Publicaties

Jeroen Bosch Ziekenhuis
2017-2018

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2017-2018

’s-Hertogenbosch, 2019

Inhoudsopgave

1 CARDIOLOGIE

Wetenschappelijke publicaties

Meuwese CL, Boulaksil M, **van Dijk J, Polad J, Meijburg HW**. Reply to "Why do you not call the condition takotsubo syndrome triggered by acute coronary ischemia?" Echocardiography. 2017 Oct;34(10):1554. doi: 10.1111/echo.13696. Epub 2017 Sep 12.
PMID: 28895176

Meuwese CL, Boulaksil M, **van Dijk J, Polad J, Meijburg HW**. Reply to "Non-ST-segment elevation myocardial infarction vs aborted myocardial infarction-triggered takotsubo syndrome?" Echocardiography. 2017 Aug;34(8):1263. doi: 10.1111/echo.13619. Epub 2017 Jul 3.
PMID: 28670734

Lorjé T, Barlo N, Reichert CLA, de Kanter W, **Sluman MA**. A 46-year-old man with recurrent embolic events. Neth Heart J. 2017 Dec;25(12):695-696. doi: 10.1007/s12471-017-1034-8.
PMID: 28864963

Valckx WJ, Lutgens SP, **Haerkens-Arends HE**, Barneveld PC, Beutler JJ, Hoogeveen EK. Listeria endocarditis: a diagnostic challenge. J Investig Med High Impact Case Rep. 2017 Apr 10;5(2) 2324709617698995.
PMID: 28491879

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PMID:27785617

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Boulaksil M, Meuwese CL, Evertz R, **Kolff-Kamphuis MGM**. Broad complex rhythm with a salty taste. Neth Heart J. 2017 May;25(5):346-347. doi: 10.1007/s12471-017-0950-y.
PMID:28108934

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Joustra R, Boulaksil M, Meijburg HW, Smeets JL. Dizziness and slow heart rate during exercise. Neth Heart J. 2017 Jul;25(7-8):461-462. doi: 10.1007/s12471-017-0983-2.
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PMID:28401473

Joustra R, van Dijk APJ, **Meijburg HWJ**, Boulaksil M. A freaky artery. Neth Heart J. 2018 Nov;26(11):577-578. doi:

10.1007/s12471-018-1189-y.
PMID: 30350002
Joustra R, van Dijk APJ, **Meijburg HWJ**, Boulaksil M. A freaky artery.
Neth Heart J. 2018 Nov;26(11):572. doi: 10.1007/s12471-018-1188-z.
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J Echocardiogr. 2017 May 2. doi: 10.1007/s12574-017-0337-5.
PMID:28466446

Meuwese CL, Boulaksil M, van Dijk J, Polad J, Meijburg HW. Transient left ventricular outflow tract obstruction with systolic anterior motion of the mitral valve: A stunning cause.
Echocardiography. 2017 Jul;34(7):1089-1091. doi: 10.1111/echo.13553. Epub 2017 May 12.
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Trefwoorden: left ventricular outflow tract obstruction; myocardial stunning; percutaneous intervention; systolic anterior motion of the mitral valve

Jansen R, van Klarenbosch BR, Cramer MJ, Meijer RCA, Westendorp PHM, **Meijburg HWJ**, Bucx JJJ, Chamuleau SAJ, Kluin J. Longitudinal echocardiographic and clinical follow-up of patients undergoing mitral valve surgery without concomitant tricuspid valve repair. Neth Heart J. 2018 Nov;26(11):552-561. doi: 10.1007/s12471-018-1159-4.
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PMID: 30266833

2 CHIRURGIE

Wetenschappelijke publicaties

Mertens AC, Tolboom RC, Zavrtanik H, **Draaisma WA**, Broeders IAMJ. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. Surg Endosc. 2019 Jul;33(7):2152-2161. doi: 10.1007/s00464-018-6494-4. Epub 2018 Oct 22.
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PMID: 28793317

Laan C, van de Vrugt M, **Olsman J**, Boucherie RJ. Static and dynamic appointment scheduling to improve patient access time.
Health Syst (Basingstoke). 2017 Nov 28;7(2):148-159. doi: 10.1080/20476965.2017.1403675. eCollection 2018.
PMID: 31214345

de Lacy FB, **van Laarhoven JJEM**, Pena R, Arroyave MC, Bravo R, Cuatrecasas M, Lacy AM. Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer. Surg Endosc. 2018 May;32(5):2442-2447. doi: 10.1007/s00464-017-5944-8. Epub 2017 Nov 3.
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van Iersel JJ, Formijne Jonkers HA, Verheijen PM, Broeders IA, Heggelman BG, Sreetharan V, Fütterer JJ, Somers I, van der Leest M, Consten EC. Comparison of dynamic magnetic resonance defaecography with rectal contrast and conventional defaecography for posterior pelvic floor compartment prolapse. Colorectal Dis. 2017 Jan;19(1):046-053. doi: 10.1111/codi.13563.
PMID: 27870169
Trefwoorden: Dynamische MRI, Defecogram

Boersma D, van Haelst ST, van Eekeren RR, Reijnen MM, de Vries JP, de Borst GJ. Macroscopic and Histologic Analysis of Vessel Wall Reaction After Mechanochemical Endovenous Ablation Using the ClariVein OC Device in an Animal Model. Eur J Vasc Endovasc Surg. 2017 Feb;53(2):290-298. doi: 10.1016/j.ejvs.2016.11.024. Epub 2016 Dec 23.
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Trefwoorden: Mechanochemical ablation; Saphenous vein; Sclerotherapy; Varicose veins; Varicose veins therapy

Nelen SD, Verhoeven RHA, Lemmens VEPP, de Wilt JHW, **Bosscha K**. Increasing survival gap between young and elderly gastric cancer patients. Gastric Cancer. 2017 Nov;20(6):919-928. doi: 10.1007/s10120-017-0708-7. Epub 2017 Mar 9.
PMID:28275933
Trefwoorden: Chemotherapy; Curative; Epidemiology; Stomach neoplasms; Surgery

Boersma D, Vink A, Moll FL, de Borst GJ. Proof-of-Concept Evaluation of the SailValve Self-Expanding Deep Venous Valve System in a Porcine Model. J Endovasc Ther. 2017 Jun;24(3):440-446. doi: 10.1177/1526602817700120. Epub 2017 Mar 30.
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Trefwoorden: animal model; deep venous thrombosis; endovascular techniques; histology; in vivo study; porcine model; prosthesis; varicose vein; venous insufficiency; venous valve

Leenstra BS, Schaap CCM, **Bessems M**, Renders NHM, **Bosscha K**. Primary Actinomycosis in the breast caused by Actinomyces neuii. A report of 2 cases. IDCases. 2017 Apr 1;8:70-72. doi: 10.1016/j.idcr.2017.03.014. eCollection 2017.
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PMID: 28138958

Witte ME, Zeebregts CJ, de Borst GJ, Reijnen MMPJ, **Boersma D**. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review. Phlebology. 2017 Dec;32(10):649-657. doi: 10.1177/0268355517702068. Epub 2017 Apr 12. Review.
PMID:28403687
Trefwoorden: Endovenous technique; mechanochemical ablation; saphenous vein; small saphenous vein

Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, Kolfschoten NE, de Jong PC, Rozema T, Wijnhoven BP, van Hillegersberg R, Wouters MW, van Sandick JW; **Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Collaborators: Bosscha K**, Cats A, Dikken JL, van Grieken NC, Hartgrink HH, Lemmens VE, Nieuwenhuijzen GA, Plukker JT, Rosman C, Siersema PD, Tetteroo G, Veldhuis PM, Voncken FE. Textbook outcome as a composite measure in oesophagogastric cancer surgery. Br J Surg. 2017 May;104(6):742-750. doi: 10.1002/bjs.10486. Epub 2017 Feb 27.
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Eur J Surg Oncol. 2017 Aug;43(8):1456-1462. doi: 10.1016/j.ejso.2017.04.012. Epub 2017 May 5.
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FE. Failure-to-rescue in patients undergoing surgery for esophageal or gastric cancer.
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PMID:28797755
Trefwoorden: Esophageal neoplasms; Esophagectomy; Failure-to-rescue; Gastrectomy; Gastric neoplasms; Quality indicators

Lam YL, De Maeseneer M, Lawson JL, De Borst GJ, **Boersma D**. Expert review on the VenaSeal® system for endovenous cyano-acrylate adhesive ablation of incompetent saphenous trunks in patients with varicose veins. Expert Rev Med Devices. 2017 Oct;14(10):755-762. doi: 10.1080/17434440.2017.1378093.
PMID:28892412
Trefwoorden: VenaSeal; non tumescent; saphenous; varicose veins; venous

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Dis Colon Rectum. 2017 Nov;60(11):1215-1223. doi: 10.1097/DCR.0000000000000895.
PMID: 28991087
Trefwoorden: Rectum prolaps, Robot Chirurgie

Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, Kroep JR, De Graaf H, Honkoop AH, Erdkamp FLG, van den Berkmortel FWPJ, de Boer M, de Roos WK, Linn SC, Imholz ALT, Seynaeve CM; **Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators. Collaborators**: Kitzen JJEM, Strobbe LJA, Kouwenhoven EA, van Dalen T, van Overbeeke AJ, Nuytinck JKS, Arntz IE, Blaisse RJB, Stockmann HBAC, Nijhuis PHA, Veldhuis GJ, Mastboom WJB, van Riel JMGH, van Dam JH, den Boer MO, Agterof MJ, de Roos MAJ, Roumen RMH, van der Hoeven JJM, Beeker A, Koelemij R, van Bochove A, Madretsma GS, Siemerink EJM, Guicherit OR, Vos AH, Nieuwenhuijzen GAP, Kehrer DFS, Valster FAA, Tanis BC, van Voorthuizen T, van der Velden AMT, Hellingman RA, Vree R, van Rossum-Schornagel Q, Meerum Terwogt JM, van Leeuwen-Breuk WG, Haasjes JG, Davidis-van Schoonhoven MA, Vriens EJC, Jagers M, Muller EW, Schiphorst PPJBM, van Groeningen CJ, van Dijk MA, Janssens-van Vliet E, Schepers EEM, Merkus JWS, van Diemen NGJ, van Doorn RC, **Bosscha K**, den Toom R, van der Velden PC, van Rossum CTAM, Oosterkamp HM, van Hillegersberg R, Jas B, Weernink EEM, Ketel JMA, Jansen JJ, Maring JK, Govaert MJPM, Kamm YJL, Vleugel MM, Hovenga S, de Boer J, Potthoff H, Sommeijer DW, van Dulken EJ. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol. 2017 Nov;18(11):1502-1511. doi: 10.1016/S1470-2045(17)30600-9. Epub 2017 Oct 12. Erratum in: Lancet Oncol. 2017 Nov;18(11):e642. Correction to Lancet Oncol 2017; 18: 1502-11. [Lancet Oncol. 2017]
PMID:29031778

van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, **Bosscha K**, Bouwense SA, Bruno MJ, Cappendijk VC, Consten EC, Dejong CH, van Eijck CH, Erkelens WG, van Goor H, van Grevenstein WMU, Haveman JW, Hofker SH, Jansen JM, Laméris JS, van Lienden KP, Meijssen MA, Mulder CJ, Nieuwenhuijs VB, Poley JW, Quispel R, de Ridder RJ, Römkens TE, Scheepers JJ, Schepers NJ, Schwartz MP, Seerden T, Spanier BWM, Straathof JWA, Strijker M, Timmer R, Venneman NG, Vleggaar FP, Voermans RP, Witteman BJ, Gooszen HG, Dijkgraaf MG, Fockens P; Dutch Pancreatitis Study Group. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet. 2018 Jan 6;391(10115):51-58. doi: 10.1016/S0140-6736(17)32404-2. Epub 2017 Nov 3.
PMID:29108721

Beck N, Busweiler LAD, Schouwenburg MG, Fiocco M, Cats A, Voncken FEM, Wijnhoven BPL, van Berge Henegouwen MI, Wouters MWJM, van Sandick JW; **Dutch Upper GI Cancer Audit (DUCA) Group and the Dutch Gastric Cancer Perioperative Therapy Study group. Collaborators: Bosscha K**, Dikken JL, van Duijvendijk P, van Grieken NCT, Gisbertz SS, Hartgrink HH, Hartemink KJ, Van Hillegersberg R, Hulsewé K, Kouwenhoven E, Lemmens VEPP, Nieuwenhuijzen GAP, Ooijen B, Plukker JT, Rosman C, Scheepers J, Siersema PD, de Steur WO, Tetteroo G, Veldhuis PMJF. Factors contributing to variation in the use of multimodality treatment in patients with gastric cancer: A Dutch population based study. Eur J Surg Oncol. 2018 Feb;44(2):260-267. doi: 10.1016/j.ejso.2017.11.023. Epub 2017 Dec 13.
PMID:29273212
Trefwoorden: Combined modality therapy; Quality assurance; Stomach neoplasms

de Rooij T, van Hilst J, **Bosscha K**, Dijkgraaf MG, Gerhards MF, Groot Koerkamp B, Hagendoorn J, de Hingh IH, Karsten TM, Lips DJ, Luyer MD, Molenaar IQ, van Santvoort HC, Tran TCK, Busch OR, Festen S, Besselink MG; Dutch Pancreatic Cancer Group. Minimally invasive versus open

pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial. Trials. 2018 Jan 3;19(1):1. doi: 10.1186/s13063-017-2423-4.
PMID:29298706
Trefwoorden: Laparoscopic; Minimally invasive; Pancreatoduodenectomy; Robot-assisted; Whipple

van der Werf LR, Dikken JL, van der Willik EM, van Berge Henegouwen MI, Nieuwenhuijzen GAP, Wijnhoven BPL; **Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Collaborators Bosscha K**, van Grieken NCT, Hartgrink HH, van Hillegersberg R, Lemmens VEPP, Plukker JT, Rosman C, van Sandick JW, Siersema PD, Tetteroo G, Veldhuis PMJF, Voncken FEM. Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study. Eur J Cancer. 2018 Mar;91:76-85. doi: 10.1016/j.ejca.2017.12.009. Epub 2018 Jan 30.
PMID:29353163
Trefwoorden: Neoadjuvant chemoradiotherapy; Oesophageal carcinoma; Oesophageal surgery; Pathological complete response; Time-to-treatment; Treatment outcome

van der Werf LR, Dikken JL, van Berge Henegouwen MI, Lemmens VEPP, Nieuwenhuijzen GAP, Wijnhoven BPL; **Dutch Upper GI Cancer Audit group. Collaborators: Bosscha K**, van Grieken NCT, Hartgrink HH, van Hillegersberg R, Lemmens VEPP, Plukker JT, Rosman C, van Sandick JW, Siersema PD, Tetteroo G, Veldhuis PMJF, Voncken FEM. A Population-based Study on Lymph Node Retrieval in Patients with Esophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit. Ann Surg Oncol. 2018 May;25(5):1211-1220. doi: 10.1245/s10434-018-6396-7. Epub 2018 Mar 9.
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PMID:29683186

Maher CF, Baessler KK, Barber MD, Cheon C, Consten ECJ, Cooper KG, Deffieux X, Dietz V, Gutman RE, **van Iersel JJ**, Nager CW, Sung VW, de Tayrac R. Summary: 2017 International Consultation on Incontinence Evidence-Based Surgical Pathway for Pelvic Organ Prolapse. Female Pelvic Med Reconstr Surg. 2018 Apr 28. doi: 10.1097/SPV.0000000000000591
PMID: 29727373
Trefwoorden: internationale richtlijn bekkenbodemverzakkingen

van Hilst J, de Rooij T, van den Boezem PB, **Bosscha K**, Busch OR, van Duijvendijk P, Festen S, Gerhards MF, de Hingh IH, Karsten TM, Kazemier G, Lips DJ, Luyer MD, Nieuwenhuijs VB, Patijn GA, Stommel MW, Zonderhuis BM, Daams F, Besselink MG; Dutch Pancreatic Cancer Group. Laparoscopic pancreatoduodenectomy with open or laparoscopic reconstruction during the learning curve: a multicenter propensity score matched study.
HPB (Oxford). 2019 Jul;21(7):857-864. doi: 10.1016/j.hpb.2018.11.003. Epub 2018 Dec 5.
PMID: 30528277

van der Meij E, Bouwsma EVA, **van den Heuvel B**, Bonjer HJ, Anema JR, Huirne JAF. Using e-health in perioperative care: a survey study investigating shortcomings in current perioperative care and possible future solutions. BMC Surg. 2017 May 23;17(1):61. doi: 10.1186/s12893-017-0254-6.
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van de Wall BJM, Stam MAW, Draaisma WA, Stellato R, Bemelman WA, Boermeester MA, Broeders IAMJ, Belgers EJ, Toorenvliet BR, **Prins HA**, Consten ECJ; DIRECT trial collaborators. Surgery versus conservative management for recurrent and ongoing left-sided diverticulitis (DIRECT trial): an open-label, multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2017 Jan;2(1):13-22. doi: 10.1016/S2468-1253(16)30109-1. Epub 2016 Oct 19.
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Trefwoorden: rectum prolaps

3 DERMATOLOGIE

Wetenschappelijke publicaties

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Maastricht Universitair Medisch Centrum (MUMC+)
4-12-2018
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Boeken

Carolina Keijsers, Rob van Marum. Klinisch redeneren bij ouderen, pp.301-318, hoofdstuk 7 Polyfarmacie bij oudere patiënten, January 2017

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van Marum RJ. Cognitieve stoornissen door medicatie. Biemond cursus (Neurologie), Noordwijkerhout, Nederland. 16 maart 2017

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Presentatie: E.T.I.A. Buisman, J.P. de Bruin, D.D.M. Braat, J.W. van der Steeg - De invloed van naalddiameter op pijn bij follikelpuncties - een gerandomiseerde studie, Gynaecongres 2018, Amersfoort

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'The ICU environment, Impact of light and noise exposure on critically ill patients'
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Trefwoorden: Hand-voet syndroom, S1 en capecitabine

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Abstracts, voordrachten en posters

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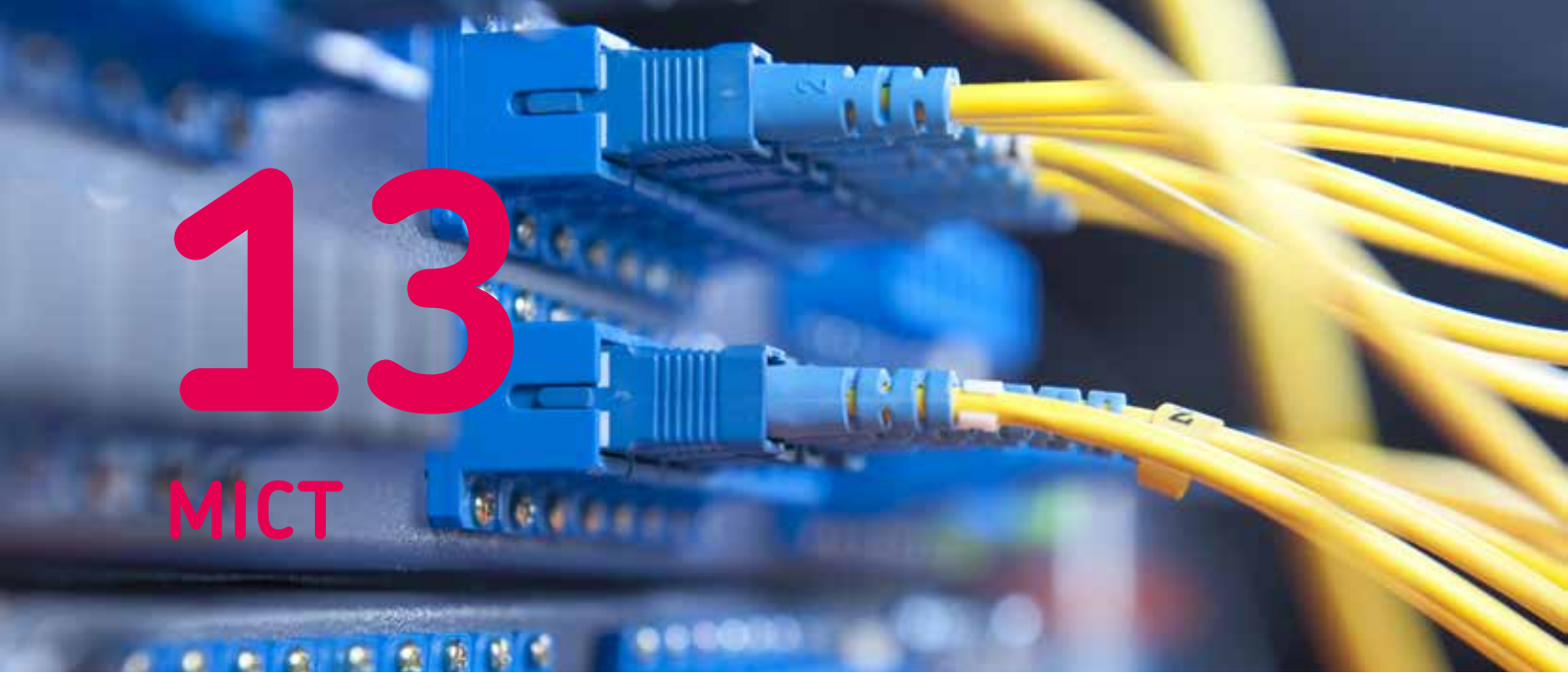

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Schulz J, P Marques J, Ter Telgte A, **van Dorst A**, de Leeuw FE, Meijer FJA, Norris DG. Clinical application of Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) imaging accelerated by simultaneous multi-slice acquisition. Eur J Radiol. 2018 Jan;98:200-206. doi: 10.1016/j.ejrad.2017.11.022. Epub 2017 Dec 2.
PMID: 29279164

Abstracts, voordrachten en posters

A.S. Turan, S.F.M. Jenniskens, L.J. Schultze Kool, J.M. Martens, **M.J.C.M. Rutten**, L.S.F. Yo, M.J.L. van Strijen, P.D. Siersema, and E.J.M. van Geenen. Antibiotic Prophylaxis in Percutaneous Transhepatic Cholangiography and Biliary Drainage (PTCD), a retrospective multicenter study. Digestive Disease Days - NVGE, maart 2018.

Rutten MJ, Maresch SJ. High-Resolution Ultrasound in peripheral nerve pathology. SWC NVVR (8 presentations: level 3) Ede, 13 Nov and 16 Nov 2018.

A.S. Turan, S.F.M. Jenniskens, L.J. Schultze Kool, J.M. Martens, **M.J.C.M. Rutten**, L.S.F. Yo, M.J.L. van Strijen, P.D. Siersema, and E.J.M. van Geenen. Antibiotic Prophylaxis in Percutaneous Transhepatic Cholangiography and Biliary Drainage (PTCD), a retrospective multicenter study. European Society of Gastrointestinal Endoscopy (ESGE) 2018, 19-21 april 2018, Budapest Hungary.

Jager GJ, **Rutten MJCM**. Hidden in plain sight. 2nd European Conference on Diagnostic Error in Medicin Society to Improve Diagnosis in Medicine (SIDM). Bern, Switzerland, 30-31 August 2018.

Publicaties (niet pubmed)

van Beijnen MTA, Zegers MJ, **van Leuken MH**, de Jager CPC, Simons KS. Association between the Hanging Chin Sign and Mortality in Critically Ill Patients, a Retrospective Observational Study. Emergency Med 2018, 8:2
DOI: 10.4172/2165-7548.1000369

Rutten MJ, Maresch SJ. Echogeleide musculoskeletale interventies. Memorad, Febr 2017.
Trefwoorden: Musculoskeletaal, interventies

Claassen B, **Rutten MJ**. Barbotage: how we do it. Memorad, Febr 2017.
Trefwoorden: Musculoskeletaal, interventies

Baardewijk van L, **Rutten MJ**. Radiologische evaluatie van artritis. Memorad, Febr 2017.
Trefwoorden: musculoskeletaal, artritis

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Trefwoorden: elastografie, borst

Overige

Rutten MJ, Maresch SJ. Teaching cases Upper Extremity Sports related radiology. Sport Radiologie Symposium Arnhem (Papendal), 7 september 2017.

