groep die de gebruikelijke follow-up onderging, zonder ondersteuning van het softwareprogramma. De resultaten laten zien dat de software veilig is wat betreft oncologische zorg; daarbij wordt het software programma positief gewaardeerd door de artsen die ermee werken.

In **hoofdstuk 4** wordt de rol van CEA bij patiënten die al zijn behandeld voor levermetastasen onderzocht. Een grote database, waarin alle patiënten die zijn behandeld voor levermetastasen van colorectale kanker tussen 1990 en 2010 zijn opgenomen, werd onderzocht op de wijze waarop de levermetastasen gevonden waren (door stijgend CEA, door routinematige beeldvorming, of door beide tegelijkertijd). Het bleek dat 23% van de patiënten een aanhoudende CEA stijging vertoonde vóór levermetastasen zichtbaar waren op routinematig beeldvormend onderzoek. Een aanvullende kostenanalyse toonde een hoge kosteneffectiviteitsratio voor het gebruik van CEA. Geconcludeerd werd dat CEA niet kan worden genegeerd bij follow-up naar leveruitzaaiingen, ondanks de verbeterende beeldvormende technieken.

Hoofdstuk 5 is het belangrijkste hoofdstuk van dit proefschrift. In een prospectieve gerandomiseerde gecontroleerde studie genaamd CEAwatch werd een nieuw follow-up protocol uitgerold in elf Nederlandse ziekenhuizen. De werkhypothese was dat recidieven eerder zouden worden opgespoord in dat protocol in vergelijking met de gebruikelijke follow-up (de huidige Nederlandse richtlijn) en dat die recidieven daardoor vaker curatief te behandelen waren. Het nieuwe protocol bestond uit tweemaandelijkse CEA metingen en beeldvorming bij een significante CEA stijging; dit schema is gebaseerd op de resultaten van de OptCEA trial. 3223 patiënten werden geïncludeerd. Na twee jaar prospectieve dataverzameling bleek dat het CEA-gebaseerde protocol is geassocieerd met de eerdere detectie van recidieven en met een hogere kans op curabele opties voor de gedetecteerde recidieven (35% versus 22%, $p < 0.001$). Hoewel de 5-jaars en 10-jaars overleving moeten worden afgewacht, laten de resultaten dus zien dat het nieuwe protocol beter is in het opsporen van terugkerende ziekte dan de huidige Nederlandse richtlijn.

Hoofdstuk 6 onderzoekt de dynamiek van CEA in het nieuwe follow-up protocol in meer detail. Het voorgestelde schema van 20% stijging per twee maanden, gevolgd door een verdere stijging vier weken later had een sensitiviteit van 55% en een specificiteit van 92% met betrekking tot de detectie van recidieven en is dus geschikt als een screenende follow-up “tool”.
Wanneer een nieuwe behandeling, in dit geval een nieuwe manier van follow-up, aangetoond effectiever is dan de tot dan toe heersende methode, moet de balans tussen het extra effect en de geassocieerde kosten worden opgemaakt om een beslissing te kunnen nemen over de implementatie van het nieuwe protocol.

In **hoofdstuk 7** worden de kosten-effectiviteits ratio’s voor het detecteren van recidieven berekend voor het nieuwe protocol en de huidige follow-up richtlijn. De kosten voor het detecteren van 1 procent meer recidieven in de het nieuwe protocol vergeleken met het controle-protocol bedragen € 94. De kosten voor de detectie van één procent extra curabele recidieven bedragen € 607. In het licht van de te verwachten kosten van een palliatieve behandeling (meestal chemotherapie) bij incurabele recidieven worden deze bedragen als acceptabel beschouwd; het nieuwe protocol is kosten-effectief.

In **hoofdstuk 8** zijn de psychologische effecten van de geïntensiveerde follow-up beschreven. Dit werd onderzocht met vragenlijsten, die alle patiënten tweemaal kregen opgestuurd. De responspercentages bedroegen respectievelijk 78.9% en 84.2%. Het nieuwe follow-up protocol heeft geen nadelige effecten op de houding van de patiënt ten aanzien van follow-up, noch op het psychisch functioneren van de patiënt. Over het algemeen waren patiënten meer angstig en nerveus aan het begin van het nieuwe protocol. Met het verstrijken van de tijd in het nieuwe protocol verminderden deze angst en nervositeit en steeg de voorkeur voor het volgen van het nieuwe follow-up programma. Geconcludeerd wordt dat patiënten de nieuwe vorm van follow-up waarderen.

Hoofdstuk 9 is een overzicht van de huidige literatuur aangaande andere tumormarkers voor colorectale kanker follow-up. Verschillende tumormarkers zijn hiervoor in de afgelopen decennia onderzocht. De literatuurstudie bracht drie andere markers aan het licht die in de richting kunnen wijzen van recidief ziekte wanneer ze verhoogd zijn bij bloedonderzoek: Tissue Polypeptide Antigeen (TPA), Carbohydrate Antigen (CA)-242 en CA 72–4. Het vergelijken van de verschillende studies bleek echter moeilijk. Daarom wordt een prospectieve studie naar deze markers noodzakelijk geacht om hun werkelijke waarde in de klinische praktijk te onderzoeken. Alle opgeslagen bloedmonsters uit de CEAwatch studie zijn nu opgenomen in een database en TPA bepalingen op deze monsters (waarvan de CEA waarden bekend zijn, en uiteraard het klinische beloop van de patiënt) zijn inmiddels verricht om de gecombineerde waarde van TPA en CEA in colorectale kanker follow-up onderzoeken.

Toekomstperspectief

Het bewijs dat er meer recidieven curatief kunnen worden behandeld door invoering van het nieuwe follow-up protocol (hoofdstuk 5) is fraai, echter de werkelijke klinische relevantie van betere follow-up strategieën ligt in verbetering van de overleving en de meest belangrijke stap op dit gebied is dus het onderzoeken van de effecten van het nieuwe follow-up protocol op zowel ziektespecifieke als overall overleving. Implementatie in de nationale richtlijn van de geïntensiveerde, CEA-gebaseerde follow-up kan niet worden uitgevoerd zonder bekende effecten op de overleving. Een grote recente Britse follow-up studie, de FACS, heeft drie schemata van meer intensieve follow-up, namelijk alleen CEA metingen, alleen CT-scans, en CEA in combinatie met CT-scans, met een minimalistische follow-up strategie vergeleken. Er werden meer behandelbare recidieven gevonden in de intensieve schemata ten opzichte van het minimalistische follow-up schema (respectievelijk 6,7%, 8,0%, 6,6% en 2,3%). De resultaten van minder recente studies die intensieve met minimale schemata vergelijken tonen consistent een gunstig effect op overleving, maar de FACS kon dit effect niet aantonen. FACS onderzoekers suggereren als mogelijke verklaring dat de patiënten in de eerdere studies wellicht bij aanvang de studie al kleine recidieven hadden die nog niet zichtbaar waren op scans; wanneer deze uitgroeiden werden ze eerder in het intensieve protocol gedetecteerd dan in de minimale follow-up. Met de verbeterde beeldvorming van tegenwoordig zouden patiënten met kleine (en eerder niet detecteerbare) recidieven niet aan de studie hebben kunnen deelnemen en zou het overlevingsvoordeel van de oudere studies verminderen of verdwijnen. Hoewel er verschillen zijn tussen FACS en CEAwatch op het gebied van randomisatie en de exacte invulling van het follow-up protocol is FACS wel het best vergelijkbare recente onderzoek.

Een Italiaanse onderzoeksgroep heeft ook overlevingsverschillen tussen verschillende follow-up strategieën onderzocht in de GILDA trial. Voorts zijn recentelijk de data van de COLOFOL trial geanalyseerd. Deze internationale prospectieve studie is bedoeld om een follow-up programma met CEA bepalingen, CT-scan van de lever en thoraxfoto's met een controleprotocol zonder CEA metingen te vergelijken. De dataverzameling van GILDA en COLOFOL is klaar; de resultaten op ziektevrije en totale overleving van de trials zijn nog niet bekendgemaakt. Na de publicatie van deze resultaten zullen meta-analyses van de overlevingsgegevens van FACS, GILDA, COLOFOL en CEAwatch moeten worden uitgevoerd; gecombineerde gegevens kunnen statistisch significante verschillen aantonen, en nog belangrijker, gecombineerde gegevens zouden de klinisch relevante invloed van follow-up op de overleving kunnen vaststellen. Daarnaast kunnen subgroep-analyses worden verricht bijvoorbeeld op niveau van tumorstadium of bepaalde patient-karakteristieken per follow-up strategie.

Daarbij moeten de invloed en rol van de verschillende soorten recidieven op de overleving duidelijker worden. Locatie, grootte en uitgebreidheid van gevonden recidieven verschillen van patiënt tot patiënt, dus gedetailleerd onderzoek naar alle recidieven die zijn gevonden tijdens de looptijd van CEAwatch is aangewezen. De precieze manier waarop tot de diagnose van een recidief is gekomen, behandelingsmogelijkheden en de definitieve, uitgevoerde behandeling (curatieve resectie of palliatieve chemotherapie) moeten worden gespecificeerd en verschillende benaderingen en behandelingen per ziekenhuis moeten worden uitgezocht.

Een groot deel van de CEA serummonsters is opgeslagen. Met de kennis van andere beschikbare veelbelovende tumormarkers voor colorectale kanker follow-up (hoofdstuk 9), kunnen andere metingen dan CEA worden uitgevoerd op deze monsters. Gegevens en inzichten over CEA waarden kunnen dan worden gecombineerd met andere tumormarkers. De eerste stap, het bepalen van het TPA in alle opgeslagen monsters is al gezet. Andere markers zoals serum p53 antilichamen en CA 19–9 kunnen ook worden bepaald op zowel hun zelfstandige waarde als hun waarde in aanvulling op CEA. Het gebruik van een combinatie van tumormarkers (een zogenoemd marker panel) met de hoogste sensitiviteit en specificiteit in follow-up ligt in het verschiet.
In het streven naar betere resultaten voor de individuele patiënt ligt wellicht informatie besloten in de ruim 18.000 CEA waardes uit de CEAwatch database. In hoofdstuk 6 is het follow-up schema al in meer detail bestudeerd aangaande de diagnostische nauwkeurigheid van CEA, maar met een sensitiviteit van 55% voor het signaleren van een recidief is het huidige schema nog niet optimaal. Mogelijk kunnen de sensitiviteit en specificiteit worden verhoogd door een model te ontwikkelen waarin patiëntkarakteristieken en tumorkarakteristieken van hen die een recidief hebben gekregen worden meegenomen; zo kan het meest voorspellende CEA stijgingspatroon per patiënt, of in ieder geval per subgroep, worden gevonden. Ook preoperatieve CEA waarden kunnen hierin worden meegenomen. De waarde van verschillende beeldvormende technieken zoals echografie en CT scans moet nader worden onderzocht; voor CEAwatch zijn ook al deze data geregistreerd. Anderzijds kan door het meenemen van deze gegevens ook een model worden geïntroduceerd die de kans op het ontstaan van recidieven voorspelt. Op deze manier kunnen we werken in de richting van individuele op maat gemaakte follow-up.
Wanneer de optimale manier van CEA follow-up op basis van de patiënt en tumorkenmerken is gemodelleerd en getoetst moet de manier waarop het wordt aangeboden aan de patiënten worden gemoderniseerd. Per ziekenhuis moet één medische professional (een nurse practitioner) alle patiënten in follow-up begeleiden en zo de regie houden; de nurse practitioner moet goed toegankelijk zijn voor alle patiënten en heeft meer tijd voor patiënten dan de medisch specialist of specialist in opleiding. Dat concept is natuurlijk niet nieuw en wordt al veelvuldig toegepast in oncologische zorg bijvoorbeeld bij patiëntes met borstkanker, maar kan zeker worden geoptimaliseerd. In de nabije toekomst moet de rol voor de nurse practitioner worden uitgebreid door het inzetten van moderne media in follow-up. Patiënten horen nu hun CEA waardes tijdens een poliklinische controle, telefonisch of per brief. Er zou een mobiele applicatie (app) voor het verzamelen, bijhouden en meedelen van de laatste waarden kunnen worden ontwikkeld. In het elektronisch dossier van de patiënt zijn alle patiënt- en tumorkarakteristieken opgenomen; een volgende stap zou dus zijn dat de app een op maat gemaakt advies levert bij de gevonden CEA waarde. De nurse practitioner kan dit advies via de app terugkoppelen aan de patiënt, of bijvoorbeeld werken met een “geen nieuws is goed nieuws” afspraak waarbij het aan de patiënt is op welke manier hij of zij wil worden geïnformeerd. Een afspraak met de medisch specialist volgt bijvoorbeeld alleen bij een afwijkende waarde en voorafgaand hieraan kan reeds de juiste vorm van beeldvorming worden verricht om de efficiëntie te verhogen. In plaats van het kiezen van echografie of CT-scan, kan het gevoeliger maar duurdere alternatief van de

PET-CT worden aangevraagd indien aan de hoogte van het CEA in combinatie met de andere parameters het vermoeden op recidief ziekte goed kan worden geschat. Met behulp van de app is de patiënt de eigenaar van zijn medische gegevens en kan hij of zij meer betrokken bij de besluitvorming. Zo kan een oude en bijna ouderwetse tumormarker herleven in de huidige tijd.

Interne Geneeskunde

Thyroid cancer treatment

Long-term effects and new developments

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van Rector Magnificus
prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 12 oktober 2016 om 16.15 uur

door

Esther Nicoline Klein Hesselink

geboren op 23 maart 1988
te Zuidhorn

Promotor: Prof. dr. T.P. Links
Copromotor: dr. J.D. Lefrandt

Beoordelingscommissie:
Prof. dr. J.W.A. Smit
Prof. dr. E. Fliers
Prof. dr. A.A. Voors

Samenvatting

Jaarlijks worden er in Nederland ongeveer 700 patiënten gediagnosticeerd met schildklierkanker.[1] In 90% betreft dit het gedifferentieerd schildkliercarcinoom (DTC), daarmee het meest voorkomende histologische type. DTC gaat uit van de folliculaire schildkliercel en bestaat uit het papillaire en folliculaire subtype. De incidentie van DTC is in de afgelopen jaren snel gestegen,[1] hetgeen hoofdzakelijk kan worden toegeschreven aan het frequenter diagnosticeren van kleine bij toeval gevonden papillaire tumoren.[2] Met een 10-jaars relatieve overleving van 95% is de prognose voor de meeste patiënten met DTC gunstig.[3] Andere histologische subtypes van schildklierkanker, zoals medullair (MTC), slecht gedifferentieerd (PDTC), en anaplastisch schildkliercarcinoom (ATC), gedragen zich agressiever. DTC's zijn meestal sporadisch (niet-familiair), en ontstaan na het optreden van mutaties in genen die coderen voor componenten van de MAPK en PI3K/AKT pathways, waardoor er een verhoogde celproliferatie, migratie, en celoverleving optreedt.[4,5] Daarnaast zijn epigenetische veranderingen betrokken bij schildklierkanker,[6-8] dit zijn veranderingen die de genexpressie beïnvloeden, maar waarbij de nucleotide volgorde gelijk blijft.

Initiële behandeling voor patiënten met DTC bestaat uit een totale thyreoidectomie en, indien geindiceerd, een halsklierdissectie. Postoperatief worden patiënten gestadieerd volgens de TNM classificatie,[9] en ondergaan ze 4 - 6 weken na de operatie een ablatietherapie met radioactief jodium (131I). Deze ablatietherapie kan plaatsvinden tijdens hypothyreoidie, waarbij na de operatie gewacht wordt met het voorschrijven van schildklierhormoon waardoor de patiënten een endogene TSH stimulatie krijgen. Ook kan gebruik worden gemaakt van recombinant humaan TSH (rhTSH). Dit laatste wordt vooral toegepast bij laag risico patiënten, en bij patiënten die de hypothyreoidie die ontstaat bij endogene TSH stimulatie niet goed kunnen verdragen.[10] Patiënten worden vervolgens ingedeeld in een laag of hoog risicogroep en er wordt gestart met de toediening van relatief hoge doses schildklierhormoon (TSH suppressietherapie). De voordelen van deze TSH suppressietherapie, net als van de ablatietherapie, staan echter steeds meer ter discussie voor DTC patiënten met een laag risico.[11,12] Bovendien worden de negatieve langetermijneffecten van deze behandelingen toenemend erkend.

Na 6 - 12 maanden worden DTC patiënten opnieuw geëvalueerd. Indien er geen aanwijzingen zijn voor ziekteactiviteit, dan wordt de patient poliklinisch vervolgd; bij persisterende ziekte kan er reden zijn voor aanvullende chirurgie of een vervolgbehandeling met radioactief jodium. Indien er sprake is van dedifferentiatie, wat kan leiden tot verminderde opname van (radioactief) jodium in kankercellen, of wanneer een lokale tumor of afstandsmetastase niet chirurgisch te behandelen is, kunnen additionele behandelingsopties worden overwogen. Tyrosine kinase remmers (TKI's) vormen een nieuwe, veelbelovende klasse van (doelgerichte) systeemtherapie.

Dit proefschrift behandelt twee belangrijke aspecten van schildklierkanker. Ten eerste zijn er toenemende aanwijzingen over de negatieve langetermijneffecten van behandeling bij patiënten met DTC (onder andere op het cardiovasculaire systeem, de speekselklieren en het beenmerg). Specifieke klinische data over langetermijneffecten van schildklierkankerbehandeling zijn echter beperkt. Daarom was het eerste doel om langetermijneffecten van DTC behandeling te onderzoeken. Het tweede doel van het onderzoek betrof de behandeling van patiënten met

schildklierkanker bij wie geen curatie kan worden bereikt. De nieuwe behandelingen die beschikbaar zijn gekomen voor deze patiënten zijn qua effectiviteit beperkt, terwijl er een aanzienlijke toxiciteit is. Meer inzicht in de pathogenese van schildklierkanker zou kunnen leiden tot de ontwikkeling van nieuwe behandelmethoden. Daarom hebben we een meta-analyse uitgevoerd naar de effectiviteit en toxiciteit van de TKI's die toegepast zijn bij schildklierkanker patiënten met progressieve ziekte, en hebben we de mate van globale DNA hypomethylatie vastgesteld in schildklierkankerweefsel van patiënten in relatie tot de prognose. **Hoofdstuk 1** bestaat uit een algemene introductie en de doelen van dit proefschrift. **Hoofdstuk 2** geeft een overzicht van de klinisch meest relevante korte- en langetermijneffecten van jodiumbehandeling en TSH suppressietherapie bij patiënten met DTC, en de toenemende tendens naar minder agressieve behandeling voor laag risico DTC patiënten.

Cardiovasculaire effecten van behandeling in patiënten met DTC
In **Hoofdstuk 3** hebben we het risico op cardiovasculaire en totale mortaliteit geëvalueerd in patiënten met DTC, en hebben we de relatie tussen TSH waarden gedurende follow-up en deze eindpunten onderzocht. TSH wordt gezien als een groeifactor voor schildklierkankercellen. Daarom werd decennialang levenslange TSH suppressietherapie geadviseerd voor alle DTC patiënten, door middel van toediening van relatief hoge doses levothyroxine (T4). Hoewel TSH suppressietherapie de kans op een recidief kan verminderen, induceert het ook een iatrogene (subklinische) hyperthyreoidie. In eerdere studies werd aangetoond dat dit geassocieerd is met nadelige cardiovasculaire effecten bij patiënten met DTC. Studies naar de specifieke klinische gevolgen hiervan zijn echter schaars. In een retrospectieve studie hebben we daarom het risico op cardiovasculaire en totale mortaliteit vergeleken tussen 524 DTC patiënten en 1572 controles die gematched waren op leeftijd en geslacht. Daarnaast werd in de DTC groep de associatie onderzocht tussen het geometrisch gemiddelde van de TSH waarden gedurende follow-up en het voorkomen van cardiovasculaire en totale mortaliteit. We vonden dat patiënten met DTC een 3,3-maal en 4,4-maal verhoogd risico hadden voor respectievelijk cardiovasculaire en totale mortaliteit in vergelijking met de controles, onafhankelijk van leeftijd, geslacht en cardiovasculaire risicofactoren. Binnen het DTC cohort waren lagere TSH waarden gedurende follow-up geassocieerd met een verhoogd risico op cardiovasculaire en totale mortaliteit. Deze significante associatie bleef na correctie voor conventionele cardiovasculaire risicofactoren en DTC tumorkarakteristieken bestaan voor cardiovasculaire mortaliteit.

In **Hoofdstuk 4** hebben we het lange termijn risico op atrium fibrilleren (AF) onderzocht bij patiënten behandeld voor DTC. Verder hebben we geëvalueerd of het voorkomen van AF gerelateerd was aan DTC behandeling. Patiënten met DTC krijgen te maken met (subklinische) hyperthyreoidie door TSH suppressietherapie gedurende tenminste een gedeelte van de follow-up. In het algemeen is (subklinische) hyperthyreoidie een risicofactor voor AF. Voor patiënten met DTC zijn data over het risico op AF echter schaars. Bovendien zijn de reeds beschikbare studies hierover slechts beperkt te interpreteren door lage patiënten aantallen of selectie op patiënten met een laag en intermediair DTC risico. Wij hebben daarom het risico op AF vergeleken in 518 DTC patiënten behandeld in het UMCG en 1563

controles gematched op leeftijd en geslacht. Alle patiënten en controles waren vrij van AF bij inclusie. We vonden dat patiënten met DTC een 2,5-maal verhoogd risico hebben op AF in vergelijking met controles, onafhankelijk van bekende risicofactoren voor AF. Binnen het DTC cohort konden we geen relatie aantonen tussen lagere TSH waarden en AF, terwijl een hogere totale dosis radioactief jodium geassocieerd was met een licht verhoogd AF risico.

In **Hoofdstuk 5** hebben we N-terminal pro Brain Natriuretic Peptide (NT-proBNP) waarden vergeleken tussen DTC patiënten en controles. Daarnaast hebben we geëvalueerd of hogere NT-proBNP waarden geassocieerd waren met een verhoogd risico op cardiovasculaire ziekte en mortaliteit gedurende followup bij patiënten met DTC. BNP wordt geproduceerd in het hart bij onder andere cardiale wand-stress en overvulling. BNP induceert vasodilatatie, natriurese en diurese, waardoor het cardiovasculaire systeem beschermd wordt tegen de effecten van overvulling. NT-proBNP is een inactief, stabiel eiwit dat vrijkomt tijdens de vorming van BNP, en is een betrouwbare voorspeller gebleken voor cardiovasculair risico en sterfte in de algemene populatie en verschillende patient categorieen. De waarde van NT-proBNP voor het bepalen van het cardiovasculaire risico in DTC patiënten is nog niet bekend. Daarom hebben we de NT-proBNP waarden gemeten bij een groep van 266 patiënten in follow-up voor DTC en de uitkomsten vergeleken met de NT-proBNP waarden van 798 controles gematched op leeftijd en geslacht. Daarnaast hebben we NT-proBNP geëvalueerd als een prognostische marker voor cardiovasculaire gebeurtenissen en sterfte bij deze groep DTC patiënten. Uit onze resultaten bleek dat NT-proBNP verhoogd is bij DTC patiënten, en dat een hogere NT-proBNP waarde geassocieerd is met een verhoogd risico op cardiovasculaire gebeurtenissen en mortaliteit bij patiënten met DTC, onafhankelijk van leeftijd, geslacht, en cardiovasculaire risicofactoren.

Effecten van radioactief jodium op de speekselklieren en beenmergfunctie in DTC patiënten

In **Hoofdstuk 6** hebben we de effecten van behandeling met radioactief jodium op de functie van de speekselklieren bij patiënten met DTC in detail onderzocht. Daarnaast hebben we gekeken of de opname van radioactief jodium in de speekselklieren (vastgesteld op diagnostische scans) correleert met veranderingen in speeksel flow rate na de behandeling. Speekselklieren bevatten de natriumjodide symporter, die ervoor zorgt dat de klier (radioactief) jodium kan opnemen. Lokale beta straling kan een inflammatoire respons veroorzaken in het secretoire klierweefsel (sialoadenitis) en de speekselkliergangen beschadigen. Gedetailleerde, prospectieve data over de effecten van radioactief jodium op de speekselklieren bij patiënten met DTC zijn schaars. Daarom hebben we een prospectieve multicenter studie uitgevoerd, waarin we patiënten hebben geïncludeerd die behandeld werden met ablatie- of vervolgbehandeling met radioactief jodium. In totaal zijn 67 patiënten vlak voor en 5 maanden na behandeling met radioactief jodium onderzocht; de meerderheid rond hun ablatietherapie. Uit onze resultaten bleek dat de functie van speekselklieren nadelig wordt beïnvloed door deze behandeling. Zowel de totale als klierspecifieke speeksel flow rates namen af, klachten van een droge mond namen toe, en veranderingen in de samenstelling van het speeksel wezen op een dysfunctie van de acini (klierbesjes). De afname van de flow rate was niet

geassocieerd met de jodium opname in de speekselklieren op diagnostische scans. Bij de 11 patiënten die een vervolgbehandeling ondergingen, vonden we geen veranderingen in speeksel parameters voor en na behandeling.

In **Hoofdstuk 7** hebben we in een algemene DTC populatie de korte- en langetermijneffecten geëvalueerd van behandeling met radioactief jodium op het perifere bloedbeeld als representant van beenmergfunctie. Verder hebben we karakteristieken geidentificeerd van patiënten die een verhoogd risico hebben op een verminderde beenmergfunctie na behandeling. Eerdere studies gaven aan dat behandeling met radioactief jodium beenmergsuppressie en zelfs ernstige pancytopenie kan veroorzaken, alhoewel deze studies beperkt waren door een geselecteerde of niet duidelijk gedefinieerde patiëntenpopulatie en een korte follow-up. In 331 DTC patiënten vergeleken wij het perifere bloedbeeld van voor de behandeling met bloedbeelden na 3 en 6 maanden, en 1 en 5 jaar na de laatste behandeling met radioactief jodium. Uit onze studie bleek dat beenmergfunctie na behandeling met radioactief jodium op de lange termijn niet gecompromitteerd is. Het aantal trombocyten en leukocyten was significant lager 6 maanden en 1 jaar na de laatste jodiumbehandeling, maar na 5 jaar normaliseerde dit geheel na naar waarden van voor de behandeling. We vonden geen afname in het hemoglobine. Risicofactoren voor de ontwikkeling van trombocytopenie na de totale behandeling waren leeftijd, T4 tumor stadium, mannelijk geslacht, en een hogere cumulatieve dosis radioactief jodium. Laatstgenoemde factor bleef onafhankelijk geassocieerd met trombocytopenie na correctie voor de bovenstaande parameters.

Nieuwe ontwikkelingen

In **Hoofdstuk 8** hebben we systematisch de effectiviteit en toxiciteit van TKI's geëvalueerd bij schildklierkanker patiënten met vergevorderde ziekte. TKI's zijn een nieuwe klasse van systeemtherapie die doelgericht werken op de signaaltransductie pathways van schildklierkanker. Een groot aantal verschillende TKI's zijn onderzocht bij schildklierkanker patiënten, maar een overzicht over de effectiviteit en toxiciteit van de verschillende middelen ontbreekt. Wij hebben daarom een systematische review en meta-analyse uitgevoerd, waarin we de respons op de behandeling en toxiciteit van TKI's bij schildklierkanker patiënten hebben geëvalueerd. We hebben systematisch alle grote databases doorzocht voor publicaties over TKI's bij schildklierkanker. Hierbij hebben we 1536 publicaties gevonden, waarvan er 22 werden geïncludeerd in de analyse. De meeste artikelen betroffen fase II studies met een enkele arm, en de meeste TKI's werden vaak in slechts 1 of 2 artikelen beschreven. Dit leidde tot een behoorlijke onzekerheid over de effecten van behandeling. Uit onze analyse bleek dat de respons op TKI behandeling (waaronder sorafenib) bij DTC patiënten beperkt is, terwijl bij MTC patiënten een redelijk aantal objectieve (hoewel partiele) responsen zijn beschreven na TKI behandeling (waaronder vandetanib en cabozantinib). De toxiciteit bij de behandeling met TKI's, zoals hand-voet syndroom, diarree en misselijkheid/braken, is aanzienlijk.

In **Hoofdstuk 9** hebben we onderzocht of globale DNA hypomethylatie verhoogd is in tumoren van patiënten met laag en hoog risico schildkliercarcinoom. Globale hypomethylatie is een epigenetisch kenmerk van kanker dat voornamelijk repetitieve DNA elementen beïnvloedt. Van deze repetitieve elementen zijn Alu repeats het

meest voorkomend. Globale hypomethylatie van DNA is gerelateerd aan instabiliteit van het genoom, en toenemende hypomethylatie is geassocieerd met zowel vroege stadia van kanker als kanker progressie. De rol van globale DNA hypomethylatie bij schildklierkanker blijft echter onduidelijk. Daarom hebben we globale Alu hypomethylatie geanalyseerd als een surrogaat marker voor globale DNA hypomethylatie in primaire schildkliertumoren en afstandsmetastasen. Hiervoor hebben we de Quantification of Unmethylated Alu repeats (QUAlu) techniek gebruikt. Verder hebben we Alu hypomethylatie gerelateerd aan schildklierkanker-specifieke en totale mortaliteit. Negentig patiënten werden geïncludeerd (28 hadden laag risico DTC, 33 DTC met afstandsmetastasen, 13 DTC op de kinderleeftijd, 7 PDTC en 9 ATC). We vonden een toenemende Alu hypomethylatie in primaire tumoren van DTC met afstandsmetastasen, PDTC en ATC, terwijl de tumoren van patiënten met laag risico DTC en DTC op de kinderleeftijd niet gehypomethyleerd waren. De Alu hypomethylatie waarde van afstandsmetastasen was vergelijkbaar aan de waarde van de primaire tumor. Hypomethylatie was verder geassocieerd met mortaliteit, maar deze associatie ging verloren na correctie voor leeftijd en schildklierkanker risicocategorie. Deze resultaten impliceren dat globale hypomethylatie mogelijk betrokken is bij tumorprogressie of dedifferentiatie van schildklierkanker.

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Kindergeneeskunde

Optimizing inhalation therapy in childhood asthma

Dissertation

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
Prof.dr. H. Brinksma,
on account of the decision of the graduation committee,
to be publicly defended
on Friday, June 24, 2016 at 14.45

by

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Samenvatting

Astma is een veel voorkomende chronische ziekte die wordt gekarakteriseerd door ontsteking en episodische vernauwing van de luchtwegen. Inspanning is een belangrijke uitlokkende factor voor luchtwegvernauwing bij astmatische kinderen. Inspanningsastma is zeer specifiek voor astma en komt frequent voor (80-90%). Veel astmatische kinderen worden hierdoor gedwongen af te haken bij sport en spel en ervaren deze klacht dan ook als zeer beperkend. Klachten van inspanningsastma zijn bij jonge kinderen aspecifiek en worden niet altijd herkend door ouders, begeleiders en behandelaars, maar ook kinderen zelf waardoor een adequate behandeling soms niet wordt gegeven. Ook kunnen kinderen met astma zich aanpassen en inspanning vermijden teneinde klachten te ontlopen. Hierdoor kunnen verschillende aspecten van de ontwikkeling van kinderen en de kwaliteit van leven in het gedrang komen. Een inspanningsprovocatietest in de koude, droge lucht kan astma klachten door inspanning objectiveren en wordt gebruikt voor diagnostiek en evaluatie van astmatische klachten. Voor de behandeling van astma wordt vaak gebruikt gemaakt van inhalatiemedicatie. In dit proefschrift onderzoeken we verschillende aspecten van inhalatietherapie bij kinderen met astma met als doel deze te optimaliseren. Een introductie van de huidige stand van zaken is te vinden in **hoofdstuk 1**.

Veel kinderen met astma hebben hun klachten matig onder controle, wat veelal veroorzaakt wordt door therapie ontrouw. Uit de literatuur blijkt een gemiddelde therapietrouw van 60% onder astmatische kinderen. Bij jonge kinderen wordt de behandeling door de ouders gegeven en kunnen zij twijfels hebben over de diagnose en de behandeling van hun kind. Deze twijfels kunnen resulteren in therapieontrouw en enkel educatie lost dit probleem niet op. Andere factoren lijken mee te spelen welke belangrijke determinanten zijn voor therapietrouw. Hierbij kan een onderscheid gemaakt worden tussen onbewuste en bewuste therapieontrouw. Onbewuste therapieontrouw is gerelateerd aan praktische barrieres in het dagelijks leven die therapietrouw in de weg staan, zoals beperkte structuur binnen de familie en problemen rondom het kind. Bewuste therapieontrouw heeft betrekking op ouders die hun eigen interpretatie geven aan de behandeling, gebaseerd op hun eigen ziekte perceptie en opvattingen over de medicatie. Ouders kunnen de controle over de klachten onder- of overschatten, omdat zij de klachten van hun kind niet goed kunnen duiden. Daardoor kunnen zij bijvoorbeeld het voorschrift van de dagelijkse medicatie naar hun eigen opvatting aanpassen.
Als ouders een inspanningsprovocatietest van hun kind bijwonen en zien dat hun kind door een korte inspanning astmatische klachten ontwikkelt, geobjectiveerd met behulp van een longfunctie meting, is het mogelijk dat zij meer doordrongen raken van de klachten van hun kind en de diagnose astma. Zij zien dat hun kind beperkt wordt in zijn/haar dagelijkse speelsituatie. Daarnaast worden ouders zich bewust van de lichamelijke symptomen van benauwdheid bij hun kind.

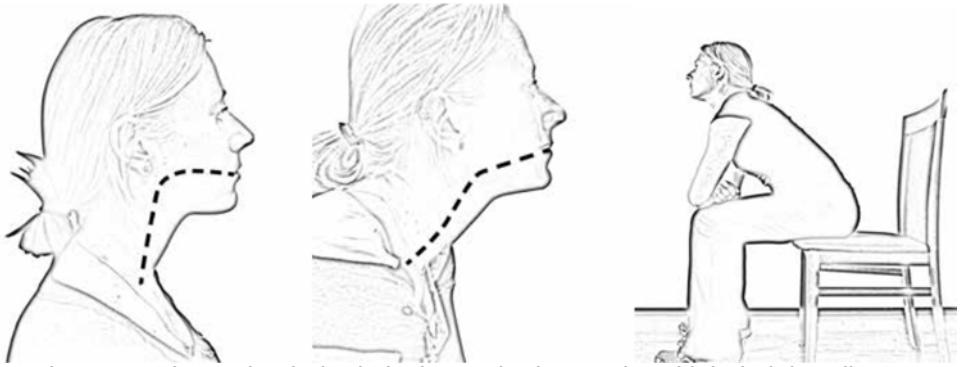
In **hoofdstuk 2** beschrijven wij een onderzoek waar we de effecten van het bespreken van het resultaat van een inspanningsprovocatietest op therapietrouw, ziekte perceptie en medicatie opvattingen van ouders analyseren. Onze hypothese was dat een kind waarbij inspanningsastma gediagnosticeerd wordt, het bewustzijn van ouders kan beïnvloeden en de therapietrouw kan verbeteren.

Negenenzeventig kinderen tussen vier en zeven jaar oud die bekend waren bij een kinderarts in verband met astmatische klachten in het Medisch Spectrum Twente in Enschede of Ziekenhuis Groep Twente in Hengelo of Almelo deden aan dit onderzoek mee. Zij voerden een inspanningsprovocatietest uit in koude, droge lucht op de overdekte ijsbaan Twente in Enschede. Voorafgaand aan de inspanningsprovocatietest hadden de kinderen zes weken lang een elektronische teller op hun medicatie inhalator gebruikt waarmee hun medicatie gebruik werd vastgelegd. Ook hadden hun ouders vragenlijsten ingevuld aangaande hun opvattingen over de ziekte en medicatie van hun kind. De uitslagen en de observaties van astma symptomen van de inspanningsprovocatietest werden direct na de test met ouders besproken, waarna opnieuw de vragenlijsten werden ingevuld. De teller op de inhalator werd tot 6 weken na de test gebruikt waarna de vragenlijsten voor de laatste maal werden ingevuld. De therapietrouw van deze groep kinderen voor de test was hoog, namelijk 83% en bleef in de periode na de test nagenoeg gelijk. Dit gold voor zowel de groep kinderen met als zonder inspanningsastma. Zowel de kinderen met een hoge als een lage therapietrouw (respectievelijk ≥ 80% en <80%) lieten na de inspanningsprovocatietest geen significante verandering zien van therapietrouw. Uit de vragenlijsten bleek dat veel ouders al overtuigd waren van de noodzaak van de medicatie. Ook bleek dat bij het overgrote merendeel van de ouders (81%) de zorgen ten aanzien van het gebruik van de medicatie ondergeschikt waren aan de noodzaak. Na de inspanningsprovocatietest bleven deze scores nagenoeg gelijk (86%). Waarschijnlijk was er in deze groep kinderen met een hoge therapietrouw en een grote overtuiging tot de noodzaak van medicatiegebruik geen mogelijkheid voor verbetering door middel van het bespreken van de resultaten van een inspanningsprovocatietest. Meest waarschijnlijk was dit te danken aan het intensieve multidisciplinaire astma zorg programma voor deze groep kinderen, waar zowel de kinderarts als de astma verpleegkundige in participeren. We veronderstellen dat in de groep met lage therapietrouw onbewuste praktische barrieres een belangrijke factor waren voor het niet verbeteren van de therapietrouw. Een intensief zorgprogramma lijkt een goed vangnet te bieden voor het voorkomen van bewuste therapieontrouw. In de toekomst zal de invloed van het bespreken van een inspanningsprovocatietestuitslag in een groep kinderen met bewuste therapie-ontrouw geanalyseerd moeten worden.
Inhalatie corticosteroiden (ICS) zijn vanwege hun ontstekingsremmende effect de standaard behandeling voor astma op alle leeftijden. Correct gebruik van de inhalatiemedicatie is een voorwaarde voor een succesvolle behandeling en fouten in het gebruik zijn geassocieerd met een verminderde astma controle. Veel astmatische kinderen inhaleren hun medicatie niet correct, zelfs na inhalatie instructie.

In **hoofdstuk 3** evalueren we de inhalatietechniek zes weken na inhalatie instructie van jonge astmatische kinderen die regelmatig op controle komen bij een kinderarts. Ook onderzochten we de relatie tussen het opleidingsniveau van ouders en inhalatietechniek van hun kind. Eenennegentig astmatische kinderen van vier tot acht jaar oud werd gevraagd hun inhalatietechniek met een aerosol inhalator met voorzetkamer te demonstreren zoals zij in de thuissituatie ook gewend waren. Fouten in de inhalatietechniek werden vastgelegd met behulp van de checklist van

het Nederlandse Longfonds. Direct na de demonstratie werden zowel de foute als de goede punten van de inhalatietechniek besproken met het kind en de ouders. Zes weken later werd de inhalatietechniek opnieuw geëvalueerd waarbij bleek dat significant meer kinderen een perfecte inhalatietechniek demonstreerden (68.5% versus 36.3% aan het begin van de studie). Desondanks waren er significant meer kinderen die de essentiele fout maakten hun inhalator niet te schudden voor gebruik (16.9% versus 6.6% aan het begin van de studie). Schudden is noodzakelijk om dosis uniformiteit na te streven voor gebruik. De inhalatietechniek van het kind bleek niet geassocieerd te zijn met het opleidingsniveau van zijn/haar ouders. Concluderend was er sprake van verdubbeling van het aantal kinderen dat zes weken na inhalatie instructie een perfecte inhalatie techniek demonstreerden. Opvallend was dat er reeds na zes weken een significante stijging was van het aantal kinderen die de fout maakten hun medicatie niet te schudden voor gebruik. Bij een inhalatie instructie dient speciale aandacht gegeven te worden aan de noodzaak van het schudden van de medicatie en de reden hiervan.
Inhalatie medicatie slaat voor een aanzienlijk deel neer in de scherpe bocht van de luchtweg in de keelholte, waardoor de hoeveelheid die de longen bereikt sterk vermindert. Bij astmatische kinderen jonger dan 12 jaar slaat 50-60% van geinhaleerd ICS met een ademgestuurde inhalator neer in de keel.

In **hoofdstuk 4** beschrijven wij een pilot onderzoek waarbij het effect van inhaleren met salbutamol op de longfunctie wordt vergeleken in of een voorover geleunde houding met het hoofd licht achterover, of in de standaard lichaamshouding. In de voorover geleunde houding (figuur 1) wordt de bovenste luchtweg grotendeels gestrekt waardoor de scherpe bocht verdwijnt. Dit effect werd gemeten door middel van het blazen van longfunctie voor en na het inhaleren van salbutamol, een luchtwegverwijder. Eenenveertig astmatische kinderen die een geplande longfunctietest ondergingen inhaleerden 200µg salbutamol, ofwel rechtop (de standaard houding) ofwel in de voorover geleunde houding. De longfunctiemetingen werden allemaal in de standaard zittende houding uitgevoerd. Dit resulteerde in een grotere reversibiliteit van FEV1 en MEF75 in de groep kinderen die voorovergeleund hadden geinhaleerd ten opzichte van de groep kinderen die in de standaard houding had geinhaleerd. FEV1 en MEF75 zijn longfunctiewaarden die informatie geven over de kracht en snelheid van uitgeblazen lucht tijdens een krachtige uitademing. Deze waarden zijn vaak verminderd bij kinderen met astmatische klachten. Dit verschil in longfunctiewaarden suggereert dat het klinische effect van salbutamol geinhaleerd met een adem gestuurde inhalator op de longen kan worden verbeterd door te inhaleren in een voorover geleunde houding met het hoofd licht achterover, waarschijnlijk ten gevolge van een grotere depositie van de medicatie in de longen.



Figuur 1: scherpe bocht in de luchtweg in de standaard inhalatiehouding versus gestrekte luchtweg in de voorovergeleunde lichaamshouding.

De pilot studie beschreven in hoofdstuk 4 is verder uitgewerkt tot een gerandomiseerde cross-over trial beschreven in **hoofdstuk 5** waarbij de kinderen 200µg en 400µg salbutamol met een adem gestuurde inhalator in zowel de voorover geleunde houding als de standaard zittende houding geinhaleerd hebben. Tweeentwintig stabiele astmatische kinderen tussen de vijf en veertien jaar oud voerden vier longfunctiemetingen uit. De voorover geleunde houding tijdens het inhaleren van salbutamol resulteerde niet in een grotere reversibiliteit van de longfunctiewaarden ten opzichte van de standaard lichaamshouding. Reversibiliteit van de FEV1 was wel significant groter bij het inhaleren van 400µg salbutamol ten opzichte van de 200µg salbutamol in de standaard lichaamshouding (4.5% +/- 7.5% vs. 9.4% +/- 9.5%, verschil 4.9%). Concluderend lijkt een voorover geleunde lichaamshouding tijdens het inhaleren van salbutamol met een adem gestuurde inhalator niet tot grotere reversibiliteit te leiden bij stabiele astmatische kinderen in tegenstelling tot wat gezien wordt bij andere methoden van inhaleren. Inhaleren van 400µg salbutamol ten opzichte van 200µg leidde wel tot een grotere reversibiliteit. Uit voorgaand onderzoek is gebleken dat een hoge enkele dosis ICS (1000-1600µg) een acute bescherming geeft tegen inspanningsastma.

Doel van de studie beschreven in **hoofdstuk 6** was om te analyseren of een veel lagere dosis van 200µg ICS in de voorover geleunde houding ook beschermt tegen inspanningsastma. Tweeëndertig astmatische kinderen tussen de vijf en zestien jaar oud met inspanningsastma, die geen corticosteroiden als onderhoudsmedicatie gebruikten, voerden twee inspanningsprovocatietesten uit op het springkussen of de loopband in de koude, droge lucht op de overdekte ijsbaan, waarbij zij vier uur van tevoren een enkele dosis 200µg ICS kregen met behulp van een adem gestuurde inhalator. Zij inhaleerden gerandomiseerd eenmaal in de standaard zittende houding en eenmaal in de voorover geleunde houding. Zowel inhaleren van 200µg ICS in de voorover geleunde houding als de standaard zittende houding beschermden significant tegen inspanningsastma (daling FEV1 zonder ICS 30.9%; daling FEV1 met ICS in standaard zittende houding 16.7%; daling FEV1 met ICS in voorover geleunde houding 15.1%). De bescherming tussen de twee houdingen verschilde niet significant. Het inhaleren in de voorover geleunde houding leidde wel tot een vertraging van het optreden van de maximale daling van de FEV1 vergeleken met

de standaard zittende houding (respectievelijk 2min 28sec +/- 58sec vs. 1min 37sec +/- 46sec). Inhaleren in de voorovergeleunde houding resulteerde in significant meer luchtwegverwijding ten opzichte van inhaleren in de standaard lichaamshouding in de vier uur periode voor de test (respectievelijk 5% +/- 9.4% vs. 1.1% +/- 7.8%). Concluderend leidde inhaleren van 200µg ICS met een adem gestuurde inhalator in een voorover geleunde houding niet tot meer bescherming tegen inspanningsastma maar wel tot een vertraging van het optreden van inspanningsastma vergeleken met inhaleren van ICS in de standaard zittende houding.
ICS worden primair als onderhoudsmedicatie gebruikt. Voorgaande studies laten zien dat een enkele hoge dosis ook een beschermend effect heeft op de luchtwegvernauwing door bijvoorbeeld inspanning.

Hoofdstuk 7 beschrijft de analyse van het beschermende effect op inspanningsastma van een enkele lage dosis ICS van 200µg. Eenendertig kinderen met inspanningsastma tussen de vijf en zestien jaar oud, die geen corticosteroiden als onderhoudsmedicatie gebruikten werden geïncludeerd. Zij voerden twee inspanningsprovocatietesten uit binnen twee weken waarbij zij vier uur voorafgaand aan de tweede inspanningsprovocatietest 200µg ICS met een adem gestuurde inhalator inhaleerden. De gemiddelde daling van de FEV1 nam significant af van 30.9% bij de eerste test, naar 16.0% na de tweede test na inhaleren van ICS. Twintig kinderen (64.5%) lieten een goede reactie zien op inhaleren van ICS (≥50% verbetering), acht kinderen lieten een gemiddelde reactie zien (25-50% verbetering) en twee kinderen lieten geheel geen reactie zien. Concluderend biedt een enkele lage dosis ICS acute bescherming tegen inspanningsastma bij de meerderheid de astmatische kinderen die geen onderhoud ICS gebruiken.
Een recente studie heeft aangetoond dat inspanning bij astmatische kinderen niet alleen kan leiden tot de bekende expiratoire luchtwegvernauwing, maar ook tot inspiratoire flow limitatie. De pathofysiologie van inspiratoire flow limitatie is nog onduidelijk. Salbutamol geeft een goede bescherming tegen expiratoire luchtwegvernauwing (gemeten middels de FEV1), door het remmende effect op degranulatie van mestcellen waarbij histamine vrij komt. Het effect van salbutamol op inspiratoire flow limitatie is echter onbekend.

Doel van het dubbel-blinde, placebo gecontroleerde, prospectieve gerandomiseerde onderzoek beschreven in **hoofdstuk 8** was het analyseren van een mogelijk beschermend effect van salbutamol tegen inspiratoire flow limitatie bij astmatische kinderen. Zestien kinderen met inspiratoire flow limitatie tussen de acht en zestien jaar inhaleerden gerandomiseerd eenmaal 200µg salbutamol en eenmaal een placebo voorafgaand aan een inspanningsprovocatietest in de koude, droge lucht op de overdekte ijsbaan. Expiratoire luchtwegvernauwing werd gedefinieerd als een daling van de FEV1 van ≥13%, en inspiratoire flow limitatie werd gedefinieerd als een daling van de mean inspiratoire flow van ≥ 25% bij 50% van de vitale capaciteit (MIF50). Salbutamol verminderde de gemiddelde daling van de MIF50 ten gevolge van inspanning significant vergeleken met placebo (17.6% vs. 24.9%), maar de helft van de kinderen liet geen significante reactie zien op het gebruik van salbutamol. Concluderend was er sprake van een grote variabiliteit in het beschermende effect van salbutamol tegen inspiratoire flow limitatie ten gevolge van inspanning wat suggereert dat de inspiratoire flow limitatie niet volledig is toe te schrijven aan

degranulatie van de mestcellen. Voor de klinische praktijk betekent dit dat aanhoudende inspanningsgebonden luchtwegklachten bij kinderen met astma ondanks profylaxe met salbutamol kunnen worden veroorzaakt door inspannings geinduceerde inspiratoire flow limitatie.
Inspanningsastma is een belangrijk symptoom van astma op de kinderleeftijd. Hoewel ICS inspanningsastma kunnen verminderen, varieert dit effect per patiënt. Op dit moment is er een tekort aan diagnostische mogelijkheden om de grootte van het individuele effect op ICS behandeling te voorspellen. De ernst van inspanningsastma correspondeert met luchtweg hyperreactiviteit die aangetoond kan worden bij een mannitol test en kan gebruikt worden om inspanningsastma te diagnosticeren en te vervolgen. Bepalen van de individuele luchtweg hyperreactiviteit gevoeligheid voor een eenmalige dosis ICS met behulp van mannitol zou een indicatie kunnen geven van het effect van ICS op de langere termijn.

Doel van het onderzoek beschreven in **hoofdstuk 9** was om de relatie te onderzoeken tussen het effect van een enkele dosis ICS en vier weken behandeling met ICS op de luchtweg hyperreactiviteit gemeten met een mannitol test. Twaalf kinderen tussen de 12 en 18 jaar oud met mild tot matig astma en symptomen van inspanningsastma die gingen starten met ICS onderhoudsbehandeling werden geïncludeerd in deze prospectieve studie. De kinderen voerden een baseline mannitol test uit en binnen een week een tweede mannitol test voorafgegaan door een enkele dosis van 200µg ICS. Na vier weken onderhoudsbehandeling met tweemaal daags ICS voerden zij een derde mannitol test uit. Twee kinderen hebben de studie niet afgemaakt. Zes van de tien overige kinderen lieten zowel een vermindering van de luchtweg hyperreactiviteit op de mannitol test zien na een enkele dosis ICS als na vier weken behandeling met ICS. De overige vier kinderen die geen verbetering lieten zien na een enkele dosis ICS, deden dit ook niet na de vier weken behandeling met ICS. De verandering van luchtweg hyperreactiviteit na een enkele dosis ICS en na vier weken behandeling met ICS bleek dus sterk gecorreleerd (intra class correlation 0.88). Dit betekent dat de uitslag van de mannitol test na 1 gift ICS sterk samenhangt met de uitslag van de mannitol test na 4 weken ICS gebruik. Dit kan in de klinische praktijk gebruikt worden om met een mannitol test na 1 gift ICS het effect te kunnen voorspellen van langdurig ICS gebruik op astmatische klachten. Deze relatie geeft mogelijkheden om te komen tot een meer individuele benadering bij de keuze van medicatie voor kinderen met astma.
Gezien het kleine aantal kinderen dat aan deze studie meegedaan heeft, gaat deze studie in de toekomst vervolgd worden met uitbreiding van het aantal deelnemers om op deze manier de betrouwbaarheid te vergroten.

Neurologie

Fluoxetine and motor imagination to facilitate recovery after ischemic stroke

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. H. Brinksma,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen op
woensdag 9 maart 2016 om 14:45 uur

door

Hanneke Irene Berends – van Genderen

Geboren op 16 januari 1980
te Enschede

Promotoren: Prof. dr. ir. M.J.A.M. van Putten
Prof. dr. M.J. IJzerman
Copromotor: Dr. K.L.L. Movig

Samenvatting
Meerdere studies suggereren dat de plasticiteit van de hersenen een cruciale rol speelt bij het herstel van de motor functie na een cerebraal vasculair accident (CVA). De hoofddoelstelling van dit proefschrift is het bestuderen van de mogelijkheid om het herstel van de motorfunctie na een CVA te verbeteren door het moduleren van de neurale plasticiteit, waarbij er vanuit wordt gegaan dat dit zal leiden tot een verbeterd herstel op de lange termijn. Twee methodes die hierbij bestudeerd worden zijn (1) het gebruik van psychoactieve medicijnen die de concentratie van neurotransmitters in de hersenen verhogen en (2) het gebruik van inbeelding van een beweging.
Wanneer de effecten van psychoactieve medicatie op de motorfunctie na een CVA bestudeerd worden, zijn er veel confounders, zoals cognitieve problemen en depressie, die de uitkomsten van de studie beïnvloeden. Andere variabelen die de effecten van de psychoactieve medicijnen op de revalidatie van de motorfunctie na een CVA kunnen beïnvloeden zijn de locatie van de CVA, de mate van handicap, de dosering van de medicatie en duur van de toediening. Het proefschrift richt zich op het beter begrijpen van de effecten van de selective serotonin reuptake inhibitor fluoxetine. Hiertoe bestuderen we de impact van fluoxetine op de motorfunctie in relatie tot veranderingen in spieractiviteit en hersenactiviteit. Zodoende willen we meer inzicht krijgen in de mogelijkheid om corticale processen te beïnvloeden die het herstel van de motorfunctie na een CVA verbeteren (**hoofdstuk 2**).

In de eerste studie, waarbij het effect van toediening van een enkele dosis fluoxetine 20 mg in chronische CVA patiënten werd bestudeerd, is een significante toename van de spieractiviteit gevonden in de aangedane arm in zowel de agonistische als de antagonistische spieren. Een effect op de motorfunctie werd echter niet gevonden. Er wordt gesuggereerd dat deze a-specifieke effecten veroorzaakt worden door het wijdverspreide effect van serotonine in de hersenen en het ruggenmerg (**hoofdstuk 3**).

De verhoging van de spieractiviteit na inname van fluoxetine zou veroorzaakt kunnen worden door veranderingen in activiteit van de motorische cortex. In de tweede studie die de effecten van fluoxetine bestudeert, zijn er trends gevonden van een verhoging van de spieractiviteit en de cocontractie van de aangedane arm na inname van fluoxetine. Bovendien werd een significant hogere hersenactiviteit gevonden in de aangedane (ipsilaterale) hemisfeer tijdens het uitvoeren van een beweging met de gezonde hand. Echter, een significante relatie tussen de veranderingen in spieractiviteit en hersenactiviteit van de motorische cortex werd niet gevonden. Motorfunctie veranderde niet na inname van fluoxetine (**hoofdstukken 4 en 6**).

Een andere interventie die mogelijk neuroplasticiteit faciliteert is het inbeelden danwel observeren van een beweging. Deze concepten veroorzaken beide een activatie van

de motorische cortex. Vergeleken met enkel het observeren van een beweging werd, bij gezonde proefpersonen, tijdens het inbeelden van een beweging in combinatie met observatie een significant hogere modificatie van de theta, alfa en beta frequentie banden gemeten met behulp van elektroencefalografie (EEG). Deze hogere activatie van de hersenen bleef bestaan gedurende de gehele periode van inbeelding en suggereert een hogere activatie van de motorische cortex en een toegevoegd effect van inbeelding van een beweging ten opzichte van enkel observeren voor het herstel van motorfunctie tijdens de revalidatie na een CVA (**hoofdstuk 5**).

Op het moment dat CVA-patiënten een specifieke beweging trachten uit te voeren is de activiteit in de motorische cortex significant hoger dan tijdens het inbeelden van de beweging. Aangezien de motorische cortex wordt geactiveerd tijdens het inbeelden van beweging wordt verondersteld dat patiënten wel degelijk in staat zijn bewegingen in te beelden, ondanks het feit dat zij niet in staat zijn dezelfde beweging uit te voeren. Tijdens de uitvoering van een beweging werd, na inname van fluoxetine, een significante desynchronisatie van de alfa frequentie band in de niet-aangedane hemisfeer gevonden. Tijdens het inbeelden van een beweging zijn trends gevonden voor dezelfde effecten (**hoofdstuk 6**). Derhalve is de combinatie van fluoxetine en inbeelden-en-observeren van een beweging een veelbelovende mogelijkheid om de revalidatie van de motorfunctie na een CVA te verbeteren.

Reumatologie

Living a good life with arthritis
Managing personal goals to improve psychological health

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. H. Brinksma,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op donderdag 6 oktober 2016 om 16.45 uur

door

Rosa Ymkje Arends

geboren 24 oktober 1984
te Kollumerland en Nieuwkruisland

Promotor: Prof. dr. M.A.F.J. van de Laar
Co-promotoren: Dr. C. Bode
Dr. E. Taal

Samenvatting

Gewrlchtsontstekingsreuma en omgaan met persoonlijke doelen

Onder de noemer gewrichtsontstekingsreuma vallen verschillende chronische gewrichtsontstekingen aan het bewegingsapparaat die alle gekenmerkt worden door immunologische betrokkenheid. Een merendeel van de aandoeningen wordt gekarakteriseerd door periodes van plotseling verhoogde ziekteactiviteit, waarbij de ontsteking en zwelling van gewrichten verergeren. Deze symptomen beïnvloeden, samen met andere symptomen zoals pijn, vermoeidheid, een verminderd fysiek functioneren, vergroeiingen, psychische stress en een lagere kwaliteit van leven, het dagelijks leven van patiënten. Het streven naar persoonlijke doelen kan hierdoor bemoeilijkt worden. Mensen met gewrichtsontstekingsreuma ervaren problemen met doelen in verschillende domeinen van het leven, bijvoorbeeld bij hun rol in de familie, werk, sociaal leven of in het dagelijks functioneren. Het streven naar en bereiken van persoonlijke doelen is voor het welbevinden belangrijk, omdat doelen het leven zin en structuur geven.

Volgens zelfregulatiemodellen is menselijk gedrag doelgericht en heeft het falen of slagen van een doel invloed op de stemming van een persoon. Dit betekent dat mensen die moeite hebben met de gevolgen van gewrichtsontstekingsreuma in het dagelijks leven niet alleen een verminderde lichamelijke gezondheid, maar ook een verminderde psychische gezondheid kunnen ervaren. Voor het streven naar doelen en het omgaan met de discrepantie tussen een doel en de werkelijke situatie kunnen verschillende strategieën ingezet worden; zogeheten doelmanagementstrategieën. Deze doelmanagementstrategieën worden ingezet om de verschillen tussen een gewenste en een feitelijke situatie te verkleinen. Mensen met een chronische aandoening gebruiken deze strategieën bij het omgaan met een situatie waarin doelen moeilijker te bereiken of onbereikbaar zijn geworden.

In het geïntegreerde model van doelmanagement (integrated model of goal management, IMGM) zijn vier doelmanagementstrategieën gecombineerd, namelijk: a) het volhouden of blijven nastreven van een doel, b) het bijstellen van een doel, c) het loslaten van een doel, en d) het zoeken naar een nieuw doel. Effectief omgaan met persoonlijke doelen kan de aanpassing aan een chronische ziekte bevorderen en hierdoor de psychische gezondheid vergroten. Belangrijk voor het behouden van een betekenisvol toekomstperspectief zijn het herkennen van bedreigde doelen, het optimaal toepassen van manieren om met de gewijzigde situatie om te gaan (doelmanagementstrategieën) en uiteindelijk het nastreven van nieuwe, waardevolle doelen. De psychische gezondheid is in dit proefschrift aan de hand van vijf indicatoren onderzocht, namelijk: depressieve symptomen, angstige symptomen, de ervaring van een zinvol leven, positieve emoties en de tevredenheid met sociale participatie. Tezamen geven deze vijf indicatoren een multidimensionaal beeld van de aanpassing aan gewrichtsontstekingsreuma.

Deel 1: De relatie tussen doelmanagement en psychische aanpassing aan gewrlchtsontstekingsreuma

In **hoofdstuk 2** en **hoofdstuk 3** van dit proefschrift is aangetoond dat doelmanagement gerelateerd is aan de indicatoren van aanpassing aan

gewrichtsontstekingsreuma. Het aanpassen van doelen bleek de gunstigste strategie voor mensen met gewrichtsontstekingsreuma; hoge niveaus van deze strategie waren gerelateerd aan positieve scores op alle vijf hierboven genoemde indicatoren van psychische gezondheid. Ook een sterkere preferentie voor de strategie doelen vasthouden was gerelateerd aan minder depressieve symptomen, een hogere ervaring van een zinvol leven en meer positieve emoties. Een grotere neiging om nieuwe doelen te zoeken was gerelateerd aan minder depressieve symptomen en een hogere tevredenheid met participatie en ervaring van een zinvol leven. Deze strategie bleek minder belangrijk voor de psychische gezondheid in onze studies dan in eerder onderzoek onder mensen met chronische aandoeningen. Vanzelfsprekend moeten mensen wel kunnen beschikken over voldoende mogelijkheden en energie om zich met nieuwe doelen te kunnen bezighouden. Een hogere neiging om doelen los te laten bleek gerelateerd aan lagere niveaus van angst, deze strategie was niet gerelateerd aan de andere indicatoren van psychische gezondheid.
Behalve relaties tussen individuele strategieën van doelmanagement en psychische gezondheid, zijn ook combinaties van meerdere strategieën onderzocht.

In **Hoofdstuk 3** zijn de resultaten van de eerste longitudinale studie naar relaties tussen doelmanagement en psychische gezondheid beschreven. In deze studie bleek het mogelijk mensen met gewrichtsontstekingsreuma in drie groepen in te delen volgens de niveaus van de vier doelmanagementstrategieën. De drie groepen verschilden gedurende een jaar in de mate van psychische gezondheid. Een breed doelmanagement repertoire (hoge niveaus van doelen vasthouden, doelen aanpassen en nieuwe doelen zoeken en gemiddeld niveau van doelen loslaten) bleek gerelateerd aan een goede psychische gezondheid. Deze uitkomst vult eerder onderzoek aan waarin flexibiliteit in het omgaan met problemen gerelateerd was aan een betere psychische gezondheid. De groep die gekenmerkt werd door een sterke preferentie voor vasthouden aan doelen gecombineerd met lage scores op de drie andere strategieën, had de laagste psychische gezondheid. In combinatie met de bevindingen in Hoofdstuk 2 betekenen deze resultaten dat een hoog niveau van doelen vasthouden samen moet gaan met hoge niveaus van doelen aanpassen en nieuwe doelen zoeken om een gunstig effect op de psychische gezondheid te hebben. Dit betekent dat het voor de psychische gezondheid belangrijk is te beschikken over een breed doelmanagement repertoire.

In **hoofdstuk 4** is een meetmethode voor domein-specifiek doelmanagement ontwikkeld. Met dit instrument kunnen de voorkeuren voor doelmanagement in verschillende domeinen, zoals de domeinen familierol, werk, sociaal leven of het dagelijks functioneren, in kaart worden gebracht bij mensen met gewrichtsontstekingsreuma. Deze studie toont aan dat de voorkeur voor doelmanagementstrategieën verschilt per domein en dat de vier doelmanagementstrategieën herkenbaar zijn en toegepast worden door mensen met gewrichtsontstekingsreuma. Deze bevindingen onderstrepen de praktische waarde van het IMGM. Verder laat dit hoofdstuk zien dat het domein-specifiek

meten van doelmanagement nuttig en relevant is bij mensen met gewrichtsontstekingsreuma.

Deel 2: Het effect van een doelmanagementprogramma op de psychische gezondheid van mensen met gewrichtsontstekingsreuma en milde depressieve klachten.
De hiervoor besproken resultaten hebben geleid tot de ontwikkeling van een psychoeducatief groepsprogramma voor mensen met gewrichtsontstekingsreuma met als doel het verbeteren van de psychische gezondheid. In dit programma 'Doelbewust ('Right on Target') staat het omgaan met bedreigde doelen centraal.

In **hoofdstuk 5** is de ontwikkeling van het programma beschreven. Bij de ontwikkeling is gebruik gemaakt van een mensgerichte benadering en zijn psychologische methoden, en gedragsveranderingstechnieken toegepast uit leer- en sociale cognitietheorieën.

In het quasi-experimentele onderzoek dat beschreven is in **hoofdstuk 6** bleken mensen die Doelbewust! gevolgd hebben geen verbetering te tonen op de primaire uitkomstmaat depressieve klachten en drie secundaire uitkomstmaten. De deelnemers van Doelbewust! verbeterden wel op de uitkomstmaat positieve emoties voor de duur van de follow-up. Deze verbetering werd bovendien gemedieerd door een stijging in de strategie 'doelen aanpassen' bij deze groep mensen.

Hoofdstuk 7 beschrijft een procesevaluatie van Doelbewust! waarin een mixed-method is toegepast. Doel van deze studie was de identificatie van de werkzame onderdelen van het programma volgens de deelnemers en een evaluatie van de uitvoering van het programma Doelbewust!. Deelnemers noemden de inhoud van het programma, de mensgerichte benadering en de sociale processen die plaatsvonden tijdens het programma, als werkzame onderdelen. De naleving van het protocol door de trainers was hoog, wel werden er verschillen gevonden in de mate waarin de beoogde coachende benadering werd toegepast en in het niveau van psychologische communicatievaardigheden. Conclusie van de procesevaluatie is dat deelnemers en trainers nog niet volledig voorbereid zijn noch zich altijd thuis voelen bij de rol die het programma van hen vraagt Aan de andere kant laat deze studie zien dat, ondanks dat de nieuwe rol als 'expert' op het gebied van de eigen gezondheid uitdagend kan zijn voor deelnemers, het merendeel klaar is om deze rol op te pakken en enkel enige begeleiding, hulpmiddelen en ondersteuning nodig heeft.

Implicaties van het proefschrift
Gezien het belang van psychische gezondheid voor de algehele gezondheid en de aanzienlijke niveaus van psychisch lijden in de populaties die bestudeerd zijn in dit proefschrift. is het duidelijk dat er bij de zorg voor chronisch zieken aandacht moet zijn voor de psychische gezondheid. Aandacht voor persoonlijke (bedreigde) doelen is hierbij een eerste aanknopingspunt. Ook adequate en tijdige screening op psychische problemen en laag welbevinden en het ter sprake brengen van de psychische gezondheid in routine consulten zijn manieren om de algehele

gezondheid te verbeteren. Een duidelijke implicatie van dit proefschrift voor de praktijk is dat het programma Doelbewust! mensen kan ondersteunen bij het ontwikkelen van kennis, vaardigheden en zelfvertrouwen, het identificeren van passende persoonlijke doelen en het ontwikkelen van een breed doelmanagement repertoire. Ook is gebleken dat een deel van de mensen met gewrichtsontstekingsreuma meer ondersteuning nodig heeft om volledig te kunnen profiteren van de benadering van Doelbewust!. Verder kunnen zorgverleners tijdens een consult bespreekbaar maken in welke mate een individuele patiënt een actieve rol wil en kan spelen bij beslissingen rondom zijn of haar eigen zorg. Om toekomstbestendige effectieve interventies gericht op het omgaan met persoonlijke doelen te ontwikkelen, moeten inzichten va nuit het medische domein, psychologische domein en het domein welbevinden samengebracht worden met technologische ontwikkelingen.

Conclusie

De studies in dit proefschrift zijn verankerd in de theorie en laten startpunten zien voor het verbeteren van de psychische gezondheid van mensen met gewrichtsontstekingsreuma. Doelmanagement en in het bijzonder het vermogen om flexibel doelen aan te passen heeft zijn praktische en klinische waarde bewezen voor de psychische gezondheid van mensen met gewrichtsontstekingsreuma. Een toename van het vermogen om doelen aan te passen van deelnemers aan Doelbewust! leidde tot een stabiele verbetering in positieve emoties. Deze resultaten onderstrepen de toegevoegde waarde van doelmanagementprogramma's voor de psychische gezondheid en geven duidelijke handvatten voor vervolgonderzoek. Om de psychische gezondheid van mensen met gewrichtsontstekingsreuma te verbeteren, dient binnen de dagelijkse zorgpraktijk behalve de vraag 'What is the matter?', ook te worden gevraagd, 'What matters to you?’