Rutten MJ, Maresch SJ. Teaching cases Lower Extremity Sports related radiology. Sport Radiologie Symposium Arnhem (Papendal), 7 september 2017.

Rutten MJ, Maresch SJ. Musculoskeletal Ultrasound Hands-on Training Course. Arnhem (Papendal), 8 september 2017.

Baardewijk L, Claassen B, **Rutten MJ**. Shoulder Barbotage clinical outcome study. Nederland-België MSK Bijeenkomst, 's-Hertogenbosch, 7 oktober 2017.

Rutten MJ. Musculoskeletal Ultrasound Master Class – Shoulder Ultrasound. Zeist (KNVB), 27 jan 2018.

De Jong-Dekkers B, Ketelaars B, **Rutten MJ.** De optimale body size index voor patiëntgebonden contrastmiddeldosering bij CT abdomen. Fontys, Eindhoven , 14 juni 2018

Rutten MJ. Automated Three-Dimensional Breast Volume Scanning: Technique, Artifacts, and Lesion Characterization. Mallorca, 5 June 2018.

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Rutten MJ. AI in Radiology. Implications for clinical practice. Radboudumc Imaging Research Meeting. Nijmegen, 20 nov 2018.

21 REUMATOLOGIE

Wetenschappelijke publicaties

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Abstracts, voordrachten en posters

Drs. Lisanne MA Janssen, drs. Thomas Macken, **dr. Marjonne CW Creemers**, dr. J. (Hans) FM Pruijt, drs. Jeroen JJ Eijk, Prof. Dr. Esther de Vries. Isolated decreased serum IgM as incidental finding: a difficult dilemma. Poster: ESID 11-14 September, Edinburgh, Scotland, 2017.

22 REVALIDATIEGENEESKUNDE

Wetenschappelijke publicaties

Kouwijzer I, Valent L, **Osterthun R**, van der Woude L, de Groot S; HandbikeBattle group. Peak power output in handcycling of individuals with a chronic spinal cord injury: predictive modeling, validation and reference values. Disabil Rehabil. 2018 Dec 3:1-10. doi: 10.1080/09638288.2018.1501097. PMID: 30507314

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23 SPOEDEISENDE GENEESKUNDE

Wetenschappelijke publicaties

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24 SPORTGENEESKUNDE

Publicaties (niet pubmed)

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Wilkens OE, **Kokshoorn APJ**, Konings T ea. Chronisch compartimentsyndroom van het laterale compartiment van de onderarm, een case report. Sport en Geneeskunde september 2018 nr3

25 UROLOGIE

Wetenschappelijke publicaties

Mannaerts CK, **Gayet M,** Verbeek JF, Engelbrecht MRW, Savci-Heijink CD, Jager GJ, Gielens MPM, van der Linden H, Beerlage HP, de Reijke TM, Wijkstra H, Roobol MJ. Prostate Cancer Risk Assessment in Biopsy-naïve Patients: The Rotterdam Prostate Cancer Risk Calculator in Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound (TRUS) Fusion Biopsy and Systematic TRUS Biopsy. Eur Urol Oncol. 2018 Jun;1(2):109-117. doi: 10.1016/j.euo.2018.02.010. Epub 2018 May 15.
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26 ZIEKENHUISFARMACIE

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Proefschriften

A.M. (Astrid) van Strien, geriater. Adverse drug reactions of antipsychotics in frail older patients. 14 september 2017. (promotor: RJ van Marum, co-promoter: CK Keijsers, **HJ Derijks**)

Abstracts, voordrachten en posters

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Van Lint J, **Hermens W**, Jessurun N. The impact of facilitated reporting of adverse drug reactions by health care professionals in hospitals as a new source of ADR information. International Society of Pharmacovigilance, ISoP P18-1282, Geneva, 11-14 November 2018

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de Rouw N, Croes S, Posthuma R, Agterhuis DE, Schoenmaekers JJ, **Derijks HJ**, Burger DM, Dingemans AM, ter Heine R, Pharmacokinetically-guided dosing of pemetrexed in a patient with renal impairment and a patient requiring hemodialysis. International workshop Clinical Pharmacology of Anticancer Drugs (ICPAD), Amsterdam, 8-9 november 2018

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27 ZIEKENHUISGENEESKUNDE

Wetenschappelijke publicaties

den Harder AM, de Boer E, Lagerweij SJ, Boomsma MF, Schilham AMR, Willemink MJ, Milles J, Leiner T, Budde RPJ, de Jong PA; Emphysema quantification using chest CT: influence of radiation dose reduction and reconstruction technique. Eur Radiol Exp 2018 Nov 7;2(1):30.
PMID 30402740
Trefwoorden: emfyseem, CT

den Harder AM, de Jong PA, de Groot MCH, Wolterink JM, Budde RPJ, Išgum I, van Solinge WW, Ten Berg MJ, Lutgens E, Veldhuis WB, Haitjema S, Hoefer IE, Leiner T. Commonly available hematological biomarkers are associated with the extent of coronary calcifications. Atherosclerosis. 2018 Aug;275:166-173.
PMID 29920437
Trefwoorden: atherosclerose, biomarkers

Chung K, Mets OM, Gerke PK, Jacobs C, **den Harder AM**, Scholten ET, Prokop M, de Jong PA, van Ginneken B, Schaefer-Prokop CM. Brock malignancy risk calculator for pulmonary nodules: validation outside a lung cancer screening population. Thorax. 2018 Sep;73(9):857-863.
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Trefwoorden: longkanker, longnodule

Kranenburg G, de Jong PA, Bartstra JW, Lagerweij SJ, Lam MG, Ossewaarde-van Norel J, Risseeuw S, van Leeuwen R, Imhof SM, Verhaar HJ, de Vries JJ, Slart RHJA, Luurtsema G, **den Harder AM**, Visseren FLJ, Mali WP, Spiering W. Etidronate for Prevention of Ectopic Mineralization in Patients With Pseudoxanthoma Elasticum. J Am Coll Cardiol. 2018 Mar 13;71(10):1117-1126.
PMID: 29519353
Trefwoorden: PXE, bisfosfanaten

den Harder AM, de Heer LM, de Jong PA, Suyker WJ, Leiner T, Budde RPJ. Frequency of abnormal findings on routine chest radiography before cardiac surgery. J Thorac Cardiovasc Surg. 2018 May;155(5):2035-2040.
PMID: 29477256
Trefwoorden: hartchirurgie, x-thorax

den Harder AM, Willemink MJ, van Doormaal PJ, Wessels FJ, Lock MTWT, Schilham AMR, Budde RPJ, Leiner T, de Jong PA. Radiation dose reduction for CT assessment of urolithiasis using iterative reconstruction: A prospective intra-individual study. Eur Radiol. 2018 Jan;28(1):143-150.
PMID: 28695359
Trefwoorden: stralingsdosis, CT

Overige

Onderzoek verricht tijdens nevenfunctie als postdoc bij de radiologie in het UMC Utrecht **den Harder AM,** Schilham AMR, Willemink MJ. CT of the Heart; Chapter “Image Reconstruction”, 2018

28 OVERIGE STAFDIENSTEN

Wetenschappelijke publicaties

Loonen AJM, Kesarsing C, Kusters R, **Hilbink M**, Wever PC, van den Brule AJC. High pneumococcal DNA load, procalcitonin and suPAR levels correlate to severe disease development in patients with pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2017 Sep;36(9):1541-1547. doi: 10.1007/s10096-017-2963-2. Epub 2017 Mar 29.
PMID: 28353184

Eijsvoogel NB, Hollegien MI, Bok VLA, Derksen Lubsen AG, Dikken FPJ, Leenders ACAP, Pijning A, Post E, Wojciechowski M, **Hilbink M**, de Vries E. Declining antibody levels after hepatitis B vaccination in Down syndrome: A need for booster vaccination? J Med Virol. 2017 Sep;89(9):1682-1685. doi: 10.1002/jmv.24813. Epub 2017 May 2.
PMID 28322457

Eijsvoogel NB, Hollegien MI, Bok LA, Derksen-Lubsen G, Dikken FPJ, Leenders ACAP, Pijning A, Post EDM, Wojciechowski M, Schmitz R, **Hilbink M, de Vries E**. Lower percentage of allergic sensitization in children with Down syndrome. Pediatr Allergy Immunol. 2017 Dec;28(8):852-857. doi: 10.1111/pai.12796. Epub 2017 Oct 3. No abstract available.
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PMID: 30521839

Jolles S, Sánchez-Ramón S, Quinti I, Soler-Palacín P, Agostini C, Florkin B, Couderc LJ, Brodszki N, Jones A, Longhurst H, Warnatz K, Haerynck F, Matucci A, **de Vries E**. Screening protocols to monitor respiratory status in primary immunodeficiency disease: findings from a European survey and subclinical infection working group. Clin Exp Immunol. 2017 Nov;190(2):226-234. doi: 10.1111/cei.13012. Epub 2017 Aug 25.
PMID: 28708268

de Vries E, Fransen L, **van den Aker M**, Meijboom BR. Preventing gatekeeping delays in the diagnosis of rare diseases.
Br J Gen Pract. 2018 Mar;68(668):145-146. doi: 10.3399/bjgp18X695225.
PMID: 29472225

Abstracts, voordrachten en posters

Drs. Lisanne MA Janssen, drs. Thomas Macken, dr. Marjonne CW Creemers, dr. J. (Hans) FM Pruijt, drs. Jeroen JJ Eijk, Prof. **Dr. Esther de Vries**. Isolated decreased serum IgM as incidental finding: a difficult dilemma. Poster: ESID 11-14 September, Edinburgh, Scotland, 2017.

WETENSCHAPSMIDDAG 2017

Programma 12e JBZ-wetenschapsmiddag 8 november 2017

15.00 uur Ontvangst + presentatie e-posters 15.20 uur Welkom	Mw. Dr. J.M.H. Timmers, adviseur Wetenschap JBZ
15.30 uur Thema presentatie: Waarheen leidt de weg tot de weten-schap?	Dhr. Prof. Dr. R.J. Kusters, klinisch chemicus
15.55 uur Thema presentatie: Hoe data science ons helpt op weg naar het hoogste cijfer voor gezondheidswelzijn in Nederland	Mw. Prof. Dr. E. de Vries, Coördinator Data Science
16.20 uur Thema presentatie: Evidence based practice: voorbeelden uit de praktijk	Mw. S. van de Ven, Procesbegeleider verpleegkundig leiderschap, EBP
16.45 uur Pauze + presentatie e-posters	
17.05 uur Uitleg Pitch en publieksstemmen	
17.15 uur 11 pitches	
1. Evaluatie van de ketenaanpak overgewicht bij kinderen in 's-Hertogenbosch- Presentatie van het studie-design	Dhr. Dr. E. van Mil, kinderarts en mw. S. de Laat, onderzoeker ketenaanpak overgewicht bij kinderen
2. Kwetsbaarheid, welbevinden, zorgcomplexiteit en ingezette verpleegkundige interventies bij ouderen die verdacht worden van een longcarcinoom	Mw. S. Vermeer-Verhagen, verpleegkundig specialist longgeneeskunde
3. Modulair organiseren van complexe zorg: op naar meer patiënt gerichte zorg	Dhr. V.J.T. Peters, PhD student, Tilburg University
4. Een derde minder prikken met "gouden labregels"	Dhr. Dr. H. Jansen, internist & mw. F. Bullens, kwaliteitsfunctionaris
5. D-dimeer POC-test in de huisartsenpraktijk bij verdenking op veneuze trombo-embolie: zinnige, zuinige en veilige zorg	Mw. E. Gemen, analist O&E, Laboratorium Klinische Chemie & Hematologie
6. Kwaliteit van zorg voor mensen met downsyndroom: het patiëntenperspectief	Mw. F. van den Driessen Mareeuw, wetenschappelijk onderzoeker Kindergeneeskunde
7. Project 0.5	Dhr. R. Roerdink, PA Orthopedie
8. Preoperatieve stadiering van pancreascarcinoom met contrast-enhanced diffusion-weighted MRI	Mw. D. Rivière, radioloog i.o.
9. Coxiella Burnetii en het risico op non-Hodgkin lymfoom	Mw. S. van Roeden, onderzoeker infectious diseases &immunity
10. MRI-echo fusiegeleide prostaatbiopten versus systematische prostaatbiopten in biopt-naïeve mannen	Mw. M. Gayet, uroloog i.o.
11. Management van postoperatieve gallekkage na laparoscopische leverresectie	Dhr. W. van der Meij, chirurg i.o.
18.30 – 19.20 Buffet (+ juryberaad)	
19.20 – 19.30 Prijsuitreiking en afsluiting (en aansluitend borrel)	Voorzitter Jury

Wedstrijd innovatieve ideeën: Project 0.5

R.L.Roerdink, namens de RVE orthopedie
Jeroen Bosch ziekenhuis, RVE orthopedie

Introductie

In het Jeroen Bosch ziekenhuis (JBZ) worden jaarlijks ongeveer 800 knie- en heupprotheses (resp. TKP en THP) geplaatst. Het grootste deel verloopt zonder problemen. Een kleine groep patiënten loopt echter een complicatie op, waaronder een prothese infectie. Prothese infecties zijn een van de meest serieuze complicaties bij gewricht vervangende operaties. Bij de orthopedie binnen ons ziekenhuis was in 2015 een plotselinge toename van prothese infecties te zien (infectiepercentage THP 2.16%, TKP 2.20% versus THP 1.30%, TKP 0.73% in 2014). Dit was een aanleiding voor evaluatie en verandering. Vanuit de oogpunten innovatie, kwaliteit, veiligheid en kosteneffectiviteit is het doel om het infectiepercentage bij primaire heup- en knieprotheses tot onder de 0.5% te brengen in 2 jaar tijd; **project 0.5**.

Methode

Met een samengestelde taskforce is er gezocht naar mogelijke interventies die van invloed kunnen zijn op het *krijgen* of *voorkomen* van een prothese infectie. De beschikbare evidence is vervolgens geevalueerd. Nieuwe handelingen / protocollen / materialen die voldoende effectief worden bevonden, worden in twee fases ingevoerd. Per 1-1-2017 zijn een nieuwe **wondsluittechniek** en een nieuw **wondzorgprotocol** geïmplementeerd. Deze werkwijze wordt herhaald voor 1-1-2018.

Resultaten

Kwalitatieve resultaten:
1. Nieuwe methode van hechten: **wondsluittechniek**
2. Aanpassing **wondzorgprotocol**

Voorlopige resultaten:

	2017 (t/m 1 okt)	2016
THP	1	7
TKP	1	3

Resultaten (vervolg)

Wondzorgprotocol

Conclusie

Dit is het eerste project dat op grote schaal verschillende infectie preventieve maatregelen en invloeden op basis van beschikbare evidence heeft samengevoegd en geïmplementeerd in de dagelijkse praktijk.
Kijkend naar de eerste resultaten leidt project 0.5 mogelijk tot een forse reductie van het aantal prothese infecties binnen het JBZ.

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BIJLAGE I

Wetenschappelijke publicaties 2015-2016 opgenomen in PubMed

PMID: 26843001

Vermeij A, Kessels RPC, Heskamp L, Simons EMF, **Dautzenberg PLJ**, Claassen JAHR. Prefrontal activation may predict working-memory training gain in normal aging and mild cognitive impairment. Brain Imaging Behav. 2017 Feb;11(1):141-154. doi: 10.1007/s11682-016-9508-7.

Cognitive training has been shown to result in improved behavioral performance in normal aging and mild cognitive impairment (MCI), yet little is known about the neural correlates of cognitive plasticity, or about individual differences in responsiveness to cognitive training. In this study, 21 healthy older adults and 14 patients with MCI received five weeks of adaptive computerized working-memory (WM) training. Before and after training, functional Near-Infrared Spectroscopy (fNIRS) was used to assess the hemodynamic response in left and right prefrontal cortex during performance of a verbal n-back task with varying levels of WM load. After training, healthy older adults demonstrated decreased prefrontal activation at high WM load, which may indicate increased processing efficiency. Although MCI patients showed improved behavioral performance at low WM load after training, no evidence was found for training-related changes in prefrontal activation. Whole-group analyses showed that a relatively strong hemodynamic response at low WM load was related to worse behavioral performance, while a relatively strong hemodynamic response at high WM load was related to higher training gain. Therefore, a 'youth-like' prefrontal activation pattern at older age may be associated with better behavioral outcome and cognitive plasticity.

PMID: 26969198

van Baaren GJ, Broekhuijsen K, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp K, Scheepers H, Bremer HA, **Rijnders R**, van Loon AJ, Perquin D, Sporken J, Papatsonis D, van Huizen ME, Vredevoogd CB, Brons J, Kaplan M, van Kaam AH, Groen H, Porath M, van den Berg PP, Mol B, Franssen M, Langenveld J; HYPITAT-II Study Group. An economic analysis of immediate delivery and expectant monitoring in women with hypertensive disorders of pregnancy, between 34 and 37 weeks of gestation (HYPITAT-II).
BJOG. 2017 Feb;124(3):453-461. doi: 10.1111/1471-0528.13957. Epub 2016 Mar 10.

OBJECTIVE: To assess the economic consequences of immediate delivery compared with expectant monitoring in women with preterm non-severe hypertensive disorders of pregnancy.
DESIGN: A cost-effectiveness analysis alongside a randomised controlled trial (HYPITAT-II).
SETTING: Obstetric departments of seven academic hospitals and 44 non-academic hospitals in the Netherlands.
POPULATION: Women diagnosed with non-severe hypertensive disorders of pregnancy between 340/7 and 370/7 weeks of gestation, randomly allocated to either immediate delivery or expectant monitoring.
METHODS: A trial-based cost-effectiveness analysis was performed from a healthcare perspective until final maternal and neonatal discharge.
MAIN OUTCOME MEASURES: Health outcomes were expressed as the prevalence of respiratory distress syndrome, defined as the need for supplemental oxygen for >24 hours combined with radiographic findings typical for respiratory distress syndrome. Costs were estimated from a healthcare perspective until maternal and neonatal discharge.
RESULTS: The average costs of immediate delivery (n = 352) were €10 245 versus €9563 for expectant monitoring (n = 351), with an average difference of €682 (95% confidence interval, 95% CI -€618 to €2126). This 7% difference predominantly originated from the neonatal admissions, which were €5672 in the immediate delivery arm and €3929 in the expectant monitoring arm.
CONCLUSION: In women with mild hypertensive disorders between 340/7 and 370/7 weeks of gestation, immediate delivery is more costly than expectant monitoring as a result of differences in neonatal admissions. These findings support expectant monitoring, as the clinical outcomes of the trial demonstrated that expectant monitoring reduced respiratory distress syndrome for a slightly increased risk of maternal complications.
TWEETABLE ABSTRACT: Expectant management in preterm hypertensive disorders is less costly compared with immediate delivery.

PMID: 27055805

Stewart T, Spelman T, Havrdova E, Horakova D, Trojano M, Izquierdo G, Duquette P, Girard M, Prat A, Lugaresi A, Grand'Maison F, Grammond P, Sola P, Shaygannejad V, Hupperts R, Alroughani R, Oreja-Guevara C, Pucci E, Boz C, Lechner-Scott J, Bergamaschi R, Van Pesch V, Iuliano G, Ramo C, Taylor B, Slee M, Spitaleri D, Granella F, Verheul F, McCombe P, Hodgkinson S, Amato MP, Vucic S, Gray O, Cristiano E, Barnett M, Sanchez Menoyo JL, **van Munster E**, Saladino ML, Olascoaga J, Prevost J, Deri N, Shaw C, Singhal B, Moore F, Rozsa C, Shuey N, Skibina O, Kister I, Petkovska-Boskova T, Ampapa R, Kermode A, Butzkueven H, Jokubaitis V, Kalincik T; MSBase Study Group. Contribution of different relapse phenotypes to disability in multiple sclerosis.

Mult Scler. 2017 Feb;23(2):266-276. doi: 10.1177/1352458516643392.

OBJECTIVE: This study evaluated the effect of relapse phenotype on disability accumulation in multiple sclerosis.

METHODS: Analysis of prospectively collected data was conducted in 19,504 patients with relapse-onset multiple sclerosis and minimum 1-year prospective follow-up from the MSBase cohort study. Multivariable linear regression models assessed associations between relapse incidence, phenotype and changes in disability (quantified with Expanded Disability Status Scale and its Functional System scores). Sensitivity analyses were conducted.

RESULTS: In 34,858 relapses recorded during 136,462 patient-years (median follow-up 5.9 years), higher relapse incidence was associated with greater disability accumulation ($\beta = 0.16$, $p < 0.001$). Relapses of all phenotypes promoted disability accumulation, with the most pronounced increase associated with pyramidal ($\beta = 0.27$ (0.25-0.29)), cerebellar ($\beta = 0.35$ (0.30-0.39)) and bowel/bladder ($\beta = 0.42$ (0.35-0.49)) phenotypes (mean (95% confidence interval)). Higher incidence of each relapse phenotype was associated with an increase in disability in the corresponding neurological domain, as well as anatomically related domains.

CONCLUSION: Relapses are associated with accumulation of neurological disability. Relapses in pyramidal, cerebellar and bowel/bladder systems have the greatest association with disability change. Therefore, prevention of these relapses is an important objective of disease-modifying therapy. The differential impact of relapse phenotypes on disability outcomes could influence management of treatment failure in multiple sclerosis.

PMID: 27135753

Ploos van Amstel FK, **Tol J**, Sessink KH, van der Graaf WT, Prins JB, Ottevanger PB. A Specific Distress Cutoff Score Shortly After Breast Cancer Diagnosis.

Cancer Nurs. 2017 May/Jun;40(3):E35-E40.

Trefwoorden: borstkanker, stress

BACKGROUND: High levels of distress are expected shortly after the diagnosis breast cancer. The Distress Thermometer (DT) is commonly used to screen for distress, using a cutoff score of 4 or 5; however, this score might not be appropriate for detecting distress in women with recently diagnosed breast cancer.

OBJECTIVES: The aims of this study were to establish the optimal DT cutoff score for detecting high distress shortly after breast cancer diagnosis and to correlate this score with the reported problems.

METHODS: We selected for this study Dutch women who completed the DT and the Hospital Anxiety and Depression Scale within 1 month after breast cancer diagnosis. Receiver operating characteristic analysis of DT scores was performed, with the Hospital Anxiety and Depression Scale being used as the criterion standard for the level of distress. The sensitivity, specificity, positive predictive value, and negative predictive value of each DT score were calculated.

RESULTS: In total, 181 women participated in the study. The optimal DT cutoff score for detecting distress was 7 with a sensitivity of 0.73, specificity of 0.84, positive predictive value of 69%, and negative predictive value of 87%. Emotional problems were the most frequently reported concerns.

CONCLUSION: We consider a cutoff score of 7, shortly after breast cancer is diagnosed, optimal to identify those women with high distress and therefore at risk of chronic distress.

IMPLICATIONS FOR PRACTICE: The findings are clinically important because they can enable healthcare professionals to direct their time and resources to those most in need of their assistance.

PMID: 27189850

Boersma D, de Borst GJ, Moll FL. A proof-of-concept study of the VeinScrew: A new percutaneous venous closure device. Vascular. 2017 Feb;25(1):105-109. doi: 10.1177/1708538116644117.

Objective This study evaluated the concept of percutaneous closure of insufficient veins using the VeinScrew principle. Methods The VeinScrew is designed to place a spring-shaped implant that contracts and clamps around the vein. The ability of the device to occlude adequately was tested in a bench model experiment. The feasibility of accurate placement and adequate venous occlusion was evaluated in an animal experiment and in a human cadaveric experiment. Results The VeinScrew implant occluded up to a pressure of 135 mmHg. In vivo studies confirmed that deployment was challenging but technically feasible, and subsequent phlebography showed closure of the vein. The cadaveric study showed that percutaneous placement of the evolved VeinScrew around the great saphenous vein was feasible and accurate. Conclusions The current studies show the feasibility of the VeinScrew concept. Future developments and translational studies are necessary to determine the potential of this technique as a new option in the phlebologist's toolbox.

PMID: 27341122

Ten Eikelder ML, van de Meent MM, Mast K, Rengerink KO, Jozwiak M, de Graaf IM, Scholtenhuis MA, Roumen FJ, Porath MM, van Loon AJ, van den Akker ES, **Rijnders RJ**, Feitsma AH, Adriaanse AH, Muller MA, de Leeuw JW, Visser H, Woiski MD, Weerd SR, van Unnik GA, Pernet PJ, Versendaal H, Mol BW, Bloemenkamp KW. Women's Experiences with and Preference for Induction of Labor with Oral Misoprostol or Foley Catheter at Term.

Objective: We assessed experience and preferences among term women undergoing induction of labor with oral misoprostol or Foley catheter. Study Design:In 18 of the 29 participating hospitals in the PROBAAT-II trial, women were asked to complete a questionnaire within 24 hours after delivery. We adapted a validated questionnaire about expectancy and experience of labor and asked women whether they would prefer the same method again in a future pregnancy. Results:The questionnaire was completed by 502 (72%) of 695 eligible women; 273 (54%) had been randomly allocated to oral misoprostol and 229 (46%) to Foley catheter. Experience of the duration of labor, pain during labor, general satisfaction with labor, and feelings of control and fear related to their expectation were comparable between both the groups. In the oral misoprostol group, 6% of the women would prefer the other method if induction is necessary in future pregnancy, versus 12% in the Foley catheter group (risk ratio: 0.70; 95% confidence interval: 0.55-0.90; p = 0.02). Conclusion: Women's experiences of labor after induction with oral misoprostol or Foley catheter are comparable. However, women in the Foley catheter group prefer more often to choose a different method for future inductions.
Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

PMID: 27412726

Custers JA, Gielissen MF, de Wilt JH, Honkoop A, **Smilde TJ**, van Spronsen DJ, van der Veld W, van der Graaf WT, Prins JB. Towards an evidence-based model of fear of cancer recurrence for breast cancer survivors.
J Cancer Surviv. 2017 Feb;11(1):41-47. doi: 10.1007/s11764-016-0558-z.

PURPOSE: In order to understand the multidimensional mechanism of fear of cancer recurrence (FCR) and to identify potential targets for interventions, it is important to empirically test the theoretical model of FCR. This study aims at assessing the validity of Lee-Jones et al.'s FCR model.
METHODS: A total of 1205 breast cancer survivors were invited to participate in this study. Participants received a questionnaire booklet including questionnaires on demographics and psychosocial variables including FCR. Data analysis consisted of the estimation of direct and indirect effects in mediator models.
RESULTS: A total of 460 women (38 %) participated in the study. Median age was 55.8 years (range 32-87). Indirect effects of external and internal cues via FCR were found for all mediation models with limited planning for the future (R 2 = .28) and body checking (R 2 = .11-.15) as behavioral response variables, with the largest effects for limited planning for the future. A direct relation was found between feeling sick and seeking professional advice, not mediated by FCR.
CONCLUSIONS: In the first tested models of FCR, all internal and external cues were associated with higher FCR. In the models with limited planning for the future and body checking as behavioral response, an indirect effect of cues via FCR was found supporting the theoretical model of Lee-Jones et al.
IMPLICATIONS FOR CANCER SURVIVORS: An evidence-based model of FCR may facilitate the development of appropriate interventions to manage FCR in breast cancer survivors.

PMID: 27454758

Zweegers J, Roosenboom B, van de Kerkhof PC, van den Reek JM, Otero ME, Atalay S, Kuijpers AL, Koetsier MI, Arnold WP, Berends MA, **Weppner-Parren L**, Bijen M, Njoo MD, Mommers JM, van Lümig PP, Driessen RJ, Kievit W, de Jong EM
Frequency and predictors of a high clinical response in patients with psoriasis on biological therapy in daily practice: results from the prospective, multicenter BioCAPTURE cohort.
Br J Dermatol. 2017 Mar;176(3):786-793.
Trefwoorden: psoriasis en biologicals

BACKGROUND: It is important to assess which patients with psoriasis are more likely to achieve high clinical responses on biologics.
OBJECTIVES: To assess the number of treatment episodes (TEs) that achieve a 100% improvement in Psoriasis Area and Severity Index (PASI 100), PASI 90 or PASI ≤ 5 at week 24 of biological treatment, and which baseline patient characteristics predict treatment response.
METHODS: Data from patients with psoriasis treated with adalimumab, etanercept, infliximab or ustekinumab were extracted from a prospective cohort. TEs with high clinical responses were described. Uni- and multivariate regression analyses were performed with the generalized estimating equation method to elucidate which baseline patient characteristics were predictors for PASI 90 and PASI ≤ 5 at week 24.
RESULTS: In total, 454 TEs were extracted (159 adalimumab; 193 etanercept; 19 infliximab; 83 ustekinumab) from 326 patients. At week 24, in 3%, 15% and 59% of TEs, respectively, PASI 100, PASI 90 and PASI ≤ 5 was reached. In TEs without a PASI 100 or PASI 90 response, PASI ≤ 5 was still achieved in 58% and 52%, respectively. Baseline PASI ≥ 10 was a strong predictor for achieving PASI 90; baseline PASI < 10 and a lower baseline body mass index (BMI) were significant predictors for PASI ≤ 5 at week 24.
CONCLUSIONS: A limited number of patients achieved PASI 100 or PASI 90 at 24 weeks of biological treatment. Including an absolute PASI score in the assessment of psoriasis severity is important. Baseline BMI was an important, modifiable predictor for a high response.

PMID: 27487525

Holleman M, **Vink M**, Nijland R, Schmand B. Effects of intensive neuropsychological rehabilitation for acquired brain injury.
Neuropsychol Rehabil. 2018 Jun;28(4):649-662. doi: 10.1080/09602011.2016.1210013.

The objective of the study was to examine the effects of a comprehensive neuropsychological rehabilitation programme (Intensive NeuroRehabilitation, INR) on the emotional and behavioural consequences of acquired brain injury (ABI). The participants were 75 adult patients suffering from ABI (33 traumatic brain injury, 14 stroke, 10 tumour, 6 hypoxia, 12 other), all of whom were admitted to the INR treatment programme. The main outcome measures were: general psychological well-being (Symptom-Checklist-90), depression and anxiety (Beck Depression Inventory-II, Hospital Anxiety and Depression Scale, State Trait Anxiety Inventory), and quality of life (Quality of Life in Brain Injury). The study was a non-blinded, waiting-list controlled trial. During the waiting-list period no or minimal care was provided. Multivariate analysis of the main outcome measures showed large effect sizes for psychological well-being (partial $\eta 2 = .191$, $p < .001$), depression (partial $\eta 2 = .168$, $p < .001$), and anxiety (partial $\eta 2 = .182$, $p < .001$), and a moderate effect size for quality of life (partial $\eta 2 = .130$, $p = .001$). Changes on neuropsychological tests did not differ between the groups. It was concluded that the INR programme improved general psychological well-being, depressive symptoms, anxiety, and quality of life. The programme does not affect cognitive functioning.

PMID: 27497436

van Balveren JA, Huijskens MJ, **Gemen EF, Péquériaux NC, Kusters R**. Effects of time and temperature on 48 routine chemistry, haematology and coagulation analytes in whole blood samples.
Ann Clin Biochem. 2017 Jul;54(4):448-462. doi: 10.1177/0004563216665868. Epub 2016 Sep 28.

Background Phlebotomy for the purpose of blood analysis is often performed at remote locations, and samples are usually temporarily stored before transport to a central laboratory for analysis. The circumstances during storage and shipment may not meet the necessary requirements. If analysed anyway, false results may be generated. We therefore examined the influence of precentrifugation time and temperature of the most frequently requested tests in whole blood. Methods Healthy volunteers donated blood in which 48 analytes were tested. Routine chemistry was performed in lithium heparin tubes, haematology in ethylenediaminetetraacetic acid tubes, coagulation in citrate tubes and glucose in sodium fluoride tubes. One tube was measured directly. The others were kept at different temperatures (4, 8, 20 or 30°C) and stored for 4, 6, 8 or 24 h before analysis. Additionally, some analytes were examined at 12, 16, 24 and 28°C. The mean percentage deviation was compared with different decision levels, including the total allowable error. Results When using the total allowable error as an acceptable limit, most of the investigated analytes remained stable. However, bicarbonate is unstable at almost all tested time-points and

temperatures. Calcium, lactate dehydrogenase, potassium and sodium are particularly affected at low temperatures, while phosphate is mainly affected at and above room temperature after 8 h. Conclusion We established the influence of time and temperature on a broad range of analytes, which may be applied to set the limits in transportation and storage of whole blood samples.

PMID: 27549241

Brooke RJ, Teunis PF, Kretzschmar ME, **Wielders CC, Schneeberger PM**, Waller LA. Use of a Dose-Response Model to Study Temporal Trends in Spatial Exposure to Coxiella burnetii: Analysis of a Multiyear Outbreak of Q Fever.
Zoonoses Public Health. 2017 Mar;64(2):118-126. doi: 10.1111/zph.12288.

The Netherlands underwent a large Q fever outbreak between 2007 and 2009. In this paper, we study spatial and temporal Coxiella burnetii exposure trends during this large outbreak as well as validate outcomes against other published studies and provide evidence to support hypotheses on the causes of the outbreak. To achieve this, we develop a framework using a dose-response model to translate acute Q fever case incidence into exposure estimates. More specifically, we incorporate a geostatistical model that accounts for spatial and temporal correlation of exposure estimates from a human Q fever dose-response model to quantify exposure trends during the outbreak. The 2051 cases, with the corresponding age, gender and residential addresses, reside in the region with the highest attack rates during the outbreak in the Netherlands between 2006 and 2009. We conclude that the multiyear outbreak in the Netherlands is caused by sustained release of infectious bacteria from the same sources, which suggests that earlier implementation of interventions may have prevented many of the cases. The model predicts the risk of infection and acute symptomatic Q fever from multiple exposure sources during a multiple-year outbreak providing a robust, evidence-based methodology to support decision-making and intervention design.

PMID: 27593688

Araújo T, Abayazid M, **Rutten MJCM**, Misra S. Segmentation and three-dimensional reconstruction of lesions using the automated breast volume scanner (ABVS).
Int J Med Robot. 2017 Sep;13(3). doi: 10.1002/rcs.1767.

BACKGROUND: Ultrasound is an effective tool for breast cancer diagnosis. However, its relatively low image quality makes small lesion analysis challenging. This promotes the development of tools to help clinicians in the diagnosis.
METHODS: We propose a method for segmentation and three-dimensional (3D) reconstruction of lesions from ultrasound images acquired using the automated breast volume scanner (ABVS). Segmentation and reconstruction algorithms are applied to obtain the lesion's 3D geometry. A total of 140 artificial lesions with different sizes and shapes are reconstructed in gelatin-based phantoms and biological tissue. Dice similarity coefficient (DSC) is used to evaluate the reconstructed shapes. The algorithm is tested using a human breast phantom and clinical data from six patients.
RESULTS: DSC values are 0.86 ± 0.06 and 0.86 ± 0.05 for gelatin-based phantoms and biological tissue, respectively. The results are validated by a specialized clinician.
CONCLUSIONS: Evaluation metrics show that the algorithm accurately segments and reconstructs various lesions. Copyright © 2016 John Wiley & Sons, Ltd.

PMID: 27611610

Govaert JA, Fiocco M, van Dijk WA, Kolfschoten NE, **Prins HA**, Dekker JWT, Tollenaar RAEM, Tanis PJ, Wouters MWJM; Dutch Value Based Healthcare Study Group. Multicenter Stratified Comparison of Hospital Costs Between Laparoscopic and Open Colorectal Cancer Resections: Influence of Tumor Location and Operative Risk.
Ann Surg. 2017 Dec;266(6):1021-1028. doi: 10.1097/SLA.0000000000002000.

OBJECTIVE: To compare actual 90-day hospital costs between elective open and laparoscopic colon and rectal cancer resection in a daily practice multicenter setting stratified for operative risk.
BACKGROUND: Laparoscopic resection has developed as a commonly accepted surgical procedure for colorectal cancer. There are conflicting data on the influence of laparoscopy on hospital costs, without separate analyses based on operative risk.
METHODS: Retrospective analyses using a population-based database (Dutch Surgical Colorectal Audit). All elective resections for a T1-3N0-2M0 stage colorectal cancer were included between 2010 and 2012 in 29 Dutch hospitals. Operative risk was stratified for age (<75 years or

≥75 years) and ASA status (I-II/III-IV). Ninety-day hospital costs were measured uniformly in all hospitals based on time-driven activity-based costing.
RESULTS: Total 90-day hospital costs ranged from &0V0556;10474 to &0V0556;20865 in the predefined subgroups. For colon cancer surgery (N = 4202), laparoscopic resection was significant less expensive than open resection in all subgroups, savings because of laparoscopy ranged from &0V0556;409 (<75 years ASA I-II) to &0V0556;1932 (≥75 years ASA I-II). In patients ≥75 years and ASA I-II, laparoscopic resection was associated with 46% less mortality (P = 0.05), 41% less severe complications (P < 0.001), 25% less hospital stay (P = 0.013), and 65% less ICU stay (P < 0.001). For rectal cancer surgery (N=2328), all laparoscopic subgroups had significantly higher total hospital costs, ranging from &0V0556;501 (<75 years ASA I-II) to &0V0556;2515 (≥75 years ASA III-IV).
CONCLUSIONS: Laparoscopic resection resulted in the largest cost reduction in patients over 75 years with ASA I-II undergoing colonic resection, and the largest cost increase in patients over 75 years with ASA III-IV undergoing rectal resection as compared with an open approach.

PMID: 27615021

van Erning FN, Janssen-Heijnen ML, Creemers GJ, **Pruijt JF**, Maas HA, Lemmens VE. Recurrence-free and overall survival among elderly stage III colon cancer patients treated with CAPOX or capecitabine monotherapy.
Int J Cancer. 2017 Jan 1;140(1):224-233. doi: 10.1002/ijc.30423.

The aim of this study is to investigate the effects of CAPOX and capecitabine on recurrence-free survival (RFS) and overall survival (OS) among elderly stage III colon cancer patients and to evaluate the effect of (non-)completion. Patients aged ≥70 years who underwent resection only or who were subsequently treated with CAPOX or capecitabine in 10 large non-academic hospitals were included. RFS and OS were analyzed with Kaplan-Meier curves and multivariable Cox regression adjusted for patient and tumor characteristics. 982 patients were included: 630 underwent surgery only, 191 received CAPOX and 161 received capecitabine. Five-year RFS and OS did not differ between capecitabine and CAPOX (RFS: 63% vs. 60% (p = 0.91), adjusted HR = 0.99 (95%CI 0.68-1.44); OS: 66% vs. 66% (p = 0.76), adjusted HR = 0.93 (95%CI 0.64-1.34)). After resection only, RFS was 38% and OS 37%. Completion rates were 48% for CAPOX and 68% for capecitabine. Three-year RFS and OS did not differ between patients who discontinued CAPOX early and patients who completed treatment with CAPOX (RFS: 61% vs. 69% (p = 0.21), adjusted HR = 1.42 (95%CI 0.85-2.37); OS: 68% vs. 78% (p = 0.41), adjusted HR = 1.17 (95%CI 0.70-1.97)). Three-year RFS and OS differed between patients who discontinued capecitabine early and patients who completed treatment with capecitabine (RFS: 54% vs. 72% (p = 0.01), adjusted HR = 2.07 (95%CI 1.11-3.84); OS: 65% vs. 80% (p = 0.01), adjusted HR = 2.00 (95%CI 1.12-3.59)). Receipt of CAPOX or capecitabine is associated with improved RFS and OS. The advantage does not differ by regimen. The addition of oxaliplatin might not be justified in elderly stage III colon cancer patients.

PMID: 27634204

Evers D, Zwaginga JJ, Tijmensen J, Middelburg RA, de Haas M, de Vooght KM, van de Kerkhof D, Visser O, **Péquériaux NC**, Hudig F, van der Bom JG. Treatments for hematologic malignancies in contrast to those for solid cancers are associated with reduced red cell alloimmunization.
Haematologica. 2017 Jan;102(1):52-59. doi: 10.3324/haematol.2016.152074.

Red cell alloimmunization may induce severe hemolytic side effects. Identification of risk-modifying conditions will help tailor preventative strategies. This study aims to quantify the associations of hematologic malignancies and solid cancers with red cell alloimmunization in patients receiving red cell transfusions. We performed a nested multicenter case-control study in a source population of 24,063 patients receiving their first and subsequent red cell transfusions during an 8-year follow-up period. Cases (n=505), defined as patients developing a first transfusion-induced red cell alloantibody, were each compared with 2 non-alloimmunized controls (n=1010) who received a similar number of red cell units. Using multivariate logistic regression analyses, we evaluated the association of various malignancies and treatment regimens with alloimmunization during a delineated 5-week risk period. The incidence of alloimmunization among patients with acute (myeloid or lymphoid) leukemia and mature (B- or T-cell) lymphoma was significantly reduced compared to patients without these malignancies: adjusted relative risks (RR) with 95% confidence interval (CI) 0.36 (range 0.19-0.68) and 0.30 (range 0.12-0.81). Associations were primarily explained by immunosuppressive treatments [RR for (any type of) chemotherapy combined with immunotherapy 0.27 (95%CI: 0.09-0.83)]. Alloimmunization risks were similarly diminished in allogeneic or autologous stem cell transplanted patients (RR 0.34, 95%CI: 0.16-0.74), at least during the six months post transplant. Alloimmunization risks of patients with other hematologic diseases or solid cancers, and their associated treatment regimens were similar to risks in the general transfused population. Our findings suggest that, in contrast to malignancies in general, hemato-oncological patients treated with dose-intensive regimens have strongly diminished risk of red cell alloimmunization.

PMID: 27659548

Razenberg LG, van Erning FN, **Pruijt HF**, Ten Tije AJ, van Riel JM, Creemers GJ, Lemmens VE. The impact of age on first-line systemic therapy in patients with metachronous metastases from colorectal cancer.
J Geriatr Oncol. 2017 Jan;8(1):37-43. doi: 10.1016/j.jgo.2016.08.003.

OBJECTIVES: The paucity of evidence for the optimal use of systemic therapy in elderly patients with metastatic colorectal cancer (mCRC) poses significant challenges to cancer specialists. The present population-based study provides insight into the impact of age on palliative systemic therapy in patients with metachronous metastases from CRC, in order to optimize the decision-making process.
METHODS: Data on the development and treatment of metachronous metastases were collected for patients with primary resected CRC diagnosed between 2003 and 2008 in the Eindhoven area of the Netherlands Cancer Registry. Patients undergoing surgery for metastases were excluded, resulting in a study population treated with palliative intent, with or without systemic therapy (n=746).
RESULTS: 385 patients received palliative systemic therapy (52%). Patients aged ≥75years were less likely to receive systemic therapy (31% ≥75years vs 73% <60years) and more likely to receive single-agent chemotherapy than combination-chemotherapy. Elderly patients (≥75years) treated with capecitabine-oxaliplatin (CAPOX) received fewer cycles (51% ≤3 oxaliplatin cycles, 43% ≤3 capecitabine cycles) and lower cumulative dosages compared to patients aged <75years, although initial dosages were similar. If capecitabine monotherapy (CapMono) was administered, starting dosages were 2414mg/m2/d<75years and 1992mg/m2/d≥75years (p<0.05), but no differences in number of received cycles or cumulative dosages were observed.
CONCLUSION: Age beginning at 75years significantly influenced palliative systemic therapy. Even in selected elderly patients, first-line treatment with CAPOX was associated with less cycles and lower cumulative dosages compared to younger patients. With single-agent fluoropyrimidine therapy, however, no such results were observed.

PMID: 27709278

Meulepas JM, Smets AMJB, Nievelstein RAJ, Gradowska P, Verbeke J, Holscher HC, **Rutten MJCM**, Kieft M, Ronckers CM, Hauptmann M. Trends and patterns of computed tomography scan use among children in The Netherlands: 1990-2012.
Eur Radiol. 2017 Jun;27(6):2426-2433. doi: 10.1007/s00330-016-4566-1. Epub 2016 Oct 5.

OBJECTIVE: To evaluate trends and patterns in CT usage among children (aged 0-17 years) in The Netherlands during the period 1990-2012.
METHODS: Lists of electronically archived paediatric CT scans were requested from the Radiology Information Systems (RIS) of Dutch hospitals which reported >10 paediatric CT scans annually in a survey conducted in 2010. Data included patient identification, birth date, gender, scan date and body part scanned. For non-participating hospitals and for years prior to electronic archiving in some participating hospitals, data were imputed by calendar year and hospital type (academic, general with <500 beds, general with ≥ 500 beds).
RESULTS: Based on 236,066 CT scans among 146,368 patients performed between 1990 and 2012, estimated annual numbers of paediatric CT scans in The Netherlands increased from 7,731 in 1990 to 26,023 in 2012. More than 70 % of all scans were of the head and neck. During the last decade, substantial increases of more than 5 % per year were observed in general hospitals with fewer than 500 beds and among children aged 10 years or older.
CONCLUSION: The estimated number of paediatric CT scans has more than tripled in The Netherlands during the last two decades.
KEY POINTS: • Paediatric CT in The Netherlands has tripled during the last two decades. • The number of paediatric CTs increased through 2012 in general hospitals. • Paediatric CTs continued to increase among children aged 10 years or older.

PMID: 27741030

Walter D, van Boeckel PG, Groenen MJ, Weusten BL, Witteman BJ, Tan G, Brink MA, Nicolai J, Tan AC, Alderliesten J, Venneman NG, Laleman W, Jansen JM, Bodelier A, Wolters FL, van der Waaij LA, Breumelhof R, Peters FT, **Scheffer RC**, Steyerberg EW, May AM, Leenders M, Hirdes MM, Vleggaar FP, Siersema PD. Higher quality of life after metal stent placement compared with plastic stent placement for malignant extrahepatic bile duct obstruction: a randomized controlled trial.
Eur J Gastroenterol Hepatol. 2017 Feb;29(2):231-237. doi: 10.1097/MEG.0000000000000762

OBJECTIVE: For palliation of extrahepatic bile duct obstruction, self-expandable metal stents (SEMS) are superior to plastic stents in terms of stent patency and occurrence of stent dysfunction. We assessed health-related quality of life (HRQoL) after stent placement to investigate whether this also results in a difference in HRQoL between patients treated with a plastic stent or SEMS.
PATIENTS AND METHODS: This randomized multicenter trial included 219 patients who were randomized to receive plastic stent (n=73) or SEMS [uncovered (n=75) and covered (n=71); n=146] placement. HRQoL was assessed with two general questionnaires (EQ-5D-3L and

QLQ-C30) and one disease-specific questionnaire (PAN-26). Scores were analyzed using linear mixed model regression and included all patients with baseline and at least one follow-up measurement.
RESULTS: HRQoL data were available in 140 of 219 patients (64%); 71 patients (32%) declined participation and in eight patients (4%) only baseline questionnaires were available. On the QLQ-C30, the interaction between follow-up time and type of stent was significantly different on two of five functional scales [physical functioning (P=0.004) and emotional functioning (P=0.01)] in favor of patients with a SEMS. In addition, patients with SEMS reported significantly less frequent symptoms of fatigue (P=0.01), loss of appetite (P=0.02), and nausea and vomiting (0.04) over time. The EQ-VAS score decreased with time in both treatment groups, indicating a statistically significant decrease in HRQoL over time.
CONCLUSION: In patients with inoperable malignant extrahepatic bile duct obstruction, SEMS placement results in better scores for general and disease-specific HRQoL over time compared with plastic stent placement.

PMID: 27761961
Kip MM, Steuten LM, Koffijberg H, IJzerman MJ, **Kusters R**. Using expert elicitation to estimate the potential impact of improved diagnostic performance of laboratory tests: a case study on rapid discharge of suspected non-ST elevation myocardial infarction patients.
J Eval Clin Pract. 2018 Feb;24(1):31-41. doi: 10.1111/jep.12626.