PubMed publicaties per vakgroep
Cardiologie

1. Time course, predictors, and prognostic implications of significant mitral regurgitation after ST-segment elevation myocardial infarction
Abate E, Hoogslag GE, Al Amri I, Debonnaire P, Wolterbeek R, Bax JJ, Delgado V, Marsan NA

Background: Ischemic mitral regurgitation (MR) is a known complication of ST-segment elevation myocardial infarction (STEMI) with important prognostic implications. We evaluated changes over time in ischemic MR after STEMI and the prevalence and predictors of significant (grade >/=2) MR at 12 months. Furthermore, the prognostic additional value of significant MR at 12-month follow-up over acute MR was assessed.
Methods: STEMI patients (n = 1,599; 77% male; 60 +/- 12 years) treated with primary percutaneous coronary intervention underwent echocardiography <48 hours of admission (baseline) and at 12 months. Mortality data were collected during long-term follow-up.
Results: At baseline, significant MR was present in 103 (6%) patients. After 12 months, MR worsened >/=1 grade in 321 (20%) patients, remained stable in 963 (60%), and improved >/=1 grade in 315 (20%). Significant MR was present in 135 patients at 12 months (8%, P = .01 vs baseline). Age, left ventricular end-systolic volume, and significant MR at baseline were independently associated with significant MR at follow-up. During follow-up (median, 50 months), 121 (8%) patients died (40% of cardiovascular cause). Significant MR at follow-up was independently associated with all-cause (hazard ratio, 1.65, 95% CI, 1.02-2.99) and cardiovascular mortality (hazard ratio, 2.47; 95% CI, 1.24-4.92), also after adjusting for significant MR at baseline.
Conclusions: The prevalence of significant MR after STEMI increases over time. Age, baseline left ventricular end-systolic volume, and baseline significant MR are independently associated with significant MR at follow-up. Significant MR at 12 months is associated with subsequent all-cause and cardiovascular mortality and shows additional prognostic value over acute MR.

Gepubliceerd: Am Heart J 2016 Aug;178:115-25
Impact factor: 4.332

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2. Effect of Chronic Kidney Disease in Women Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents: A Patient-Level Pooled Analysis of Randomized Controlled Trials
Baber U, Giustino G, Sartori S, Aquino M, Stefanini GG, Steg PG, Windecker S, Leon MB, Wijns W, Serruys PW, Valgimigli M, Stone GW, Dangas GD, Morice MC, Camenzind E, Weisz G, Smits PC, Kandzari D, von Birgelen C, Mastoris I, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Mehran R

Objectives: This study sought to evaluate: 1) the effect of impaired renal function on long-term clinical outcomes in women undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES); and 2) the safety and efficacy of new-generation compared with early-generation DES in women with chronic kidney disease (CKD).
Background: The prevalence and effect of CKD in women undergoing PCI with DES is unclear.
Methods: We pooled patient-level data for women enrolled in 26 randomized trials. The study population was categorized by creatinine clearance (CrCl) <45 ml/min, 45 to 59 ml/min, and >/=60 ml/min. The primary endpoint was the 3-year rate of major adverse cardiovascular events (MACE). Participants for whom baseline creatinine was missing were excluded from the analysis.
Results: Of 4,217 women included in the pooled cohort treated with DES and for whom serum creatinine was available, 603 (14%) had a CrCl <45 ml/min, 811 (19%) had a CrCl 45 to 59 ml/min, and 2,803 (66%) had a CrCl >/=60 ml/min. A significant stepwise gradient in risk for MACE was observed with worsening renal function (26.6% vs. 15.8% vs. 12.9%; p < 0.01). Following multivariable adjustment, CrCl <45 ml/min was independently associated with a higher risk of MACE (adjusted hazard ratio: 1.56; 95% confidence interval: 1.23 to 1.98) and all-cause mortality (adjusted hazard ratio: 2.67; 95% confidence interval: 1.85 to 3.85). Compared with older-generation DES, the use of newer-generation DES was associated with a reduction in the risk of cardiac death, myocardial infarction, or stent thrombosis in women with CKD. The effect of new-generation DES on outcomes was uniform, between women with or without CKD, without evidence of interaction.
Conclusions: Among women undergoing PCI with DES, CKD is a common comorbidity associated with a strong and independent risk for MACE that is durable over 3 years. The benefits of newer-generation DES are uniform in women with or without CKD.

Gepubliceerd: JACC Cardiovasc Interv 2016 Jan 11;9(1):28-38
Impact factor: 7.630

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3. 'Elevated' hemidiaphragm due to a pericardial cyst
Borghouts VA, Stevenhagen YJ, Wagenaar LJ, Bouman DE, Verhorst PM

Gepubliceerd: Neth Heart J 2016;24(4):298-9
Impact factor: 2.062

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4. Prognostic Value of Coronary Computed Tomography Imaging in Patients at High Risk Without Symptoms of Coronary Artery Disease
Dedic A, Ten Kate GJ, Roos CJ, Neefjes LA, de Graaf MA, Spronk A, Delgado V, van Lennep JE, Moelker A, Ouhlous M, Scholte AJ, Boersma E, Sijbrands EJ, Nieman K, Bax JJ, de Feijter PJ

At present, traditional risk factors are used to guide cardiovascular management of asymptomatic subjects. Intensified surveillance may be warranted in those identified as high risk of developing cardiovascular disease (CVD). This study aims to determine the prognostic value of coronary computed tomography (CT) angiography (CCTA) next to the coronary artery calcium score (CACS) in patients at high CVD risk without symptoms suspect for coronary artery disease (CAD). A total of 665 patients at high risk (mean age 56 +/- 9 years, 417 men), having at least one important CVD risk factor (diabetes mellitus, familial hypercholesterolemia, peripheral artery disease, or severe hypertension) or a calculated European systematic coronary risk evaluation of >10% were included from outpatient clinics at 2 academic centers. Follow-up was performed for the occurrence of adverse events including all-cause mortality, nonfatal myocardial infarction, unstable angina, or coronary revascularization. During a median follow-up of 3.0 (interquartile range 1.3 to 4.1) years, adverse events occurred in 40 subjects (6.0%). By multivariate analysis, adjusted for age, gender, and CACS, obstructive CAD on CCTA (>/=50% luminal stenosis) was a significant predictor of adverse events (hazard ratio 5.9 [CI 1.3 to 26.1]). Addition of CCTA to age, gender, plus CACS, increased the C statistic from 0.81 to 0.84 and resulted in a total net reclassification index of 0.19 (p <0.01). In conclusion, CCTA has incremental prognostic value and risk reclassification benefit beyond CACS in patients without CAD symptoms but with high risk of developing CVD.

Gepubliceerd: Am J Cardiol 2016 Mar 1;117(5):768-74
Impact factor: 3.154

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5. Correlates and Impact of Coronary Artery Calcifications in Women Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents: From the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration

Giustino G, Mastoris I, Baber U, Sartori S, Stone GW, Leon MB, Serruys PW, Kastrati A, Windecker S, Valgimigli M, Dangas GD, von Birgelen C, Smits PC, Kandzari D, Galatius S, Wijns W, Steg PG, Stefanini GG, Aquino M, Morice MC, Camenzind E, Weisz G, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Chieffo A, Mehran R

Objectives: The aim of this study was to investigate the clinical correlates and prognostic impact of coronary artery calcification (CAC) in women undergoing percutaneous coronary intervention with drug-eluting stents (DES).
Background: The clinical correlates and the prognostic significance of CAC in women undergoing percutaneous coronary intervention with DES remain unclear.
Methods: Patient-level data from female participants in 26 randomized trials of DES were pooled. Study population was categorized according to the presence of moderate or severe versus mild or no target lesion CAC, assessed through coronary angiography. Co-primary endpoints of interest were the composite of death, myocardial infarction (MI), or target lesion revascularization and death, MI, or stent thrombosis at 3-year follow-up.

Results: Among 11,557 women included in the pooled dataset, CAC status was available in 6,371 women. Of these, 1,622 (25.5%) had moderate or severe CAC. In fully adjusted models, independent correlates of CAC were age, hypertension, hypercholesterolemia, smoking, previous coronary artery bypass graft surgery, and worse left ventricular and renal function. At 3 years, women with CAC were at higher risk for death, MI, or target lesion revascularization (18.2% vs. 13.1%; adjusted hazard ratio: 1.56; 95% confidence interval: 1.33 to 1.84; $p < 0.0001$) and death, MI, or stent thrombosis (12.7% vs. 8.6%; adjusted hazard ratio: 1.48; 95% confidence interval: 1.21 to 1.80; $p = 0.0001$). The adverse effect of CAC on ischemic outcomes appeared to be consistent across clinical and angiographic subsets of women, including new-generation DES.
Conclusions: Women undergoing PCI of calcified lesions tend to have worse clinical profile and remain at increased ischemic risk, irrespective of new-generation DES.

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Impact factor: 7.630

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6. Safety and Efficacy of New-Generation Drug-Eluting Stents in Women at High Risk for Atherothrombosis: From the Women in Innovation and Drug-Eluting Stents Collaborative Patient-Level Pooled Analysis
Giustino G, Baber U, Salianski O, Sartori S, Stone GW, Leon MB, Aquino M, Stefanini GG, Steg PG, Windecker S, O' Donoghue M, Wijns W, Serruys PW, Valgimigli M, Morice MC, Camenzind E, Weisz G, Smits PC, Kandzari D, von Birgelen C, Dangas GD, Cha JY, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Genereux P, Chieffo A, Mehran R

Background: The safety and efficacy of new-generation drug-eluting stents (DES) in women with multiple atherothrombotic risk (ATR) factors is unclear.
Methods and Results: We pooled patient-level data for women enrolled in 26 randomized trials. Study population was categorized based on the presence or absence of high ATR, which was defined as having history of diabetes mellitus, prior percutaneous or surgical coronary revascularization, or prior myocardial infarction. The primary end point was major adverse cardiovascular events defined as a composite of all-cause mortality, myocardial infarction, or target lesion revascularization at 3 years of follow-up. Out of 10,449 women included in the pooled database, 5333 (51%) were at high ATR. Compared with women not at high ATR, those at high ATR had significantly higher risk of major adverse cardiovascular events (15.8% versus 10.6%; adjusted hazard ratio: 1.53; 95% confidence interval: 1.34-1.75; P=0.006) and all-cause mortality. In high-ATR risk women, the use of new-generation DES was associated with significantly lower risk of 3-year major adverse cardiovascular events (adjusted hazard ratio: 0.69; 95% confidence interval: 0.52-0.92) compared with early-generation DES. The benefit of new-generation DES on major adverse cardiovascular events was uniform between high-ATR and non-high-ATR women, without evidence of interaction (Pinteraction=0.14). At landmark analysis, in high-ATR women, stent thrombosis rates were comparable between

DES generations in the first year, whereas between 1 and 3 years, stent thrombosis risk was lower with new-generation devices.
Conclusions: Use of new-generation DES even in women at high ATR is associated with a benefit consistent over 3 years of follow-up and a substantial improvement in very-late thrombotic safety.

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Impact factor: 5.706

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7. Safety and Efficacy of New-Generation Drug-Eluting Stents in Women Undergoing Complex Percutaneous Coronary Artery Revascularization: From the WIN-DES Collaborative Patient-Level Pooled Analysis
Giustino G, Baber U, Aquino M, Sartori S, Stone GW, Leon MB, Genereux P, Dangas GD, Chandrasekhar J, Kimura T, Salianski O, Stefanini GG, Steg PG, Windecker S, Wijns W, Serruys PW, Valgimigli M, Morice MC, Camenzind E, Weisz G, Smits PC, Kandzari DE, Galatius S, von Birgelen C, Saporito R, Jeger RV, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Mehran R

Objectives: The purpose of this study was to investigate the safety and efficacy of new-generation drug-eluting stents (DES) versus early-generation DES in women undergoing complex percutaneous coronary intervention (CPCI).
Background: Whether the benefits of new-generation DES are preserved in women undergoing complex percutaneous revascularization is unknown.
Methods: We pooled patient-level data from women enrolled in 26 randomized trials of DES. Study population was categorized according to the presence or absence of CPCI, which was defined as the composite of total stent length >30 mm, >/=2 stents implanted, >/=2 lesions treated, or bifurcation lesion as target vessel. The primary endpoint was major adverse cardiovascular events (MACE) defined as a composite of all-cause mortality, myocardial infarction, or target lesion revascularization at 3 years of follow-up.
Results: Of 10,241 women included in the pooled database, 4,629 (45%) underwent CPCI. Compared with non-CPCI, women who underwent CPCI had a higher 3-year risk of MACE (adjusted hazard ratio [HR]: 1.63; 95% confidence interval [CI]: 1.45 to 1.83; p < 0.0001). In women who underwent CPCI, use of new-generation DES was associated with significantly lower 3-year risk of MACE (adjusted HR: 0.81; 95% CI: 0.68 to 0.96), target lesion revascularization (adjusted HR: 0.74; 95% CI: 0.57 to 0.95), and definite or probable stent thrombosis (ST) (adjusted HR: 0.50; 95% CI: 0.30 to 0.83). The benefit of new-generation DES on efficacy and safety outcomes was uniform between CPCI and non-CPCI groups, without evidence of interaction. By landmark analysis, new-generation DES were associated with low rates (</=0.4%) of very-late ST irrespective of procedural complexity.
Conclusions: Women undergoing CPCI remain at higher risk of adverse events. The long-term ischemic benefits of new-generation DES platforms are uniform among complex and non-complex percutaneous revascularization procedures in women.

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Impact factor: 7.630

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8. Prognostic Implications of Elevated Pulmonary Artery Pressure After ST-Segment Elevation Myocardial Infarction
Haeck ML, Hoogslag GE, Boden H, Velders MA, Katsanos S, Al Amri I, Debonnaire P, Schalij MJ, Vliegen HW, Bax JJ, Marsan NA, Delgado V

Elevated systolic pulmonary artery pressure (SPAP) after ST-segment elevation myocardial infarction (STEMI) has been associated with adverse outcome. However, little is known about the development of increased SPAP after STEMI treated with primary percutaneous coronary intervention. The aims of this study were to investigate the incidence and determinants of elevated SPAP (SPAP >/=36 mm Hg at 12 months) after first STEMI and to analyze its prognostic implications. A total of 705 patients (60 +/- 12 years; 75% men; left ventricular ejection fraction [LVEF] 47 +/- 9%) with first STEMI treated with primary percutaneous coronary intervention were evaluated. Two-dimensional echocardiography was available at baseline and 12-month follow-up. Data on all-cause mortality were collected at long-term follow-up. Incident elevated SPAP was present in 5% (n = 38) of patients. Patients with incident elevated SPAP were older (66 +/- 12 vs 60 +/- 11 years, p = 0.001), had more systemic hypertension (58% vs 30%, p <0.001) and lower LVEF (43 +/- 9% vs 48 +/- 8%, p <0.001) than their counterparts. Left atrial volume was larger (23 +/- 11 vs 18 +/- 6 ml/m(2), p = 0.006), and moderate to severe mitral regurgitation was more prevalent in patients with incident elevated SPAP (16% vs 7%, p = 0.05). Independent correlates of incident elevated SPAP at 12-month follow-up were age (odds ratio [OR] 1.04, 95% CI 1.01 to 1.08, p = 0.01), hypertension (OR 2.52, 95% CI 1.23 to 5.14, p = 0.01), baseline LVEF (OR 0.94, 95% CI 0.90 to 0.98, p = 0.003), and baseline left atrial volume (OR 1.08, 95% CI 1.03 to 1.12, p = 0.001). Incident elevated SPAP was independently associated with all-cause mortality (hazard ratio 3.84, 95% CI 1.76 to 8.39, p = 0.001). In conclusion, although the incidence of elevated SPAP after STEMI is low, its presence is independently associated with increased risk of all-cause mortality at follow-up.

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Impact factor: 3.154

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9. Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial
Haude M, Ince H, Abizaid A, Toelg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Neumann FJ, Kaiser C, Eeckhout E, Lim ST, Escaned J, Garcia-Garcia HM, Waksman R

Background: Absorbable scaffolds were designed to overcome the limitations of conventional, non-absorbable metal-based drug-eluting stents. So far, only polymeric absorbable scaffolds are commercially available. We aimed to assess the safety and performance of a novel second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in patients with de-novo coronary artery lesions.
Methods: We did this prospective, multicentre, non-randomised, first-in-man trial at 13 percutaneous coronary intervention centres in Belgium, Brazil, Denmark, Germany, Singapore, Spain, Switzerland, and the Netherlands. Eligible patients had stable or unstable angina or documented silent ischaemia, and a maximum of two de-novo lesions with a reference vessel diameter between 2.2 mm and 3.7 mm. Clinical follow-up was scheduled at months 1, 6, 12, 24, and 36. Patients were scheduled for angiographic follow-up at 6 months, and a subgroup of patients was scheduled for intravascular ultrasound, optical coherence tomography, and vasomotion assessment. All patients were recommended to take dual antiplatelet treatment for at least 6 months. The primary endpoint was in-segment late lumen loss at 6 months. We did analysis by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01960504.
Findings: Between Oct 8, 2013, and May 22, 2015, we enrolled 123 patients with 123 coronary target lesions. At 6 months, mean in-segment late lumen loss was 0.27 mm (SD 0.37), and angiographically discernable vasomotion was documented in 20 (80%) of 25 patients. Intravascular ultrasound assessments showed a preservation of the scaffold area (mean 6.24 mm2 [SD 1.15] post-procedure vs 6.21 mm2 [1.22] at 6 months) with a low mean neointimal area (0.08 mm2 [0.09]), and optical coherence tomography did not detect any intraluminal mass. Target lesion failure occurred in four (3%) patients: one (<1%) patient died from cardiac death, one (<1%) patient had periprocedural myocardial infarction, and two (2%) patients needed clinically driven target lesion revascularisation. No definite or probable scaffold thrombosis was observed.
Interpretation: Our findings show that implantation of the DREAMS 2G device in de-novo coronary lesions is feasible, with favourable safety and performance outcomes at 6 months. This novel absorbable metal scaffold could be an alternative to absorbable polymeric scaffolds for treatment of obstructive coronary disease.
Funding: Biotronik AG.

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Impact factor: 44.002

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10. Sustained safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de novo coronary lesions: 12-month clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial
Haude M, Ince H, Abizaid A, Toelg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Neumann FJ, Kaiser C, Eeckhout E, Lim ST, Escaned J, Onuma Y, Garcia-Garcia HM, Waksman R

Aims: Metal absorbable scaffolds constitute a conceptually attractive alternative to polymeric scaffolds. Promising 6-month outcomes of a second-generation drug-eluting absorbable metal scaffold (DREAMS 2G), consisting of an absorbable

magnesium scaffold backbone, have been reported. We assessed the 12-month safety and performance of this novel device.
Methods and Results: The prospective, international, multi-centre, first-in-man BIOSOLVE-II trial enrolled 123 patients with up to two de novo lesions with a reference diameter between 2.2 and 3.7 mm. All patients were scheduled for angiographic follow-up at 6 months, and-if subjects consented-at 12 months. Dual antiplatelet therapy was recommended for 6 months. Quantitative coronary angiography (QCA) parameters remained stable from 6 to 12 months [paired data of 42 patients: in-segment late lumen loss 0.20 +/- 0.21 mm vs. 0.25 +/- 0.22 mm, P = 0.117, Delta 0.05 +/- 0.21 mm (95% CI: -0.01;0.12); in-scaffold late lumen loss 0.37 +/- 0.25 mm vs. 0.39 +/- 0.27 mm, P = 0.446, Delta 0.03 +/- 0.22 (95% CI: -0.04;0.10), respectively]. Intravascular ultrasound and optical coherence tomography findings corroborated the QCA results. Target lesion failure occurred in four patients (3.4%), consisting of one death of unknown cause, one target-vessel myocardial infarction, and two clinically driven target lesion revascularization. No additional event occurred beyond the 6-month follow-up. During the entire follow-up of 12 months, none of the patients experienced a definite or probable scaffold thrombosis.
Conclusion: The novel drug-eluting metal absorbable scaffold DREAMS 2G showed a continuous favourable safety profile up to 12 months and stable angiographic parameters between 6 and 12 months.
ClinicalTrialsGov Identifier: NCT01960504.

Gepubliceerd: Eur Heart J 2016 Sep 14;37(35):2701-9
Impact factor: 15.064

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11. Assessment of global left ventricular excursion using three-dimensional dobutamine stress echocardiography to identify significant coronary artery disease
Hoogslag GE, Joyce E, Bax JJ, Ajmone Marsan N, Delgado V

Background: Quantitative three-dimensional (3D) dobutamine stress echocardiography (DSE) for myocardial ischemia detection may be an adjuvant to left ventricular (LV) wall-motion analysis. The aim of the current study was to assess the association between global 3D LV excursion during DSE and the presence of significant coronary artery disease (CAD) on coronary angiography.
Methods: Three-dimensional DSE was performed in 40 patients (67+/-12 years, 68% male) who underwent subsequent coronary angiography (median 1.6 months later). Using 3D echocardiography, global LV excursion was measured (in a total of 680 segments) at rest and peak dose and the change between stages was calculated (peak-rest=global LV excursion). Significant CAD was defined as >70% stenosis on coronary angiography.
Results: In total, 25 patients (63%) demonstrated significant CAD on coronary angiography. At rest, global LV excursion was similar in patients with and without significant CAD (5.1+/-0.2 vs 5.0+/-0.2 mm, P=.74). However, patients with significant CAD demonstrated a worsening in global LV excursion from rest to peak stress (from 5.1+/-0.2 to 4.1+/-0.2 mm, P<.001), while global LV excursion in

patients without significant CAD remained unchanged (from 5.0+/-0.2 to 5.5+/-0.2 mm, P=.10). After adjusting for clinically relevant characteristics, global LV excursion was independently associated with significant CAD (odds ratio 0.29, 95% confidence interval 0.12-0.72, P=.008).
Conclusions: Analysis of 3D echocardiographic LV excursion at global level on full-protocol DSE may be a helpful tool to detect CAD on coronary angiography.

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Impact factor: 1.432

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12. Impact of severe lesion calcification on clinical outcome of patients with stable angina, treated with newer generation permanent polymer-coated drug-eluting stents: A patient-level pooled analysis from TWENTE and DUTCH PEERS (TWENTE II)
Huisman J, van der Heijden LC, Kok MM, Danse PW, Jessurun GA, Stoel MG, van Houwelingen KG, Lowik MM, Hautvast RW, IJzerman MJ, Doggen CJ, von Birgelen C

Background: The outcome of percutaneous coronary intervention with newer generation permanent polymer-coated drug-eluting stents (DES) in patients with severely calcified lesions is greatly unknown. We assessed the impact of severe lesion calcification on clinical outcome in patients with stable angina who underwent percutaneous coronary intervention with newer generation DES.
Methods: TWENTE and DUTCH PEERS randomized trials enrolled 1423 patients with stable angina, who were categorized into patients with versus without severe target lesion calcification. A patient-level pooled analysis assessed clinical outcome, including target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization (TVR).
Results: Patients with severe calcification (n = 342) were older (66.6 +/- 9.1 vs 64.2 +/- 9.8 years, P < .001) and had more diabetes (25.7% vs 20.4%, P = .04) than other patients (n = 1081). Patients with calcified lesions had higher rates of TVF (16.4% vs 9.8%, pLogrank = .001), cardiac death (4.4% vs 1.5%, P = .03), target vessel myocardial infarction (7.6% vs 3.4%, P = .001), and definite stent thrombosis (1.8% vs 0.4%, P = .02). Multivariate analysis demonstrated that severe calcification was an independent risk factor of 2-year TVF (HR 1.42, 95% CI: 1.02-1.99, pLogrank = .04); landmark analysis showed that this was based on a difference during the first year (periprocedural: 5.8% vs. 3.1%, pLogrank = .02; first year: 7.5% vs. 3.8%, pLogrank = .007; second year: 4.1% vs. 3.3%, pLogrank = .54).
Conclusion: In patients with stable angina, severe target lesion calcification is associated with an increased risk of adverse cardiovascular events following treatment with newer generation permanent polymer-coated DES. This increase in risk is restricted to the first year of follow-up, which is an encouraging finding.

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Impact factor: 4.332

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13. Reducing Microvascular Dysfunction in Revascularized Patients with ST-Elevation Myocardial Infarction by Off-Target Properties of Ticagrelor versus Prasugrel. Rationale and Design of the REDUCE-MVI Study
Janssens GN, van Leeuwen MA, van der Hoeven NW, de Waard GA, Nijveldt R, Diletti R, Zijlstra F, von Birgelen C, Escaned J, Valgimigli M, van Royen N

Microvascular injury is present in a large proportion of patients with ST-elevation myocardial infarction (STEMI) despite successful revascularization. Ticagrelor potentially mitigates this process by exerting additional adenosine-mediated effects. This study aims to determine whether ticagrelor is associated with a better microvascular function compared to prasugrel as maintenance therapy after STEMI. A total of 110 patients presenting with STEMI and additional intermediate stenosis in another coronary artery will be studied after successful percutaneous coronary intervention (PCI) of the infarct-related artery. Patients will be randomized to treatment with ticagrelor or prasugrel for 1 year. FFR-guided PCI of the non-infarct-related artery will be performed at 1 month. Microvascular function will be assessed by measurement of the index of microcirculatory resistance (IMR) in the infarct-related artery and non-infarct-related artery, immediately after primary PCI and after 1 month. The REDUCE-MVI study will establish whether ticagrelor as a maintenance therapy may improve microvascular function in patients after revascularized STEMI.

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Impact factor: 3.197

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14. Three cases of hepatocellular carcinoma in Fontan patients: Review of the literature and suggestions for hepatic screening
Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP

The Fontan procedure has been used since 1971 as a palliative treatment for various (functionally) univentricular hearts. The systemic venous blood flows passively to the pulmonary arteries, without passing through a functional ventricle. This results in chronic systemic venous congestion, which may lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. This review discusses possible screening modalities for liver fibrosis and cirrhosis in the Fontan population and proposes a screening protocol. We suggest starting screening for progression of fibrosis and cirrhosis in collaboration with the hepatologist circa 10 years after Fontan completion. The screening programme will consist of a yearly evaluation of liver laboratory tests in conjunction with imaging of the liver with ultrasound or MRI every two years. In case of liver fibrosis or cirrhosis, (reversible) causes should be ruled out (e.g. obstruction in the Fontan circuit). In case of severe fibrosis or cirrhosis, other complications of portal hypertension should be evaluated and screening for hepatocellular carcinoma is required on a regular (6-12 months) basis. As regards hepatocellular carcinoma, treatment should be discussed in a multidisciplinary team, before deciding a treatment modality.

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Impact factor: 4.638

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15. Endothelial Dysfunction After ST-segment Elevation Myocardial Infarction and Long-term Outcome: A Study With Reactive Hyperemia Peripheral Artery Tonometry

Kandhai-Ragunath JJ, Doggen CJ, Jorstad HT, Doelman C, de Wagenaar B, IJzerman MJ, Peters RJ, von Birgelen C

Introduction and Objectives: Long-term data on the relationship between endothelial dysfunction after ST-segment elevation myocardial infarction and future adverse clinical events are scarce. The aim of this study was to noninvasively assess whether endothelial dysfunction 4 weeks to 6 weeks after primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction predicts future clinical events.
Methods: This prospective cohort study was performed in 70 patients of the RESPONSE randomized trial, who underwent noninvasive assessment of endothelial function 4 weeks to 6 weeks after primary percutaneous coronary intervention. Endothelial function was measured by the reactive hyperemia peripheral artery tonometry method; an index<1.67 identified endothelial dysfunction.
Results: The reactive hyperemia peripheral artery tonometry index measured on average 1.90+/-0.58. A total of 35 (50%) patients had endothelial dysfunction and 35 (50%) patients had normal endothelial function. Periprocedural "complications" (eg, cardiogenic shock, total atrioventricular block) were more common in patients with endothelial dysfunction than in those without (25.7% vs 2.9%; P<.01). During 4.0+/-1.7 years of follow-up, 20 (28.6%) patients had major adverse cardiovascular events: events occurred in 9 (25.7%) patients with endothelial dysfunction and in 11 (31.5%) patients with normal endothelial function (P=.52). There was an association between the prevalence of diabetes mellitus at baseline and the occurrence of major adverse cardiovascular events during follow-up (univariate analysis: hazard ratio=2.8; 95% confidence interval, 1.0-7.8; P<.05), and even in multivariate analyses the risk appeared to be increased, although not significantly (multivariate analysis: hazard ratio=2.5; 95% confidence interval, 0.8-7.5).
Conclusions: In this series of patients who survived an ST-segment elevation myocardial infarction, endothelial dysfunction, as assessed by reactive hyperemia peripheral artery tonometry 4 weeks to 6 weeks after myocardial infarction, did not predict future clinical events during a mean follow-up of 4 years.

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Impact factor: 4.596

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16. Sex Difference in Chest Pain After Implantation of Newer Generation Coronary Drug-Eluting Stents: A Patient-Level Pooled Analysis From the TWENTE and DUTCH PEERS Trials

Kok MM, van der Heijden LC, Sen H, Danse PW, Lowik MM, Anthonio RL, Louwerenburg JH, de Man FH, Linssen GC, IJzerman MJ, Doggen CJ, Maas AH, Mehran R, von Birgelen C

Objectives: This study sought to assess sex differences in chest pain after percutaneous coronary intervention (PCI) with newer generation drug-eluting stents (DES). **Background:** Sex-based data on chest pain after PCI with DES are scarce. **Methods:** The authors performed a patient-level pooled analysis of the TWENTE and DUTCH PEERS randomized trials, in which patients were treated with newer generation permanent polymer-coated DES. At 1 and 2 years, clinical follow-up was available in 99.8% and patient-reported chest pain data in 94.1% and 93.6%, respectively.
Results: Among all 3,202 patients, the 871 (27.2%) women were older (67.5 +/- 10.2 years vs. 62.8 +/- 10.6 years; p < 0.001) and had more cardiovascular risk factors: diabetes (24.2% vs. 17.8%; p < 0.001), hypertension (63.6% vs. 51.6%; p < 0.001), and positive family history (54.5% vs. 50.1%; p = 0.03). At 1- and 2-year follow-up, women reported more clinically relevant chest pain (16.3% vs. 10.5%; p < 0.001, and 17.2% vs. 11.1%; p < 0.001, respectively). Multivariate analysis demonstrated that female sex independently predicted clinically relevant chest pain at 1- and 2-year follow-up both during daily activities and at minimum physical exertion/at rest (1 year adjusted odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.2 to 2.4; p = 0.002; and adjusted OR: 1.8; 95% CI: 1.3 to 2.5; p < 0.001; 2-year adjusted OR: 1.8; 95% CI: 1.3 to 2.6; p < 0.001; and adjusted OR: 1.7; 95% CI: 1.3 to 2.3; p = 0.001). Nevertheless, the 2-year rates of death, myocardial infarction, revascularization, stent thrombosis, and various composite clinical endpoints were similar for both sexes.
Conclusions: Although the incidence of adverse cardiovascular events was low and similar for both sexes, women showed a statistically significantly higher prevalence of clinically relevant chest pain, which might be largely related to mechanisms other than epicardial coronary obstruction.

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Impact factor: 7.630

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17. The telephone lifestyle intervention 'Hartcoach' has modest impact on coronary risk factors: A randomised multicentre trial
Leemrijse CJ, Peters RJ, von Birgelen C, van Dijk J, van Hal JM, Kuijper AF, Snaterse M, Veenhof C

Background: Unhealthy diets and inactivity are still common among patients with cardiovascular diseases. This study evaluates the effects of the telephonic lifestyle intervention 'Hartcoach' on risk factors and self-management in patients with recent coronary events. DESIGN: This was a randomised trial in five Dutch hospitals.
Methods: Patients (18-80 years), less than eight weeks after hospitalisation for acute myocardial infarction or (un)stable angina pectoris were randomised to the Hartcoach-group, who received telephonic coaching every four weeks for a period of six months (in addition to usual care), and a control group receiving usual care only.

Simple random allocation was used (without relation to prior assignment). Measurements were taken by research nurses blinded for group allocation. Differences after six months of participation were compared using linear or logistic regression models with treatment-group and baseline score for the outcome under analysis as covariates, resulting in adjusted mean change (b).
Results: Altogether 374 patients were randomised (173 Hartcoach + usual care, 201 usual care only). Follow-up was obtained in 331 patients who still participated after six months. Hartcoach had significant favourable effects on body mass index (BMI) (b = -0.32; 95% CI:(-0.63- -0.003)), waist circumference (b = -1.71; 95% CI:(-2.73- -0.70)), physical activity (b = 15.08 (score); 95% CI:(0.13, 30.04)) daily intake of vegetables (b = 13.41; 95% CI:(1.10-25.71)), self-management (b = 0.11; 95% CI:(0.00-0.23)) and anxiety (b = -0.65; 95% CI:(-1.25- -0.06)). Hartcoach slightly increased the total number of risk scores on target (b = 0.45; 95% CI:(0.17-0.73)).
Conclusions: Hartcoach has modest impact on BMI, waist circumference, physical activity, intake of vegetables, self-management and anxiety. Therefore, it may be a useful maintenance programme in addition to usual care, to support patients with recent coronary events to improve self-management and reduce risk factors.

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Impact factor: 3.361

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18. Coronary angiography after cardiac arrest: Rationale and design of the COACT trial

Lemkes JS, Janssens GN, Straaten HM, Elbers PW, van der Hoeven NW, Tijssen JG, Otterspoor LC, Voskuil M, van der Heijden JJ, Meuwissen M, Rijpstra TA, Vlachojannis GJ, van der Vleugel RM, Nieman K, Jewbali LS, Bleeker GB, Baak R, Beishuizen B, Stoel MG, van der Harst P, Camaro C, Henriques JP, Vink MA, Gosselink MT, Bosker HA, Crijns HJ, van Royen N

Background: Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography (CAG) and percutaneous coronary intervention (PCI) after restoration of spontaneous circulation following cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains debated.
Hypothesis: We hypothesize that immediate CAG and PCI, if indicated, will improve 90-day survival in post-cardiac arrest patients without signs of STEMI. DESIGN: In a prospective, multicenter, randomized controlled clinical trial, 552 post-cardiac arrest patients with restoration of spontaneous circulation and without signs of STEMI will be randomized in a 1:1 fashion to immediate CAG and PCI (within 2 hours) versus initial deferral with CAG and PCI after neurological recovery. The primary end point of the study is 90-day survival. The secondary end points will include 90-day survival with good cerebral performance or minor/moderate disability, myocardial injury, duration of inotropic support, occurrence of acute kidney injury, need for renal replacement therapy, time to targeted temperature control, neurological status at intensive care unit discharge, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, and reasons for discontinuation of treatment.

Summary: The COACT trial is a multicenter, randomized, controlled clinical study that will evaluate the effect of an immediate invasive coronary strategy in post-cardiac arrest patients without STEMI on 90-day survival.

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Impact factor: 4.332

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19. Safety and efficacy of everolimus-eluting bioresorbable vascular scaffolds versus durable polymer everolimus-eluting metallic stents assessed at 1-year follow-up: A systematic review and meta-analysis of studies
Mukete BN, van der Heijden LC, Tandjung K, Baydoun H, Yadav K, Saleh QA, Doggen CJ, Abi Rafeh N, Le Jemtel TH, von Birgelen C

Background: The Absorb bioresorbable vascular scaffold (BVS) was developed to address long-term safety issues of metallic drug-eluting stents. However, it may be associated with an increased event risk during the first year.
Methods: A systematic literature search was performed (in MEDLINE/PubMed, Cochrane CENTRAL, EMBASE, and scientific meeting abstracts) to identify studies that compared BVS and cobalt-chromium durable polymer everolimus-eluting stents (EES). For randomized clinical trials and non-randomized propensity score matched studies that reported 1-year outcome data, fixed/random-effects models were used to generate pooled estimates of outcomes, presented as odds ratios (OR) with 95%-confidence intervals (CI).
Results: The 1-year follow-up data of 6 trials with 5588 patients were analyzed. A device-oriented composite endpoint (DOCE - cardiac death, target vessel myocardial infarction (MI), or target lesion revascularization (TLR)) was reached by 308 BVS or EES patients (195/3253 vs. 113/2315). Meta-analysis showed that patients who received BVS had an increased risk of MI (4.3% vs. 2.3%; OR:1.63, 95%-CI: 1.18-2.25, p<0.01) and definite-or-probable scaffold thrombosis (1.3% vs. 0.6%; OR:2.10, 95%-CI: 1.13-3.87, p=0.02). However, there was no significant between-group difference in risk of DOCE (6.0% vs. 4.9%; OR:1.19, 95%-CI: 0.94-1.52, p=0.16), cardiac death (0.8% vs. 0.7%; OR:1.14, 95%-CI: 0.54-2.39, p=0.73), or TLR (2.5% vs. 2.5%; OR: 0.98, 95%-CI:0.69-1.40, p=0.92).
Conclusions: During the first year of follow-up, patients treated with BVS had a higher incidence of MI and scaffold thrombosis. The risk of DOCE was not significantly different. As BVS may pay off later, future robust data on long-term clinical outcome will be of paramount importance.

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20. Chronic fatigue syndrome in women assessed with combined cardiac magnetic resonance imaging
Olimulder MA, Galjee MA, Wagenaar LJ, van Es J, van der Palen J, Visser FC, Vermeulen RC, von Birgelen C

Objective: In chronic fatigue syndrome (CFS), only a few imaging and histopathological studies have previously assessed either cardiac dimensions/function or myocardial tissue, suggesting smaller left ventricular (LV) dimensions, LV wall motion abnormalities and occasionally viral persistence that may lead to cardiomyopathy. The present study with cardiac magnetic resonance (CMR) imaging is the first to use a contrast-enhanced approach to assess cardiac involvement, including tissue characterisation of the LV wall.
Methods: CMR measurements of 12 female CFS patients were compared with data of 36 age-matched, healthy female controls. With cine imaging, LV volumes, ejection fraction (EF), mass, and wall motion abnormalities were assessed. T2-weighted images were analysed for increased signal intensity, reflecting oedema (i. e. inflammation). In addition, the presence of contrast enhancement, reflecting fibrosis (i. e. myocardial damage), was analysed.
Results: When comparing CFS patients and healthy controls, LVEF (57.9 +/- 4.3 % vs. 63.7 +/- 3.7 %; $p < 0.01$), end-diastolic diameter (44 +/- 3.7 mm vs. 49 +/- 3.7 mm; $p < 0.01$), as well as body surface area corrected LV end-diastolic volume (77.5 +/- 6.2 ml/m2 vs. 86.0 +/- 9.3 ml/m2; $p < 0.01$), stroke volume (44.9 +/- 4.5 ml/m2 vs. 54.9 +/- 6.3 ml/m2; $p < 0.001$), and mass (39.8 +/- 6.5 g/m2 vs. 49.6 +/- 7.1 g/m2; $p = 0.02$) were significantly lower in patients. Wall motion abnormalities were observed in four patients and contrast enhancement (fibrosis) in three; none of the controls showed wall motion abnormalities or contrast enhancement. None of the patients or controls showed increased signal intensity on the T2-weighted images.
Conclusion: In patients with CFS, CMR demonstrated lower LV dimensions and a mildly reduced LV function. The presence of myocardial fibrosis in some CFS patients suggests that CMR assessment of cardiac involvement is warranted as part of the scientific exploration, which may imply serial non-invasive examinations.

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Impact factor: 2.062

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21. QRS Prolongation after Premature Stimulation is Associated with Polymorphic Ventricular Tachycardia in Nonischemic Cardiomyopathy: Results from the Leiden Nonischemic Cardiomyopathy Study
Piers SR, Askar SF, Venlet J, Androulakis AF, Kapel GF, de Riva Silva M, Jongbloed JJ, van Tintelen JP, Schalij MJ, Pijnappels DA, Zeppenfeld K

Background: Progressive activation delay after premature stimulation has been associated with ventricular fibrillation in nonischemic cardiomyopathy (NICM).
Objective: The purpose of this study was to (1) investigate prolongation of the paced QRS duration (QRSd) after premature stimulation as a marker of activation delay in NICM, (2) assess its relation to induced ventricular arrhythmias, and (3) analyze its underlying substrate by late gadolinium enhancement CMR (LGE-CMR) and endomyocardial biopsy.
Methods: Patients with NICM were prospectively enrolled in the Leiden Nonischemic Cardiomyopathy Study and underwent a comprehensive evaluation including LGE-CMR, electrophysiological study (EPS) and endomyocardial biopsy. Patients without structural heart disease served as controls for EPS.

Results: Forty patients with NICM were included (age 57+/-14 years, 83% male, LVEF 30+/-13%). After the 400 ms drive train and progressively premature stimulation, the maximum increase in QRSd was larger in NICM than in controls (35+/-18ms vs. 23+/-12ms, p=0.005) and the coupling interval window with QRSd prolongation was wider (47+/-23ms vs. 31+/-14ms, p=0.005). The maximum paced QRSd exceeded the ventricular refractory period allowing for pacing before the QRS offset in 20/39 NICM patients vs. 1/20 controls (p<0.001). In NICM, QRSd prolongation was associated with polymorphic VT inducibility (16/39 patients), and was related to long thick strands of fibrosis in biopsies, but not to focal enhancement on LGE-CMR.
Conclusions: QRSd is a simple parameter to quantify activation delay after premature stimulation, and its prolongation is associated with the inducibility of polymorphic VT and with the pattern of myocardial fibrosis in biopsies. CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov. Identifier: NCT01940081.

Gepubliceerd: Heart Rhythm 2016;13(4):860-9
Impact factor: 4.391

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22. Safety and long-term effects of renal denervation: Rationale and design of the Dutch registry

Sanders MF, Blankestijn PJ, Voskuil M, Spiering W, Vonken EJ, Rotmans JI, van der Hoeven BL, Daemen J, van den Meiracker AH, Kroon AA, de Haan MW, Das M, Bax M, van der Meer IM, van Overhagen H, van den Born BJ, van Brussel PM, van der Valk PH, Smak Gregoor PJ, Meuwissen M, Gomes ME, Oude Ophuis T, Troe E, Tonino WA, Konings CJ, de Vries PA, van Balen A, Heeg JE, Smit JJ, Elvan A, Steggerda R, Niamut SM, Peels JO, de Swart JB, Wardeh AJ, Groeneveld JH, van der Linden E, Hemmelder MH, Folkeringa R, Stoel MG, Kant GD, Herrman JP, van Wissen S, Deinum J, Westra SW, Aengevaeren WR, Parlevliet KJ, Schramm A, Jessurun GA, Rensing BJ, Winkens MH, Wierema TK, Santegoets E, Lipsic E, Houwerzijl E, Kater M, Allaart CP, Nap A, Bots ML

Background: Percutaneous renal denervation (RDN) has recently been introduced as a treatment for therapy-resistant hypertension. Also, it has been suggested that RDN may be beneficial for other conditions characterised by increased sympathetic nerve activity. There are still many uncertainties with regard to efficacy, safety, predictors for success and long-term effects. To answer these important questions, we initiated a Dutch RDN registry aiming to collect data from all RDN procedures performed in the Netherlands.
Methods: The Dutch RDN registry is an ongoing investigator-initiated, prospective, multicentre cohort study. Twenty-six Dutch hospitals agreed to participate in this registry. All patients who undergo RDN, regardless of the clinical indication or device that is used, will be included. Data are currently being collected on eligibility and screening, treatment and follow-up.
Results: Procedures have been performed since August 2010. At present, data from 306 patients have been entered into the database. The main indication for RDN was hypertension (n = 302, 99%). Patients had a mean office blood pressure of 177/100 (+/-29/16) mmHg with a median use of three (range 0-8) blood pressure

lowering drugs. Mean 24-hour blood pressure before RDN was 157/93 (+/-18/13) mmHg. RDN was performed with different devices, with the Simplicity catheter currently used most frequently.
Conclusion: Here we report on the rationale and design of the Dutch RDN registry. Enrolment in this investigator-initiated study is ongoing. We present baseline characteristics of the first 306 participants.

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Impact factor: 1.489

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23. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology
Sliwa K, van Hagen IM, Budts W, Swan L, Sinagra G, Caruana M, Blanco MV, Wagenaar LJ, Johnson MR, Webb G, Hall R, Roos-Hesselink JW

Aims: To describe the outcomes of pregnancy in women with pulmonary hypertension.
Methods and Results: In 2007 the European Registry on Pregnancy and Heart Disease was initiated by the European Society of Cardiology. Consecutive patients with all forms of cardiovascular disease, presenting with pregnancy, were enrolled with the aim of investigating the pregnancy outcomes. This subgroup of the cohort included 151 women with pulmonary hypertension (PH) either diagnosed by right heart catheterization or diagnosed as possible PH by echocardiographic signs, with 26% having pulmonary arterial hypertension (PAH), in three subgroups: idiopathic (iPAH), associated with congenital heart disease (CHD-PAH), or associated with other disease (oPAH), and 74% having PH caused by left heart disease (LHD-PH, n = 112). Maternal mean age was 29.2 +/- 5.6 years and 37% were nulliparous. Right ventricular systolic pressure was <50 mmHg in 59.6% of patients, 50-70 mmHg in 28.5% and >70 mmHg in 11.9%. In more than 75% of patients, the diagnosis of PH had been made before pregnancy. Maternal death up to 1 week after delivery occurred in five patients (3.3%), with another two out of 78 patients who presented for follow-up (2.6%), dying within 6 months after delivery. The highest mortality was found in iPAH (3/7, 43%). During pregnancy, heart failure occurred in 27%. Caesarean section was performed in 63.4% (23.9% as emergency). Therapeutic abortion was performed in 4.0%. Complications included miscarriage (5.6%), fetal mortality (2%), premature delivery (21.7%), low birth weight (19.0%), and neonatal mortality (0.7%).
Conclusion: Mortality in this group of patients with various forms of PH was lower than previously reported as specialized care during pregnancy and delivery was available. However, maternal and fetal mortality remains prohibitively high in women with iPAH, although this conclusion is restricted by limited numbers. Early advice on contraception, pregnancy risk and fetal outcome remains paramount.

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24. Baseline MDCT findings after prosthetic heart valve implantation provide important complementary information to echocardiography for follow-up purposes
Sucha D, Chamuleau SA, Symersky P, Meijs MF, van den Brink RB, de Mol BA, Mali WP, Habets J, van Herwerden LA, Budde RP

Objectives: Recent studies have proposed additional multidetector-row CT (MDCT) for prosthetic heart valve (PHV) dysfunction. References to discriminate physiological from pathological conditions early after implantation are lacking. We present baseline MDCT findings of PHVs 6 weeks post implantation.
Methods: Patients were prospectively enrolled and TTE was performed according to clinical guidelines. 256-MDCT images were systematically assessed for leaflet excursions, image quality, valve-related artefacts, and pathological and additional findings.
Results: Forty-six patients were included comprising 33 mechanical and 16 biological PHVs. Overall, MDCT image quality was good and relevant regions remained reliably assessable despite mild-moderate PHV-artefacts. MDCT detected three unexpected valve-related pathology cases: (1) prominent subprosthetic tissue, (2) pseudoaneurysm and (3) extensive pseudoaneurysms and valve dehiscence. The latter patient required valve surgery to be redone. TTE only showed trace periprosthetic regurgitation, and no abnormalities in the other cases. Additional findings were: tilted aortic PHV position (n = 3), pericardial haematoma (n = 3) and pericardial effusion (n = 3). Periaortic induration was present in 33/40 (83 %) aortic valve patients.
Conclusions: MDCT allowed evaluation of relevant PHV regions in all valves, revealed baseline postsurgical findings and, despite normal TTE findings, detected three cases of unexpected, clinically relevant pathology. KEY POINTS: * Postoperative MDCT presents baseline morphology relevant for prosthetic valve follow-up. * 83 % of patients show periaortic induration 6 weeks after aortic valve replacement. * MDCT detected three cases of clinically relevant pathology not found with TTE. * Valve dehiscence detection by MDCT required redo valve surgery in one patient. * MDCT is a suitable and complementary imaging tool for follow-up purposes.

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Impact factor: 3.640

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25. Diagnostic evaluation and treatment strategy in patients with suspected prosthetic heart valve dysfunction: The incremental value of MDCT
Sucha D, Symersky P, van den Brink RB, Tanis W, Laufer EM, Meijs MF, Habets J, de Mol BA, Mali WP, Chamuleau SA, van Herwerden LA, Budde RP

Background: In patients with suspected prosthetic heart valve (PHV) dysfunction, routine evaluation echocardiography and fluoroscopy may provide unsatisfactory results for identifying the cause of dysfunction. This study assessed the value of

MDCT as a routine, complementary imaging modality in suspected PHV-dysfunction for diagnosing the cause of PHV dysfunction and proposing a treatment strategy.
Methods: Patients with suspected PHV dysfunction were prospectively recruited. All patients underwent routine diagnostic work-up (TTE, TEE +/- fluoroscopy) and additional MDCT imaging. An expert panel reviewed all cases and assessed the diagnosis and treatment strategy, first based on routine evaluation only, second with additional MDCT information.
Results: Forty-two patients were included with suspected PHV obstruction (n = 30) and PHV regurgitation (n = 12). The addition of MDCT showed incremental value to routine evaluation in 26/30 (87%) cases for detecting the specific cause of PHV obstruction and in 7/12 (58%) regurgitation cases for assessment of complications and surgical planning. The addition of MDCT resulted in treatment strategy change in 8/30 (27%) patients with suspected obstruction and 3/12 (25%) patients with regurgitation.
Conclusion: In addition to echocardiography and fluoroscopy, MDCT may identify the cause of PHV dysfunction and alter the treatment strategy.

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Impact factor: 2.472

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26. Evaluation of vascular healing of polymer-free sirolimus-eluting stents in native coronary artery stenosis: a serial follow-up at three and six months with optical coherence tomography imaging
Suwannasom P, Onuma Y, Benit E, Gach O, von Birgelen C, Hofma SH, Sotomi Y, Bo X, Zhang YJ, Gao R, Garcia-Garcia HM, Wykrzykowska JJ, de Winter RJ, Serruys PW

Aims: Our aim was to assess vascular response after polymer-free sirolimus-eluting stent (SES) implantation by using an optical coherence tomography (OCT)-derived vascular healing score (HS), quantifying the deficiency of healing.
Methods and Results: In a prospective, multicentre, single-arm, open-label study, OCT examinations were performed at three months in 45 patients (47 lesions). Per protocol, 24 lesions which had not reached adequate vascular healing according to study criteria were scheduled for OCT examination at six months. The HS was calculated at two time points. Serial OCT imaging demonstrated that the proportion of covered stent struts increased from a median of 87.1% at three months to 98.6% at six months ($p<0.001$). The neointimal thickness increased from a median of 82.8 microm to 112.2 microm ($p<0.001$), whereas the median percentages of malapposed struts were 0.2% and 0.0% at the two respective time points. Neointimal volume obstruction increased from 6.3% to 12.8%, and the HS decreased from a median of 28.1 at three months to 2.4 at six months.
Conclusions: In patients who had inadequate vascular healing three months after polymer-free SES implantation, serial OCT showed almost complete vascular healing at six months.

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Impact factor: 3.863

27. Value of the SYNTAX score for periprocedural myocardial infarction according to WHO and the third universal definition of myocardial infarction: insights from the TWENTE trial
Tandjung K, Lam MK, Sen H, de Man FH, Louwerenburg JH, Stoel MG, van Houwelingen KG, Linssen GC, van der Palen J, Doggen CJ, von Birgelen C

Aims: The SYNTAX score is a tool to quantify the complexity of coronary artery disease. We investigated the relation between the SYNTAX score and the occurrence of a periprocedural myocardial infarction (PMI) according to the historical definition of the World Health Organization (WHO) and the recently updated universal definition of MI.
Methods and Results: The SYNTAX score was calculated in 1,243 patients enrolled in TWENTE, a randomised trial which assessed second-generation drug-eluting stents. PMI was defined by the WHO definition and the third universal definition of MI. Patients were divided into tertiles of the SYNTAX score: </=7 (n=430); >7 and <15 (n=390); >/=15 (n=423). PMI according to the WHO definition occurred more frequently in patients in the highest SYNTAX score tertile (7.3% vs. 3.1% vs. 1.6%, p<0.001) compared to the mid and lowest tertile. Similar findings were seen for universal PMI (9.9% vs. 7.7% vs. 3.7%, p<0.01). After multivariate analysis, SYNTAX score was a significant independent correlate of PMI for both definitions: the highest SYNTAX score tertile had an almost five times higher risk for WHO PMI, and a three times higher risk for universal PMI.
Conclusions: In a broad patient population treated with second-generation DES, the SYNTAX score was able to stratify the risk of PMI.

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Impact factor: 3.863

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28. Non-sustained ventricular tachycardia in patients with congenital heart disease: An important sign?
Teuwen CP, Ramdjan TT, Gotte M, Brundel BJ, Evertz R, Vriend JW, Molhoek SG, Reinhart Dorman HG, van Opstal JM, Konings TC, van der Voort P, Delacretaz E, Wolfhagen NJ, van Gastel V, de Klerk P, Theuns DA, Witsenburg M, Roos-Hesselink JW, Triedman JK, Bogers AJ, de Groot NM

Background: Sustained ventricular tachycardia (susVT) and ventricular fibrillation (VF) are observed in adult patients with congenital heart disease (CHD). These dysrhythmias may be preceded by non-sustained ventricular tachycardia (NSVT). The aims of this study are to examine the 1] time course of ventricular tachyarrhythmia (VTA) in a large cohort of patients with various CHDs and 2] the development of susVT/VF after NSVT.
Methods: In this retrospective study, patients with VTA on ECG, 24-hour Holter or ICD-printout or an out-of-hospital-cardiac arrest due to VF were included. In patients with an ICD, the number of shocks was studied.

Results: Patients (N=145 patients, 59% male) initially presented with NSVT (N=103), susVT (N=25) or VF (N=17) at a mean age of 40 +/- 14 years. Prior to VTA, 58 patients had intraventricular conduction delay, 14 an impaired ventricular dysfunction and 3 had coronary artery disease. susVT/VF rarely occurred in patients with NSVT (N=5). Fifty-two (36%) patients received an ICD; appropriate and inappropriate shocks, mainly due to supraventricular tachycardia (SVT), occurred in respectively 15 (29%) (NSVT: N=1, susVT: N=9, VF: N=5) and 12 (23%) (NSVT: N=4, susVT: N=5, VF: N=3) patients.
Conclusions: VTA in patients with CHD appear on average at the age of 40 years. susVT/VF rarely developed in patients with only NSVT, whereas recurrent episodes of susVT/VF frequently developed in patients initially presenting with susVT/VF. Hence, a wait-and-see treatment strategy in patients with NSVT and aggressive therapy of both episodes of VTA and SVT in patients with susVT/VF seems justified.

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Impact factor: 4.638

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29. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study
Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JH, Holm NR, Wijns W

Objectives: The aim of this prospective multicenter study was to identify the optimal approach for simple and fast fractional flow reserve (FFR) computation from radiographic coronary angiography, called quantitative flow ratio (QFR).
Background: A novel, rapid computation of QFR pullbacks from 3-dimensional quantitative coronary angiography was developed recently.
Methods: QFR was derived from 3 flow models with: 1) fixed empiric hyperemic flow velocity (fixed-flow QFR [fQFR]); 2) modeled hyperemic flow velocity derived from angiography without drug-induced hyperemia (contrast-flow QFR [cQFR]); and 3) measured hyperemic flow velocity derived from angiography during adenosine-induced hyperemia (adenosine-flow QFR [aQFR]). Pressure wire-derived FFR, measured during maximal hyperemia, served as the reference. Separate independent core laboratories analyzed angiographic images and pressure tracings from 8 centers in 7 countries.
Results: The QFR and FFR from 84 vessels in 73 patients with intermediate coronary lesions were compared. Mean angiographic percent diameter stenosis (DS%) was 46.1 +/- 8.9%; 27 vessels (32%) had FFR </= 0.80. Good agreement with FFR was observed for fQFR, cQFR, and aQFR, with mean differences of 0.003 +/- 0.068 (p = 0.66), 0.001 +/- 0.059 (p = 0.90), and -0.001 +/- 0.065 (p = 0.90), respectively. The overall diagnostic accuracy for identifying an FFR of </=0.80 was 80% (95% confidence interval [CI]: 71% to 89%), 86% (95% CI: 78% to 93%), and 87% (95% CI: 80% to 94%). The area under the receiver-operating characteristic curve was higher for cQFR than fQFR (difference: 0.04; 95% CI: 0.01 to 0.08; p < 0.01), but did not differ significantly between cQFR and aQFR (difference: 0.01; 95%

CI: -0.04 to 0.06; p = 0.65). Compared with DS%, both cQFR and aQFR increased the area under the receiver-operating characteristic curve by 0.20 (p < 0.01) and 0.19 (p < 0.01). The positive likelihood ratio was 4.8, 8.4, and 8.9 for fQFR, cQFR, and aQFR, with negative likelihood ratio of 0.4, 0.3, and 0.2, respectively.
Conclusions: The QFR computation improved the diagnostic accuracy of 3-dimensional quantitative coronary angiography-based identification of stenosis significance. The favorable results of cQFR that does not require pharmacologic hyperemia induction bears the potential of a wider adoption of FFR-based lesion assessment through a reduction in procedure time, risk, and costs.

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Impact factor: 7.630

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30. Prognostic value of coronary computed tomography angiography in diabetic patients without chest pain syndrome
van den Hoogen IJ, de Graaf MA, Roos CJ, Leen AC, Kharagjitsingh AV, Wolterbeek R, Kroft LJ, Wouter JJ, Bax JJ, Scholte AJ

Aims: Diabetic patients with coronary artery disease (CAD) are often free of chest pain syndrome. A useful modality for non-invasive assessment of CAD is coronary computed tomography angiography (CTA). However, the prognostic value of CAD on coronary CTA in diabetic patients without chest pain syndrome is relatively unknown. Therefore, the aim was to investigate the long-term prognostic value of coronary CTA in a large population diabetic patients without chest pain syndrome.
Methods: Between 2005 and 2013, 525 diabetic patients without chest pain syndrome were prospectively included to undergo coronary artery calcium (CAC)-scoring followed by coronary CTA. During follow-up, the composite endpoint of all-cause mortality, non-fatal myocardial infarction (MI), and late revascularization (>90 days) was registered.
Results: In total, CAC-scoring was performed in 410 patients and coronary CTA in 444 patients (431 interpretable). After median follow-up of 5.0 (IQR 2.7-6.5) years, the composite endpoint occurred in 65 (14%) patients. Coronary CTA demonstrated a high prevalence of CAD (85%), mostly non-obstructive CAD (51%). Furthermore, patients with a normal CTA had an excellent prognosis (event-rate 3%). An incremental increase in event-rate was observed with increasing CAC-risk category or coronary stenosis severity. Finally, obstructive (50-70%) or severe CAD (>70%) was independently predictive of events (HR 11.10 [2.52;48.79] (P = .001), HR 15.16 [3.01;76.36] (P = .001)). Obstructive (50-70%) or severe CAD (>70%) provided increased value over baseline risk factors.
Conclusion: Coronary CTA provided prognostic value in diabetic patients without chest pain syndrome. Most importantly, the prognosis of patients with a normal CTA was excellent.

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Impact factor: 2.929

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31. Bifurcation treatment with novel, highly flexible drug-eluting coronary stents in all-comers: 2-year outcome in patients of the DUTCH PEERS trial
van der Heijden LC, Kok MM, Lam MK, Danse PW, Schramm AR, Jessurun GA, Tjon Joe Gin RM, van Houwelingen KG, Hautvast RW, Linssen GC, Sen H, Lowik MM, IJzerman MJ, Doggen CJ, von Birgelen C

Background: Percutaneous coronary intervention (PCI) in bifurcated lesions with second-generation drug-eluting stents (DES) was associated with increased myocardial infarction (MI) rates. Flexible stent designs that accommodate well to vessel tapering may be of benefit in challenging anatomies such as bifurcated target lesions, but so far data are scarce.
Methods: We analyzed the 2-year follow-up data of the DUTCH PEERS (TWENTE II) trial, which randomized 1811 all-comer patients to PCI with newer generation resolute integrity zotarolimus-eluting (Medtronic) or promus element everolimus-eluting stents (Boston Scientific). In bifurcated lesions, provisional stenting was generally performed. Target vessel failure is a composite endpoint, consisting of cardiac death, target vessel MI, or target vessel revascularization.
Results: Patients with at least one bifurcated lesion (n = 465, 25.7 %) versus patients with non-bifurcated target lesions only (n = 1346, 74.3 %) showed similar rates of clinical endpoints including target vessel failure (9.2 versus 7.9 %, p = 0.36) and definite stent thrombosis (0.4 versus 1.0 %, p = 0.38). Target vessel MI was more common in patients with bifurcated lesions (3.4 versus 1.6 %, p = 0.02); but after multivariate analysis with propensity score adjustment, bifurcation treatment was found not to be an independent predictor of target vessel MI (HR 1.40, 95 % CI 0.71-2.76; p = 0.34). Among patients with bifurcated lesions, DES type and side-branch size did not affect outcome, but periprocedural MI occurred more often after two-stent approaches (9.0 versus 2.1 %; p = 0.002).
Conclusion: All-comer patients treated for bifurcated and non-bifurcated target lesions showed similar and low rates of clinical endpoints, suggesting that the DES used are efficacious and safe for treating bifurcated target lesions.

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Impact factor: 4.324

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32. Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: Insights from 2-year DUTCH PEERS (TWENTE II) randomized trial
van der Heijden LC, Kok MM, Danse PW, Schramm AR, Hartmann M, Lowik MM, Linssen GC, Stoel MG, Doggen CJ, von Birgelen C

Background: Treatment of lesions in small vessels was associated with worse clinical outcome, and various definitions of "small vessels" have been used. Data with novel drug-eluting stents are scarce.
Methods: To compare the outcome of patients with vs without small-vessel treatment, we assessed 2-year follow-up data of the DUTCH PEERS randomized trial (ClinicalTrials.gov: NCT01331707), in which 1,811 all-comers were treated with contemporary zotarolimus-eluting (Resolute Integrity) or everolimus-eluting (Promus

Element) stents. Primary end point was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, and target lesion revascularization.
Results: The rates of TLF (9.5% vs 5.4%; P log rank = .001) and 2 individual components thereof-target vessel myocardial infarction (3.1% vs 1.3%; P log rank = .006) and target lesion revascularization (4.8% vs 2.8%; P log rank = .02)-were higher among 798 (44.1%) patients treated in at least one small vessel (<2.50 mm by quantitative coronary angiography). Multivariate analysis with propensity score adjustment demonstrated that treatment of small-vessel lesions independently predicted TLF at 2-year follow-up (hazard ratio 1.60, 95% CI 1.09-2.34). Patients with the smallest target vessel being <2.25 mm had TLF rates similar to patients with smallest target vessels of 2.25 to <2.50 mm; however, patients treated in vessels no smaller than 2.50 to <3.00 mm and patients treated in vessels >/=3.00 mm had lower TLF rates (9.3%, 9.8%, 5.0%, and 5.8%, respectively; P log rank = .009).
Conclusion: Patients treated with novel drug-eluting stents in small-vessel lesions had higher adverse event rates than did patients who had no small-vessel treatment. Our data suggest that with current stents, a vessel diameter <2.50 mm is a suitable threshold to identify small target vessels.

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Impact factor: 4.332

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33. Long-term outcome and chest pain in patients with true versus non-true bifurcation lesions treated with second-generation drug-eluting stents in the TWENTE trial
van Houwelingen KG, van der Heijden LC, Lam MK, Kok MM, Lowik MM, Louwerenburg JW, Linssen GC, IJzerman MJ, Doggen CJ, von Birgelen C

The objective of this study is to assess 3-year clinical outcome of patients with true bifurcation lesions (TBLs) versus non-true bifurcation lesions (non-TBLs) following treatment with second-generation drug-eluting stents (DES). TBLs are characterized by the obstruction of both main vessel and side-branch. Limited data are available on long-term clinical outcome following TBL treatment with newer-generation DES. We performed an explorative sub-study of the randomized TWENTE trial among 287 patients who had bifurcated target lesions with side-branches >/=2.0 mm. Patients were categorized into TBL (Medina classes: 1.1.1; 1.0.1; 0.1.1) versus non-TBL to compare long-term clinical outcome. A total of 116 (40.4 %) patients had TBL, while 171 (59.6 %) had non-TBL only. Target-lesion revascularization rates were similar (3.5 vs. 3.5 %; p = 1.0), and definite-or-probable stent thrombosis rates were low (both <1.0 %). The target-vessel myocardial infarction (MI) rate was 11.3 versus 5.3 % (p = 0.06), mostly driven by (periprocedural) MI </=48 h from PCI. All-cause mortality and cardiac death rates were 8.7 versus 3.5 % (p = 0.06) and 3.5 versus 1.2 % (p = 0.22), respectively. The 3-year major adverse cardiac event rate for patients with TBL versus non-TBL was 20.0 versus 11.7 % (p = 0.05). At 1-, 2-, and 3-year follow-up, 6.5, 13.0, and 11.0 % of patients reported chest pain at less than or equal moderate physical effort, respectively, without any between-group

difference. Patients treated with second-generation DES for TBL had somewhat higher adverse event rates than patients with non-TBL, but dissimilarities did not reach statistical significance. Up to 3-year follow-up, the vast majority of patients of both groups remained free from chest pain.

Gepubliceerd: Heart Vessels 2016 Nov;31(11):1731-9
Impact factor: 2.293

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34. Outcome After Myocardial Infarction Treated With Resolute Integrity and Promus Element Stents: Insights From the DUTCH PEERS (TWENTE II) Randomized Trial
van Houwelingen KG, Lam MK, Lowik MM, Danse PW, Tjon Joe Gin RM, Jessurun GA, Anthonio RL, Sen H, Linssen GC, IJzerman MJ, Doggen CJ, von Birgelen C

Introduction and Objectives: In acute myocardial infarction (MI), novel highly deliverable drug-eluting stents (DES) may be particularly valuable as their flexible stent designs might reduce device-induced traumas to culprit lesions. The aim of the study was to assess the safety and efficacy of percutaneous coronary interventions with 2 novel durable polymer-coated DES in patients with acute MI.
Methods: The prospective, randomized DUTCH PEERS (TWENTE II) multicenter trial compares Resolute Integrity and Promus Element stents in 1811 all-comer patients, of whom 817 (45.1%) were treated for ST-segment elevation MI or non-ST-segment elevation MI and the 2-year outcome is available in 99.9%. The primary clinical endpoint is target vessel failure (TVF), a composite of cardiac death, target vessel related MI, or target vessel revascularization.
Results: Of all 817 patients treated for acute MI, 421 (51.5%) were treated with Resolute Integrity and 396 (48.5%) with Promus Element stents. At the 2-year follow-up, the rates of TVF (7.4% vs 6.1%; P = .45), target lesion revascularization (3.1% vs 2.8%; P = .79), and definite stent thrombosis (1.0% vs 0.5%; P = .69) were low for both stent groups. Consistent with these findings in all patients with acute MI, outcomes for the 2 DES were favorable and similar in both, with 370 patients with ST-segment elevation MI (TVF, 5.1% vs 4.9%; P = .81) and 447 patients with non-ST-segment elevation MI (TVF, 9.0% vs 7.5%; P = .56).
Conclusions: Resolute Integrity and Promus Element stents were both safe and efficacious in treating patients with acute MI. The present 2-year follow-up data underline the safety of using these devices in this particular clinical setting.