Early health technology assessment can provide insight in the potential cost-effectiveness of new tests to guide further development decisions. This can increase their potential benefit but often requires evidence which is lacking in early test development stages. Then, expert elicitation may be used to generate evidence on the impact of tests on patient management. This is illustrated in a case study on a new triple biomarker test (copeptin, heart-type fatty acid binding protein, and high-sensitivity troponin [HsTn]) at hospital admission. The elicited evidence enables estimation of the impact of using the triple biomarker on time to exclusion of non-ST elevation myocardial infarction compared with current serial HsTn measurement (performed 0, 2, and 6 h after admission). Cardiologists were asked to estimate the effect of the triple biomarker on patient's discharge rates and interventions performed, depending on its diagnostic performance. This elicited evidence was combined with Dutch reimbursement data and published evidence into a decision analytic model. Direct hospital costs and patients' discharge rates were assessed for 3 testing strategies including this triple biomarker (ie, only at admission or combined with HsTn measurements after 2 and 6 h). Direct hospital costs of suspected non-ST elevation myocardial infarction patients using serial HsTn measurements are estimated at €1825 per patient. Combining this triple biomarker with HsTn measurements after 2 and 6 hours is expected to be the most cost-effective strategy. Depending on the diagnostic performance of the triple biomarker, this strategy is estimated to reduce costs with €66 to €205 per patient (ie, 3.6%-11.3% reduction). Expert elicitation can be a valuable tool for early health technology assessment to provide an initial estimate of the cost-effectiveness of new tests prior to their implementation in clinical practice. As demonstrated in our case study, improved diagnostic performance of the triple biomarker may have benefits that should be further explored.

PMID: 27784131
van Eijk JJ, Groothuis JT, van Alfen N. Reply.
Muscle Nerve. 2017 Mar;55(3):447. doi: 10.1002/mus.25449. Epub 2016 Nov 16.
No abstract available.

PMID:27785617
Joustra R, Polderman FN, Smeets JL, **Daniëls MC, Boulaksil M**. Typical ECG findings in an unconscious patient. Neth Heart J. 2017 Mar;25(3):215-216. doi: 10.1007/s12471-016-0909-4.
No abstract available.

PMID:27785621
Joustra R, Polderman FN, Smeets JL, **Daniëls MC, Boulaksil M**. Typical ECG findings in an unconscious patient. Neth Heart J. 2017 Mar;25(3):221-222. doi: 10.1007/s12471-016-0910-y.
No abstract available.

PMID: 27870169

van Iersel JJ, Formijne Jonkers HA, Verheijen PM, Broeders IA, Heggelman BG, Sreetharan V, Fütterer JJ, Somers I, van der Leest M, Consten EC. Comparison of dynamic magnetic resonance defaecography with rectal contrast and conventional defaecography for posterior pelvic floor compartment prolapse.
Colorectal Dis. 2017 Jan;19(1):046-053. doi: 10.1111/codi.13563.
Trefwoorden: Dynamische MRI, Defecogram

AIM: This study compared the diagnostic capabilities of dynamic magnetic resonance defaecography (D-MRI) with conventional defaecography (CD, reference standard) in patients with symptoms of prolapse of the posterior compartment of the pelvic floor.
METHOD: Forty-five consecutive patients underwent CD and D-MRI. Outcome measures were the presence or absence of rectocele, enterocele, intussusception, rectal prolapse and the descent of the anorectal junction on straining, measured in millimetres. Cohen's Kappa, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the positive and negative likelihood ratio of D-MRI were compared with CD. Cohen's Kappa and Pearson's correlation coefficient were calculated and regression analysis was performed to determine inter-observer agreement.
RESULTS: Forty-one patients were available for analysis. D-MRI underreported rectocele formation with a difference in prevalence (CD 77.8% vs D-MRI 55.6%), mean protrusion (26.4 vs 22.7 mm, P = 0.039) and 11 false negative results, giving a low sensitivity of 0.62 and a NPV of 0.31. For the diagnosis of enterocele, D-MRI was inferior to CD, with five false negative results, giving a low sensitivity of 0.17 and high specificity (1.0) and PPV (1.0). Nine false positive intussusceptions were seen on D-MRI with only two missed.
CONCLUSION: The accuracy of D-MRI for diagnosing rectocele and enterocele is less than that of CD. D-MRI, however, appears superior to CD in identifying intussusception. D-MRI and CD are complementary imaging techniques in the evaluation of patients with symptoms of prolapse of the posterior compartment.

PMID: 27787599

van der Linden YT, Govaert JA, Fiocco M, van Dijk WA, **Lips DJ, Prins HA**. Single center cost analysis of single-port and conventional laparoscopic surgical treatment in colorectal malignant diseases.
Int J Colorectal Dis. 2017 Feb;32(2):233-239. doi: 10.1007/s00384-016-2692-5. Epub 2016 Oct 27.

BACKGROUND AND PURPOSE: Single-port laparoscopy (SPL) is a relatively new technique, used in various procedures. There is limited knowledge about the cost effectiveness and the learning curve of this technique. The primary aim of this study was to compare hospital costs between SPL and conventional laparoscopic resections (CLR) for colorectal cancer; the secondary aim was to identify a learning curve of SPL.
METHODS: All elective colorectal cancer SPL and CLR performed in a major teaching hospital between 2011 and 2012 that were registered in the Dutch Surgical Colorectal Audit were included (n = 267). The economic evaluation was conducted from a hospital perspective, and costs were calculated using time-driven activity-based costing methodology up to 90 days after discharge. When looking at SPL only, the introduction year (2011) was compared to the next year (2012).
RESULTS: SPL (n = 78) was associated with lower mortality, lower reintervention rates, and more complications as compared to CLR (n = 189); however, none of these differences were statistically significant. A significant shorter operating time was seen in the SPL. Total costs were higher for SPL group as compared to CLR; however, this difference was not statistically significant. For the SPL group, most clinical outcomes improved between 2011 and 2012; moreover, total hospital costs for SPL in 2012 became comparable to CLR.
CONCLUSION: No significant differences in financial outcomes between SPL and CLR were identified. After the introduction period, SPL showed similar results as compared to CLR. Conclusions are based on a small single-port group and the conclusions of this manuscript should be an impetus for further research.

PMID: 27792243

Zwertbroek EF, Broekhuijsen K, Langenveld J, van Baaren GJ, van den Berg PP, Bremer HA, Ganzevoort W, van Loon AJ, Mol BW, van Pampus MG, Perquin DA, **Rijnders RJ**, Scheepers HC, Sikkema MJ, Woiski MD, Groen H, Franssen MT; HYPITAT-II Study Group. Prediction of progression to severe disease in women with late preterm hypertensive disorders of pregnancy.
Acta Obstet Gynecol Scand. 2017 Jan;96(1):96-105. doi: 10.1111/aogs.13051.

INTRODUCTION: If hypertensive disorders of pregnancy are diagnosed before term, the benefits of immediate delivery need to be weighed against the neonatal consequences of preterm delivery. If we are able to predict which women are at high risk of progression to severe disease, they could be targeted for delivery and maternal complications might be reduced. In addition, this may prevent unnecessary preterm births in

women at low risk.
MATERIAL AND METHODS: We developed a prediction model using data from the HYPITAT-II trail, which evaluated immediate delivery vs. expectant monitoring in women with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation. Univariate and multivariate logistic regression analysis were used to identify relevant variables from clinical and laboratory parameters. The performance of the resulting prediction model was assessed by receiver operating characteristic analysis, calibration and bootstrapping, using the average predicted probabilities.
RESULTS: We included 519 women, 115 (22.2%) of whom developed severe hypertensive disorders of pregnancy. The prediction model included: maternal age (odds ratio 0.92 per year), gestational age (odds ratio 0.87 per week), systolic blood pressure (odds ratio 1.05 per mmHg), the presence of chronic hypertension (odds ratio 2.4), platelet count (odds ratio 0.996), creatinine (odds ratio 1.02) and lactate dehydrogenase (odds ratio 1.003). The model showed good fit ($p = 0.64$), fair discrimination (area under the curve 0.76, 95% confidence interval 0.73-0.81, $p < 0.001$) and could stratify women in three risk groups of average, intermediate and high risk (predicted probabilities <0.22, <0.44 and >0.45, respectively).
CONCLUSION: In women with non-severe hypertension in pregnancy near term, progression to severe disease can be predicted. This model requires external validation before it can be applied in practice.

PMID: 27973688

Nieuwesteeg A, Hartman E, Emons W, van Bakel H, Aanstoot HJ, **van Mil E**, Pouwer F. Paediatric parenting stress in fathers and mothers of young children with Type 1 diabetes: a longitudinal study.
Diabet Med. 2017-34(6):821-827.

AIM: To compare levels of paediatric parenting stress in the fathers and mothers of young children with Type 1 diabetes and study the variation in this stress over time.
METHODS: One hundred and twelve parents (56 mothers and 56 fathers) of young children (0-7 years) with Type 1 diabetes participated in this study. They completed the Pediatric Inventory for Parents to assess paediatric parenting stress (frequency and difficulty scores on the Communication, Emotional Distress, Medical Care and Role Functioning subscales and Total Score); 44 mothers (79%) and 31 fathers (55%) completed the questionnaire again, 1 year later. Independent and paired sample t-tests were used to examine the differences between fathers and mothers and the changes over time. Cohen's d effect sizes were also calculated.
RESULTS: Mothers scored significantly higher than fathers on the stress subscales for Communication frequency and difficulty, Emotional Distress frequency and difficulty, Medical Care frequency and Total Score frequency and difficulty (d ranged from -0.44 to -0.56). Furthermore, fathers reported a decrease in Medical Care frequency (d = 0.10) and an increase in Emotional Distress difficulty (d = -0.32) and Total Score difficulty (d = -0.29), whereas mothers reported a decrease in Emotional Distress frequency, Medical Care frequency and Total Score frequency (d ranged from 0.31 to 0.66) over a 1-year period.
CONCLUSIONS: These results show that within families with a young child with Type 1 diabetes, the burden of care increases in fathers and decreases in mothers, suggesting that fathers assume more responsibility for care of their child with Type 1 diabetes as the child grows.

PMID: 27993999

van Eekelen R, Scholten I, Tjon-Kon-Fat RI, **van der Steeg JW, Steures P**, Hompes P, van Wely M, van der Veen F, Mol BW, Eijkemans MJ, Te Velde ER, van Geloven N. Natural conception: repeated predictions over time.
Hum Reprod. 2017 Feb;32(2):346-353. doi: 10.1093/humrep/dew309. Epub 2016 Dec 18.

STUDY QUESTION: How can we predict chances of natural conception at various time points in couples diagnosed with unexplained subfertility?
SUMMARY ANSWER: We developed a dynamic prediction model that can make repeated predictions over time for couples with unexplained subfertility that underwent a fertility workup at a fertility clinic.
WHAT IS KNOWN ALREADY: The most frequently used prediction model for natural conception (the 'Hunault model') estimates the probability of natural conception only once per couple, that is, after completion of the fertility workup. This model cannot be used for a second or third time for couples who wish to know their renewed chances after a certain period of expectant management.
STUDY DESIGN, SIZE, DURATION: A prospective cohort studying the long-term follow-up of subfertile couples included in 38 centres in the Netherlands between January 2002 and February 2004. Couples with bilateral tubal occlusion, anovulation or a total motile sperm count <1 × 106 were excluded.
PARTICIPANTS/MATERIALS, SETTING, METHODS: The primary endpoint was time to natural conception, leading to an ongoing pregnancy.

Follow-up time was censored at the start of treatment or at the last date of contact. In developing the new dynamic prediction model, we used the same predictors as the Hunault model, i.e. female age, duration of subfertility, female subfertility being primary or secondary, sperm motility and referral status. The performance of the model was evaluated in terms of calibration and discrimination. Additionally, we assessed the utility of the model in terms of the variability of the calculated predictions.
MAIN RESULTS AND THE ROLE OF CHANCE: Of the 4999 couples in the cohort, 1053 (21%) women reached a natural conception leading to an ongoing pregnancy within a mean follow-up of 8 months (5th and 95th percentile: 1-21). Our newly developed dynamic prediction model estimated the median probability of conceiving in the first year after the completion of the fertility workup at 27%. For couples not yet pregnant after half a year, after one year and after one and a half years of expectant management, the median probability of conceiving over the next year was estimated at 20, 15 and 13%, respectively. The model performed fair in an internal validation. The prediction ranges were sufficiently broad to aid in counselling couples for at least two years after their fertility workup.
LIMITATIONS, REASONS FOR CAUTION: The dynamic prediction model needs to be validated in an external population.
WIDER IMPLICATIONS OF THE FINDINGS: This dynamic prediction model allows reassessment of natural conception chances after various periods of unsuccessful expectant management. This gives valuable information to counsel couples with unexplained subfertility that are seen for a fertility workup.
STUDY FUNDING/COMPETING INTERESTS: This study was facilitated by grant 945/12/002 from ZonMW, The Netherlands Organization for Health Research and Development, The Hague, The Netherlands. No competing interests.

PMID: 28003177

van der Meij E, Huirne JA, Bouwsma EV, van Dongen JM, Terwee CB, van de Ven PM, den Bakker CM, van der Meij S, van Baal WM, Leclercq WK, Geomini PM, Consten EC, Schraffordt Koops SE, van Kesteren PJ, Stockmann HB, Ten Cate AD, Davids PH, Scholten PC, **van den Heuvel B**, Schaafsma FG, Meijerink WJ, Bonjer HJ, Anema JR. Substitution of Usual Perioperative Care by eHealth to Enhance Postoperative Recovery in Patients Undergoing General Surgical or Gynecological Procedures: Study Protocol of a Randomized Controlled Trial.
JMIR Res Protoc. 2016 Dec 21;5(4):e245. doi: 10.2196/resprot.6580.

BACKGROUND: Due to the strong reduction in the length of hospital stays in the last decade, the period of in-hospital postoperative care is limited. After discharge from the hospital, guidance and monitoring on recovery and resumption of (work) activities are usually not provided. As a consequence, return to normal activities and work after surgery is hampered, leading to a lower quality of life and higher costs due to productivity loss and increased health care consumption.
OBJECTIVE: With this study we aim to evaluate whether an eHealth care program can improve perioperative health care in patients undergoing commonly applied abdominal surgical procedures, leading to accelerated recovery and to a reduction in costs in comparison to usual care.
METHODS: This is a multicenter randomized, single-blinded, controlled trial. At least 308 patients between 18 and 75 years old who are on the waiting list for a laparoscopic cholecystectomy, inguinal hernia surgery, or laparoscopic adnexal surgery for a benign indication will be included. Patients will be randomized to an intervention or control group. The intervention group will have access to an innovative, perioperative eHealth care program. This intervention program consists of a website, mobile phone app, and activity tracker. It aims to improve patient self-management and empowerment by providing guidance to patients in the weeks before and after surgery. The control group will receive usual care and will have access to a nonintervention (standard) website consisting of the digital information brochure about the surgical procedure being performed. Patients are asked to complete questionnaires at 5 moments during the first 6 months after surgery. The primary outcome measure is time to return to normal activities based on a patient-specific set of 8 activities selected from the Patient-Reported Outcomes Measurement Information System (PROMIS) physical functioning item bank version 1.2. Secondary outcomes include social participation, self-rated health, duration of return to work, physical activity, length of recovery, pain intensity, and patient satisfaction. In addition, an economic evaluation alongside this randomized controlled trial will be performed from the societal and health care perspective. All statistical analyses will be conducted according to the intention-to-treat principle.
RESULTS: The enrollment of patients started in September 2015. The follow-up period will be completed in February 2017. Data cleaning and analyses have not begun as of the time this article was submitted.
CONCLUSIONS: We hypothesize that patients receiving the intervention program will resume their normal activities sooner than patients in the control group and costs will be lower.
CLINICALTRIAL: Netherlands Trial Registry NTC4699; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4699 (Archived by WebCite at http://www.webcitation.org/6mcCBZmwy).

Paul JM van Kesteren, Hein BAC Stockmann, A Dorien ten Cate, Paul HP Davids, Petrus C Scholten, Baukje van den Heuvel, Frederieke G Schaafsma, Wilhelmus JHJ Meijerink, H Jaap Bonjer, Johannes R Anema. Originally published in JMIR Research Protocols (http://www.researchprotocols.org), 21.12.2016.

PMID: 28017787

Peters S, Stahel RA, Dafni U, Ponce Aix S, Massutí B, Gautschi O, Coate L, López Martín A, van Heemst R, Berghmans T, Meldgaard P, Cobo Dols M, Garde Noguera J, Curioni-Fontecedro A, Rauch D, Mark MT, Cuffe S, **Biesma B**, van Henten AM, Juan Vidal Ó, Palmero Sanchez R, Villa Guzmán JC, Collado Martin R, Peralta S, Insa A, Summers Y, Láng I, Horgan A, Ciardiello F, de Hosson S, Pieterman R, Groen HJ, van den Berg PM, Zielinski CC, Chittazhathu Kurian Kuruvilla Y, Gasca-Ruchti A, Kassapian M, Novello S, Torri V, Tsourti Z, Gregorc V, Smit EF; EMPHASIS-lung Collaborative Group. Randomized Phase III Trial of Erlotinib versus Docetaxel in Patients with Advanced Squamous Cell Non-Small Cell Lung Cancer Failing First-Line Platinum-Based Doublet Chemotherapy Stratified by VeriStrat Good versus VeriStrat Poor. The European Thoracic Oncology Platform (ETOP) EMPHASIS-lung
Trial. J Thorac Oncol. 2017 Apr;12(4):752-762. doi: 10.1016/j.jtho.2016.12.017.

INTRODUCTION: Docetaxel and erlotinib are registered second-line treatments for wild-type EGFR NSCLC. Previous studies suggested a predictive value of the VeriStrat test in second-line therapy of NSCLC, classifying patients as either VeriStrat good or VeriStrat poor. EMPHASIS-lung aimed at exploring this predictive effect in patients with squamous cell NSCLC. The trial closed prematurely because of low accrual and results from other trials. Our analysis includes an exploratory combined analysis with results from the PROSE trial.
METHODS: EMPHASIS-lung was a randomized phase III multicenter trial exploring the differential effect of second-line erlotinib versus docetaxel on progression-free survival (PFS) in VeriStrat good versus VeriStrat poor patients with squamous cell NSCLC.
RESULTS: A total of 80 patients were randomized, with 72.5% categorized as VeriStrat good. Patient characteristics were balanced between VeriStrat status and treatment groups. The median PFS times with docetaxel and erlotinib treatment in the VeriStrat good cohort were 4.1 and 1.6 months, respectively, versus 1.9 and 2.1 months, respectively, in the VeriStrat poor cohort. The median overall survival (OS) times with docetaxel and erlotinib treatment in the VeriStrat good cohort were 7.8 and 8.4 months, respectively, and 4.4 and 5.2 months, respectively, in the VeriStrat poor cohort. An additional exploratory analysis was performed; in it, 47 patients from the squamous cell subgroup of PROSE were included in a combined analysis, contributing with 45 PFS and 41 OS events.
CONCLUSIONS: The final analysis of EMPHASIS-lung did not show a differential effect on PFS for erlotinib versus docetaxel stratified by VeriStrat status. Similarly, in the combined analysis, no significant treatment by VeriStrat status interaction was observed (interaction p = 0.24 for PFS and 0.45 for OS, stratified by study).

PMID:28025005

Boersma D, Van Haelst ST, Van Eekeren RR, Reijnen MM, De Vries JP, De Borst GJ. Macroscopic and Histologic Analysis of Vessel Wall Reaction After Mechanochemical Endovenous Ablation Using the ClariVein OC Device in an Animal Model.
Eur J Vasc Endovasc Surg. 2017 Feb;53(2):290-298. doi: 10.1016/j.ejvs.2016.11.024. Epub 2016 Dec 23.
Trefwoorden:Mechanochemical ablation; Saphenous vein; Sclerotherapy; Varicose veins; Varicose veins therapy

OBJECTIVE/BACKGROUND:Mechanochemical endovenous ablation (MOCA) has been developed as a tumescentless technique to ablate saphenous veins and to avoid heat induced complications and post-procedural pain. The mechanism of action of MOCA is poorly understood. The present experiments were conducted to determine the effect of MOCA on vein wall injury and sclerosis in an animal model.
METHODS:A total of 36 lateral saphenous veins (LSVs) were treated in 18 goats according to the human protocol. Veins from nine goats were evaluated 45 min after the procedure, while in the remaining nine, the treated veins were evaluated 6 weeks later. All treated veins were divided equally over three treatment groups: (i) MOCA, (ii) mechanical ablation without the sclerosant, and (iii) liquid sclerotherapy alone. The histological effects of treatment on the vein wall were systematically evaluated.
RESULTS: The average diameter of the LSV was 4.0 ± 0.5 mm. Technical success was achieved in all but one LSV (35/36; 97%), with a median procedure time of 14 min (range 9-22 min). In the acute group, histological examination showed that mechanical ablation (alone or MOCA) induced severe injury to the endothelium in 82% but no damage to other layers of the vein wall. Mechanical ablation led to vasoconstriction. After 6 weeks follow-up, four of six MOCA treated veins were occluded. The occluded segments consisted mainly of fibrotic lesions probably evolved from organised thrombus. No occlusions were observed after sclerotherapy or mechanical treatment alone. No major complications occurred during procedures or follow-up.
CONCLUSION:MOCA is associated with an increased occlusion rate compared with its separated components of mechanical ablation or

sclerotherapy. The occlusion consists of cellular fibrotic material likely to be evolved from organised thrombus with fibrotic alterations to the surrounding media and adventitia. This study underlines the hypothesis that the additive use of MOCA increases the effectiveness of sclerosants alone by inducing endothelial damage and probably vasoconstriction.

PMID:28050772
Boulaksil M, Gevers RM. Enlarged jugular veins.
Neth Heart J. 2017 Apr;25(4):280-281. doi: 10.1007/s12471-016-0940-5.
No abstract available.

PMID: 28068157
Huibertse LJ, van Eenbergen M, de Rooij BH, Bastiaens MT, Fossion LM, de la Fuente RB, Kil PJ, Koldewijn EL, Meier AH, Mommers RJ, Niemer AQ, **Oddens JR**, Oomens EH, Prins M, de Roos KP, Thissen MR, Timmermans MW, Wijsman BP, van de Poll-Franse LV, Ezendam NP. Cancer survivors' preference for follow-up care providers: a cross-sectional study from the population-based PROFILES-registry.
Acta Oncol. 2017 Feb;56(2):278-287. doi: 10.1080/0284186X.2016.1267398. Epub 2017 Jan 9.

BACKGROUND: The best practice for the organization of follow-up care in oncology is under debate, due to growing numbers of cancer survivors. Understanding survivors' preferences for follow-up care is elementary for designing patient-centred care. Based on data from prostate cancer and melanoma survivors, this study aims to identify: 1) preferences for follow-up care providers, for instance the medical specialist, the oncology nurse or the general practitioner; 2) characteristics associated with these preferences and 3) the preferred care provider to discuss cancer-related problems.
MATERIAL AND METHODS: Survivors diagnosed with prostate cancer (N = 535) and melanoma (N = 232) between 2007 and 2013 as registered in The Netherlands Cancer Registry returned a questionnaire (response rate was 71% and 69%, respectively). A latent class cluster model analysis was used to define preferences and a multinomial logistic regression analysis was used to identify survivor-related characteristics associated with these preferences.
RESULTS: Of all survivors, 29% reported no preference, 40% reported a preference for the medical specialist, 20% reported a preference for both the medical specialist and the general practitioner and 11% reported a preference for both the medical specialist and the oncology nurse. Survivors who were older, lower/intermediate educated and women were more likely to have a preference for the medical specialist. Lower educated survivors were less likely to have a preference for both the medical specialist and the general practitioner. Overall, survivors prefer to discuss diet, physical fitness and fatigue with the general practitioner, and hereditary and recurrence with the medical specialist. Only a small minority favored to discuss cancer-related problems with the oncology nurse.
CONCLUSION: Survivors reported different preferences for follow-up care providers based on age, education level, gender and satisfaction with the general practitioner, showing a need for tailored follow-up care in oncology. The results indicate an urgency to educate patients about transitions in follow-up care.

PMID: 28081723
Heeres RH, **Hoogeveen EK**, Geleijnse JM, de Goede J, Kromhout D, Giltay EJ Kidney dysfunction, systemic inflammation and mental well-being in elderly post-myocardial infarction patients. BMC Psychol. 2017;5:1. doi: 10.1186/s40359-016-0170-z.

BACKGROUND: The aim was to investigate whether mild kidney dysfunction and low-grade inflammation in post-myocardial infarction patients are independently associated with markers of mental well-being (i.e. depressive and apathy symptoms, and dispositional optimism).
METHODS: In post-myocardial infarction patients, kidney function was assessed by estimated glomerular filtration rate (eGFR) calculated from the combined CKD-EPI formula based on serum levels of both creatinine and cystatine C. Systemic inflammation was assessed using high sensitivity C-reactive protein (hs-CRP) levels. The 15-item Geriatric Depression Scale (GDS-15), the 3-item apathy subscale and the 4-item optimism questionnaire (4Q) were used to measure mental well-being and were analyzed using linear multivariable regression analysis.
RESULTS: Of the 2355 patients, mean age was 72.3 (range 63-84) years and 80.1% were men. After multivariable adjustment, a poorer kidney function was associated with more depressive symptoms ($\beta = -0.084$, $p < 0.001$), more apathy symptoms ($\beta = -0.101$, $p < 0.001$), and less dispositional optimism ($\beta = 0.072$, $p = 0.002$). Moreover, higher levels of hs-CRP were associated with more depressive symptoms ($\beta = 0.051$, $p = 0.013$), more apathy symptoms ($\beta = 0.083$, $p < 0.001$) and less dispositional optimism ($\beta = -0.047$ $p = 0.024$). Apathy showed the strongest independent relation with both low eGFR and high hs-CRP.

CONCLUSIONS: In post-myocardial infarction patients, impaired kidney function and systemic inflammation showed a stronger association with apathy than with depressive symptoms and dispositional optimism.

PMID: 28087236

Wassenaar A, van den Boogaard M, **Underpin-Icu Study Group**, Schoonhoven L, Pickkers P. Determination of the feasibility of a multicomponent intervention program to prevent delirium in the Intensive Care Unit: A modified RAND Delphi study.
Aust Crit Care. 2017 Nov;30(6):321-327. doi: 10.1016/j.aucc.2016.12.004. Epub 2017 Jan 10.

BACKGROUND: Delirium is common in Intensive Care Unit (ICU) patients and associated with poor outcome. In non-ICU patients a multicomponent intervention program with non-pharmacological interventions has shown to reduce delirium. Currently, there is insufficient evidence regarding the effects of such a program in ICU patients. We developed a draft program based on a review. As most studies were conducted in non-ICU patients, the feasibility of the program in ICU patients needs to be assessed before investigating its effectiveness.
OBJECTIVES: To determine experts' opinion and to achieve group consensus on the feasibility and completeness of the multicomponent intervention program for ICU patients.
METHODS: A modified RAND/UCLA Appropriateness Method Delphi study was used. A total of 38 experts were selected following purposive sampling. Round one informed the experts about the draft program and asked for their opinion about its feasibility and completeness. In round two the experts were asked to reconsider their opinion based on changes made, and to rank the interventions in order of importance. The feasibility was scored using a 9-point Likert scale. A disagreement index (DI) and panel median were calculated to determine the level of agreement.
RESULTS: During Delphi round one 100% of the questionnaires was completed, during round two 79%. After two rounds the experts agreed on the feasibility of the interventions targeting sleep deprivation (panel median 7.00, DI 0.26), immobility (panel median 8.00, DI 0.22), visual and hearing impairment (panel median 8.00, DI 0.19), and cognitive impairment (panel median 8.00, DI 0.23), except for cognitive training (panel median 5.00, DI 0.52).
CONCLUSIONS: During this study a feasible multicomponent intervention program to prevent ICU delirium was developed based on expert consensus. As no consensus was reached on cognitive training, a pilot study is planned to determine the feasibility of cognitive training in the ICU.

PMID: 28102094

Kwakman JJM, Baars A, Boot H, **Pruijt JFM**, Winther SB, Pfeiffer P, Punt CJA. Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients.
Acta Oncol. 2017 Jul;56(7):1023-1026. doi: 10.1080/0284186X.2016.1278459. Epub 2017 Jan 19.
No abstract available.
Trefwoorden: Hand-voet syndroom, S1 en capecitabine

PMID: 28106666

Ferwerda M, van Beugen S, van Middendorp H, Spillekom-van Koulil S, Donders ART, Visser H, Taal E, **Creemers MCW**, van Riel PCLM, Evers AWM. A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial.
Pain. 2017 May;158(5):868-878. doi: 10.1097/j.pain.0000000000000845.

For patients with chronic pain conditions such as rheumatoid arthritis (RA), who experience elevated levels of distress, tailored-guided internet-based cognitive-behavioral treatment may be effective in improving psychological and physical functioning, and reducing the impact of RA on daily life. A multicenter, randomized controlled trial was conducted for RA patients with elevated levels of distress as assessed by a disease-specific measure. The control group (n = 71) received standard care and the intervention group (n = 62) additionally received an internet-based tailored cognitive-behavioral intervention. Main analyses were performed using a linear mixed model estimating differences between the intervention and control groups in scores of psychological functioning, physical functioning, and impact of RA on daily life at preassesment and postassessment, and at 3, 6, 9, and 12 months. Patients who received the internet-based intervention reported a larger improvement in psychological functioning compared with the control group, indicating less depressed mood ($P < 0.001$, $d = 0.54$), negative mood ($P = 0.01$, $d = 0.38$), and anxiety ($P < 0.001$, $d = 0.48$) during the course of the 1-year follow-up period. Regarding physical functioning,

a trend was found for the intervention group reporting less fatigue than the control group (P = 0.06, d = 0.24), whereas no effect was found on pain. No effects were found for the impact of RA on daily life, except for the intervention group experiencing fewer role limitations due to emotional problems (P < 0.001, d = 0.53). Offering guided internet-based cognitive-behavioral therapy is a promising development to aid patients with psychological distress particularly in improving psychological functioning. Further research on adherence and specific intervention ingredients is warranted.

PMID:28108934

Boulaksil M, Meuwese CL, Evertz R, **Kolff-Kamphuis MGM**. Broad complex rhythm with a salty taste.
Neth Heart J. 2017 May;25(5):346-347. doi: 10.1007/s12471-017-0950-y.
No abstract available.

PMID:28108935

Boulaksil M, Meuwese CL, Evertz R, **Kolff-Kamphuis MGM**. Broad complex rhythm with a salty taste.
Neth Heart J. 2017 May;25(5):350-351. doi: 10.1007/s12471-017-0951-x.
No abstract available.

PMID: 28128518

Van Oostwaard MF, van Eerden L, de Laat MW, Duvekot JJ, Erwich J, Bloemenkamp K, Bolte AC, Bosma J, Koenen SV, Kornelisse RF, Rethans B, van Runnard Heimel P, Scheepers H, Ganzevoort W, Mol B, de Groot CJ, **Gaugler-Senden I**. Maternal and neonatal outcomes in women with severe early onset pre-eclampsia before 26 weeks of gestation, a case series.
BJOG. 2017 Jan 27. doi: 10.1111/1471-0528.14512. [Epub ahead of print]
Trefwoorden: Vroege pre-eclampsie, uitkomsten

OBJECTIVE: To describe the maternal and neonatal outcomes and prolongation of pregnancies with severe early onset pre-eclampsia before 26 weeks of gestation.
DESIGN: Nationwide case series.
SETTING: All Dutch tertiary perinatal care centres.
POPULATION: All women diagnosed with severe pre-eclampsia who delivered between 22 and 26 weeks of gestation in a tertiary perinatal care centre in the Netherlands, between 2008 and 2014.
METHODS: Women were identified through computerised hospital databases. Data were collected from medical records.
MAIN OUTCOME MEASURES: Maternal complications [HELLP (haemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, eclampsia, pulmonary oedema, cerebrovascular incidents, hepatic capsular rupture, placenta abruption, renal failure, and maternal death], neonatal survival and complications (intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis, bronchopulmonary dysplasia, and sepsis), and outcome of subsequent pregnancies (recurrent pre-eclampsia, premature delivery, and neonatal survival).
RESULTS: We studied 133 women, delivering 140 children. Maternal complications occurred frequently (54%). Deterioration of HELLP syndrome during expectant care occurred in 48%, after 4 days. Median prolongation was 5 days (range: 0-25 days). Neonatal survival was poor (19%), and was worse (6.6%) if the mother was admitted before 24 weeks of gestation. Complications occurred frequently among survivors (84%). After active support, neonatal survival was comparable with the survival of spontaneous premature neonates (54%). Pre-eclampsia recurred in 31%, at a mean gestational age of 32 weeks and 6 days.
CONCLUSIONS: Considering the limits of prolongation, women need to be counselled carefully, weighing the high risk for maternal complications versus limited neonatal survival and/or extreme prematurity and its sequelae. The positive prospects regarding maternal and neonatal outcome in future pregnancies can supplement counselling.
TWEETABLE ABSTRACT: Severe early onset pre-eclampsia comes with high maternal complication rates and poor neonatal survival.

PMID: 28133768

Jessurun N, van Puijenbroek EP, Otten LS, Mikes O, **Vermeulen Windsant A, van Marum RJ**, Grootens K, **Derijks HJ**. Inhibition of CYP2D6 with low dose (5 mg) paroxetine in patients with high 10-hydroxynortriptyline serum levels - a review of routine practice.
Br J Clin Pharmacol. 2017 May;83(5):1149-1151. doi: 10.1111/bcp.13201. Epub 2017 Jan 29.
No abstract available.

PMID: 28138958

Wong-Lun-Hing EM, van Dam RM, van Breukelen GJ, Tanis PJ, Ratti F, van Hillegersberg R, Slooter GD, de Wilt JH, Liem MS, de Boer MT, Klaase JM, Neumann UP, Aldrighetti LA, Dejong CH; **ORANGE II Collaborative Group. Collaborators**: Terkivatan T, Verhoef C, Porte RJ, Haverman JW, Busch OR, Boermeester MA, Besselink MG, Molenaar IQ, Borel Rinkes IH, **Bosscha K**, van der Vorst JR, de Waard JW, Gerhards MF, Patijn GA, Schmeding M, Primrose JN, Abu Hilal M, Dagher I, Laurent A, Topal B, Edwin B, Lassen K, van Duyn EB, Ambergen AW, Olde Damink SW, Bemelmans MH. Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study). Br J Surg. 2017 Apr;104(5):525-535. doi: 10.1002/bjs.10438. Epub 2017 Jan 31.

BACKGROUND: Laparoscopic left lateral sectionectomy (LLLS) has been associated with shorter hospital stay and reduced overall morbidity compared with open left lateral sectionectomy (OLLS). Strong evidence has not, however, been provided.
METHODS: In this multicentre double-blind RCT, patients (aged 18-80 years with a BMI of 18-35 kg/m2 and ASA fitness grade of III or below) requiring left lateral sectionectomy (LLS) were assigned randomly to OLLS or LLLS within an enhanced recovery after surgery (ERAS) programme. All randomized patients, ward physicians and nurses were blinded to the procedure undertaken. A parallel prospective registry (open non-randomized (ONR) versus laparoscopic non-randomized (LNR)) was used to monitor patients who were not enrolled for randomization because of doctor or patient preference. The primary endpoint was time to functional recovery. Secondary endpoints were length of hospital stay (LOS), readmission rate, overall morbidity, composite endpoint of liver surgery-specific morbidity, mortality, and reasons for delay in discharge after functional recovery.
RESULTS: Between January 2010 and July 2014, patients were recruited at ten centres. Of these, 24 patients were randomized at eight centres, and 67 patients from eight centres were included in the prospective registry. Owing to slow accrual, the trial was stopped on the advice of an independent Data and Safety Monitoring Board in the Netherlands. No significant difference in median (i.q.r.) time to functional recovery was observed between laparoscopic and open surgery in the randomized or non-randomized groups: 3 (3-5) days for OLLS versus 3 (3-3) days for LLLS; and 3 (3-3) days for ONR versus 3 (3-4) days for LNR. There were no significant differences with regard to LOS, morbidity, reoperation, readmission and mortality rates.
CONCLUSION: This RCT comparing open and laparoscopic LLS in an ERAS setting was not able to reach a conclusion on time to functional recovery, because it was stopped prematurely owing to slow accrual. Registration number: NCT00874224 (https://www.clinicaltrials.gov).

PMID: 28160528

Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM; **EVAR-1, DREAM, OVER and ACE Trialists (Rutten MJ)**. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years.
Br J Surg. 2017 Feb;104(3):166-178. doi: 10.1002/bjs.10430. Erratum in: Br J Surg. 2018 Aug;105(9):1222.

BACKGROUND: The erosion of the early mortality advantage of elective endovascular aneurysm repair (EVAR) compared with open repair of abdominal aortic aneurysm remains without a satisfactory explanation.
METHODS:An individual-patient data meta-analysis of four multicentre randomized trials of EVAR versus open repair was conducted to a prespecified analysis plan, reporting on mortality, aneurysm-related mortality and reintervention.
RESULTS: The analysis included 2783 patients, with 14 245 person-years of follow-up (median 5·5 years). Early (0-6 months after randomization) mortality was lower in the EVAR groups (46 of 1393 versus 73 of 1390 deaths; pooled hazard ratio 0·61, 95 per cent c.i. 0·42 to 0·89; P = 0·010), primarily because 30-day operative mortality was lower in the EVAR groups (16 deaths versus 40 for open repair; pooled odds ratio 0·40, 95 per cent c.i. 0·22 to 0·74). Later (within 3 years) the survival curves converged, remaining converged to 8 years. Beyond 3 years, aneurysm-related mortality was significantly higher in the EVAR groups (19 deaths versus 3 for open repair; pooled hazard ratio 5·16, 1·49 to 17·89; P = 0·010). Patients with moderate renal dysfunction or previous coronary artery disease had no early survival advantage under EVAR. Those with peripheral artery disease had lower mortality under open repair (39 deaths versus 62 for EVAR; P = 0·022) in the period from 6 months to 4 years after randomization.
CONCLUSION: The early survival advantage in the EVAR group, and its subsequent erosion, were confirmed. Over 5 years, patients of marginal fitness had no early survival advantage from EVAR compared with open repair. Aneurysm-related mortality and patients with low ankle : brachial pressure index contributed to the erosion of the early survival advantage for the EVAR group. Trial registration numbers: EVAR-1, ISRCTN55703451; DREAM (Dutch Randomized Endovascular Aneurysm Management), NCT00421330; ACE (Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothèse), NCT00224718; OVER (Open Versus Endovascular Repair Trial for Abdominal Aortic Aneurysms), NCT00094575.

PMID: 28163063

Van Grinsven J, van Brunschot S, van Santvoort HC; **Dutch Pancreatitis Study Group (Cappendijk VC)**. The Value of a 24/7 Online Nationwide Multidisciplinary Expert Panel for Acute Necrotizing Pancreatitis. Gastroenterology. 2017 Mar;152(4):685-688.e6. doi: 10.1053/j.gastro.2017.01.040. Epub 2017 Feb 3.

No abstract available.

PMID: 28179203

Jansen AFM, Schoffelen T, Textoris J, Mege JL, Bleeker-Rovers CP, Roest HIJ, **Wever PC**, Joosten LAB, Netea MG, van de Vosse E, van Deuren M. Involvement of matrix metalloproteinases in chronic Q fever. Clin Microbiol Infect 2017;23:487.e7-487.e13.

OBJECTIVES: Chronic Q fever is a persistent infection with the intracellular Gram-negative bacterium Coxiella burnetii, which can lead to complications of infected aneurysms. Matrix metalloproteinases (MMPs) cleave extracellular matrix and are involved in infections as well as aneurysms. We aimed to study the role of MMPs in the pathogenesis of chronic Q fever.

METHODS: We investigated gene expression of MMPs through microarray analysis and MMP production with ELISA in C. burnetii-stimulated peripheral blood mononuclear cells (PBMCs) of patients with chronic Q fever and healthy controls. Twenty single nucleotide polymorphisms (SNPs) of MMP and tissue inhibitor of MMP genes were genotyped in 139 patients with chronic Q fever and 220 controls with similar cardiovascular co-morbidity. Additionally, circulating MMPs levels in patients with chronic Q fever were compared with those in cardiovascular controls with and without a history of past Q fever.

RESULTS: In healthy controls, the MMP pathway involving four genes (MMP1, MMP7, MMP10, MMP19) was significantly up-regulated in C. burnetii-stimulated but not in Escherichia coli lipopolysaccharide -stimulated PBMCs. Coxiella burnetii induced MMP-1 and MMP-9 production in PBMCs of healthy individuals (both $p<0.001$), individuals with past Q fever ($p<0.05$, $p<0.01$, respectively) and of patients with chronic Q fever (both $p<0.001$). SNPs in MMP7 (rs11568810) ($p<0.05$) and MMP9 (rs17576) ($p<0.05$) were more common in patients with chronic Q fever. Circulating MMP-7 serum levels were higher in patients with chronic Q fever (median 33.5 ng/mL, interquartile range 22.3-45.7 ng/mL) than controls (20.6 ng/mL, 15.9-33.8 ng/mL).

CONCLUSION: Coxiella burnetii-induced MMP production may contribute to the development of chronic Q fever.

PMID: 28182761

Hoogeveen EK, Geleijnse JM, Giltay EJ, Soedamah-Muthu SS, de Goede J, Oude Griep LM, Stijnen T, Kromhout D. Kidney function and specific mortality in 60-80 years old post-myocardial infarction patients: A 10-year follow-up study. PLoS One. 2017 Feb 9;12(2):e0171868. doi: 10.1371/journal.pone.0171868.

Chronic kidney disease (CKD) is highly prevalent among older post-myocardial infarction (MI) patients. It is not known whether CKD is an independent risk factor for mortality in older post-MI patients with optimal cardiovascular drug-treatment. Therefore, we studied the relation between kidney function and all-cause and specific mortality among older post-MI patients, without severe heart failure, who are treated with state-of-the-art pharmacotherapy. From 2002-2006, 4,561 Dutch post-MI patients were enrolled and followed until death or January 2012. We estimated Glomerular Filtration Rate (eGFR) with cystatin C (cysC) and creatinine (cr) using the CKD-EPI equations and analyzed the relation with any and major causes of death using Cox models and restricted cubic splines. Mean (SD) for age was 69 years (5.6), 79% were men, 17% smoked, 21% had diabetes, 90% used antihypertensive drugs, 98% used antithrombotic drugs and 85% used statins. Patients were divided into four categories of baseline eGFRcysC: ≥90 (33%; reference), 60-89 (47%), 30-59 (18%), and <30 (2%) ml/min/1.73m2. Median follow-up was 6.4 years. During follow-up, 873 (19%) patients died: 370 (42%) from cardiovascular causes, 309 (35%) from cancer, and 194 (22%) from other causes. After adjustment for age, sex and classic cardiovascular risk factor, hazard ratios (95%-confidence intervals) for any death according to the four eGFRcysC categories were: 1 (reference), 1.4 (1.1-1.7), 2.9 (2.3-3.6) and 4.4 (3.0-6.4). The hazard ratios of all-cause and cause-specific mortality increased linearly below kidney functions of 80 ml/min/1.73 m2. Weaker results were obtained for eGFRcr. To conclude, we found in optimal cardiovascular drug-treated post-MI patients an inverse graded relation between kidney function and mortality for both cardiovascular as well as non-cardiovascular causes. Risk of mortality increased linearly below kidney function of about 80 ml/min/1.73 m2.

PMID: 28198344
Boot EM, Hanny KH, Meijer FJ, **van Eijk JJ**. [A woman with reversible encephalopathy]. Ned Tijdschr Geneeskd. 2017;161:D690. Dutch.

A 72-year-old woman who recently had been treated with metronidazole presented with subacute dysarthria, gait ataxia and encephalopathy with severe anxiety. Head MRI showed symmetrical T2-hyperintensities. Under suspicion of a metronidazole-induced encephalopathy, metronidazole was stopped immediately. The patient recovered completely and follow-up MRI showed complete resolution of T2-hyperintensities.

PMID: 28199701
Zhou X, Huang F, Xu L, Lin Z, de Vrij FMS, Ayo-Martin AC, van der Kroeg M, Zhao M, Yin Y, Wang W, Cao W, Wang Y, Kushner SA, Marie Peron J, Alric L, de Man RA, Jacobs BC, **van Eijk JJ**, Aronica EMA, Sprengers D, Metselaar HJ, de Zeeuw CI, Dalton HR, Kamar N, Peppelenbosch MP, Pan Q. Hepatitis E Virus Infects Neurons
and Brains.
J Infect Dis. 2017 Apr 15;215(8):1197-1206. doi: 10.1093/infdis/jix079.

Hepatitis E virus (HEV), as a hepatotropic virus, is supposed to exclusively infect the liver and only cause hepatitis. However, a broad range of extrahepatic manifestations (in particular, idiopathic neurological disorders) have been recently reported in association with its infection. In this study, we have demonstrated that various human neural cell lines (embryonic stem cell-derived neural lineage cells) induced pluripotent stem cell-derived human neurons and primary mouse neurons are highly susceptible to HEV infection. Treatment with interferon-α or ribavirin, the off-label antiviral drugs for chronic hepatitis E, exerted potent antiviral activities against HEV infection in neural cells. More importantly, in mice and monkey peripherally inoculated with HEV particles, viral RNA and protein were detected in brain tissues. Finally, patients with HEV-associated neurological disorders shed the virus into cerebrospinal fluid, indicating a direct infection of their nervous system. Thus, HEV is neurotropic in vitro, and in mice, monkeys, and possibly humans. These results challenge the dogma of HEV as a pure hepatotropic virus and suggest that HEV infection should be considered in the differential diagnosis of idiopathic neurological disorders.

PMID: 28203304
de Rouw HJ, Jessurun NT, Masen-Poos LJ, **Derijks HJ**. Muscle spasms: an unexpected adverse drug reaction of pemetrexed? Ther Adv Med Oncol 2017; 9(2): 138-41.

In this report we describe a 53-year-old woman with advanced non-small cell lung cancer, treated with pemetrexed and cisplatin combination therapy, followed by pemetrexed monotherapy. The patient developed severe muscle spasms at least twice, shortly after administration of pemetrexed monotherapy. A possible explanation for this observation is that in combination with cisplatin therapy, the patient was hyperhydrated before administration to promote renal excretion and reduce toxicity. Pemetrexed is also renally excreted, which supports the finding that toxicity did not occur when the patient was hyperhydrated. After discontinuation of pemetrexed the symptoms did not reoccur. All aspects of this case point to a possible relationship between pemetrexed and an adverse drug reaction (ADR). We conclude that muscle spasms are a rare, but possibly dose-related ADR of pemetrexed-based therapy.

PMID:28240357
Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, Kolfschoten NE, de Jong PC, Rozema T, Wijnhoven BP, van Hillegersberg R, Wouters MW, van Sandick JW; Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Collaborators: **Bosscha K**, Cats A, Dikken JL, van Grieken NC, Hartgrink HH, Lemmens VE, Nieuwenhuijzen GA, Plukker JT, Rosman C, Siersema PD, Tetteroo G, Veldhuis PM, Voncken FE. Textbook outcome as a composite measure in oesophagogastric cancer surgery.
Br J Surg. 2017 May;104(6):742-750. doi: 10.1002/bjs.10486. Epub 2017 Feb 27.

BACKGROUND: Quality assurance is acknowledged as a crucial factor in the assessment of oncological surgical care. The aim of this study was to develop a composite measure of multiple outcome parameters defined as 'textbook outcome', to assess quality of care for patients undergoing oesophagogastric cancer surgery.

METHODS: Patients with oesophagogastric cancer, operated on with the intent of curative resection between 2011 and 2014, were identified from a national database (Dutch Upper Gastrointestinal Cancer Audit). Textbook outcome was defined as the percentage of patients who underwent a complete tumour resection with at least 15 lymph nodes in the resected specimen and an uneventful postoperative course, without hospital readmission. Hospital variation in textbook outcome was analysed after adjustment for case-mix factors.
RESULTS: In total, 2748 patients with oesophageal cancer and 1772 with gastric cancer were included in this study. A textbook outcome was achieved in 29·7 per cent of patients with oesophageal cancer and 32·1 per cent of those with gastric cancer. Adjusted textbook outcomerates varied from 8·5 to 52·4 per cent between hospitals. The outcome parameter 'at least 15 lymph nodes examined' had the greatest negative impact on a textbook outcome both for patients with oesophageal cancer and for those with gastric cancer.
CONCLUSION: Most patients did not achieve a textbook outcome and there was wide variation between hospitals.