Gepubliceerd: Rev Esp Cardiol (Engl Ed) 2016 Aug 29;69(12):1152-9
Impact factor: 4.596

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35. Oversized post-dilatation of current bioresorbable vascular scaffolds: kill or cure?
von Birgelen C, Basalus MW

Gepubliceerd: EuroIntervention 2016 Mar;11(12):1330-3
Impact factor: 3.863

36. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial

von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin RM, Somi S, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JH, Hartmann M, Zocca P, Linssen GC, van der Palen J, Doggen CJ, Lowik MM

Background: In patients with coronary artery disease, treated with durable polymer-coated drug-eluting stents, the life-long presence of the polymer might delay arterial healing. Novel very thin strut biodegradable polymer stents, which leave only a bare metal stent after polymer resorption, might improve long-term outcome. We investigated in allcomers the safety and efficacy of three stents eluting either everolimus, sirolimus, or zotarolimus, often clinically used but never compared, of which the biodegradable polymer everolimus-eluting stent was never before assessed in allcomers.
Methods: The large-scale, investigator-initiated, multicentre, assessor and patient blinded, three-arm, randomised, BIO-RESORT non-inferiority trial was done at four clinical sites in the Netherlands. All-comer patients were aged 18 years or older, capable of providing informed consent, and required a percutaneous coronary intervention with drug-eluting stent implantation according to clinical guidelines or the operators' judgment. Exclusion criteria were: participation in another randomised drug or device study before reaching the primary endpoint of that study; planned surgery necessitating interruption of dual antiplatelet therapy within the first 6 months; known intolerance to components of the investigational product or medication required; uncertainty about the adherence to follow-up procedures or an assumed life expectancy of less than 1 year; or known pregnancy. Web-based computer-generated allocation sequences randomly assigned patients (1:1:1) to treatment with very thin strut biodegradable polymer everolimus-eluting or sirolimus-eluting stents (which differ substantially in type, amount, distribution, and resorption speed of their respective coating), or thin strut durable polymer zotarolimus-eluting stents. The primary endpoint was a composite of safety (cardiac death or target vessel-related myocardial infarction) and efficacy (target vessel revascularisation) at 12 months of follow up with a very thin strut biodegradable polymer of either everolimus-eluting or sirolimus-eluting stents, compared with durable polymer zotarolimus-eluting stents, analysed by intention to treat (non-inferiority margin 3.5%). This trial was registered with ClinicalTrials.gov, number NCT01674803.
Findings: From Dec 21, 2012, to Aug 24, 2015, 3514 patients were enrolled and analysed, of whom 2449 (70%) had acute coronary syndromes, which included 1073 (31%) ST-elevation myocardial infarctions. 12 month follow-up of 3490 (99%) patients (three lost to follow-up; 21 withdrawals) was available. The primary endpoint was met by 55 (5%) of 1172 patients assigned to everolimus-eluting stents, 55 (5%) of 1169 assigned to sirolimus-eluting stents and 63 (5%) of 1173 assigned to zotarolimus-eluting stents. Non-inferiority of the everolimus-eluting stents and sirolimus-eluting stents compared with zotarolimus-eluting stents was confirmed (both -0.7% absolute risk difference, 95% CI -2.4 to 1.1; upper limit of one sided

95% CI 0.8%, pnon-inferiority<0.0001). Definite stent thrombosis (defined by the Academic Research Consortium) occurred in four (0.3%) of 1172 patients who were allocated to everolimus-eluting stents, four (0.3%) of 1169 patients who were allocated to sirolimus-eluting stents, and three (0.3%) of 1173 patients who were allocated to zotarolimus-eluting stents (log-rank p=0.70 for both comparisons with zotarolimus-eluting stents).
Interpretation: At 12 month follow-up, both very thin strut drug-eluting stents with dissimilar biodegradable polymer coatings (eluting either everolimus or sirolimus) were non-inferior to the durable polymer stent (eluting zotarolimus) in treating allcomers with a high proportion of patients with acute coronary syndromes. The absence of a loss of 1 year safety and efficacy with the use of these two biodegradable polymer-coated stents is a prerequisite before assessing their potential longer-term benefits. FUNDING: Biotronik, Boston Scientific, and Medtronic.

Gepubliceerd: Lancet 2016 Oct 28;388(10060):2607-17
Impact factor: 44.002

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37. A Comparison of the Quality of Life of Patients With an Entirely Subcutaneous Implantable Defibrillator System Versus a Transvenous System (from the EFFORTLESS S-ICD Quality of Life Substudy)
Pedersen SS, Mastenbroek MH, Carter N, Barr C, Neuzil P, Scholten M, Lambiase PD, Boersma L, Johansen JB, Theuns DA

The first clinical results from the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the subcutaneous implantable cardioverter defibrillator (EFFORTLESS S-ICD) Registry on the entirely S-ICD system are promising, but the impact of the S-ICD system on patients' quality of life (QoL) is not known. We evaluated the QoL of patients with an S-ICD against an unrelated cohort with a transvenous (TV)-ICD system during 6 months of follow-up. Consecutively implanted patients with an S-ICD system were matched with patients with a TV-ICD system on a priori selected variables including baseline QoL. QoL was measured with the Short-Form Health Survey at baseline, 3, and 6 months after implant and compared using multivariable modeling with repeated measures. Patients with an S-ICD (n = 167) versus a TV-ICD system (n = 167) did not differ significantly on physical (p = 0.8157) and mental QoL scores (p = 0.9080) across baseline, 3, and 6 months after implantation in adjusted analyses. The evolution in physical (p = 0.0503) and mental scores (p = 0.3772) during follow-up was similar for both cohorts, as indicated by the nonsignificant interaction effect for ICD system by time. Both patients with an S-ICD system and a TV-ICD system experienced significant improvements in physical and mental QoL between time of implant and 3 months (both p's <0.0001) and between time of implant and 6 months (both p's <0.0001) but not between 3 and 6 months (both p's >0.05). In conclusion, these first results show that the QoL of patients with an S-ICD versus TV-ICD system is similar and that patients with either system experience improvements in QoL on the short term.

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Impact factor: 3.154

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38. Patient preference regarding assessment of clinical follow-up after percutaneous coronary intervention: the PAPAYA study
Kok MM, von Birgelen C, Lam MK, Lowik MM, van Houwelingen KG, Stoel MG, Louwerenburg JH, de Man FH, Hartmann M, Doggen CJ, van Til JA, IJzerman MJ

Aims: To keep patients in long-term clinical follow-up programmes after percutaneous coronary intervention (PCI), knowledge of the patient-preferred mode for follow-up assessment is crucial. We systematically assessed patient preference, and explored potential relationships with age and gender.
Methods and Results: In the prospective, observational PAPAYA study (ClinicalTrials.gov: NCT02189070), 2,566 patients, treated by PCI between June 2008 and May 2012, were invited to participate in a postal survey on the patient-preferred mode (postal questionnaire, telephone or e-mail consultation) and frequency of follow-up assessment. A total of 1,797 (70.0%) patients responded. The vast majority preferred completing postal questionnaires (1,248 [69.9%]) as compared to telephone (240 [13.4%]) or e-mail-based approaches (227 [12.7%]) ($p<0.001$). With increasing age, there was a gradual decline in preference for e-mail ($p<0.001$); the youngest patients (</=60 years) preferred e-mail-based follow-up more often than the oldest (21.1% vs. 3.1%). Nevertheless, 79.9% of the youngest preferred to be approached in ways other than by e-mail. Women more often preferred approaches other than e-mail (94.1% vs. 87.3%, $p<0.001$).
Conclusions: Patients showed a distinct preference for completing postal questionnaires rather than being approached by telephone or e-mail. Younger patients accepted e-mail-based follow-up more often, but the majority of the youngest patients still preferred approaches other than by e-mail.

Gepubliceerd: EuroIntervention 2016 Apr 20;11(13):1487-94
Impact factor: 3.863

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39. The learning curve associated with the introduction of the subcutaneous implantable defibrillator
Knops RE, Brouwer TF, Barr CS, Theuns DA, Boersma L, Weiss R, Neuzil P, Scholten M, Lambiase PD, Leon AR, Hood M, Jones PW, Wold N, Grace AA, Olde Nordkamp LR, Burke MC

Aims: The subcutaneous implantable cardioverter defibrillator (S-ICD) was introduced to overcome complications related to transvenous leads. Adoption of the S-ICD requires implanters to learn a new implantation technique. The aim of this study was to assess the learning curve for S-ICD implanters with respect to implant-related complications, procedure time, and inappropriate shocks (IASs).
Methods and Results: In a pooled cohort from two clinical S-ICD databases, the IDE Trial and the EFFORTLESS Registry, complications, IASs at 180 days follow-up and implant procedure duration were assessed. Patients were grouped in quartiles based on experience of the implanter and Kaplan-Meier estimates of complication

and IAS rates were calculated. A total of 882 patients implanted in 61 centres by 107 implanters with a median of 4 implants (IQR 1,8) were analysed. There were a total of 59 patients with complications and 48 patients with IAS. The complication rate decreased significantly from 9.8% in Quartile 1 (least experience) to 5.4% in Quartile 4 (most experience) (P = 0.02) and non-significantly for IAS from 7.9 to 4.8% (P = 0.10). Multivariable analysis demonstrated a hazard ratio of 0.78 (P = 0.045) for complications and 1.01 (P = 0.958) for IAS. Dual-zone programming increased with experience of the individual implanter (P < 0.001), which reduced IAS significantly in the multivariable model (HR 0.44, P = 0.01). Procedure time decreased from 75 to 65 min (P < 0.001). The complication rate and procedure time stabilized after Quartile 2 (>13 implants).
Conclusion: There is a short and significant learning curve associated with physicians adopting the S-ICD. Performance stabilizes after 13 implants.

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Impact factor: 4.021

Totale impact factor: 250.748
Gemiddelde impact factor: 6.429

Aantal artikelen 1e, 2e of laatste auteur: 18
Totale impact factor: 110.147
Gemiddelde impact factor: 6.119

Gynaecologie

1. The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids
Brolmann H, Bongers M, Garza-Leal JG, Gupta J, Veersema S, Quartero R, Toub D

The FAST-EU Trial was designed to establish the effectiveness and confirm the safety of transcervical intrauterine sonography-guided radiofrequency ablation with the VizAblate System in the treatment of symptomatic uterine fibroids. This was a multicenter, prospective, single-arm trial involving academic and community hospitals in the United Kingdom, the Netherlands, and Mexico. Women with qualifying uterine fibroids and heavy menstrual bleeding underwent intrauterine sonography-guided transcervical radiofrequency ablation (RFA) with the VizAblate System; anesthesia was individualized. Patients were required to have up to five fibroids from 1 to 5 cm in diameter. The primary trial endpoint was the percentage change in perfused fibroid volume, as assessed by contrast-enhanced MRI at 3 months by an independent core laboratory. Secondary endpoints, evaluated at 6 and 12 months, included safety, percentage reductions in the Menstrual Pictogram (MP) score, and the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire, along with the rate of surgical reintervention for abnormal uterine bleeding and the mean number of days to return to normal activity. Additional assessments included the Health-Related Quality of Life (HRQOL) subscale of the UFS-QOL, nonsurgical reintervention for abnormal uterine bleeding, anesthesia regimen, patient satisfaction, and pain during the recovery period. An additional MRI study was performed at 12 months on a subgroup of patients. Fifty patients (89 fibroids) underwent transcervical radiofrequency ablation with the VizAblate System. At 3 and 12 months, perfused fibroid volumes were reduced from baseline by an average of 68.1 +/- 28.6 and 67.4 +/- 31.9 %, respectively, while total fibroid volumes were reduced from baseline by an average of 54.7 +/- 37.4 and 66.6 +/- 32.1 %, respectively (all P < .001 compared with baseline; Wilcoxon signed-rank test). At 12 months, mean MP score and SSS decreased by 53.8 +/- 50.5 and 55.1 +/- 41.0 %, respectively; the mean HRQOL score increased by 277 +/- 483 %. There were four surgical reinterventions (8 %) within 12 months. This is the first report of the 12-month follow-up for patients in the FAST-EU Trial. In concert with previously reported 3- and 6-month endpoint data, the 12-month results of the FAST-EU Trial suggest that in addition to substantially reducing the perfused and total volume of targeted uterine fibroids, the VizAblate System is safe and effective through 12 months in providing relief of abnormal uterine bleeding associated with submucous, intramural, and transmural fibroids.

Gepubliceerd: Gynecol Surg 2016;13:27-35
Impact factor: 3.560

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2. Randomized Trial of a Lifestyle Program in Obese Infertile Women
Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, Koks CA, van Golde R, Kaaijk EM, Schierbeek JM, Oosterhuis GJ, Broekmans

FJ, Bemelmans WJ, Lambalk CB, Verberg MF, Van der Veen F, Klijn NF, Mercelina PE, van Kasteren YM, Nap AW, Brinkhuis EA, Vogel NE, Mulder RJ, Gondrie ET, de Bruin JP, Sikkema JM, de Greef MH, ter Bogt NC, Land JA, Mol BW, Hoek A

Background: Small lifestyle-intervention studies suggest that modest weight loss increases the chance of conception and may improve perinatal outcomes, but large randomized, controlled trials are lacking.
Methods: We randomly assigned infertile women with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 29 or higher to a 6-month lifestyle intervention preceding treatment for infertility or to prompt treatment for infertility. The primary outcome was the vaginal birth of a healthy singleton at term within 24 months after randomization.
Results: We assigned women who did not conceive naturally to one of two treatment strategies: 290 women were assigned to a 6-month lifestyle-intervention program preceding 18 months of infertility treatment (intervention group) and 287 were assigned to prompt infertility treatment for 24 months (control group). A total of 3 women withdrew consent, so 289 women in the intervention group and 285 women in the control group were included in the analysis. The discontinuation rate in the intervention group was 21.8%. In intention-to-treat analyses, the mean weight loss was 4.4 kg in the intervention group and 1.1 kg in the control group (P<0.001). The primary outcome occurred in 27.1% of the women in the intervention group and 35.2% of those in the control group (rate ratio in the intervention group, 0.77; 95% confidence interval, 0.60 to 0.99).
Conclusions: In obese infertile women, a lifestyle intervention preceding infertility treatment, as compared with prompt infertility treatment, did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization. (Funded by the Netherlands Organization for Health Research and Development; Netherlands Trial Register number, NTR1530.).

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Impact factor: 59.558

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3. Parasitic myoma after laparoscopic morcellation: a systematic review of the literature
Van der Meulen JF, Pijnenborg J, Boomsma CM, Verberg M, Geomini P, Bongers MY

Background: Laparoscopic morcellation is frequently used for tissue removal after laparoscopic hysterectomy or myomectomy and may result in parasitic myomas, due to seeding of remained tissue fragments in the abdominal cavity. However, little is known about the incidence and risk factors of this phenomenon. **Objectives:** To identify the incidence and risk factors for the development of parasitic myoma after laparoscopic morcellation.
Search strategy: A systematic review of the literature in Pubmed (MEDLINE) and Embase was conducted. Reference lists of identified relevant articles were checked for missing case reports.

Selection criteria: Studies reporting on incidence or cases of parasitic myoma diagnosed after laparoscopic morcellation were selected. Studies were excluded when history of laparoscopic morcellation was lacking or final pathology demonstrated a malignancy or endometriosis.
Data collection and analysis: Data were extracted and analysed on incidence of parasitic myomas and characteristics of case reports.
Main results: Fourty-four studies were included. Sixty-nine women diagnosed with parasitic myomas after laparoscopic morcellation were identified. Mean age was 40.8 (+/- 7.5) years (range 24-57), median time between surgery and diagnosis was 48.0 months (range 1-192) and mean number of parasitic myomas was 2.9 (+/- 3.3) (range 1-16). The overall incidence of parasitic myomas after laparoscopic morcellation was 0.12-0.95%.
Conclusion: Although the incidence is relatively low, it is important to discuss the risk of parasitic myoma after laparoscopic morcellation with women and balance towards alternative treatment options. The duration of steroid exposure after laparoscopic morcellation might be a risk factor for development of parasitic myomas.
Tweetable abstract: Systematic review on the incidence and risk factors for parasitic myoma after laparoscopic morcellation.

Gepubliceerd: BJOG 2016;123(1):69-75
Impact factor: 3.720

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4. Spontaneous Regression of Clear Cell Carcinoma of the Endometrium
Kankava K, Baidoshvili A, Schutter E, van der Meer S, Makaridze D

This report documents a rare case of complete spontaneous regression of clear cell carcinoma of the endometrium. An elderly woman with paranoid schizophrenia was admitted to the hospital because of vaginal bleeding. Diagnostic curetting and biopsy were performed and she was diagnosed with clear cell carcinoma of endometrium. Anti-tumour therapy was not possible because of her poor psychiatric status. 13 months later the woman died of a natural cause and at autopsy the endometrial tumour could no longer be identified. Myocardial infarction, aggravated by poor functional status of organism due to sepsis, was concluded to be the cause of death.

Gepubliceerd: J Cancer Ther 2016;7:635-45
Impact factor: 0

Totale impact factor: 66.838
Gemiddelde impact factor: 16.710

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

Heelkunde

1. Magnetic Technique for Sentinel Lymph Node Biopsy in Melanoma: The MELAMAG Trial
Anninga B, White SH, Moncrieff M, Dziewulski P, Geh LC, Klaase J, Garmo H, Castro F, Pinder S, Pankhurst QA, Hall-Craggs MA, Douek M

Background: Sentinel lymph node biopsy (SLNB) in melanoma is currently performed using the standard dual technique (radioisotope and blue dye). The magnetic technique is non-radioactive and provides a brown color change in the sentinel lymph node (SLN) through an intradermal injection of a magnetic tracer, and utilizes a handheld magnetometer. The MELAMAG Trial compared the magnetic technique with the standard technique for SLNB in melanoma.
Methods: Clinically node-negative patients with primary cutaneous melanoma were recruited from four centers. SLNB was undertaken after intradermal administration of both the standard (blue dye and radioisotope) and magnetic tracers. The SLN identification rate per patient, with the two techniques, was compared.
Results: A total of 133 patients were recruited, 129 of which were available for final analysis. The sentinel node identification rate was 97.7 % (126/129) with the standard technique and 95.3 % (123/129) with the magnetic technique [2.3 % difference; 95 % upper confidence limit (CL) 6.4; 5.4 % discordance]. With radioisotope alone, the SLN identification rate was 95.3 % (123/129), as with the magnetic technique (0 % difference; 95 % upper CL 4.5; 7.8 % discordance). The lymph node retrieval rate was 1.99 nodes per patient overall, 1.78 with the standard technique and 1.87 with the magnetic technique.
Conclusions: The magnetic technique is feasible for SLNB in melanoma with a high SLN identification rate, but is associated with skin staining. When compared with the standard dual technique, it did not reach our predefined non-inferiority margin.

Gepubliceerd: Ann Surg Oncol 2016 Feb 19;23(6):2070-8
Impact factor: 3.655

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2. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer
Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, Klaase JM

Background: The prevalence of colorectal cancer in the elderly is increasing and, therefore, surgical interventions with a risk of potential complications are more frequently performed. This study investigated the role of low skeletal muscle mass (sarcopenia), muscle quality, and the sarcopenic obesity as prognostic factors for postoperative complications and survival in patients with resectable colon cancer.
Methods: We conducted a retrospective chart review of 91 consecutive patients who underwent an elective open colon resection for cancer with primary anastomosis between 2011 and 2013. Skeletal muscle mass was measured as total psoas area (TPA) and total abdominal muscle area (TAMA) at three anatomical

levels on the preoperative CT scan. Skeletal muscle quality was measured using corresponding mean Hounsfield units (HU) for TAMA. Their relation with complications (none vs one or more), severe complications, and survival was analyzed.
Results: The study included 91 patients with a mean age of 71.2 +/- 9.7 years. Complications were noted in 55 patients (60 %), of which 15 (16.4 %) were severe. Lower HU for TAMA, as an indicator for impaired skeletal muscle quality, was an independent risk factor for one or more complications (all P </= 0.002), while sarcopenic obesity (TPA) was an independent risk factor for severe complications (all P </= 0.008). Sarcopenia was an independent predictor of worse overall survival (HR 8.54; 95 % confidence interval (CI) 1.07-68.32).
Conclusion: Skeletal muscle quality is a predictor for overall complications, whereas sarcopenic obesity is a predictor for severe postoperative complications after open colon resection for cancer. Sarcopenia on itself is a predictor for worse overall survival.

Gepubliceerd: Int J Colorectal Dis 2016 Feb 15;31(6):1117-24
Impact factor: 2.383

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3. Prophylactic mesh placement to prevent parastomal hernia, early results of a prospective multicentre randomized trial
Brandsma HT, Hansson BM, Aufenacker TJ, van Geldere D, van Lammeren FM, Mahabier C, Steenvoorde P, de Vries Reilingh TS, Wiezer RJ, de Wilt JH, Bleichrodt RP, Rosman C

Purpose: Parastomal hernia (PSH) is a common complication after colostomy formation. Recent studies indicate that mesh implantation during formation of a colostomy might prevent a PSH. To determine if placement of a retromuscular mesh at the colostomy site is a feasible, safe and effective procedure in preventing a parastomal hernia, we performed a multicentre randomized controlled trial in 11 large teaching hospitals and three university centres in The Netherlands.
Methods: Augmentation of the abdominal wall with a retromuscular light-weight polypropylene mesh (Parietene Light, Covidien) around the trephine was compared with traditional colostomy formation. Patients undergoing elective open formation of a permanent end-colostomy were eligible. 150 patients were randomized between 2010 and 2012. Primary endpoint of the PREVENT trial is the incidence of parastomal hernia. Secondary endpoints are morbidity, pain, quality of life, mortality and cost-effectiveness. This article focussed on the early results of the PREVENT trial and, therefore, operation time, postoperative morbidity, pain, and quality of life were measured.
Results: Outcomes represent results after 3 months of follow-up. A total of 150 patients were randomized. Mean operation time of the mesh group (N = 72) was significantly longer than in the control group (N = 78) (182.6 vs. 156.8 min; P = 0.018). Four (2.7 %) peristomal infections occurred of which one (1.4 %) in the mesh group. No infection of the mesh occurred. Most of the other infections were infections of the perineal wound, equally distributed over both groups. No statistical

differences were discovered in stoma or mesh-related complications, fistula or stricture formation, pain, or quality of life.
Conclusions: During open and elective formation of an end-colostomy, primary placement of a retromuscular light-weight polypropylene mesh for prevention of a parastomal hernia is a safe and feasible procedure. The PREVENT trial is registered at: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2018.

Gepubliceerd: Hernia 2015 Oct 28;20(4):535-41
Impact factor: 2.050

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4. Impact of a Nationwide Training Program in Minimally Invasive Distal Pancreatectomy (LAELAPS)
de Rooij T, van Hilst J, Boerma D, Bonsing BA, Daams F, van Dam RM, Dijkgraaf MG, van Eijck CH, Festen S, Gerhards MF, Koerkamp BG, van der Harst E, de Hingh IH, Kazemier G, Klaase J, de Kleine RH, van Laarhoven CJ, Lips DJ, Luyer MD, Molenaar IQ, Patijn GA, Roos D, Scheepers JJ, van der Schelling GP, Steenvoorde P, Vriens MR, Wijsman JH, Gouma DJ, Busch OR, Hilal MA, Besselink MG

Objective: To study the feasibility and impact of a nationwide training program in minimally invasive distal pancreatectomy (MIDP). SUMMARY OF BACKGROUND DATA: Superior outcomes of MIDP compared with open distal pancreatectomy have been reported. In the Netherlands (2005 to 2013) only 10% of distal pancreatectomies were in a minimally invasive fashion and 85% of surgeons welcomed MIDP training. The feasibility and impact of a nationwide training program is unknown.
Methods: From 2014 to 2015, 32 pancreatic surgeons from 17 centers participated in a nationwide training program in MIDP, including detailed technique description, video training, and proctoring on-site. Outcomes of MIDP before training (2005-2013) were compared with outcomes after training (2014-2015).
Results: In total, 201 patients were included; 71 underwent MIDP in 9 years before training versus 130 in 22 months after training (7-fold increase, P < 0.001). The conversion rate (38% [n = 27] vs 8% [n = 11], P < 0.001) and blood loss were lower after training and more pancreatic adenocarcinomas were resected (7 [10%] vs 28 [22%], P = 0.03), with comparable R0-resection rates (4/7 [57%] vs 19/28 [68%], P = 0.67). Clavien-Dindo score >/=III complications (15 [21%] vs 19 [15%], P = 0.24) and pancreatic fistulas (20 [28%] vs 41 [32%], P = 0.62) were not significantly different. Length of hospital stay was shorter after training (9 [7-12] vs 7 [5-8] days, P < 0.001). Thirty-day mortality was 3% vs 0% (P = 0.12).
Conclusion: A nationwide MIDP training program was feasible and followed by a steep increase in the use of MIDP, also in patients with pancreatic cancer, and decreased conversion rates. Future studies should determine whether such a training program is applicable in other settings.

Gepubliceerd: Ann Surg 2016 Nov;264(5):754-62
Impact factor: 8.569

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5. Outcomes of Distal Pancreatectomy for Pancreatic Ductal Adenocarcinoma in the Netherlands: A Nationwide Retrospective Analysis
de Rooij T, Tol JA, van Eijck CH, Boerma D, Bonsing BA, Bosscha K, van Dam RM, Dijkgraaf MG, Gerhards MF, van Goor H, van der Harst E, de Hingh IH, Kazemier G, Klaase JM, Molenaar IQ, Patijn GA, van Santvoort HC, Scheepers JJ, van der Schelling GP, Sieders E, Busch OR, Besselink MG

Background: Large multicenter series on outcomes and predictors of survival after distal pancreatectomy (DP) for pancreatic ductal adenocarcinoma (PDAC) are scarce.
Methods: Adults who underwent DP for PDAC in 17 Dutch pancreatic centers between January 2005 and September 2013 were analyzed retrospectively. The primary outcome was survival, and predictors of survival were identified using Cox regression analysis.
Results: In total, 761 consecutive patients after DP were assessed, of whom 620 patients were excluded because of non-PDAC histopathology (n = 616) or a lack of data (n = 4), leaving a total of 141 patients included in the study [45 % (n = 63) male, mean age 64 years (SD = 10)]. Multivisceral resection was performed in 43 patients (30 %) and laparoscopic resection was performed in 7 patients (5 %). A major complication (Clavien-Dindo score of III or higher) occurred in 46 patients (33 %). Mean tumor size was 44 mm (SD 23), and histopathological examination showed 70 R0 resections (50 %), while 30-day and 90-day mortality was 3 and 6 %, respectively. Overall, 63 patients (45 %) received adjuvant chemotherapy. Median survival was 17 months [interquartile range (IQR) 13-21], with a median follow-up of 17 months (IQR 8-29). Cumulative survival at 1, 3 and 5 years was 64, 29, and 22 %, respectively. Independent predictors of worse postoperative survival were R1/R2 resection [hazard ratio (HR) 1.6, 95 % confidence interval (CI) 1.1-2.4], pT3/pT4 stage (HR 1.9, 95 % CI 1.3-2.9), a major complication (HR 1.7, 95 % CI 1.1-2.5), and not receiving adjuvant chemotherapy (HR 1.5, 95 % CI 1.0-2.3).
Conclusion: Survival after DP for PDAC is poor and is related to resection margin, tumor stage, surgical complications, and adjuvant chemotherapy. Further studies should assess to what extent prevention of surgical complications and more extensive use of adjuvant chemotherapy can improve survival.

Gepubliceerd: Ann Surg Oncol 2016 Feb;23(2):585-91
Impact factor: 3.655

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6. EndoAnchors to Resolve Persistent Type Ia Endoleak Secondary to Proximal Cuff With Parallel Graft Placement
Donselaar EJ, van der Vijver-Coppen RJ, van den Ham LH, Lardenoye JW, Reijnen MM

PURPOSE: To describe 2 patients with a distally migrated endograft causing a type Ia endoleak and treatment with a proximal cuff and chimney grafts that required EndoAnchors to finally seal the leak.

Case report: Two men, ages 86 and 72 years, presented with stent-graft migration and type Ia endoleak at 5 and 15 years after endovascular repair, respectively. Both were treated with a proximal cuff in combination with a chimney graft to the left renal artery. In both cases, the type Ia endoleak persisted, likely due to gutter formation. Both patients were treated in the same setting with EndoAnchors that instantly resolved the endoleak. At 1-year follow-up, there was no recurrent endoleak or migration, with patent chimney grafts and renal arteries and stable renal function. **Conclusion:** EndoAnchors may effectively resolve a persistent type Ia endoleak arising from gutter formation after placement of a proximal cuff and chimney grafts.

Gepubliceerd: J Endovasc Ther 2016;23(1):228
Impact factor: 3.128

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7. [Preference for endovascular aortic aneurysm repair: results of RCTs versus nationwide audits]
Geelkerken RH, Hamming JF

This short comment puts into perspective the value of randomised controlled clinical trials in comparison with nationwide audits in the field of aortic aneurysm treatment. RCTs represent greater scientific value but nationwide audits represent daily practices and seem to be more appropriate for shared decision-making.

Gepubliceerd: Ned Tijdschr Geneeskd 2016;160:A9290
Impact factor: 0

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8. The state of the art in breast imaging using the Twente Photoacoustic Mammoscope: results from 31 measurements on malignancies
Heijblom M, Piras D, van den Engh FM, van der Schaaf M, Klaase JM, Steenbergen W, Manohar S

Objectives: Photoacoustic mammography is potentially an ideal technique, however, the amount of patient data is limited. To further our understanding of the in vivo performance of the method and to guide further research and development, we imaged 33 breast malignancies using the research system - the Twente Photoacoustic Mammoscope (PAM).
Methods: Thirty-one patients participated in this retrospective, observational study. The study and informed consent procedure were approved by the local ethics committee. PAM uses 1,064 nm light for excitation with a planar, 588-element, 1-MHz ultrasound array for detection. Photoacoustic lesion visibility and appearance were compared with conventional imaging (x-ray mammography and ultrasonography) findings, histopathology and patient demographics.
Results: Of 33 malignancies 32 were visualized with high contrast and good co-localization with conventional imaging. The contrast of the detected malignancies was independent of radiographic breast density, and size estimation was reasonably good with an average 28 % deviation from histology. However, the presence of contrast areas outside the malignant region is suggestive for low specificity of the

current system. Statistical analyses did not reveal any further relationship between PAM results and patient demographics nor lesion characteristics.
Conclusions: The results confirm the high potential of photoacoustic mammography in future breast care.
KEY POINTS: *Photoacoustic breast imaging visualizes malignancies with high imaging contrast. *Photoacoustic lesion contrast is independent of the mammographically estimated breast density. *No clear relationship exists between photoacoustic characteristics and lesion type, grade, etc. *Photoacoustic specificity to breast cancer from some cases is not yet optimal.

Gepubliceerd: Eur Radiol 2016 Mar 5;26(11):3874-87
Impact factor: 3.640

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9. Imaging After Nellix Endovascular Aneurysm Sealing: A Consensus Document
Holden A, Savlovskis J, Winterbottom A, van den Ham LH, Hill A, Krievins D, Hayes PD, Reijnen MM, Bockler D, de Vries JP, Carpenter JP, Thompson MM

Endovascular aneurysm sealing (EVAS) using the Nellix system is a new and different method of abdominal aortic aneurysm repair. Normal postoperative imaging has unique appearances that change with time; complications also have different and specific appearances. This consensus document on the imaging findings after Nellix EVAS is based on the collective experience of the sites involved in the Nellix EVAS Global Forward Registry and the US Investigational Device Exemption Trial. The normal findings on computed tomography (CT), duplex ultrasound, magnetic resonance imaging, and plain radiography are described. With time, endobag appearances change on CT due to contrast migration to the margins of the hydrogel polymer within the endobag. Air within the endobag also has unique appearances that change over time. Among the complications after Nellix EVAS, type I endoleak usually presents as a curvilinear area of flow between the endobag and aortic wall, while type II endoleak is typically small and usually occurs where an aortic branch artery lies adjacent to an irregular aortic blood lumen that is not completely filled by the endobag. Procedural aortic injury is an uncommon but important complication that occurs as a result of overfilling of the endobags during Nellix EVAS. The optimum imaging surveillance algorithm after Nellix EVAS has yet to be defined but is largely CT-based, especially in the first year postprocedure. However, duplex ultrasound also appears to be a sensitive modality in identifying normal appearances and complications.

Gepubliceerd: J Endovasc Ther 2015 Nov 12;23(1):7-20
Impact factor: 3.128

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10. Episodic Abdominal Pain Characteristics Are Not Associated with Clinically Relevant Improvement of Health Status After Cholecystectomy
Lamberts MP, Kievit W, Gerritsen JJ, Roukema JA, Westert GP, Drenth JP, van Laarhoven CJ

Background: Cholecystectomy is the therapy of first choice in patients with uncomplicated symptomatic cholecystolithiasis, but it remains unclear which patients truly benefit in terms of health status improvement. Patients generally present with episodic abdominal pain of varying frequency, duration, and intensity. We assessed whether characteristics of abdominal pain episodes are determinants of clinically relevant improvement of health status after cholecystectomy.
Methods: In a post hoc analysis of a prospective multicenter cohort study, patients of >/=18 years of age with uncomplicated symptomatic cholecystolithiasis subjected to cholecystectomy were included. Preoperatively, patients received a structured interview and a questionnaire consisting of the visual analogue scale (VAS; range 0-100) and gastrointestinal quality of life index (GIQLI). At 12 weeks after cholecystectomy, the GIQLI was again administered. Logistic regression analyses were performed to determine significant associations.
Results: Questionnaires were sent to 261 and returned by 166 (63.6 %) patients (128 females, mean age at surgery 49.5 +/- 13.8). A total of 131 (78.9 %) patients reported a clinically relevant improvement of health status. The median (interquartile range) frequency, duration, and intensity of abdominal pain episodes were 0.38 (0.18-0.75) a week, 4.00 (2.00-8.00) hours, and 92 (77-99), respectively. None of the characteristics was associated with a clinically relevant improvement of health status at 12 weeks after cholecystectomy.
Conclusions: Characteristics of abdominal pain episodes cannot be used to inform patients with symptomatic cholecystolithiasis who are skeptic about the timing of cholecystectomy for optimal benefit. Timing of cholecystectomy should therefore be based on other characteristics and preferences.

Gepubliceerd: J Gastrointest Surg 2016 Jul;20(7):1350-8
Impact factor: 2.807

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11. Pancreatoduodenectomy with colon resection for cancer: A nationwide retrospective analysis
Marsman EM, de Rooij T, van Eijck CH, Boerma D, Bonsing BA, van Dam RM, van Dieren S, Erdmann JI, Gerhards MF, de Hingh IH, Kazemier G, Klaase J, Molenaar IQ, Patijn GA, Scheepers JJ, Tanis PJ, Busch OR, Besselink MG

Background: Microscopically radical (R0) resection of pancreatic, periampullary, or colon cancer may occasionally require a pancreatoduodenectomy with colon resection (PD-colon), but the benefits of this procedure have been disputed, and multicenter studies on morbidity and oncologic outcomes after PD-colon are lacking. This study aimed to assess complications and survival after PD-colon.
Methods: Patients who had undergone PD-colon from 2004-2014 in 1 of 13 centers were analyzed retrospectively. Ninety-day morbidity was scored using the Clavien-Dindo score and the Comprehensive Complication Index (CCI, 0 = no complications, 100 = death). Survival was analyzed per histopathologic diagnosis.
Results: After screening 3,218 consecutive PDs, 50 (1.6%) PD-colon patients (median age 66 years [interquartile range 55-72], 33 [66%] men) were included. Twenty-three (46%) patients had pancreatic ductal adenocarcinoma (PDAC), 19

(38%) other pathology, and 8 (16%) colon cancer. Ninety-day Clavien-Dindo >/=3 complications occurred in 30 (60%) patients without differences per diagnosis (P > .99); mean CCI was 39 (standard deviation 27). Colonic anastomosis leak, pancreatic fistula, and 90-day mortality occurred in 3 (6%), 2 (4%), and 4 (8%) patients, respectively. A total of 11/23 (48%) patients with PDAC and 8/8 (100%) patients with colon cancer underwent an R0 resection. Patients with PDAC had a median postoperative survival of 13 months (95% confidence interval = 5-21). One-, 3-, and 5-year cumulative survival was 56%, 21%, and 14%, respectively. Median survival after R0 resection for PDAC was 21 months (95% confidence interval = 6-35). All patients with colon cancer were alive at end of follow-up (median 24 months [95% confidence interval = 9-110]).
Conclusion: In this retrospective, multicenter study, PD-colon was associated with considerable complications and acceptable survival rates when a tumor negative resection margin was achieved.

Gepubliceerd: Surgery 2016 Jul;160(1):145-52
Impact factor: 3.309

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12. A nurse-initiated pain protocol in the ED improves pain treatment in patients with acute musculoskeletal pain
Pierik JG, Berben SA, IJzerman MJ, Gaakeer MI, van Eenennaam FL, van Vugt AB, Doggen CJ

While acute musculoskeletal pain is a frequent complaint, its management is often neglected. An implementation of a nurse-initiated pain protocol based on the algorithm of a Dutch pain management guideline in the emergency department might improve this. A pre-post intervention study was performed as part of the prospective PROTACT follow-up study. During the pre- (15 months, n = 504) and post-period (6 months, n = 156) patients' self-reported pain intensity and pain treatment were registered. Analgesic provision in patients with moderate to severe pain (NRS >/=4) improved from 46.8% to 68.0%. Over 10% of the patients refused analgesics, resulting into an actual analgesic administration increase from 36.3% to 46.1%. Median time to analgesic decreased from 10 to 7 min (P < 0.05), whereas time to opioids decreased from 37 to 15 min (P < 0.01). Mean pain relief significantly increased to 1.56 NRS-points, in patients who received analgesic treatment even up to 2.02 points. The protocol appeared to lead to an increase in analgesic administration, shorter time to analgesics and a higher clinically relevant pain relief. Despite improvements, suffering moderate to severe pain at ED discharge was still common. Protocol adherence needs to be studied in order to optimize pain management.

Gepubliceerd: Int Emerg Nurs 2016 Jul;27:3-10
Impact factor: 0.974

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13. Incidence and prognostic factors of chronic pain after isolated musculoskeletal extremity injury

Pierik JG, IJzerman MJ, Gaakeer MI, Vollenbroek-Hutten MM, **van Vugt AB**, Doggen CJ

Background: Chronic pain in patients is usually related to an episode of pain following acute injury, emphasizing the need to prevent progression from acute to chronic pain. Multiple factors in the acute phase might be responsible for perpetuating the pain. The presentation of patients at the emergency department (ED) presents a prime opportunity to identify patients at high risk for chronic pain and to start appropriate treatment.
Methods: The PROTACT study is a prospective follow-up study aiming to estimate the incidence and prognostic factors responsible for the development of chronic pain after musculoskeletal injury. Data including sociodemographic, pain, clinical, injury- or treatment-related and psychological factors of 435 patients were collected from registries and questionnaires at ED visit, 6-week, 3- and 6-month follow-up.
Results: At 6 months post-injury, 43.9% of the patients had some degree of pain (Numeric Rating Scale (NRS) >/=1) and 10.1% had chronic pain (NRS >/=4). Patients aged over 40 years, in poor physical health, with pre-injury chronic pain, pain catastrophizing, high urgency level and severe pain at discharge were found to be at high risk for chronic pain.
Conclusions: Two prognostic factors, severe pain at discharge and pain catastrophizing, are potentially modifiable. The implementation of a pain protocol in the ED and the use of cognitive-behavioural techniques involving reducing catastrophizing might be useful.

Gepubliceerd: Eur J Pain 2015 Oct 22;20(5):711-22
Impact factor: 2.928

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14. Ex vivo sentinel lymph node mapping in colorectal cancer using a magnetic nanoparticle tracer to improve staging accuracy: a pilot study
Pouw JJ, Grootendorst MR, Klaase JM, van Baarlen J, Ten Haken B

Aim: Nodal status is the most important prognostic factor in colorectal cancer (CRC). Small occult metastases may remain undetected on conventional histopathological examination, potentially resulting in undertreatment. Ex vivo sentinel lymph node mapping (SLNM) can be used to improve the accuracy of nodal staging, but the currently used tracers suffer from drawbacks, which hamper implementation of the technique in routine clinical practice. Magnetic tracers are the optimal size for sentinel lymph node (SLN) retention and allow objective quantitative selection of SLNs; they therefore have great potential for SLNM in CRC. The study evaluates the feasibility of ex vivo magnetic SLNM and compares the performance of this technique with blue dye SLNM.
Method: Twenty-eight ex vivo SLNM procedures were performed in 27 histological node-negative patients with CRC using a magnetic tracer and blue dye. A magnetometer was used to select magnetic SLNs after formalin fixation of the CRC specimen. Both magnetic and blue SLNs were subjected to serial sectioning and immunohistochemical staining to reveal occult metastases.

Results: At least one SLN was successfully identified in 27/28 (96%) and 25/28 (89%) of the cases with the magnetic technique and blue dye. Isolated tumour cells were detected in 10 patients. This was predicted with 100% sensitivity and accuracy using the magnetic technique, and with 91% sensitivity and 96% accuracy using the blue dye technique.
Conclusion: This study demonstrates that ex vivo magnetic SLNM is a feasible technique for use in routine clinical practice, improving nodal staging accuracy of CRC patients.

Gepubliceerd: Colorectal Dis 2016 Dec;18(12):1147-53
Impact factor: 2.452

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15. Phantom study quantifying the depth performance of a handheld magnetometer for sentinel lymph node biopsy
Pouw JJ, Bastiaan DM, Klaase JM, Ten Haken B

Purpose: The use of a magnetic nanoparticle tracer and handheld magnetometer for sentinel lymph node biopsy (SLNB) was recently introduced to overcome drawbacks associated with the use of radioisotope tracers. Unlike the gamma probe, the used magnetometers are not only sensitive to the tracer, but also the diamagnetic human body. This potentially limits the performance of the magnetometer when used clinically.
Methods: A phantom, mimicking the magnetic and mechanical properties of the human axilla, was constructed. The depth performance of two current generation magnetometers was evaluated in this phantom. LN-phantoms with tracer uptake ranging from 5 to 500mug iron were placed at clinically relevant depths of 2.5, 4 and 5.5cm. Distance-response curves were obtained to quantify the depth performance of the probes.
Results: The depth performance of both probes was limited. In the absence of diamagnetic material and forces on the probe (ideal conditions) a LN-phantom with high uptake (500mug iron) could first be detected at 3.75cm distance. In the phantom, only superficially placed LNs (2.5cm) with high uptake (500mug iron) could be detected from the surface. The penetration depth was insufficient to detect LNs with lower uptake, or which were located deeper.
Conclusion: The detection distance of the current generation magnetometers is limited, and does not meet the demands formulated by the European Association for Nuclear Medicine for successful transcutaneous SLN localization. Future clinical trials should evaluate whether the limited depth sensitivity is of influence to the clinical outcome of the SLNB procedure.

Gepubliceerd: Phys Med 2016 Jul;32(7):926-31
Impact factor: 1.763

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16. Preoperative exercise therapy in surgical care: a scoping review
Pouwels S, Hageman D, Gommans LN, Willigendael EM, Nienhuijs SW, Scheltinga MR, Teijink JA

Objectives: Several systematic reviews have focused on the role of preoperative exercise therapy (PET) in various fields of surgical care. Aims of the present scoping review are to summarize research findings and to identify gaps in existing literature.
Methods: Two authors independently conducted a comprehensive literature search on systematic reviews regarding PET. The risk of bias was assessed using "the methodology checklist for systematic reviews and meta-analyses of the Scottish Intercollegiate Guidelines Network (SIGN)." Findings of the included systematic reviews were summarized according to type of surgery and type of PET.
Results: Twenty-one reviews on PET with a low risk of bias were included. Seven reviews investigated PET in multiple surgical fields and 14 in just a single surgical field. PET was studied before cardiac surgery (n = 9), orthopedic surgery (n = 8), abdominal surgery (n = 8), thoracic surgery (n = 8), vascular surgery (n = 3), and urologic surgery (n = 1).
Conclusion: Overall, it seems that PET exerts beneficial effects on physical fitness and postoperative outcome measures. Gaps in current literature are the heterogeneity in selected patient populations and outcome measures as well as lack of guidelines on the specific PET regimes. Therefore, there is increasing need for multicenter randomized trials with specifically designed PET programs and a carefully selected patient population to strengthen current evidence.

Gepubliceerd: J Clin Anesth 2016 Sep;33:476-90
Impact factor: 1.284

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17. Symptomatic abdominal aortic aneurysm repair: to wait or not to wait
Ten Bosch JA, Koning SW, Willigendael EM, van Sambeek MR, Stokmans RA, Prins MH, Teijink JA

Background: In patients with a symptomatic abdominal aortic aneurysm (sAAA), acute intervention theoretically reduces rupture risk prior to surgery whereas delayed intervention provides surgery under optimised conditions. In the present study we evaluated differences in 30-day mortality in patients with a sAAA operated within 12 hours compared to patients who received treatment after 12 hours and who were optimized for surgery.
Methods: All patients with a sAAA who were treated within one week after presentation were included in the analyses. The 30-day mortality rates of patients operated within 12 hours were compared to those operated after 12 hours, adjusted for type of operation and for all potential confounders.
Results: Of the 89 included patients, 37 patients received surgery within 12 hours. In patients treated within 12 hours, 30-day mortality rate was 6 (16.2%) compared to 3 (5.8%) in patients treated after 12 hours (odds ratio 0.316; CI 0.074-1.358). When adjusted for type of operation and other confounders, odds ratios were 0.305 (CI 0.066-1.405) and 0.270 (CI 0.015-4.836), respectively.
Conclusions: In a substantial amount of patients with an alleged symptomatic AAA, delayed surgery with patient optimisation might be justified. However, specific criteria in order to select patients that might benefit from delayed surgery need further investigation.

Gepubliceerd: J Cardiovasc Surg (Torino) 2016 Dec;57(6):830-8
Impact factor: 1.632

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18. Treatment of an Infrarenal Aneurysm with an Eccentric Calcified Lesion in the Infrarenal Neck Using the Nellix Endoprosthesis
van den Ham LH, Smeets L, Reijnen MM

Gepubliceerd: J Vasc Interv Radiol 2016 Feb;27(2):290-3
Impact factor: 2.570

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19. Treatment of Type IIIb Endoleaks After EVAR Using the Nellix EndoVascular Aneurysm Sealing System
van den Ham LH, Wiersema AM, Kievit JK, Reijnen MM

Purpose: To describe the successful endovascular treatment of 2 patients with type IIIb endoleak using the Nellix EndoVascular Aneurysm Sealing (EVAS) System.
Case Report: Two men aged 75 and 83 years presented with type IIIb endoleak several years (8 and 3, respectively) after initial endovascular aneurysm repair. Dual Nellix endoprosthesis were deployed in the stent-grafts, and the endobags were filled with polymer to seal the defect and eliminate the endoleak. The perioperative periods were uneventful. At up to 6-month follow-up, no endoleaks were detected, aneurysm diameters were unchanged, and the endografts were patent. One patient died 7 months after revision due to a metastatic malignancy.
Conclusion: The Nellix EVAS System may prove useful for the treatment of type IIIb endoleak.

Gepubliceerd: J Endovasc Ther 2016;23(1):29-32
Impact factor: 3.128

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20. Prospective nationwide outcome audit of surgery for suspected acute appendicitis
van Rossem CC, Bolmers MD, Schreinemacher MH, van Geloven AA, Bemelman WA, Snapshot Appendicitis Collaborative Study Group (Includes Klaase JM)

Background: Studies comparing laparoscopic and open appendicectomy are difficult to interpret owing to several types of bias, and the results often seem of limited clinical importance. National audits can be valuable to provide insight into outcomes following appendicectomy at a population level.
Methods: A prospective, observational, resident-led, nationwide audit was carried out over a period of 2 months, including all consecutive adult patients who had surgery for suspected acute appendicitis. Complications after laparoscopic and open appendicectomy were compared by means of logistic regression analysis; subgroup analyses were performed for patients with complicated appendicitis.

Results: A total of 1975 patients were included from 62 participating Dutch hospitals. A normal appendix was seen in 3.3 per cent of patients. Appendicectomy was performed for acute appendicitis in 1378 patients, who were analysed. All but three patients underwent preoperative imaging. Laparoscopy was used in 79.5 per cent of patients; the conversion rate was 3.4 per cent. A histologically normal appendix was found in 2.2 per cent. Superficial surgical-site infection was less common in the laparoscopic group (odds ratio 0.25, 95 per cent c.i. 0.14 to 0.44; P < 0.001). The rate of intra-abdominal abscess formation was not significantly different following laparoscopic or open surgery (odds ratio 1.71, 0.80 to 3.63; P = 0.166). Similar findings were observed in patients with complicated appendicitis.
Conclusion: Management of acute appendicitis in the Netherlands is preferably performed laparoscopically, characterized by a low conversion rate. Fewer superficial surgical-site infections occurred with laparoscopy, although the rate of abscess formation was no different from that following open surgery. A low normal appendix rate is the presumed effect of a mandatory preoperative imaging strategy.

Gepubliceerd: Br J Surg 2016 Jan;103(1):144-51
Impact factor: 5.596

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21. Correct positioning of percutaneous iliosacral screws with computer-navigated versus fluoroscopically guided surgery in traumatic pelvic ring fractures
Verbeek J, Hermans E, van Vugt A, Frolke JP

Objectives: To assess the correct positioning of iliosacral screw in patients with unstable traumatic pelvic ring injury by comparing fluoroscopically guided computer-navigated surgery (CNS) with conventional fluoroscopy (CF) through reviewing post-operative CT scans and clinical indicators. DESIGN: A comparative multicenter cohort study. SETTING: Two level I Trauma Centers in The Netherlands. PATIENTS: The computer-navigated group (n=56) and the conventional fluoroscopy group (n=24) were comparable regarding age (mean, 43 yr), gender (58%, male), BMI (25 kg/m2), ISS (27), injury-to-surgery interval (7 days) and OTA classification (40% 61-B, 60% 61-C). MAIN OUTCOME MEASUREMENTS: The position of the iliosacral screws was evaluated on postoperative CT scans. Additionally, clinical morbidity and re-operation were assessed.
Results: In the CNS group, a total of 111 screws were placed (2.0 per patient), of which 83% were placed correctly. In the CF group, 39 screws (1.6 per patient) were placed, 82% of them correctly.Inadequate fixation included neural foramina hit (12 screws (11%) in the CNS group vs. 3 screws (8%) in the CF group, p = 0.76) and extra osseous dislocation (7 screws (6%) vs. 4 screws (10%), respectively, p = 0.47). Five patients required re-operation, all in the computer-navigated surgery group, p = 0.32. We observed more adequate positioning with increased surgical experience, p = 0.12.
Conclusions: In contrast to what has been suggested by previous studies, we found no benefit from computer-navigated iliosacral screw fixation compared to fluoroscopically guided surgery regarding the correct positioning of iliosacral screw on postoperative CT scans and related morbidity. LEVEL OF EVIDENCE:

Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Gepubliceerd: J Orthop Trauma 2016;30(6):331-5
Impact factor: 1.840

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22. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial
Versteijne E, van Eijck CH, Punt CJ, Suker M, Zwinderman AH, Dohmen MA, Groothuis KB, Busch OR, Besselink MG, de Hingh IH, Ten Tije AJ, Patijn GA, Bonsing BA, de Vos-Geelen J, Klaase JM, Festen S, Boerma D, Erdmann JI, Molenaar IQ, van der Harst E, van der Kolk MB, Rasch CR, van Tienhoven G

Background: Pancreatic cancer is the fourth largest cause of cancer death in the United States and Europe with over 100,000 deaths per year in Europe alone. The overall 5-year survival ranges from 2-7 % and has hardly improved over the last two decades. Approximately 15 % of all patients have resectable disease at diagnosis, and of those, only a subgroup has a resectable tumour at surgical exploration. Data from cohort studies have suggested that outcome can be improved by preoperative radiochemotherapy, but data from well-designed randomized studies are lacking. Our PREOPANC phase III trial aims to test the hypothesis that median overall survival of patients with resectable or borderline resectable pancreatic cancer can be improved with preoperative radiochemotherapy.
Methods/Design: The PREOPANC trial is a randomized, controlled, multicentric superiority trial, initiated by the Dutch Pancreatic Cancer Group. Patients with (borderline) resectable pancreatic cancer are randomized to A: direct explorative laparotomy or B: after negative diagnostic laparoscopy, preoperative radiochemotherapy, followed by explorative laparotomy. A hypofractionated radiation scheme of 15 fractions of 2.4 gray (Gy) is combined with a course of gemcitabine, 1,000 mg/m(2)/dose on days 1, 8 and 15, preceded and followed by a modified course of gemcitabine. The target volumes of radiation are delineated on a 4D CT scan, where at least 95 % of the prescribed dose of 36 Gy in 15 fractions should cover 98 % of the planning target volume. Standard adjuvant chemotherapy is administered in both treatment arms after resection (six cycles in arm A and four in arm B). In total, 244 patients will be randomized in 17 hospitals in the Netherlands. The primary endpoint is overall survival by intention to treat. Secondary endpoints are (R0) resection rate, disease-free survival, time to locoregional recurrence or distant metastases and perioperative complications. Secondary endpoints for the experimental arm are toxicity and radiologic and pathologic response.
Discussion: The PREOPANC trial is designed to investigate whether preoperative radiochemotherapy improves overall survival by means of increased (R0) resection rates in patients with resectable or borderline resectable pancreatic cancer. TRIAL REGISTRATION: Trial open for accrual: 3 April 2013 The Netherlands National Trial Register - NTR3709 (8 November 2012) EU Clinical Trials Register - 2012-003181-40 (11 December 2012).

Gepubliceerd: Trials 2016;17(1):127
Impact factor: 1.859

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23. Meta-analysis of sentinel lymph node biopsy in breast cancer using the magnetic technique
Zada A, Peek MC, Ahmed M, Anninga B, Baker R, Kusakabe M, Sekino M, Klaase JM, Ten Haken B, Douek M

Background: The standard for sentinel lymph node biopsy (SLNB), the dual technique (radiolabelled tracer and blue dye), has several drawbacks. A novel magnetic technique without these drawbacks has been evaluated in a number of clinical trials. It uses a magnetic tracer and a handheld magnetometer to identify and excise sentinel lymph nodes. A systematic review and meta-analysis was performed to assess the performance and utility of the magnetic in comparison to the standard technique.
Methods: MEDLINE, PubMed, Embase and the Cochrane online literature databases were used to identify all original articles evaluating the magnetic technique for SLNB published up to April 2016. Studies were included if they were prospectively conducted clinical trials comparing the magnetic with the standard technique for SLNB in patients with breast cancer.
Results: Seven studies were included. The magnetic technique was non-inferior to the standard technique ($z = 3.87$, $P < 0.001$), at a 2 per cent non-inferiority margin. The mean identification rates for the standard and magnetic techniques were 96.8 (range 94.2-99.0) and 97.1 (94.4-98.0) per cent respectively (risk difference (RD) 0.00, 95 per cent c.i. -0.01 to 0.01; $P = 0.690$). The total lymph node retrieval was significantly higher with the magnetic compared with the standard technique: 2113 (1.9 per patient) versus 2000 (1.8 per patient) (RD 0.05, 0.03 to 0.06; $P = 0.003$). False-negative rates were 10.9 (range 6-22) per cent for the standard technique and 8.4 (2-22) per cent for the magnetic technique (RD 0.03, 0.00 to 0.06; $P = 0.551$). The mean discordance rate was 3.9 (range 1.7-6.9) per cent.
Conclusion: The magnetic technique for SLNB is non-inferior to the standard technique, with a high identification rate but with a significantly higher lymph node retrieval rate.

Gepubliceerd: Br J Surg 2016 Oct;103(11):1409-19
Impact factor: 5.596

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24. The Effect of Unenhanced MRI on the Surgeons' Decision-Making Process in Females with Suspected Appendicitis
Ziedses des Plantes CM, van Veen MJ, van der Palen J, Klaase JM, Gielkens HA, Geelkerken RH

Background: This prospective study evaluated the impact of the results of unenhanced magnetic resonance imaging (MRI) on the surgeon's diagnosis of acute appendicitis in potentially fertile females.

Methods: 112 female patients, aged 12-55, with suspected appendicitis underwent MRI of the abdomen. At three defined intervals; admission and clinical re-evaluation before and after revealing the MRI results, the surgeon recorded the attendance of each patient in operative treatment, observation or discharge. Appendicitis was confirmed or declined by pathology or by telephone follow-up in case of non-intervention.
Findings: Appendicitis was confirmed in 29 of 112 patients. At admission the surgeon's disposition had a sensitivity of 97 % and specificity of 29 %. After knowing the MRI results, sensitivity was 97 % and specificity 64 %. The sensitivity and specificity of MRI alone were 89 and 100 %, with a negative and positive predictive value of 96 and 100 %, respectively.
Conclusion: We believe that MRI should perhaps be standard in all female patients during their reproductive years with suspected appendicitis. It avoids an operation in 32 % of cases and allows earlier planning for patients with an equivocal clinical picture. Trial number: OND1292733 (Narcis.nl).

Gepubliceerd: World J Surg 2016 Dec;40(12):2881-7
Impact factor: 2.532

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25. An international study comparing conventional versus mRNA level testing (TargetPrint) for ER, PR, and HER2 status of breast cancer
Wesseling J, Tinterri C, Sapino A, Zanconati F, Lutke-Holzik M, Nguyen B, Deck KB, Querzoli P, Perin T, Giardina C, Seitz G, Guinebretiere JM, Barone J, Dekker L, de Snoo F, Stork-Sloots L, Roepman P, Watanabe T, Cusumano P

To compare results from messenger RNA (mRNA)-based TargetPrint testing with those from immunohistochemistry (IHC) and in situ hybridization (ISH) conducted according to local standard procedures at hospitals worldwide. Tumor samples were prospectively obtained from 806 patients at 22 hospitals. The mRNA level of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was assessed by TargetPrint quantitative gene expression readouts. IHC/ISH assessments were performed according to local standards at the participating hospitals. TargetPrint readout showed a high concordance with IHC/ISH of 95 % (kappa 0.81) for ER, 81 % (kappa 0.56) for PR, and 94 % (kappa 0.76) for HER2. The positive/negative agreement between TargetPrint and IHC for ER, PR, and HER2 was 96 %/87 %, 84 %/74 %, and 74 %/98 %, respectively. The concordance rate in IHC/ISH results between hospitals varied: 88-100 % for ER (kappa 0.50-1.00); 50-100 % for PR (kappa 0.20-1.00); and 90-100 % for HER2 (kappa 0.59-1.00). mRNA readout of ER, PR, and HER2 status by TargetPrint was largely comparable to local IHC/ISH analysis. However, there was substantial discordance in IHC/ISH results between different hospitals. When results are discordant, the use of TargetPrint would improve the reliability of hormone receptor and HER2 results by prompting retesting in a reference laboratory.

Gepubliceerd: Virchows Arch 2016 Sep;469(3):297-304
Impact factor: 2.613

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26. Traumatische fractuur van een talar beak bij tarsale coalitie
Boer BC, Bulut T, Klazen CA, Hogeboom WR

Tarsal coalition is an uncommon condition and consists of complete or partial union between two or more bones in the midfoot and hindfoot. A talar beak results from impaired subtalar joint motion and should not be confused with degenerative osteophytic changes. Different radiographic findings could lead to the recognition of a talar beak and subsequently the diagnosis of a tarsal coalition. A fractured talar beak in tarsal coalition may lead to impaired bone healing.

Gepubliceerd: Ned Tijdschr Traumachirurgie 2016;24(3):9-11
Impact factor: 0

Totale impact factor: 73.091
Gemiddelde impact factor: 2.811

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 8.043
Gemiddelde impact factor: 1.609

Intensive Care

1. Perioperative glutamine supplementation restores disturbed renal arginine synthesis after open aortic surgery: a randomized controlled clinical trial
Brinkmann SJ, Buijs N, Vermeulen MA, Oosterink E, Schierbeek H, Beishuizen A, de Vries JP, Wisselink W, van Leeuwen PA

Postoperative renal failure is a common complication after open repair of an abdominal aortic aneurysm. The amino acid arginine is formed in the kidneys from its precursor citrulline, and citrulline is formed from glutamine in the intestines. Arginine enhances the function of the immune and cardiovascular systems, which is important for recovery after surgery. We hypothesized that renal arginine production is diminished after ischemia-reperfusion injury caused by clamping of the aorta during open abdominal aortic surgery and that parenteral glutamine supplementation might compensate for this impaired arginine synthesis. This open-label clinical trial randomized patients who underwent clamping of the aorta during open abdominal aortic surgery to receive a perioperative supplement of intravenous alanyl-glutamine (0.5 g.kg(-1).day(-1); group A, n = 5) or no supplement (group B, n = 5). One day after surgery, stable isotopes and tracer methods were used to analyze the metabolism and conversion of glutamine, citrulline, and arginine. Whole body plasma flux of glutamine, citrulline, and arginine was significantly higher in group A than in group B (glutamine: 391 +/- 34 vs. 258 +/- 19 mumol.kg(-1).h(-1), citrulline: 5.7 +/- 0.4 vs. 2.8 +/- 0.4 mumol.kg(-1).h(-1), and arginine: 50 +/- 4 vs. 26 +/- 2 mumol.kg(-1).h(-1), P < 0.01), as was the synthesis of citrulline from glutamine (4.8 +/- 0.7 vs. 1.6 +/- 0.3 mumol.kg(-1).h(-1)), citrulline from arginine (2.3 +/- 0.3 vs. 0.96 +/- 0.1 mumol.kg(-1).h(-1)), and arginine from glutamine (7.7 +/- 0.4 vs. 2.8 +/- 0.2 mumol.kg(-1).h(-1)), respectively (P < 0.001 for all). In conclusion, the production of citrulline and arginine is severely reduced after clamping during aortic surgery. This study shows that an intravenous supplement of glutamine increases the production of citrulline and arginine and compensates for the inhibitory effect of ischemia-reperfusion injury.

Gepubliceerd: Am J Physiol Renal Physiol 2016 Sep 1;311(3):F567-F575
Impact factor: 3.390

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2. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial
de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EM, de Smet AM, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW

Background: In critically ill patients, antibiotic therapy is of great importance but long duration of treatment is associated with the development of antimicrobial

resistance. Procalcitonin is a marker used to guide antibacterial therapy and reduce its duration, but data about safety of this reduction are scarce. We assessed the efficacy and safety of procalcitonin-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.
Methods: We did a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. Critically ill patients aged at least 18 years, admitted to the ICU, and who received their first dose of antibiotics no longer than 24 h before inclusion in the study for an assumed or proven infection were eligible to participate. Patients who received antibiotics for presumed infection were randomly assigned (1:1), using a computer-generated list, and stratified (according to treatment centre, whether infection was acquired before or during ICU stay, and dependent on severity of infection [ie, sepsis, severe sepsis, or septic shock]) to receive either procalcitonin-guided or standard-of-care antibiotic discontinuation. Both patients and investigators were aware of group assignment. In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0.5 mug/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols. Primary endpoints were antibiotic daily defined doses and duration of antibiotic treatment. All analyses were done by intention to treat. Mortality analyses were completed for all patients (intention to treat) and for patients in whom antibiotics were stopped while being on the ICU (per-protocol analysis). Safety endpoints were reinstitution of antibiotics and recurrent inflammation measured by C-reactive protein concentrations and they were measured in the population adhering to the stopping rules (per-protocol analysis). The study is registered with ClinicalTrials.gov, number NCT01139489, and was completed in August, 2014.
Findings: Between Sept 18, 2009, and July 1, 2013, 1575 of the 4507 patients assessed for eligibility were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785). In 538 patients (71%) in the procalcitonin-guided group antibiotics were discontinued in the ICU. Median consumption of antibiotics was 7.5 daily defined doses (IQR 4.0-12.7) in the procalcitonin-guided group versus 9.3 daily defined doses (5.0-16.6) in the standard-of-care group (between-group absolute difference 2.69, 95% CI 1.26-4.12, p<0.0001). Median duration of treatment was 5 days (3-9) in the procalcitonin-guided group and 7 days (4-11) in the standard-of-care group (between-group absolute difference 1.22, 0.65-1.78, p<0.0001). Mortality at 28 days was 149 (20%) of 761 patients in the procalcitonin-guided group and 196 (25%) of 785 patients in the standard-of-care group (between-group absolute difference 5.4%, 95% CI 1.2-9.5, p=0.0122) according to the intention-to-treat analysis, and 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6.6%, 1.3-11.9, p=0.0154) in the per-protocol analysis. 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided and 196 (43%) of 457 patients in the standard-of-care groups (between-group absolute difference 7.4, 1.3-13.8, p=0.0188).
Interpretation: Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality. Procalcitonin

concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship. FUNDING: Thermo Fisher Scientific.

Gepubliceerd: Lancet Infect Dis 2016 Jul;16(7):819-27
Impact factor: 21.372

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3. Neutrophil CD64 expression as a longitudinal biomarker for severe disease and acute infection in critically ill patients
de Jong E, de Lange DW, Beishuizen A, van de Ven PM, Girbes AR, Huisman A

Intoduction: Neutrophilic granulocytes express cluster of differentiation 64 (CD64) antigen upon activation. CD64 can be used as a marker of bacterial infection and sepsis. The goal of this study was to determine whether CD64 is a useful biomarker for critically ill patients and analyze longitudinal measurements with regard to outcome and sepsis severity.
Methods: In this prospective observational study, CD64 analysis was performed daily until discharge from ICU or death. Demographics, clinical, laboratory data, and outcome defined as 28-day survival were recorded. Patients were included when admitted to the ICU with sepsis, severe sepsis, or septic shock and within 24 h from start of antibiotic treatment.
Results: Hundred and fifty-five consecutive patients were enrolled. At baseline, a difference in CD64 of 2.26 (1.33-4.47) vs. 1.49 (0.89-2.24) (P = 0.004) was seen between patients with a positive culture and negative culture. CD64 at day 1 was higher with patients with septic shock when compared with sepsis (P = 0.012). No difference of CD64 between survivors and nonsurvivors was seen.
Conclusion: This study demonstrated that CD64 discriminates between critically ill patients with culture positive and negative sepsis and correlates with severity of disease. However, CD64 index is not a good predictor for 28-day mortality in the critically ill patient.

Gepubliceerd: Int J Lab Hematol 2016 Oct;38(5):576-84
Impact factor: 2.401

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4. Procalcitonin to guide antibiotic stewardship in intensive care - Authors'reply
de Jong E, van Oers JA, Beishuizen A, Girbes AR, Nijsten MW, de Lange DW

Gepubliceerd: Lancet Infect Dis 2016 Aug;16(8):889-90
Impact factor: 21.372

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5. Genomic Characterization of Colistin Heteroresistance in Klebsiella pneumoniae during a Nosocomial Outbreak
Halaby T, Kucukkose E, Janssen AB, Rogers MR, Doorduijn DJ, van der Zanden AG, Al Naiemi N, Vandenbroucke-Grauls CM, van Schaik W

Klebsiella pneumoniae is emerging as an important nosocomial pathogen due to its rapidly increasing multidrug resistance, which has led to a renewed interest in polymyxin antibiotics, such as colistin, as antibiotics of last resort. However, heteroresistance (i.e., the presence of a subpopulation of resistant bacteria in an otherwise susceptible culture) may hamper the effectiveness of colistin treatment in patients. In a previous study, we showed that colistin resistance among extended-spectrum-beta-lactamase (ESBL)-producing K. pneumoniae isolates emerged after the introduction of selective digestive tract decontamination (SDD) in an intensive care unit (ICU). In this study, we investigated heteroresistance to colistin among ESBL-producing K. pneumoniae isolates by using population analysis profiles (PAPs). We used whole-genome sequencing (WGS) to identify the mutations that were associated with the emergence of colistin resistance in these K. pneumoniae isolates. We found five heteroresistant subpopulations, with colistin MICs ranging from 8 to 64 mg/liter, which were derived from five clonally related, colistin-susceptible clinical isolates. WGS revealed the presence of mutations in the lpxM, mgrB, phoQ, and yciM genes in colistin-resistant K. pneumoniae isolates. In two strains, mgrB was inactivated by an IS3-like or ISKpn14 insertion sequence element. Complementation in trans with the wild-type mgrB gene resulted in these strains reverting to colistin susceptibility. The MICs for colistin-susceptible strains increased 2- to 4-fold in the presence of the mutated phoQ, lpxM, and yciM alleles. In conclusion, the present study indicates that heteroresistant K. pneumoniae subpopulations may be selected for upon exposure to colistin. Mutations in mgrB and phoQ have previously been associated with colistin resistance, but we provide experimental evidence for roles of mutations in the yciM and lpxM genes in the emergence of colistin resistance in K. pneumoniae.