PMID: 28245951

van Kampen RJW, Ramaekers BLT, Lobbezoo DJA, de Boer M, Dercksen MW, van den Berkmortel F, **Smilde TJ**, van de Wouw AJ, Peters FPJ, van Riel JMG, Peters NAJB, Tjan-Heijnen VCG, Joore MA. Real-world and trial-based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients: a study of the Southeast Netherlands Breast Cancer Consortium.
Eur J Cancer. 2017 Jul;79:238-246. doi: 10.1016/j.ejca.2017.01.027. Epub 2017 Feb 27.

INTRODUCTION: The aim of our analysis was to assess the real-world cost-effectiveness of bevacizumab in addition to taxane treatment versus taxane monotherapy for HER2-negative metastatic breast cancer compared with the cost-effectiveness based on the efficacy results from a trial.
METHODS: A state transition model was built to estimate costs, life years (LYs) and quality-adjusted life years (QALYs) for both treatments. Two scenarios were examined: a real-world scenario and a trial-based scenario in which transition probabilities were primarily based on a real-world cohort study and the E2100 trial, respectively. In both scenarios, costs and utility parameter estimates were extracted from the real-world cohort study. Moreover, the Dutch health care perspective was adopted.
RESULTS: In both the real-world and trial scenarios, bevacizumab-taxane is more expensive (incremental costs of €56,213 and €52,750, respectively) and more effective (incremental QALYs of 0.362 and 0.189, respectively) than taxane monotherapy. In the real-world scenario, bevacizumab-taxane compared to taxane monotherapy led to an incremental cost-effectiveness ratio (ICER) of €155,261 per QALY gained. In the trial scenario, the ICER amounted to €278,711 per QALY gained.
CONCLUSION: According to the Dutch informal threshold, bevacizumab in addition to taxane treatment was not considered cost-effective for HER2-negative metastatic breast cancer both in a real-world and in a trial scenario.

PMID: 28267549

van Zelst JCM, Tan T, Platel B, **de Jong M**, Steenbakkers A, Mourits M, Grivegnee A, Borelli C, Karssemeijer N, Mann RM. Improved cancer detection in automated breast ultrasound by radiologists using Computer Aided Detection.
Eur J Radiol. 2017 Apr;89:54-59. doi: 10.1016/j.ejrad.2017.01.021. Epub 2017 Jan 22.

OBJECTIVE: To investigate the effect of dedicated Computer Aided Detection (CAD) software for automated breast ultrasound (ABUS) on the performance of radiologists screening for breast cancer.
METHODS: 90 ABUS views of 90 patients were randomly selected from a multi-institutional archive of cases collected between 2010 and 2013. This dataset included normal cases (n=40) with >1year of follow up, benign (n=30) lesions that were either biopsied or remained stable, and malignant lesions (n=20). Six readers evaluated all cases with and without CAD in two sessions. CAD-software included conventional CAD-marks and an intelligent minimum intensity projection of the breast tissue. Readers reported using a likelihood-of-malignancy scale from 0 to 100. Alternative free-response ROC analysis was used to measure the performance.
RESULTS: Without CAD, the average area-under-the-curve (AUC) of the readers was 0.77 and significantly improved with CAD to 0.84 (p=0.001). Sensitivity of all readers improved (range 5.2-10.6%) by using CAD but specificity decreased in four out of six readers (range 1.4-5.7%). No significant difference was observed in the AUC between experienced radiologists and residents both with and without CAD.
CONCLUSIONS: Dedicated CAD-software for ABUS has the potential to improve the cancer detection rates of radiologists screening for breast cancer.

PMID: 28274327

van Strien AM, Souverein PC, **Keijsers CK**, Heerdink ER, Derijks HJ, **van Marum RJ**. Antipsychotic drug use associated with urinary tract infections in older women. Maturitas. 2017 Apr;98:46-50. doi: 10.1016/j.maturitas.2017.01.009. Epub 2017 Jan 27.

OBJECTIVES: Antipsychotic drugs are frequently prescribed to elderly patients, but they are associated with serious adverse effects. The objective of the current study was to investigate the association between use of antipsychotics by elderly women and the risk of urinary tract infections (UTIs).
COHORT STUDY SETTING: Dispensing data were obtained from the PHARMO Database Network for the period 1998-2008.
PARTICIPANTS: Ambulatory Dutch women (≥65 years) with current and past use of antipsychotics.
MEASUREMENTS: Incidence rates of UTIs, as defined by use of nitrofurantoin, was calculated within and outside the period of exposure to antipsychotic drugs. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate crude and adjusted hazard ratios (HRs).
RESULTS: During the study period, 18,541 women with a first prescription of an antipsychotic were identified. Current use of antipsychotics was associated with an increased risk of UTI compared to past use: HR, adjusted for age and history of UTIs, 1.33, 95% CI 1.27-1.39. A strong temporal relationship was found: the risk of being treated for a UTI was higher in the first week after the start of the treatment (adjusted HR 3.03, 95% CI 2.63-3.50) and decreased after 3 months (adjusted HR 1.22, 95% CI 1.17-1.28). Cumulative exposure was not associated with an increased risk of UTIs. There was no difference in effect between conventional and atypical antipsychotics.
CONCLUSION: Our results show an increased risk of uncomplicated UTIs during antipsychotic use in older female patients, especially in the first week of treatment.

PMID:28275933

Nelen SD, Verhoeven RHA, Lemmens VEPP, de Wilt JHW, **Bosscha K**. Increasing survival gap between young and elderly gastric cancer patients.
Gastric Cancer. 2017 Nov;20(6):919-928. doi: 10.1007/s10120-017-0708-7. Epub 2017 Mar 9.
Trefwoorden:Chemotherapy; Curative; Epidemiology; Stomach neoplasms; Surgery

INTRODUCTION: This study investigates the treatment and survival of young versus elderly potentially curable gastric cancer patients in the Netherlands.
PATIENTS AND METHODS: All noncardia gastric cancer patients with potentially curable gastric cancer according to stage (cTx-3, cNx-3, and cMx-0) diagnosed between 1989 and 2013 were selected from the Netherlands Cancer Registry. Trends in treatment and overall survivalwere compared between young patients (younger than 70 years) and elderly patients (70 years or older). Multivariable logistic regression analysis was used to examine the probability of patients undergoing surgery and chemotherapy in the most recent period. Multivariable Cox regression analysis was used to identify independent factors associated with survival.
RESULTS: In total, 8107 young and 13,814 elderly gastric cancer patients were included. There was a major increase in the proportion of patients treated with resection and chemotherapy after 2004-2008. In young patients the increase was from 2.6% in 1999-2003 to 63% in 2009-2013 ($p < 0.01$). Also an increase was noticed among elderly patients, from 0.1% to 16% ($p < 0.01$). Median survival increased from 2004 to 2008 onward particularly in young patients and to a lesser extent in elderly patients (from 28 to 41 months vs from 11 to 13 months). Multivariable Cox regression analyses confirmed that overall survival improved for young and elderly patients.
DISCUSSION: Young patients experienced a stronger improvement in survival than elderly patients, resulting in an increasing survival gap. The literature shows this is a problem not only in the Netherlands but also throughout Europe. The dissimilarity in treatment between youngand elderly patients could be the reason for this difference.

PMID: 28276328

Vuik FE, Koehestanie P, **Herbers AHE, Terhaar Sive Droste JS**. Chronic use of metamizole: not so safe after all? Neth J Med. 2017 Mar;75(2):81-83.

Metamizole can be used in both short- and long-term pain relief therapies and has a relatively favourable safety profile compared with classic NSAIDs. Metamizole is also infamous because of its potential fatal adverse drug reaction, agranulocytosis. Although this risk varies, it is estimated to occur in less than one million metamizole prescriptions. We describe a case of a 68-year-old patient who developed leukopenia after using metamizole.

PMID: 28280089

Dolstra H, Roeven MWH, Spanholtz J, Hangalapura BN, Tordoir M, Maas F, Leenders M, Bohme F, Kok N, Trilsbeek C, Paardekooper J, van der Waart AB, Westerweel PE, Snijders TJF, Cornelissen J, Bos G, **Pruijt HFM**, de Graaf AO, van der Reijden BA, Jansen JH, van der Meer A, Huls G, Cany J, Preijers F, Blijlevens NMA, Schaap NM. Successful Transfer of Umbilical Cord Blood CD34+ Hematopoietic Stem and Progenitor-derived NK Cells in Older Acute Myeloid Leukemia Patients.
Clin Cancer Res. 2017 Aug 1;23(15):4107-4118. doi: 10.1158/1078-0432.CCR-16-2981. Epub 2017 Mar 9.
Trefwoorden: Navelstrengtransplantatie, NK-cellen

Purpose: Older acute myeloid leukemia (AML) patients have a poor prognosis; therefore, novel therapies are needed. Allogeneic natural killer (NK) cells have been adoptively transferred with promising clinical results. Here, we report the first-in-human study exploiting a unique scalable NK-cell product generated ex vivo from CD34+ hematopoietic stem and progenitor cells (HSPC) from partially HLA-matched umbilical cord blood units.
Experimental Design: Ten older AML patients in morphologic complete remission received an escalating HSPC-NK cell dose (between 3 and 30 × 106/kg body weight) after lymphodepleting chemotherapy without cytokine boosting.
Results: HSPC-NK cell products contained a median of 75% highly activated NK cells, with <1 × 104 T cells/kg and <3 × 105 B cells/kg body weight. HSPC-NK cells were well tolerated, and neither graft-versus-host disease nor toxicity was observed. Despite no cytokine boosting being given, transient HSPC-NK cell persistence was clearly found in peripheral blood up to 21% until day 8, which was accompanied by augmented IL15 plasma levels. Moreover, donor chimerism up to 3.5% was found in bone marrow. Interestingly, in vivo HSPC-NK cell maturation was observed, indicated by the rapid acquisition of CD16 and KIR expression, while expression of most activating receptors was sustained. Notably, 2 of 4 patients with minimal residual disease (MRD) in bone marrow before infusion became MRD negative (<0.1%), which lasted for 6 months.
Conclusions: These findings indicate that HSPC-NK cell adoptive transfer is a promising, potential "off-the-shelf" translational immunotherapy approach in AML. Clin Cancer Res; 23(15); 4107-18. ©2017 AACR.

PMID: 28283195

de Rooij BH, Ezendam NPM, Nicolaije KAH, Caroline Vos M, Pijnenborg JMA, Boll D, Boss EA, Hermans RHM, Engelhart KCM, Haartsen JE, **Pijlman BM**, van Loon-Baelemans IEAM, Mertens HJMM, Nolting WE, van Beek JJ, Roukema JA, Kruitwagen RFPM, van de Poll-Franse LV. Effects of Survivorship Care Plans on patient reported outcomes in ovarian cancer during 2-year follow-up - The ROGY care trial.
Gynecol Oncol. 2017 May;145(2):319-328. doi: 10.1016/j.ygyno.2017.02.041. Epub 2017 Mar 7.

OBJECTIVE: The aim of this study was to assess the long-term impact of an automatically generated Survivorship Care Plan (SCP) on patient reported outcomes in ovarian cancer in routine clinical practice. Outcome measures included satisfaction with information provision and care, illness perceptions and health care utilization.
METHODS: In this pragmatic cluster randomized trial, twelve hospitals in the South of the Netherlands were randomized to 'SCP care' or 'usual care'. All newly diagnosed ovarian cancer patients in the 'SCP care' arm received an SCP that was automatically generated by the oncology provider, by clicking a button in the web-based Registrationsystem Oncological GYnecology (ROGY). Ovarian cancer patients (N=174, mean age 63.3, SD=11.4; all stages) completed questionnaires directly after initial treatment and after 6, 12 and 24months.
RESULTS: First questionnaires were returned from 61 (67%) ovarian cancer patients in the 'SCP care' arm and 113 (72%) patients in the 'usual care' arm. In the 'SCP care' arm, 66% (N=41) of the patients reported receipt of an SCP. No overall differences were observed between the trial arms on satisfaction with information provision, satisfaction with care or health care utilization. Regarding illness perceptions, patients in the 'SCP care' arm had lower beliefs that the treatment would help to cure their disease (overall, 6.7 vs. 7.5, P<0.01).
CONCLUSIONS: SCPs did not increase satisfaction with information provision or care in ovarian cancer patients. Our trial results suggest that ovarian cancer patients may not benefit from an SCP.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01185626.

PMID: 28319018

Groenewoud ER, Macklon NS, Cohlen BJ; **ANTARCTICA Study Group (de Bruin JP)**.
The effect of elevated progesterone levels before HCG triggering in modified natural cycle frozen-thawed embryo transfer cycles.
Reprod Biomed Online. 2017 May;34(5):546-554. doi: 10.1016/j.rbmo.2017.02.008. Epub 2017 Feb 28.

Recent studies suggest that elevated late follicular phase progesterone concentrations after ovarian stimulation for IVF may result in embryo-endometrial asynchrony, reducing the chance of successful implantation after fresh embryo transfer. It remains unclear to what extent elevated late follicular phase progesterone levels may occur in unstimulated cycles before frozen-thawed embryo transfer, or what affect they may have on outcomes. In this cohort study, 271 patients randomized to the modified natural cycle arm of a randomized controlled trial comparing two endometrial preparation regimens underwent late follicular phase progesterone and LH testing. A receiver operating characteristic curve was constructed to identify a progesterone cut-off level with the best predictive value for live birth (progesterone level ≥4.6 nmol/l). A total of 24.4% of patients revealed an isolated elevated serum progesterone of 4.6 nmol/l or greater, and 44.3% showed an elevated progesterone level in association with a rise in LH. Neither endocrine disruption affected outcomes, with live birth rates of 12.9% versus 10.6% (OR 0.6, 95% CI 0.19 to 1.9) and 11.9% versus 17.5% (OR 1.6, 95% CI 0.79 to 3.1), respectively. Whether monitoring of progesterone and LH in natural cycle frozen-thawed embryo transfer has added clinical value should studied further.

PMID 28322457

Eijsvoogel NB, Hollegien MI, Bok VLA, Derksen Lubsen AG, Dikken FPJ, **Leenders ACAP**, Pijning A, Post E, Wojciechowski M, **Hilbink M, de Vries E**. Declining antibody levels after hepatitis B vaccination in Down syndrome: A need for booster vaccination? J Med Virol. 2017 Sep;89(9):1682-1685. doi: 10.1002/jmv.24813. Epub 2017 May 2.

We determined the anti-HBs titer in 227 children of all ages with Down syndrome (DS). Only 48.1% (95%CI: 35.1-61.3) of the DS children aged 7-10 years and 31.9% (95%CI: 22.1-43.6) of the DS children aged >10 years had a protective anti-HBs titer (≥10 IU/L). The geometric mean anti-HBs titer was significantly lower in the DS children; this suggests booster vaccination for HBV may be needed.

PMID: 28349891

Scholten I, van Zijl M, Custers IM, **Brandes M**, Gianotten J, van der Linden PJQ, Hompes PGA, van der Veen F, Mol BWJ. The effectiveness of intrauterine insemination: A matched cohort study.
Eur J Obstet Gynecol Reprod Biol. 2017 May;212:91-95. doi: 10.1016/j.ejogrb.2017.03.028. Epub 2017 Mar 18.

OBJECTIVE: To study the effectiveness of an intrauterine insemination (IUI) program compared to no treatment in subfertile couples with unexplained subfertility and a poor prognosis on natural conception.
STUDY DESIGN: A retrospective matched cohort study in which ongoing pregnancy rates in 72 couples who voluntarily dropped out of treatment with IUI were compared to ongoing pregnancy rates in 144 couples who continued treatment with IUI. Couples with unexplained subfertility, mild male subfertility or cervical factor subfertility who started treatment with IUI between January 2000 and December 2008 were included. Couples were matched on hospital, age, duration of subfertility, primary or secondary subfertility and diagnosis. Primary outcome was cumulative ongoing pregnancy rate after three years. Time to pregnancy was censored at the moment couples were lost to follow up or when their child wish ended and, for the no-treatment group, when couples re-started treatment.
RESULTS: After three years, there were 18 pregnancies in the stopped treatment group (25%) versus 41 pregnancies in the IUI group (28%) (RR 1.1 (0.59-2.2)(p=0.4)). The cumulative pregnancy rate after three years was 40% in both groups, showing no difference in time to ongoing pregnancy (shared frailty model p=0.86).
CONCLUSIONS: In couples with unexplained subfertility and a poor prognosis for natural conception, treatment with IUI does not to add to expectant management. There is need for a randomized clinical trial comparing IUI with expectant management in these couples.

PMID: 28353184

Loonen AJM, Kesarsing C, **Kusters R, Hilbink M, Wever PC, van den Brule AJC**. High pneumococcal DNA load, procalcitonin and suPAR levels correlate to severe disease development in patients with pneumococcal pneumonia.
Eur J Clin Microbiol Infect Dis. 2017 Sep;36(9):1541-1547. doi: 10.1007/s10096-017-2963-2. Epub 2017 Mar 29.

Community-acquired pneumonia (CAP) is mostly caused by Streptococcus pneumoniae. Identification of the pathogen causing CAP can be achieved by conventional culture techniques of sputum and/or blood, antigen detection from urine or molecular analysis. However, it remains difficult to determine patients who are at risk of severe disease development (intensive care unit [ICU] admittance and/or death). In this retrospective study, 121 patients admitted to the emergency department with pneumonia symptoms were included. Several markers of infection (pneumococcal DNA load in blood (real-time LytA PCR), white blood cell (WBC) count, C-reactive protein (CRP), procalcitonin (PCT) and soluble urokinase plasminogen activator receptor (suPAR) levels) were assessed for their ability to predict severe disease development. Of 121 patients, 6 were excluded from the study because of an alternative diagnosis, whereas 8 were excluded from biomarker analysis because of the presence of co-morbidities. Of the 115 patients analysed by the LytA PCR, 23 were positive. PCR detected S. pneumoniae DNA in 82% of patients with positive blood culture for S. pneumoniae. PCR missed three samples from patients in which S. pneumoniae was recovered by blood cultures. However, eight additional LytA PCR-positive samples were detected from patients whose blood cultures remained negative. Pneumococcal DNA load was also monitored in time for 31 patients, of whom 11 had positive PCR results. For 10 out of 11 (91%) positive PCR patients, a clear increase in Ct-values was observed, indicating a lower pneumococcal DNA load in the blood as a result of antibiotic therapy. Biomarker analysis was performed in 107 patients, of whom 29 showed severe disease development. Pneumococcal DNA load ($p = 0.026$), PCT ($p = 0.046$) and suPAR ($p = 0.001$) levels most reliably predicted severe disease development. In conclusion, in patients with CAP, higher pneumococcal DNA load, PCT and suPAR values are associated with severe disease development (ICU admission and/or death). These biomarkers may be useful tools for triage of patients suspected of having CAP in the emergency department.

PMID:28355935

Boersma D, Vink A, Moll FL, de Borst GJ. Proof-of-Concept Evaluation of the SailValve Self-Expanding Deep Venous Valve System in a Porcine Model.
J Endovasc Ther. 2017 Jun;24(3):440-446. doi: 10.1177/1526602817700120. Epub 2017 Mar 30.
Trefwoorden: animal model; deep venous thrombosis; endovascular techniques; histology; in vivo study; porcine model; prosthesis; varicose vein; venous insufficiency; venous valve

PURPOSE:To evaluate the SailValve, a new self-expanding deep venous valve concept based on a single polytetrafluoroethylene cusp floating up and down in the bloodstream like a sail, acting as a flow regulator and allowing minimal reflux to reduce thrombogenicity.
METHODS:Both iliac veins of 5 pigs were implanted with SailValve devices; the first animal was an acute pilot experiment to show the feasibility of accurately positioning the SailValve via a femoral access. The other 4 animals were followed for 2 weeks (n=2) or 4 weeks (n=2) under a chronic implantation protocol. Patency and valve function were evaluated directly in all animals using ascending and descending phlebography after device placement and at termination in the chronic implant animals. For reasons of clinical relevance, a regimen of clopidogrel and calcium carbasalate was administered. Histological analysis was performed according to a predefined protocol by an independent pathologist.
RESULTS:Deployment was technically feasible in all 10 iliac veins, and all were patent directly after placement. No perioperative or postoperative complications occurred. Ascending phlebograms in the follow-up animals confirmed the patency of all valves after 2 or 4 weeks. Descending phlebograms showed full function in 5 of 8 valves. Limited reflux was seen in 1 valve (4-week group), and the function in the remaining 2 valves (2-week group) was insufficient because of malpositioning. No macroscopic thrombosis was noted on histology. Histology in the follow-up groups revealed a progressive inflammatory reaction to the valves.
CONCLUSION:This animal study shows the potential of the SailValve concept with sufficient valve function after adequate positioning and no (thrombogenic) occlusions after short-term follow-up. Future research is essential to optimize valve material and long-term patency.

PMID: 28370076

Benoist GE, van der Meulen E, Lubberman FJE, Gerritsen WR, **Smilde TJ**, Schalken JA, Beumer JH, Burger DM, van Erp NP.
Analytical challenges in quantifying abiraterone with LC-MS/MS in human plasma.
Biomed Chromatogr. 2017 Nov;31(11). doi: 10.1002/bmc.3986. Epub 2017 May 16.

A method was developed and validated to quantify abiraterone in human plasma. During assay development, several analytical challenges were encountered: limited stability in patient samples, adsorption to glass, coelution with metabolites and carry-over issues. Limited stability (2 h)

was found for abiraterone in fresh plasma as well as whole blood at ambient temperature. When kept at 2-8°C, abiraterone in plasma was stable for 24 h and in whole blood for 8 h. Adsorption of abiraterone to glass materials was addressed by using polypropylene throughout the method. Carry-over was reduced to acceptable limits by incorporating a third mobile phase into the gradient. The chromatographic separation of abiraterone with its multiple metabolites was addressed by using a longer analytical column and adjusting the gradient. Abiraterone was extracted by protein precipitation, separated on a C18 column with gradient elution and analyzed with tandem quadrupole mass spectrometry in positive ion mode. A stable deuterated isotope was used as the internal standard. The assay ranges from 1 to 500 ng/mL. Within- and-between-day precisions and accuracies were below 13.4% and within 95-102%. This bioanalytical method was successfully validated and applied to determine plasma concentrations of abiraterone in clinical studies and in regular patient care for patients with metastatic castration-resistant prostate cancer.

PMID: 28371278

Witjes M, Kotsopoulos A, Herold IHF, Otterspoor L, **Simons KS**, van Vliet J, de Blauw M, Festen B, Eijkenboom JJA, Jansen NE, van der Hoeven JG, Abdo WF. The Influence of End-of-Life Care on Organ Donor Potential Am J Transplant. 2017 Jul;17(7) 1922-1927

Trefwoorden; Orgaandonatie, IC opname

Many patients with acute devastating brain injury die outside intensive care units and could go unrecognized as potential organ donors. We conducted a prospective observational study in seven hospitals in the Netherlands to define the number of unrecognized potential organ donors outside intensive care units, and to identify the effect that end-of-life care has on organ donor potential. Records of all patients who died between January 2013 and March 2014 were reviewed. Patients were included if they died within 72 h after hospital admission outside the intensive care unit due to devastating brain injury, and fulfilled the criteria for organ donation. Physicians of included patients were interviewed using a standardized questionnaire regarding logistics and medical decisions related to end-of-life care. Of the 5170 patients screened, we found 72 additional potential organ donors outside intensive care units. Initiation of end-of-life care in acute settings and lack of knowledge and experience in organ donation practices outside intensive care units can result in under-recognition of potential donors equivalent to 11-34% of the total pool of organ donors. Collaboration with the intensive care unit and adjusting the end-of-life path in these patients is required to increase the likelihood of organ donation.

PMID:28388963

de Rooij T, van Hilst J, Vogel JA, van Santvoort HC, de Boer MT, Boerma D, van den Boezem PB, Bonsing BA, **Bosscha K**, Coene PP, Daams F, van Dam RM, Dijkgraaf MG, van Eijck CH, Festen S, Gerhards MF, Groot Koerkamp B, Hagendoorn J, van der Harst E, de Hingh IH, Dejong CH, Kazemier G, Klaase J, de Kleine RH, van Laarhoven CJ, Lips DJ, Luyer MD, Molenaar IQ, Nieuwenhuijs VB, Patijn GA, Roos D, Scheepers JJ, van der Schelling GP, Steenvoorde P, Swijnenburg RJ, Wijsman JH, Abu Hilal M, Busch OR, Besselink MG; Dutch Pancreatic Cancer Group. Minimally invasive versus open distal pancreatectomy (LEOPARD): study protocol for a randomized controlled trial.
Trials. 2017 Apr 8;18(1):166. doi: 10.1186/s13063-017-1892-9.

Trefwoorden: Distal pancreatectomy; Laparoscopic; Minimally invasive; Pancreatic cancer; Pancreatic surgery; Robot-assisted

BACKGROUND:Observational cohort studies have suggested that minimally invasive distal pancreatectomy (MIDP) is associated with better short-term outcomes compared with open distal pancreatectomy (ODP), such as less intraoperative blood loss, lower morbidity, shorter length of hospital stay, and reduced total costs. Confounding by indication has probably influenced these findings, given that case-matched studies failed to confirm the superiority of MIDP. This accentuates the need for multicenter randomized controlled trials, which are currently lacking. We hypothesize that time to functional recovery is shorter after MIDP compared with ODP even in an enhanced recovery setting.
METHODS:LEOPARD is a randomized controlled, parallel-group, patient-blinded, multicenter, superiority trial in all 17 centers of the DutchPancreatic Cancer Group. A total of 102 patients with symptomatic benign, premalignant or malignant disease will be randomly allocated to undergo MIDP or ODP in an enhanced recovery setting. The primary outcome is time (days) to functional recovery, defined as all of the following: independently mobile at the preoperative level, sufficient pain control with oral medication alone, ability to maintain sufficient (i.e. >50%) daily required caloric intake, no intravenous fluid administration and no signs of infection. Secondary outcomes are operative and postoperative outcomes, including clinically relevant complications, mortality, quality of life and costs.
DISCUSSION:The LEOPARD trial is designed to investigate whether MIDP reduces the time to functional recovery compared with ODP in an enhanced recovery setting.
TRIAL REGISTRATION:Dutch Trial Register, NTR5188 . Registered on 9 April 2015.

PMID: 28399110

Janssen A, Verkleij CPM, **van der Vlist A**, Mathijssen RHJ, Bloemendal HJ, Ter Heine R. Towards better dose individualisation: metabolic phenotyping to predict cabazitaxel pharmacokinetics in men with prostate cancer.
Br J Cancer. 2017 May 9;116(10):1312-1317. doi: 10.1038/bjc.2017.91. Epub 2017 Apr 11.

BACKGROUND: Cabazitaxel is approved for treatment of castration-resistant metastatic prostate cancer. The current dosing strategy of cabazitaxel is based on body surface area (BSA). Body surface area is known as a poor predictor for total systemic exposure to drugs, since it does not take into account variability in activity of metabolising enzymes, necessary for clearance of drugs. As exposure to cabazitaxel is related to treatment response, it is essential to develop a better individualised dosing strategy.
METHODS: Ten patients with metastatic castration-resistant prostate cancer, who received cabazitaxel dosed on BSA as a part of routine palliative care, were enrolled in this study. Midazolam was administered as phenotyping probe for cytochrome P450 isoenzyme 3A (CYP3A). The relationship between midazolam and cabazitaxel clearance was investigated using non-linear mixed effects modelling.
RESULTS: The clearance of Midazolam highly correlated with cabazitaxel clearance (R=0.74). Midazolam clearance significantly (P<0.004) explained the majority (~60%) of the inter-individual variability in cabazitaxel clearance in the studied population.
CONCLUSIONS: Metabolic phenotyping of CYP3A using midazolam is a promising strategy to individualise cabazitaxel dosing. Before clinical application, a randomised study is warranted.

PMID:28401472

Joustra R, Boulaksil M, Meijburg HW, Smeets JL. Dizziness and slow heart rate during exercise. Neth Heart J. 2017 Jul;25(7-8):461-462. doi: 10.1007/s12471-017-0983-2.
No abstract available.

PMID:28401473

Joustra R, Boulaksil M, Meijburg HW, Smeets JL. Dizziness and slow heart rate during exercise. Neth Heart J. 2017 Jul;25(7-8):465-466. doi: 10.1007/s12471-017-0985-0.
No abstract available.

PMID:28403687

Witte ME, Zeebregts CJ, de Borst GJ, Reijnen MMPJ, **Boersma D**. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review.
Phlebology. 2017 Dec;32(10):649-657. doi: 10.1177/0268355517702068. Epub 2017 Apr 12. Review.
Trefwoorden: Endovenous technique; mechanochemical ablation; saphenous vein; small saphenous vein

Objective To systematically review all available English literature on mechanochemical endovenous ablation and to report on the anatomical, technical, and clinical success. Methods A systematic literature search was performed in PubMed, EMBASE, and the Cochrane Library on mechanochemical endovenous ablation for the treatment of insufficient great and/or small saphenous vein. Methodological quality of the included studies was evaluated using the MINORS score. The primary outcome measure was anatomical success, defined as closure of the treated vein on follow-up duplex ultrasound imaging. Secondary outcomes were technical and clinical success, and major complications defined as deep venous thrombosis, pulmonary embolisms or paresthesia. Results The literature search identified 759 records, of which 13 were included, describing 10 unique cohorts. A total of 1521 veins (1267 great saphenous vein and 254 small saphenous vein) were included, with cohort sizes ranging from 30 to 570 veins. The pooled anatomical success rate after short-term follow up was 92% (95% CI 90-94%) (n = 1314 veins). After 6 and 12 months these numbers were 92% (95% CI 88-95%) (n = 284) and 91% (95% CI 86-94%) (n = 228), respectively. The long-term anatomical success rates at 2 and 3 years were 91% (95% CI 85-95%) (n = 136) and 87% (95% CI 75-94%) (n = 48), respectively. Major complications and especially nerve injury were very rare (≤ 0.2%). All studies were of moderate or good quality using the MINORS scoring scale. Conclusions Mechanochemical endovenous ablation using the ClariVein in combination with liquid sclerosant is associated with an anatomical success rate ranging from 87% to 92% and good clinical success. To date, no randomized controlled trials are available studying the anatomical success after mechanochemical ablation, compared to the endothermal ablation. The risk of major complications is very low after the procedure.

PMID: 28404008

van de Wall BJM, Stam MAW, Draaisma WA, Stellato R, Bemelman WA, Boermeester MA, Broeders IAMJ, Belgers EJ, Toorenvliet BR, **Prins HA**, Consten ECJ; DIRECT trial collaborators. Surgery versus conservative management for recurrent and ongoing left-sided diverticulitis (DIRECT trial): an open-label, multicentre, randomised controlled trial.
Lancet Gastroenterol Hepatol. 2017 Jan;2(1):13-22. doi: 10.1016/S2468-1253(16)30109-1. Epub 2016 Oct 19.

BACKGROUND: Patients with recurrent or persisting complaints after an episode of left-sided diverticulitis are managed with either conservative measures or elective sigmoidectomy. To date, there are no data from randomised trials. We aimed to establish which treatment leads to a better quality of life for patients with diverticulitis.
METHODS: We did an open-label, multicentre, randomised controlled trial (DIRECT trial) in 24 teaching and two academic hospitals in the Netherlands. Patients aged 18-75 years presenting with either recurrent (three or more presentations with clinical signs of acute diverticulitis within 2 years) or persistent abdominal complaints (ongoing lower left abdominal pain or persistent change in bowel habits for ≥3 months) after an episode of left-sided diverticulitis, confirmed by CT, ultrasound, or endoscopy, were included. Patients were excluded if they had previous elective or emergency surgery for acute sigmoid diverticulitis, an absolute operation indication, suspicion of a colorectal malignancy, with a preoperative or postoperative risk greater than III (on the American Society of Anesthesiologists classification), or were unable to complete questionnaire or follow-up. Patients were randomly assigned (3:3) to receive conservative management or elective (laparoscopic) sigmoidectomy using a digital randomisation system, stratified by type of disease and centre, with a block size of six. Patients, physicians, and researchers were not masked to treatment allocation. Our primary endpoint was health-related quality of life, measured by the Gastrointestinal Quality of Life Index (GIQLI) at 6 months after inclusion or surgery, depending on randomisation group. This trial is registered with trialregister.nl, number NTR1478, and is closed for inclusion.
FINDINGS: Between July 1, 2010, and April 1, 2014, we randomly assigned 109 patients to receive surgical treatment (resection; n=53) or conservative management (n=56), after which the Data Safety and Monitoring Board prematurely terminated the trial because of increasing difficulties in recruitment. 47 (89%) of 53 patients received surgical treatment and 43 (77%) of 56 patients received conservative management. The GIQLI score at 6 months' follow-up was significantly higher in patients randomly assigned to receive surgical treatment (mean 114·4 [SD 22·3]) than conservative management (100·4 [22·7]; mean difference 14·2, 95% CI 7·2-21·1, p<0·0001). 43 (38%) of 109 patients had a severe adverse event in the first 6 months after treatment (18 [34%] of 53 patients in the surgical treatment group vs 23 [40%] of 57 patients in the conservative treatment group). Seven (15%) patients who received surgical treatment developed anastomotic leakage. Of the 56 patients assigned to be treated conservatively, 13 (23%) ultimately underwent elective resection due to ongoing abdominal complaints, with no anastomotic leakage. We recorded no patient deaths.
INTERPRETATION: Elective sigmoidectomy, despite its inherent risk of complications, results in better quality of life than conservative management in patients with recurrent and persisting abdominal complaints after an episode of diverticulitis.
FUNDING: Netherlands Organisation for Health Research and Development.

PMID: 28406555

Jacobs BC, van den Berg B, Verboon C, Chavada G, Cornblath DR, Gorson KC, Harbo T, Hartung HP, Hughes RAC, Kusunoki S, van Doorn PA, Willison HJ; **IGOS Consortium (Garssen MJP)**. International Guillain-Barré Syndrome Outcome Study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome.
J Peripher Nerv Syst. 2017 Jun;22(2):68-76. doi: 10.1111/jns.12209.

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy with a highly variable clinical presentation, course, and outcome. The factors that determine the clinical variation of GBS are poorly understood which complicates the care and treatment of individual patients. The protocol of the ongoing International GBS Outcome Study (IGOS), a prospective, observational, multicenter cohort study that aims to identify the clinical and biological determinants and predictors of disease onset, subtype, course and outcome of GBS is presented here. Patients fulfilling the diagnostic criteria for GBS, regardless of age, disease severity, variant forms, or treatment, can participate if included within 2 weeks after onset of weakness. Information about demography, preceding infections, clinical features, diagnostic findings, treatment, course, and outcome is collected. In addition, cerebrospinal fluid and serial blood samples for serum and DNA is collected at standard time points. The original aim was to include at least 1,000 patients with a follow-up of 1-3 years. Data are collected via a web-based data entry system and stored anonymously. IGOS started in May 2012 and by January 2017 included more than 1,400 participants from 143 active centers in 19 countries across 5 continents. The IGOS data/biobank is available for research projects conducted by expertise groups focusing on specific topics including epidemiology, diagnostic criteria, clinimetrics, electrophysiology, antecedent events, antibodies, genetics, prognostic modeling, treatment effects, and long-term outcome of GBS. The IGOS will help to standardize the international collection of data and biosamples for future research of GBS.
TRIAL REGISTRATION: ClinicalTrials.gov NCT01582763.

PMID: 28411255
Evers D, van der Bom JG, Tijmensen J, de Haas M, Middelburg RA, de Vooght KMK, van de Kerkhof D, Visser O, **Péquériaux NCV**, Hudig F, Zwaginga JJ. Absence of the spleen and the occurrence of primary red cell alloimmunization in humans. Haematologica. 2017 Aug;102(8):e289-e292. doi: 0.3324/haematol.2016.162685. Epub 2017 Apr 14.
No abstract available.

PMID: 28420357
van den Driessen Mareeuw FA, **Hollegien MI**, Coppus AMW, Delnoij DMJ, de Vries E. In search of quality indicators for Down syndrome healthcare: a scoping review.
BMC Health Serv Res. 2017 Apr 18;17(1):284. doi: 10.1186/s12913-017-2228-x. Review.

BACKGROUND: The medical care chain around Down syndrome (DS) is complex, with many multidisciplinary challenges. The current quality of care is unknown. Outcome-oriented quality indicators have the potential to improve medical practice and evaluate whether innovations are successful. This is particularly interesting for the evolving care for people with DS and intellectual disabilities (ID). The aim of this study was to identify existing indicators for medical DS care, by reviewing the literature.
METHODS: We systematically searched six databases (PubMed, EMBASE, Web of Science, CINAHL, PsycINFO, Google Scholar) for studies concerning the development and implementation of quality indicators for DS and/or ID care, published until February 1st 2015. The scoping review method was used, including systematic data extraction and stakeholder consultation.
RESULTS: We identified 13 studies concerning quality indicators for ID care that obtained data originating from questionnaires (patient/family/staff), medical files and/or national databases. We did not find any indicator sets specifically for DS care. Consulted stakeholders did not come up with additional indicator sets. Existing indicators for ID care predominantly focus on support services. Indicators in care for people with ID targeting medical care are scarce. Of the 70 indicators within the 13 indicator sets, 10% are structure indicators, 34% process, 32% outcome and 24% mixed. Ten of the 13 sets include indicators on the WHO quality dimensions 'patient-centeredness', 'effectiveness' and 'efficiency' of care. 'Accessibility' is covered by nine sets, 'equitability' by six, and 'safety' by four. Most studies developed indicators in a multidisciplinary manner in a joint effort with all relevant stakeholders; some used focus groups to include people with ID.
CONCLUSION: To our knowledge, this is the first review that searched for studies on quality indicators in DS care. Hence, the study contributes to existing knowledge on DS care as well as on measuring quality of care. Future research should address the development of a compact set of quality indicators for the DS care chain as a whole. Indicators should preferably be patient-centred and outcome-oriented, including user perspectives, while developed in a multidisciplinary way to achieve successful implementation.

PMID: 28429438
de Vaan MD, Mol BWJ. Re: Induction of labour with retrievable prostaglandin vaginal inserts: outcomes following retrieval due to an intrapartum adverse event and Induction of labour: many choices, but still in search of the perfect protocol. BJOG. 2017 May;124(6):985. doi: 10.1111/1471-0528.14404.
No abstract available.

PMID: 28432161
Storms I, van den Brand M, **Schneeberger P**, van 't Hullenaar N. Aggregatibacter actinomycetemcomitans pneumonia with chest and abdominal wall involvement. BMJ Case Rep. 2017 Apr 21;2017. pii: bcr-2016-217377. doi: 10.1136/bcr-2016-217377.

A 54-year-old man presented with a productive cough, chest pain, fever and weight loss. Initial analysis revealed a palpable chest wall mass and consolidation in the left lower lobe and pleural abnormalities on imaging. At that point no infectious cause or malignancy was identified. Microbiological analysis of a needle biopsy from a newly developed abdominal wall mass revealed growth of Aggregatibacter actinomycetemcomitans The patient was successfully treated with antibiotic therapy for 1 year. Aggregatibacter actinomycetemcomitans is a Gram-negative coccobacillus and is part of the normal oral flora. It is capable of causing infections in humans including periodontitis, soft tissue abscesses and systemic invasive infections, most commonly endocarditis.

PMID: 28434653

Bensdorp AJ, **van der Steeg JW, Steures P**, Habbema JDF, Hompes PGA, Bossuyt PMM, van der Veen F, Mol BWJ, Eijkemans MJC; CECERM study group. A revised prediction model for natural conception.
Reprod Biomed Online. 2017 Jun;34(6):619-626. doi: 10.1016/j.rbmo.2017.03.014. Epub 2017 Mar 28.

One of the aims in reproductive medicine is to differentiate between couples that have favourable chances of conceiving naturally and those that do not. Since the development of the prediction model of Hunault, characteristics of the subfertile population have changed. The objective of this analysis was to assess whether additional predictors can refine the Hunault model and extend its applicability. Consecutive subfertile couples with unexplained and mild male subfertility presenting in fertility clinics were asked to participate in a prospective cohort study. We constructed a multivariable prediction model with the predictors from the Hunault model and new potential predictors. The primary outcome, natural conception leading to an ongoing pregnancy, was observed in 1053 women of the 5184 included couples (20%). All predictors of the Hunault model were selected into the revised model plus an additional seven (woman's body mass index, cycle length, basal FSH levels, tubal status,history of previous pregnancies in the current relationship (ongoing pregnancies after natural conception, fertility treatment or miscarriages), semen volume, and semen morphology. Predictions from the revised model seem to concur better with observed pregnancy rates compared with the Hunault model; c-statistic of 0.71 (95% CI 0.69 to 0.73) compared with 0.59 (95% CI 0.57 to 0.61).

PMID:28462153

Leenstra BS, Schaap CCM, **Bessems M, Renders NHM, Bosscha K**. Primary Actinomycosis in the breast caused by Actinomyces neuii. A report of 2 cases.
IDCases. 2017 Apr 1;8:70-72. doi: 10.1016/j.idcr.2017.03.014. eCollection 2017.

ABSTRACT:Actinomycosis is a slowly progressive infection caused by anaerobic bacteria, primarily from the genus Actinomyces. Primary actinomycosisof the breast is rare and presents as a mass like density which can mimic malignancy. Mammography, ultrasonography and histopathologic examination is required for diagnosis. Treatment should consist of high doses of antibacterials for a prolonged period of time and possibly surgical drainage. Primary actinomycosis infections are commonly caused by A. israelii. Actinomyces neuii is a less common cause of classical actinomycosis. We present two cases of primary actinomycosis of the breast in two female patients caused by A. neuii.

PMID: 28462739

Kip MMA, Noltes AM, Koffijberg H, IJzerman MJ, **Kusters R**. Improving early exclusion of acute coronary syndrome in primary care: the added value of point-of-care troponin as stated by general practitioners.
Prim Health Care Res Dev. 2017 Jul;18(4):386-397. doi: 10.1017/S1463423617000135. Epub 2017 May 2.

Aim To investigate general practitioners' (GPs') desire and perceived added value of point-of-care (POC) troponin, its effect on referral decisions, and test requirements.
BACKGROUND: Excluding acute coronary syndrome (ACS) in primary care remains a diagnostic challenges for GPs. Consequently, referral rates of chest pain patients are high, while the incidence of a cardiovascular problem is only 8-15%. Previous studies have shown that GPs are interested in a POC troponin test. This test could enhance rapid exclusion of ACS, thereby preventing unnecessary patient distress, without compromising safety and while reducing costs. However, using this test is not recommended in current guidelines due to uncertainty in the test's potential added value, and the lower sensitivity early after symptom onset as compared with troponin tests in a regular laboratory.
METHODS: An online survey containing 34 questions was distributed among 837 Dutch GPs in June 2015. Findings A total of 126 GPs (15.1%) completed at least 75% of the questions. 67.1% of GPs believe that POC troponin tests have moderate to very high added value. Although the availability of a POC test is expected to increase the frequency at which troponin tests are used, it likely decreases (immediate) referral rates. Of the responding GPs, 78.3% only accept 10 min as the maximum test duration, 78.1% think reimbursement of the POC device is required for implementation, and 68.9% consider it necessary that it can be performed with a finger prick blood sample. In conclusion, according to GPs, the POC troponin test can be of added value to exclude ACS early on. Actual test implementation will depend on test characteristics, including test duration, type of blood sample required, and reimbursement of the analyzer.

PMID: 28462869

Menting J, Tack CJ, van Bon AC, **Jansen HJ**, van den Bergh JP, Mol MJTM, Goedendorp MM, Donders R, Knoop H. Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial.

Lancet Diabetes Endocrinol. 2017 Jun;5(6):448-456. doi: 10.1016/S2213-8587(17)30098-0. Epub 2017 Apr 24.

Trefwoorden: Moeheid en type 1 diabetes mellitus.

BACKGROUND: Fatigue in type 1 diabetes is prevalent and persistent, but so far, no evidence-based treatments are available. We aimed to investigate the efficacy of cognitive behavioural therapy (CBT) in reducing fatigue severity in patients with type 1 diabetes.

METHODS: We did a multicentre randomised controlled trial at one university medical centre and four large teaching hospitals in the Netherlands. Eligible patients were aged 18-70 years and had type 1 diabetes for at least 1 year and chronic fatigue for at least 6 months. We randomly assigned patients (1:1) to CBT or waiting list using computer-generated blocked randomisation, stratified by type of enrolment. The CBT intervention (Dia-Fit) was given for 5 months in blended form, consisting of face-to-face and web-based sessions. The primary outcome was fatigue severity assessed 5 months after randomisation, directly after the intervention or waiting list period, with the Checklist Individual Strength fatigue severity subscale. Secondary outcomes were functional impairment (assessed with the total score of the Sickness Impact Profile-8), glycaemic control (HbA1c), and glucose variability. Analyses were done by intention to treat. This trial is registered with the Nederlands Trial Register, number NTR4312.

FINDINGS: Between Feb 6, 2014, and March 24, 2016, we randomly assigned 120 eligible patients to either CBT (n=60) or waiting list (n=60), all of whom were included in the intention-to-treat analyses. Compared with patients in the waiting list group, those in the CBT group had significantly lower fatigue severity scores (mean difference 13·8, 95% CI 10·0-17·5; p<0·0001) and significantly lower scores for functional impairment (mean difference 513, 95% CI 340-686; p<0·0001) after 5 months. HbA1c and glucose variability did not change after treatment and there was no difference between groups. Five patients in the CBT group and seven in the waiting list group reported adverse events; none were deemed to be related to the study intervention.

INTERPRETATION: Although our findings need to be confirmed in larger and longer-term studies, they suggest that CBT can effectively reduce fatigue severity and functional impairment in type 1 diabetes.

FUNDING: Dutch Diabetes Research Foundation (Diabetes Fonds).

PMID:28466446

Boxma RPJ, Kolff-Kamphuis MGM, Gevers RMM, Boulaksil M. Subacute right ventricular pacemaker lead perforation: evaluation by echocardiography and cardiac CT.

J Echocardiogr. 2017 May 2. doi: 10.1007/s12574-017-0337-5.

No abstract available.

PMID: 28476109

van Bommel RMG, Weber R, Voogd AC, Nederend J, Louwman MWJ, Venderink D, Strobbe LJA, **Rutten MJC**, Plaisier ML, Lohle PN, Hooijen MJH, Tjan-Heijnen VCG, Duijm LEM. Interval breast cancer characteristics before, during and after the transition from screen-film to full-field digital screening mammography.

BMC Cancer. 2017 May 5;17(1):315. doi: 10.1186/s12885-017-3294-5.

BACKGROUND: To determine the proportion of "true" interval cancers and tumor characteristics of interval breast cancers prior to, during and after the transition from screen-film mammography screening (SFM) to full-field digital mammography screening (FFDM).

METHODS: We included all women with interval cancers detected between January 2006 and January 2014. Breast imaging reports, biopsy results and breast surgery reports of all women recalled at screening mammography and of all women with interval breast cancers were collected. Two experienced screening radiologists reviewed the diagnostic mammograms, on which the interval cancers were diagnosed, as well as the prior screening mammograms and determined whether or not the interval cancer had been missed on the most recent screening mammogram. If not missed, the cancer was considered an occult ("true") interval cancer.

RESULTS: A total of 442 interval cancers had been diagnosed, of which 144 at SFM with a prior SFM (SFM-SFM), 159 at FFDM with a prior SFM (FFDM-SFM) and 139 at FFDM with a prior FFDM (FFDM-FFDM). The transition from SFM to FFDM screening resulted in the diagnosis of more occult ("true") interval cancers at FFDM-SFM than at SFM-SFM (65.4% (104/159) versus 49.3% (71/144), P < 0.01), but this increase was no longer statistically significant in women who had been screened digitally for the second time (57.6% (80/139) at FFDM-FFDM versus 49.3% (71/144) at SFM-SFM). Tumor characteristics were comparable for the three interval cancer cohorts, except of a lower porportion (75.7

and 78.0% versus 67.2% af FFDM-FFDM, P < 0.05) of invasive ductal cancers at FFDM with prior FFDM.
CONCLUSIONS: An increase in the proportion of occult interval cancers is observed during the transition from SFM to FFDM screening mammography. However, this increase seems temporary and is no longer detectable after the second round of digital screening. Tumor characteristics and type of surgery are comparable for interval cancers detected prior to, during and after the transition from SFM to FFDM screening mammography, except of a lower proportion of invasive ductal cancers after the transition.