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Impact factor: 4.415

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6. Coronary angiography after cardiac arrest: Rationale and design of the COACT trial

Lemkes JS, Janssens GN, Straaten HM, Elbers PW, van der Hoeven NW, Tijssen JG, Otterspoor LC, Voskuil M, van der Heijden JJ, Meuwissen M, Rijpstra TA, Vlachojannis GJ, van der Vleugel RM, Nieman K, Jewbali LS, Bleeker GB, Baak R, Beishuizen B, Stoel MG, van der Harst P, Camaro C, Henriques JP, Vink MA, Gosselink MT, Bosker HA, Crijns HJ, van Royen N

Background: Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography (CAG) and percutaneous coronary intervention (PCI) after restoration of spontaneous circulation following cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains debated.
Hypothesis: We hypothesize that immediate CAG and PCI, if indicated, will improve 90-day survival in post-cardiac arrest patients without signs of STEMI. DESIGN: In a prospective, multicenter, randomized controlled clinical trial, 552 post-cardiac arrest patients with restoration of spontaneous circulation and without signs of STEMI will be randomized in a 1:1 fashion to immediate CAG and PCI (within 2 hours) versus

initial deferral with CAG and PCI after neurological recovery. The primary end point of the study is 90-day survival. The secondary end points will include 90-day survival with good cerebral performance or minor/moderate disability, myocardial injury, duration of inotropic support, occurrence of acute kidney injury, need for renal replacement therapy, time to targeted temperature control, neurological status at intensive care unit discharge, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, and reasons for discontinuation of treatment.
Summary: The COACT trial is a multicenter, randomized, controlled clinical study that will evaluate the effect of an immediate invasive coronary strategy in post-cardiac arrest patients without STEMI on 90-day survival.

Gepubliceerd: Am Heart J 2016 Oct;180:39-45
Impact factor: 4.332

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7. A prospective multicenter evaluation of direct molecular detection of blood stream infection from a clinical perspective
Nieman AE, Savelkoul PH, Beishuizen A, Henrich B, Lamik B, MacKenzie CR, Kindgen-Milles D, Helmers A, Diaz C, Sakka SG, Schade RP

Background: Rapid diagnosis and appropriate antimicrobial therapy are of major importance to decrease morbidity and mortality in patients with blood stream infections (BSI). Blood culture, the current gold standard for detecting bacteria in blood, requires at least 24-48 hours and has limited sensitivity if obtained during antibiotic treatment of the patient. The aim of this prospective multicenter study was to clinically evaluate the application of a commercial universal 16S/18S rDNA PCR, SepsiTest (PCR-ST), directly on whole blood.
Methods: In total 236 samples from 166 patients with suspected sepsis were included in the study. PCR-ST results were compared to blood culture, the current gold standard for detecting BSI. Because blood cultures can give false-negative results, we performed an additional analysis to interpret the likelihood of bloodstream infection by using an evaluation based on clinical diagnosis, other diagnostic tests and laboratory parameters.
Results: Clinical interpretation of results defined the detected organism to be contaminants in 22 of 43 positive blood cultures (51.2 %) and 21 of 47 positive PCR-ST results (44.7 %). Excluding these contaminants resulted in an overall sensitivity and specificity of the PCR-ST of 66.7 and 94.4 % respectively. Of the 36 clinically relevant samples, 11 BSI were detected with both techniques, 15 BSI were detected with PCR-ST only and 10 with blood culture only. Therefore, in this study, SepsiTest detected an additional 71 % BSI compared to blood culture alone.
Conclusions: More clinically relevant BSI were diagnosed by molecular detection, which might influence patient treatment. An improved SepsiTest assay suited for routine use can have additional value to blood culture in diagnosing bacteremia in septic patients.

Gepubliceerd: BMC Infect Dis 2016 Jun 30;16:314
Impact factor: 2.690

8. [Agranulocytosis and septic shock after metamizole use]
Oude Munnik TH, Annink-Smoors M, Hom HW, Sportel ET

Background: Metamizole is an analgesic, the orally administered form of which was withdrawn in the Netherlands in 1989 due to an unacceptably high incidence of agranulocytosis. However, later studies showed a much lower incidence and since 2013 the use of metamizole has been recommended by the national guideline on postoperative pain.
Case description: A 58-year-old woman was referred by her general practitioner to our hospital with suspected diverticulitis. Three days previously the patient had returned from a four-week period of rehabilitation at a German spa following hip replacement surgery. She had been using metamizole since the operation. Within hours of admission, the patient developed septic shock and was transferred to the intensive care unit. Laboratory tests revealed severe neutropenia of 0.2 x 10(9)/l. Treatment consisted of filgrastim, piperacillin/tazobactam and haemodynamic support. After five days the patient was sufficiently recovered to return to the ward.
Conclusion: Metamizole-related agranulocytosis is rare but potentially life-threatening. This condition is expected to occur more frequently as the use of metamizole in the Netherlands increases.

Gepubliceerd: Ned Tijdschr Geneeskd 2016;160:A9464
Impact factor: 0

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9. Continuous EEG Monitoring for Early Detection of Delayed Cerebral Ischemia in Subarachnoid Hemorrhage: A Pilot Study
Rots ML, van Putten MJ, Hoedemaekers CW, Horn J

Intoduction: Early identification of delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (aSAH) is a major challenge. The aim of this study was to investigate whether quantitative EEG (qEEG) features can detect DCI prior to clinical or radiographic findings.
Methods: A prospective cohort study was performed in aSAH patients in whom continuous EEG (cEEG) was recorded. We studied 12 qEEG features. We compared the time point at which qEEG changed with the time point that clinical deterioration occurred or new ischemia was noted on CT scan.
Results: Twenty aSAH patients were included of whom 11 developed DCI. The alpha/delta ratio (ADR) was the most promising feature that showed a significant difference in change over time in the DCI group (median -62 % with IQR -87 to -39 %) compared to the control group (median +27 % with IQR -32 to +104 %, p = 0.013). Based on the ROC curve, a threshold was chosen for a combined measure of ADR and alpha variability (AUC: 91.7, 95 % CI 74.2-100). The median time that elapsed between change of qEEG and clinical DCI diagnosis was seven hours (IQR -11-25). Delay between qEEG and CT scan changes was 44 h (median, IQR 14-117).

Conclusion: In this study, ADR and alpha variability could detect DCI development before ischemic changes on CT scan was apparent and before clinical deterioration was noted. Implementation of cEEG in aSAH patients can probably improve early detection of DCI.

Gepubliceerd: Neurocrit Care 2016;24(2):207-16
Impact factor: 2.488

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10. Gastric feeding intolerance is not caused by mucosal ischemia measured by intragastric air tonometry in the critically ill
Streefkerk JO, Beishuizen A, Groeneveld AB

Background: Gastric mucosal ischemia may be a risk factor for gastrointestinal intolerance to early feeding in the critically ill. AIMS: To study intragastric PCO2 air tonometry and gastric residual volumes (GRV) before and after the start of gastric feeding.
Methods: This is a two-center study in intensive care units of a university and teaching hospital. Twenty-nine critically ill, consecutive and consenting patients scheduled to start gastric feeding were studied after insertion of a gastric tonometry catheter and prior to and after start of gastric feeding (500 ml over 1 h), when clinically indicated.
Results: Blood gasometry and intragastric tonometry were performed prior to and 2 h after gastric feeding. The intragastric to arterial PCO2 gap (normal <8 mm Hg) was elevated in 41% of patients prior to feeding and measured (mean +/- standard deviation) 13 +/- 20 and 16 +/- 23 mm Hg in patients with normal (<100 ml, 42 +/- 34 ml, n = 19) and elevated GRV (250 +/- 141 ml, n = 10, P = 0.75), respectively. After feeding, the gradient did not increase and measured 27 +/- 25 and 23 +/- 34 mm Hg, respectively (P = 0.80).
Conclusion: Gastric mucosal ischemia is not a major risk factor for intolerance to early gastric feeding in the critically ill.

Gepubliceerd: Clin Nutr 2016 Jun;35(3):731-4
Impact factor: 4.487

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11. Additional postoperative cell salvage of shed mediastinal blood in cardiac surgery does not reduce allogeneic blood transfusions: a cohort study
Vermeijden WJ, Hagenaars JA, Scheeren TW, de Vries AJ

Objectives: Does additional postoperative collection and processing of mediastinal shed blood with a cell salvage device reduce the number of allogeneic blood transfusions compared to intraoperative cell salvage alone?
Methods: A single-centre cohort study in which adult patients with coronary artery bypass grafting or aortic valve replacement were allocated to either a C.A.T.S(R) group with intraoperative blood processing only or a CardioPat(R) group with both intra- and postoperative blood processing. The primary endpoint was the number of allogeneic blood transfusions during hospital admission.

Results: The study included 99 patients; 50 in the C.A.T.S(R) and 49 in the CardioPat(R) group.There was no difference in the number of red blood cells (RBC) (C.A.T.S(R) group 43 units versus CardioPat(R) 50 units, p=0.74), fresh frozen plasma (C.A.T.S(R) 8 units versus CardioPat(R) 8 units, p=1.00) or platelets (C.A.T.S(R) 5 units versus CardioPat(R) 4 units, p=1.00) transfused during the hospital stay.Cardiac creatinine kinase (CK-MB) and troponin levels did not differ between the groups although a significant time effect (p<0.001) was present. Creatinine kinase (CK) levels were not different between the groups three hours after arrival in the intensive care unit (ICU) (CardioPat(R) group versus C.A.T.S(R) group, p=0.17). But, compared to the C.A.T.S(R) group on the first (350 [232-469] IU/L) and second postoperative days (325 [201-480] IU/L), the increase in CK levels was more in the CardioPat(R) group on the first (431 [286-642] IU/L, p=0.02) and second postoperative days (406 [239-760] IU/L, p=0.05), resulting in a difference between the groups (p=0.04)
Conclusions: Postoperative cell salvage does not reduce transfusion requirements compared to intraoperative cell salvage alone, but results in elevated total CK levels that suggest haemolysis.

Gepubliceerd: Perfusion 2015 Oct 22;31(5):384-90
Impact factor: 0.935

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12. Enteral Glutamine Administration in Critically Ill Nonseptic Patients Does Not Trigger Arginine Synthesis
Vermeulen MA, Brinkmann SJ, Buijs N, Beishuizen A, Bet PM, Houdijk AP, van Goudoever JB, van Leeuwen PA

Glutamine supplementation in specific groups of critically ill patients results in favourable clinical outcome. Enhancement of citrulline and arginine synthesis by glutamine could serve as a potential mechanism. However, while receiving optimal enteral nutrition, uptake and enteral metabolism of glutamine in critically ill patients remain unknown. Therefore we investigated the effect of a therapeutically relevant dose of L-glutamine on synthesis of L-citrulline and subsequent L-arginine in this group. Ten versus ten critically ill patients receiving full enteral nutrition, or isocaloric isonitrogenous enteral nutrition including 0.5 g/kg L-alanyl-L-glutamine, were studied using stable isotopes. A cross-over design using intravenous and enteral tracers enabled splanchnic extraction (SE) calculations. Endogenous rate of appearance and SE of glutamine citrulline and arginine was not different (SE controls versus alanyl-glutamine: glutamine 48 and 48%, citrulline 33 versus 45%, and arginine 45 versus 42%). Turnover from glutamine to citrulline and arginine was not higher in glutamine-administered patients. In critically ill nonseptic patients receiving adequate nutrition and a relevant dose of glutamine there was no extra citrulline or arginine synthesis and glutamine SE was not increased. This suggests that for arginine synthesis enhancement there is no need for an additional dose of glutamine when this population is adequately fed. This trial is registered with NTR2285.

Gepubliceerd: J Nutr Metab 2016;2016:1373060
Impact factor: 4.450

13. Reply
Vermeijden WJ, de Vries AJ

Gepubliceerd: Ann Thorac Surg 2016 May;101(5):2020
Impact factor: 3.021

Totale impact factor: 75.353
Gemiddelde impact factor: 5.796

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 15.346
Gemiddelde impact factor: 3.069

Interne Geneeskunde

1. Angiotensin II-Receptor Inhibition With Candesartan to Prevent Trastuzumab-Related Cardiotoxic Effects in Patients With Early Breast Cancer: A Randomized Clinical Trial

Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, Los M, Smit WM, Nieboer P, Smorenburg CH, Mandigers CM, van der Wouw AJ, Kessels L, van der Velden AW, Ottevanger PB, Smilde T, de Boer J, van Veldhuisen DJ, Kema IP, de Vries EG, Schellens JH

Importance: This is the first randomized placebo-controlled evaluation of a medical intervention for the prevention of trastuzumab-related cardiotoxic effects.
Objective: To determine as the primary end point whether angiotensin II antagonist treatment with candesartan can prevent or ameliorate trastuzumab-related cardiotoxic effects, defined as a decline in left ventricular ejection fraction (LVEF) of more than 15% or a decrease below the absolute value 45%.
Design: This randomized, placebo-controlled clinical study was conducted between October 2007 and October 2011 in 19 hospitals in the Netherlands, enrolling 210 women with early breast cancer testing positive for human epidermal growth factor receptor 2 (HER2) who were being considered for adjuvant systemic treatment with anthracycline-containing chemotherapy followed by trastuzumab.
Interventions: A total of 78 weeks of candesartan (32 mg/d) or placebo treatment; study treatment started at the same day as the first trastuzumab administration and continued until 26 weeks after completion of trastuzumab treatment.
Main Outcomes and Measures: The primary outcome was LVEF. Secondary end points included whether the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) can be used as surrogate markers and whether genetic variability in germline ERBB2 (formerly HER2 or HER2/neu) correlates with trastuzumab-related cardiotoxic effects.
Results: A total of 206 participants were evaluable (mean age, 49 years; age range, 25-69 years) 103 in the candesartan group (mean age, 50 years; age range, 25-69 years) and 103 in the placebo group (mean age, 50 years; age range, 30-67 years). Of these, 36 manifested at least 1 of the 2 primary cardiac end points. There were 3.8% more cardiac events in the candesartan group than in the placebo group (95% CI, -7% to 15%; P = .58): 20 events (19%) and 16 events (16%), respectively. The 2-year cumulative incidence of cardiac events was 0.28 (95% CI, 0.13-0.40) in the candesartan group and 0.16 (95% CI, 0.08-0.22) in the placebo group (P = .56). Candesartan did not affect changes in NT-proBNP and hs-TnT values, and these biomarkers were not associated with significant changes in LVEF. The Ala1170Pro homozygous ERBB2 genotype was associated with a lower likelihood of the occurrence of a cardiac event compared with Pro/Pro + Ala/Pro genotypes in multivariate analysis (odds ratio, 0.09; 95% CI, 0.02-0.45; P = .003).
Conclusions and Relevance: The findings do not support the hypothesis that concomitant use of candesartan protects against a decrease in left ventricular ejection fraction during or shortly after trastuzumab treatment in early breast cancer. The ERBB2 germline Ala1170Pro single nucleotide polymorphism may be used to identify patients who are at increased risk of trastuzumab-related cardiotoxic effects.

Trial registration: clinicaltrials.gov Identifier: NCT00459771.

Gepubliceerd: JAMA Oncol 2016 Aug 1;2(8):1030-7
Impact factor: 0

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2. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands
Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJ, Haanen JB, Gelderblom H, Uyl-de Groot CA, Aarts MJ, van den Berkmortel FW, Blokx WA, Cardous-Ubbink MC, Groenewegen G, de Groot JW, Hospers GA, Kapiteijn E, Koornstra RH, Kruit WH, Louwman MW, Piersma D, van Rijn RS, Ten Tije AJ, Vreugdenhil G, Wouters MW, van der Hoeven JJ

Background: In recent years, the treatment of metastatic melanoma has changed dramatically due to the development of immune checkpoint and mitogen-activated protein (MAP) kinase inhibitors. A population-based registry, the Dutch Melanoma Treatment Registry (DMTR), was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands. This article describes the design and objectives of the DMTR and presents some results of the first 2 years of registration.
Methods: The DMTR documents detailed information on all Dutch patients with unresectable stage IIIc or IV melanoma. This includes tumour and patient characteristics, treatment patterns, clinical outcomes, quality of life, healthcare utilisation, informal care and productivity losses. These data are used for clinical auditing, increasing the transparency of melanoma care, providing insights into real-world cost-effectiveness and creating a platform for research.
Results: Within 1 year, all melanoma centres were participating in the DMTR. The quality performance indicators demonstrated that the BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands with toxicity rates that were consistent with the phase III trials conducted. The median overall survival of patients treated with systemic therapy was 10.1 months (95% confidence interval [CI] 9.1-11.1) in the first registration year and 12.7 months (95% CI 11.6-13.7) in the second year.
Conclusion: The DMTR is the first comprehensive multipurpose nationwide registry and its collaboration with all stakeholders involved in melanoma care reflects an integrative view of cancer management. In future, the DMTR will provide insights into challenging questions regarding the definition of possible subsets of patients who benefit most from the new drugs.

Gepubliceerd: Eur J Cancer 2016 Dec 25;72:156-65
Impact factor: 6.163

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3. How did partners experience cancer patients' participation in a phase I study? An observational study after a patient's death
Langenberg SM, Peters ME, van der Graaf WT, Wymenga AN, Prins JB, van Herpen CM

Objective: It can be assumed that patients' participation in a phase I study will have an important impact on their partners' life. However, evaluation of partners' experiences while patients are undergoing experimental treatment and of their well-being after the patient's death is lacking. We aimed to explore partners' experience of patients' participation in phase I studies and to investigate their well-being after a patient's death.
Method: This was an observational study conducted after the patient's death. Partners of deceased patients who had participated in a phase I study completed a questionnaire designed by us for experience evaluation and the Beck Depression Inventory for Primary Care, the Hospital Anxiety and Depression Scale, the Inventory of Traumatic Grief, and the RAND-36 Health Survey.
Results: The median age of the 58 participating partners was 58 years (range: 51-65), and 67% was female. Partners reported negative effects on patients' quality of life, but only 5% of partners regretted patients' participation. Approximately two years after the patients' death, 19% of partners scored for depression, 36% for psychological distress, and 46% for complicated grief, and partners generally scored significantly lower on social and mental functioning compared to normative comparators. **Significance of Results:** Although partners reported negative consequences on patients' quality of life, most did not regret patients' participation in the phase I studies. Prevalence of depression, psychological distress, and complicated grief seemed important problems after a patient's death, and these must be considered when shaping further support for partners of patients participating in phase I trials.

Gepubliceerd: Palliat Support Care 2016 Jun;14(3):241-9
Impact factor: 2.230

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4. Safety and long-term effects of renal denervation: Rationale and design of the Dutch registry

Sanders MF, Blankestijn PJ, Voskuil M, Spiering W, Vonken EJ, Rotmans JI, van der Hoeven BL, Daemen J, van den Meiracker AH, Kroon AA, de Haan MW, Das M, Bax M, van der Meer IM, van Overhagen H, van den Born BJ, van Brussel PM, van der Valk PH, Smak Gregoor PJ, Meuwissen M, Gomes ME, Oude Ophuis T, Troe E, Tonino WA, Konings CJ, de Vries PA, van Balen A, Heeg JE, Smit JJ, Elvan A, Steggerda R, Niamut SM, Peels JO, de Swart JB, Wardeh AJ, Groeneveld JH, van der Linden E, Hemmelder MH, Folkeringa R, Stoel MG, Kant GD, Herrman JP, van Wissen S, Deinum J, Westra SW, Aengevaeren WR, Parlevliet KJ, Schramm A, Jessurun GA, Rensing BJ, Winkens MH, Wierema TK, Santegoets E, Lipsic E, Houwerzijl E, Kater M, Allaart CP, Nap A, Bots ML

Background: Percutaneous renal denervation (RDN) has recently been introduced as a treatment for therapy-resistant hypertension. Also, it has been suggested that RDN may be beneficial for other conditions characterised by increased sympathetic nerve activity. There are still many uncertainties with regard to efficacy, safety, predictors for success and long-term effects. To answer these important questions, we initiated a Dutch RDN registry aiming to collect data from all RDN procedures performed in the Netherlands.

Methods: The Dutch RDN registry is an ongoing investigator-initiated, prospective, multicentre cohort study. Twenty-six Dutch hospitals agreed to participate in this registry. All patients who undergo RDN, regardless of the clinical indication or device that is used, will be included. Data are currently being collected on eligibility and screening, treatment and follow-up.
Results: Procedures have been performed since August 2010. At present, data from 306 patients have been entered into the database. The main indication for RDN was hypertension (n = 302, 99%). Patients had a mean office blood pressure of 177/100 (+/-29/16) mmHg with a median use of three (range 0-8) blood pressure lowering drugs. Mean 24-hour blood pressure before RDN was 157/93 (+/-18/13) mmHg. RDN was performed with different devices, with the Simplicity catheter currently used most frequently.
Conclusion: Here we report on the rationale and design of the Dutch RDN registry. Enrolment in this investigator-initiated study is ongoing. We present baseline characteristics of the first 306 participants.

Gepubliceerd: Neth J Med 2016 Jan;74(1):5-15
Impact factor: 1.489

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5. Willingness to accept chemotherapy and attitudes towards costs of cancer treatment; A multisite survey study in the Netherlands
van Dijk EF, Coskunturk M, Zuur AT, van der Palen J, van der Graaf WT, Timmer-Bonte JN, Wymenga AN

Background: In the past years, interest in patient treatment preferences is growing. Our objectives were: (1) to assess and compare the minimal required benefit for patients with cancer, patients without cancer and healthcare professionals to make chemotherapy acceptable and (2) to obtain insight into attitudes towards societal costs of cancer treatment. PATIENTS AND
Methods: We performed a prospective survey consisting of hypothetical scenarios among patients with cancer, patients without cancer and healthcare professionals. Participants were asked to indicate the minimal desired benefit in terms of chance of cure, life prolongation and symptom relief which would make intensive and mild chemotherapy regimens acceptable. In two other scenarios, attitudes towards monthly costs for chemotherapy treatment were examined.
Results: The minimal benefit required to make chemotherapy acceptable did not differ between cancer and non-cancer patients, with respect to chance of cure (mean 57%), life prolongation (median 24 months) and symptom relief (mean 50%); healthcare providers were likely to accept the same chemotherapy regimen at lower thresholds ($p < 0.01$). Education level was an important explanatory variable and the differences between patients and healthcare professionals disappeared when corrected for education level. Opinions about the maximum acceptable costs for chemotherapy displayed a large spread between the groups.
Conclusions: Minimal benefits to accept chemotherapy were not different between cancer and non-cancer patients, but are beyond what can generally can be achieved. Healthcare professionals were willing to accept chemotherapy for less benefit. This difference may be attributed to a difference in education level between

the groups. Healthcare professionals rated the maximum acceptable societal cost for chemotherapy lower than patients.

Gepubliceerd: Neth J Med 2016 Aug;74(7):292-300
Impact factor: 1.489

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6. Fatigue following Acute Q-Fever: A Systematic Literature Review
Morroy G, Keijmel SP, Delsing CE, Bleijenberg G, Langendam M, Timen A, Bleeker-Rovers CP

Background: Long-term fatigue with detrimental effects on daily functioning often occurs following acute Q-fever. Following the 2007-2010 Q-fever outbreak in the Netherlands with over 4000 notified cases, the emphasis on long-term consequences of Q-fever increased. The aim of this study was to provide an overview of all relevant available literature, and to identify knowledge gaps regarding the definition, diagnosis, background, description, aetiology, prevention, therapy, and prognosis, of fatigue following acute Q-fever.
Design: A systematic review was conducted through searching Pubmed, Embase, and PsycInfo for relevant literature up to 26th May 2015. References of included articles were hand searched for additional documents, and included articles were quality assessed.
Results: Fifty-seven articles were included and four documents classified as grey literature. The quality of most studies was low. The studies suggest that although most patients recover from fatigue within 6-12 months after acute Q-fever, approximately 20% remain chronically fatigued. Several names are used indicating fatigue following acute Q-fever, of which Q-fever fatigue syndrome (QFS) is most customary. Although QFS is described to occur frequently in many countries, a uniform definition is lacking. The studies report major health and work-related consequences, and is frequently accompanied by nonspecific complaints. There is no consensus with regard to aetiology, prevention, treatment, and prognosis.
Conclusions: Long-term fatigue following acute Q-fever, generally referred to as QFS, has major health-related consequences. However, information on aetiology, prevention, treatment, and prognosis of QFS is underrepresented in the international literature. In order to facilitate comparison of findings, and as platform for future studies, a uniform definition and diagnostic work-up and uniform measurement tools for QFS are proposed.

Gepubliceerd: PLoS One 2016;11(5):e0155884
Impact factor: 3.540

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7. Phenotypic and clinical implications of variants in the dihydropyrimidine dehydrogenase gene
Kuilenburg AB, Meijer J, Tanck MW, Dobritzsch D, Zoetekouw L, Dekkers LL, Roelofsen J, Meinsma R, Wymenga M, Kulik W, Buchel B, Hennekam RC, Largiader CR

Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the catabolism of the pyrimidine bases uracil, thymine and the antineoplastic agent 5-fluorouracil. Genetic variations in the gene encoding DPD (DPYD) have emerged as predictive risk alleles for 5FU-associated toxicity. Here we report an in-depth analysis of genetic variants in DPYD and their consequences for DPD activity and pyrimidine metabolites in 100 Dutch healthy volunteers. 34 SNPs were detected in DPYD and 15 SNPs were associated with altered plasma concentrations of pyrimidine metabolites. DPD activity was significantly associated with the plasma concentrations of uracil, the presence of a specific DPYD mutation (c.1905+1G>A) and the combined presence of three risk variants in DPYD (c.1905+1G>A, c.1129-5923C>G, c.2846A>T), but not with an altered uracil/dihydrouracil (U/UH2) ratio. Various haplotypes were associated with different DPD activities (haplotype D3, a decreased DPD activity; haplotype F2, an increased DPD activity). Functional analysis of eight recombinant mutant DPD enzymes showed a reduced DPD activity, ranging from 35% to 84% of the wild-type enzyme. Analysis of a DPD homology model indicated that the structural effect of the novel p.G401R mutation is most likely minor. The clinical relevance of the p.D949V mutation was demonstrated in a cancer patient heterozygous for the c.2846A>T mutation and a novel nonsense mutation c.1681C>T (p.R561X), experiencing severe grade IV toxicity. Our studies showed that the endogenous levels of uracil and the U/UH2 ratio are poor predictors of an impaired DPD activity. Loading studies with uracil to identify patients with a DPD deficiency warrants further investigation.

Gepubliceerd: Biochim Biophys Acta 2016 Apr;1862(4):754-62
Impact factor: 5.340

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8. Pooled Analysis of the Prognostic Relevance of Circulating Tumor Cells in Primary Breast Cancer

Janni WJ, Rack B, Terstappen LW, Pierga JY, Taran FA, Fehm T, Hall C, de Groot MR, Bidard FC, Friedl TW, Fasching PA, Brucker SY, Pantel K, Lucci A

Purpose: Although unequivocal evidence has shown the prognostic relevance of circulating tumor cells (CTC) in the peripheral blood of patients with metastatic breast cancer, less evidence is available for the prognostic relevance of CTCs at the time of primary diagnosis.
Experimental design: We conducted a pooled analysis of individual data from 3,173 patients with nonmetastatic (stage I-III) breast cancer from five breast cancer institutions. The prevalence and numbers of CTCs were assessed at the time of primary diagnosis with the FDA-cleared CellSearch System (Janssen Diagnostics, LLC). Patient outcomes were analyzed using meta-analytic procedures, univariate log-rank tests, and multivariate Cox proportional hazard regression analyses. The median follow-up duration was 62.8 months.
Results: One or more CTCs were detected in 20.2% of the patients. CTC-positive patients had larger tumors, increased lymph node involvement, and a higher histologic tumor grade than did CTC-negative patients (all $P < 0.002$). Multivariate Cox regressions, which included tumor size, nodal status, histologic tumor grade, and hormone receptor and HER2 status, confirmed that the presence of CTCs was

an independent prognostic factor for disease-free survival [HR, 1.82; 95% confidence interval (CI), 1.47-2.26], distant disease-free survival (HR, 1.89; 95% CI, 1.49-2.40), breast cancer-specific survival (HR, 2.04; 95% CI, 1.52-2.75), and overall survival (HR, 1.97; 95% CI, 1.51-2.59).
Conclusions: In patients with primary breast cancer, the presence of CTCs was an independent predictor of poor disease-free, overall, breast cancer-specific, and distant disease-free survival. Clin Cancer Res; 22(10); 2583-93. (c)2016 AACR.

Gepubliceerd: Clin Cancer Res 2016 May 15;22(10):2583-93
Impact factor: 8.738

Totale impact factor: 28.989
Gemiddelde impact factor: 3.624

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.489
Gemiddelde impact factor: 1.489

Kindergeneeskunde

1. Dysglycaemia in small-for-gestational-age neonates: a matched case-control study in monochorionic twins
de Bruin CD, van der Lugt NM, Visser R, Oostdijk W, van Zwet EW, Te Pas AB, Lopriore E

Objective: Small-for-gestational-age (SGA) neonates (birth weight <10th centile) are at higher risk of altered glucose homeostasis compared to appropriate for gestational age (AGA) neonates. The aim of this matched case-control study was to estimate the incidence of hypoglycaemia and/or hyperglycaemia in monochorionic (MC) twins with selective intrauterine growth restriction (sIUGR).
Methods: We included all MC twins with sIUGR (2002-2013). Neonates in the SGA group were matched with their AGA co-twin. We recorded the occurrence of hypoglycaemia and hyperglycaemia in the first 48 h after birth and studied the association with SGA.
Results: In this retrospective study were 126 twin pairs included. The incidence of hypoglycaemia in the SGA group and AGA group was 29.6% and 17.4%, respectively, hyperglycaemia occurred in 8.7% of the SGA neonates and in 2.6% of the AGA co-twins. Multivariate analysis showed an independent association of SGA with hypoglycaemia (OR 1.97, CI 1.23-3.18, p </= 0.01), but not with hyperglycaemia (OR 2.57, CI 1.64-10.28, p = 0.182). Low gestational age (GA) at birth (OR 1.65, CI 1.09-2.48, p = 0.02) showed an independent association with hyperglycaemia.
Conclusions: The risk of hypoglycaemia is almost twofold higher in SGA neonates compared to their MC AGA twins. Low GA appeared to be an independent risk factor for hyperglycaemia in SGA neonates.

Gepubliceerd: J Matern Fetal Neonatal Med 2016;29(13):2114-9
Impact factor: 0.770

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2. Can a single dose response predict the effect of montelukast on exercise-induced bronchoconstriction?
Kersten ET, Akkerman-Nijland AM, Driessen JM, Diamant Z, Thio BJ

Rationale: Exercise-induced bronchoconstriction (EIB) can be prevented by a single dose of montelukast (MLK). The effect is variable, similar to the variable responsiveness observed after daily treatment with MLK. We hypothesized that the effect of a single MLK-dose (5 or 10 mg) on EIB could predict the clinical effectiveness of longer term once daily treatment.
Methods: This was a prospective, open-label study. Twenty-four asthmatic adolescents (12-17 years) suboptimally controlled by low-dose inhaled corticosteroids, with >/=10% post-exercise fall in FEV1 , were included. They performed an exercise test at baseline, 20 hr after a single MLK-dose and 40-44 hr after the last dose of 4 weeks once daily treatment. The correlations between the

effect of a single dose and 4 weeks treatment on area under the curve (AUC) and maximum % fall in FEV1 were calculated.
Results: AUC0-20 min decreased significantly after a single MLK-dose (P = 0.001, CI: 64.9-218.2), but not after 4 weeks of treatment (P = 0.080, CI: -12.2 to 200.4). There was a moderate correlation between the effect of a single MLK-dose and 4 weeks treatment on AUC0-20 min , r = 0.49 (P = 0.011), and maximum % fall in FEV1 , r = 0.40 (P = 0.035).
Conclusion: The protection provided by a single MLK-dose against EIB only modestly predicts the effect of regular treatment against EIB in adolescent asthmatics on low-dose inhaled corticosteroids. If used on a daily base, MLK offered clinically significant protection against EIB in two thirds of adolescents suboptimally controlled by low-dose ICS. Pediatr Pulmonol. 2015;9999:XX-XX. (c) 2015 Wiley Periodicals, Inc.

Gepubliceerd: Pediatr Pulmonol 2016;51(5):470-7
Impact factor: 2.850

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3. Adherence to Oral Maintenance Treatment in Adolescents with Inflammatory Bowel Disease: A Systematic Review
Spekhorst LM, Hummel TZ, Benninga MA, Van Rheenen PF, Kindermann A

Objectives: To systematically review the rates of non-adherence to oral maintenance treatment in adolescents with inflammatory bowel disease (IBD), and to describe perceived barriers to adherence and psychosocial factors involved. DESIGN: Systematic review.
Methods: Studies published in Medline, Embase and Psychinfo up to March 2015. INCLUSION CRITERIA: Studies that had collected data on adherence to thiopurines or aminosalicylates in a cohort of adolescents with IBD. Case reports and case series were excluded.
Results: 25 studies were included. Lack of uniformity of outcome measures made pooling of data impossible. Rates of medication non-adherence ranged from 2% to 93%. The most frequently reported barriers were 'just forgot', 'wasn't home' and 'interferes with activity'. Family dysfunction, peer victimization, poor health related quality of life, poor child coping strategies, anxiety and depressive symptoms were associated with medication non-adherence.
Conclusions: Non-adherence to oral maintenance therapy in adolescents with IBD is a significant health care problem, and can lead to unnecessary escalation in therapy. Difficulties in family and social interactions, as well as psychosocial dysfunction can jeopardize IBD treatment outcome and should receive attention early in the course of disease.

Gepubliceerd: J Pediatr Gastroenterol Nutr 2016;62(2):264-70
Impact factor: 2.400

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4. [Dysphagia in children]
Ten Velde E, Gonera-de Jong BC

In this case report we discuss two children with dysphagia. Both presented with difficulties in swallowing and oesophageal impaction of solid food. The first case involves a 16-year-old boy who suffered from dysphagia for many years. After a long diagnostic journey, during which a psychogenic cause was suspected, he was diagnosed with oesophageal achalasia. After a balloon dilatation of the lower oesophageal sphincter his complaints persisted and the treatment procedure was repeated. The second case involves a 15-year-old girl, who presented with a food impaction in the distal oesophagus. After biopsies, she was diagnosed with eosinophilic esophagitis. After short-term acid suppression and treatment with budesonide her symptoms were in remission. The lesson is that there are many causes of dysphagia, including anatomical, functional and psychogenic disorders. In children with dysphagia it is important to rule out somatic disorders before consideration of psychogenic disorders, and to be aware of 'red flag' symptoms such as weight loss.

Gepubliceerd: Ned Tijdschr Geneeskd 2016;160(0):D557
Impact factor: 0

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5. Lidocaine response rate in aEEG-confirmed neonatal seizures: Retrospective study of 413 full-term and preterm infants

Weeke LC, Toet MC, van Rooij LG, Groenendaal F, Boylan GB, Pressler RM, Hellstrom-Westas L, van den Broek MP, de Vries LS

Objective: To investigate the seizure response rate to lidocaine in a large cohort of infants who received lidocaine as second- or third-line antiepileptic drug (AED) for neonatal seizures.
Methods: Full-term (n = 319) and preterm (n = 94) infants, who received lidocaine for neonatal seizures confirmed on amplitude-integrated EEG (aEEG), were studied retrospectively (January 1992-December 2012). Based on aEEG findings, the response was defined as good (>4 h no seizures, no need for rescue medication); intermediate (0-2 h no seizures, but rescue medication needed after 2-4 h); or no clear response (rescue medication needed <2 h).
Results: Lidocaine had a good or intermediate effect in 71.4%. The response rate was significantly lower in preterm (55.3%) than in full-term infants (76.1%, $p < 0.001$). In full-term infants the response to lidocaine was significantly better than midazolam as second-line AED (21.4% vs. 12.7%, $p = 0.049$), and there was a trend for a higher response rate as third-line AED (67.6% vs. 57%, $p = 0.086$). Both lidocaine and midazolam had a higher response rate as third-line AED than as second-line AED ($p < 0.001$). Factors associated with a good response to lidocaine were the following: higher gestational age, longer time between start of first seizure and administration of lidocaine, lidocaine as third-line AED, use of new lidocaine regimens, diagnosis of stroke, use of digital aEEG, and hypothermia. Multivariable analysis of seizure response to lidocaine included lidocaine as second- or third-line AED and seizure etiology.
Significance: Seizure response to lidocaine was seen in ~70%. The response rate was influenced by gestational age, underlying etiology, and timing of administration.

Lidocaine had a significantly higher response rate than midazolam as second-line AED, and there was a trend for a higher response rate as third-line AED. Both lidocaine and midazolam had a higher response rate as third-line compared to second-line AED, which could be due to a pharmacologic synergistic mechanism between the two drugs.

Gepubliceerd: Epilepsia 2016 Feb;57(2):233-42
Impact factor: 4.706

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6. The prevalence of irritable bowel syndrome-type symptoms in paediatric inflammatory bowel disease, and the relationship with biochemical markers of disease activity

Diederen K, Hoekman DR, Hummel TZ, de Meij TG, Koot BG, Tabbers MM, Vlieger AM, Kindermann A, Benninga MA

Background: A large proportion (25-46%) of adults with inflammatory bowel disease in remission has symptoms of irritable bowel syndrome (IBS), which are thought to reflect ongoing inflammation. Data on paediatric inflammatory bowel disease patients are lacking.
Aim: To investigate (i) the prevalence of IBS-type symptoms in paediatric inflammatory bowel disease patients in remission and (ii) the relationship of IBS-type symptoms with biochemical markers of disease activity.
Methods: This cross-sectional study included all patients (<18 years) with Crohn's disease or ulcerative colitis attending the out-patient clinic of one of three Dutch hospitals between March 2014 and June 2015. Clinical disease activity was determined using the abbreviated-PCDAI or PUCAI. Biochemical disease activity was assessed using faecal calprotectin and serum CRP. IBS-symptoms were assessed using physician-administered Rome III-questionnaires.
Results: We included 184 patients (92 female; mean age: 14.5 years) (Crohn's disease: 123, ulcerative colitis: 61). The prevalence of IBS-type symptoms in children with inflammatory bowel disease in clinical remission was 6.4% (95% CI: 2.5-11.1%; Crohn's disease: 4.5%; ulcerative colitis: 10.8%). Prevalence of IBS-type symptoms in children with faecal calprotectin <250 mug/g was 16.1% (95% CI: 7.6-25.8%; Crohn's disease: 16.7%; ulcerative colitis: 10.8%). No difference in faecal calprotectin or CRP was found between patients in clinical remission with or without IBS-type symptoms (faecal calprotectin: IBS+ median 58 mug/g, IBS- 221 mug/g, P = 0.12; CRP: IBS+ median 1.4 mg/L, IBS- 1.1 mg/L, P = 0.63).
Conclusions: The prevalence of IBS-type symptoms in children with inflammatory bowel disease is highly dependent on the definition of remission. Nonetheless, the prevalence is much lower than that previously reported in studies in adult inflammatory bowel disease patients. IBS-type symptoms appear to be unrelated to gastrointestinal inflammation.

Gepubliceerd: Aliment Pharmacol Ther 2016 Jul;44(2):181-8
Impact factor: 6.320

Totale impact factor: 17.046
Gemiddelde impact factor: 2.841

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 5.250
Gemiddelde impact factor: 1.750

Klinische Chemie

1. Comparison of eight routine unpublished LC-MS/MS methods for the simultaneous measurement of testosterone and androstenedione in serum
Buttler RM, Martens F, Ackermans MT, Davison AS, van Herwaarden AE, Kortz L, Krabbe JG, Lentjes EG, Syme C, Webster R, Blankenstein MA, Heijboer AC

Background: Liquid-chromatography tandem mass spectrometry (LC-MS/MS) has become the method of choice in steroid hormone measurement. However, little information on the mutual agreement of LC-MS/MS methods is available. We compared eight routine unpublished LC-MS/MS methods for the simultaneous measurement of testosterone and androstenedione.
Methods: Sixty random serum samples from male and female volunteers were analysed in duplicate by eight routine LC-MS/MS methods. We performed Passing-Bablok regression analyses and calculated Pearson's correlation coefficients to assess the agreement of the methods investigated with one published method known to be accurate. Intra-assay CV of each method was calculated from duplicate results, recoveries for each method were calculated from six spiked samples. Furthermore, a CV between the investigated methods was calculated.
Results: The concentrations ranged from 0.05-1.26 nmol/L, 6.15-24.44 nmol/L and 0.15-4.78 nmol/L for testosterone in females, testosterone in males and androstenedione, respectively. The intra-assay CVs were between 3.7-16.0%, 0.9-5.2% and 1.2-9.5% for testosterone in females, testosterone in males and androstenedione, respectively. The slopes of the regression lines ranged between 0.90-1.25, 0.87-1.24 and 0.94-1.31 for testosterone concentrations in females, all testosterone values and androstenedione, respectively. Inter-method CVs were 24%, 14% and 29% for testosterone for concentrations in females and males and androstenedione, respectively. These compare unfavourably to the variation found earlier in published methods.
Conclusion: Although most routine LC-MS/MS methods investigated here showed a reasonable agreement, some of the assays showed a high variation. The observed differences in standardization should be taken into account when applying reference values, or should, preferably, be solved.

Gepubliceerd: Clin Chim Acta 2016 Feb 15;454:112-8
Impact factor: 2.799

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2. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial
de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EM, de Smet AM, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW

Background: In critically ill patients, antibiotic therapy is of great importance but long duration of treatment is associated with the development of antimicrobial resistance. Procalcitonin is a marker used to guide antibacterial therapy and reduce its duration, but data about safety of this reduction are scarce. We assessed the efficacy and safety of procalcitonin-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.
Methods: We did a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. Critically ill patients aged at least 18 years, admitted to the ICU, and who received their first dose of antibiotics no longer than 24 h before inclusion in the study for an assumed or proven infection were eligible to participate. Patients who received antibiotics for presumed infection were randomly assigned (1:1), using a computer-generated list, and stratified (according to treatment centre, whether infection was acquired before or during ICU stay, and dependent on severity of infection [ie, sepsis, severe sepsis, or septic shock]) to receive either procalcitonin-guided or standard-of-care antibiotic discontinuation. Both patients and investigators were aware of group assignment. In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0.5 mug/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols. Primary endpoints were antibiotic daily defined doses and duration of antibiotic treatment. All analyses were done by intention to treat. Mortality analyses were completed for all patients (intention to treat) and for patients in whom antibiotics were stopped while being on the ICU (per-protocol analysis). Safety endpoints were reinstitution of antibiotics and recurrent inflammation measured by C-reactive protein concentrations and they were measured in the population adhering to the stopping rules (per-protocol analysis). The study is registered with ClinicalTrials.gov, number NCT01139489, and was completed in August, 2014.
Findings: Between Sept 18, 2009, and July 1, 2013, 1575 of the 4507 patients assessed for eligibility were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785). In 538 patients (71%) in the procalcitonin-guided group antibiotics were discontinued in the ICU. Median consumption of antibiotics was 7.5 daily defined doses (IQR 4.0-12.7) in the procalcitonin-guided group versus 9.3 daily defined doses (5.0-16.6) in the standard-of-care group (between-group absolute difference 2.69, 95% CI 1.26-4.12, p<0.0001). Median duration of treatment was 5 days (3-9) in the procalcitonin-guided group and 7 days (4-11) in the standard-of-care group (between-group absolute difference 1.22, 0.65-1.78, p<0.0001). Mortality at 28 days was 149 (20%) of 761 patients in the procalcitonin-guided group and 196 (25%) of 785 patients in the standard-of-care group (between-group absolute difference 5.4%, 95% CI 1.2-9.5, p=0.0122) according to the intention-to-treat analysis, and 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6.6%, 1.3-11.9, p=0.0154) in the per-protocol analysis. 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided and 196 (43%) of 457 patients in the standard-of-care groups (between-group absolute difference 7.4, 1.3-13.8, p=0.0188).

Interpretation: Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality. Procalcitonin concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship. FUNDING: Thermo Fisher Scientific.

Gepubliceerd: Lancet Infect Dis 2016 Jul;16(7):819-27
Impact factor: 21.372

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3. Various calibration procedures result in optimal standardization of routinely used 25(OH)D ID-LC-MS/MS methods
Dirks NF, Vesper HW, van Herwaarden AE, van den Ouweland JM, Kema IP, Krabbe JG, Heijboer AC

Background: The variety of LC-MS/MS methods measuring total 25(OH)D used today is vast and the comparability among these methods is still not well assessed.
Methods: Here, we performed a comparison in samples of healthy donors between the currently routinely used 25(OH)D LC-MS/MS methods in the Netherlands and the Ghent University reference measurement procedure to address this issue (n=40). Additionally, an interlaboratory comparison in patient serum samples assessed agreement between the Dutch diagnostic methods (n=37).
Results: The overall correlation of the routine methods for 25(OH)D3 with the reference measurement procedures and with the mean of all diagnostic methods was excellent (r>0.993 and r>0.989, respectively). Three out of five methods aligned perfectly with both the reference measurement procedure and the median of all methods. One of the routine methods showed a small positive bias, while another showed a small negative bias consistently in both comparisons.
Conclusion: The biases most probably originated from differences in calibration procedure and may be obviated by reassessing calibration of stock standards and/or calibrator matrices. In conclusion, five diagnostic centers have performed a comparison with the 25(OH)D Ghent University reference measurement procedure in healthy donor serum samples and a comparison among themselves in patient serum samples. Both analyses showed a high correlation and specificity of the routine LC-MS/MS methods, yet did reveal some small standardization issues that could not be traced back to the technical details of the different methods. Hence, this study indicates various calibration procedures can result in perfect alignment.

Gepubliceerd: Clin Chim Acta 2016 Aug 25;462:49-54
Impact factor: 2.799

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4. Endothelial Dysfunction After ST-segment Elevation Myocardial Infarction and Long-term Outcome: A Study With Reactive Hyperemia Peripheral Artery Tonometry
Kandhai-Ragunath JJ, Doggen CJ, Jorstad HT, Doelman C, de Wagenaar B, IIzerman MJ, Peters RJ, von Birgelen C

Introduction and Objectives: Long-term data on the relationship between endothelial dysfunction after ST-segment elevation myocardial infarction and future adverse clinical events are scarce. The aim of this study was to noninvasively assess whether endothelial dysfunction 4 weeks to 6 weeks after primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction predicts future clinical events.
Methods: This prospective cohort study was performed in 70 patients of the RESPONSE randomized trial, who underwent noninvasive assessment of endothelial function 4 weeks to 6 weeks after primary percutaneous coronary intervention. Endothelial function was measured by the reactive hyperemia peripheral artery tonometry method; an index<1.67 identified endothelial dysfunction.
Results: The reactive hyperemia peripheral artery tonometry index measured on average 1.90+/-0.58. A total of 35 (50%) patients had endothelial dysfunction and 35 (50%) patients had normal endothelial function. Periprocedural "complications" (eg, cardiogenic shock, total atrioventricular block) were more common in patients with endothelial dysfunction than in those without (25.7% vs 2.9%; P<.01). During 4.0+/-1.7 years of follow-up, 20 (28.6%) patients had major adverse cardiovascular events: events occurred in 9 (25.7%) patients with endothelial dysfunction and in 11 (31.5%) patients with normal endothelial function (P=.52). There was an association between the prevalence of diabetes mellitus at baseline and the occurrence of major adverse cardiovascular events during follow-up (univariate analysis: hazard ratio=2.8; 95% confidence interval, 1.0-7.8; P<.05), and even in multivariate analyses the risk appeared to be increased, although not significantly (multivariate analysis: hazard ratio=2.5; 95% confidence interval, 0.8-7.5).
Conclusions: In this series of patients who survived an ST-segment elevation myocardial infarction, endothelial dysfunction, as assessed by reactive hyperemia peripheral artery tonometry 4 weeks to 6 weeks after myocardial infarction, did not predict future clinical events during a mean follow-up of 4 years.

Gepubliceerd: Rev Esp Cardiol (Engl Ed) 2016 Jul;69(7):664-71
Impact factor: 4.596

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5. Analytical evaluation of a second generation assay for chromogranin A; a dual-site study
Krabbe JG, Monaghan PJ, Russell J, de Rijke YB

Gepubliceerd: Clin Chem Lab Med 2016;54(4):e139-e142
Impact factor: 3.017

Totale impact factor: 34.583
Gemiddelde impact factor: 6.917

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.017

Gemiddelde impact factor: 3.017

Klinische Farmacie

1. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients experiencing a severe exacerbation of COPD: a pilot study
Assink MD, de Saegher ME, Nijdam L, van der Valk PD, Brusse-Keizer MG, Brummelhuis-Visser P, Movig KL

Objective: To investigate the safety and tolerability of nebulized amoxicillin + clavulanic acid twice a day in patients experiencing a severe exacerbation of copd. Single-dose nebulization of amoxicillin + clavulanic acid has shown to be safe in patients having stable copd.
Design: Prospective, single-arm, observational intervention study.
Methods: Eight subjects nebulized doses of 200 + 40 mg amoxicillin + clavulanic acid twice a day for a maximum of seven days. Safety was evaluated by spirometry before and after the first nebulization. Tolerability was evaluated by a questionnaire filled in by the subjects after every nebulization. Plasma and expectorated sputum samples were assayed for amoxicillin concentration.
Results: Spirometry showed no clinically relevant reduction in forced expiratory volume in 1 second (fev1) after nebulization with amoxicillin + clavulanic acid. In 47% of the nebulizations no adverse events were reported. The adverse events that were reported, were minor in 32%, moderate in 8% and acceptable in 12% of the nebulizations. Most reported adverse events were cough, shortness of breath and bitter taste. 15 (out of 16) sputum samples showed an amoxicillin concentration above the mic90 for potential pathogenic micro-organisms in exacerbations of copd. All 7 collected plasma samples showed an amoxicillin concentration < 1.0 mg/L.
Conclusion: Based on the results of the spirometry and the reported side effects, inhalation of nebulized amoxicillin + clavulanic acid seems to be safe and well tolerated in patients experiencing a severe exacerbation of copd. Nebulizing amoxicillin + clavulanic acid 200 + 40 mg leads to sputum concentrations well above the mic90 for potential pathogenic micro-organisms with low concentrations in the central compartment..

Gepubliceerd: PW Wetenschappelijk Platform 2016;9:a1539
Impact factor: 0

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2. Statins and morbidity and mortality in COPD in the COMIC study: a prospective COPD cohort study
Citgez E, van der Palen J, Koehorst-Ter Huurne K, Movig K, van der Valk PD, Brusse-Keizer M

Background: Both chronic inflammation and cardiovascular comorbidity play an important role in the morbidity and mortality of patients with chronic obstructive pulmonary disease (COPD). Statins could be a potential adjunct therapy. The additional effects of statins in COPD are, however, still under discussion. The aim of this study is to further investigate the association of statin use with clinical outcomes in a well-described COPD cohort.

Methods: 795 patients of the Cohort of Mortality and Inflammation in COPD (COMIC) study were divided into statin users or not. Statin use was defined as having a statin for at least 90 consecutive days after inclusion. Outcome parameters were 3-year survival, based on all-cause mortality, time until first hospitalisation for an acute exacerbation of COPD (AECOPD) and time until first community-acquired pneumonia (CAP). A sensitivity analysis was performed without patients who started a statin 3 months or more after inclusion to exclude immortal time bias.
Results: Statin use resulted in a better overall survival (corrected HR 0.70 (95% CI 0.51 to 0.96) in multivariate analysis), but in the sensitivity analysis this association disappeared. Statin use was not associated with time until first hospitalisation for an AECOPD (cHR 0.95, 95% CI 0.74 to 1.22) or time until first CAP (cHR 1.1, 95% CI 0.83 to 1.47).
Conclusions: In the COMIC study, statin use is not associated with a reduced risk of all-cause mortality, time until first hospitalisation for an AECOPD or time until first CAP in patients with COPD.

Gepubliceerd: BMJ Open Respir Res 2016;3(1):e000142
Impact factor: 0

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3. Quality of life and adherence to inhaled corticosteroids and tiotropium in COPD are related
Koehorst-Ter Huurne K, Kort S, van der Palen J, van Beurden WJ, Movig KL, van der Valk PD, Brusse-Keizer M

Background: Poor adherence to inhaled medications in COPD patients seems to be associated with an increased risk of death and hospitalization. Knowing the determinants of nonadherence to inhaled medications is important for creating interventions to improve adherence. **Objectives:** To identify disease-specific and health-related quality of life (HRQoL) factors, associated with adherence to inhaled corticosteroids (ICS) and tiotropium in COPD patients.
Methods: Adherence of 795 patients was recorded over 3 years and was deemed optimal at >75%-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). Health-related quality of life was measured with the Clinical COPD Questionnaire and the EuroQol-5D questionnaire.
Results: Patients with a higher forced expiratory volume in 1 second (FEV1)/vital capacity (VC) (odds ratio [OR] =1.03) and >/=1 hospitalizations in the year prior to inclusion in this study (OR =2.67) had an increased risk of suboptimal adherence to ICS instead of optimal adherence. An increased risk of underuse was predicted by a higher FEV1/VC (OR =1.05). Predictors for the risk of overuse were a lower FEV1 (OR =0.49), higher scores on Clinical COPD Questionnaire-question 3 (anxiety for dyspnea) (OR =1.26), and current smoking (OR =1.73). Regarding tiotropium, predictors for suboptimal use were a higher FEV1/VC (OR =1.03) and the inability to perform usual activities as asked by the EuroQol-5D questionnaire (OR =3.09). A higher FEV1/VC also was a predictor for the risk of underuse compared to optimal adherence (OR =1.03). The risk of overuse increased again with higher scores on Clinical COPD Questionnaire-question 3 (OR =1.46).

Conclusion: Several disease-specific and quality of life factors are related to ICS and tiotropium adherence, but a clear profile of a nonadherent patient cannot yet be outlined. Overusers of ICS and tiotropium experience more anxiety.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2016;11:1679-88
Impact factor: 3.046

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4. The influence of type of inhalation device on adherence of COPD patients to inhaled medication
Koehorst-Ter Huurne K, Movig K, van der Valk PD, van der Palen J, Brusse-Keizer M

Objective: To study the influence of type of inhalation device on medication adherence of COPD patients.
Methods: Adherence to inhalation medication of 795 patients was recorded from pharmacy records over 3 years. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Since most patients used more than one device, 1379 medication periods were analyzed.
Results: Patients using a Metered Dose Inhaler (MDI) or Diskus had a 2.3-fold and 2.2-fold increased risk, respectively, of suboptimal adherence versus good adherence, compared to Handihaler and a 2.1-fold and 2.2-fold increased risk, respectively, of underuse versus good adherence compared to Handihaler. Turbuhaler, MDI, Respimat had a 7.9-fold, 3.5-fold, and 2.0-fold increased risk, of overuse versus good adherence compared to Handihaler.
Conclusions: In COPD, adherence to inhalation medication is device-related. Overuse was most pronounced for devices without a dose counter, devices with the ability to load a dosage without actual inhalation, or devices lacking feedback of correct inhalation. The design of the device seems to be related to underuse and overuse of inhaled medication. Future research might investigate whether prescribing a different device with similar medication improves therapy adherence.

Gepubliceerd: Expert Opin Drug Deliv 2016;13(4):469-75
Impact factor: 5.434

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5. Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel - proton pump inhibitor interaction
Kruik-Kolloffel WJ, van der Palen J, Kruik HJ, van Herk-Sukel MP, Movig KL

Safety concerns of the concomitant use of clopidogrel and proton pump inhibitors (PPIs) were published in 2009 and 2010 by the medicines regulatory agencies, including a direct healthcare professional communication. We examined the association between various safety statements and prescription behavior for gastroprotective drugs in naive patients in the Netherlands during the years 2008-2011. Data from the PHARMO Database Network were analyzed with interrupted time series analyses to estimate the impact of each communication on drug

prescriptions. Dispensings were used as a proxy variable for prescription behavior. After the early communication in January 2009, 15.5% (95% CI 7.8, 23.4) more patients started concomitantly with (es)omeprazole and 13.8% (95% CI 6.5, 21.2) less with other PPIs. Directly after the first statement in June 2009, we found a steep increase in histamine 2-receptor antagonists (H2RA) peaking at 25%, placing those patients at risk for gastrointestinal events. This effect for H2RA faded away after a few months. In February 2010, when the official advice via an adjusted statement was to avoid (es)omeprazole, we found a decrease of 11.9% (95% CI 5.7, 18.2) for (es)omeprazole and an increase of +16.0% (95% CI 10.3, 21.7) for other PPIs. Still 22.6% (95% CI 19.5, 25.7) of patients started on (es)omeprazole in February 2010, placing them at risk for cardiovascular events. Advices of regulatory authorities were followed, however, reluctantly and not fully, probably partly because of the existing scientific doubt about the interaction.

Gepubliceerd: Pharmacol Res Perspect 2016 Aug;4(4):e00242
Impact factor: 0

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6. Safety and Tolerability of Nebulized Amoxicillin-Clavulanic Acid in Patients with COPD (STONAC 1 and STONAC 2)
Nijdam LC, Assink MD, Kuijvenhoven JC, de Saegher ME, van der Valk PD, van der Palen J, Brusse-Keizer MG, Movig KL

The safety and tolerability of nebulized amoxicillin clavulanic acid were determined in patients with stable COPD and during severe exacerbations of COPD. Nine stable COPD patients received doses ranging from 50:10 mg up to 300:60 mg amoxicillin clavulanic acid and eight patients hospitalised for a COPD exacerbation received fixed doses 200/40 mg twice daily. Safety was evaluated by spirometry before and after inhalation. Tolerability was evaluated by questionnaire. Plasma and expectorated sputum samples were assayed for amoxicillin content. Seventeen patients underwent in total 100 nebulizations with amoxicillin clavulanic acid. In this safety and tolerability study no clinically relevant deteriorations in FEV1 were observed. Nebulized amoxicillin clavulanic acid produces sputum concentrations well above the Minimal Inhibiting Concentration of 90% for potential pathogenic micro-organisms, with low concentrations in the central compartment (low systemic exposure). Based on spirometry and reported side effects, inhalation of nebulized amoxicillin clavulanic acid seems to be safe and well tolerated, both in stable patients with COPD as in those experiencing a severe exacerbation. Levels of amoxicillin were adequate.

Gepubliceerd: COPD 2016 Aug;13(4):448-54
Impact factor: 2.160

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7. [Agranulocytosis and septic shock after metamizole use]
Oude Munnik TH, Annink-Smoors M, Hom HW, Sportel ET

Background: Metamizole is an analgesic, the orally administered form of which was withdrawn in the Netherlands in 1989 due to an unacceptably high incidence of agranulocytosis. However, later studies showed a much lower incidence and since 2013 the use of metamizole has been recommended by the national guideline on postoperative pain.
Case description: A 58-year-old woman was referred by her general practitioner to our hospital with suspected diverticulitis. Three days previously the patient had returned from a four-week period of rehabilitation at a German spa following hip replacement surgery. She had been using metamizole since the operation. Within hours of admission, the patient developed septic shock and was transferred to the intensive care unit. Laboratory tests revealed severe neutropenia of 0.2 x 10(9)/l. Treatment consisted of filgrastim, piperacillin/tazobactam and haemodynamic support. After five days the patient was sufficiently recovered to return to the ward.
Conclusion: Metamizole-related agranulocytosis is rare but potentially life-threatening. This condition is expected to occur more frequently as the use of metamizole in the Netherlands increases.

Gepubliceerd: Ned Tijdschr Geneeskd 2016;160:A9464
Impact factor: 0

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8. Therapeutic Drug Monitoring of Monoclonal Antibodies in Inflammatory and Malignant Disease - Translating TNF-alpha Experience to Oncology
Oude Munnink TH, Henstra MJ, Segerink LI, Movig KL, Brummelhuis-Visser P

Lack of response to monoclonal antibodies (mAbs) has been associated with inadequate mAb serum concentrations. Therapeutic drug monitoring (TDM) of mAbs has the potential to guide to more effective dosing in individual patients. This review discusses the mechanisms responsible for interpatient variability of mAb pharmacokinetics, summarizes exposure-response data of mAbs used in inflammatory and malignant disease, presents current evidence of mAb-TDM in inflammatory disease, and provides hurdles and required future steps for further implementing mAb-TDM. This article is protected by copyright. All rights reserved.

Gepubliceerd: Clin Pharmacol Ther 2016;99(4):419-31
Impact factor: 7.268

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9. Involving Patients in Weighting Benefits and Harms of Treatment in Parkinson's Disease
Weernink MG, van Til JA, van Vugt JP, Movig KL, Groothuis-Oudshoorn CG, IJzerman MJ

Intoduction: Little is known about how patients weigh benefits and harms of available treatments for Parkinson's Disease (oral medication, deep brain stimulation, infusion therapy). In this study we have (1) elicited patient preferences for benefits, side effects and process characteristics of treatments and (2) measured patients' preferred and perceived involvement in decision-making about treatment.

Methods: Preferences were elicited using a best-worst scaling case 2 experiment. Attributes were selected based on 18 patient-interviews: treatment modality, tremor, slowness of movement, posture and balance problems, drowsiness, dizziness, and dyskinesia. Subsequently, a questionnaire was distributed in which patients were asked to indicate the most and least desirable attribute in nine possible treatment scenarios. Conditional logistic analysis and latent class analysis were used to estimate preference weights and identify subgroups. Patients also indicated their preferred and perceived degree of involvement in treatment decision-making (ranging from active to collaborative to passive).
Results: Two preference patterns were found in the patient sample (N = 192). One class of patients focused largely on optimising the process of care, while the other class focused more on controlling motor-symptoms. Patients who had experienced advanced treatments, had a shorter disease duration, or were still employed were more likely to belong to the latter class. For both classes, the benefits of treatment were more influential than the described side effects. Furthermore, many patients (45%) preferred to take the lead in treatment decisions, however 10.8% perceived a more passive or collaborative role instead.
Discussion: Patients weighted the benefits and side effects of treatment differently, indicating there is no "one-size-fits-all" approach to choosing treatments. Moreover, many patients preferred an active role in decision-making about treatment. Both results stress the need for physicians to know what is important to patients and to share treatment decisions to ensure that patients receive the treatment that aligns with their preferences.

Gepubliceerd: PLoS One 2016;11(8):e0160771
Impact factor: 3.540

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10. Antibiotic information application offers nurses quick support
Wentzel J, van Drie-Pierik R, Nijdam L, Geesing J, Sanderman R, van Gemert-Pijnen JE

Background: Nurses can be crucial contributors to antibiotic stewardship programs (ASPs), interventions aimed at improving antibiotic use, but nurse empowerment in ASPs adds to their job complexity. Nurses work in complex settings with high cognitive loads, which ask for easily accessible information. An information application (app) was developed to support nurses in ASPs. The efficiency, effectiveness, and user satisfaction regarding this antibiotic app were tested in a pilot study.
Methods: The app was introduced into 2 lung wards of a local teaching hospital. During the 8-month pilot study, the 62 nurses of the wards had access to the app. Changes in user satisfaction regarding information support, safety attitudes, and ASP behavior were assessed with a questionnaire. At baseline, 28 nurses completed the (e-mail) questionnaire; after the study, 18 nurses participated. Scenario-based tests were done to assess app efficiency and effectiveness at baseline (n = 16) and in a randomized control (without the app, n = 17) and intervention condition (with the app, n = 17).

Results: Significant improvements were found regarding task support (P = .041), reliability (P = .004), unobtrusiveness (P = .000), relevance (P = .002), user friendliness (P = .000), speed, and hyperlinks (P = .001). An improvement in communication was observed regarding nurse-physician understanding (P = .034). With the app, nurses solved the scenarios faster than without it.
Conclusions: The human-centered design approach and persuasive strategy of task support were effective in reducing time needed to find information. Stewardship-related behaviors need active education strategies.

Gepubliceerd: Am J Infect Control 2016 Jun 1;44(6):677-84
Impact factor: 2.170

Totale impact factor: 23.618
Gemiddelde impact factor: 2.362

Aantal artikelen 1e, 2e of laatste auteur: 7
Totale impact factor: 17.032
Gemiddelde impact factor: 2.433

KNO

1. Intracochlear Position of Cochlear Implants Determined Using CT Scanning versus Fitting Levels: Higher Threshold Levels at Basal Turn
van der Beek FB, Briaire JJ, van der Marel KS, Verbist BM, Frijns JH

Objectives: In this study, the effects of the intracochlear position of cochlear implants on the clinical fitting levels were analyzed. DESIGN: A total of 130 adult subjects who used a CII/HiRes 90K cochlear implant with a HiFocus 1/1J electrode were included in the study. The insertion angle and the distance to the modiolus of each electrode contact were determined using high-resolution CT scanning. The threshold levels (T-levels) and maximum comfort levels (M-levels) at 1 year of follow-up were determined. The degree of speech perception of the subjects was evaluated during routine clinical follow-up.
Results: The depths of insertion of all the electrode contacts were determined. The distance to the modiolus was significantly smaller at the basal and apical cochlear parts compared with that at the middle of the cochlea ($p < 0.05$). The T-levels increased toward the basal end of the cochlea (3.4 dB). Additionally, the M-levels, which were fitted in our clinic using a standard profile, also increased toward the basal end, although with a lower amplitude (1.3 dB). Accordingly, the dynamic range decreased toward the basal end (2.1 dB). No correlation was found between the distance to the modiolus and the T-level or the M-level. Furthermore, the correlation between the insertion depth and stimulation levels was not affected by the duration of deafness, age at implantation or the time since implantation. Additionally, the T-levels showed a significant correlation with the speech perception scores ($p < 0.05$).
Conclusions: The stimulation levels of the cochlear implants were affected by the intracochlear position of the electrode contacts, which were determined using postoperative CT scanning. Interestingly, these levels depended on the insertion depth, whereas the distance to the modiolus did not affect the stimulation levels. The T-levels increased toward the basal end of the cochlea. The level profiles were independent of the overall stimulation levels and were not affected by the biographical data of the patients, such as the duration of deafness, age at implantation or time since implantation. Further research is required to elucidate how fitting using level profiles with an increase toward the basal end of the cochlea benefits speech perception. Future investigations may elucidate an explanation for the effects of the intracochlear electrode position on the stimulation levels and might facilitate future improvements in electrode design.

Gepubliceerd: Audiol Neurootol 2016;21(1):54-67
Impact factor: 2.070

Totale impact factor: 2.070
Gemiddelde impact factor: 2.070

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.070

Laboratorium voor Microbiologie

1. Genomic Characterization of Colistin Heteroresistance in Klebsiella pneumoniae during a Nosocomial Outbreak
Halaby T, Kucukkose E, Janssen AB, Rogers MR, Doorduijn DJ, van der Zanden AG, Al Naiemi N, Vandenbroucke-Grauls CM, vanSchaik W

Klebsiella pneumoniae is emerging as an important nosocomial pathogen due to its rapidly increasing multidrug resistance, which has led to a renewed interest in polymyxin antibiotics, such as colistin, as antibiotics of last resort. However, heteroresistance (i.e., the presence of a subpopulation of resistant bacteria in an otherwise susceptible culture) may hamper the effectiveness of colistin treatment in patients. In a previous study, we showed that colistin resistance among extended-spectrum-beta-lactamase (ESBL)-producing K. pneumoniae isolates emerged after the introduction of selective digestive tract decontamination (SDD) in an intensive care unit (ICU). In this study, we investigated heteroresistance to colistin among ESBL-producing K. pneumoniae isolates by using population analysis profiles (PAPs). We used whole-genome sequencing (WGS) to identify the mutations that were associated with the emergence of colistin resistance in these K. pneumoniae isolates. We found five heteroresistant subpopulations, with colistin MICs ranging from 8 to 64 mg/liter, which were derived from five clonally related, colistin-susceptible clinical isolates. WGS revealed the presence of mutations in the lpxM, mgrB, phoQ, and yciM genes in colistin-resistant K. pneumoniae isolates. In two strains, mgrB was inactivated by an IS3-like or ISKpn14 insertion sequence element. Complementation in trans with the wild-type mgrB gene resulted in these strains reverting to colistin susceptibility. The MICs for colistin-susceptible strains increased 2- to 4-fold in the presence of the mutated phoQ, lpxM, and yciM alleles. In conclusion, the present study indicates that heteroresistant K. pneumoniae subpopulations may be selected for upon exposure to colistin. Mutations in mgrB and phoQ have previously been associated with colistin resistance, but we provide experimental evidence for roles of mutations in the yciM and lpxM genes in the emergence of colistin resistance in K. pneumoniae.

Gepubliceerd: Antimicrob Agents Chemother 2016 Nov;60(11):6837-43
Impact factor: 4.415

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2. Gram-positive cocci in Dutch ICUs with and without selective decontamination of the oropharyngeal and digestive tract: a retrospective database analysis
van der Bij AK, Frentz D, Bonten MJ, ISIS-AR Study Group (inludes Halaby T)

Objectives: The objective of this study was to determine time trends in the rate of Gram-positive cocci in 42 Dutch ICUs that continuously used or did not use selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) and ICUs that introduced SOD/SDD.

Methods: The Dutch Surveillance System on Antibiotic Resistance was used to determine monthly rates of Staphylococcus aureus, Enterococcus faecalis and Enterococcus faecium isolates, including resistant phenotypes, in blood and respiratory tract specimens from 2008 to 2013. Per patient, the last isolate per species per month was selected, and cumulative rates per 100 beds per month were determined. Time trends were analysed by multilevel Poisson regression.
Results: Eighteen ICUs used SOD/SDD (1296 months), 13 did not use SOD/SDD (936 months) and 11 introduced SOD/SDD (373 months before and 419 months after introduction). There was no significant increase in the rate of Gram-positive cocci in ICUs that used SOD/SDD. Introduction of SOD/SDD was associated with increased rates of S. aureus (beta = 0.018, 95% CI 0.006-0.030) and E. faecalis isolates (beta = 0.028, 95% CI 0.006-0.051) in respiratory tract specimens. Numbers of resistant phenotypes remained low, and an observed increase in E. faecium isolates (beta = 0.033, 95% CI 0.012-0.054), 97% of which were resistant to ampicillin, in the absence of SOD/SDD disappeared after the introduction of SOD/SDD.
Conclusions: In ICUs with a low endemicity of resistance, introduction of SOD/SDD was associated with increased rates of S. aureus and E. faecalis isolates, but not with resistant phenotypes. Continuous 5 year use of SOD/SDD was not associated with increased isolation of Gram-positive cocci.

Gepubliceerd: J Antimicrob Chemother 2016 Mar;71(3):816-20
Impact factor: 4.919

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3. Ernstige opportunistische infectieuze complicaties vele jaren na niertransplantatie
Mulder B, Pickkers P, Meis JF

Een niertransplantatiepatient ontwikkelde acht jaar na de transplantatie opeenvolgende infecties met Nocardia asteroides, Mycobacterium kansasii en Cryptococcus neoformans. Hoewel deze infecties klinisch konden worden genezen, overleed de patient vervolgens aan een Epstein-Barr virus gerelateerd maligne B-cellymfoom van de hersenen.

Gepubliceerd: Nederlands Tijdschrift voor Medische Microbiologie 2016;24:35-6
Impact factor: 0

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4. Detection and epidemiology of carbapenemase producing Enterobacteriaceae in the Netherlands in 2013-2014
Vlek AL, Frentz D, Haenen A, Bootsma HJ, Notermans DW, Frakking FN, de Greeff SC, Leenstra T, ISIS-AR study group (incl.Halaby A)

Laboratory detection of carbapenemase-producing Enterobacteriaceae (CPE) is complicated. Screening with MIC values below clinical breakpoints followed by genotypic confirmation is recommended. We evaluated the application of recommended CPE screening and confirmation methods and provide an overview of

CPE epidemiology in E. coli and K. pneumoniae in the Netherlands. Data on E. coli and K. pneumoniae isolates with elevated meropenem (>0.25 mg/L) and/or imipenem (>1 mg/L) MIC values in 2013-2014 were selected from the Infectious Disease Surveillance Information System for Antibiotic Resistance. Laboratories were requested to provide additional results of any confirmatory testing performed. Confirmation of elevated carbapenem MIC values using gradient testing was performed in 59.8 % of eligible isolates. Confirmatory testing showed elevated MIC values in 8 % of E. coli and 32 % of K. pneumoniae isolates. The overall proportion of confirmed non-susceptible E. coli and K. pneumoniae was 0.01 % and 0.16 %, respectively. Genotypic confirmation was performed in 61.0 % of isolates with confirmed elevated carbapenem MIC values. A carbapenemase gene was identified in 47 % of E. coli and 65 % of K. pneumoniae isolates. OXA-48, NDM and KPC were the most frequently found carbapenemase genes. The majority (62 %) of CPE isolates was detected through targeted screening. CPE are a rare finding in the Netherlands. Adherence to the national guideline is suboptimal and differs between laboratories, implying a risk of inadequate CPE detection. Since accurate identification of CPE is the first step in prevention of CPE spread, successful implementation of guidelines for testing and reporting of CPE is essential.

Gepubliceerd: Eur J Clin Microbiol Infect Dis 2016 Jul;35(7):1089-96
Impact factor: 2.857

Totale impact factor: 12.191
Gemiddelde impact factor: 3.048

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 4.415
Gemiddelde impact factor: 2.208

Longgeneeskunde

1. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients experiencing a severe exacerbation of COPD: a pilot study
Assink MD, de Saegher ME, Nijdam L, van der Valk PD, Brusse-Keizer MG, Brummelhuis-Visser P, Movig KL

Objective: To investigate the safety and tolerability of nebulized amoxicillin + clavulanic acid twice a day in patients experiencing a severe exacerbation of copd. Single-dose nebulization of amoxicillin + clavulanic acid has shown to be safe in patients having stable copd.
Design: Prospective, single-arm, observational intervention study.
Methods: Eight subjects nebulized doses of 200 + 40 mg amoxicillin + clavulanic acid twice a day for a maximum of seven days. Safety was evaluated by spirometry before and after the first nebulization. Tolerability was evaluated by a questionnaire filled in by the subjects after every nebulization. Plasma and expectorated sputum samples were assayed for amoxicillin concentration.
Results: Spirometry showed no clinically relevant reduction in forced expiratory volume in 1 second (fev1) after nebulization with amoxicillin + clavulanic acid. In 47% of the nebulizations no adverse events were reported. The adverse events that were reported, were minor in 32%, moderate in 8% and acceptable in 12% of the nebulizations. Most reported adverse events were cough, shortness of breath and bitter taste. 15 (out of 16) sputum samples showed an amoxicillin concentration above the mic90 for potential pathogenic micro-organisms in exacerbations of copd. All 7 collected plasma samples showed an amoxicillin concentration < 1.0 mg/L.
Conclusion: Based on the results of the spirometry and the reported side effects, inhalation of nebulized amoxicillin + clavulanic acid seems to be safe and well tolerated in patients experiencing a severe exacerbation of copd. Nebulizing amoxicillin + clavulanic acid 200 + 40 mg leads to sputum concentrations well above the mic90 for potential pathogenic micro-organisms with low concentrations in the central compartment..

Gepubliceerd: PW Wetenschappelijk Platform 2016;9:a1539
Impact factor: 0

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2. Comparing the 2007 and 2011 GOLD Classifications as Predictors of all-Cause Mortality and Morbidity in COPD
Brusse-Keizer M, Klatte M, Zuur-Telgen M, Koehorst-Ter Huurne K, van der Palen J, van der Valk PD

To better classify patients with chronic obstructive pulmonary disease (COPD) for prognostic purposes and to tailor treatment, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification was revised in 2011. The primary aim of the current data analyses was to evaluate the accuracy of the GOLD 2007 and 2011 GOLD classifications to predict all-cause mortality and morbidity in a well-described COPD cohort. The prognostic values of both GOLD classifications,

expressed as the C-statistic, were assessed in the Cohort of Mortality and Inflammation in COPD (COMIC) study of 795 COPD patients, with a follow-up of 3 years. Outcomes were all-cause mortality and morbidity. Morbidity was defined as time until first COPD-related hospitalisation and time until first community-acquired pneumonia (CAP). The prognostic value of the GOLD 2011 classification was compared between symptom classification based on the modified Medical Research Council (mMRC) score and the Clinical COPD Questionnaire (CCQ) scores with two different thresholds. Although the GOLD 2011 CCQ classification had the highest accuracy to predict mortality and morbidity in our study, the C-statistics differed only numerically. Furthermore, our study showed that the instrument used to determine the level of symptoms in the GOLD 2011 classification has not only important consequences on the mortality prognosis, but also affects the morbidity prognosis in COPD. Therefore, patients' estimated prognosis could alter when different types of tools are used to evaluate the prognosis.

Gepubliceerd: COPD 2016 Jul 21;14(1):7-14
Impact factor: 2.160

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3. Statins and morbidity and mortality in COPD in the COMIC study: a prospective COPD cohort study

Citgez E, van der Palen J, Koehorst-Ter Huurne K, Movig K, van der Valk PD, Brusse-Keizer M

Background: Both chronic inflammation and cardiovascular comorbidity play an important role in the morbidity and mortality of patients with chronic obstructive pulmonary disease (COPD). Statins could be a potential adjunct therapy. The additional effects of statins in COPD are, however, still under discussion. The aim of this study is to further investigate the association of statin use with clinical outcomes in a well-described COPD cohort.
Methods: 795 patients of the Cohort of Mortality and Inflammation in COPD (COMIC) study were divided into statin users or not. Statin use was defined as having a statin for at least 90 consecutive days after inclusion. Outcome parameters were 3-year survival, based on all-cause mortality, time until first hospitalisation for an acute exacerbation of COPD (AECOPD) and time until first community-acquired pneumonia (CAP). A sensitivity analysis was performed without patients who started a statin 3 months or more after inclusion to exclude immortal time bias.
Results: Statin use resulted in a better overall survival (corrected HR 0.70 (95% CI 0.51 to 0.96) in multivariate analysis), but in the sensitivity analysis this association disappeared. Statin use was not associated with time until first hospitalisation for an AECOPD (cHR 0.95, 95% CI 0.74 to 1.22) or time until first CAP (cHR 1.1, 95% CI 0.83 to 1.47).
Conclusions: In the COMIC study, statin use is not associated with a reduced risk of all-cause mortality, time until first hospitalisation for an AECOPD or time until first CAP in patients with COPD.

Gepubliceerd: BMJ Open Respir Res 2016;3(1):e000142
Impact factor: 0

4. Definition of a COPD self-management intervention: International Expert Group consensus
Effing TW, Vercoulen JH, Bourbeau J, Trappenburg J, Lenferink A, Cafarella P, Coultas D, Meek P, van der Valk PD, Bischoff EW, Bucknall C, Dewan NA, Early F, Fan V, Frith P, Janssen DJ, Mitchell K, Morgan M, Nici L, Patel I, Walters H, Rice KL, Singh S, Zuwallack R, Benzo R, Goldstein R, Partridge MR, van der Palen J

There is an urgent need for consensus on what defines a chronic obstructive pulmonary disease (COPD) self-management intervention. We aimed to obtain consensus regarding the conceptual definition of a COPD self-management intervention by engaging an international panel of COPD self-management experts using Delphi technique features and an additional group meeting.In each consensus round the experts were asked to provide feedback on the proposed definition and to score their level of agreement (1=totally disagree; 5=totally agree). The information provided was used to modify the definition for the next consensus round. Thematic analysis was used for free text responses and descriptive statistics were used for agreement scores.In total, 28 experts participated. The consensus round response rate varied randomly over the five rounds (ranging from 48% (n=13) to 85% (n=23)), and mean definition agreement scores increased from 3.8 (round 1) to 4.8 (round 5) with an increasing percentage of experts allocating the highest score of 5 (round 1: 14% (n=3); round 5: 83% (n=19)).In this study we reached consensus regarding a conceptual definition of what should be a COPD self-management intervention, clarifying the requisites for such an intervention. Operationalisation of this conceptual definition in the near future will be an essential next step.

Gepubliceerd: Eur Respir J 2016 Jul;48(1):46-54
Impact factor: 8.332

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5. Obstructive Sleep Apnea Syndrome in Company Workers: Development of a Two-Step Screening Strategy with a New Questionnaire
Eijsvogel MM, Wiegersma S, Randerath W, Verbraecken J, Wegter-Hilbers E, van der Palen J

Study Objectives: To develop and evaluate a screening questionnaire and a two-step screening strategy for obstructive sleep apnea syndrome (OSAS) in healthy workers. DESIGN: Cross-sectional study.
Setting and participants: A total of 1,861 employees comprising healthy blue- and white-collar workers in two representative plants in the Netherlands from a worldwide consumer electronic company were approached to participate.
Interventions: Employees were invited to complete various sleep questionnaires, and undergo separate single nasal flow recording and home polysomnography on 2 separate nights. **Measurements and Results:** Of the 1,861 employees, 249 provided informed consent and all nasal flow and polysomnography data were available from 176 (70.7%). OSAS was diagnosed in 65 (36.9%). A combination of age, absence of insomnia, witnessed breathing stops, and three-way scoring of the

Berlin and STOPBANG questionnaires best predicted OSAS. Factor analysis identified a six-factor structure of the resulting new questionnaire: snoring, snoring severity, tiredness, witnessed apneas, sleep quality, and daytime well-being. Subsequently, some questions were removed, and the remaining questions were used to construct a new questionnaire. A scoring algorithm, computing individual probabilities of OSAS as high, intermediate, or low risk, was developed. Subsequently, the intermediate risk group was split into low and high probability for OSAS, based on nasal flow recording. This two-step approach showed a sensitivity of 63.1%, and a specificity of 90.1%. Specificity is important for low prevalence populations.
Conclusion: A two-step screening strategy with a new questionnaire and subsequent nasal flow recording is a promising way to screen for OSAS in a healthy worker population.
Trial registration: Development and validation of a screening instrument for Obstructive Sleep Apnea Syndrome in healthy workers. Netherlands Trial Register (www.trailregister.nl), number: NTR2675.

Gepubliceerd: J Clin Sleep Med 2016;12(4):555-64
Impact factor: 2.710

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6. Volumetric capnography in the exclusion of pulmonary embolism at the emergency department: a pilot study
Fabius TM, Eijsvogel MM, van der Lee I, Brusse-Keizer MG, de Jongh FH

The analysis of the [Formula: see text] in expired air as a function of the exhaled volume (volumetric capnography) might result in a more specific exclusion tool for pulmonary embolism (PE) in addition to the Wells-score and D-dimer. A novel combination of volumetric capnography parameters ([Formula: see text]) should be decreased in PE and could possibly be used to decrease the number of requested computed tomography pulmonary angiograms (CTPA). Volumetric capnography measurements were performed on consecutive patients seen in the emergency department for which, due to suspected PE (due to increased D-dimer level or Wells-score), a CTPA was ordered. A total of 30 subjects were included, of which in 13 PE was seen on CTPA. Median [Formula: see text] was 4.36 kPa (IQR 3.92-4.88) in the no PE group versus 4.07 kPa (IQR 3.37-4.39) in the PE group (p = 0.086). Median of the novel parameter [Formula: see text] was 1.85 min.kPa dl-1 (IQR 1.21-3.00) in the no PE group versus 1.18 min.kPa dl-1 (IQR 0.61-1.38) in the PE group (p = 0.006). Using a threshold for the new parameter of 1.90 min.kPa dl-1 or higher to exclude PE resulted in a negative predictive value of 100% (95% CI: 77%-100%) and would have potentially excluded PE in 47% (95% CI: 26%-69%) of the no PE group without the need for CTPA. This pilot study introduces a novel parameter [Formula: see text] which is significantly decreased in PE subjects. Future studies regarding validation and addressing aspects such as reproducibility and normalization after treatment are needed to confirm its usability in excluding PE in the emergency department.

Gepubliceerd: J Breath Res 2016 Dec 17;10(4):046016

Impact factor: 4.177

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7. Electroanatomical Mapping of the Urinary Bladder
Farag F, Koens M, Tijssen M, de Jong S, Fabius T, Tromp J, van Breda H, Smeets J, Feitz W, Heesakkers J

A noncontact mapping system (EnSite) was used for electroanatomical mapping of the bladder simultaneously with pressure flow study in three women with lower urinary tract symptoms. We selected the periods of obvious detrusor activity. Data were processed to remove baseline drift, and an envelope of electrovesicography (EVG) data was created. The correlation coefficient for the correlation between between the EVG envelope and the detrusor pressure (Pdet) was calculated. Bladder geometry was successfully created in all 3 patients. Simultaneous recording of EVG and pressure flow data was successful in 1 patient. Scatter plots were made of the highest correlation coefficient, showing a positive correlation between the Pdet and the envelope, and negative correlation between abdominal pressure (Pabd) and the envelope. Minimal electrical activity could be observed. Significant weak to moderate correlation coefficients were found for the correlations between Pdet and EVG and between Pabd and EVG.

Gepubliceerd: Int Neurourol J 2016 Jun;20(2):164-7
Impact factor: 1.344

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8. Quality of life and adherence to inhaled corticosteroids and tiotropium in COPD are related
Koehorst-Ter Huurne K, Kort S, van der Palen J, van Beurden WJ, Movig KL, van der Valk PD, Brusse-Keizer M

Background: Poor adherence to inhaled medications in COPD patients seems to be associated with an increased risk of death and hospitalization. Knowing the determinants of nonadherence to inhaled medications is important for creating interventions to improve adherence. **Objectives:** To identify disease-specific and health-related quality of life (HRQoL) factors, associated with adherence to inhaled corticosteroids (ICS) and tiotropium in COPD patients.
Methods: Adherence of 795 patients was recorded over 3 years and was deemed optimal at >75%-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). Health-related quality of life was measured with the Clinical COPD Questionnaire and the EuroQol-5D questionnaire.
Results: Patients with a higher forced expiratory volume in 1 second (FEV1)/vital capacity (VC) (odds ratio [OR] =1.03) and >/=1 hospitalizations in the year prior to inclusion in this study (OR =2.67) had an increased risk of suboptimal adherence to ICS instead of optimal adherence. An increased risk of underuse was predicted by a higher FEV1/VC (OR =1.05). Predictors for the risk of overuse were a lower FEV1 (OR =0.49), higher scores on Clinical COPD Questionnaire-question 3 (anxiety for dyspnea) (OR =1.26), and current smoking (OR =1.73). Regarding tiotropium, predictors for suboptimal use were a higher FEV1/VC (OR =1.03) and the inability to

perform usual activities as asked by the EuroQol-5D questionnaire (OR =3.09). A higher FEV1/VC also was a predictor for the risk of underuse compared to optimal adherence (OR =1.03). The risk of overuse increased again with higher scores on Clinical COPD Questionnaire-question 3 (OR =1.46).
Conclusion: Several disease-specific and quality of life factors are related to ICS and tiotropium adherence, but a clear profile of a nonadherent patient cannot yet be outlined. Overusers of ICS and tiotropium experience more anxiety.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2016;11:1679-88
Impact factor: 3.046

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9. The influence of type of inhalation device on adherence of COPD patients to inhaled medication
Koehorst-Ter Huurne K, Movig K, van der Valk PD, van der Palen J, Brusse-Keizer M

Objective: To study the influence of type of inhalation device on medication adherence of COPD patients.
Methods: Adherence to inhalation medication of 795 patients was recorded from pharmacy records over 3 years. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Since most patients used more than one device, 1379 medication periods were analyzed.
Results: Patients using a Metered Dose Inhaler (MDI) or Diskus had a 2.3-fold and 2.2-fold increased risk, respectively, of suboptimal adherence versus good adherence, compared to Handihaler and a 2.1-fold and 2.2-fold increased risk, respectively, of underuse versus good adherence compared to Handihaler. Turbuhaler, MDI, Respimat had a 7.9-fold, 3.5-fold, and 2.0-fold increased risk, of overuse versus good adherence compared to Handihaler.
Conclusions: In COPD, adherence to inhalation medication is device-related. Overuse was most pronounced for devices without a dose counter, devices with the ability to load a dosage without actual inhalation, or devices lacking feedback of correct inhalation. The design of the device seems to be related to underuse and overuse of inhaled medication. Future research might investigate whether prescribing a different device with similar medication improves therapy adherence.

Gepubliceerd: Expert Opin Drug Deliv 2016;13(4):469-75
Impact factor: 5.434

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10. Construct Validity of the Dutch Version of the 12-Item Partners in Health Scale: Measuring Patient Self-Management Behaviour and Knowledge in Patients with Chronic Obstructive Pulmonary Disease
Lenferink A, Effing T, Harvey P, Battersby M, Frith P, van Beurden WJ, van der Palen J, Paap MC

Objective: The 12-item Partners in Health scale (PIH) was developed in Australia to measure self-management behaviour and knowledge in patients with chronic diseases, and has undergone several changes. Our aim was to assess the construct validity and reliability of the latest PIH version in Dutch COPD patients.
Methods: The 12 items of the PIH, scored on a self-rated 9-point Likert scale, are used to calculate total and subscale scores (knowledge; coping; recognition and management of symptoms; and adherence to treatment). We used forward-backward translation of the latest version of the Australian PIH to define a Dutch PIH (PIH(Du)). Mokken Scale Analysis and common Factor Analysis were performed on data from a Dutch COPD sample to investigate the psychometric properties of the Dutch PIH; and to determine whether the four-subscale solution previously found for the original Australian PIH could be replicated for the Dutch PIH.
Results: Two subscales were found for the Dutch PIH data (n = 118); 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment. The correlation between the two Dutch subscales was 0.43. The lower-bound of the reliability of the total scale equalled 0.84. Factor analysis indicated that the first two factors explained a larger percentage of common variance (39.4% and 19.9%) than could be expected when using random data (17.5% and 15.1%).
Conclusion: We recommend using two PIH subscale scores when assessing self-management in Dutch COPD patients. Our results did not support the four-subscale structure as previously reported for the original Australian PIH.

Gepubliceerd: PLoS One 2016;11(8):e0161595
Impact factor: 3.540

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11. Safety and Tolerability of Nebulized Amoxicillin-Clavulanic Acid in Patients with COPD (STONAC 1 and STONAC 2)
Nijdam LC, Assink MD, Kuijvenhoven JC, de Saegher ME, van der Valk PD, van der Palen J, Brusse-Keizer MG, Movig KL

The safety and tolerability of nebulized amoxicillin clavulanic acid were determined in patients with stable COPD and during severe exacerbations of COPD. Nine stable COPD patients received doses ranging from 50:10 mg up to 300:60 mg amoxicillin clavulanic acid and eight patients hospitalised for a COPD exacerbation received fixed doses 200/40 mg twice daily. Safety was evaluated by spirometry before and after inhalation. Tolerability was evaluated by questionnaire. Plasma and expectorated sputum samples were assayed for amoxicillin content. Seventeen patients underwent in total 100 nebulizations with amoxicillin clavulanic acid. In this safety and tolerability study no clinically relevant deteriorations in FEV1 were observed. Nebulized amoxicillin clavulanic acid produces sputum concentrations well above the Minimal Inhibiting Concentration of 90% for potential pathogenic micro-organisms, with low concentrations in the central compartment (low systemic exposure). Based on spirometry and reported side effects, inhalation of nebulized amoxicillin clavulanic acid seems to be safe and well tolerated, both in stable patients with COPD as in those experiencing a severe exacerbation. Levels of amoxicillin were adequate.

Gepubliceerd: COPD 2016 Aug;13(4):448-54
Impact factor: 2.160

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12. Effect of Minimally Invasive Surfactant Therapy on Lung Volume and Ventilation in Preterm Infants
van der Burg PS, de Jongh FH, Miedema M, Frerichs I, van Kaam AH

Objective: To assess the changes in (regional) lung volume and gas exchange during minimally invasive surfactant therapy (MIST) in preterm infants with respiratory distress syndrome. STUDY DESIGN: In this prospective observational study, infants requiring a fraction of inspired oxygen (FiO2) >/=0.30 during nasal continuous positive airway pressure of 6 cmH2O were eligible for MIST. Surfactant (160-240 mg/kg) was administered in supine position in 1-3 minutes via an umbilical catheter placed 2 cm below the vocal cords. Changes in end-expiratory lung volume (EELV), tidal volume, and its distribution were recorded continuously with electrical impedance tomography before and up to 60 minutes after MIST. Changes in transcutaneous oxygen saturation (SpO2) and partial carbon dioxide pressure, FiO2, respiratory rate, and minute ventilation were recorded.
Results: A total of 16 preterm infants were included. One patient did not finish study protocol because of severe apnea 10 minutes after MIST. In the remaining infants (gestational age 29.8 +/- 2.8 weeks, body weight 1545 +/- 481 g) EELV showed a rapid and sustained increase, starting in the dependent lung regions, followed by the nondependent regions approximately 5 minutes later. Oxygenation, expressed as the SpO2/FiO2 ratio, increased from 233 (IQR 206-257) to 418 (IQR 356-446) after 60 minutes (P < .001). This change was significantly correlated with the change in EELV (rho = 0.70, P < .01). Tidal volume and minute volume decreased significantly after MIST, but transcutaneous partial carbon dioxide pressure was comparable with pre-MIST values. Ventilation distribution remained unchanged.
Conclusions: MIST results in a rapid and homogeneous increase in EELV, which is associated with an improvement in oxygenation.

Gepubliceerd: J Pediatr 2016;170:67-72
Impact factor: 3.890

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13. The effect of prolonged lateral positioning during routine care on regional lung volume changes in preterm infants
van der Burg PS, de Jongh FH, Miedema M, Frerichs I, van Kaam AH

Intoduction: During routine nursing care, preterm infants are often placed in lateral position for several hours, but the effect of this---- procedure on regional lung volume and ventilation is unknown. In our study we examined this effect during 3 hrs of lateral positioning in stable preterm infants.
Methods: Preterm infants on non-invasive respiratory support were eligible for the study. Infants were placed in supine position and subsequently transferred to right or left lateral position, according to their individual routine nursing schedule. Changes in end-expiratory lung volume (EELV), tidal volume (VT) and ventilation distribution

were recorded using electrical impedance tomography (EIT), starting 10 min before and up to 180 min after the positional change. Additionally, oxygen requirement, transcutaneous oxygen saturation and respiratory rate were recorded.
Results: 15 infants were included (GA 28.9 +/- 2.0 wk, BW 1167 +/- 290 g). EELV increased significantly after changing to lateral position, stabilizing at a median value of 40.8 (IQR 29.0-99.3) AU/kg at 30 min. This increase could almost be exclusively attributed to the non-dependent lung regions. Tidal volume, oxygenation, and respiratory rate remained stable. Changing to the right, but not the left, lateral position resulted in a rapid but transient shift in ventilation to the dependent lung regions. After 180 min there were no differences in ventilation distribution between lateral and supine positioning.
Conclusion: This study shows that lateral position up to 3 hours, as part of normal nursing care of preterm infants, has no adverse effects on lung volumes and its regional distribution. Pediatr Pulmonol. (c) 2015 Wiley Periodicals, Inc.

Gepubliceerd: Pediatr Pulmonol 2016;51(3):280-5
Impact factor: 2.850

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14. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices
van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, Wilkinson T, Stonham C, Chauhan AJ, Imber V, Zhu CQ, Svedsater H, Barnes NC

Errors in the use of different inhalers were investigated in patients naive to the devices under investigation in a multicentre, single-visit, randomised, open-label, cross-over study. Patients with chronic obstructive pulmonary disease (COPD) or asthma were assigned to ELLIPTA vs DISKUS (Accuhaler), metered-dose inhaler (MDI) or Turbuhaler. Patients with COPD were also assigned to ELLIPTA vs Handihaler or Breezhaler. Patients demonstrated inhaler use after reading the patient information leaflet (PIL). A trained investigator assessed critical errors (i.e., those likely to result in the inhalation of significantly reduced, minimal or no medication). If the patient made errors, the investigator demonstrated the correct use of the inhaler, and the patient demonstrated inhaler use again. Fewer COPD patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS, 9/171 (5%) vs 75/171 (44%); MDI, 10/80 (13%) vs 48/80 (60%); Turbuhaler, 8/100 (8%) vs 44/100 (44%); Handihaler, 17/118 (14%) vs 57/118 (48%); Breezhaler, 13/98 (13%) vs 45/98 (46%; all P<0.001). Most patients (57-70%) made no errors using ELLIPTA and did not require investigator instruction. Instruction was required for DISKUS (65%), MDI (85%), Turbuhaler (71%), Handihaler (62%) and Breezhaler (56%). Fewer asthma patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS (3/70 (4%) vs 9/70 (13%), P=0.221); MDI (2/32 (6%) vs 8/32 (25%), P=0.074) and significantly fewer vs Turbuhaler (3/60 (5%) vs 20/60 (33%), P<0.001). More asthma and COPD patients preferred ELLIPTA over the other devices (all P0.002). Significantly, fewer COPD patients using ELLIPTA made critical errors after reading the PIL vs other inhalers. More asthma and COPD patients preferred ELLIPTA over comparator inhalers.

Gepubliceerd: NPJ Prim Care Respir Med 2016 Nov 24;26:16079
Impact factor: 1.447

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15. Stable State Proadrenomedullin Level in COPD Patients: A Validation Study
Zuur-Telgen M, van der Valk PD, van der Palen J, Kerstjens HA, Brusse-Keizer M

In patients with stable COPD, proadrenomedullin (MR-proADM) has been shown to be a good predictor for mortality. This study aims to provide an external validation of earlier observed cut-off values used by Zuur-Telgen et al. and Stolz.et al. in COPD patients in stable state and at hospitalization for an acute exacerbation of COPD (AECOPD). From the COMIC cohort study we included 545 COPD patients with a blood sample obtained in stable state (n = 490) and/or at hospitalization for an AECOPD (n = 101). Time to death was compared between patients with MR-proADM cut-off scores 0.71 and 0.75 nmol/L for stable state or 0.79 and 0.84 nmol/l for AECOPD. The predictive value of MR-proADM for survival was represented by the C statistic. Risk ratios were corrected for sex, age, BMI, presence of heart failure, and GOLD stage. Patients above the cut-off of 0.75 nmol/l had a 2-fold higher risk of dying than patient below this cut-off (95% CI: 1.20-3.41). The cut-off of 0.71 nmol/l showed only a borderline significantly higher risk of 1.67 (95% CI: 0.98-2.85). The corrected odds ratios for one-year mortality were 3.15 (95% CI 1.15-8.64) and 3.70 (95% CI 1.18-11.6) in patients with MR-proADM levels above versus below the cut-off of respectively 0.75 and 0.71 nmol/l measured in stable state. MR-proADM levels in samples at hospitalization for an AECOPD were not predictive for mortality in this validation cohort. MR-proADM in stable state is a powerful predictor for mortality.

Gepubliceerd: COPD 2016 Nov 23;1-9
Impact factor: 2.160

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16. (Cost-)effectiveness of self-treatment of exacerbations in patients with COPD: 2 years follow-up of a RCT
Zwerink M, Kerstjens HA, van der Palen J, van der Valk PD, Brusse-Keizer M, Zielhuis G, Effing T

Background and Objective: Long-term effectiveness of action plans in patients with chronic obstructive pulmonary disease (COPD) is minimally investigated. We have evaluated the (cost-)effectiveness of a self-management programme with or without self-treatment of exacerbations after 2 years follow-up.
Methods: Self-management with or without self-treatment of exacerbations was randomly assigned to patients. All patients participated in four self-management meetings. Patients in the self-treatment group (STG) also learned to use an action plan to start a course of prednisolone and/or antibiotics in case of worsening of symptoms. Primary outcome was the duration and severity of exacerbations.

Results: Data of 70 COPD patients in the STG and 72 patients in the control group (CG) were analysed. Over 2 years, the median number of exacerbation days was significantly lower in the STG (50, IQR: 32-115) compared with the CG (82, IQR: 22-186) (P = 0.047), as was the mean symptom score of an exacerbation (STG: 43.4, IQR 27.2-68.6 vs CG: 55.9, IQR: 31.2-96.8) (P = 0.029). Also, patients in the STG visited the respiratory physician and emergency department less frequently than patients in the CG with incidence rate ratios of 1.52 (95% CI: 1.28-1.79) and 2.27 (95% CI: 1.11-4.62), respectively. Direct medical costs per patient over 2 years were euro1078 lower in the STG.
Conclusion: Self-treatment of exacerbations is beneficial in COPD patients without significant comorbidities because it reduces exacerbation duration, exacerbation severity and health-care utilization leading to considerable cost savings.

Gepubliceerd: Respirology 2016;21(3):497-503
Impact factor: 3.078

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17. Cost-Effectiveness of a Community-Based Exercise Programme in COPD Self-Management
Zwerink M, Effing T, Kerstjens HA, van der Valk PD, Brusse-Keizer M, Zielhuis G, van der Palen J

Intoduction: Information regarding cost-effectiveness of community-based exercise programmes in COPD is scarce. Therefore, we have investigated whether a community-based exercise programme is a cost-effective component of self-management for patients with COPD after 2 years of follow-up.
Methods: All included COPD patients participated in four self-management sessions. Additionally, patients in the COPE-active group participated in an 11-month community-based exercise programme led by physiotherapists. Patients trained 3 times/week for 6 months and two times/week during the subsequent 5 months. In both periods, one of these weekly training sessions was home-based (unsupervised). No formal physiotherapy sessions were offered to COPE-active patients in the second year. A decision analytical model with a 24-month perspective was used to evaluate cost-effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness planes were created.
Results: Data of 77 patients participating in the exercise programme and 76 patients in the control group were analysed. The ICER for an additional patient prevented from deteriorating at least 47.5 meters on the ISWT was euro6257. The ICER for an additional patient with a clinically relevant improvement (>/= 500 steps/day) in physical activity was euro1564, and the ICER for an additional quality-adjusted life year (QALY) was euro10 950.
Conclusion: Due to a lack of maintenance of beneficial effects on our primary outcome exercise capacity after 2 years of follow-up and higher costs of the programme, the community-based exercise programme cannot be considered cost-effective compared to self-management programmes only. Nevertheless, the ICERs for the secondary outcomes physical activity and QALY are generally considered acceptable.

Gepubliceerd: COPD 2016;13(2):214-23
Impact factor: 2.160

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18. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial
Den Exter PL, Zondag W, Klok FA, Brouwer RE, Dolsma J, Eijsvogel M, Faber LM, van Gerwen M, Grootenboers MJ, Heller-Baan R, Hovens MM, Jonkers GJ, van Kralingen KW, Melissant CF, Peltenburg H, Post JP, van de Ree MA, Vlasveld LT, de Vreede MJ, Huisman MV

Rationale: Outpatient treatment of pulmonary embolism (PE) may lead to improved patient satisfaction and reduced healthcare costs. However, trials to assess its safety and the optimal method for patient selection are scarce.
Objectives: To validate the utility and safety of selecting patients with PE for outpatient treatment by the Hestia criteria and to compare the safety of the Hestia criteria alone with the Hestia criteria combined with N-terminal pro-brain natriuretic peptide (NT-proBNP) testing.
Methods: We performed a randomized noninferiority trial in 17 Dutch hospitals. We randomized patients with PE without any of the Hestia criteria to direct discharge or additional NT-proBNP testing. We discharged the latter patients as well if NT-proBNP did not exceed 500 ng/L or admitted them if NT-proBNP was greater than 500 ng/L. The primary endpoint was 30-day adverse outcome defined as PE- or bleeding-related mortality, cardiopulmonary resuscitation, or intensive care unit admission. The noninferiority margin for the primary endpoint was 3.4%.
Measurements and main results: We randomized 550 patients. In the NT-proBNP group, 34 of 275 (12%) had elevated NT-proBNP values and were managed as inpatients. No patient (0 of 34) with an elevated NT-proBNP level treated in hospital (0%; 95% confidence interval [CI], 0-10.2%), versus no patient (0 of 23) with a post hoc-determined elevated NT-proBNP level from the direct discharge group (0%; 95% CI, 0-14.8%), experienced the primary endpoint. In both trial cohorts, the primary endpoint occurred in none of the 275 patients (0%; 95% CI, 0-1.3%) subjected to NT-proBNP testing, versus in 3 of 275 patients (1.1%; 95% CI, 0.2-3.2%) in the direct discharge group (P = 0.25). During the 3-month follow-up, recurrent venous thromboembolism occurred in two patients (0.73%; 95% CI, 0.1-2.6%) in the NT-proBNP group versus three patients (1.1%; 95% CI, 0.2-3.2%) in the direct discharge group (P = 0.65).
Conclusions: Outpatient treatment of patients with PE selected on the basis of the Hestia criteria alone was associated with a low risk of adverse events. Given the low number of patients with elevated NT-proBNP levels, this trial was unable to draw definite conclusions regarding the incremental value of NT-proBNP testing in patients who fulfill the Hestia criteria. Clinical trial registered with www.trialregister.nl/trialreg/admin/rctview.asp?TC=2603 (NTR2603).

Gepubliceerd: Am J Respir Crit Care Med 2016 Oct 15;194(8):998-1006
Impact factor: 13.118

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19. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

Walter JE, Heuvelmans MA, de Jong PA, Vliegenthart R, van Ooijen PM, Peters RB, Ten Haaf K, Yousaf-Khan U, van der Aalst CM, de Bock GH, Mali W, Groen HJ, de Koning HJ, Oudkerk M

Background: US guidelines now recommend lung cancer screening with low-dose CT for high-risk individuals. Reports of new nodules after baseline screening have been scarce and are inconsistent because of differences in definitions used. We aimed to identify the occurrence of new solid nodules and their probability of being lung cancer at incidence screening rounds in the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).
Methods: In the ongoing, multicentre, randomised controlled NELSON trial, between Dec 23, 2003, and July 6, 2006, 15 822 participants who had smoked at least 15 cigarettes a day for more than 25 years or ten cigarettes a day for more than 30 years and were current smokers, or had quit smoking less than 10 years ago, were enrolled and randomly assigned to receive either screening with low-dose CT (n=7915) or no screening (n=7907). From Jan 28, 2004, to Dec 18, 2006, 7557 individuals underwent baseline screening with low-dose CT; 7295 participants underwent second and third screening rounds. We included all participants with solid non-calcified nodules, registered by the NELSON radiologists as new or smaller than 15 mm(3) (study detection limit) at previous screens. Nodule volume was generated semiautomatically by software. We calculated the maximum volume doubling time for nodules with an estimated percentage volume change of 25% or more, representing the minimum growth rate for the time since the previous scan. Lung cancer diagnosis was based on histology, and benignity was based on histology or stable size for at least 2 years. The NELSON trial is registered at trialregister.nl, number ISRCTN63545820.
Findings: We analysed data for participants with at least one solid non-calcified nodule at the second or third screening round. In the two incidence screening rounds, the NELSON radiologists registered 1222 new solid nodules in 787 (11%) participants. A new solid nodule was lung cancer in 49 (6%) participants with new solid nodules and, in total, 50 lung cancers were found, representing 4% of all new solid nodules. 34 (68%) lung cancers were diagnosed at stage I. Nodule volume had a high discriminatory power (area under the receiver operating curve 0.795 [95% CI 0.728-0.862]; p<0.0001). Nodules smaller than 27 mm(3) had a low probability of lung cancer (two [0.5%] of 417 nodules; lung cancer probability 0.5% [95% CI 0.0-1.9]), nodules with a volume of 27 mm(3) up to 206 mm(3) had an intermediate probability (17 [3.1%] of 542 nodules; lung cancer probability 3.1% [1.9-5.0]), and nodules of 206 mm(3) or greater had a high probability (29 [16.9%] of 172 nodules; lung cancer probability 16.9% [12.0-23.2]). A volume cutoff value of 27 mm(3) or greater had more than 95% sensitivity for lung cancer.
Interpretation: Our study shows that new solid nodules are detected at each screening round in 5-7% of individuals who undergo screening for lung cancer with low-dose CT. These new nodules have a high probability of malignancy even at a small size. These findings should be considered in future screening guidelines, and

new solid nodules should be followed up more aggressively than nodules detected at baseline screening. Funding: Zorgonderzoek Nederland Medische Wetenschappen and Koningin Wilhelmina Fonds Kankerbestrijding.

Gepubliceerd: Lancet Oncol 2016 Jul;17(7):907-16
Impact factor: 26.509

Totale impact factor: 99.609
Gemiddelde impact factor: 5.243

Aantal artikelen 1e, 2e of laatste auteur: 11
Totale impact factor: 56.476
Gemiddelde impact factor: 5.134

MDL

1. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps
IJspeert JE, Bastiaansen BA, van Leerdam ME, Meijer GA, van Eeden S, Sanduleanu S, Schoon EJ, Bisseling TM, Spaander MC, van Lelyveld N, Bargeman M, Wang J, Dekker E

Objective: Accurate endoscopic differentiation would enable to resect and discard small and diminutive colonic lesions, thereby increasing cost-efficiency. Current classification systems based on narrow band imaging (NBI), however, do not include neoplastic sessile serrated adenomas/polyps (SSA/Ps). We aimed to develop and validate a new classification system for endoscopic differentiation of adenomas, hyperplastic polyps and SSA/Ps <10 mm.
Design: We developed the Workgroup serrAted polypS and Polyposis (WASP) classification, combining the NBI International Colorectal Endoscopic classification and criteria for differentiation of SSA/Ps in a stepwise approach. Ten consultant gastroenterologists predicted polyp histology, including levels of confidence, based on the endoscopic aspect of 45 polyps, before and after participation in training in the WASP classification. After 6 months, the same endoscopists predicted polyp histology of a new set of 50 polyps, with a ratio of lesions comparable to daily practice.
Results: The accuracy of optical diagnosis was 0.63 (95% CI 0.54 to 0.71) at baseline, which improved to 0.79 (95% CI 0.72 to 0.86, p<0.001) after training. For polyps diagnosed with high confidence the accuracy was 0.73 (95% CI 0.64 to 0.82), which improved to 0.87 (95% CI 0.80 to 0.95, p<0.01). The accuracy of optical diagnosis after 6 months was 0.76 (95% CI 0.72 to 0.80), increasing to 0.84 (95% CI 0.81 to 0.88) considering high confidence diagnosis. The combined negative predictive value with high confidence of diminutive neoplastic lesions (adenomas and SSA/Ps together) was 0.91 (95% CI 0.83 to 0.96).
Conclusions: We developed and validated the first integrative classification method for endoscopic differentiation of small and diminutive adenomas, hyperplastic polyps and SSA/Ps. In a still image evaluation setting, introduction of the WASP classification significantly improved the accuracy of optical diagnosis overall as well as SSA/P in particular, which proved to be sustainable after 6 months.

Gepubliceerd: Gut 2016;65(6):963-70
Impact factor: 14.660

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2. Three cases of hepatocellular carcinoma in Fontan patients: Review of the literature and suggestions for hepatic screening
Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP

The Fontan procedure has been used since 1971 as a palliative treatment for various (functionally) univentricular hearts. The systemic venous blood flows

passively to the pulmonary arteries, without passing through a functional ventricle. This results in chronic systemic venous congestion, which may lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. This review discusses possible screening modalities for liver fibrosis and cirrhosis in the Fontan population and proposes a screening protocol. We suggest starting screening for progression of fibrosis and cirrhosis in collaboration with the hepatologist circa 10 years after Fontan completion. The screening programme will consist of a yearly evaluation of liver laboratory tests in conjunction with imaging of the liver with ultrasound or MRI every two years. In case of liver fibrosis or cirrhosis, (reversible) causes should be ruled out (e.g. obstruction in the Fontan circuit). In case of severe fibrosis or cirrhosis, other complications of portal hypertension should be evaluated and screening for hepatocellular carcinoma is required on a regular (6-12 months) basis. As regards hepatocellular carcinoma, treatment should be discussed in a multidisciplinary team, before deciding a treatment modality.

Gepubliceerd: Int J Cardiol 2016 Mar 1;206:21-6
Impact factor: 4.638

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3. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial
Schepers NJ, Bakker OJ, Besselink MG, Bollen TL, Dijkgraaf MG, van Eijck CH, Fockens P, van Geenen EJ, van Grinsven J, Hallensleben ND, Hansen BE, van Santvoort HC, Timmer R, Anten MP, Bolwerk CJ, van Delft F, van Dullemen HM, Erkelens GW, van Hooft JE, Laheij R, van der Hulst RW, Jansen JM, Kubben FJ, Kuiken SD, Perk LE, de Ridder RJ, Rijk MC, Romkens TE, Schoon EJ, Schwartz MP, Spanier BW, Tan AC, Thijs WJ, Venneman NG, Vleggaar FP, van de Vrie W, Witteman BJ, Gooszen HG, Bruno MJ

Background: Acute pancreatitis is mostly caused by gallstones or sludge. Early decompression of the biliary tree by endoscopic retrograde cholangiography (ERC) with sphincterotomy may improve outcome in these patients. Whereas current guidelines recommend early ERC in patients with concomitant cholangitis, early ERC is not recommended in patients with mild biliary pancreatitis. Evidence on the role of routine early ERC with endoscopic sphincterotomy in patients without cholangitis but with biliary pancreatitis at high risk for complications is lacking. We hypothesize that early ERC with sphincterotomy improves outcome in these patients.
Methods/Design: The APEC trial is a randomized controlled, parallel group, superiority multicenter trial. Within 24 hours after presentation to the emergency department, patients with biliary pancreatitis without cholangitis and at high risk for complications, based on an Acute Physiology and Chronic Health Evaluation (APACHE-II) score of 8 or greater, Modified Glasgow score of 3 or greater, or serum C-reactive protein above 150 mg/L, will be randomized. In 27 hospitals of the Dutch Pancreatitis Study Group, 232 patients will be allocated to early ERC with sphincterotomy or to conservative treatment. The primary endpoint is a composite of major complications (that is, organ failure, pancreatic necrosis, pneumonia, bacteremia, cholangitis, pancreatic endocrine, or exocrine insufficiency) or death

within 180 days after randomization. Secondary endpoints include ERC-related complications, infected necrotizing pancreatitis, length of hospital stay and an economical evaluation.
Discussion: The APEC trial investigates whether an early ERC with sphincterotomy reduces the composite endpoint of major complications or death compared with conservative treatment in patients with biliary pancreatitis at high risk of complications.
Trial registration: Current Controlled Trials ISRCTN97372133 (date registration: 17-12-2012).

Gepubliceerd: Trials 2016 Jan 5;17:5
Impact factor: 1.859

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4. Equivalent Helicobacter pylori infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer
Soer EC, Leicher LW, Langers AM, van de Meeberg PC, van der Wouden EJ, Koornstra JJ, Bigirwamungu-Bargeman M, Vasen HF, de Vos tot Nederveen Cappel WH

Background: Patients with Lynch syndrome (LS) are at an increased risk of developing gastric cancer. In 2010, a guideline that recommended to screen all patients for Helicobacter pylori was implemented in the Netherlands. H. pylori is an important risk factor in the development of gastric cancer in the general population, and eradication of the bacterium reduces this risk. We aimed to assess the proportion of LS patients being tested and the yield and also addressed the question whether H. pylori infection is more prevalent in LS families with known cases of gastric cancer.
Methods: Proven mutation carriers from five different Dutch hospitals were included. The implementation of H. pylori screening and its outcome was examined. The observation period was 2008-2013. The presence of first-degree family members with gastric cancer was noted, and it was observed if H. pylori infection was more prevalent in Lynch families with known cases of gastric cancer. Obtainable endoscopy reports were reviewed.
Results: Four hundred forty-three (male, 184) proven mutation carriers were included. The proportion of patients screened increased after 2010, from 37 to 68%. Twenty percent of the patients were infected. The 25 patients who had a first-degree family member with gastric cancer did not have a higher infection rate. In 30% of cases, an endoscopy was performed; in four patients, intestinal metaplasia and in eight patients, gastric cancer was found.
Conclusion: The recommendation to screen for H. pylori is increasingly followed. The prevalence of infection in this patient group does not differ from the general population. Patients who had a first-degree family member with gastric cancer did not have a higher infection rate.

Gepubliceerd: Int J Colorectal Dis 2016 Mar;31(3):693-7
Impact factor: 2.383

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5. A large variety of clinical features and concomitant disorders in celiac disease - A cohort study in the Netherlands
Spijkerman M, Tan IL, Kolkman JJ, Withoff S, Wijmenga C, Visschedijk MC, Weersma RK

Background and Aims: Celiac disease (CeD) is a gluten triggered, immune-mediated disease of the small intestine. Few clinical cohort descriptions are available, despite the diverse clinical picture. This study provides an overview of a large Dutch CeD cohort focusing on presenting symptoms, co-occurrence of immune mediated diseases (IMD) and malignancies.
Methods: We performed a retrospective study in a Dutch university and a non-university medical hospital and included only biopsy proven (>/=Marsh type 2 classification) CeD patients.
Results: 412 patients were included, selected from 9468 small-bowel biopsy pathology reports and financial codes. Classical symptoms were present in approximately one third of the cohort (diarrhea (37.4%), fatigue (35.0%), weight loss (31.6%), abdominal pain (33.3%)). Atypical symptoms as constipation (10.4%) and reflux (12.4%) were reported as well. 11.7% was diagnosed without reported symptoms. In 25.2% concomitant IMD occurred (most prevalent: type 1 diabetes mellitus (4.9%), microscopic colitis (4.9%), immune mediated-thyroid disease (4.1%)). CeD patients with a concomitant IMD were diagnosed at a significantly higher age compared to those without (P=0.002). Malignancies occurred in 53 cases (12.9%), including eight Enteropathy Associated T-cell Lymphomas.
Conclusion: This is the first study describing a CeD cohort in such detail in the Netherlands and highlights the clinical heterogeneity and importance of screening for concomitant diseases in CeD.

Gepubliceerd: Dig Liver Dis 2016 May;48(5):499-505
Impact factor: 2.719

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6. The Prevalence of Nodular Regenerative Hyperplasia in Inflammatory Bowel Disease Patients Treated with Thioguanine Is Not Associated with Clinically Significant Liver Disease
van Asseldonk DP, Jharap B, Verheij J, den Hartog G, Westerveld DB, Becx MC, Russel MG, Engels LG, de Jong DJ, Witte BI, Mulder CJ, van Nieuwkerk CM, Bloemena E, de Boer NK, van Bodegraven AA

Background: Nodular regenerative hyperplasia (NRH) of the liver is associated with inflammatory-mediated diseases and certain drugs. There is conflicting data on the prevalence of NRH and its clinical implications in inflammatory bowel disease (IBD) patients treated with thioguanine.
Methods: A retrospective cohort study involving 7 Dutch centers comprised all IBD patients who were being treated with thioguanine and underwent a liver biopsy as part of the standard toxicity screening. Liver biopsy specimens were reviewed by 2 experienced liver pathologists. Clinical data as well as liver chemistry, blood counts, and abdominal imaging were collected.

Results: One hundred eleven IBD patients who submitted to liver biopsy were treated with thioguanine in a daily dose of 0.3 mg/kg for a median duration of 20 (4-64) months. NRH was detected in 6% of patients (7; 95% confidence interval, 3-14 patients). Older age (P = 0.02), elevated gamma-glutamyl transferase (P = 0.01) and alkaline phosphatase (P = 0.01) levels, a higher mean corpuscular volume (P = 0.02), and a lower platelet or leukocyte count (P < 0.01 and P = 0.02, respectively) were associated with NRH. Three of the 7 patients with NRH did not have any associated clinical symptoms or signs. The other 4 had minor biochemical abnormalities only. Ultrasonography revealed splenomegaly in 3 of the 78 patients (4%; 95% confidence interval, 0%-9%), only one of whom had NRH. There was no clinically overt portal hypertension.
Conclusions: The prevalence of NRH was 6% in liver biopsies obtained from IBD patients treated with thioguanine. Histopathological irregularities including NRH were not associated with clinically significant findings over the period of observation.

Gepubliceerd: Inflamm Bowel Dis 2016 Sep;22(9):2112-20
Impact factor: 4.358

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7. Safety of Tioguanine During Pregnancy in Inflammatory Bowel Disease
van den Berg SA, de Boer M, van der Meulen-de Jong AE, Jansen JM, Hoentjen F, Russel MG, Mahmmod N, van Bodegraven AA, van der Woude CJ, Mulder CJ, de Boer NK

Background and Aims: Conventional thiopurine [azathioprine and mercaptopurine] treatment during pregnancy in patients with inflammatory bowel disease [IBD] is considered to be safe; however data on the safety and teratogenicity of the non-conventional thiopurine tioguanine [TG] in pregnant IBD patients are lacking. We aim to describe the safety and teratogenicity of TG treatment during pregnancy in IBD patients.
Methods: This was a retrospective, multicentre descriptive case series of female IBD patients using TG during pregnancy. Data on disease and medication history, pregnancy complications, pregnancy outcome, mode of delivery, preterm birth, birthweight, congenital abnormalities, laboratory signs of myelosuppression or hepatotoxicity, and 6-thioguaninenucleotide [6-TGN] concentrations in mother and neonate were collected.
Results: In all, 13 patients [77% Crohn's disease, 23% ulcerative colitis] used TG [median dose 18g/day] during pregnancy; 19 pregnancies, including 1 twin pregnancy, were included. Spontaneous abortion occurred in three pregnancies. In 7 of the 16 ongoing pregnancies a caesarean section was performed. One neonate had a mild congenital abnormality [distal shaft hypospadias]. In the singleton pregnancies, the median birthweight was 3410g at a median of gestational age of 39 weeks. No preterm birth [< 37 weeks] or low birthweight [< 2500 g] was observed in the singleton newborns. In the twin pregnancy an induction of labour was performed at 35 + 1 weeks of gestation because of pre-eclampsia. Both neonates had a low birthweight.

Conclusions: This relatively small case series supports safe use of TG in pregnant IBD patients. Still, consideration should be given to the indication and continuation of TG during pregnancy.

Gepubliceerd: J Crohns Colitis 2016;10(2):159-65
Impact factor: 6.585

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8. Willingness to accept chemotherapy and attitudes towards costs of cancer treatment; A multisite survey study in the Netherlands
van Dijk EF, Coskunturk M, Zuur AT, van der Palen J, van der Graaf WT, Timmer-Bonte JN, Wymenga AN

Background: In the past years, interest in patient treatment preferences is growing. Our objectives were: (1) to assess and compare the minimal required benefit for patients with cancer, patients without cancer and healthcare professionals to make chemotherapy acceptable and (2) to obtain insight into attitudes towards societal costs of cancer treatment. PATIENTS AND
Methods: We performed a prospective survey consisting of hypothetical scenarios among patients with cancer, patients without cancer and healthcare professionals. Participants were asked to indicate the minimal desired benefit in terms of chance of cure, life prolongation and symptom relief which would make intensive and mild chemotherapy regimens acceptable. In two other scenarios, attitudes towards monthly costs for chemotherapy treatment were examined.
Results: The minimal benefit required to make chemotherapy acceptable did not differ between cancer and non-cancer patients, with respect to chance of cure (mean 57%), life prolongation (median 24 months) and symptom relief (mean 50%); healthcare providers were likely to accept the same chemotherapy regimen at lower thresholds ($p < 0.01$). Education level was an important explanatory variable and the differences between patients and healthcare professionals disappeared when corrected for education level. Opinions about the maximum acceptable costs for chemotherapy displayed a large spread between the groups.
Conclusions: Minimal benefits to accept chemotherapy were not different between cancer and non-cancer patients, but are beyond what can generally can be achieved. Healthcare professionals were willing to accept chemotherapy for less benefit. This difference may be attributed to a difference in education level between the groups. Healthcare professionals rated the maximum acceptable societal cost for chemotherapy lower than patients.

Gepubliceerd: Neth J Med 2016 Aug;74(7):292-300
Impact factor: 1.489

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9. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression
Kastelein F, van Olphen SH, Steyerberg EW, Spaander MC, Bruno MJ, ProBar-Study Group (inlc Kolkman JJ)

Objective: Endoscopic surveillance for Barrett's oesophagus (BO) is under discussion given the overall low incidence of neoplastic progression and lack of evidence that it prevents advanced oesophageal adenocarcinoma (OAC). The aim of this study was to evaluate the impact of endoscopic BO surveillance on tumour stage and survival of patients with neoplastic progression.
Design: 783 patients with BO of at least 2 cm were included in a multicentre prospective cohort and followed during surveillance according to the American College of Gastroenterology guidelines. Cases of high-grade dysplasia and OAC were identified during follow-up. OAC staging was performed according to the 7th UICC-AJCC classification. Survival data were collected and crosschecked using death and municipal registries. Data from patients with OAC in the general population were obtained from the Dutch cancer registry. We compared survival of patients with BO with neoplastic progression during surveillance with those of patients without neoplastic progression and patients with OAC in the general population.
Results: 53 patients with BO developed high-grade dysplasia or OAC during surveillance. Thirty-five (66%) were classified as stage 0, 14 (26%) as stage 1 and 4 (8%) as stage 2. OAC was diagnosed at an earlier stage during BO surveillance than in the general population ($p<0.001$). Survival of patients with BO with neoplastic progression was not significantly worse than those of patients without neoplastic progression and similar to survival of patients with stage 0 or stage 1 OAC in the general population.
Conclusions: OAC is detected at an earlier stage during BO surveillance than in the general population with good survival rates.

Gepubliceerd: Gut 2016 Apr;65(4):548-54
Impact factor: 14.660

Totale impact factor: 55.351
Gemiddelde impact factor: 6.150

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

Medical School Twente

1. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients experiencing a severe exacerbation of COPD: a pilot study
Assink MD, de Saegher ME, Nijdam L, van der Valk PD, Brusse-Keizer MG, Brummelhuis-Visser P, Movig KL

Objective: To investigate the safety and tolerability of nebulized amoxicillin + clavulanic acid twice a day in patients experiencing a severe exacerbation of copd. Single-dose nebulization of amoxicillin + clavulanic acid has shown to be safe in patients having stable copd.
Design: Prospective, single-arm, observational intervention study.
Methods: Eight subjects nebulized doses of 200 + 40 mg amoxicillin + clavulanic acid twice a day for a maximum of seven days. Safety was evaluated by spirometry before and after the first nebulization. Tolerability was evaluated by a questionnaire filled in by the subjects after every nebulization. Plasma and expectorated sputum samples were assayed for amoxicillin concentration.
Results: Spirometry showed no clinically relevant reduction in forced expiratory volume in 1 second (fev1) after nebulization with amoxicillin + clavulanic acid. In 47% of the nebulizations no adverse events were reported. The adverse events that were reported, were minor in 32%, moderate in 8% and acceptable in 12% of the nebulizations. Most reported adverse events were cough, shortness of breath and bitter taste. 15 (out of 16) sputum samples showed an amoxicillin concentration above the mic90 for potential pathogenic micro-organisms in exacerbations of copd. All 7 collected plasma samples showed an amoxicillin concentration < 1.0 mg/L.
Conclusion: Based on the results of the spirometry and the reported side effects, inhalation of nebulized amoxicillin + clavulanic acid seems to be safe and well tolerated in patients experiencing a severe exacerbation of copd. Nebulizing amoxicillin + clavulanic acid 200 + 40 mg leads to sputum concentrations well above the mic90 for potential pathogenic micro-organisms with low concentrations in the central compartment..

Gepubliceerd: PW Wetenschappelijk Platform 2016;9:a1539
Impact factor: 0

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2. Prognostic assessment in COPD without lung function: the B-AE-D indices
Boeck L, Soriano JB, Brusse-Keizer M, Blasi F, Kostikas K, Boersma W, Milenkovic B, Louis R, Lacoma A, Djamin R, Aerts J, Torres A, Rohde G, Welte T, Martinez-Camblor P, Rakic J, Scherr A, Koller M, van der Palen J, Marin JM, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluna JJ, de Torres JP, Miravitlles M, Celli BR, Tamm M, Stolz D

Several composite markers have been proposed for risk assessment in chronic obstructive pulmonary disease (COPD). However, choice of parameters and score complexity restrict clinical applicability. Our aim was to provide and validate a simplified COPD risk index independent of lung function.The PROMISE study

(n=530) was used to develop a novel prognostic index. Index performance was assessed regarding 2-year COPD-related mortality and all-cause mortality. External validity was tested in stable and exacerbated COPD patients in the ProCOLD, COCOMICS and COMIC cohorts (total n=2988).Using a mixed clinical and statistical approach, body mass index (B), severe acute exacerbations of COPD frequency (AE), modified Medical Research Council dyspnoea severity (D) and copeptin (C) were identified as the most suitable simplified marker combination. 0, 1 or 2 points were assigned to each parameter and totalled to B-AE-D or B-AE-D-C. It was observed that B-AE-D and B-AE-D-C were at least as good as BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity), ADO (age, dyspnoea, airflow obstruction) and DOSE (dyspnoea, obstruction, smoking, exacerbation) indices for predicting 2-year all-cause mortality (c-statistic: 0.74, 0.77, 0.69, 0.72 and 0.63, respectively; Hosmer-Lemeshow test all p>0.05). Both indices were COPD specific (c-statistic for predicting COPD-related 2-year mortality: 0.87 and 0.89, respectively). External validation of B-AE-D was performed in COCOMICS and COMIC (c-statistic for 1-year all-cause mortality: 0.68 and 0.74; c-statistic for 2-year all-cause mortality: 0.65 and 0.67; Hosmer-Lemeshow test all p>0.05).The B-AE-D index, plus copeptin if available, allows a simple and accurate assessment of COPD-related risk.

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Impact factor: 8.332

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3. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer

Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, Klaase JM

Background: The prevalence of colorectal cancer in the elderly is increasing and, therefore, surgical interventions with a risk of potential complications are more frequently performed. This study investigated the role of low skeletal muscle mass (sarcopenia), muscle quality, and the sarcopenic obesity as prognostic factors for postoperative complications and survival in patients with resectable colon cancer.
Methods: We conducted a retrospective chart review of 91 consecutive patients who underwent an elective open colon resection for cancer with primary anastomosis between 2011 and 2013. Skeletal muscle mass was measured as total psoas area (TPA) and total abdominal muscle area (TAMA) at three anatomical levels on the preoperative CT scan. Skeletal muscle quality was measured using corresponding mean Hounsfield units (HU) for TAMA. Their relation with complications (none vs one or more), severe complications, and survival was analyzed.
Results: The study included 91 patients with a mean age of 71.2 +/- 9.7 years. Complications were noted in 55 patients (60 %), of which 15 (16.4 %) were severe. Lower HU for TAMA, as an indicator for impaired skeletal muscle quality, was an independent risk factor for one or more complications (all P </= 0.002), while sarcopenic obesity (TPA) was an independent risk factor for severe complications

(all P </= 0.008). Sarcopenia was an independent predictor of worse overall survival (HR 8.54; 95 % confidence interval (CI) 1.07-68.32).
Conclusion: Skeletal muscle quality is a predictor for overall complications, whereas sarcopenic obesity is a predictor for severe postoperative complications after open colon resection for cancer. Sarcopenia on itself is a predictor for worse overall survival.

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Impact factor: 2.383

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4. Comparing the 2007 and 2011 GOLD Classifications as Predictors of all-Cause Mortality and Morbidity in COPD
Brusse-Keizer M, Klatte M, Zuur-Telgen M, Koehorst-Ter Huurne K, van der Palen J, van der Valk PD

To better classify patients with chronic obstructive pulmonary disease (COPD) for prognostic purposes and to tailor treatment, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification was revised in 2011. The primary aim of the current data analyses was to evaluate the accuracy of the GOLD 2007 and 2011 GOLD classifications to predict all-cause mortality and morbidity in a well-described COPD cohort. The prognostic values of both GOLD classifications, expressed as the C-statistic, were assessed in the Cohort of Mortality and Inflammation in COPD (COMIC) study of 795 COPD patients, with a follow-up of 3 years. Outcomes were all-cause mortality and morbidity. Morbidity was defined as time until first COPD-related hospitalisation and time until first community-acquired pneumonia (CAP). The prognostic value of the GOLD 2011 classification was compared between symptom classification based on the modified Medical Research Council (mMRC) score and the Clinical COPD Questionnaire (CCQ) scores with two different thresholds. Although the GOLD 2011 CCQ classification had the highest accuracy to predict mortality and morbidity in our study, the C-statistics differed only numerically. Furthermore, our study showed that the instrument used to determine the level of symptoms in the GOLD 2011 classification has not only important consequences on the mortality prognosis, but also affects the morbidity prognosis in COPD. Therefore, patients' estimated prognosis could alter when different types of tools are used to evaluate the prognosis.

Gepubliceerd: COPD 2016 Jul 21;14(1):7-14
Impact factor: 2.160

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5. Statins and morbidity and mortality in COPD in the COMIC study: a prospective COPD cohort study
Citgez E, van der Palen J, Koehorst-Ter Huurne K, Movig K, van der Valk PD, Brusse-Keizer M

Background: Both chronic inflammation and cardiovascular comorbidity play an important role in the morbidity and mortality of patients with chronic obstructive

pulmonary disease (COPD). Statins could be a potential adjunct therapy. The additional effects of statins in COPD are, however, still under discussion. The aim of this study is to further investigate the association of statin use with clinical outcomes in a well-described COPD cohort.
Methods: 795 patients of the Cohort of Mortality and Inflammation in COPD (COMIC) study were divided into statin users or not. Statin use was defined as having a statin for at least 90 consecutive days after inclusion. Outcome parameters were 3-year survival, based on all-cause mortality, time until first hospitalisation for an acute exacerbation of COPD (AECOPD) and time until first community-acquired pneumonia (CAP). A sensitivity analysis was performed without patients who started a statin 3 months or more after inclusion to exclude immortal time bias.
Results: Statin use resulted in a better overall survival (corrected HR 0.70 (95% CI 0.51 to 0.96) in multivariate analysis), but in the sensitivity analysis this association disappeared. Statin use was not associated with time until first hospitalisation for an AECOPD (cHR 0.95, 95% CI 0.74 to 1.22) or time until first CAP (cHR 1.1, 95% CI 0.83 to 1.47).
Conclusions: In the COMIC study, statin use is not associated with a reduced risk of all-cause mortality, time until first hospitalisation for an AECOPD or time until first CAP in patients with COPD.

Gepubliceerd: BMJ Open Respir Res 2016;3(1):e000142
Impact factor: 0

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6. Definition of a COPD self-management intervention: International Expert Group consensus
Effing TW, Vercoulen JH, Bourbeau J, Trappenburg J, Lenferink A, Cafarella P, Coultas D, Meek P, van der Valk PD, Bischoff EW, Bucknall C, Dewan NA, Early F, Fan V, Frith P, Janssen DJ, Mitchell K, Morgan M, Nici L, Patel I, Walters H, Rice KL, Singh S, Zuwallack R, Benzo R, Goldstein R, Partridge MR, van der Palen J

There is an urgent need for consensus on what defines a chronic obstructive pulmonary disease (COPD) self-management intervention. We aimed to obtain consensus regarding the conceptual definition of a COPD self-management intervention by engaging an international panel of COPD self-management experts using Delphi technique features and an additional group meeting.In each consensus round the experts were asked to provide feedback on the proposed definition and to score their level of agreement (1=totally disagree; 5=totally agree). The information provided was used to modify the definition for the next consensus round. Thematic analysis was used for free text responses and descriptive statistics were used for agreement scores.In total, 28 experts participated. The consensus round response rate varied randomly over the five rounds (ranging from 48% (n=13) to 85% (n=23)), and mean definition agreement scores increased from 3.8 (round 1) to 4.8 (round 5) with an increasing percentage of experts allocating the highest score of 5 (round 1: 14% (n=3); round 5: 83% (n=19)).In this study we reached consensus regarding a conceptual definition of what should be a COPD self-management intervention, clarifying the requisites for such an intervention. Operationalisation of this conceptual definition in the near future will be an essential next step.

Gepubliceerd: Eur Respir J 2016 Jul;48(1):46-54
Impact factor: 8.332

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7. Obstructive Sleep Apnea Syndrome in Company Workers: Development of a Two-Step Screening Strategy with a New Questionnaire
Eijsvogel MM, Wiegersma S, Randerath W, Verbraecken J, Wegter-Hilbers E, van der Palen J

Study Objectives: To develop and evaluate a screening questionnaire and a two-step screening strategy for obstructive sleep apnea syndrome (OSAS) in healthy workers.
Design: Cross-sectional study.
Setting and participants: A total of 1,861 employees comprising healthy blue- and white-collar workers in two representative plants in the Netherlands from a worldwide consumer electronic company were approached to participate.
Interventions: Employees were invited to complete various sleep questionnaires, and undergo separate single nasal flow recording and home polysomnography on 2 separate nights.
Measurements and Results: Of the 1,861 employees, 249 provided informed consent and all nasal flow and polysomnography data were available from 176 (70.7%). OSAS was diagnosed in 65 (36.9%). A combination of age, absence of insomnia, witnessed breathing stops, and three-way scoring of the Berlin and STOPBANG questionnaires best predicted OSAS. Factor analysis identified a six-factor structure of the resulting new questionnaire: snoring, snoring severity, tiredness, witnessed apneas, sleep quality, and daytime well-being. Subsequently, some questions were removed, and the remaining questions were used to construct a new questionnaire. A scoring algorithm, computing individual probabilities of OSAS as high, intermediate, or low risk, was developed. Subsequently, the intermediate risk group was split into low and high probability for OSAS, based on nasal flow recording. This two-step approach showed a sensitivity of 63.1%, and a specificity of 90.1%. Specificity is important for low prevalence populations.
Conclusion: A two-step screening strategy with a new questionnaire and subsequent nasal flow recording is a promising way to screen for OSAS in a healthy worker population.
Trial registration: Development and validation of a screening instrument for Obstructive Sleep Apnea Syndrome in healthy workers. Netherlands Trial Register (www.trailregister.nl), number: NTR2675.

Gepubliceerd: J Clin Sleep Med 2016;12(4):555-64
Impact factor: 2.710

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8. Volumetric capnography in the exclusion of pulmonary embolism at the emergency department: a pilot study
Fabius TM, Eijsvogel MM, van der Lee I, Brusse-Keizer MG, de Jongh FH

The analysis of the [Formula: see text] in expired air as a function of the exhaled volume (volumetric capnography) might result in a more specific exclusion tool for pulmonary embolism (PE) in addition to the Wells-score and D-dimer. A novel combination of volumetric capnography parameters ([Formula: see text]) should be decreased in PE and could possibly be used to decrease the number of requested computed tomography pulmonary angiograms (CTPA). Volumetric capnography measurements were performed on consecutive patients seen in the emergency department for which, due to suspected PE (due to increased D-dimer level or Wells-score), a CTPA was ordered. A total of 30 subjects were included, of which in 13 PE was seen on CTPA. Median [Formula: see text] was 4.36 kPa (IQR 3.92-4.88) in the no PE group versus 4.07 kPa (IQR 3.37-4.39) in the PE group (p = 0.086). Median of the novel parameter [Formula: see text] was 1.85 min.kPa dl-1 (IQR 1.21-3.00) in the no PE group versus 1.18 min.kPa dl-1 (IQR 0.61-1.38) in the PE group (p = 0.006). Using a threshold for the new parameter of 1.90 min.kPa dl-1 or higher to exclude PE resulted in a negative predictive value of 100% (95% CI: 77%-100%) and would have potentially excluded PE in 47% (95% CI: 26%-69%) of the no PE group without the need for CTPA. This pilot study introduces a novel parameter [Formula: see text] which is significantly decreased in PE subjects. Future studies regarding validation and addressing aspects such as reproducibility and normalization after treatment are needed to confirm its usability in excluding PE in the emergency department.

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Impact factor: 4.177

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9. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H

Background: The aim of this study is to analyze the impact of first degree relative (FDR) of young breast cancer patients.
Methods: Data were used from our prospective population-based cohort study which started in 1983. The family history (FH) was registered with regard to FDR: the presence or absence of invasive breast cancer in none vs. one or more FDRs at any age.
Results: A total of 1109 women, </=50 years with 1128 breast conserving treatments was seen. The incidence of FDR was 17.0% for one FDR and 3.2% >/=2 FDR. The three groups, none, 1 or >/=2 FDR, were comparable. The local failure rate is comparable for all three groups. Women with a positive FH and metachronous bilateral breast cancer (MBBC) showed a lower local failure (HR 0.2; 95% CI 0.05-0.8). A positive FH was an independent predictor for a better disease-specific survival (HR 0.6; 95% CI 0.4-0.9).
Conclusion: A positive FH, based on FDR implies a better prognosis in relation to survival for young women treated with BCT. In contrast to no FH for FDR, MBBC in women with a positive FH was not associated with an increased risk of local recurrence.

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Impact factor: 3.730

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10. Characteristics of effective self-management interventions in patients with COPD: individual patient data meta-analysis
Jonkman NH, Westland H, Trappenburg JC, Groenwold RH, Bischoff EW, Bourbeau J, Bucknall CE, Coultas D, Effing TW, Epton M, Gallefoss F, Garcia-Aymerich J, Lloyd SM, Monninkhof EM, Nguyen HQ, van der Palen J, Rice KL, Sedeno M, Taylor SJ, Troosters T, Zwar NA, Hoes AW, Schuurmans MJ

It is unknown whether heterogeneity in effects of self-management interventions in patients with chronic obstructive pulmonary disease (COPD) can be explained by differences in programme characteristics. This study aimed to identify which characteristics of COPD self-management interventions are most effective.Systematic search in electronic databases identified randomised trials on self-management interventions conducted between 1985 and 2013. Individual patient data were requested for meta-analysis by generalised mixed effects models.14 randomised trials were included (67% of eligible), representing 3282 patients (75% of eligible). Univariable analyses showed favourable effects on some outcomes for more planned contacts and longer duration of interventions, interventions with peer contact, without log keeping, without problem solving, and without support allocation. After adjusting for other programme characteristics in multivariable analyses, only the effects of duration on all-cause hospitalisation remained. Each month increase in intervention duration reduced risk of all-cause hospitalisation (time to event hazard ratios 0.98, 95% CI 0.97-0.99; risk ratio (RR) after 6 months follow-up 0.96, 95% CI 0.92-0.99; RR after 12 months follow-up 0.98, 95% CI 0.96-1.00).Our results showed that longer duration of self-management interventions conferred a reduction in all-cause hospitalisations in COPD patients. Other characteristics are not consistently associated with differential effects of self-management interventions across clinically relevant outcomes.

Gepubliceerd: Eur Respir J 2016 Jul;48(1):55-68
Impact factor: 8.332

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11. Do self-management interventions in COPD patients work and which patients benefit most? An individual patient data meta-analysis
Jonkman NH, Westland H, Trappenburg JC, Groenwold RH, Bischoff EW, Bourbeau J, Bucknall CE, Coultas D, Effing TW, Epton MJ, Gallefoss F, Garcia-Aymerich J, Lloyd SM, Monninkhof EM, Nguyen HQ, van der Palen J, Rice KL, Sedeno M, Taylor SJ, Troosters T, Zwar NA, Hoes AW, Schuurmans MJ

Background: Self-management interventions are considered effective in patients with COPD, but trials have shown inconsistent results and it is unknown which patients benefit most. This study aimed to summarize the evidence on effectiveness of self-management interventions and identify subgroups of COPD patients who benefit most.

Methods: Randomized trials of self-management interventions between 1985 and 2013 were identified through a systematic literature search. Individual patient data of selected studies were requested from principal investigators and analyzed in an individual patient data meta-analysis using generalized mixed effects models.
Results: Fourteen trials representing 3,282 patients were included. Self-management interventions improved health-related quality of life at 12 months (standardized mean difference 0.08, 95% confidence interval [CI] 0.00-0.16) and time to first respiratory-related hospitalization (hazard ratio 0.79, 95% CI 0.66-0.94) and all-cause hospitalization (hazard ratio 0.80, 95% CI 0.69-0.90), but had no effect on mortality. Prespecified subgroup analyses showed that interventions were more effective in males (6-month COPD-related hospitalization: interaction P=0.006), patients with severe lung function (6-month all-cause hospitalization: interaction P=0.016), moderate self-efficacy (12-month COPD-related hospitalization: interaction P=0.036), and high body mass index (6-month COPD-related hospitalization: interaction P=0.028 and 6-month mortality: interaction P=0.026). In none of these subgroups, a consistent effect was shown on all relevant outcomes.
Conclusion: Self-management interventions exert positive effects in patients with COPD on respiratory-related and all-cause hospitalizations and modest effects on 12-month health-related quality of life, supporting the implementation of self-management strategies in clinical practice. Benefits seem similar across the subgroups studied and limiting self-management interventions to specific patient subgroups cannot be recommended.

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Impact factor: 3.046

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12. Can a single dose response predict the effect of montelukast on exercise-induced bronchoconstriction?
Kersten ET, Akkerman-Nijland AM, Driessen JM, Diamant Z, Thio BJ

Rationale: Exercise-induced bronchoconstriction (EIB) can be prevented by a single dose of montelukast (MLK). The effect is variable, similar to the variable responsiveness observed after daily treatment with MLK. We hypothesized that the effect of a single MLK-dose (5 or 10 mg) on EIB could predict the clinical effectiveness of longer term once daily treatment.
Methods: This was a prospective, open-label study. Twenty-four asthmatic adolescents (12-17 years) suboptimally controlled by low-dose inhaled corticosteroids, with >/=10% post-exercise fall in FEV1 , were included. They performed an exercise test at baseline, 20 hr after a single MLK-dose and 40-44 hr after the last dose of 4 weeks once daily treatment. The correlations between the effect of a single dose and 4 weeks treatment on area under the curve (AUC) and maximum % fall in FEV1 were calculated.
Results: AUC0-20 min decreased significantly after a single MLK-dose (P = 0.001, CI: 64.9-218.2), but not after 4 weeks of treatment (P = 0.080, CI: -12.2 to 200.4). There was a moderate correlation between the effect of a single MLK-dose and 4 weeks treatment on AUC0-20 min , r = 0.49 (P = 0.011), and maximum % fall in FEV1 , r = 0.40 (P = 0.035).

Conclusion: The protection provided by a single MLK-dose against EIB only modestly predicts the effect of regular treatment against EIB in adolescent asthmatics on low-dose inhaled corticosteroids. If used on a daily base, MLK offered clinically significant protection against EIB in two thirds of adolescents suboptimally controlled by low-dose ICS. Pediatr Pulmonol. 2015;9999:XX-XX. (c) 2015 Wiley Periodicals, Inc.

Gepubliceerd: Pediatr Pulmonol 2016;51(5):470-7
Impact factor: 2.850

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13. Quality of life and adherence to inhaled corticosteroids and tiotropium in COPD are related
Koehorst-Ter Huurne K, Kort S, van der Palen J, van Beurden WJ, Movig KL, van der Valk PD, Brusse-Keizer M

Background: Poor adherence to inhaled medications in COPD patients seems to be associated with an increased risk of death and hospitalization. Knowing the determinants of nonadherence to inhaled medications is important for creating interventions to improve adherence. **Objectives:** To identify disease-specific and health-related quality of life (HRQoL) factors, associated with adherence to inhaled corticosteroids (ICS) and tiotropium in COPD patients.
Methods: Adherence of 795 patients was recorded over 3 years and was deemed optimal at >75%-</=125%, suboptimal at >/=50%-<75%, and poor at <50% (underuse) or >125% (overuse). Health-related quality of life was measured with the Clinical COPD Questionnaire and the EuroQol-5D questionnaire.
Results: Patients with a higher forced expiratory volume in 1 second (FEV1)/vital capacity (VC) (odds ratio [OR] =1.03) and >/=1 hospitalizations in the year prior to inclusion in this study (OR =2.67) had an increased risk of suboptimal adherence to ICS instead of optimal adherence. An increased risk of underuse was predicted by a higher FEV1/VC (OR =1.05). Predictors for the risk of overuse were a lower FEV1 (OR =0.49), higher scores on Clinical COPD Questionnaire-question 3 (anxiety for dyspnea) (OR =1.26), and current smoking (OR =1.73). Regarding tiotropium, predictors for suboptimal use were a higher FEV1/VC (OR =1.03) and the inability to perform usual activities as asked by the EuroQol-5D questionnaire (OR =3.09). A higher FEV1/VC also was a predictor for the risk of underuse compared to optimal adherence (OR =1.03). The risk of overuse increased again with higher scores on Clinical COPD Questionnaire-question 3 (OR =1.46).
Conclusion: Several disease-specific and quality of life factors are related to ICS and tiotropium adherence, but a clear profile of a nonadherent patient cannot yet be outlined. Overusers of ICS and tiotropium experience more anxiety.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2016;11:1679-88
Impact factor: 3.046

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14. The influence of type of inhalation device on adherence of COPD patients to inhaled medication

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

Objective: To study the influence of type of inhalation device on medication adherence of COPD patients.
Methods: Adherence to inhalation medication of 795 patients was recorded from pharmacy records over 3 years. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Since most patients used more than one device, 1379 medication periods were analyzed.
Results: Patients using a Metered Dose Inhaler (MDI) or Diskus had a 2.3-fold and 2.2-fold increased risk, respectively, of suboptimal adherence versus good adherence, compared to Handihaler and a 2.1-fold and 2.2-fold increased risk, respectively, of underuse versus good adherence compared to Handihaler. Turbuhaler, MDI, Respimat had a 7.9-fold, 3.5-fold, and 2.0-fold increased risk, of overuse versus good adherence compared to Handihaler.
Conclusions: In COPD, adherence to inhalation medication is device-related. Overuse was most pronounced for devices without a dose counter, devices with the ability to load a dosage without actual inhalation, or devices lacking feedback of correct inhalation. The design of the device seems to be related to underuse and overuse of inhaled medication. Future research might investigate whether prescribing a different device with similar medication improves therapy adherence.

Gepubliceerd: Expert Opin Drug Deliv 2016;13(4):469-75
Impact factor: 5.434

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15. Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel - proton pump inhibitor interaction
Kruik-Kolloffel WJ, van der Palen J, Kruik HJ, van Herk-Sukel MP, Movig KL

Safety concerns of the concomitant use of clopidogrel and proton pump inhibitors (PPIs) were published in 2009 and 2010 by the medicines regulatory agencies, including a direct healthcare professional communication. We examined the association between various safety statements and prescription behavior for gastroprotective drugs in naive patients in the Netherlands during the years 2008-2011. Data from the PHARMO Database Network were analyzed with interrupted time series analyses to estimate the impact of each communication on drug prescriptions. Dispensings were used as a proxy variable for prescription behavior. After the early communication in January 2009, 15.5% (95% CI 7.8, 23.4) more patients started concomitantly with (es)omeprazole and 13.8% (95% CI 6.5, 21.2) less with other PPIs. Directly after the first statement in June 2009, we found a steep increase in histamine 2-receptor antagonists (H2RA) peaking at 25%, placing those patients at risk for gastrointestinal events. This effect for H2RA faded away after a few months. In February 2010, when the official advice via an adjusted statement was to avoid (es)omeprazole, we found a decrease of 11.9% (95% CI 5.7, 18.2) for (es)omeprazole and an increase of +16.0% (95% CI 10.3, 21.7) for other PPIs. Still 22.6% (95% CI 19.5, 25.7) of patients started on (es)omeprazole in February 2010,

placing them at risk for cardiovascular events. Advices of regulatory authorities were followed, however, reluctantly and not fully, probably partly because of the existing scientific doubt about the interaction.

Gepubliceerd: Pharmacol Res Perspect 2016 Aug;4(4):e00242
Impact factor: 0

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16. Construct Validity of the Dutch Version of the 12-Item Partners in Health Scale: Measuring Patient Self-Management Behaviour and Knowledge in Patients with Chronic Obstructive Pulmonary Disease
Lenferink A, Effing T, Harvey P, Battersby M, Frith P, van Beurden WJ, van der Palen J, Paap MC

Objective: The 12-item Partners in Health scale (PIH) was developed in Australia to measure self-management behaviour and knowledge in patients with chronic diseases, and has undergone several changes. Our aim was to assess the construct validity and reliability of the latest PIH version in Dutch COPD patients.
Methods: The 12 items of the PIH, scored on a self-rated 9-point Likert scale, are used to calculate total and subscale scores (knowledge; coping; recognition and management of symptoms; and adherence to treatment). We used forward-backward translation of the latest version of the Australian PIH to define a Dutch PIH (PIH(Du)). Mokken Scale Analysis and common Factor Analysis were performed on data from a Dutch COPD sample to investigate the psychometric properties of the Dutch PIH; and to determine whether the four-subscale solution previously found for the original Australian PIH could be replicated for the Dutch PIH.
Results: Two subscales were found for the Dutch PIH data (n = 118); 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment. The correlation between the two Dutch subscales was 0.43. The lower-bound of the reliability of the total scale equalled 0.84. Factor analysis indicated that the first two factors explained a larger percentage of common variance (39.4% and 19.9%) than could be expected when using random data (17.5% and 15.1%).
Conclusion: We recommend using two PIH subscale scores when assessing self-management in Dutch COPD patients. Our results did not support the four-subscale structure as previously reported for the original Australian PIH.

Gepubliceerd: PLoS One 2016;11(8):e0161595
Impact factor: 3.540

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17. Does the postcoital test predict pregnancy in WHO II anovulatory women? A prospective cohort study
Nahuis MJ, Weiss NS, Van der Velde M, Oosterhuis JJ, Hompes PG, Kaaijk EM, van der Palen J, Van der Veen F, Mol BW, van Wely M

Objective: To assess the capacity of the postcoital test (PCT) to predict pregnancy in WHO II anovulatory women who are ovulatory on clomiphene citrate (CC). In

these women, an abnormal PCT result could be associated with lower pregnancy chances, but this has never been proven or refuted.
Study design: Prospective cohort study was performed between December 2009 and September 2012 for all women who started ovulation induction with CC in one university clinic and two teaching hospitals in the Netherlands. A PCT was performed in one of the first three ovulatory cycles. Ovulation induction with CC was continued for at least six cycles. The PCT was judged to be positive if at least one progressive motile spermatozo was seen in one of five high power fields at 400x magnification. The primary outcome was time to ongoing pregnancy, within six ovulatory cycles.
Results: In 152 women the PCT was performed. 135 women had a reliable, well-timed PCT. The ongoing pregnancy rate was 44/107 (41%) for a positive and 10/28 (36%) for a negative PCT. The hazard rate for ongoing pregnancy was 1.3 (95% CI 0.64-2.5) for a positive versus a negative PCT. Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not clear (HR 2.0; 95% CI 1.02-3.84, p=0.04).
Conclusion: The present study suggests that the outcome of the postcoital test in women with WHO-II anovulation that undergo ovulation induction with CC does not have a large effect on ongoing pregnancy chances over time.

Gepubliceerd: Eur J Obstet Gynecol Reprod Biol 2016 Feb 1;199:127-31
Impact factor: 1.662

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18. Safety and Tolerability of Nebulized Amoxicillin-Clavulanic Acid in Patients with COPD (STONAC 1 and STONAC 2)
Nijdam LC, Assink MD, Kuijvenhoven JC, de Saegher ME, van der Valk PD, van der Palen J, Brusse-Keizer MG, Movig KL

The safety and tolerability of nebulized amoxicillin clavulanic acid were determined in patients with stable COPD and during severe exacerbations of COPD. Nine stable COPD patients received doses ranging from 50:10 mg up to 300:60 mg amoxicillin clavulanic acid and eight patients hospitalised for a COPD exacerbation received fixed doses 200/40 mg twice daily. Safety was evaluated by spirometry before and after inhalation. Tolerability was evaluated by questionnaire. Plasma and expectorated sputum samples were assayed for amoxicillin content. Seventeen patients underwent in total 100 nebulizations with amoxicillin clavulanic acid. In this safety and tolerability study no clinically relevant deteriorations in FEV1 were observed. Nebulized amoxicillin clavulanic acid produces sputum concentrations well above the Minimal Inhibiting Concentration of 90% for potential pathogenic micro-organisms, with low concentrations in the central compartment (low systemic exposure). Based on spirometry and reported side effects, inhalation of nebulized amoxicillin clavulanic acid seems to be safe and well tolerated, both in stable patients with COPD as in those experiencing a severe exacerbation. Levels of amoxicillin were adequate.

Gepubliceerd: COPD 2016 Aug;13(4):448-54
Impact factor: 2.160

19. Chronic fatigue syndrome in women assessed with combined cardiac magnetic resonance imaging
Olimulder MA, Galjee MA, Wagenaar LJ, van Es J, van der Palen J, Visser FC, Vermeulen RC, von Birgelen C

Objective: In chronic fatigue syndrome (CFS), only a few imaging and histopathological studies have previously assessed either cardiac dimensions/function or myocardial tissue, suggesting smaller left ventricular (LV) dimensions, LV wall motion abnormalities and occasionally viral persistence that may lead to cardiomyopathy. The present study with cardiac magnetic resonance (CMR) imaging is the first to use a contrast-enhanced approach to assess cardiac involvement, including tissue characterisation of the LV wall.
Methods: CMR measurements of 12 female CFS patients were compared with data of 36 age-matched, healthy female controls. With cine imaging, LV volumes, ejection fraction (EF), mass, and wall motion abnormalities were assessed. T2-weighted images were analysed for increased signal intensity, reflecting oedema (i. e. inflammation). In addition, the presence of contrast enhancement, reflecting fibrosis (i. e. myocardial damage), was analysed.
Results: When comparing CFS patients and healthy controls, LVEF (57.9 +/- 4.3 % vs. 63.7 +/- 3.7 %; $p < 0.01$), end-diastolic diameter (44 +/- 3.7 mm vs. 49 +/- 3.7 mm; $p < 0.01$), as well as body surface area corrected LV end-diastolic volume (77.5 +/- 6.2 ml/m2 vs. 86.0 +/- 9.3 ml/m2; $p < 0.01$), stroke volume (44.9 +/- 4.5 ml/m2 vs. 54.9 +/- 6.3 ml/m2; $p < 0.001$), and mass (39.8 +/- 6.5 g/m2 vs. 49.6 +/- 7.1 g/m2; $p = 0.02$) were significantly lower in patients. Wall motion abnormalities were observed in four patients and contrast enhancement (fibrosis) in three; none of the controls showed wall motion abnormalities or contrast enhancement. None of the patients or controls showed increased signal intensity on the T2-weighted images.
Conclusion: In patients with CFS, CMR demonstrated lower LV dimensions and a mildly reduced LV function. The presence of myocardial fibrosis in some CFS patients suggests that CMR assessment of cardiac involvement is warranted as part of the scientific exploration, which may imply serial non-invasive examinations.

Gepubliceerd: Neth Heart J 2016 Aug 25;24(12):709-16
Impact factor: 2.062

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20. The COPD-SIB: a newly developed disease-specific item bank to measure health-related quality of life in patients with chronic obstructive pulmonary disease
Paap MC, Lenferink LI, Herzog N, Kroeze KA, van der Palen J

Background: Health-related quality of life (HRQoL) is widely used as an outcome measure in the evaluation of treatment interventions in patients with chronic obstructive pulmonary disease (COPD). In order to address challenges associated with existing fixed-length measures (e.g., too long to be used routinely, too short to

ensure both content validity and reliability), a COPD-specific item bank (COPD-SIB) was developed.
Methods: Items were selected based on literature review and interviews with Dutch COPD patients, with a strong focus on both content validity and item comprehension. The psychometric quality of the item bank was evaluated using Mokken Scale Analysis and parametric Item Response Theory, using data of 666 COPD patients.
Results: The final item bank contains 46 items that form a strong scale, tapping into eight important themes that were identified based on literature review and patient interviews: Coping with disease/symptoms, adaptability; Autonomy; Anxiety about the course/end-state of the disease, hopelessness; Positive psychological functioning; Situations triggering or enhancing breathing problems; Symptoms; Activity; Impact.
Conclusions: The 46-item COPD-SIB has good psychometric properties and content validity. Items are available in Dutch and English. The COPD-SIB can be used as a stand-alone instrument, or to inform computerised adaptive testing.

Gepubliceerd: Health Qual Life Outcomes 2016 Jun 27;14:97
Impact factor: 2.212

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21. Using the Three-Step Test Interview to understand how patients perceive the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
Paap MC, Lange L, van der Palen J, Bode C

Purpose: The aim of this study was to assess the experiences of patients with chronic obstructive pulmonary disease (COPD) while they were completing the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), using qualitative research methods.
Methods: Twenty Dutch COPD patients were recruited through pulmonary physicians [13 women; mean age = 63.3 years (SD = 11.4)]. A trained interviewer applied the Three-Step Test Interview which allowed the interviewer to follow the thought process of the patient filling out the SGRQ-C. The official Dutch translation of the SGRQ-C was used.
Results: Patients missed a recall period for the Symptoms subscale; were uncertain how to interpret specific words and phrases like "good days", "games", and "housework"; were confused by long-item stems that included a list of activities; and were frustrated by the dichotomous format used for the majority of SGRQ-C items (true/false).
Conclusions: Overall, patients were satisfied with the SGRQ-C. Nevertheless, making minor adjustments could further increase its quality. This includes reintroducing a recall period in the first set of items such as used in the previous version and splitting up items consisting of multiple activities. Furthermore, we recommend using the same response format (4 or 5 response categories) for all items.

Gepubliceerd: Qual Life Res 2016;25(6):1561-70
Impact factor: 2.486

22. Nonfocal Symptoms in Patients with Transient Ischemic Attack or Ischemic Stroke: Occurrence, Clinical Determinants, and Association with Cardiac History
Plas GJ, Booij HA, Brouwers PJ, Brusse-Keizer M, Koudstaal PJ, Dippel DW, den Hertog HM

Background: Transient ischemic attacks (TIAs) accompanied by nonfocal symptoms are associated with a higher risk of cardiovascular events, in particular cardiac events. Reported frequencies of TIAs accompanied by nonfocal symptoms range from 18 to 53%. We assessed the occurrence of nonfocal symptoms in patients with TIA or minor ischemic stroke in a neurological outpatient clinic in terms of clinical determinants, cardiac history, and atrial fibrillation (AF).
Methods: We included 1,265 consecutive patients with TIA or minor stroke who visited the outpatient clinic. During these visits, we systematically asked for nonfocal symptoms. Nonfocal symptoms included decreased consciousness, amnesia, positive visual phenomena, non-rotatory dizziness, and paresthesias. Relative risks for the presence of nonfocal symptoms in relation to clinical determinants, AF, and cardiac history were calculated.
Results: In 243 (19%) of 1,265 patients, TIA or minor ischemic stroke was accompanied by one or more nonfocal symptoms. Non-rotatory dizziness, paresthesia, and amnesia were the most common nonfocal symptoms. In patients with an event of the posterior circulation or obesity, the qualifying TIA or minor stroke was more frequently accompanied by nonfocal symptoms, and in patients with significant carotid stenosis, nonfocal symptoms occurred less frequently. AF was related only with amnesia.
Conclusion: Nonfocal symptoms are present in one out of 5 patients with TIA or ischemic stroke, in particular when located in the posterior circulation. A cardiac history or AF was not directly related to nonfocal symptoms. A heterogeneous etiology is suggested.

Gepubliceerd: Cerebrovasc Dis 2016;42(5-6):439-45
Impact factor: 3.359

23. Dealing with missing behavioral endpoints in health promotion research by modeling cognitive parameters in cost-effectiveness analyses of behavioral interventions: a validation study
Prenger R, Pieterse ME, Braakman-Jansen AL, Feenstra TL, Smit ES, Hoving C, de Vries H, van Ommeren JK, Evers SM, van der Palen J

Cost-effectiveness analyses (CEAs) of behavioral interventions typically use physical outcome criteria. However, any progress in cognitive antecedents of behavior change may be seen as a beneficial outcome of an intervention. The aim of this study is to explore the feasibility and validity of incorporating cognitive parameters of behavior change in CEAs. The CEA from a randomized controlled trial on smoking cessation was reanalyzed. First, relevant cognitive antecedents of

behavior change in this dataset were identified. Then, transition probabilities between combined states of smoking and cognitions at 6 weeks and corresponding 6 months smoking status were obtained from the dataset. These rates were extrapolated to the period from 6 to 12 months in a decision analytic model. Simulated results were compared with the 12 months' observed cost-effectiveness results. Self-efficacy was the strongest time-varying predictor of smoking cessation. Twelve months' observed CEA results for the multiple tailoring intervention versus usual care showed euro3188 had to be paid for each additional quitter versus euro10,600 in the simulated model. The simulated CEA showed largely similar but somewhat more conservative results. Using self-efficacy to enhance the estimation of the true behavioral outcome seems a feasible and valid way to estimate future cost-effectiveness. Copyright (c) 2014 John Wiley & Sons, Ltd.

Gepubliceerd: Health Econ 2016;25(1):24-39
Impact factor: 2.151

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24. Study protocol for a non-inferiority trial of a blended smoking cessation treatment versus face-to-face treatment (LiveSmokefree-Study)
Siemer L, Pieterse ME, Brusse-Keizer MG, Postel MG, Ben Allouch S, Sanderman R

Background: Smoking cessation can significantly reduce the risk of developing smoking-related diseases. Several face-to-face and web-based treatments have shown to be effective. Blending of web-based and face-to-face treatment is expected to improve smoking cessation treatment. The primary objective of this study is to compare the prolonged abstinence rate of the blended smoking cessation treatment with the face-to-face treatment. Secondary objectives are to assess the benefits of blended treatment in terms of cost effectiveness and patient satisfaction, and to identify mechanisms underlying successful smoking cessation.
Methods/Design: This study will be a single-center randomized controlled non-inferiority-trial with parallel group design. Patients (n = 344) will be randomly assigned to either the blended or the face-to-face group. Both treatments will consist of ten sessions with equal content held within 6 months. In the blended treatment five out of ten sessions will be delivered online. The treatments will cover the majority of behavior change techniques that are evidence-based within smoking cessation counseling. All face-to-face sessions in both treatments will take place at the outpatient smoking cessation clinic of a hospital. The primary outcome parameter will be biochemically validated prolonged abstinence at 15 months from the start of the smoking cessation treatment.
Discussion: This RCT will be the first study to examine the effectiveness of a blended smoking cessation treatment. It will also be the first study to explore patient satisfaction, adherence, cost-effectiveness, and the clinically relevant influencing factors of a blended smoking cessation treatment. The findings of this RCT are expected to substantially strengthen the base of evidence available to inform the development and delivery of smoking cessation treatment.
Trial registration: Nederlands Trialregister NTR5113 . Registered 24 March 2015.

Gepubliceerd:BMC Public Health 2016 Nov 24;16(1):1187
Impact factor: 2.209

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25. Value of the SYNTAX score for periprocedural myocardial infarction according to WHO and the third universal definition of myocardial infarction: insights from the TWENTE trial
Tandjung K, Lam MK, Sen H, de Man FH, Louwerenburg JH, Stoel MG, van Houwelingen KG, Linssen GC, van der Palen J, Doggen CJ, von Birgelen C

Aims: The SYNTAX score is a tool to quantify the complexity of coronary artery disease. We investigated the relation between the SYNTAX score and the occurrence of a periprocedural myocardial infarction (PMI) according to the historical definition of the World Health Organization (WHO) and the recently updated universal definition of MI.
Methods and Results: The SYNTAX score was calculated in 1,243 patients enrolled in TWENTE, a randomised trial which assessed second-generation drug-eluting stents. PMI was defined by the WHO definition and the third universal definition of MI. Patients were divided into tertiles of the SYNTAX score: </=7 (n=430); >7 and <15 (n=390); >/=15 (n=423). PMI according to the WHO definition occurred more frequently in patients in the highest SYNTAX score tertile (7.3% vs. 3.1% vs. 1.6%, p<0.001) compared to the mid and lowest tertile. Similar findings were seen for universal PMI (9.9% vs. 7.7% vs. 3.7%, p<0.01). After multivariate analysis, SYNTAX score was a significant independent correlate of PMI for both definitions: the highest SYNTAX score tertile had an almost five times higher risk for WHO PMI, and a three times higher risk for universal PMI.
Conclusions: In a broad patient population treated with second-generation DES, the SYNTAX score was able to stratify the risk of PMI.

Gepubliceerd: EuroIntervention 2016;12(4):431-40
Impact factor: 3.863

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26. Cost-Effectiveness of a Community-Based Exercise Programme in COPD Self-Management
Zwerink M, Effing T, Kerstjens HA, van der Valk PD, Brusse-Keizer M, Zielhuis G, van der Palen J

Intoduction: Information regarding cost-effectiveness of community-based exercise programmes in COPD is scarce. Therefore, we have investigated whether a community-based exercise programme is a cost-effective component of self-management for patients with COPD after 2 years of follow-up.
Methods: All included COPD patients participated in four self-management sessions. Additionally, patients in the COPE-active group participated in an 11-month community-based exercise programme led by physiotherapists. Patients trained 3 times/week for 6 months and two times/week during the subsequent 5 months. In both periods, one of these weekly training sessions was home-based (unsupervised). No formal physiotherapy sessions were offered to COPE-active

patients in the second year. A decision analytical model with a 24-month perspective was used to evaluate cost-effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness planes were created.
Results: Data of 77 patients participating in the exercise programme and 76 patients in the control group were analysed. The ICER for an additional patient prevented from deteriorating at least 47.5 meters on the ISWT was euro6257. The ICER for an additional patient with a clinically relevant improvement (>/= 500 steps/day) in physical activity was euro1564, and the ICER for an additional quality-adjusted life year (QALY) was euro10 950.
Conclusion: Due to a lack of maintenance of beneficial effects on our primary outcome exercise capacity after 2 years of follow-up and higher costs of the programme, the community-based exercise programme cannot be considered cost-effective compared to self-management programmes only. Nevertheless, the ICERs for the secondary outcomes physical activity and QALY are generally considered acceptable.

Gepubliceerd: COPD 2016;13(2):214-23
Impact factor: 2.160

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27. How does injury compensation affect health and disability in patients with complaints of whiplash? A qualitative study among rehabilitation experts-professionals
van der Meer S, Pieterse M, Reneman M, Verhoeven J, van der Palen J

Purpose: To explore rehabilitation professionals' opinions about the influence and the pathways of injury compensation (IC) on health and disability in patients with whiplash associated disorder (WAD).
Methods: Semi-structured interviews were performed among a purposeful selected sample of Dutch expert-professionals in the field of rehabilitation of patients with WAD. Inclusion continued until saturation was reached. Inductive and deductive thematic analyses were performed.
Results: Ten rehabilitation expert-professionals (five females), working as physician, psychologist or physiotherapist, were interviewed. All expert-professionals acknowledged that IC can influence rehabilitation, health and disability. The expert-professionals provided three causal pathways; a pathway through prolonged distress, a behavioral pathway, and patient characteristics that may either attenuate or worsen their response. They assess the influence of IC mainly with interview techniques. Most professionals discuss the potential influence of IC with their patients, because they want to give clear information to the patient. Some emphasize that their role is neutral in relation with the IC. Others mention that financial consequences can accompany functional improvement.
Conclusions: Rehabilitation expert-professionals believe that IC may affect rehabilitation, health and disability in patients with WAD. Three pathways are mentioned by the experts-professionals. Implications for Rehabilitation According to rehabilitation expert-professionals, an injury compensation (IC) can lead to distress, by creating a (conscious or unconscious) conflict of interests within a patient between striving for compensation on one hand, and recovery on the other hand.

Patient characteristics can either attenuate or worsen IC-related distress. Reliable and valid tools need to be developed to assess the influence of IC on health, disability and rehabilitation, and to limit the negative effects. Rehabilitation professionals can discuss the possible unintended effects of IC with their patients to clarify their current situation.

Gepubliceerd: Disabil Rehabil 2016 Feb;38(3):211-7
Impact factor: 1.919

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28. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices
van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, Wilkinson T, Stonham C, Chauhan AJ, Imber V, Zhu CQ, Svedsater H, Barnes NC

Errors in the use of different inhalers were investigated in patients naive to the devices under investigation in a multicentre, single-visit, randomised, open-label, cross-over study. Patients with chronic obstructive pulmonary disease (COPD) or asthma were assigned to ELLIPTA vs DISKUS (Accuhaler), metered-dose inhaler (MDI) or Turbuhaler. Patients with COPD were also assigned to ELLIPTA vs Handihaler or Breezhaler. Patients demonstrated inhaler use after reading the patient information leaflet (PIL). A trained investigator assessed critical errors (i.e., those likely to result in the inhalation of significantly reduced, minimal or no medication). If the patient made errors, the investigator demonstrated the correct use of the inhaler, and the patient demonstrated inhaler use again. Fewer COPD patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS, 9/171 (5%) vs 75/171 (44%); MDI, 10/80 (13%) vs 48/80 (60%); Turbuhaler, 8/100 (8%) vs 44/100 (44%); Handihaler, 17/118 (14%) vs 57/118 (48%); Breezhaler, 13/98 (13%) vs 45/98 (46%; all P<0.001). Most patients (57-70%) made no errors using ELLIPTA and did not require investigator instruction. Instruction was required for DISKUS (65%), MDI (85%), Turbuhaler (71%), Handihaler (62%) and Breezhaler (56%). Fewer asthma patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS (3/70 (4%) vs 9/70 (13%), P=0.221); MDI (2/32 (6%) vs 8/32 (25%), P=0.074) and significantly fewer vs Turbuhaler (3/60 (5%) vs 20/60 (33%), P<0.001). More asthma and COPD patients preferred ELLIPTA over the other devices (all P0.002). Significantly, fewer COPD patients using ELLIPTA made critical errors after reading the PIL vs other inhalers. More asthma and COPD patients preferred ELLIPTA over comparator inhalers.

Gepubliceerd: NPJ Prim Care Respir Med 2016 Nov 24;26:16079
Impact factor: 1.447

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29. Willingness to accept chemotherapy and attitudes towards costs of cancer treatment; A multisite survey study in the Netherlands
van Dijk EF, Coskunturk M, Zuur AT, van der Palen J, van der Graaf WT, Timmer-Bonte JN, Wymenga AN

Background: In the past years, interest in patient treatment preferences is growing. Our objectives were: (1) to assess and compare the minimal required benefit for patients with cancer, patients without cancer and healthcare professionals to make chemotherapy acceptable and (2) to obtain insight into attitudes towards societal costs of cancer treatment. PATIENTS AND
Methods: We performed a prospective survey consisting of hypothetical scenarios among patients with cancer, patients without cancer and healthcare professionals. Participants were asked to indicate the minimal desired benefit in terms of chance of cure, life prolongation and symptom relief which would make intensive and mild chemotherapy regimens acceptable. In two other scenarios, attitudes towards monthly costs for chemotherapy treatment were examined.
Results: The minimal benefit required to make chemotherapy acceptable did not differ between cancer and non-cancer patients, with respect to chance of cure (mean 57%), life prolongation (median 24 months) and symptom relief (mean 50%); healthcare providers were likely to accept the same chemotherapy regimen at lower thresholds ($p < 0.01$). Education level was an important explanatory variable and the differences between patients and healthcare professionals disappeared when corrected for education level. Opinions about the maximum acceptable costs for chemotherapy displayed a large spread between the groups.
Conclusions: Minimal benefits to accept chemotherapy were not different between cancer and non-cancer patients, but are beyond what can generally can be achieved. Healthcare professionals were willing to accept chemotherapy for less benefit. This difference may be attributed to a difference in education level between the groups. Healthcare professionals rated the maximum acceptable societal cost for chemotherapy lower than patients.

Gepubliceerd: Neth J Med 2016 Aug;74(7):292-300
Impact factor: 1.489

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30. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial

von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin RM, Somi S, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JH, Hartmann M, Zocca P, Linssen GC, van der Palen J, Doggen CJ, Lowik MM

Background: In patients with coronary artery disease, treated with durable polymer-coated drug-eluting stents, the life-long presence of the polymer might delay arterial healing. Novel very thin strut biodegradable polymer stents, which leave only a bare metal stent after polymer resorption, might improve long-term outcome. We investigated in allcomers the safety and efficacy of three stents eluting either everolimus, sirolimus, or zotarolimus, often clinically used but never compared, of which the biodegradable polymer everolimus-eluting stent was never before assessed in allcomers.

Methods: The large-scale, investigator-initiated, multicentre, assessor and patient blinded, three-arm, randomised, BIO-RESORT non-inferiority trial was done at four clinical sites in the Netherlands. All-comer patients were aged 18 years or older, capable of providing informed consent, and required a percutaneous coronary intervention with drug-eluting stent implantation according to clinical guidelines or the operators' judgment. Exclusion criteria were: participation in another randomised drug or device study before reaching the primary endpoint of that study; planned surgery necessitating interruption of dual antiplatelet therapy within the first 6 months; known intolerance to components of the investigational product or medication required; uncertainty about the adherence to follow-up procedures or an assumed life expectancy of less than 1 year; or known pregnancy. Web-based computer-generated allocation sequences randomly assigned patients (1:1:1) to treatment with very thin strut biodegradable polymer everolimus-eluting or sirolimus-eluting stents (which differ substantially in type, amount, distribution, and resorption speed of their respective coating), or thin strut durable polymer zotarolimus-eluting stents. The primary endpoint was a composite of safety (cardiac death or target vessel-related myocardial infarction) and efficacy (target vessel revascularisation) at 12 months of follow up with a very thin strut biodegradable polymer of either everolimus-eluting or sirolimus-eluting stents, compared with durable polymer zotarolimus-eluting stents, analysed by intention to treat (non-inferiority margin 3.5%). This trial was registered with ClinicalTrials.gov, number NCT01674803.
Findings: From Dec 21, 2012, to Aug 24, 2015, 3514 patients were enrolled and analysed, of whom 2449 (70%) had acute coronary syndromes, which included 1073 (31%) ST-elevation myocardial infarctions. 12 month follow-up of 3490 (99%) patients (three lost to follow-up; 21 withdrawals) was available. The primary endpoint was met by 55 (5%) of 1172 patients assigned to everolimus-eluting stents, 55 (5%) of 1169 assigned to sirolimus-eluting stents and 63 (5%) of 1173 assigned to zotarolimus-eluting stents. Non-inferiority of the everolimus-eluting stents and sirolimus-eluting stents compared with zotarolimus-eluting stents was confirmed (both -0.7% absolute risk difference, 95% CI -2.4 to 1.1; upper limit of one sided 95% CI 0.8%, pnon-inferiority<0.0001). Definite stent thrombosis (defined by the Academic Research Consortium) occurred in four (0.3%) of 1172 patients who were allocated to everolimus-eluting stents, four (0.3%) of 1169 patients who were allocated to sirolimus-eluting stents, and three (0.3%) of 1173 patients who were allocated to zotarolimus-eluting stents (log-rank p=0.70 for both comparisons with zotarolimus-eluting stents).
Interpretation: At 12 month follow-up, both very thin strut drug-eluting stents with dissimilar biodegradable polymer coatings (eluting either everolimus or sirolimus) were non-inferior to the durable polymer stent (eluting zotarolimus) in treating allcomers with a high proportion of patients with acute coronary syndromes. The absence of a loss of 1 year safety and efficacy with the use of these two biodegradable polymer-coated stents is a prerequisite before assessing their potential longer-term benefits. FUNDING: Biotronik, Boston Scientific, and Medtronic.

Gepubliceerd: Lancet 2016 Oct 28;388(10060):2607-17
Impact factor: 44.002

31. The Effect of Unenhanced MRI on the Surgeons' Decision-Making Process in Females with Suspected Appendicitis
Ziedses des Plantes CM, van Veen MJ, van der Palen J, Klaase JM, Gielkens HA, Geelkerken RH

Background: This prospective study evaluated the impact of the results of unenhanced magnetic resonance imaging (MRI) on the surgeon's diagnosis of acute appendicitis in potentially fertile females.
Methods: 112 female patients, aged 12-55, with suspected appendicitis underwent MRI of the abdomen. At three defined intervals; admission and clinical re-evaluation before and after revealing the MRI results, the surgeon recorded the attendance of each patient in operative treatment, observation or discharge. Appendicitis was confirmed or declined by pathology or by telephone follow-up in case of non-intervention.
Findings: Appendicitis was confirmed in 29 of 112 patients. At admission the surgeon's disposition had a sensitivity of 97 % and specificity of 29 %. After knowing the MRI results, sensitivity was 97 % and specificity 64 %. The sensitivity and specificity of MRI alone were 89 and 100 %, with a negative and positive predictive value of 96 and 100 %, respectively.
Conclusion: We believe that MRI should perhaps be standard in all female patients during their reproductive years with suspected appendicitis. It avoids an operation in 32 % of cases and allows earlier planning for patients with an equivocal clinical picture. Trial number: OND1292733 (Narcis.nl).

Gepubliceerd:World J Surg 2016 Dec;40(12):2881-7
Impact factor: 2.532

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32. Stable State Proadrenomedullin Level in COPD Patients: A Validation Study
Zuur-Telgen M, van der Valk PD, van der Palen J, Kerstjens HA, Brusse-Keizer M

In patients with stable COPD, proadrenomedullin (MR-proADM) has been shown to be a good predictor for mortality. This study aims to provide an external validation of earlier observed cut-off values used by Zuur-Telgen et al. and Stolz.et al. in COPD patients in stable state and at hospitalization for an acute exacerbation of COPD (AECOPD). From the COMIC cohort study we included 545 COPD patients with a blood sample obtained in stable state (n = 490) and/or at hospitalization for an AECOPD (n = 101). Time to death was compared between patients with MR-proADM cut-off scores 0.71 and 0.75 nmol/L for stable state or 0.79 and 0.84 nmol/l for AECOPD. The predictive value of MR-proADM for survival was represented by the C statistic. Risk ratios were corrected for sex, age, BMI, presence of heart failure, and GOLD stage. Patients above the cut-off of 0.75 nmol/l had a 2-fold higher risk of dying than patient below this cut-off (95% CI: 1.20-3.41). The cut-off of 0.71 nmol/l showed only a borderline significantly higher risk of 1.67 (95% CI: 0.98-2.85). The corrected odds ratios for one-year mortality were 3.15 (95% CI 1.15-8.64) and 3.70 (95% CI 1.18-11.6) in patients with MR-proADM levels above versus below

the cut-off of respectively 0.75 and 0.71 nmol/l measured in stable state. MR-proADM levels in samples at hospitalization for an AECOPD were not predictive for mortality in this validation cohort. MR-proADM in stable state is a powerful predictor for mortality.

Gepubliceerd: COPD 2016 Nov 23;1-9
Impact factor: 2.160

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33. (Cost-)effectiveness of self-treatment of exacerbations in patients with COPD: 2 years follow-up of a RCT
Zwerink M, Kerstjens HA, van der Palen J, van der Valk PD, Brusse-Keizer M, Zielhuis G, Effing T

Background and Objective: Long-term effectiveness of action plans in patients with chronic obstructive pulmonary disease (COPD) is minimally investigated. We have evaluated the (cost-)effectiveness of a self-management programme with or without self-treatment of exacerbations after 2 years follow-up.
Methods: Self-management with or without self-treatment of exacerbations was randomly assigned to patients. All patients participated in four self-management meetings. Patients in the self-treatment group (STG) also learned to use an action plan to start a course of prednisolone and/or antibiotics in case of worsening of symptoms. Primary outcome was the duration and severity of exacerbations.
Results: Data of 70 COPD patients in the STG and 72 patients in the control group (CG) were analysed. Over 2 years, the median number of exacerbation days was significantly lower in the STG (50, IQR: 32-115) compared with the CG (82, IQR: 22-186) (P = 0.047), as was the mean symptom score of an exacerbation (STG: 43.4, IQR 27.2-68.6 vs CG: 55.9, IQR: 31.2-96.8) (P = 0.029). Also, patients in the STG visited the respiratory physician and emergency department less frequently than patients in the CG with incidence rate ratios of 1.52 (95% CI: 1.28-1.79) and 2.27 (95% CI: 1.11-4.62), respectively. Direct medical costs per patient over 2 years were euro1078 lower in the STG.
Conclusion: Self-treatment of exacerbations is beneficial in COPD patients without significant comorbidities because it reduces exacerbation duration, exacerbation severity and health-care utilization leading to considerable cost savings.

Gepubliceerd: Respirology 2016;21(3):497-503
Impact factor: 3.078

Totale impact factor: 135.023
Gemiddelde impact factor: 4.092

Aantal artikelen 1e, 2e of laatste auteur: 16
Totale impact factor: 41.973
Gemiddelde impact factor: 2.623

Mond- kaak- en aangezichtschirurgie

1. Multiple giant cell lesions in a patient with Noonan syndrome with multiple lentigines
van den Berg H, Schreuder WH, Jongmans M, van Bommel-Slee D, Witsenburg B, de Lange J

A patient with Noonan syndrome with multiple lentigines (NSML) and multiple giant cell lesions (MGCL) in mandibles and maxillae is described. A mutation p.Thr468Met in the PTPN11-gene was found. This is the second reported NSML patient with MGCL. Our case adds to the assumption that, despite a different molecular pathogenesis and effect on the RAS/MEK pathway, NSML shares the development of MGCL, with other RASopathies.

Gepubliceerd: Eur J Med Genet 2016 Aug;59(8):425-8
Impact factor: 1.810

Totale impact factor: 1.810
Gemiddelde impact factor: 1.810

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

Neurochirurgie

1. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation
Duarte RV, Andronis L, Lenders MW, de Vos CC

Purpose: This study aims to explore the changes in pain intensity and quality of life (QoL) experienced by patients with painful diabetic neuropathy (PDN) treated with spinal cord stimulation (SCS) and conventional medical practice (CMP).
Methods: Patient-reported pain intensity and QoL data were obtained from participants in an international multicentre randomised controlled trial comparing SCS versus CMP. Data were collected at randomisation and 6 month follow up by means of a visual analogue scale for pain intensity, the EuroQoL Visual Analogue Scale (EQ VAS) and the EuroQol EQ-5D index. Quality-adjusted life years (QALYs) were calculated for each treatment using the 'area under the curve' method. Differences in QALYs were calculated after adjusting for between-treatment imbalances in baseline QoL.
Results: At 6 months, patients allocated to SCS reported larger reductions in pain intensity and improvements in QoL measured by the EQ-5D utility score and EQ VAS as compared to those allocated to CMP. Initial calculations of QALYs for the SCS and CMP groups suggested no statistical differences between the groups. Adjusting for imbalances in baseline EQ-5D scores showed SCS to be associated with significantly higher QALYs compared to CMP.
Conclusions: SCS resulted in significant improvement in pain intensity and QoL in patients with PDN, offering further support for SCS as an effective treatment for patients suffering from PDN. From a methodological point of view, different results would have been obtained if QALY calculations were not adjusted for baseline EQ-5D scores, highlighting the need to account for imbalances in baseline QoL.

Gepubliceerd: Qual Life Res 2016 Jul;25(7):1771-7
Impact factor: 2.486

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2. Intermanual transfer in an artist with Parkinson's disease
Kho KH, Janssen N

A professional right-handed painter with Parkinson's disease (PD) broke his right arm and continued to paint with his left hand, showing an intact intermanual transfer of skills. This neurocognitive process is related to the supplementary motor area, a brain region that has also been shown to be involved in PD. This observation raises questions about the exact neural underpinnings of intermanual transfer and the possible impact of neurodegenerative disease and medication.

Gepubliceerd: Neurocase 2016;22(1):119-21
Impact factor: 1.225

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3. Early Complete Remitters After Electroconvulsive Therapy: Profile and Prognosis
Spaans HP, Verwijk E, Stek ML, Kho KH, Bouckaert F, Kok RM, Sienaert P

Objective: To investigate the prevalence, characteristics, and prognosis of depressive patients who show early complete remission after right unilateral (ultra)brief pulse electroconvulsive therapy (ECT).
Methods: Early complete remitters (ECRs) were those patients who were rated 1 on the Clinical Global Impression Scale (maximum score, 7) within 4 ECT sessions and achieved remission (Montgomery Asberg Depression Rating Scale score, <10). The ECRs were compared with late complete remitters (LCRs), which fulfilled the same criteria after 9 to 12 ECT sessions and with the nonremitters/nonresponders (NRs).
Results: Of the 87 patients who completed the index treatment phase, 50 (57.5%) achieved remission. Of these remitters, 12 (14%) were ECRs and 9 (10%) were LCRs. The ECRs were characterized by a higher mean age (71.0 vs 53.9 years; P = 0.008), a shorter current depressive episode (mean, 5.8 vs 15.4 months; P = 0.042), and more psychotic features (75% vs 22%; P = 0.030) and were treated more often with brief pulse ECT (P = 0.030) compared with the LCRs. Although not significant, cognitive performances of ECRs were lower than that of LCRs at baseline with a large effect size: Autobiographical Memory Interview (P = 0.099; d = 0.83), Amsterdam Media Questionnaire (P = 0.114; d = 0.84), and Letter fluency (P = 0.071; d = 0.95). The ECR group had a lower relapse rate during 6 months' follow-up: 10% (1 of 10) versus 62.5% (5 of 8) (P = 0.043). No significant differences in demographic and clinical characteristics were found between LCRs (n = 9) and NRs (n = 27).
Conclusions: Older patients with a psychotic depression and a profile of cognitive slowing have a high chance of achieving complete remission within 4 ECT sessions, with a favorable 6-month prognosis.

Gepubliceerd: J ECT 2016 Jun;32(2):82-7
Impact factor: 1.833

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4. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation
Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MW

Objective: Spinal cord stimulation (SCS) is used for treating intractable neuropathic pain. It has been suggested that burst SCS (five pulses at 500 Hz, delivered 40 times per second) suppresses neuropathic pain at least as well as conventional tonic SCS, but without evoking paraesthesia. The efficacy of paraesthesia-free high and low amplitude burst SCS for the treatment of neuropathic pain in patients who are already familiar with tonic SCS was evaluated. MATERIALS AND
Methods: Forty patients receiving conventional (30-120 Hz) tonic SCS for at least six months were included. All patients received high and low amplitude burst SCS, for a two-week period in a double blind randomized crossover design, with a two-week period of tonic stimulation in between. The average visual analogue scale

(VAS) scores for pain during the last three days of each stimulation period were evaluated as well as quality of life (QoL) scores, and patient's preferences.
Results: Average VAS score for pain were lower during high (40, p = 0.013) and low amplitude burst stimulation (42, p = 0.053) compared with tonic stimulation (52). QoL scores did not differ significantly. At the individual level 58% of the patients experienced significant additional pain reduction (>30% decrease in VAS for pain) during high and/or low amplitude burst stimulation. Eleven patients preferred tonic stimulation, fifteen high, and fourteen low amplitude burst stimulation.
Conclusion: Burst stimulation is in general more effective than tonic stimulation. Individual patients can highly benefit from burst stimulation; however, the therapeutic range of burst stimulation amplitudes requires individual assessment.

Gepubliceerd: Neuromodulation 2016 Jul;19(5):492-7
Impact factor: 2.409

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5. How Many Patients would Benefit from Steering Technology for Deep Brain Stimulation?
Contarino MF, Brinke TR, Mosch A, Lelieveld W, Postma M, Odekerken VJ, Steendam-Oldekamp TE, Van Laar T, Kuijf ML, Tjepkema-Cloostermans MC, Schuurman PR

Gepubliceerd: Brain Stimul 2016 Jan;9(1):144-5
Impact factor: 4.793

Totale impact factor: 12.692
Gemiddelde impact factor: 2.538

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 6.120
Gemiddelde impact factor: 2.040

Neurologie

1. Asymmetries in reactive and anticipatory balance control are of similar magnitude in Parkinson's disease patients
Boonstra TA, van Kordelaar J, Engelhart D, van Vugt JP, van der Kooij H

Many Parkinson's disease (PD) patients show asymmetries in balance control during quiet stance and in response to perturbations (i.e., reactive balance control) in the sagittal plane. In addition, PD patients show a reduced ability to anticipate to self-induced disturbances, but it is not clear whether these anticipatory responses can be asymmetric too. Furthermore, it is not known how reactive balance control and anticipatory balance control are related in PD patients. Therefore, we investigated whether reactive and anticipatory balance control are asymmetric to the same extent in PD patients. 14 PD patients and 10 controls participated. Reactive balance control (RBC) was investigated by applying external platform and force perturbations and relating the response of the left and right ankle torque to the body sway angle at the excited frequencies. Anticipatory postural adjustments (APAs) were investigated by determining the increase in the left and right ankle torque just before the subjects released a force exerted with the hands against a force sensor. The symmetry ratio between the contribution of the left and right ankle was used to express the asymmetry in reactive and anticipatory balance control; the correlation between the two ratio's was investigated with Spearman's rank correlation coefficients. PD patients were more asymmetric in anticipatory (p=0.026) and reactive balance control (p=0.004) compared to controls and the symmetry ratios were significantly related (rho=0.74; p=0.003) in PD patients. These findings suggest that asymmetric reactive balance control during bipedal stance may share a common pathophysiology with asymmetries in the anticipation of voluntary perturbations during, for instance, gait initiation.

Gepubliceerd: Gait Posture 2016 Jan;43:108-13
Impact factor: 2.286

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2. Clinical Practice Variation Needs to be Considered in Cost-Effectiveness Analyses: A Case Study of Patients with a Recent Transient Ischemic Attack or Minor Ischemic Stroke
Buisman LR, Rijnsburger AJ, den Hertog HM, van der Lugt A, Redekop WK

Background and Objective: The cost-effectiveness of clinical interventions is often assessed using current care as the comparator, with national guidelines as a proxy. However, this comparison is inadequate when clinical practice differs from guidelines, or when clinical practice differs between hospitals. We examined the degree of variation in the way patients with a recent transient ischemic attack (TIA) or minor ischemic stroke are assessed and used the results to illustrate the importance of investigating possible clinical practice variation, and the need to perform hospital-level cost-effectiveness analyses (CEAs) when variation exists.

Methods: Semi-structured interviews were conducted with 16 vascular neurologists in hospitals throughout the Netherlands. Questions were asked about the use of initial and confirmatory diagnostic imaging tests to assess carotid stenosis in patients with a recent TIA or minor ischemic stroke, criteria to perform confirmatory tests, and criteria for treatment. We also performed hospital-level CEAs to illustrate the consequences of the observed diagnostic strategies in which the diagnostic test costs, sensitivity and specified were varied according to the local hospital conditions.
Results: 56 % (9/16) of the emergency units and 63 % (10/16) of the outpatient clinics use the initial and confirmatory diagnostic tests to assess carotid stenosis in accordance with the national guidelines. Of the hospitals studied, only one uses the recommended criteria for use of a confirmatory test, 38 % (6/16) follow the guidelines for treatment. The most cost-effective diagnostic test strategy differs between hospitals.
Conclusions: If important practice variation exists, hospital-level CEAs should be performed. These CEAs should include an assessment of the feasibility and costs of switching to a different strategy.

Gepubliceerd: Appl Health Econ Health Policy 2016;14(1):67-75
Impact factor: 0

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3. Single and paired pulse transcranial magnetic stimulation in drug naive epilepsy
de Goede AA, Ter Braack EM, van Putten MJ

Transcranial magnetic stimulation (TMS) measures cortical excitability and is therefore potentially suitable as an additional tool for epilepsy diagnostics and therapy evaluation. In this review we discuss the application of TMS in epilepsy research and systematically analyze single and paired pulse TMS outcomes from 31 drug naive patient studies. Despite a large variety in used TMS protocols, there was no relation between specific protocol aspects and the occurrence of significant results. Protocols were often not in accordance with latest guidelines and recommendations. Cortical excitability, as measured by TMS, was increased in drug naive epilepsy patients, being most prominent for generalized epilepsy. Single pulse TMS indicated a trend towards a lower resting motor threshold (rMT) and a prolonged cortical silent period (CSP) for generalized epilepsy, while inconclusive results were found for focal epilepsy. The paired pulse TMS outcomes, short intracortical inhibition (SICI) and long intracortical inhibition (LICI), showed the most consistent significant increase in cortical excitability in generalized and focal epilepsy patients. Future epilepsy research should especially focus on the interstimulus intervals 2 and 5ms for SICI, and 250 and 300ms for LICI. Furthermore, combining TMS with electroencephalography (EEG) may contribute to analysis on an individual patient level.

Gepubliceerd: Clin Neurophysiol 2016 Sep;127(9):3140-55
Impact factor: 3.426

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4. Non-Hospitalized Patients with Mild Traumatic Brain Injury: The Forgotten Minority
de Koning ME, Scheenen ME, van der Horn HJ, Hageman G, Roks G, Spikman JM, van der Naalt J

Non-hospitalized mild traumatic brain injury (mTBI) patients comprise a substantial part of the trauma population. For these patients, guidelines recommend specialized follow-up only in the case of persistent complaints or problems in returning to previous activities. This study describes injury and outcome characteristics of non-hospitalized mTBI patients, and the possibility of predicting which of the non-hospitalized patients will return to the outpatient neurology clinic. Data from all non-hospitalized mTBI patients (Glasgow Coma Scale [GCS] score 13-15, n = 462) from a prospective follow-up study on mTBI (UPFRONT-study) conducted in three level 1 trauma centers were analyzed. At 2 weeks, and 3 and 6 months after injury, patients completed questionnaires on post-traumatic complaints, depression, anxiety, outpatient follow-up, and resumption of activities. Most patients were male (57%), with a mean age of 40 years (range 16-91 years). Injuries were most often caused by traffic accidents (32%) or falls (39%). Six months after injury, 36% showed incomplete recovery as defined by the Glasgow Outcome Scale - Extended (GOS-E). Twenty-five percent of the non-hospitalized patients returned to the outpatient neurology clinic within 6 months after injury, of which one third had not completely resumed pre-injury activities. Regression analyses showed an increased risk for outpatient follow-up for patients scoring above the cutoff value for anxiety (odds ratio [OR] = 3.0), depression (OR = 3.5), or both (OR = 3.7) 2 weeks after injury. Our findings underline that clinicians and researchers should be aware of recovery for all mTBI patients, preventing their transition into a forgotten minority.

Gepubliceerd: J Neurotrauma 2017 Jan 1;34(1):257-61
Impact factor: 4.377

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5. A Biophysical Model for Cytotoxic Cell Swelling
Dijkstra K, Hofmeijer J, van Gils SA, van Putten MJ

We present a dynamic biophysical model to explain neuronal swelling underlying cytotoxic edema in conditions of low energy supply, as observed in cerebral ischemia. Our model contains Hodgkin-Huxley-type ion currents, a recently discovered voltage-gated chloride flux through the ion exchanger SLC26A11, active KCC2-mediated chloride extrusion, and ATP-dependent pumps. The model predicts changes in ion gradients and cell swelling during ischemia of various severity or channel blockage with realistic timescales. We theoretically substantiate experimental observations of chloride influx generating cytotoxic edema, while sodium entry alone does not. We show a tipping point of Na+/K+-ATPase functioning, where below cell volume rapidly increases as a function of the remaining pump activity, and a Gibbs-Donnan-like equilibrium state is reached. This precludes a return to physiological conditions even when pump strength returns to baseline. However, when voltage-gated sodium channels are temporarily blocked, cell volume and membrane potential normalize, yielding a potential therapeutic

strategy. SIGNIFICANCE STATEMENT: Cytotoxic edema most commonly results from energy shortage, such as in cerebral ischemia, and refers to the swelling of brain cells due to the entry of water from the extracellular space. We show that the principle of electroneutrality explains why chloride influx is essential for the development of cytotoxic edema. With the help of a biophysical model of a single neuron, we show that a tipping point of the energy supply exists, below which the cell volume rapidly increases. We simulate realistic time courses to and reveal critical components of neuronal swelling in conditions of low energy supply. Furthermore, we show that, after transient blockade of the energy supply, cytotoxic edema may be reversed by temporary blockade of Na+ channels.

Gepubliceerd: J Neurosci 2016 Nov 23;36(47):11881-90
Impact factor: 5.924

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6. Prehospital paths and hospital arrival time of patients with acute coronary syndrome or stroke, a prospective observational study
Doggen CJ, Zwerink M, Droste HM, Brouwers PJ, van Houwelingen GK, van Eenennaam FL, Egberink RE

Background: Patients with a presumed diagnosis of acute coronary syndrome (ACS) or stroke may have had contact with several healthcare providers prior to hospital arrival. The aim of this study was to describe the various prehospital paths and the effect on time delays of patients with ACS or stroke.
Methods: This prospective observational study included patients with presumed ACS or stroke who may choose to contact four different types of health care providers. Questionnaires were completed by patients, general practitioners (GP), GP cooperatives, ambulance services and emergency departments (ED). Additional data were retrieved from hospital registries.
Results: Two hundred two ACS patients arrived at the hospital by 15 different paths and 243 stroke patients by ten different paths. Often several healthcare providers were involved (60.8 % ACS, 95.1 % stroke). Almost half of all patients first contacted their GP (47.5 % ACS, 49.4 % stroke). Some prehospital paths were more frequently used, e.g. GP (cooperative) and ambulance in ACS, and GP or ambulance and ED in stroke. In 65 % of all events an ambulance was involved. Median time between start of symptoms and hospital arrival for ACS patients was over 6 h and for stroke patients 4 h. Of ACS patients 47.7 % waited more than 4 h before seeking medical advice compared to 31.6 % of stroke patients. Median time between seeking medical advice to arrival at hospital was shortest in paths involving the ambulance only (60 min ACS, 54 min stroke) or in combination with another healthcare provider (80 to 100 min ACS, 99 to 106 min stroke).
Conclusions: Prehospital paths through which patients arrived in hospital are numerous and often complex, and various time delays occurred. Delays depend on the entry point of the health care system, and dialing the emergency number seems to be the best choice. Since reducing patient delay is difficult and noticeable differences exist between various prehospital paths, further research into reasons for these different entry choices may yield possibilities to optimize paths and reduce overall time delay.

Gepubliceerd:BMC Emerg Med 2016 Jan 9;16:3
Impact factor: 0

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7. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation
Duarte RV, Andronis L, Lenders MW, de Vos CC

Purpose: This study aims to explore the changes in pain intensity and quality of life (QoL) experienced by patients with painful diabetic neuropathy (PDN) treated with spinal cord stimulation (SCS) and conventional medical practice (CMP).
Methods: Patient-reported pain intensity and QoL data were obtained from participants in an international multicentre randomised controlled trial comparing SCS versus CMP. Data were collected at randomisation and 6 month follow up by means of a visual analogue scale for pain intensity, the EuroQoL Visual Analogue Scale (EQ VAS) and the EuroQol EQ-5D index. Quality-adjusted life years (QALYs) were calculated for each treatment using the 'area under the curve' method. Differences in QALYs were calculated after adjusting for between-treatment imbalances in baseline QoL.
Results: At 6 months, patients allocated to SCS reported larger reductions in pain intensity and improvements in QoL measured by the EQ-5D utility score and EQ VAS as compared to those allocated to CMP. Initial calculations of QALYs for the SCS and CMP groups suggested no statistical differences between the groups. Adjusting for imbalances in baseline EQ-5D scores showed SCS to be associated with significantly higher QALYs compared to CMP.
Conclusions: SCS resulted in significant improvement in pain intensity and QoL in patients with PDN, offering further support for SCS as an effective treatment for patients suffering from PDN. From a methodological point of view, different results would have been obtained if QALY calculations were not adjusted for baseline EQ-5D scores, highlighting the need to account for imbalances in baseline QoL.

Gepubliceerd: Qual Life Res 2016 Jul;25(7):1771-7
Impact factor: 2.486

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8. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial
Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama ANG, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de VJ, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW

Importance: Intra-arterial treatment (IAT) for acute ischemic stroke caused by intracranial arterial occlusion leads to improved functional outcome in patients treated within 6 hours after onset. The influence of treatment delay on treatment effect is not yet known.
Objective: To evaluate the influence of time from stroke onset to the start of treatment and from stroke onset to reperfusion on the effect of IAT.
Design, setting, and participants: The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) was a multicenter, randomized clinical open-label trial of IAT vs no IAT in 500 patients. The time to the start of treatment was defined as the time from onset of symptoms to groin puncture (TOG). The time from onset of treatment to reperfusion (TOR) was defined as the time to reopening the vessel occlusion or the end of the procedure in cases for which reperfusion was not achieved. Data were collected from December 3, 2010, to June 3, 2014, and analyzed (intention to treat) from July 1, 2014, to September 19, 2015.
Main outcomes and measures: Main outcome was the modified Rankin Scale (mRS) score for functional outcome (range, 0 [no symptoms] to 6 [death]). Multiple ordinal logistic regression analysis estimated the effect of treatment and tested for the interaction of time to randomization, TOG, and TOR with treatment. The effect of treatment as a risk difference on reaching independence (mRS score, 0-2) was computed as a function of TOG and TOR. Calculations were adjusted for age, National Institutes of Health Stroke Scale score, previous stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion.
Results: Among 500 patients (58% male; median age, 67 years), the median TOG was 260 (interquartile range [IQR], 210-311) minutes; median TOR, 340 (IQR, 274-395) minutes. An interaction between TOR and treatment (P = .04) existed, but not between TOG and treatment (P = .26). The adjusted risk difference (95% CI) was 25.9% (8.3%-44.4%) when reperfusion was reached at 3 hours, 18.8% (6.6%-32.6%) at 4 hours, and 6.7% (0.4%-14.5%) at 6 hours.
Conclusion and relevance: For every hour of reperfusion delay, the initially large benefit of IAT decreases; the absolute risk difference for a good outcome is reduced by 6% per hour of delay. Patients with acute ischemic stroke require immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.
Trial registration: trialregister.nl Identifier: NTR1804.

Gepubliceerd: JAMA Neurol 2016 Feb;73(2):190-6
Impact factor: 8.230

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9. Quantification of EEG reactivity in comatose patients
Hermans MC, Westover MB, van Putten MJ, Hirsch LJ, Gaspard N

Objective: EEG reactivity is an important predictor of outcome in comatose patients. However, visual analysis of reactivity is prone to subjectivity and may benefit from quantitative approaches.
Methods: In EEG segments recorded during reactivity testing in 59 comatose patients, 13 quantitative EEG parameters were used to compare the spectral

characteristics of 1-minute segments before and after the onset of stimulation (spectral temporal symmetry). Reactivity was quantified with probability values estimated using combinations of these parameters. The accuracy of probability values as a reactivity classifier was evaluated against the consensus assessment of three expert clinical electroencephalographers using visual analysis.
Results: The binary classifier assessing spectral temporal symmetry in four frequency bands (delta, theta, alpha and beta) showed best accuracy (Median AUC: 0.95) and was accompanied by substantial agreement with the individual opinion of experts (Gwet's AC1: 65-70%), at least as good as inter-expert agreement (AC1: 55%). Probability values also reflected the degree of reactivity, as measured by the inter-experts' agreement regarding reactivity for each individual case.
Conclusion: Automated quantitative EEG approaches based on probabilistic description of spectral temporal symmetry reliably quantify EEG reactivity.
SIGNIFICANCE: Quantitative EEG may be useful for evaluating reactivity in comatose patients, offering increased objectivity.

Gepubliceerd:Clin Neurophysiol 2016;127(1):571-80
Impact factor: 3.426

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10. Author Response
Hofmeijer J, van Putten MJ

Gepubliceerd: Neurology 2016 Jan 5;86(1):108-9
Impact factor: 8.166

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11. EEG in postanoxic coma: Prognostic and diagnostic value
Hofmeijer J, van Putten MJ

Evolution of the EEG background pattern is a robust contributor to prediction of poor or good outcome of comatose patients after cardiac arrest. At 24h, persistent isoelectricity, low voltage activity, or burst-suppression with identical bursts predicts a poor outcome without false positives. Rapid recovery toward continuous patterns within 12h is strongly associated with a good neurological outcome. Predictive values are highest in the first 24h, despite the use of mild therapeutic hypothermia and sedative medication. Studies on reactivity or mismatch negativity have not included the EEG background pattern. Therefore, the additional predictive value of reactivity parameters remains unclear. Whether or not treatment of electrographic status epilepticus improves outcome is studied in the randomized multicenter Treatment of Electroencephalographic STatus epilepticus After cardiopulmonary Resuscitation (TELSTAR) trial (NCT02056236).

Gepubliceerd: Clin Neurophysiol 2016 Apr;127(4):2047-55
Impact factor: 3.426

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12. Progression of Neuronal Damage in an In Vitro Model of the Ischemic Penumbra
Le Feber J, Tzafi Pavlidou S, Erkamp N, van Putten MJ, Hofmeijer J

Improvement of neuronal recovery in the ischemic penumbra around a brain infarct has a large potential to advance clinical recovery of patients with acute ischemic stroke. However, pathophysiological mechanisms leading to either recovery or secondary damage in the penumbra are not completely understood. We studied neuronal dynamics in a model system of the penumbra consisting of networks of cultured cortical neurons exposed to controlled levels and durations of hypoxia. Short periods of hypoxia (pO2 approximately 20mmHg) reduced spontaneous activity, due to impeded synaptic function. After approximately 6 hours, activity and connectivity partially recovered, even during continuing hypoxia. If the oxygen supply was restored within 12 hours, changes in network connectivity were completely reversible. For longer periods of hypoxia (12-30 h), activity levels initially increased, but eventually decreased and connectivity changes became partially irreversible. After approximately 30 hours, all functional connections disappeared and no activity remained. Since this complete silence seemed unrelated to hypoxic depths, but always followed an extended period of low activity, we speculate that irreversible damage (at least partly) results from insufficient neuronal activation. This opens avenues for therapies to improve recovery by neuronal activation.

Gepubliceerd: PLoS One 2016;11(2):e0147231
Impact factor: 3.540

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13. Long-term depressive symptoms and anxiety after transient ischaemic attack or ischaemic stroke in young adults
Maaijwee NA, Tendolkar I, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Dorresteijn LD, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE

Background and purpose: Few studies exist on long-term post-stroke depressive symptoms and anxiety in young adults, although these young patients have a particular interest in their long-term prognosis, given their usually long life expectancy and being in the midst of an active social, working and family life. The aims of this study were to investigate the prevalence of depressive symptoms and anxiety and their association with clinical and demographic variables and with functional outcome after stroke in young adults.
Methods and Results: Long-term prevalence of depressive symptoms and anxiety was calculated in 511 patients with a transient ischaemic attack or ischaemic stroke, aged 18-50 years, using the Hospital Anxiety and Depression scale, compared with 147 controls. Functional outcome was assessed with the modified Rankin Score (mRS) and the Instrumental Activities of Daily Living scale (IADL). 16.8% of patients had depressive symptoms and 23.0% had anxiety, versus 6.1% (P = 0.001) and 12.2% (P < 0.001) in controls. In ischaemic stroke patients, depressive symptoms and anxiety were associated with poor functional outcome (mRS > 2 or IADL < 8).
Conclusion: Even a decade after stroke at young age, depressive symptoms and anxiety were prevalent and associated with poor functional outcome. Therefore,

even in the long term, treating physicians should be aware of the long-term presence of these symptoms as their recognition may be the first step in improving long-term functional independence.

Gepubliceerd: Eur J Neurol 2016 Aug;23(8):1262-8
Impact factor: 3.956

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14. Single Pulse Electrical Stimulation to identify epileptogenic cortex: Clinical information obtained from early evoked responses
Mouthaan BE, van 't Klooster MA, Keizer D, Hebbink GJ, Leijten FS, Ferrier CH, van Putten MJ, Zijlmans M, Huiskamp GJ

Objective: Single Pulse Electrical Stimulation (SPES) probes epileptogenic cortex during electrocorticography. Two SPES responses are described: pathological delayed responses (DR, >100ms) associated with the seizure onset zone (SOZ) and physiological early responses (ER, <100ms) that map cortical connectivity. We analyzed properties of ERs, including frequencies >80Hz, in the SOZ and seizure propagation areas.
Methods: We used data from 12 refractory epilepsy patients. SPES consisted of 10 pulses of 1ms, 4-8mA and 5s interval on adjacent electrodes pairs. Data were available at 2048samples/s for six and 512samples/s (22 bits) for eight patients and analyzed in the time-frequency (TF) and time-domain (TD).
Results: Electrodes with ERs were stronger associated with SOZ than non-SOZ electrodes. ERs with frequency content >80Hz exist and are specific for SOZ channels. ERs evoked by stimulation of seizure onset electrodes were associated with electrodes involved in seizure propagation.
Conclusion: Analysis of ERs can reveal aspects of pathology, manifested by association with seizure propagation and areas with high ER numbers that coincide with the SOZ. SIGNIFICANCE: Not only DRs, but also ERs could have clinical value for mapping epileptogenic cortex and help to unravel aspects of the epileptic network.

Gepubliceerd: Clin Neurophysiol 2016;127(2):1088-98
Impact factor: 3.426

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15. Glucose in prediabetic and diabetic range and outcome after stroke
Osei E, Fonville S, Zandbergen AA, Koudstaal PJ, Dippel DW, den Hertog HM

Objectives: Newly diagnosed disturbed glucose metabolism is highly prevalent in patients with stroke. Limited data are available on their prognostic value on outcome after stroke. We aimed to assess the association of glucose in the prediabetic and diabetic range with unfavourable short-term outcome after stroke. MATERIALS AND **Methods:** We included 839 consecutive patients with ischemic stroke and 168 patients with intracerebral haemorrhage. In all nondiabetic patients, fasting glucose levels were determined on day 2-4. Prediabetic range was defined as fasting glucose of 5.6-6.9 mmol/L, diabetic range as >/=7.0 mmol/L, pre-existent diabetes

as the use of anti-diabetic medication prior to admission. Outcome measures were poor functional outcome or death defined as modified Rankin Scale (mRS) score >2 and discharge not to home. The association of prediabetic range, diabetic range and pre-existent diabetes (versus normal glucose) with unfavourable outcome was expressed as odds ratios, estimated with multiple logistic regression, with adjustment for prognostic factors.
Results: Compared with normal glucose, prediabetic range (aOR 1.8; 95%CI 1.1-2.8), diabetic range (aOR 2.5; 95%CI 1.3-4.9) and pre-existent diabetes (aOR 2.6; 95%CI 1.6-4.0) were associated with poor functional outcome or death. Patients in the prediabetic range (aOR 0.6; 95%CI 0.4-0.9), diabetic range (aOR 0.4; 95%CI 0.2-0.9) and pre-existent diabetes (aOR 0.6; 95%CI 0.4-0.9) were more likely not to be discharged to home.
Conclusions: Patients with glucose in the prediabetic and diabetic range have an increased risk of unfavourable short-term outcome after stroke. These findings illustrate the potential impact of early detection and treatment of these patients.

Gepubliceerd: Acta Neurol Scand 2017 Feb;135(2):170-5
Impact factor: 2.559

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16. Increased admission and fasting glucose are associated with unfavorable short-term outcome after intra-arterial treatment of ischemic stroke in the MR CLEAN pretrial cohort
Osei E, den Hertog HM, Berkhemer OA, Fransen PS, Roos YB, Beumer D, van Oostenbrugge RJ, Schonewille WJ, Boiten J, Zandbergen AA, Koudstaal PJ, Dippel DW

Background: Limited data are available on the impact of fasting glucose on outcome after intra-arterial treatment (IAT). We studied whether hyperglycemia on admission and impaired fasting glucose (IFG) are associated with unfavorable outcome after IAT in acute ischemic stroke.
Methods: Patients were derived from the pretrial registry of the MR CLEAN-trial. Hyperglycemia on admission was defined as glucose>7.8mmol/L, IFG as fasting glucose>5.5mmol/L in the first week of admission. 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 discharge, estimated with ordinal logistic regression, adjusted for common prognostic factors.
Results: Of the 335 patients in which glucose on admission was available, 86 (26%) were hyperglycemic, 148 of the 240 patients with available fasting glucose levels (62%) had IFG. Median admission glucose was 6.8mmol/L (IQR 6-8). Increased admission glucose (acOR 1.2, 95%CI 1.1-1.3), hyperglycemia on admission (acOR 2.6, 95%CI 1.5-4.6) and IFG (acOR 2.8, 95%CI 1.4-5.6) were associated with worse functional outcome at discharge.
Conclusion: Increased glucose on admission and IFG in the first week after stroke onset are associated with unfavorable short-term outcome after IAT of acute ischemic stroke.

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Impact factor: 2.126

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17. Nonfocal Symptoms in Patients with Transient Ischemic Attack or Ischemic Stroke: Occurrence, Clinical Determinants, and Association with Cardiac History
Plas GJ, Booij HA, Brouwers PJ, Brusse-Keizer M, Koudstaal PJ, Dippel DW, den Hertog HM

Background: Transient ischemic attacks (TIAs) accompanied by nonfocal symptoms are associated with a higher risk of cardiovascular events, in particular cardiac events. Reported frequencies of TIAs accompanied by nonfocal symptoms range from 18 to 53%. We assessed the occurrence of nonfocal symptoms in patients with TIA or minor ischemic stroke in a neurological outpatient clinic in terms of clinical determinants, cardiac history, and atrial fibrillation (AF).
Methods: We included 1,265 consecutive patients with TIA or minor stroke who visited the outpatient clinic. During these visits, we systematically asked for nonfocal symptoms. Nonfocal symptoms included decreased consciousness, amnesia, positive visual phenomena, non-rotatory dizziness, and paresthesias. Relative risks for the presence of nonfocal symptoms in relation to clinical determinants, AF, and cardiac history were calculated.
Results: In 243 (19%) of 1,265 patients, TIA or minor ischemic stroke was accompanied by one or more nonfocal symptoms. Non-rotatory dizziness, paresthesia, and amnesia were the most common nonfocal symptoms. In patients with an event of the posterior circulation or obesity, the qualifying TIA or minor stroke was more frequently accompanied by nonfocal symptoms, and in patients with significant carotid stenosis, nonfocal symptoms occurred less frequently. AF was related only with amnesia.
Conclusion: Nonfocal symptoms are present in one out of 5 patients with TIA or ischemic stroke, in particular when located in the posterior circulation. A cardiac history or AF was not directly related to nonfocal symptoms. A heterogeneous etiology is suggested.

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Impact factor: 3.359

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18. Cognitive impairment and associated loss in brain white microstructure in aircrew members exposed to engine oil fumes
Reneman L, Schagen SB, Mulder M, Mutsaerts HJ, Hageman G, de Ruiter MB

Cabin air in airplanes can be contaminated with engine oil contaminants. These contaminations may contain organophosphates (OPs) which are known neurotoxins to brain white matter. However, it is currently unknown if brain white matter in aircrew is affected. We investigated whether we could objectify cognitive complaints in aircrew and whether we could find a neurobiological substrate for their complaints. After medical ethical approval from the local institutional review board, informed consent was obtained from 12 aircrew (2 females, on average aged 44.4 years,

8,130 flying hours) with cognitive complaints and 11 well matched control subjects (2 females, 43.4 years, 233 flying hours). Depressive symptoms and self-reported cognitive symptoms were assessed, in addition to a neuropsychological test battery. State of the art Magnetic Resonance Imaging (MRI) techniques were administered that assess structural and functional changes, with a focus on white matter integrity. In aircrew we found significantly more self-reported cognitive complaints and depressive symptoms, and a higher number of tests scored in the impaired range compared to the control group. We observed small clusters in the brain in which white matter microstructure was affected. Also, we observed higher cerebral perfusion values in the left occipital cortex, and reduced brain activation on a functional MRI executive function task. The extent of cognitive impairment was strongly associated with white matter integrity, but extent of estimated number of flight hours was not associated with cognitive impairment nor with reductions in white matter microstructure. Defects in brain white matter microstructure and cerebral perfusion are potential neurobiological substrates for cognitive impairments and mood deficits reported in aircrew.

Gepubliceerd: Brain Imaging Behav 2016 Jun;10(2):437-44
Impact factor: 3.667

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19. Continuous EEG Monitoring for Early Detection of Delayed Cerebral Ischemia in Subarachnoid Hemorrhage: A Pilot Study
Rots ML, van Putten MJ, Hoedemaekers CW, Horn J

Intoduction: Early identification of delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (aSAH) is a major challenge. The aim of this study was to investigate whether quantitative EEG (qEEG) features can detect DCI prior to clinical or radiographic findings.
Methods: A prospective cohort study was performed in aSAH patients in whom continuous EEG (cEEG) was recorded. We studied 12 qEEG features. We compared the time point at which qEEG changed with the time point that clinical deterioration occurred or new ischemia was noted on CT scan.
Results: Twenty aSAH patients were included of whom 11 developed DCI. The alpha/delta ratio (ADR) was the most promising feature that showed a significant difference in change over time in the DCI group (median -62 % with IQR -87 to -39 %) compared to the control group (median +27 % with IQR -32 to +104 %, p = 0.013). Based on the ROC curve, a threshold was chosen for a combined measure of ADR and alpha variability (AUC: 91.7, 95 % CI 74.2-100). The median time that elapsed between change of qEEG and clinical DCI diagnosis was seven hours (IQR -11-25). Delay between qEEG and CT scan changes was 44 h (median, IQR 14-117).
Conclusion: In this study, ADR and alpha variability could detect DCI development before ischemic changes on CT scan was apparent and before clinical deterioration was noted. Implementation of cEEG in aSAH patients can probably improve early detection of DCI.

Gepubliceerd: Neurocrit Care 2016;24(2):207-16

Impact factor: 2.488

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20. Remote Lower White Matter Integrity Increases the Risk of Long-Term Cognitive Impairment After Ischemic Stroke in Young Adults
Schaapsmeerders P, Tuladhar AM, Arntz RM, Franssen S, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, Kessels RP, de Leeuw FE

Background and purpose: Poststroke cognitive impairment occurs frequently in young patients with ischemic stroke (18 through 50 years of age). Accumulating data suggest that stroke is associated with lower white matter integrity remote from the stroke impact area, which might explain why some patients have good long-term cognitive outcome and others do not. Given the life expectancy of decades in young patients, we therefore investigated remote white matter in relation to long-term cognitive function.
Methods: We included all consecutive first-ever ischemic stroke patients, left/right hemisphere, without recurrent stroke or transient ischemic attack during follow-up, aged 18 through 50 years, admitted to our university medical center between 1980 and 2010. One hundred seventeen patients underwent magnetic resonance imaging scanning including a T1-weighted scan, a diffusion tensor imaging scan, and completed a neuropsychological assessment. Patients were compared with a matched stroke-free control group (age, sex, and education matched). Cognitive impairment was defined as >1.5 SD below the mean cognitive index score of controls and no cognitive impairment as </=1 SD. Tract-Based Spatial Statistics was used to assess the white matter integrity (fractional anisotropy and mean diffusivity).
Results: About 11 years after ischemic stroke, lower remote white matter integrity was associated with a worse long-term cognitive performance. A lower remote white matter integrity, even in the contralesional hemisphere, was observed in cognitively impaired patients (n=25) compared with cognitively unimpaired patients (n=71).
Conclusions: These findings indicate that although stroke has an acute onset, it might have long lasting effects on remote white matter integrity and thereby increases the risk of long-term cognitive impairment.

Gepubliceerd: Stroke 2016 Oct;47(10):2517-25
Impact factor: 5.460

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21. Patients "At Risk" of Suffering from Persistent Complaints after Mild Traumatic Brain Injury: The Role of Coping, Mood Disorders, and Post-Traumatic Stress
Scheenen ME, Spikman JM, de Koning ME, van der Horn HJ, Roks G, Hageman G, van der Naalt J

Although most patients recover fully following mild traumatic brain injury (mTBI), a minority (15-25%) of all patients develop persistent post-traumatic complaints (PTC) that interfere with the resumption of previous activities. An early identification of patients who are at risk for PTC is currently performed by measuring the number of

complaints in the acute phase. However, only part of this group will actually develop persisting complaints, stressing the need for studies on additional risk factors. This study aimed to compare this group of patients with many complaints with patients with few and no complaints to identify potential additional discriminating characteristics and to evaluate which of these factors have the most predictive value for being at risk. We evaluated coping style, presence of psychiatric history, injury characteristics, mood-related symptoms, and post-traumatic stress. We included 820 patients (Glasgow Coma Scale [GCS] score 13-15) admitted to three level-1 trauma centers as part of the UPFRONT-study. At 2 weeks after injury, 60% reported three or more complaints (PTC-high), 25% reported few complaints (PTC-low), and 15% reported no complaints (PTC-zero). Results showed that PTC-high consisted of more females (78% vs. 73% and 52%, $p < 0.001$), were more likely to have a psychiatric history (7% vs. 2% and 5%), and had a higher number of reported depression (22% vs. 6% and 3%, $p < 0.001$), anxiety (25% vs. 7% and 5%), and post-traumatic stress (37% vs. 27% and 19%, $p < 0.001$) than the PTC-low and PTC-zero groups. We conclude that in addition to reported complaints, psychological factors such as coping style, depression, anxiety, and post-traumatic stress symptoms had the highest predictive value and should be taken into account in the identification of at-risk patients for future treatment studies.

Gepubliceerd: J Neurotrauma 2017 Jan 1;34(1):31-7
Impact factor: 4.377

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22. Acyl Ghrelin Improves Synapse Recovery in an In Vitro Model of Postanoxic Encephalopathy
Stoyanova II, Hofmeijer J, van Putten MJ, Le Feber J

Comatose patients after cardiac arrest have a poor prognosis. Approximately half never awakes as a result of severe diffuse postanoxic encephalopathy. Several neuroprotective agents have been tested, however without significant effect. In the present study, we used cultured neuronal networks as a model system to study the general synaptic damage caused by temporary severe hypoxia and the possibility to restrict it by ghrelin treatment. Briefly, we applied hypoxia (pO2 lowered from 150 to 20 mmHg) during 6 h in 55 cultures. Three hours after restoration of normoxia, half of the cultures were treated with ghrelin for 24 h, while the other, non-supplemented, were used as a control. All cultures were processed immunocytochemically for detection of the synaptic marker synaptophysin. We observed that hypoxia led to drastic decline of the number of synapses, followed by some recovery after return to normoxia, but still below the prehypoxic level. Additionally, synaptic vulnerability was selective: large- and small-sized neurons were more susceptible to synaptic damage than the medium-sized ones. Ghrelin treatment significantly increased the synapse density, as compared with the non-treated controls or with the prehypoxic period. The effect was detected in all neuronal subtypes. In conclusion, exogenous ghrelin has a robust impact on the recovery of cortical synapses after hypoxia. It raises the possibility that ghrelin or its analogs may have a therapeutic potential for treatment of postanoxic encephalopathy.

Gepubliceerd: Mol Neurobiol 2016 Nov;53(9):6136-43
Impact factor: 5.397

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23. Early TMS evoked potentials in epilepsy: A pilot study
Ter Braack EM, Koopman AW, van Putten MJ

Objective: To explore if the TMS evoked potential is different in patients with epilepsy compared to healthy subjects.
Methods: Eighteen healthy subjects and thirteen epilepsy patients participated in this study. Single TMS pulses were applied to the left and right motor cortex. For each target we applied 75 pulses at 110% of the resting motor threshold (RMT), and continuously measured the EEG. Resting motor threshold and the TMS evoked potential (TEP) were compared between patients and healthy subjects.
Results: Epilepsy patients had a higher left RMT than healthy subjects (88.5% vs. 81.8%, p=0.048). For left motor cortex stimulation, the N100 was larger in amplitude in epilepsy patients than in healthy subjects (p=0.0073). For right motor cortex stimulation, the P180 was larger in amplitude in epilepsy patients than in healthy subjects (p=0.006). The differences in these late TEP components were localized in the centro-parietal areas. No significant differences were found for other TEP components.
Conclusions: In this pilot study, we found a significant higher MT and higher TEP amplitudes in epilepsy patients compared to healthy subjects. SIGNIFICANCE: Changes in cortical excitability may assist in epilepsy diagnostics or evaluation of the efficacy of anti-epileptic drugs.

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Impact factor: 3.426

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24. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation
Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MW

Objective: Spinal cord stimulation (SCS) is used for treating intractable neuropathic pain. It has been suggested that burst SCS (five pulses at 500 Hz, delivered 40 times per second) suppresses neuropathic pain at least as well as conventional tonic SCS, but without evoking paraesthesia. The efficacy of paraesthesia-free high and low amplitude burst SCS for the treatment of neuropathic pain in patients who are already familiar with tonic SCS was evaluated. MATERIALS AND
Methods: Forty patients receiving conventional (30-120 Hz) tonic SCS for at least six months were included. All patients received high and low amplitude burst SCS, for a two-week period in a double blind randomized crossover design, with a two-week period of tonic stimulation in between. The average visual analogue scale (VAS) scores for pain during the last three days of each stimulation period were evaluated as well as quality of life (QoL) scores, and patient's preferences.

Results: Average VAS score for pain were lower during high (40, p = 0.013) and low amplitude burst stimulation (42, p = 0.053) compared with tonic stimulation (52). QoL scores did not differ significantly. At the individual level 58% of the patients experienced significant additional pain reduction (>30% decrease in VAS for pain) during high and/or low amplitude burst stimulation. Eleven patients preferred tonic stimulation, fifteen high, and fourteen low amplitude burst stimulation.
Conclusion: Burst stimulation is in general more effective than tonic stimulation. Individual patients can highly benefit from burst stimulation; however, the therapeutic range of burst stimulation amplitudes requires individual assessment.

Gepubliceerd: Neuromodulation 2016 Jul;19(5):492-7
Impact factor: 2.409

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25. Stimulus induced bursts in severe postanoxic encephalopathy
Tjepkema-Cloostermans MC, Wijers ET, van Putten MJ

Objective: To report on a distinct effect of auditory and sensory stimuli on the EEG in comatose patients with severe postanoxic encephalopathy.
Methods: In two comatose patients admitted to the Intensive Care Unit (ICU) with severe postanoxic encephalopathy and burst-suppression EEG, we studied the effect of external stimuli (sound and touch) on the occurrence of bursts.
Results: In patient A bursts could be induced by either auditory or sensory stimuli. In patient B bursts could only be induced by touching different facial regions (forehead, nose and chin). When stimuli were presented with relatively long intervals, bursts persistently followed the stimuli, while stimuli with short intervals (<1s) did not induce bursts. In both patients bursts were not accompanied by myoclonia. Both patients deceased.
Conclusions: Bursts in patients with a severe postanoxic encephalopathy can be induced by external stimuli, resulting in stimulus-dependent burst-suppression. SIGNIFICANCE: Stimulus induced bursts should not be interpreted as prognostic favourable EEG reactivity.

Clin Neurophysiol 2016 Nov;127(11):3492-7
Impact factor: 3.426

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26. Plasma tPA-Activity and Progression of Cerebral White Matter Hyperintensities in Lacunar Stroke Patients
van Overbeek EC, Staals J, Knottnerus IL, ten Cate H, van Oostenbrugge RJ

Intoduction: Tissue plasminogen activator (tPA)-activity and plasminogen activator inhibitor type 1 (PAI-1) antigen are considered to be haemostasis-related markers of endothelial activation and relate to presence of cerebral white matter hyperintensities (WMH) as was earlier shown in a cross-sectional study. We investigated whether tPA-activity and PAI-1 levels are associated with WMH progression in a longitudinal study.

Methods: In 127 first-ever lacunar stroke patients in whom baseline brain MRI and plasma levels of tPA-activity and PAI-1-antigen were available, we obtained a 2-year follow-up MRI. We assessed WMH progression by a visual WMH change scale. We determined the relationship between levels of tPA-activity and PAI-1 and WMH progression, by logistic regression analysis.
Results: Plasma tPA-activity was associated with periventricular WMH progression (OR 2.36, 95% CI 1.01-5.49, with correction for age and sex and baseline presence of WMH), but not with deep or any (periventricular and/or deep) WMH progression. PAI-1 levels were lower in patients with WMH progression, but these results were not significant.
Conclusion: We found a relationship between plasma tPA-activity and progression of periventricular WMH. More research is needed to determine whether there is a (direct) role of tPA in the development and progression of WMH.

Gepubliceerd: PLoS One 2016;11(3):e0150740
Impact factor: 3.540

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27. EEG Monitoring in Cerebral Ischemia: Basic Concepts and Clinical Applications
van Putten MJ, Hofmeijer J

EEG is very sensitive to changes in neuronal function resulting from ischemia. The authors briefly review essentials of EEG generation and the effects of ischemia on the underlying neuronal processes. They discuss the differential sensitivity of various neuronal processes to energy limitations, including synaptic disturbances. The clinical applications reviewed include continuous EEG monitoring during carotid surgery and acute ischemic stroke, and EEG monitoring for prognostication after cardiac arrest.

Gepubliceerd: J Clin Neurophysiol 2016 Jun;33(3):203-10
Impact factor: 1.337

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28. Involving Patients in Weighting Benefits and Harms of Treatment in Parkinson's Disease
Weernink MG, van Til JA, van Vugt JP, Movig KL, Groothuis-Oudshoorn CG, IJzerman MJ

Intoduction: Little is known about how patients weigh benefits and harms of available treatments for Parkinson's Disease (oral medication, deep brain stimulation, infusion therapy). In this study we have (1) elicited patient preferences for benefits, side effects and process characteristics of treatments and (2) measured patients' preferred and perceived involvement in decision-making about treatment.
Methods: Preferences were elicited using a best-worst scaling case 2 experiment. Attributes were selected based on 18 patient-interviews: treatment modality, tremor, slowness of movement, posture and balance problems, drowsiness, dizziness, and dyskinesia. Subsequently, a questionnaire was distributed in which patients were

asked to indicate the most and least desirable attribute in nine possible treatment scenarios. Conditional logistic analysis and latent class analysis were used to estimate preference weights and identify subgroups. Patients also indicated their preferred and perceived degree of involvement in treatment decision-making (ranging from active to collaborative to passive).
Results: Two preference patterns were found in the patient sample (N = 192). One class of patients focused largely on optimising the process of care, while the other class focused more on controlling motor-symptoms. Patients who had experienced advanced treatments, had a shorter disease duration, or were still employed were more likely to belong to the latter class. For both classes, the benefits of treatment were more influential than the described side effects. Furthermore, many patients (45%) preferred to take the lead in treatment decisions, however 10.8% perceived a more passive or collaborative role instead.
Discussion: Patients weighted the benefits and side effects of treatment differently, indicating there is no "one-size-fits-all" approach to choosing treatments. Moreover, many patients preferred an active role in decision-making about treatment. Both results stress the need for physicians to know what is important to patients and to share treatment decisions to ensure that patients receive the treatment that aligns with their preferences.

Gepubliceerd: PLoS One 2016;11(8):e0160771
Impact factor: 3.540

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29. Feasibility of external rhythmic cueing with the Google Glass for improving gait in people with Parkinson's disease
Zhao Y, Nonnekes J, Storcken EJ, Janssen S, van Wegen EE, Bloem BR, Dorresteijn LD, van Vugt JP, Heida T, van Wezel RJ

New mobile technologies like smartglasses can deliver external cues that may improve gait in people with Parkinson's disease in their natural environment. However, the potential of these devices must first be assessed in controlled experiments. Therefore, we evaluated rhythmic visual and auditory cueing in a laboratory setting with a custom-made application for the Google Glass. Twelve participants (mean age = 66.8; mean disease duration = 13.6 years) were tested at end of dose. We compared several key gait parameters (walking speed, cadence, stride length, and stride length variability) and freezing of gait for three types of external cues (metronome, flashing light, and optic flow) and a control condition (no-cue). For all cueing conditions, the subjects completed several walking tasks of varying complexity. Seven inertial sensors attached to the feet, legs and pelvis captured motion data for gait analysis. Two experienced raters scored the presence and severity of freezing of gait using video recordings. User experience was evaluated through a semi-open interview. During cueing, a more stable gait pattern emerged, particularly on complicated walking courses; however, freezing of gait did not significantly decrease. The metronome was more effective than rhythmic visual cues and most preferred by the participants. Participants were overall positive about the usability of the Google Glass and willing to use it at home. Thus, smartglasses like the Google Glass could be used to provide personalized mobile cueing to

support gait; however, in its current form, auditory cues seemed more effective than rhythmic visual cues.

Gepubliceerd: J Neurol 2016 Jun;263(6):1156-65
Impact factor: 3.408

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30. Determinants of intention to change health-related behavior and actual change in patients with TIA or minor ischemic stroke
Brouwer-Goossensen D, van Genugten L, Lingsma H, Dippel D, Koudstaal P, den Hertog H

Objective: To assess determinants of intention to change health-related behavior and actual change in patients with TIA or ischemic stroke.
Methods: In this prospective cohort study, 100 patients with TIA or minor ischemic stroke completed questionnaires on behavioral intention and sociocognitive factors including perception of severity, susceptibility, fear, response-efficacy and self-efficacy at baseline. Questionnaires on physical activity, diet and smoking were completed at baseline and at 3 months. Associations between sociocognitive factors and behavioral intention and actual change were studied with multivariable linear and logistic regression.
Results: Self-efficacy, response efficacy, and fear were independently associated with behavioral intention, with self-efficacy as the strongest determinant of intention to increase physical activity (aBeta 0.40; 95% CI 0.12-0.71), adapt a healthy diet (aBeta 0.49; 95% CI 0.23-0.75), and quit smoking (aBeta 0.51; 95% CI 0.13-0.88). Intention to change tended to be associated with actual health-related behavior change.
Conclusion: Self-efficacy, fear, and response-efficacy were determinants of intention to change health-related behavior after TIA or ischemic stroke. PRACTICE IMPLICATIONS: These determinants of intention to change health-related behavior after TIA or ischemic stroke should be taken into account in the development of future interventions promoting health-related behavior change in these group of patients.

Gepubliceerd: Patient Educ Couns 2016 Apr;99(4):644-50
Impact factor: 2.232

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31. Persistence and adherence in multiple sclerosis patients starting glatiramer acetate treatment: assessment of relationship with care received from multiple disciplines
Jongen PJ, Lemmens WA, Hupperts R, Hoogervorst EL, Schrijver HM, Slettenaar A, de Schryver EL, Boringa J, van Noort E, Donders R

Background: In multiple sclerosis patients, the persistence of, and adherence to, disease-modifying treatment are often insufficient. The degree of persistence and adherence may relate to the care received from various disciplines.
Methods: In an observational study of 203 patients treated with glatiramer acetate 20 mg subcutaneous daily, we assess the persistence and adherence in relation to

the amount of care received in various disciplines. The frequencies and durations of care per discipline were reported by patients online, as were missed doses and eventual treatment discontinuation. The associations between the care provided by neurologists, nurses, psychologists, pharmacists, and rehabilitative doctors and persistence and adherence were the primary outcomes; the associations between care received from general practitioners, occupational therapists, physiotherapists, social workers, dieticians, home caregivers, informal caregivers, other medical specialists, and other caregivers and persistence and adherence were secondary outcomes.
Results: It was found that the 12-month persistence rate was 62% and that 85% of the persistent patients were 95% adherent (missed <5% of doses). Patients who discontinued treatment in the fourth quarter (Q) had received less-frequent and shorter psychological care in Q3 than persistent patients (P=0.0018 and P=0.0022). Adherent patients had received more frequent home care and informal care than nonadherent patients (P=0.0074 and P=0.0198), as well as longer home care and informal care (P=0.0074 and P=0.0318). Associations between care in other disciplines and persistence or adherence were not observed. As to the relationship between adherence and persistence, nonadherence in Q2 was related to discontinuation after Q2 (P=0.0001).
Conclusion: We obtained no evidence that, in multiple sclerosis patients, persistence of and adherence to disease-modifying treatment are associated with the amount of neurological, nursing, pharmaceutical, or rehabilitative care. However, findings suggest that the treatment of psychological problems in Q3 may relate to persistence and that home care and informal care may relate to adherence.

Gepubliceerd: Patient Prefer Adherence 2016;10:909-17
Impact factor: 2.180

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32. Automated Entire Thrombus Density Measurements for Robust and Comprehensive Thrombus Characterization in Patients with Acute Ischemic Stroke
Santos EM, Niessen WJ, Yoo AJ, Berkhemer OA, Beenen LF, Majoie CB, Marquering HA, MR CLEAN Investigators (incl. den Hertog HM)

Background and Purpose: In acute ischemic stroke (AIS) management, CT-based thrombus density has been associated with treatment success. However, currently used thrombus measurements are prone to inter-observer variability and oversimplify the heterogeneous thrombus composition. Our aim was first to introduce an automated method to assess the entire thrombus density and then to compare the measured entire thrombus density with respect to current standard manual measurements.
Materials and Method: In 135 AIS patients, the density distribution of the entire thrombus was determined. Density distributions were described using medians, interquartile ranges (IQR), kurtosis, and skewedness. Differences between the median of entire thrombus measurements and commonly applied manual measurements using 3 regions of interest were determined using linear regression.

Results: Density distributions varied considerably with medians ranging from 20.0 to 62.8 HU and IQRs ranging from 9.3 to 55.8 HU. The average median of the thrombus density distributions (43.5 +/- 10.2 HU) was lower than the manual assessment (49.6 +/- 8.0 HU) ($p<0.05$). The difference between manual measurements and median density of entire thrombus decreased with increasing density ($r = 0.64$; $p<0.05$), revealing relatively higher manual measurements for low density thrombi such that manual density measurement tend overestimates the real thrombus density.
Conclusions: Automatic measurements of the full thrombus expose a wide variety of thrombi density distribution, which is not grasped with currently used manual measurement. Furthermore, discrimination of low and high density thrombi is improved with the automated method.

Gepubliceerd: PLoS One 2016;11(1):e0145641
Impact factor: 3.540

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33. Thrombus Permeability Is Associated With Improved Functional Outcome and Recanalization in Patients With Ischemic Stroke
Santos EM, Marquering HA, den Blanken MD, Berkhemer OA, Boers AM, Yoo AJ, Beenen LF, Treurniet KM, Wismans C, van NK, Lingsma HF, Dippel DW, van der Lugt A, van Zwam WH, Roos YB, van Oostenbrugge RJ, Niessen WJ, Majoie CB, MR CLEAN Investigators (incl. den Hertog HM)

Background and Purpose: Preclinical studies showed that thrombi can be permeable and may, therefore, allow for residual blood flow in occluded arteries of patients having acute ischemic stroke. This perviousness may increase tissue oxygenation, improve thrombus dissolution, and augment intra-arterial treatment success. We hypothesize that the combination of computed tomographic angiography and noncontrast computed tomography imaging allows measurement of contrast agent penetrating a permeable thrombus, and it is associated with improved outcome.
Methods: Thrombus and contralateral artery attenuations in noncontrast computed tomography and computed tomographic angiography images were measured in 184 Multicenter Randomized Clinical trial of Endovascular treatment of acute ischemic stroke in the Netherlands (MR CLEAN) patients with thin-slice images. Two quantitative estimators of the thrombus permeability were introduced: computed tomographic angiography attenuation increase (Delta) and thrombus void fraction (epsilon). Patients were dichotomized as having a pervious or impervious thrombus and associated with outcome, recanalization, and final infarct volume.
Results: Patients with Delta>/=10.9 HU (n=81 [44%]) and epsilon>/=6.5% (n=77 [42%]) were classified as having a pervious thrombus. These patients were 3.2 (95% confidence interval, 1.7-6.4) times more likely to have a favorable outcome, and 2.5 (95% confidence interval, 1.3-4.8) times more likely to recanalyze, for Delta based classification, and similarly for epsilon. These odds ratios were independent from intravenous or intra-arterial treatment. Final infarct volume was negatively correlated with both perviousness estimates (correlation coefficient, -0.39 for Delta and -0.40 for epsilon).

Conclusions: This study shows that simultaneous measurement of thrombus attenuation in noncontrast computed tomography and computed tomographic angiography allows for quantification of thrombus perviousness. Thrombus perviousness is strongly associated with improved functional outcome, smaller final infarct volume, and higher recanalization rate.

Gepubliceerd: Stroke 2016 Mar;47(3):732-41
Impact factor: 5.460

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34. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke

Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, Lingsma HF, Sprengers ME, Jenniskens SF, Lycklama A Nijeholt GJ, van Walderveen MA, van den Berg R, Bot JC, Beenen LF, Boers AM, Slump CH, Roos YB, van Oostenbrugge RJ, Dippel DW, van der Lugt A, van Zwam WH, Marquering HA, Majoie CB, MR CLEAN Investigators (incl. den Hertog HM)

Background and Purpose: Recent randomized trials have proven the benefit of intra-arterial treatment (IAT) with retrievable stents in acute ischemic stroke. Patients with poor or absent collaterals (preexistent anastomoses to maintain blood flow in case of a primary vessel occlusion) may gain less clinical benefit from IAT. In this post hoc analysis, we aimed to assess whether the effect of IAT was modified by collateral status on baseline computed tomographic angiography in the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN).
Methods: MR CLEAN was a multicenter, randomized trial of IAT versus no IAT. Primary outcome was the modified Rankin Scale at 90 days. The primary effect parameter was the adjusted common odds ratio for a shift in direction of a better outcome on the modified Rankin Scale. Collaterals were graded from 0 (absent) to 3 (good). We used multivariable ordinal logistic regression analysis with interaction terms to estimate treatment effect modification by collateral status.
Results: We found a significant modification of treatment effect by collaterals (P=0.038). The strongest benefit (adjusted common odds ratio 3.2 [95% confidence intervals 1.7-6.2]) was found in patients with good collaterals (grade 3). The adjusted common odds ratio was 1.6 [95% confidence intervals 1.0-2.7] for moderate collaterals (grade 2), 1.2 [95% confidence intervals 0.7-2.3] for poor collaterals (grade 1), and 1.0 [95% confidence intervals 0.1-8.7] for patients with absent collaterals (grade 0).
Conclusions: In MR CLEAN, baseline computed tomographic angiography collateral status modified the treatment effect. The benefit of IAT was greatest in patients with good collaterals on baseline computed tomographic angiography. Treatment benefit appeared less and may be absent in patients with absent or poor collaterals. CLINICAL TRIAL REGISTRATION: URL: http://www.trialregister.nl and http://www.controlled-trials.com. Unique identifier: (NTR)1804 and ISRCTN10888758, respectively.

Gepubliceerd: Stroke 2016 Mar;47(3):768-76
Impact factor: 5.460

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35. Early effect of intra-arterial treatment in ischemic stroke on aphasia recovery in MR CLEAN

Crijnen YS, Nouwens F, de Lau LM, Visch-Brink EG, van de Sandt-Koenderman MW, Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Majoie CB, Dippel DW, MR CLEAN Investigators (incl. den Hertog HM)

Objective: To investigate the effect of intra-arterial treatment (IAT) on early recovery from aphasia in acute ischemic stroke. We hypothesized that the early effect of IAT on aphasia is smaller than the effect on motor deficits.
Methods: We included patients with aphasia from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), in which 500 patients with a proximal anterior circulation stroke were randomized to usual care plus IAT (<6 hours after stroke, mainly stent retrievers) or usual care alone. We estimated the effect of IAT on the shift on the NIH Stroke Scale (NIHSS) item language and the NIHSS item motor arm at 24 hours and 1 week after stroke with multivariable ordinal logistic regression as a common odds ratio, adjusted for prognostic variables (acOR). Differences between the effect of IAT on aphasia and on motor deficits were tested in a multilevel model with a multiplicative interaction term.
Results: Of the 288 patients with aphasia, 126 were assigned to IAT and 162 to usual care alone. The acOR for improvement of language score at 24 hours was 1.65 (95% confidence interval [CI] 1.05-2.60), and at 1 week 1.86 (95% CI 1.18-2.94). The acOR for improvement of motor deficit at 24 hours was 2.44 (95% CI 1.54-3.88), and at 1 week 2.32 (95% CI 1.43-3.77). The effect of IAT on language deficits was significantly different from the effect on motor deficits at 24 hours and 1 week ($p = 0.005$ and $p = 0.011$).
Conclusions: IAT results in better early recovery from aphasia than usual care alone. The early effect of IAT on aphasia is smaller than the effect on motor deficits. CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for patients with acute ischemic stroke IAT increases early recovery from aphasia and that the early effect on aphasia, as measured by the NIHSS, is smaller than the effect on motor deficits.

Gepubliceerd: Neurology 2016 May 31;86(22):2049-55
Impact factor: 8.166

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36. The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN

Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama A Nijeholt GJ, Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van Oostenbrugge

RJ, Majoie CB, Dippel DW, Roos YB, MR CLEAN Investigators (incl. den Hertog HM)

Background: The aim of the current study was to assess the influence of anesthetic management on the effect of treatment in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).
Methods: MR CLEAN was a multicenter, randomized, open-label trial of intra-arterial therapy (IAT) vs no IAT. The intended anesthetic management at the start of the procedure was used for this post hoc analysis. The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the modified Rankin Scale (mRS) at 90 days, estimated with multivariable ordinal logistic regression analysis, which included a term for general anesthesia (GA).
Results: GA was associated with significant (p = 0.011) effect modification, resulting in estimated decrease of 51% (95% confidence interval [CI] 31%-86%) in treatment effect compared to non-GA. We found a shift in the distribution on the mRS in favor of non-GA compared to control group (acOR 2.18 [95% CI 1.49-3.20]). The shift in distribution between GA and control group was in a similar direction (acOR 1.12 [95% CI 0.71-1.78]) with loss of statistical significance.
Conclusions: In this post hoc analysis, we found that the type of anesthetic management influences outcome following IAT. Only treatment without general anesthesia was associated with a significant treatment benefit in MR CLEAN. CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for patients with acute ischemic stroke undergoing IAT, mRS scores at 90 days improve only in patients treated without GA.

Gepubliceerd: Neurology 2016 Aug 16;87(7):656-64
Impact factor: 8.166

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37. Clot Burden Score on Baseline Computerized Tomographic Angiography and Intra-Arterial Treatment Effect in Acute Ischemic Stroke
Treurniet KM, Yoo AJ, Berkhemer OA, Lingsma HF, Boers AM, Fransen PS, Beumer D, van den Berg LA, Sprengers ME, Jenniskens SF, Lycklama A Nijeholt GJ, van Walderveen MA, Bot JC, Beenen LF, van den Berg R, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Dippel DW, Roos YB, Marquering HA, Majoie CB, MR CLEAN Investigators (incl. den Hertog HM)

Background and Purpose: A high clot burden score (CBS) is associated with favorable outcome after intravenous treatment for acute ischemic stroke. The added benefit of intra-arterial treatment might be less in these patients. The aim of this exploratory post hoc analysis was to assess the relation of CBS with neurological improvement and endovascular treatment effect.
Methods: For 499 of 500 patients in the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), the CBS was determined. Ordinal logistic regression models with and without main baseline prognostic variables were used to assess the association between CBS (continuous or dichotomized at CBS of 6) and a shift toward better

outcome on the modified Rankin Scale. The model without main baseline prognostic variables only included treatment allocation and CBS. Models with and without a multiplicative interaction term of CBS and treatment were compared using the chi2 test to assess treatment effect modification by CBS.
Results: Higher CBS was associated with a shift toward better outcome on the modified Rankin Scale; adjusted common odds ratio per point CBS was 1.12 (95% confidence interval, 1.04-1.20]. Dichotomized CBS had an adjusted common odds ratio of 1.67 (95% confidence interval, 1.12-2.51). Both effect estimates were slightly attenuated by adding baseline prognostic variables. The addition of the interaction terms did not significantly improve the fit of the models. There was a small and insignificant increase of intra-arterial treatment efficacy in the high CBS group.
Conclusions: A higher CBS is associated with improved outcome and may be used as a prognostic marker. We found no evidence that CBS modifies the effect of intra-arterial treatment. CLINICAL TRIAL REGISTRATION: URL: http://www.trialregister.nl. Unique identifier: NTR1804. URL: http://www.controlled-trials.com. Unique identifier: ISRCTN10888758.

Gepubliceerd: Stroke 2016 Dec;47(12):2972-8
Impact factor: 5.460

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38. Clinical manifestations of intermediate allele carriers in Huntington disease
Cubo E, Ramos-Arroyo MA, Martinez-Horta S, Martinez-Descalls A, Calvo S, Gil-Polo C, European HD Network (incl. Van Vugt JP)

Objective: There is controversy about the clinical consequences of intermediate alleles (IAs) in Huntington disease (HD). The main objective of this study was to establish the clinical manifestations of IA carriers for a prospective, international, European HD registry.
Methods: We assessed a cohort of participants at risk with <36 CAG repeats of the huntingtin (HTT) gene. Outcome measures were the Unified Huntington's Disease Rating Scale (UHDRS) motor, cognitive, and behavior domains, Total Functional Capacity (TFC), and quality of life (Short Form-36 [SF-36]). This cohort was subdivided into IA carriers (27-35 CAG) and controls (<27 CAG) and younger vs older participants. IA carriers and controls were compared for sociodemographic, environmental, and outcome measures. We used regression analysis to estimate the association of age and CAG repeats on the UHDRS scores.
Results: Of 12,190 participants, 657 (5.38%) with <36 CAG repeats were identified: 76 IA carriers (11.56%) and 581 controls (88.44%). After correcting for multiple comparisons, at baseline, we found no significant differences between IA carriers and controls for total UHDRS motor, SF-36, behavioral, cognitive, or TFC scores. However, older participants with IAs had higher chorea scores compared to controls ($p = 0.001$). Linear regression analysis showed that aging was the most contributing factor to increased UHDRS motor scores ($p = 0.002$). On the other hand, 1-year follow-up data analysis showed IA carriers had greater cognitive decline compared to controls ($p = 0.002$).

Conclusions: Although aging worsened the UHDRS scores independently of the genetic status, IAs might confer a late-onset abnormal motor and cognitive phenotype. These results might have important implications for genetic counseling. CLINICALTRIALSGOV IDENTIFIER: NCT01590589.

Gepubliceerd: Neurology 2016 Aug 9;87(6):571-8
Impact factor: 8.166

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39. Psychiatric and social outcome after deep brain stimulation for advanced Parkinson's disease
Boel JA, Odekerken VJ, Geurtsen GJ, Schmand BA, Cath DC, Figee M, van den Munckhof P, de Haan RJ, Schuurman PR, de Bie RM, NSTAPS study group (incl. Van Vugt JP)

Background: The aim of this study was to assess psychiatric and social outcome 12 months after bilateral deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and subthalamic nucleus (STN) for advanced Parkinson's disease (PD).
Methods: We randomly assigned patients to receive GPi DBS (n = 65) or STN DBS (n = 63). Standardized psychiatric and social questionnaires were assessed at baseline and after 12 months.
Results: No differences were found between GPi DBS and STN DBS on psychiatric evaluation. Within-group comparisons showed small but statistically significant changes on several measures in both groups. Descriptive statistics indicated slight changes in social functioning. Marital satisfaction of patients and partners remained relatively stable after GPi and STN DBS.
Conclusions: We found neither differences in psychiatric and social outcome between GPi DBS and STN DBS nor any relevant within-group differences. The decision for GPi DBS or STN DBS cannot be based on expected psychiatric or social effects.

Gepubliceerd: Mov Disord 2016 Mar;31(3):409-13
Impact factor: 6.010

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40. GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up
Odekerken VJ, Boel JA, Schmand BA, de Haan RJ, Figee M, van den Munckhof P, Schuurman PR, de Bie RM, NSTAPS study group (incl. Van Vugt JP)

Objective: To compare motor symptoms, cognition, mood, and behavior 3 years after deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and subthalamic nucleus (STN) in advanced Parkinson disease (PD).
Methods: Patients with PD eligible for DBS were randomized to bilateral GPi DBS and bilateral STN DBS (1:1). The primary outcome measures were (1) improvement in motor symptoms in off-drug phase measured with the Unified Parkinson Disease

Rating Scale (UPDRS) and (2) a composite score for cognitive, mood, and behavioral effects, and inability to complete follow-up at 36 months after surgery.
Results: Of the 128 patients enrolled, 90 were able to complete the 3-year follow-up. We found significantly more improvement of motor symptoms after STN DBS (median [interquartile range (IQR)] at 3 years, GPi 33 [23-41], STN 28 [20-36], p = 0.04). No between-group differences were observed on the composite score (GPi 83%, STN 86%). Secondary outcomes showed larger improvement in off-drug functioning in the AMC Linear Disability Scale score after STN DBS (mean +/- SD, GPi 65.2 +/- 20.1, STN 72.6 +/- 18.0, p = 0.05). Medication was reduced more after STN DBS (median levodopa equivalent dose [IQR] at 3 years, GPi 1,060 [657-1,860], STN 605 [411-875], p < 0.001). No differences in adverse effects were recorded, apart from more reoperations to a different target after GPi DBS (GPi n = 8, STN n = 1).
Conclusions: Off-drug phase motor symptoms and functioning improve more after STN DBS than after GPi DBS. No between-group differences were observed on a composite score for cognition, mood, and behavior, and the inability to participate in follow-up. CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that STN DBS provides more off-phase motor improvement than GPi DBS, but with a similar risk for cognitive, mood, and behavioral complications.

Gepubliceerd: Neurology 2016 Feb 23;86(8):755-61
Impact factor: 8.166

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41. Cognitive and psychiatric outcome 3 years after globus pallidus pars interna or subthalamic nucleus deep brain stimulation for Parkinson's disease
Boel JA, Odekerken VJ, Schmand BA, Geurtsen GJ, Cath DC, Figee M, van den Munckhof P, de Haan RJ, Schuurman PR, de Bie RM, NSTAPS study group (incl. Van Vugt JP)

Background: Effects on non-motor symptoms, mainly cognitive and psychiatric side effects, could influence the decision for either globus pallidus pars interna (GPi) or subthalamic nucleus (STN) deep brain stimulation (DBS) for patients with Parkinson's disease (PD). OBJECTIVE: 1) To compare cognitive and psychiatric outcomes 3 years after GPi DBS versus STN DBS, and 2) to report on occurrence of suicidal ideation, psychiatric diagnoses, social functioning, and marital satisfaction 3 years after DBS.
Methods: Patients were randomized to receive GPi DBS (n = 65) or STN DBS (n = 63). Standardized assessments were performed at baseline, 1 year, and 3 years. We used linear mixed model analyses to investigate between-group differences on the Mattis Dementia Rating Scale (MDRS), neuropsychological tests, and psychiatric questionnaires 3 years after DBS.
Results: Eighty-seven patients (68%) completed at least one neuropsychological test after 3 years. No significant between-group differences were found on the MDRS (p = 0.61), neuropsychological tests (p-values between 0.17 and 0.87), and psychiatric questionnaires (p-values between 0.23 and 0.88) 3 years after DBS. The Mini International Neuropsychiatric Interview did not indicate a substantial number of

psychiatric diagnoses after 3 years. Social functioning and marital satisfaction were comparable in both groups.
Conclusions: Three years after GPi DBS and STN DBS no pronounced between-group differences on measures of cognitive and psychiatric functioning could be demonstrated. Overall, cognitive and psychiatric outcome 3 years after DBS do not provide a clear direction for clinicians when considering which of these two surgical targets to choose.

Gepubliceerd: Parkinsonism Relat Disord 2016 Dec;33:90-5
Impact factor: 3.794

Totale impact factor: 169.988
Gemiddelde impact factor: 4.146

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 46.790
Gemiddelde impact factor: 3.342

Orthopedie

1. The less invasive anterior approach for total hip arthroplasty: a comparison to other approaches and an evaluation of the learning curve - a systematic review
den Hartog YM, Mathijssen NM, Vehmeijer SB

There is still discussion about possible advantages and disadvantages of the less invasive anterior approach for total hip arthroplasty (THA). The purpose of our systematic review was to evaluate literature regarding the anterior approach in comparison to other approaches. Furthermore, we investigated if there is a description of a learning curve for the anterior approach.Data were obtained from EMBASE, Cochrane, PsycINFO, CINAHL, Web-of-Science, Scopus, Google scholar, and PubMed since their inception up to June 2015. 2 reviewers independently selected the studies and independently conducted the quality assessment. Because studies were considered heterogeneous regarding outcome measures, determinants studied, and methodological quality, we decided to perform a "best evidence synthesis". A total of 64 studies met the inclusion criteria.Strong evidence for no difference in component placement between the anterior approach and other approaches was found. Also, strong evidence for faster postoperative recovery and less need for assistive devices after the anterior approach were found. All other studied parameters only demonstrated conflicting evidence. Although the learning curve for the anterior approach is not yet clear, this learning curve should not to be neglected.In conclusion, the less invasive anterior approach provides benefits in the early postoperative period only, when compared to other approaches.

Gepubliceerd: Hip Int 2016 Mar;26(2):105-20
Impact factor: 0.889

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2. Means of enhancing bone fracture healing: optimal cell source, isolation methods and acoustic stimulation
Ghebes CA, Braham MV, Zeegers AV, Renard AJ, Fernandes H, Saris DB

Background: The human body has an extensive capacity to regenerate bone tissue after trauma. However large defects such as long bone fractures of the lower limbs cannot be restored without intervention and often lead to nonunion. Therefore, the aim of the present study was to assess the pool and biological functions of human mesenchymal stromal cells (hMSCs) isolated from different bone marrow locations of the lower limbs and to identify novel strategies to prime the cells prior to their use in bone fracture healing. Following, bone marrow from the ilium, proximal femur, distal femur and proximal tibia was aspirated and the hMSCs isolated. Bone marrow type, volume, number of mononuclear cells/hMSCs and their self-renewal, multilineage potential, extracellular matrix (ECM) production and surface marker profiling were analyzed. Additionally, the cells were primed to accelerate bone fracture healing either by using acoustic stimulation or varying the initial hMSCs isolation conditions.

Results: We found that the more proximal the bone marrow aspiration location, the larger the bone marrow volume was, the higher the content in mononuclear cells/hMSCs and the higher the self-renewal and osteogenic differentiation potential of the isolated hMSCs were. Acoustic stimulation of bone marrow, as well as the isolation of hMSCs in the absence of fetal bovine serum, increased the osteogenic and ECM production potential of the cells, respectively.
Conclusion: We showed that bone marrow properties change with the aspiration location, potentially explaining the differences in bone fracture healing between the tibia and the femur. Furthermore, we showed two new priming methods capable of enhancing bone fracture healing.

Gepubliceerd: BMC Biotechnol 2016 Dec 12;16(1):89
Impact factor: 2.452

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3. Recognizing the elbow prosthesis on conventional radiographs
Oflazoglu K, Koenrades N, Somford MP, van den Bekerom MP

The objective of this study was to make an overview that can be useful in determining which type and brand of prosthesis a patient has when visiting the emergency department or outpatient clinic with a periprosthetic fracture, dislocation, or implant failure. The commonly used prostheses in Europe are opted for this list. The radiographs used for this list are obtained either from the company or from our own patients. This list contains the Coonrad/Morrey total elbow prosthesis, the Nexel total elbow prosthesis, the GSB III Elbow Prosthesis, the iBP Total Elbow System, the Discovery Elbow System, the NESimplavit Elbow System, the Latitude Elbow prosthesis, the Solar Elbow, and the Souter-Strathclyde total elbow. The characteristics of each prosthesis are described.

Gepubliceerd: Strategies Trauma Limb Reconstr 2016 Nov;11(3):161-8
Impact factor: 1.050

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4. Nationwide review of mixed and non-mixed components from different manufacturers in total hip arthroplasty
Peters RM, van Steenbergen LN, Bulstra SK, Zeegers AV, Stewart RE, Poolman RW, Hosman AH

Background and purpose - Combining components from different manufacturers in total hip arthroplasty (THA) is common practice worldwide. We determined the proportion of THAs used in the Netherlands that consist of components from different manufacturers, and compared the revision rates of these mixed THAs with those of non-mixed THAs. Patients and methods - Data on primary and revision hip arthroplasty are recorded in the LROI, the nationwide population-based arthroplasty register in the Netherlands. We selected all 163,360 primary THAs that were performed in the period 2007-2014. Based on the manufacturers of the components, 4 groups were discerned: non-mixed THAs with components from the same manufacturer (n = 142,964); mixed stem-head THAs with different manufacturers for

the femoral stem and head (n = 3,663); mixed head-cup THAs with different head and cup manufacturers (n = 12,960), and mixed stem-head-cup THAs with different femoral stem, head, and cup manufacturers (n = 1,773). Mixed prostheses were defined as THAs (stem, head, and cup) composed of components made by different manufacturers. Results - 11% of THAs had mixed components (n = 18,396). The 6-year revision rates were similar for mixed and non-mixed THAs: 3.4% (95% CI: 3.1w-3.7) for mixed THAs and 3.5% (95% CI: 3.4-3.7) for non-mixed THAs. Revision of primary THAs due to loosening of the acetabulum was more common in mixed THAs (16% vs. 12%). Interpretation - Over an 8-year period in the Netherlands, 11% of THAs had mixed components-with similar medium-term revision rates to those of non-mixed THAs.

Gepubliceerd: Acta Orthop 2016 Aug;87(4):356-62
Impact factor: 2.617

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5. The Bristow-Latarjet procedure, a historical note on a technique in comeback
van der Linde JA, van Wijngaarden R, Somford MP, van Deurzen DF, van den Bekerom MP

The Bristow-Latarjet procedure is a well-known surgical technique designed to treat shoulder instability. In this procedure, the coracoid process is transferred to the glenoid rim, to serve as augmentation of an associated bony defect. Because long-term results following a soft tissue procedure (Bankart repair) reveal that up to 21 and 33 % of the patients might experience recurrent instability and with the advent of the arthroscopic coracoid transfer, there is renewed interest in this procedure to treat shoulder instability. The aim of this study is to provide a historical overview, with emphasis on the original inventors Bristow and Latarjet, the complications and following modifications regarding the surgical approach, the coracoid transfer and the arthroscopic technique. Level of evidence V.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc 2016 Feb;24(2):470-8
Impact factor: 3.097

Totale impact factor: 10.105
Gemiddelde impact factor: 2.021

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 0.889
Gemiddelde impact factor: 0.889

Pathologie

1. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H

Background: The aim of this study is to analyze the impact of first degree relative (FDR) of young breast cancer patients.
Methods: Data were used from our prospective population-based cohort study which started in 1983. The family history (FH) was registered with regard to FDR: the presence or absence of invasive breast cancer in none vs. one or more FDRs at any age.
Results: A total of 1109 women, </=50 years with 1128 breast conserving treatments was seen. The incidence of FDR was 17.0% for one FDR and 3.2% >/=2 FDR. The three groups, none, 1 or >/=2 FDR, were comparable. The local failure rate is comparable for all three groups. Women with a positive FH and metachronous bilateral breast cancer (MBBC) showed a lower local failure (HR 0.2; 95% CI 0.05-0.8). A positive FH was an independent predictor for a better disease-specific survival (HR 0.6; 95% CI 0.4-0.9).
Conclusion: A positive FH, based on FDR implies a better prognosis in relation to survival for young women treated with BCT. In contrast to no FH for FDR, MBBC in women with a positive FH was not associated with an increased risk of local recurrence.

Gepubliceerd: Acta Oncol 2016;55(4):449-54
Impact factor: 3.730

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2. Quantifying prion disease penetrance using large population control cohorts
Minikel EV, Vallabh SM, Lek M, Estrada K, Samocha KE, Sathirapongsasuti JF, McLean CY, Tung JY, Yu LP, Gambetti P, Blevins J, Zhang S, Cohen Y, Chen W, Yamada M, Hamaguchi T, Sanjo N, Mizusawa H, Nakamura Y, Kitamoto T, Collins SJ, Boyd A, Will RG, Knight R, Ponto C, Zerr I, Kraus TF, Eigenbrod S, Giese A, Calero M, de Pedro-Cuesta J, Haik S, Laplanche JL, Bouaziz-Amar E, Brandel JP, Capellari S, Parchi P, Poleggi A, Ladogana A, O'Donnell-Luria AH, Karczewski KJ, Marshall JL, Boehnke M, Laakso M, Mohlke KL, Kahler A, Chambert K, McCarroll S, Sullivan PF, Hultman CM, Purcell SM, Sklar P, van der Lee SJ, Rozemuller A, Jansen C, Hofman A, Kraaij R, van Rooij JG, Ikram MA, Uitterlinden AG, van Duijn CM, Daly MJ, MacArthur DG

More than 100,000 genetic variants are reported to cause Mendelian disease in humans, but the penetrance-the probability that a carrier of the purported disease-causing genotype will indeed develop the disease-is generally unknown. We assess the impact of variants in the prion protein gene (PRNP) on the risk of prion disease by analyzing 16,025 prion disease cases, 60,706 population control exomes, and 531,575 individuals genotyped by 23andMe Inc. We show that missense variants in

PRNP previously reported to be pathogenic are at least 30 times more common in the population than expected on the basis of genetic prion disease prevalence. Although some of this excess can be attributed to benign variants falsely assigned as pathogenic, other variants have genuine effects on disease susceptibility but confer lifetime risks ranging from <0.1 to ~100%. We also show that truncating variants in PRNP have position-dependent effects, with true loss-of-function alleles found in healthy older individuals, a finding that supports the safety of therapeutic suppression of prion protein expression.

Gepubliceerd: Sci Transl Med 2016 Jan 20;8(322):322ra9
Impact factor: 16.264

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3. Tumor stroma-containing 3D spheroid arrays: A tool to study nanoparticle penetration

Priwitaningrum DL, Blonde JG, Sridhar A, van Baarlen J, Hennink WE, Storm G, Le GS, Prakash J

Nanoparticle penetration through tumor tissue after extravasation is considered as a key issue for tumor distribution and therapeutic effects. Most tumors possess abundant stroma, a fibrotic tissue composed of cancer-associated fibroblasts (CAFs) and extracellular matrix (ECM), which acts as a barrier for nanoparticle penetration. There is however a lack of suitable in vitro systems to study the tumor stroma penetration of nanoparticles. In the present study, we developed and thoroughly characterized a 3D co-culture spheroidal array to mimic tumor stroma and investigated the penetration of silica and PLGA nanoparticles in these spheroids. First, we examined human breast tumor patient biopsies to characterize the content and organization of stroma and found a high expression of alpha-smooth muscle actin (alpha-SMA; 40% positive area) and collagen-1 (50% positive area). Next, we prepared homospheroids of 4T1 mouse breast cancer cells or 3T3 mouse fibroblasts alone as well as heterospheroids combining 3T3 and 4T1 cells in different ratios (1:1 and 5:1) using a microwell array platform. Confocal live imaging revealed that fibroblasts distributed and reorganized within 48h in heterospheroids. Furthermore, immunohistochemical staining and gene expression analysis showed a proportional increase of alpha-SMA and collagen in heterospheroids with higher fibroblast ratios attaining 35% and 45% positive area at 5:1 (3T3:4T1) ratio, in a good match with the clinical breast tumor stroma. Subsequently, we studied the penetration of high and low negatively charged fluorescent silica nanoparticles (30nm; red and 100 or 70nm; green; zeta potential: -40mV and -20mV) and as well as Cy5-conjugated pegylated PLGA nanoparticles (200nm, -7mV) in both homo- and heterospheroid models. Fluorescent microscopy on spheroid cryosections after incubation with silica nanoparticles showed that 4T1 homospheroids allowed a high penetration of about 75-80% within 24h, with higher penetration in case of the 30nm nanoparticles. In contrast, spheroids with increasing fibroblast amounts significantly inhibited NP penetration. Silica nanoparticles with a less negative zeta potential exhibited lesser penetration compared to highly negative charged nanoparticles. Subsequently, similar experiments were conducted using Cy5-conjugated pegylated PLGA nanoparticles and confocal laser scanning microscopy; an increased nanoparticle

penetration was found in 4T1 homospheroids until 48h, but significantly lower penetration in heterospheroids. Furthermore, we also developed human homospheroids (MDA-MB-231 or Panc-1 tumor cells) and heterospheroids (MDA-MB-231/BJ-hTert and Panc-1/pancreatic stellate cells) and performed silica nanoparticle (30 and 100nm) penetration studies. As a result, heterospheroids had significantly a lesser penetration of the nanoparticles compared to homospheroids. In conclusion, our data demonstrate that tumor stroma acts as a strong barrier for nanoparticle penetration. The 30-nm nanoparticles with low zeta potential favor deeper penetration. Furthermore, the herein proposed 3D co-culture platform that mimics the tumor stroma, is ideally suited to systematically investigate the factors influencing the penetration characteristics of newly developed nanomedicines to allow the design of nanoparticles with optimal penetration characteristics.

Gepubliceerd: J Control Release 2016 Dec 28;244(Pt B):257-68
Impact factor: 7.441

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4. Spontaneous Regression of Clear Cell Carcinoma of the Endometrium
Kankava K, Baidoshvili A, Schutter E, van der Meer S, Makaridze D

This report documents a rare case of complete spontaneous regression of clear cell carcinoma of the endometrium. An elderly woman with paranoid schizophrenia was admitted to the hospital because of vaginal bleeding. Diagnostic curetting and biopsy were performed and she was diagnosed with clear cell carcinoma of endometrium. Anti-tumour therapy was not possible because of her poor psychiatric status. 13 months later the woman died of a natural cause and at autopsy the endometrial tumour could no longer be identified. Myocardial infarction, aggravated by poor functional status of organism due to sepsis, was concluded to be the cause of death.

Gepubliceerd: J Cancer Ther 2016;7:635-45
Impact factor: 0

Totale impact factor: 27.435
Gemiddelde impact factor: 6.859

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

Plastische chirurgie

1. Single-stage breast reconstruction using Strattice: A retrospective study
Dikmans RE, El Morabit F, Ottenhof MJ, Tuinder SM, Twisk JW, Moues C, Bouman MB, Mullender MG

Introduction: Strattice, a porcine acellular dermal matrix, has emerged as a product to augment implant-based breast reconstruction. It aims to resolve problems related to poor tissue coverage of the implant. Presently, evidence justifying the use of Strattice in breast reconstruction is lacking. The objective of this study is to assess the clinical outcomes of a patient cohort that underwent single-stage implant-based breast reconstruction with the additional use of Strattice.
Methods: We conducted a retrospective chart review of patients who underwent single-stage breast reconstruction with the use of Strattice. All cases of breast reconstruction after oncologic or prophylactic mastectomy between 2010 and 2014 in one of eight different centres in the Netherlands were included. Patient demographics, treatment characteristics and clinical outcome data were collected. The outcomes were presented using descriptive statistics, and the associations were evaluated using Fisher's exact test.
Results: Eighty-eight patients who underwent either unilateral (60 patients) or bilateral (25 patients) (n = 110 breasts) single-stage breast reconstruction with the use of Strattice were identified. The indication for mastectomy was therapeutic in 69.1% (76) of cases and prophylactic in 30.9% (34) of cases. The reported minor complications included seroma (20.9%), skin necrosis (20.0%), wound dehiscence (11.8%), erythema/inflammation (14.5%) and infection (11.8%). In 22 breasts (22.7%), reoperation was necessary, with explantation of the implant in 11 breasts (11.8%).
Conclusions: In this cohort, the total complication rate was very high (78%). Although most complications were minor, reoperation was performed in 22.7%, with explantation of the implant in 11.8% of breasts. We suggest that patient selection, experience of the surgeon and handling of early complications are factors playing a crucial role in the success of the operation. The use of a Strattice sheet in single-stage implant-based breast reconstruction may be a promising technique, but more evidence from prospective, randomized studies is necessary to justify its use. Level of evidence: IV.

Gepubliceerd: J Plast Reconstr Aesthet Surg 2016;69(2):227-33
Impact factor: 1.743

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2. [Complicated course of a felon: prevention is better than surgical reconstruction]
Letsch MT, Kreulen M, Rakhorst HA

Infections of the hand can result in significant limitation of the function of the hand, and may even require partial amputation of a digit. A felon is an abscess of the distal pulp of the fingertip, which can spread rapidly through the flexor tendon sheath when

not treated appropriately. Knowledge of the anatomy and the correct method of physical examination are essential when assessing a patient suspected of having a felon or flexor tendon sheath infection. Here we present two patients with a complicated felon resulting in palmar necrosis of the distal phalanx of the thumb, in which a groin flap was used to reconstruct the thumb. This article describes the relevant anatomy, physical examination and treatment of a felon and flexor tendon sheath infection to prevent a complicated course.

Gepubliceerd: Ned Tijdschr Geneeskd 2016;160:D192
Impact factor: 0

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3. Microvascular reconstruction of facial defects in settings where resources are limited
Rodgers W, Lloyd T, Mizen K, Fourie L, Nishikawa H, Rakhorst H, Schmidt A, Kuoraite D, Bulstrode N, Dunaway D

The surgical treatment of defects caused by noma is challenging for the surgeon and the patient. Local flaps are preferred, but sometimes, because of the nature of the disease, there is not enough local tissue available. We describe our experience of free tissue transfer in Ethiopia. Between 2008 and 2014, 34 microsurgical procedures were done over 11 missions with the charity Facing Africa, predominantly for the treatment of defects caused by noma (n=32). The mean duration of operation was 442minutes (range 200 - 720). Six minor wound infections were treated conservatively and did not affect outcome, a return to theatre was required in 4 patients with wound infections and one with a haemorrhage; 2 flaps failed and 2 partially failed, one patient developed an oronasal fistula, and one had an infection at the donor site that required a repeat graft. In settings where resources are limited, free flaps can be used when local tissue is not available and they cause less morbidity than pedicled tissue transfer.

Gepubliceerd: Br J Oral Maxillofac Surg 2016 Jan;54(1):51-6
Impact factor: 1.237

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4. In Defense of the International Collaboration of Breast Registry Activities (ICOBRA)
Cooter R, Barnett R, Deva A, Magnusson MR, McNeil J, Perks G, Rakhorst H, Verheyden C

Gepubliceerd: Aesthet Surg J 2016 Jul;36(7):NP225-NP227
Impact factor: 0.66

Totale impact factor: 3.640
Gemiddelde impact factor: 0.910

Aantal artikelen 1e, 2e of laatste auteur: 1

Totale impact factor: 0
Gemiddelde impact factor: 0

Radiologie

1. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer
Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, Klaase JM

Background: The prevalence of colorectal cancer in the elderly is increasing and, therefore, surgical interventions with a risk of potential complications are more frequently performed. This study investigated the role of low skeletal muscle mass (sarcopenia), muscle quality, and the sarcopenic obesity as prognostic factors for postoperative complications and survival in patients with resectable colon cancer.
Methods: We conducted a retrospective chart review of 91 consecutive patients who underwent an elective open colon resection for cancer with primary anastomosis between 2011 and 2013. Skeletal muscle mass was measured as total psoas area (TPA) and total abdominal muscle area (TAMA) at three anatomical levels on the preoperative CT scan. Skeletal muscle quality was measured using corresponding mean Hounsfield units (HU) for TAMA. Their relation with complications (none vs one or more), severe complications, and survival was analyzed.
Results: The study included 91 patients with a mean age of 71.2 +/- 9.7 years. Complications were noted in 55 patients (60 %), of which 15 (16.4 %) were severe. Lower HU for TAMA, as an indicator for impaired skeletal muscle quality, was an independent risk factor for one or more complications (all P </= 0.002), while sarcopenic obesity (TPA) was an independent risk factor for severe complications (all P </= 0.008). Sarcopenia was an independent predictor of worse overall survival (HR 8.54; 95 % confidence interval (CI) 1.07-68.32).
Conclusion: Skeletal muscle quality is a predictor for overall complications, whereas sarcopenic obesity is a predictor for severe postoperative complications after open colon resection for cancer. Sarcopenia on itself is a predictor for worse overall survival.

Gepubliceerd: Int J Colorectal Dis 2016 Feb 15;31(6):1117-24
Impact factor: 2.383

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2. 'Elevated' hemidiaphragm due to a pericardial cyst
Borghouts VA, Stevenhagen YJ, Wagenaar LJ, Bouman DE, Verhorst PM

Gepubliceerd: Neth Heart J 2016;24(4):298-9
Impact factor: 2.062

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3. Radiologic extranodal spread and matted nodes: Important predictive factors for development of distant metastases in patients with high-risk head and neck cancer
de Bree R, Ljumanovic R, Hazewinkel MJ, Witte BI, Castelijns JA

Background: Different clinical high-risk factors for the development of distant metastases have been identified but not tested in the same cohort of patients with head and neck squamous cell carcinoma (HNSCC).
Methods: In 145 patients with previously identified clinical high risk factors, the presence of extranodal spread (ENS) and matted node on pretreatment CT (n = 96) and/or MRI (n = 111) were determined.
Results: Of 145 patients, ENS was detected in 87 patients (60.0%) and matted nodes in 53 patients (36.6%). Kaplan-Meier curves for presence or absence of ENS (on CT and/or MRI) and matted nodes (on CT) differ significantly. In a Cox regression analysis, only ENS was a significant risk factor (hazard ratio [HR] = 3.3; 95% confidence interval [CI] = 2.0-5.5; p < .001).
Conclusion: In patients with high-risk HNSCC with clinically (palpably or radiologically) ENS and matted nodes, both determined radiologically, are high risk factors for development of distant metastases. (c) 2015 Wiley Periodicals, Inc. Head Neck, 2015.

Gepubliceerd: Head Neck 2016;38(Suppl 1):E1452-E1458
Impact factor: 2.760

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4. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial

Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama ANG, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de VJ, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW

Importance: Intra-arterial treatment (IAT) for acute ischemic stroke caused by intracranial arterial occlusion leads to improved functional outcome in patients treated within 6 hours after onset. The influence of treatment delay on treatment effect is not yet known.
Objective: To evaluate the influence of time from stroke onset to the start of treatment and from stroke onset to reperfusion on the effect of IAT.
Design, setting, and participants: The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) was a multicenter, randomized clinical open-label trial of IAT vs no IAT in 500 patients. The time to the start of treatment was defined as the time from onset of symptoms to groin puncture (TOG). The time from onset of treatment to reperfusion (TOR) was defined as the time to reopening the vessel occlusion or the end of the procedure in cases for which reperfusion was not achieved. Data were collected

from December 3, 2010, to June 3, 2014, and analyzed (intention to treat) from July 1, 2014, to September 19, 2015.
Main outcomes and measures: Main outcome was the modified Rankin Scale (mRS) score for functional outcome (range, 0 [no symptoms] to 6 [death]). Multiple ordinal logistic regression analysis estimated the effect of treatment and tested for the interaction of time to randomization, TOG, and TOR with treatment. The effect of treatment as a risk difference on reaching independence (mRS score, 0-2) was computed as a function of TOG and TOR. Calculations were adjusted for age, National Institutes of Health Stroke Scale score, previous stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion.
Results: Among 500 patients (58% male; median age, 67 years), the median TOG was 260 (interquartile range [IQR], 210-311) minutes; median TOR, 340 (IQR, 274-395) minutes. An interaction between TOR and treatment (P = .04) existed, but not between TOG and treatment (P = .26). The adjusted risk difference (95% CI) was 25.9% (8.3%-44.4%) when reperfusion was reached at 3 hours, 18.8% (6.6%-32.6%) at 4 hours, and 6.7% (0.4%-14.5%) at 6 hours.
Conclusion and relevance: For every hour of reperfusion delay, the initially large benefit of IAT decreases; the absolute risk difference for a good outcome is reduced by 6% per hour of delay. Patients with acute ischemic stroke require immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.
Trial registration: trialregister.nl Identifier: NTR1804.

Gepubliceerd: JAMA Neurol 2016 Feb;73(2):190-6
Impact factor: 8.230

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5. The state of the art in breast imaging using the Twente Photoacoustic Mammoscope: results from 31 measurements on malignancies
Heijblom M, Piras D, van den Engh FM, van der Schaaf M, Klaase JM, Steenbergen W, Manohar S

Objectives: Photoacoustic mammography is potentially an ideal technique, however, the amount of patient data is limited. To further our understanding of the in vivo performance of the method and to guide further research and development, we imaged 33 breast malignancies using the research system - the Twente Photoacoustic Mammoscope (PAM).
Methods: Thirty-one patients participated in this retrospective, observational study. The study and informed consent procedure were approved by the local ethics committee. PAM uses 1,064 nm light for excitation with a planar, 588-element, 1-MHz ultrasound array for detection. Photoacoustic lesion visibility and appearance were compared with conventional imaging (x-ray mammography and ultrasonography) findings, histopathology and patient demographics.
Results: Of 33 malignancies 32 were visualized with high contrast and good co-localization with conventional imaging. The contrast of the detected malignancies was independent of radiographic breast density, and size estimation was reasonably good with an average 28 % deviation from histology. However, the presence of contrast areas outside the malignant region is suggestive for low specificity of the

current system. Statistical analyses did not reveal any further relationship between PAM results and patient demographics nor lesion characteristics.
Conclusions: The results confirm the high potential of photoacoustic mammography in future breast care.
Key Points: *Photoacoustic breast imaging visualizes malignancies with high imaging contrast. *Photoacoustic lesion contrast is independent of the mammographically estimated breast density.
*No clear relationship exists between photoacoustic characteristics and lesion type, grade, etc. *Photoacoustic specificity to breast cancer from some cases is not yet optimal.

Gepubliceerd: Eur Radiol 2016 Mar 5;26(11):3874-87
Impact factor: 3.640

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6. Three cases of hepatocellular carcinoma in Fontan patients: Review of the literature and suggestions for hepatic screening
Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP

The Fontan procedure has been used since 1971 as a palliative treatment for various (functionally) univentricular hearts. The systemic venous blood flows passively to the pulmonary arteries, without passing through a functional ventricle. This results in chronic systemic venous congestion, which may lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. This review discusses possible screening modalities for liver fibrosis and cirrhosis in the Fontan population and proposes a screening protocol. We suggest starting screening for progression of fibrosis and cirrhosis in collaboration with the hepatologist circa 10 years after Fontan completion. The screening programme will consist of a yearly evaluation of liver laboratory tests in conjunction with imaging of the liver with ultrasound or MRI every two years. In case of liver fibrosis or cirrhosis, (reversible) causes should be ruled out (e.g. obstruction in the Fontan circuit). In case of severe fibrosis or cirrhosis, other complications of portal hypertension should be evaluated and screening for hepatocellular carcinoma is required on a regular (6-12 months) basis. As regards hepatocellular carcinoma, treatment should be discussed in a multidisciplinary team, before deciding a treatment modality.

Gepubliceerd: Int J Cardiol 2016 Mar 1;206:21-6
Impact factor: 4.638

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7. The Effect of Unenhanced MRI on the Surgeons' Decision-Making Process in Females with Suspected Appendicitis
Ziedses des Plantes CM, van Veen MJ, van der Palen J, Klaase JM, Gielkens HA, Geelkerken RH

Background: This prospective study evaluated the impact of the results of unenhanced magnetic resonance imaging (MRI) on the surgeon's diagnosis of acute appendicitis in potentially fertile females.

Methods: 112 female patients, aged 12-55, with suspected appendicitis underwent MRI of the abdomen. At three defined intervals; admission and clinical re-evaluation before and after revealing the MRI results, the surgeon recorded the attendance of each patient in operative treatment, observation or discharge. Appendicitis was confirmed or declined by pathology or by telephone follow-up in case of non-intervention.
Findings: Appendicitis was confirmed in 29 of 112 patients. At admission the surgeon's disposition had a sensitivity of 97 % and specificity of 29 %. After knowing the MRI results, sensitivity was 97 % and specificity 64 %. The sensitivity and specificity of MRI alone were 89 and 100 %, with a negative and positive predictive value of 96 and 100 %, respectively.
Conclusion: We believe that MRI should perhaps be standard in all female patients during their reproductive years with suspected appendicitis. It avoids an operation in 32 % of cases and allows earlier planning for patients with an equivocal clinical picture. Trial number: OND1292733 (Narcis.nl).

Gepubliceerd: World J Surg 2016 Dec;40(12):2881-7
Impact factor: 2.532

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8. Traumatische fractuur van een talar beak bij tarsale coalitie
Boer BC, Bulut T, Klazen CA, Hogeboom WR

Tarsal coalition is an uncommon condition and consists of complete or partial union between two or more bones in the midfoot and hindfoot. A talar beak results from impaired subtalar joint motion and should not be confused with degenerative osteophytic changes. Different radiographic findings could lead to the recognition of a talar beak and subsequently the diagnosis of a tarsal coalition. A fractured talar beak in tarsal coalition may lead to impaired bone healing.

Gepubliceerd: Ned Tijdschr Traumachirurgie 2016;24(3):9-11
Impact factor: 0

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9. Hemangioma in the Male Breast
Mojtahedia FF, Bulut T, Oosterhof-Berktas R, Bezooijen R

We saw a 52-year-old Caucasian male in our breast care clinic. The patient had noticed a small mass in his right breast for the past couple of months without any symptoms. After undergoing several diagnostic tests, the diagnosis was a breast hemangioma. This is a rare finding in male patients, and only a couple of cases have been described before.

Gepubliceerd: J Med Cases 2016;7(8):323-5
Impact factor: 0.010

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10. Coronary or thoracic artery calcium score in provoked and unprovoked pulmonary embolism: a case-control study
van der Bijl N, Klok FA, Huisman MV, de Roos A, Kroft LJ

Essentials Patients with unprovoked pulmonary embolism (PE) are at increased risk of arterial thromboembolism. Coronary and thoracic aorta calcium were evaluated in patients with and without (unprovoked) PE. No association was found between (unprovoked) PE and coronary or aortic calcification. Assessment of both calcium scores on computed tomography pulmonary angiography was highly reproducible.
Objective: To evaluate the potential association between (unprovoked) pulmonary embolism (PE) and the presence and extent of coronary artery calcium (CAC) and thoracic aorta calcium (TAC).
Methods: CAC and TAC derived from computed tomography pulmonary angiography of 100 patients with PE were compared to that of 100 patients in whom PE was ruled out.
Results: Intraobserver and interobserver agreements for both TAC and CAC were excellent (intraclass correlation > 0.95 for both). In patients with PE vs. patients without PE, no significant differences were found in the presence of CAC or TAC (CAC 64% vs. 67%, odds ratio [OR] 1.0, 95% confidence interval [CI] 0.67-1.6; TAC 46% vs. 59%, OR 1.2, 95% CI 0.80-2.1). Mean CAC and TAC scores were significantly lower in patients with PE than in patients without PE (CAC 3.4 vs. 4.9, absolute difference 1.5, 95% CI 0.2-2.8; TAC 1.1 vs. 1.8, absolute difference 0.9, 95% CI 0.2-1.2). No significant differences were found in the presence of CAC or TAC or in mean CAC and TAC scores between patients with unprovoked PE vs. patients with provoked PE, or between patients with unprovoked PE vs. no PE.
Conclusion: No significant differences were found between the extent of CAC and TAC in patients with unprovoked PE compared to those with provoked PE or without PE. The observed difference in the extend of CAC and TAC between patients with and without PE was dependent on prevalent cardiovascular risk factors.

Gepubliceerd: J Thromb Haemost 2016 May;14(5):931-5
Impact factor: 5.565

Totale impact factor: 31.820
Gemiddelde impact factor: 3.182

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 5.575
Gemiddelde impact factor: 1.858

Radiotherapie

1. Fractionated high-dose-rate brachytherapy as monotherapy in prostate cancer: Does implant displacement and its correction influence acute and late toxicity?
Aluwini S, Busser WM, Baartman LE, Bhawanie A, Alemayehu WG, Boormans JL, Kolkman-Deurloo IK

Purpose: In fractionated high-dose-rate brachytherapy (HDR-BT) for prostate cancer (PCa) with one implant for several fractions, dose delivery relies on reproducibility of catheter positions. However, caudal displacement of implanted catheters does occur between fractions and needs to be corrected. Our protocol prescribes correction of displacements > 3 mm. We investigated whether displacement and its corrections influence acute and late toxicity incidences.
Methods and Materials: We analyzed 162 PCa patients treated with HDR-BT monotherapy between 2007 and 2013. The implant remained in situ between the 4 fractions. Catheter displacement was assessed before each fraction using lateral X-ray images and corrected if needed. Genitourinary (GU) and gastrointestinal (GI) acute and late toxicities were assessed using clinical record forms and patient self-assessment questionnaires.
Results: Implant displacement corrections (DC) were needed in 71 patients (43.8%) whereas no DCs were needed in 91 patients (56.2%). No statistically significant differences were seen in acute and late grade >/= 2 GU and GI toxicity incidences between DC and no DC groups. The maximum displacement nor the number of corrections had any influence on toxicity.
Conclusions: The occurrence and subsequent correction of implant displacements exceeding 3 mm during fractionated HDR-BT monotherapy for PCa did not lead to increased incidences of acute or late GU and GI toxicity. This indicates that our clinical protocol to correct displacements > 3 mm results in safe treatment regarding organ at risk toxicity.

Gepubliceerd: Brachytherapy 2016 Nov;15(6):707-13
Impact factor: 2.088

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2. Revisiting classification of pain from bone metastases as mild, moderate, or severe based on correlation with function and quality of life
Chow E, Ding K, Parulekar WR, Wong RK, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, Nabid A, Ong F, van Tienhoven G, Babington S, Demas WF, Wilson CF, Brundage M, Zhu L, Meyer RM

Purpose: The objective of our study was to determine the optimal cut points for classification of pain scores as mild, moderate, and severe based on interference with function and quality of life (QOL).
Methods: We evaluated 822 patients who completed the Brief Pain Inventory (BPI) and/or the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire Core 30 (QLQ-C30) prior to receiving repeat radiation therapy

for previously irradiated painful bone metastases. Optimal cut points for mild, moderate, and severe pain were determined by the MANOVA that yielded the largest F ratio for the between category effect on the seven interference items of BPI and the six functional domains of QOL (physical, role, emotional, cognitive, social functioning, and global QOL) as indicated by Pillai's Trace, Wilk's lambda, and Hostelling's Trace F statistics.
Results: For BPI and for QOL domains separately, the two largest F ratios for Wilk's lambda, Pillai's Trace, and Hotelling's Trace F statistics were from the cut points 4, 8 and 6,**8.** When combining both, the optimal cut points were 4, 8 with 1-4 (mild), 5-8 (moderate), and 9-10 (severe). With this classification, the mean scores of all the seven interference items in BPI and the six functional domains were all highly statistically different. Patients with severe pain survived significantly shorter than those with mild and moderate pain ($p < 0.0001$).
Conclusion: Our analysis supports the classification of pain scores as follows: 1-4 as mild pain, 5-8 as moderate pain, and 9-10 as severe pain. This may facilitate conduct of future clinical trials.

Gepubliceerd: Support Care Cancer 2016;24(4):1617-23
Impact factor: 2.535

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3. Progression of a solitary plasmacytoma to multiple myeloma. A population-based registry of the northern Netherlands
de Waal EG, Leene M, Veeger N, Vos HJ, Ong F, Smit WG, Hovenga S, Hoogendoorn M, Hogenes M, Beijert M, Diepstra A, Vellenga E

Plasmacytoma is characterized by a local accumulation of monoclonal plasma cells without criteria for multiple myeloma (MM). The current treatment regimen is local radiotherapy. However, more than 50% of patients develop MM within 2 years after treatment. A population-based registry was consulted for the diagnosis of solitary plasmacytoma between 1988 and 2011. Progression to MM and prognostic features for progression to MM were scored, including hypoxia inducible factors (HIF), vascular endothelial growth factor (VEGF, also termed VEGFA) and micro-vessel density (MVD) expression in biopsy material. A total of 76 patients were included, 34% having extramedullary plasmacytoma (EMP) while 66% had a solitary plasmacytoma of the bone (SBP). Median follow-up was 89 months, (7-293 months). In Seventy per cent of SBP patients developed MM with a median time to progression of 19 months (5-293). Three patients (12%) with EMP developed MM. High expression of VEGF and HIF-2alpha (also termed EPAS1) was demonstrated in conjunction with an increased MVD in 66% of the patients. No association could be shown between angiogenesis parameters and progression to MM. In conclusion, this population-based study demonstrates that SBP patients have a higher risk of developing MM following local radiotherapy, indicating that this group might benefit from added systemic chemotherapy.

Gepubliceerd: Br J Haematol 2016 Nov;175(4):661-7
Impact factor: 4.942

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4. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial
Lutgens LC, Koper PC, Jobsen JJ, van der Steen-Banasik EM, Creutzberg CL, van den Berg HA, Ottevanger PB, van Rhoon GC, van Doorn HC, Houben R, van der Zee J

Background: Chemoradiation (RT-CT) is standard treatment for locally advanced cervical cancer (LACC). This study tried to establish if radiotherapy combined with hyperthermia (RT-HT) should be preferred in bulky and/or FIGO-stage III.
Methods: In this open-label, multicenter randomized trial, patients with LACC were randomly assigned by a computer-generated, biased coin minimization technique to RT-CT or RT-HT. Central randomization was done with stratification by FIGO-stage, tumour diameter and nodal status. Primary endpoint was event free survival (EFS). Secondary endpoints were pelvic recurrence free survival (PRFS), overall survival (OS) and treatment related toxicity. Analysis was done by intention to treat.
Results: The trial was closed prematurely (87 of 376 planned patients enrolled: 43 RT-CT; 44 RT-HT). Median follow-up time was 7.1 years. The cumulative incidence of an event was 33% in the RT-CT group and 35% in the RT-HT group. The corresponding hazard rate (HR) for EFS was 1.15 (CI: 0.56-2.36, p=0.7). Also the hazards for PRFS (0.94; CI 0.36-2.44) and OS (1.04; CI 0.48-2.23) at 5 years were comparable between both treatment arms as was grade 3 radiation related late toxicity (6 RT-CT and 5 RT-HT patients).
Conclusion: After 25% of intended accrual, data suggest comparable outcome for RT-CT and RT-HT.

Gepubliceerd: Radiother Oncol 2016 Sep;120(3):378-82
Impact factor: 4.817

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5. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts
Stelloo E, Nout RA, Osse EM, Jurgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Nijman HW, Putter H, Bosse T, Creutzberg CL, Smit VT

Purpose: Recommendations for adjuvant treatment for women with early-stage endometrial carcinoma are based on clinicopathologic features. Comprehensive genomic characterization defined four subgroups: p53-mutant, microsatellite instability (MSI), POLE-mutant, and no specific molecular profile (NSMP). We aimed to confirm the prognostic capacity of these subgroups in large randomized trial populations, investigate potential other prognostic classifiers, and integrate these into an integrated molecular risk assessment guiding adjuvant therapy.
Experimental design: Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, beta-catenin, L1CAM, PTEN, ER, and PR was undertaken on 947 available early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials, mostly high-intermediate risk (n = 614). Prognostic value was determined using univariable and multivariable Cox

proportional hazard models. AUCs of different risk stratification models were compared.
Results: Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of high-intermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant).
Conclusions: Integrating clinicopathologic and molecular factors improves the risk assessment of patients with early-stage endometrial carcinoma. Assessment of this integrated risk profile is feasible in daily practice, and holds promise to reduce both overtreatment and undertreatment. Clin Cancer Res; 22(16); 4215-24. (c)2016 AACR.

Gepubliceerd: Clin Cancer Res 2016 Aug 15;22(16):4215-24
Impact factor: 8.738

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6. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers
van den Broek AJ, van 't Veer LJ, Hooning MJ, Cornelissen S, Broeks A, Rutgers EJ, Smit VT, Cornelisse CJ, van Beek M, Janssen-Heijnen ML, Seynaeve C, Westenend PJ, Jobsen JJ, Siesling S, Tollenaar RA, van Leeuwen FE, Schmidt MK

Purpose: To determine prospectively overall and age-specific estimates of contralateral breast cancer (CBC) risk for young patients with breast cancer with or without BRCA1/2 mutations. PATIENTS AND
Methods: A cohort of 6,294 patients with invasive breast cancer diagnosed under 50 years of age and treated between 1970 and 2003 in 10 Dutch centers was tested for the most prevalent BRCA1/2 mutations. We report absolute risks and hazard ratios within the cohort from competing risk analyses.
Results: After a median follow-up of 12.5 years, 578 CBCs were observed in our study population. CBC risk for BRCA1 and BRCA2 mutation carriers was two to three times higher than for noncarriers (hazard ratios, 3.31 [95% CI, 2.41 to 4.55; P < .001] and 2.17 [95% CI,1.22 to 3.85; P = .01], respectively). Ten-year cumulative CBC risks were 21.1% (95% CI, 15.4 to 27.4) for BRCA1, 10.8% (95% CI, 4.7 to 19.6) for BRCA2 mutation carriers and 5.1% (95% CI, 4.5 to 5.7) for noncarriers. Age at diagnosis of the first breast cancer was a significant predictor of CBC risk in BRCA1/2 mutation carriers only; those diagnosed before age 41 years had a 10-year cumulative CBC risk of 23.9% (BRCA1: 25.5%; BRCA2: 17.2%) compared with 12.6% (BRCA1: 15.6%; BRCA2: 7.2%) for those 41 to 49 years of age (P = .02); our review of published studies showed ranges of 24% to 31% before age 40 years (BRCA1: 24% to 32%; BRCA2:17% to 29%) and 8% to 21% after 40 years (BRCA1: 11% to 52%; BRCA2: 7% to 18%), respectively.

Conclusion: Age at first breast cancer is a strong risk factor for cumulative CBC risk in BRCA1/2 mutation carriers. Considering the available evidence, age-specific risk estimates should be included in counseling.

Gepubliceerd: J Clin Oncol 2016;34(5):409-18
Impact factor: 20.982

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7. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study
van Maaren MC, de ML, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, Poortmans P, Strobbe LJ, Siesling S

Background: Investigators of registry-based studies report improved survival for breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer. As these studies did not present long-term overall and breast cancer-specific survival, the effect of breast-conserving surgery plus radiotherapy might be overestimated. In this study, we aimed to evaluate 10 year overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy compared with mastectomy in Dutch women with early breast cancer.
Methods: In this population-based study, we selected all women from the Netherlands Cancer Registry diagnosed with primary, invasive, stage T1-2, N0-1, M0 breast cancer between Jan 1, 2000, and Dec 31, 2004, given either breast-conserving surgery plus radiotherapy or mastectomy, irrespective of axillary staging or dissection or use of adjuvant systemic therapy. Primary outcomes were 10 year overall survival in the entire cohort and breast cancer-specific survival in a representative subcohort of patients diagnosed in 2003 with characteristics similar to the entire cohort. We estimated breast cancer-specific survival by calculating distant metastasis-free and relative survival for every tumour and nodal category. We did multivariable Cox proportional hazard analysis to estimate hazard ratios (HRs) for overall and distant metastasis-free survival. We estimated relative survival by calculating excess mortality ratios using life tables of the general population. We did multiple imputation to account for missing data.
Findings: Of the 37 207 patients included in this study, 21 734 (58%) received breast-conserving surgery plus radiotherapy and 15 473 (42%) received mastectomy. The 2003 representative subcohort consisted of 7552 (20%) patients, of whom 4647 (62%) received breast-conserving surgery plus radiotherapy and 2905 (38%) received mastectomy. For both unadjusted and adjusted analysis accounting for various confounding factors, breast-conserving surgery plus radiotherapy was significantly associated with improved 10 year overall survival in the whole cohort overall compared with mastectomy (HR 0.51 [95% CI 0.49-0.53]; p<0.0001; adjusted HR 0.81 [0.78-0.85]; p<0.0001), and this improvement remained significant for all subgroups of different T and N stages of breast cancer. After adjustment for confounding variables, breast-conserving surgery plus radiotherapy did not significantly improve 10 year distant metastasis-free survival in the 2003 cohort overall compared with mastectomy (adjusted HR 0.88 [0.77-1.01]; p=0.07), but did in the T1N0 subgroup (adjusted 0.74 [0.58-0.94]; p=0.014). Breast-

conserving surgery plus radiotherapy did significantly improve 10 year relative survival in the 2003 cohort overall (adjusted 0.76 [0.64-0.91]; p=0.003) and in the T1N0 subgroup (adjusted 0.60 [0.42-0.85]; p=0.004) compared with mastectomy. **Interpretation:** Adjusting for confounding variables, breast-conserving surgery plus radiotherapy showed improved 10 year overall and relative survival compared with mastectomy in early breast cancer, but 10 year distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. These results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to overall survival and may influence treatment decision making for patients with early breast cancer. FUNDING: None.

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Impact factor: 26.509

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8. Breast-conserving therapy versus mastectomy in T1-2N2 stage breast cancer: a population-based study on 10-year overall, relative, and distant metastasis-free survival in 3071 patients
van Maaren MC, de Munck L, Jobsen JJ, Poortmans P, de Bock GH, Siesling S, Strobbe LJ

Purpose: Our previous study demonstrated breast-conserving surgery with radiation therapy (BCT) to be at least equivalent to mastectomy in T1-2N0-1 breast cancer. Yet, 10-year survival rates after BCT and mastectomy with radiation therapy (MAST) in T1-2N2 breast cancer specifically have not been examined. Our study aimed to determine 10-year overall (OS), relative (RS), and distant metastasis-free survival (DMFS) in T1-2N2 breast cancer after BCT and MAST, stratified for T category. **Methods:** All women diagnosed with primary invasive T1-2N2 breast cancer in 2000-2004, treated with BCT or MAST, both with axillary dissection and RT, were selected from the Netherlands Cancer Registry. Ten-year OS and DMFS were estimated using multivariable Cox regression. Excess mortality ratios (EMR) were calculated to estimate RS, using life tables of the general population. OS and RS were determined on the whole cohort, and DMFS on the 2003 cohort with completed follow-up. Missing data were imputed. **Results:** Of 3071 patients, 1055 (34.4 %) received BCT and 2016 (65.7 %) MAST. BCT and MAST showed equal 10-year OS and RS. After stratification, BCT was significantly associated with improved 10-year OS [HRadjusted 0.82 (95 % CI 0.71-0.96)] and RS (EMRadjusted 0.81 (95 % CI 0.67-0.97]) in T2N2, but not in T1N2. Ten-year DMFS was equal for both treatments [HRadjusted 0.87 (95 % CI 0.64-1.18)] in the 2003 cohort (n = 594), which was representative for the full cohort. **Conclusion:** BCT showed at least equal 10-year OS, RS, and DMFS compared to MAST. These results confirm that BCT is a good treatment option in T1-2N2 breast cancer.

Gepubliceerd: Breast Cancer Res Treat 2016 Dec;160(3):511-21
Impact factor: 4.085

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9. Course of Quality of Life After Radiation Therapy for Painful Bone Metastases: A Detailed Analysis From the Dutch Bone Metastasis Study
Westhoff PG, Verdam MG, Oort FJ, Jobsen JJ, van Vulpen M, Leer JW, Marijnen CA, de Graeff A, van der Linden YM

Purpose: To study the course of quality of life (QoL) after radiation therapy for painful bone metastases.
Patients and methods: The Dutch Bone Metastasis Study randomized 1157 patients with painful bone metastases between a single fraction of 8 Gy and 6 fractions of 4 Gy between 1996 and 1998. The study showed a comparable pain response of 74%. Patients filled out weekly questionnaires for 13 weeks, then monthly for 2 years. In these analyses, physical, psychosocial, and functional QoL domain scores and a score of general health were studied. Mixed modeling was used to model the course of QoL and to study the influence of several characteristics.
Results: In general, QoL stabilized after 1 month. Psychosocial QoL improved after treatment. The level of QoL remained stable, steeply deteriorating at the end of life. For most QoL domains, a high pain score and intake of opioids were associated with worse QoL, with small effect sizes (-0.11 to -0.27). A poor performance score was associated with worse functional QoL, with a medium effect size (0.41). There is no difference in QoL between patients receiving a single fraction of 8 Gy and 6 fractions of 4 Gy, except for a temporary worsening of physical QoL after 6 fractions.
Conclusion: Although radiation therapy for painful bone metastases leads to a meaningful pain response, most domains of QoL do not improve after treatment. Only psychosocial QoL improves slightly after treatment. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterward a sharp decrease, starting only a few weeks before the end of life. Six fractions of 4 Gy lead to a temporary worse physical QoL compared with a single fraction of 8 Gy.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2016 Aug 1;95(5):1391-8
Impact factor: 4.495

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10. Photoacoustic-guided focused ultrasound for accurate visualization of brachytherapy seeds with the photoacoustic needle
Singh MK, Parameshwarappa V, Hendriksen E, Steenbergen W, Manohar S

Gepubliceerd: J Biomed Opt 2016 Dec 1;21(12):120501
Impact factor: 2.556

Totale impact factor: 81.747
Gemiddelde impact factor: 8.175

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

Gemiddelde impact factor: 0

Reumatologie

1. Barriers and facilitators to disease-modifying antirheumatic drug use in patients with inflammatory rheumatic diseases: a qualitative theory-based study
Voshaar M, Vriezekolk J, van DS, van den Bemt B, van de Laar M

Background: Although disease-modifying anti-rheumatic drugs (DMARDs) are the cornerstone of treatment for inflammatory rheumatic diseases, medication adherence to DMARDs is often suboptimal. Effective interventions to improve adherence to DMARDs are lacking, and new targets are needed to improve adherence. The aim of the present study was to explore patients' barriers and facilitators of optimal DMARD use. These factors might be used as targets for adherence interventions.
Methods: In a mixed method study design, patients (n = 120) with inflammatory arthritis (IA) completed a questionnaire based on an existing adapted Theoretical Domains Framework (TDF) to identify facilitators and barriers of DMARD use. A subgroup of these patients (n = 21) participated in focus groups to provide insights into their facilitators and barriers. The answers to the questionnaires and responses of the focus groups were thematically coded by three researchers independently and subsequently categorized.
Results: The barriers and facilitators that were reported by IA patients presented large inter-individual variations. The identified barriers and facilitators could be captured in the following domains based on an adapted TDF: (i) knowledge, (ii) emotions, (iii) attention, memory, and decision processes, (iv) social influences, (v) beliefs about capability, (vi) beliefs about consequences, (vii) motivation and goals, (viii) goal conflict, (ix) environmental context and resources, and (x) skills.
Conclusions: Patients with IA have a variety of barriers and facilitators with regard to their DMARD use. All of these barriers and facilitators could be categorized into adapted domains of the TDF. Interventions that address individual facilitators and barriers, based on capability, opportunity, and motivation, are needed to develop strategies for medication adherence that are tailored to individual patient needs.

Gepubliceerd: BMC Musculoskelet Disord 2016 Oct 21;17(1):442
Impact factor: 1.684

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2. The longitudinal relation between patterns of goal management and psychological health in people with arthritis: The need for adaptive flexibility
Arends RY, Bode C, Taal E, van de Laar MA

Objectives: Due to their disease, patients with polyarthritis face the task of reconciling their threatened personal goals with their capabilities. Previous cross-sectional research on patients with chronic disease related higher levels of goal management strategies to lower levels of distress and higher levels of well-being. This study was the first to focus longitudinally on goal management patterns that combined strategies originating from different goal management theories. Our first

study objective was to identify patterns that consisted of various strategies of goal management among patients with polyarthritis. Subsequently, the cross-sectional and longitudinal relationships between these patterns and the psychological health of the patients were studied.
Methods: A longitudinal questionnaire study with three measurements of goal management and psychological health was conducted among 331 patients with polyarthritis. Stability of goal management over time was analysed with ANOVAs. Patterns were identified using cluster analysis at baseline, based on the following strategies: Goal maintenance, goal adjustment, goal disengagement, and goal reengagement. Longitudinal relationships between the patterns and psychological health (specifically: Depression, anxiety, purpose in life, positive affect, and social participation) were analysed using a generalized estimating equations analysis.
Results: Three goal management patterns were found: 'Moderate engagement', 'Broad goal management repertoire', and 'Holding on'. Patients with the 'Broad goal management repertoire' pattern had the highest level of psychological health. The 'Holding on' pattern was identified as the most unfavourable in terms of psychological health. Over time, stable differences in levels of psychological health between the patterns were found.
Conclusions: This study was the first to reveal patterns of several goal management strategies and their longitudinal relationship to psychological health. Psychosocial support for arthritis patients with lower psychological health should focus on helping patients to become familiar with a broad range of goal management strategies when dealing with threatened goals. STATEMENT OF CONTRIBUTION: What is already known on this subject? Polyarthritis is a collective term for a variety of disorders associated with autoimmune pathologies that may affect all aspects of a person's physical, psychological, and social functioning. Patients often experience difficulties in maintaining and achieving goals in several domains of life due to disease symptoms. The process of emotional adaptation to polyarthritis is characterized by searching equilibrium between desires and constraints and reacting constructive to stressors. Goal management strategies are ways to minimize the perceived disparity between the actual and the preferred situation with regard to personal goals and are applied both consciously and unconsciously. Cross-sectional, higher levels of goal management strategies have been related to lower levels of distress and higher levels of well-being both in patients with polyarthritis and in other patient groups. What does this study add? Contributes to our understanding of how combinations of goal management strategies relate to psychological health. Identifies patterns of goal management that are longitudinally related to psychological health. Provides clear guidance for improving psychological health of people with polyarthritis.

Gepubliceerd: Br J Health Psychol 2016 May;21(2):469-89
Impact factor: 2.895

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3. Exploring Fatigue Trajectories in Early Symptomatic Knee and Hip Osteoarthritis: 6-year Results from the CHECK Study
Botterman J, Bode C, Siemons L, van de Laar MA, Dekker J

Objective: To examine whether different groups of fatigue trajectories can be identified among patients with early symptomatic osteoarthritis (OA) of the knee or hip, to describe the level of fatigue severity within each of these fatigue groups, and to investigate the involvement of age, sex, use of medication, comorbidity, and OA severity in relation to group membership.
Methods: Six years of followup data on fatigue (Medical Outcomes Study Short Form-36 Vitality scale) came from the Cohort Hip and Cohort Knee (CHECK) cohort. Growth mixture modeling was applied to identify distinct fatigue trajectories as well as to take into account the effects of the patient characteristics.
Results: Three fatigue trajectories were identified: low fatigue, low-to-high fatigue, and high fatigue. Latter trajectories showed considerable overlap from years 2 to 6, but differed in some patient characteristics in comparison with each other and in comparison with the low fatigue group. Comorbidity, medication use, and sex were significantly associated with the identified trajectories. Women, individuals with a comorbid disease, and those who used medication were more likely to follow a high fatigue trajectory.
Conclusion: These findings suggest heterogeneous development of fatigue in the early OA population associated with varying patient characteristics. Further, this study shows that a considerable number of patients with OA already experience elevated levels of fatigue at an early stage of OA. While these findings need to be replicated, the identification of these trajectories with differing patient characteristics may warrant tailored psychosocial interventions for patients with elevated levels of fatigue.

Gepubliceerd: J Rheumatol 2016 Jul;43(7):1413-20
Impact factor: 3.236

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4. Development of Preliminary Remission Criteria for Gout Using Delphi and 1000Minds(R) Consensus Exercises
de Lautour H, Taylor WJ, Adebajo A, Alten R, Burgos-Vargas R, Chapman P, Cimmino MA, da Rocha Castelar Pinheiro G, Day R, Harrold LR, Helliwell P, Janssen M, Kerr G, Kavanaugh A, Khanna D, Khanna PP, Lin C, Louthrenoo W, McCarthy G, Vazquez-Mellado J, Mikuls TR, Neogi T, Ogdie A, Perez-Ruiz F, Schlesinger N, Schumacher HR, Scire CA, Singh JA, Sivera F, Slot O, Stamp LK, Tausche AK, Terkeltaub R, Uhlig T, van de Laar M, White D, Yamanaka H, Zeng X, Dalbeth N

Objectives: The aim of this study was to establish consensus for potential remission criteria for use in clinical trials of gout.
Methods: Experts (n=88) in gout from multiple countries were invited to participate in a web-based questionnaire study. Three rounds of Delphi consensus exercises were conducted using SurveyMonkey(R) followed by a discrete choice experiment using 1000Minds(R). The exercises focused on identifying domains, definitions for each domain and the timeframe over which remission should be defined.
Results: There were 49 respondents (56% response) to the initial survey with subsequent response rates ranging from 57% to 90%. Consensus was reached for the inclusion of serum urate (98% agreement), flares (96%), tophi (92%), pain (83%)

and patient global assessment (93%) of disease activity as measurement domains in remission criteria. Consensus was also reached for domain definitions including serum urate (< 0.36mM), pain (<2 on a 10-point scale) and patient global assessment (<2 on a 10-point scale), all of which should be measured at least twice over a set time interval. Consensus was not achieved in the Delphi exercise for the timeframe for remission with equal responses for six months (51%) and one year (49%). In the discrete choice experiment, there was a preference towards 12 months as a timeframe for remission.
Conclusion: These consensus exercises have identified domains and provisional definitions for gout remission criteria. Based on the results of these exercises, preliminary remission criteria are proposed with domains of serum urate, acute flares, tophus, pain and patient global assessment. These preliminary criteria now require testing in clinical datasets.

Gepubliceerd: Arthritis Care Res (Hoboken) 2016;68(5):667-72
Impact factor: 4.713

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5. Measuring the Therapeutic Relationship in Internet-Based Interventions
Ferwerda M, van Beugen S, van Riel PC, van de Kerkhof PC, de Jong EM, Smit JV, Zeeuwen-Franssen ME, Kroft EB, Visser H, Vonkeman HE, Creemers MC, van Middendorp H, Evers AW

Gepubliceerd: Psychother Psychosom 2016;85(1):47-9
Impact factor: 0.080

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6. Stopping Tumor Necrosis Factor Inhibitor Treatment in Patients With Established Rheumatoid Arthritis in Remission or With Stable Low Disease Activity: A Pragmatic Multicenter, Open-Label Randomized Controlled Trial
Ghiti Moghadam M, Vonkeman HE, Ten Klooster PM, Tekstra J, van Schaardenburg D, Starmans-Kool M, Brouwer E, Bos R, Lems WF, Colin EM, Allaart CF, Meek IL, Landewe R, Bernelot Moens HJ, van Riel PL, van de Laar MA, Jansen TL

Objective: Tumor necrosis factor inhibitor (TNFi) biologic agents are an effective treatment for rheumatoid arthritis (RA). It is unclear whether patients whose disease is in remission or who have stable low disease activity need to continue use of TNFi or can stop this treatment. This study was undertaken to assess whether patients with established RA who are in remission or have stable low disease activity can effectively and safely stop their TNFi therapy.
Methods: The study was designed as a pragmatic multicenter, open-label randomized controlled trial. Inclusion criteria were a diagnosis of RA according to the American College of Rheumatology 1987 classification criteria, as well as use of a TNFi for at least 1 year along with a stable dose of disease-modifying antirheumatic drugs and a Disease Activity Score in 28 joints (DAS28) of <3.2 over the 6 months preceding trial inclusion. Patients were randomized in a 2:1 ratio to either stop or continue treatment with their current TNFi. Flare was defined as a

DAS28 of >/=3.2 during the 12-month follow-up period and an increase in score of >/=0.6 compared to the baseline DAS28.
Results: In total, 531 patients were allocated to the stop group and 286 to the TNFi continuation group. At 12 months, more patients had experienced a flare in the stop group (272 [51.2%] of 531) than in the continuation group (52 [18.2%] of 286; P < 0.001). The hazard ratio for occurrence of a flare after stopping TNFi was 3.50 (95% confidence interval [95% CI] 2.60-4.72). The mean DAS28 in the stop group was significantly higher during the follow-up period compared to that in the continuation group (P < 0.001). Of the 195 patients who restarted TNFi treatment after experiencing a flare and within 26 weeks after stopping, 165 (84.6%) had regained a DAS28 of <3.2 by 6 months later, and the median time to a regained DAS28 of <3.2 was 12 weeks (95% CI 10.7-13.3). There were more hospitalizations in the stop group than in the continuation group (6.4% versus 2.4%).
Conclusion: Stopping TNFi treatment results in substantially more flares than does continuation of TNFi in patients with established RA in remission or with stable low disease activity.

Gepubliceerd: Arthritis Rheumatol 2016 Aug;68(8):1810-7
Impact factor: 6.009

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7. The Minimum Clinically Important Improvement and Patient-acceptable Symptom State in the BASDAI and BASFI for Patients with Ankylosing Spondylitis
Kviatkovsky MJ, Ramiro S, Landewe R, Dougados M, Tubach F, Bellamy N, Hochberg M, Ravaud P, Martin-Mola E, Awada H, Bombardier C, Felson D, Hajjaj-Hassouni N, Logeart I, Matucci-Cerinic M, van de Laar M, van der Heijde D

Objective: To establish cutoffs for the minimum clinically important improvement (MCII) and the patient-acceptable symptom state (PASS) for the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in patients with ankylosing spondylitis (AS).
Methods: Patients with AS who started nonsteroidal antiinflammatory drugs were included. After 4 weeks, the PASS and the MCII were defined using external anchor questions (for the PASS, patients considering their condition of AS over the prior 48 h as "acceptable" forever; and for the MCII, those reporting moderate or slightly important improvement). Consistency of the MCII and PASS were tested according to HLA-B27 status, presence/absence of SpA extraarticular manifestations, age, sex, disease duration, and baseline BASDAI/BASFI score. The 75th percentile of the cumulative distribution was used to determine the MCII and PASS.
Results: In total, 283 patients from a multinational cohort were included. Overall cutoffs for the PASS were 4.1 in the BASDAI and 3.8 in the BASFI. Cutoffs for the MCII were 0.7 and 0.4 for the BASDAI and BASFI, respectively. Subgroup analyses revealed that disease duration and baseline BASDAI/BASFI were significantly associated with the PASS and MCII. In a subanalysis limited to patients with active disease (baseline BASDAI >/= 4), the MCII was 1.1 for the BASDAI and 0.6 for the BASFI.

Conclusion: The conceptual viability of the PASS for the BASDAI is questionable because levels approach those required for the start of biological therapy. Because the MCII is less variable than the PASS, we propose its exclusive use, with cutoffs of 1.1/0.6 for the BASDAI/BASFI in patients with active disease. Because these values are based on a subset of the study population, we recommend confirmation in larger studies focused on patients with baseline BASDAI >/= 4.

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Impact factor: 3.236

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8. Effectiveness of Tumor Necrosis Factor Inhibitors in Combination with Various csDMARD in the Treatment of Rheumatoid Arthritis: Data from the DREAM Registry
Manders SH, Kievit W, Jansen TL, Stolk JN, Visser H, Schilder AM, Vonkeman HE, Adang E, van de Laar MA, van Riel PL

Objective: To analyze and compare the effectiveness and drug survival in patients with rheumatoid arthritis, as measured by 28-joint Disease Activity Score (DAS28) and Health Assessment Questionnaire-Disability Index (HAQ-DI), of tumor necrosis factor inhibitor (TNFi) monotherapy, TNFi + leflunomide (LEF), TNFi + sulfasalazine (SSZ), TNFi + other conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and TNFi + methotrexate (MTX) therapy, in daily practice.
Methods: Data were collected from the DREAM registry. Patients beginning their first TNFi treatment were included in the study: TNFi monotherapy (n = 320), TNFi + SSZ (n = 103), TNFi + LEF (n = 80), TNFi + other csDMARD (n = 99), TNFi + MTX alone (n = 919), TNFi + MTX + other csDMARD (n = 412). Treatment effectiveness was analyzed using DAS28 and HAQ-DI with linear mixed models and the TNFi drug survival was analyzed using Kaplan-Meier curves and Cox regression. All analyses have been corrected for confounders.
Results: The patients who received TNFi + MTX had significantly better DAS28 and HAQ-DI values over time (both $p < 0.001$) and longer TNFi drug survival than TNFi monotherapy ($p < 0.001$). TNFi + SSZ and TNFi + other csDMARD had significantly better DAS28 values over time ($p = 0.001$) and longer drug survival ($p = 0.001$) versus TNFi monotherapy. TNFi + LEF was not significantly better compared to monotherapy. Adding other csDMARD to the TNFi + MTX combination provided no added value.
Conclusion: Preferably, TNFi should be prescribed together with MTX. If this is not possible, we advise the use of other csDMARD.

Gepubliceerd: J Rheumatol 2016 Oct;43(10):1787-94
Impact factor: 3.236

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9. Arthritis patients' motives for (not) wanting to be involved in medical decision-making and the factors that hinder or promote patient involvement
Nota I, Drossaert CH, Taal E, van de Laar MA

The aim of this study is to gain insight into arthritis patients' motives for (not) wanting to be involved in medical decision-making (MDM) and the factors that hinder or promote patient involvement. In-depth semi-structured interviews were conducted with 29 patients suffering from Rheumatoid Arthritis (RA). Many patients perceived the questions about involvement in MDM as difficult, mostly because they were unaware of having a choice. Shared decision-making (SDM) was generally preferred, but the preferred level of involvement varied between and within individuals. Preference regarding involvement may vary according to the type of treatment and the severity of the complaints. A considerable group of respondents would have liked more participation than they had experienced in the past. Perceived barriers could be divided into doctor-related (e.g. a paternalistic attitude), patient-related (e.g. lack of knowledge) and context-related (e.g. too little time to decide) factors. This study demonstrates the complexity of predicting patients' preferences regarding involvement in MDM: most RA patients prefer SDM, but their preference may vary according to the situation they are in and the extent to which they experience barriers in getting more involved. Unawareness of having a choice is still a major barrier for patient participation. The attending physician seems to have an important role as facilitator in enhancing patient participation by raising awareness and offering options, but implementing SDM is a shared responsibility; all parties need to be involved and educated.

Gepubliceerd: Clin Rheumatol 2016 May;35(5):1225-35
Impact factor: 2.042

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10. Evaluation of a patient decision aid for initiating disease modifying anti-rheumatic drugs

Nota I, Drossaert CH, Taal E, Vonkeman HE, Haagsma CJ, van de Laar MA

Background: According to international guidelines, treatment of inflammatory arthritis should be based on a shared decision between patient and rheumatologist. Furthermore, patients with inflammatory arthritis have high need of information and want to be more actively involved in medical decision-making. To facilitate shared decision-making and support patients in choosing between disease modifying anti-rheumatic drugs (DMARDs), a web-based patient decision aid (PtDA) was developed. This study evaluated use, appreciation and effect of this PtDA.
Methods: A post-test only study with a historical comparison group was conducted. In a two-year period, all patients diagnosed with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis, who were deciding whether to start a (different) DMARD were invited to participate. In the first year, patients received standard information (comparison group). In the second year, patients were referred to the PtDA (intervention group). In both groups, a questionnaire was sent four weeks after consulting the rheumatologist. Patient characteristics included sociodemographic, health-related and preference-related variables. Process measures were for use and appraisal of the PtDA (intervention group only). The primary outcome measure was patients' perceived role in medical decision-making. Secondary outcome measures comprised satisfaction with the decision-making process and the decision, beliefs about medication, adherence to medication and trust in the physician.

Results: We received 158/232 questionnaires (68 %) from the comparison group and 123/200 (61 %) from the intervention group. The PtDA was used by 69/123 patients (57 %) in the intervention group. Patients who used the PtDA highly appreciated it and perceived it as easy to use and helpful. Relative to the comparison group, patients in the intervention group perceived a more active role in medical decision-making and decisions were more in line with patients' personal preferences. Other outcomes showed no significant difference between the two groups.
Conclusion: The web-based PtDA was highly appreciated and perceived as helpful for decision-making. Implementation of the PtDA in rheumatology practice was associated with a significantly larger proportion of patients perceiving an active role in medical decision-making and decisions were more in line with patients' personal preferences. The PtDA can be a valuable aid in improving patient participation in decision-making about DMARDs.

Gepubliceerd: Arthritis Res Ther 2016 Oct 28;18(1):252
Impact factor: 3.979

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11. Development and Validation of a Short Form of the Social Role Participation Questionnaire in Patients with Ankylosing Spondylitis
Oude Voshaar MA, van Onna M, van Genderen S, van de Laar M, van der Heijde D, Heuft L, Spoorenberg A, Luime J, Gignac M, Boonen A

Objective: The Social Role Participation Questionnaire (SRPQ) assesses the influence of health on 11 specific roles and 1 general role along 4 dimensions. In this study, a shortened version of the SRPQ (s-SRPQ) was developed in patients with ankylosing spondylitis (AS) to facilitate data collection in clinical studies and practice.
Methods: Using data from 246 patients with AS and population controls, the fit of each role to the different participation dimensions, the contribution of each role to the measurement precision, and the correlation between dimensions were evaluated using item response theory. Representation of the 3 participation chapters of the International Classification of Functioning, Disability, and Health was ensured. Reliability of each dimension of both versions of the SRPQ was compared by correlating scores to the Medical Outcomes Study Short Form-36 (SF-36) and the Satisfaction With Life Scale (SWLS), and by comparing ability to discriminate between patients and controls and between patients with low and high disease activity (Bath Ankylosing Spondylitis Disease Activity Index >/= 4).
Results: The s-SRPQ, which assesses participation across 6 social roles along 2 dimensions (physical difficulty and satisfaction with performance), was proposed. Both dimensions of the s-SRPQ were highly reliable (r >/= 0.86) and were shown to have construct validity as indicated by a similar pattern of correlations with the SF-36 and SWLS as the original SRPQ dimensions. Both versions discriminated well between patients and controls and between patients with high versus low disease activity (relative validity >/= 0.72).
Conclusion: The s-SRPQ retains the measurement properties of the original SRPQ and seems useful for measuring the effect of AS on participation.

Gepubliceerd: J Rheumatol 2016 Jul;43(7):1386-92
Impact factor: 3.236

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12. Further Simplification of the Simple Erosion Narrowing Score With Item Response Theory Methodology
Oude Voshaar MA, Schenk O, Ten Klooster PM, Vonkeman HE, Bernelot Moens HJ, Boers M, van de Laar MA

Objective: To further simplify the simple erosion narrowing score (SENS) by removing scored areas that contribute the least to its measurement precision according to analysis based on item response theory (IRT) and to compare the measurement performance of the simplified version to the original.
Methods: Baseline and 18-month data of the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial were modeled using longitudinal IRT methodology. Measurement precision was evaluated across different levels of structural damage. SENS was further simplified by omitting the least reliably scored areas. Discriminant validity of SENS and its simplification were studied by comparing their ability to differentiate between the COBRA and sulfasalazine arms. Responsiveness was studied by comparing standardized change scores between versions.
Results: SENS data showed good fit to the IRT model. Carpal and feet joints contributed the least statistical information to both erosion and joint space narrowing scores. Omitting the joints of the foot reduced measurement precision for the erosion score in cases with below-average levels of structural damage (relative efficiency compared with the original version ranged 35-59%). Omitting the carpal joints had minimal effect on precision (relative efficiency range 77-88%). Responsiveness of a simplified SENS without carpal joints closely approximated the original version (i.e., all Delta standardized change scores were </=0.06). Discriminant validity was also similar between versions for both the erosion score (relative efficiency = 97%) and the SENS total score (relative efficiency = 84%).
Conclusion: Our results show that the carpal joints may be omitted from the SENS without notable repercussion for its measurement performance.

Gepubliceerd: Arthritis Care Res (Hoboken) 2016 Aug;68(8):1206-10
Impact factor: 3.229

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13. Validation of automatic joint space width measurements in hand radiographs in rheumatoid arthritis
Schenk O, Huo Y, Vincken KL, van de Laar MA, Kuper IH, Slump KC, Lafeber FP, Bernelot Moens HJ

Computerized methods promise quick, objective, and sensitive tools to quantify progression of radiological damage in rheumatoid arthritis (RA). Measurement of joint space width (JSW) in finger and wrist joints with these systems performed comparable to the Sharp-van der Heijde score (SHS). A next step toward clinical use, validation of precision and accuracy in hand joints with minimal damage, is

described with a close scrutiny of sources of error. A recently developed system to measure metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints was validated in consecutive hand images of RA patients. To assess the impact of image acquisition, measurements on radiographs from a multicenter trial and from a recent prospective cohort in a single hospital were compared. Precision of the system was tested by comparing the joint space in mm in pairs of subsequent images with a short interval without progression of SHS. In case of incorrect measurements, the source of error was analyzed with a review by human experts. Accuracy was assessed by comparison with reported measurements with other systems. In the two series of radiographs, the system could automatically locate and measure 1003/1088 (92.2%) and 1143/1200 (95.3%) individual joints, respectively. In joints with a normal SHS, the average (SD) size of MCP joints was [Formula: see text] and [Formula: see text] in the two series of radiographs, and of PIP joints [Formula: see text] and [Formula: see text]. The difference in JSW between two serial radiographs with an interval of 6 to 12 months and unchanged SHS was [Formula: see text], indicating very good precision. Errors occurred more often in radiographs from the multicenter cohort than in a more recent series from a single hospital. Detailed analysis of the 55/1125 (4.9%) measurements that had a discrepant paired measurement revealed that variation in the process of image acquisition (exposure in 15% and repositioning in 57%) was a more frequent source of error than incorrect delineation by the software (25%). Various steps in the validation of an automated measurement system for JSW of MCP and PIP joints are described. The use of serial radiographs from different sources, with a short interval and limited damage, is helpful to detect sources of error. Image acquisition, in particular repositioning, is a dominant source of error.

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14. Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry

Steunebrink LM, Versteeg GA, Vonkeman HE, Ten Klooster PM, Kuper HH, Zijlstra TR, van Riel PL, van de Laar MA

Background: Treat to target (T2T) is widely accepted as the standard of care for patients with rheumatoid arthritis (RA) and has been shown to be more effective than traditional routine care. The objective of this study was to compare the effectiveness of two T2T strategies in patients with early RA: a step-up approach starting with methotrexate (MTX) monotherapy (cohort I) versus an initial disease-modifying antirheumatic drug combination approach (cohort II).
Methods: A total of 128 patients from cohort II were case-control-matched with 128 patients from cohort I on gender, age, and baseline disease activity. Twelve-month follow-up data were available for 121 patients in both cohorts. The primary outcome was the proportion of patients having reached at least one 28-joint Disease Activity Score (DAS28) score <2.6 (remission) during 12 months of follow-up. Secondary

outcomes were time until remission was achieved and mean DAS28 scores at 6- and 12-month follow-up.
Results: After 12 months of follow-up, remission was reached at least once in 77.3 % of the patients in cohort II versus 71.9 % in cohort I (P = 0.31). Median time until first remission was 17 weeks in cohort II versus 27 weeks in cohort I (P = 0.04). A significant time by strategy interaction was found in mean DAS28 scores. Post hoc analysis revealed a significant difference in mean DAS28 scores between both cohorts at 6 months (P = 0.04), but not at 12 months (P = 0.36).
Conclusions: The initial combination strategy resulted in a comparable remission rate after 1 year but a significantly shorter time until remission. At 6 months, mean DAS28 scores were lower in patients with initial combination treatment than in those with step-up therapy. At 12 months, no significant differences remained in mean DAS28 scores or the proportion of patients in remission.

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15. Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry
Steunebrink LM, Vonkeman HE, Ten Klooster PM, Hoekstra M, van Riel PL, van de Laar MA

Despite considerable evidence on the efficacy and safety of early aggressive treat-to-target (T2T) strategies in early rheumatoid arthritis (RA), a proportion of patients still fail to reach remission. The goal of this study is to examine remission rates and predictors of remission in a real life T2T cohort of consecutive patients with a recent diagnosis of RA. Baseline demographics, clinical, laboratory and patient-reported variables and 1-year follow-up disease activity data were used from patients with early RA included in the DREAM remission induction cohort II study. Survival analyses and simple and multivariable logistic regression analyses were used to examine remission rates and significant predictors of achieving remission. A total of 137 recently diagnosed consecutive RA patients were available for this study. During the first year after inclusion, DAS28 remission was achieved at least once in 77.2 % of the patients and the median time to first remission was 17 weeks. None of the examined baseline variables were robustly associated with achieving remission within 1 year and in the multivariable analysis only lower ESR (p = 0.005) remained significantly associated with achieving fast remission within 17 weeks. During the first year of their disease a high proportion of recently diagnosed RA patient achieved remission, with only a small percentage of patients needing bDMARD therapy. Combined with the absence of baseline predictors of remission, this suggests that clinicians in daily clinical practice may focus on DAS28 scores only, without needing to take other patients characteristics into account.

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Thoraxchirurgie

1. Erratum to: 'Modified transesophageal echocardiography of the dissected thoracic aorta; a novel diagnostic approach'
Jansen Klomp WW, Peelen LM, Brandon Bravo Bruinsma GJ, Van't Hof AW, Grandjean JG, Nierich AP

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2. Imaging Techniques for Diagnosis of Thoracic Aortic Atherosclerosis
Jansen Klomp WW, Brandon Bravo Bruinsma GJ, van 't Hof AW, Grandjean JG, Nierich AP

The most severe complications after cardiac surgery are neurological complications including stroke which is often caused by emboli merging from atherosclerosis in the ascending aorta to the brain. Information about the thoracic aorta is crucial in reducing the embolization risk for both surgical open and closed chest procedures such as transaortic heart valve implantation. Several techniques are available to screen the ascending aorta, for example, transesophageal echocardiography (TEE), epiaortic ultrasound, TEE A-view method, manual palpation, computed tomography, and magnetic resonance imaging. This paper provides a description of the advantages and disadvantages of these imaging techniques.

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3. Modified transesophageal echocardiography of the dissected thoracic aorta; a novel diagnostic approach
Jansen Klomp WW, Peelen LM, Brandon Bravo Bruinsma GJ, Van't Hof AW, Grandjean JG, Nierich AP

Background: Transesophageal echocardiography (TEE) is a key diagnostic modality in patients with acute aortic dissection, yet its sensitivity is limited by a "blind-spot" caused by air in the trachea. After placement of a fluid-filled balloon in the trachea visualization of the thoracic aorta becomes possible. This method, modified TEE, has been shown to be an accurate test for the diagnosis of upper aortic atherosclerosis. In this study we discuss how we use modified TEE for the diagnosis and management of patients with (suspected) acute aortic dissection. **Novel diagnostic approach of the dissected aorta**: Modified TEE provides the possibility to obtain a complete echocardiographic overview of the thoracic aorta and its branching vessels with anatomical and functional information. It is a bedside test, and can thus be applied in hemodynamic instable patients who cannot undergo computed tomography. Visualization of the aortic arch allows differentiation between Stanford type A and B dissections and visualization of the proximal cerebral vessels

enables a timely identification of impaired cerebral perfusion. During surgery modified TEE can be applied to identify the true lumen for cannulation, and to assure that the true lumen is perfused. Also, the innominate- and carotid arteries can be assessed for structural integrity and adequate perfusion during multiple phases of the surgical repair.
Conclusions: Modified TEE can reveal the "blind-spot" of conventional TEE. In patients with (suspected) aortic dissection it is thus possible to obtain a complete echocardiographic overview of the thoracic aorta and its branches. This is of specific merit in hemodynamically unstable patients who cannot undergo CT. Modified TEE can guide also guide the surgical management and monitor perfusion of the cerebral arteries.

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4. A European Multicenter Study of 616 Patients Receiving the Freedom Solo Stentless Bioprosthesis
Thalmann M, Grubitzsch H, Matschke K, Glauber M, Tan E, Francois K, Amorim MJ, Hensens AG, Cesari F, Feyrer R, Diegeler A, Veit F, Repossini A

Background: The purpose of this study was to evaluate the safety and performance of the Freedom Solo valve in aortic valve replacement by clinical and hemodynamic outcomes.
Methods: Six hundred sixteen patients underwent aortic valve replacement in 18 European centers; mean age was 74.5 +/- 5.9 years, 54.1% of the patients were male, and concomitant procedures were performed in 43.2% of the patients. The majority (69%) of the implanted sizes were 23 mm and 25 mm.
Results: At 1 year, overall survival was 94.0%, whereas freedom from valve-related death was 98.6%. There were 9 (1.5%) early (</=30 days) and 27 (4.4%) late (>30 days) deaths. Early and late valve-related mortality was 0.3% (n = 2) and 1.1% (n = 7), respectively. Freedom from explant was 97.6%; 10 valves were explanted for endocarditis and 4 for paravalvular leak. There were 10 (1.6%) early and 5 (0.8%) late strokes. Atrioventricular block requiring pacemaker implant occurred in 8 (1.3%) and 1 (0.2%) patients in the early and late postoperative period, respectively. Thrombocytopenia was seen in 27 cases (4.4%) in the early postoperative period. Preoperatively, 93.8% of patients were in New York Heart Association functional classes II through IV, whereas at 1 year 96.9% of patients were in New York Heart Association functional classes I and II. At 1-year follow-up, mean and peak pressure gradients were 7.2 and 14.6 mm Hg, respectively. Indexed left ventricular mass decreased by 12% from 138 g/m(2) at discharge to 122 g/m(2) at 1 year.
Conclusions: At 1-year follow-up after Freedom Solo implantation, we found acceptable clinical results with low mortality and morbidity and good hemodynamic performance, confirming safety and effectiveness in this multicenter experience.

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