PMID: 28481766
van Strien AM, Schrijver EJM, **Keijsers CKJPW, Péquériaux NC**, Nanayakkara PWB, **Derijks HJJ, van Marum RJ**. Haloperidol Does Not Activate Thrombogenic Factors in Older, Nonpsychotic Hospitalized Patients. J Clin Psychopharmacol. 2017 Aug;37(4):487-488. doi: 10.1097/JCP.0000000000000716.
No abstract available.

PMID: 28491879
Valckx WJ, Lutgens SP, Haerkens-Arends HE, Barneveld PC, Beutler JJ, Hoogeveen EK. Listeria endocarditis: a diagnostic challenge.
J Investig Med High Impact Case Rep. 2017 Apr 10;5(2) 2324709617698995.

A 74-year-old hemodialysis patient with a history of an atrial septum defect closure, coronary bypass surgery, and a St. Jude aortic prosthetic valve was diagnosed with pneumonia and volume overload. Blood cultures were positive for Listeria monocytogenes, and amoxicillin was given for 2 weeks. Immediately after discontinuation of amoxicillin, fever relapsed. Transthoracic and transesophageal echocardiography showed no sign of endocarditis. Given the fever relapse and 3 positive minor Duke criteria, an 18F-FDG PET-CT scan (18F-fluorodeoxyglucose-positron emission tomography-computed tomography) scan was performed. This scan showed activity at the aortic root, proximal ascending aorta, and inferior wall of the heart, making Listeria monocytogenes endocarditis a likely explanation. Amoxicillin was given for 6 weeks with good clinical result. Diagnosing a life-threatening Listeria monocytogenes endocarditis can be challenging and an 18F-FDG PET-CT scan can be helpful.

PMID:28497565
Meuwese CL, Boulaksil M, van Dijk J, Polad J, Meijburg HW. Transient left ventricular outflow tract obstruction with systolic anterior motion of the mitral valve: A stunning cause.
Echocardiography. 2017 Jul;34(7):1089-1091. doi: 10.1111/echo.13553. Epub 2017 May 12.
Trefwoorden: left ventricular outflow tract obstruction; myocardial stunning; percutaneous intervention; systolic anterior motion of the mitral valve

Left ventricular outflow tract obstruction (LVOTO) and systolic anterior motion (SAM) of the mitral valve may have various etiologies, of which hypertrophic cardiomyopathy is the most common. More rarely, an acute coronary syndrome, myocardial stunning, and takotsubo cardiomyopathy may give rise to LVOTO and SAM. Here, we present a 70-year-old female patient with a non-ST-elevation acute coronary syndrome treated with percutaneous coronary intervention. Echocardiography the day after, because of dyspnea and hypotension, revealed apical akinesia, LVOTO, and SAM, which proved completely reversible after treatment with a β-blocker and a 2-month follow-up period. It was concluded that postischemic apical stunning had caused LVOTO and SAM.© 2017, Wiley Periodicals, Inc.

PMID 28515215
Bosch T, **Lutgens SPM, Hermans MHA, Wever PC, Schneeberger PM, Renders NHM, Leenders ACAP**, Kluytmans JAJW, Schoffelen A, Notermans D, Witteveen S, Bathoorn E, Schouls LM. An outbreak of NDM-1 producing Klebsiella pneumoniae in a Dutch hospital with interspecies transfer of the resistance plasmid and unexpected occurrence in unrelated healthcare centers. J Clin Microbiol. 2017 Aug;55(8):2380-2390. doi: 10.1128/JCM.00535-17. Epub 2017 May 17

In the Netherlands, the number of cases of infection with New Delhi metallo-beta-lactamase (NDM)-positive Enterobacteriaceae is low. Here, we report an outbreak of NDM-1-producing Klebsiella pneumoniae infection in a Dutch hospital with interspecies transfer of the resistance plasmid and unexpected occurrence in other unrelated health care centers (HCCs). Next-generation sequencing was performed on 250 carbapenemase-producing Enterobacteriaceae isolates, including 42 NDM-positive isolates obtained from 29 persons at the outbreak site. Most outbreak isolates were K. pneumoniae (n = 26) and Escherichia coli (n = 11), but 5 isolates comprising three other Enterobacteriaceae

species were also cultured. The 26 K. pneumoniae isolates had sequence type 873 (ST873), as did 7 unrelated K. pneumoniae isolates originating from five geographically dispersed HCCs. The 33 ST873 isolates that clustered closely together using whole-genome multilocus sequence typing (wgMLST) carried the same plasmids and had limited differences in the resistome. The 11 E. coli outbreak isolates showed great variety in STs, did not cluster using wgMLST, and showed considerable diversity in resistome and plasmid profiles. The blaNDM-1 gene-carrying plasmid present in the ST873 K. pneumoniae isolates was found in all the other Enterobacteriaceae species cultured at the outbreak location and in a single E. coli isolate from another HCC. We describe a hospital outbreak with an NDM-1-producing K. pneumoniae strain from an unknown source that was also found in patients from five other Dutch HCCs in the same time frame without an epidemiological link. Interspecies transfer of the resistance plasmid was observed in other Enterobacteriaceae species isolated at the outbreak location and in another HCC.

PMID:28520519

Dreyer K, van Rijswijk J, Mijatovic V, Goddijn M, Verhoeve HR, van Rooij IAJ, Hoek A, Bourdrez P, Nap AW, Rijnsaardt-Lukassen HGM, Timmerman CCM, Kaplan M, Hooker AB, Gijsen AP, van Golde R, van Heteren CF, Sluijmer AV, **de Bruin JP**, Smeenk JMJ, de Boer JAM, Scheenjes E, Duijn AEJ, Mozes A, Pelinck MJ, Traas MAF, van Hooff MHA, van Unnik GA, de Koning CH, van Geloven N, Twisk JWR, Hompes PGA, Mol BWJ. Oil-Based or Water-Based Contrast for Hysterosalpingography in Infertile Women.
N Engl J Med. 2017 May 25;376(21):2043-2052. doi: 10.1056/NEJMoa1612337. Epub 2017 May 18.

BACKGROUND: Pregnancy rates among infertile women have been reported to increase after hysterosalpingography, but it is unclear whether the type of contrast medium used (oil-based or water-soluble contrast) influences this potential therapeutic effect.
METHODS: We performed a multicenter, randomized trial in 27 hospitals in the Netherlands in which infertile women who were undergoing hysterosalpingography were randomly assigned to undergo this procedure with the use of oil-based or water-based contrast. Subsequently, couples received expectant management or the women underwent intrauterine insemination. The primary outcome was ongoing pregnancy within 6 months after randomization. Outcomes were analyzed according to the intention-to-treat principle.
RESULTS: A total of 1119 women were randomly assigned to hysterosalpingography with oil contrast (557 women) or water contrast (562 women). A total of 220 of 554 women in the oil group (39.7%) and 161 of 554 women in the water group (29.1%) had an ongoing pregnancy (rate ratio, 1.37; 95% confidence interval [CI], 1.16 to 1.61; P<0.001), and 214 of 552 women in the oil group (38.8%) and 155 of 552 women in the water group (28.1%) had live births (rate ratio, 1.38; 95% CI, 1.17 to 1.64; P<0.001). Rates of adverse events were low and similar in the two groups.
CONCLUSIONS: Rates of ongoing pregnancy and live births were higher among women who underwent hysterosalpingography with oil contrast than among women who underwent this procedure with water contrast. (Netherlands Trial Register number, NTR3270 .).

PMID: 28521567

Roerdink RL, Dietvorst M. Prognostic factors associated with mortality in patients with arthritis: a descriptive cohort study - comments on the article by Andreasen et al. Scand J Rheumatol. 2017 Jul;46(4):331-332. doi: 10.1080/03009742.2017.1309454. Epub 2017 May 18.
No abstract available.

PMID: 28522775

Dautzenberg KHW, Polderman FN, van Suylen RJ, Moviat MAM. Purpura fulminans mimicking toxic epidermal necrolysis – additional value of 16S rRNA sequencing and skin biopsy.
Neth J Med. 2017 May;75(4):165-168.

Both purpura fulminans and toxic epidermal necrolysis (TEN) are rare and life-threatening disorders with a high mortality. We present a case of suspected rapidly progressive, severe pneumococcal sepsis-induced purpura fulminans complicated by multiple organ failure, severe epidermolysis and cutaneous necrosis. We show the diagnostic challenge to differentiate between purpura fulminans and TEN, as the extensive epidermolysis in purpura fulminans may mimic TEN and we highlight the additional value of repeated skin biopsies and 16S rRNA gene sequencing.

PMID: 28528566

Heine M, Verschuren O, Hoogervorst EL, **van Munster E**, Hacking HG, Visser-Meily A, Twisk JW, Beckerman H, de Groot V, Kwakkel G; TREFAMS-ACE study group. Does aerobic training alleviate fatigue and improve societal participation in patients with multiple sclerosis? A randomized controlled trial.
Mult Scler. 2017 Oct;23(11):1517-1526. doi: 10.1177/1352458517696596. Epub 2017 May 22.

BACKGROUND: Evidence supporting the effectiveness of aerobic training, specific for fatigue, in severely fatigued patients with multiple sclerosis (MS) is lacking.
OBJECTIVE: To estimate the effectiveness of aerobic training on MS-related fatigue and societal participation in ambulant patients with severe MS-related fatigue.
METHODS: Patients (N = 90) with severe MS-related fatigue were allocated to 16-week aerobic training or control intervention. Primary outcomes were perceived fatigue (Checklist Individual Strength (CIS20r) fatigue subscale) and societal participation. An improvement of ≥8 points on the CIS20r fatigue subscale was considered clinically relevant. Outcomes were assessed by a blinded observer at baseline, 2, 4, 6 and 12 months.
RESULTS: Of the 89 patients that started treatment (median Expanded Disability Status Scale (interquartile range), 3.0 (2.0-3.6); mean CIS20r fatigue subscale (standard deviation (SD)), 42.6 (8.0)), 43 received aerobic training and 46 received the control intervention. A significant post-intervention between-group mean difference (MD) on the CIS20r fatigue subscale of 4.708 (95% confidence interval (CI) = 1.003-8.412; p = 0.014) points was found in favour of aerobic training that, however, was not sustained during follow-up. No effect was found on societal participation.
CONCLUSION: Aerobic training in MS patients with severe fatigue does not lead to a clinically meaningful reduction in fatigue or societal participation when compared to a low-intensity control intervention.

PMID: 28529886

Mooren VHJF, Bleeker MWP, van Ingen J, Hermans MHA, **Wever PC**. Disseminated Mycobacterium abscessus infection in a peritoneal dialysis patient.
IDCases. 2017 May 4;9:6-7.
Trefwoorden: Mycobacterium abscessus, dialyse patiënt.

A disseminated peritoneal dialysis-related Mycobacterium abscessus infection is very rare. M. abscessus belongs to the rapidly growing mycobacteria and can be misidentified as a diphtheroid bacterium, which in our case delayed diagnosis and optimal treatment. Due to intrinsic resistance to most antimicrobials, therapeutic options in M. abscessus infections are limited. Infection often leads to catheter loss. A fatal outcome, like in our case, is not exceptional.

PMID: 28535763

van der Meij E, Bouwsma EVA, **van den Heuvel B**, Bonjer HJ, Anema JR, Huirne JAF. Using e-health in perioperative care: a survey study investigating shortcomings in current perioperative care and possible future solutions.
BMC Surg. 2017 May 23;17(1):61. doi: 10.1186/s12893-017-0254-6.

BACKGROUND: An e-health care program has previously shown to have a positive effect on return to work, quality of life and pain in patients who underwent gynaecological surgery. Plausibly, providing the care program to a population undergoing other types of surgery will be beneficial as well. The objectives of this study are to evaluate patients' opinions, needs and preferences regarding the information and guidance supplied to patients during the perioperative period, to investigate whether e-health may be of assistance and to explore if gender specific needs exist.
METHODS: A questionnaire was sent to all patients between 18 and 75 years (n = 362), who underwent various forms of abdominal surgery between August 2013 to September 2014 in a university hospital in the Netherlands. The questionnaire contained questions about the current situation in perioperative care and questions about patients' preferences in an e-health care program. Gender differences were evaluated.
RESULTS: Two hundred seven participants (57.2%) completed the survey. The majority of the participants were relatively satisfied with the perioperative care they received (68.6%). Most reported shortcomings in perioperative care concerning the supply of information regarding the resumption of activities and guidance during the recovery course. An e-health care program was expected to be of added value in perioperative care by 78% of the participants; a website was reported as most useful. In particular practical functions on a website focusing on the preparation to surgery and monitoring after surgery were appraised to be highly valuable. Overall, women had slightly more needs for extra information and support during the perioperative course than men.

CONCLUSIONS: In abdominal surgery, there is a need for an e-health care program, which should focus mainly on the supply of information about the resumption of activities as well as guidance in the postoperative course.

PMID: 28536921

Gieselbach RJ, Muller-Hansma AH, Wijburg MT, de Bruin-Weller MS, van Oosten BW, **Nieuwkamp DJ**, Coenjaerts FE, Wattjes MP, Murk JL. Progressive multifocal leukoencephalopathy in patients treated with fumaric acid esters: a review of 19 cases. J Neurol. 2017 Jun;264(6):1155-1164. doi: 10.1007/s00415-017-8509-9. Epub 2017 May 23. Review. Erratum in: J Neurol. 2017 Jul 15.

Progressive multifocal leukoencephalopathy (PML) is a rare and potentially fatal condition caused by a brain infection with JC polyomavirus (JCV). PML develops almost exclusively in immunocompromised patients and has recently been associated with use of fumaric acid esters (FAEs), or fumarates. We reviewed the literature and the Dutch and European pharmacovigilance databases in order to identify all available FAE-associated PML cases and distinguish possible common features among these patients. A total of 19 PML cases associated with FAE use were identified. Five cases were associated with FAE use for multiple sclerosis and 14 for psoriasis. Ten patients were male and nine were female. The median age at PML diagnosis was 59 years. The median duration of FAE therapy to PML symptom onset or appearance of first PML lesion on brain imaging was 31 months (range 6-110). In all cases a certain degree of lymphocytopenia was reported. The median duration of lymphocytopenia to PML symptom onset was 23 months (range 6-72). The median lymphocyte count at PML diagnosis was 414 cells/μL. CD4 and CD8 counts were reported in ten cases, with median cell count of 137 and 39 cells/μL, respectively. Three patients died (16% mortality). The association between occurrence of PML in patients with low CD4 and CD8 counts is reminiscent of PML cases in the HIV population and suggests that loss of T cells is the most important risk factor.

PMID: 28546336

Kouijzer IJE, Kampschreur LM, **Wever PC, Hoekstra C**, van Kasteren MEE, de Jager-Leclerq MGL, Nabuurs-Franssen MH, Wegdam-Blans MCA, Ammerlaan HSM, Buijs J, de Geus-Oei L-F, Oyen WJG, Bleeker-Rovers CP.
The value of 18F-FDG PET/CT in diagnosis and during follow-up in 273 patients with chronic Q fever.
J Nucl Med 2018;59:127-133.

In 1%-5% of all acute Q fever infections, chronic Q fever develops, mostly manifesting as endocarditis, infected aneurysms, or infected vascular prostheses. In this study, we investigated the diagnostic value of 18F-FDG PET/CT in chronic Q fever at diagnosis and during follow-up. Methods: All adult Dutch patients suspected of chronic Q fever who were diagnosed since 2007 were retrospectively included until March 2015, when at least one 18F-FDG PET/CT scan was obtained. Clinical data and results from 18F-FDG PET/CT at diagnosis and during follow-up were collected. 18F-FDG PET/CT scans were prospectively reevaluated by 3 nuclear medicine physicians using a structured scoring system. Results: In total, 273 patients with possible, probable, or proven chronic Q fever were included. Of all 18F-FDG PET/CT scans performed at diagnosis, 13.5% led to a change in diagnosis. Q fever-related mortality rate in patients with and without vascular infection based on 18F-FDG PET/CT was 23.8% and 2.1%, respectively (P = 0.001). When 18F-FDG PET/CT was added as a major criterion to the modified Duke criteria, 17 patients (1.9-fold increase) had definite endocarditis. At diagnosis, 19.6% of 18F-FDG PET/CT scans led to treatment modification. During follow-up, 57.3% of 18F-FDG PET/CT scans resulted in treatment modification. Conclusion:18F-FDG PET/CT is a valuable technique in diagnosis of chronic Q fever and during follow-up, often leading to a change in diagnosis or treatment modification and providing important prognostic information on patient survival.

PMID: 28550023

Danhof NA, van Wely M, Koks CAM, Gianotten J, **de Bruin JP**, Cohlen BJ, van der Ham DP, Klijn NF, van Hooff MHA, Broekmans FJM, Fleischer K, Janssen CAH, Rijn van Weert JM, van Disseldorp J, Twisk M, Traas M, Verberg MFG, Pelinck MJ, Visser J, Perquin DAM, Boks DES, Verhoeve HR, van Heteren CF, Mol BWJ, Repping S, van der Veen F, Mochtar MH. The SUPER study: protocol for a randomised controlled trial comparing follicle-stimulating hormone and clomiphene citrate for ovarian stimulation in intrauterine insemination.
BMJ Open. 2017 May 25;7(5):e015680. doi: 10.1136/bmjopen-2016-015680.

OBJECTIVE: To study the effectiveness of four cycles of intrauterine insemination (IUI) with ovarian stimulation (OS) by follicle-stimulating hormone (FSH) or by clomiphene citrate (CC), and adherence to strict cancellation criteria.

SETTING: Randomised controlled trial among 22 secondary and tertiary fertility clinics in the Netherlands.
PARTICIPANTS: 732 women from couples diagnosed with unexplained or mild male subfertility and an unfavourable prognosis according to the model of Hunault of natural conception.
INTERVENTIONS: Four cycles of IUI-OS within a time horizon of 6 months comparing FSH 75 IU with CC 100 mg. The primary outcome is ongoing pregnancy conceived within 6 months after randomisation, defined as a positive heartbeat at 12 weeks of gestation. Secondary outcomes are cancellation rates, number of cycles with a monofollicular or with multifollicular growth, number of follicles >14 mm at the time of ovulation triggering, time to ongoing pregnancy, clinical pregnancy, miscarriage, live birth and multiple pregnancy. We will also assess if biomarkers such as female age, body mass index, smoking status, antral follicle count and endometrial aspect and thickness can be used as treatment selection markers.
ETHICS AND DISSEMINATION: The study has been approved by the Medical Ethical Committee of the Academic Medical Centre and from the Dutch Central Committee on Research involving Human Subjects (CCMO NL 43131-018-13). Results will be disseminated through peer-reviewed publications and presentations at international scientific meetings.
TRIAL REGISTRATION NUMBER: NTR4057.

PMID: 28558849

van Lieshout A, Rutten MJCM, Jager GJ. [Characterisation of breast lesions with VTIQ elastography: a new elastography method to evaluate the stiffness of tissues].
Ned Tijdschr Geneeskd. 2017;161:D1122. Dutch.

B-mode ultrasound is used as an adjunct to mammography to differentiate between benign and malignant breast lesions. An additional ultrasound technique is elastography which can evaluate the stiffness of tissues. It is believed that malignant lesions are generally stiffer than benign lesions. Virtual touch tissue Quantification (VTIQ) is a new elastography method for measuring the stiffness of tissue. Because this method does not depend on the degree of compression, measurements are reliable and reproducible. VTIQ - in combination with ultrasonography - has the potential to characterise abnormalities in more detail. Adding elastography to regular B-mode ultrasound improves the diagnostic specificity without loss of sensitivity. This suggests that VTIQ might change patient management and avoid unnecessary biopsies. However, further research involving a greater variety of abnormalities and larger study populations is indicated.

PMID: 28572122

Derks JL, **van Suylen RJ**, Thunnissen E, den Bakker MA, Groen HJ, Smit EF, Damhuis RA, van den Broek EC, Speel EM, Dingemans AC; PALGA group. Chemotherapy for pulmonary large cell neuroendocrine carcinomas: does the regimen matter?
Eur Respir J. 2017 Jun 1;49(6). pii: 1601838. doi: 10.1183/13993003.01838-2016. Print 2017 Jun.

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is rare. Chemotherapy for metastatic LCNEC ranges from small cell lung carcinoma (SCLC) regimens to nonsmall cell lung carcinoma (NSCLC) chemotherapy regimens. We analysed outcomes of chemotherapy treatments for LCNEC.The Netherlands Cancer Registry and Netherlands Pathology Registry (PALGA) were searched for patients with stage IV chemotherapy-treated LCNEC (2003-2012). For 207 patients, histology slides were available for pathology panel review. First-line platinum-based combined chemotherapy was clustered as "NSCLC-t", comprising gemcitabine, docetaxel, paclitaxel or vinorelbine; "NSCLC-pt", with pemetrexed treatment only; and "SCLC-t", consisting of etoposide chemotherapy.A panel review diagnosis of LCNEC was established in 128 out of 207 patients. NSCLC-t chemotherapy was administered in 46% (n=60), NSCLC-pt in 16% (n=20) and SCLC-t in 38% (n=48) of the patients.
The median (95% CI) overall survival for NSCLC-t chemotherapy was 8.5 (7.0-9.9) months, significantly longer than patients treated with NSCLC-pt, with a median survival of 5.9 (5.0-6.9) months (hazard ratio 2.51, 95% CI 1.39-4.52; p=0.002) and patients treated with SCLC-t chemotherapy, with a median survival of 6.7 (5.0-8.5) months (hazard ratio 1.66, 95% CI 1.08-2.56; p=0.020).In patients with LCNEC, NSCLC-t chemotherapy results in longer overall survival compared to NSCLC-pt and SCLC-t chemotherapy.

PMID:28576463

Sloothaak DAM, van der Linden RLA, van de Velde CJH, Bemelman WA, Lips DJ, van der Linden JC, Doornewaard H, Tanis PJ, Bosscha K, van der Zaag ES, Buskens CJ. Prognostic implications of occult nodal tumour cells in stage I and II colon cancer: The correlation between micrometastasis and disease recurrence.
Eur J Surg Oncol. 2017 Aug;43(8):1456-1462. doi: 10.1016/j.ejso.2017.04.012. Epub 2017 May 5.
Trefwoorden: Coloncancer; Lymph nodes; Micrometastasis; Occult tumour cells

INTRODUCTION: Occult nodal tumour cells should be categorised as micrometastasis (MMs) and isolated tumour cells (ITCs). A recent meta-analysis demonstrated that MMs, but not ITCs, are prognostic for disease recurrence in patients with stage I/II colon cancer.
AIMS & METHODS: The objective of this retrospective multicenter study was to correlate MMs and ITCs to characteristics of the primary tumour, and to determine their prognostic value in patients with stage I/II colon cancer.
RESULTS: One hundred ninety two patients were included in the study with a median follow up of 46 month (IQR 33-81 months). MMs were found in eight patients (4.2%), ITCs in 37 (19.3%) and occult tumour cells were absent in 147 patients (76.6%). Between these groups, tumour differentiation and venous or lymphatic invasion was equally distributed. Advanced stage (pT3/pT4) was found in 66.0% of patients without occult tumour cells (97/147), 72.9% of patients with ITCs (27/37), and 100% in patients with MMs (8/8), although this was a non-significant trend. Patients with MMs showed a significantly reduced 3 year-disease free survival compared to patients with ITCs or patients without occult tumour cells (75.0% versus 88.0% and 94.8%, respectively, p = 0.005). When adjusted for T-stage, MMs independently predicted recurrence of cancer (OR 7.6 95% CI 1.5-37.4, p = 0.012).
CONCLUSION: In this study, the incidence of MMs and ITCs in patients with stage I/II colon cancer was 4.2% and 19.3%, respectively. MMs were associated with an reduced 3 year disease free survival rate, but ITCs were not.

PMID: 28576620

van Zelst JCM, Balkenhol M, Tan T, **Rutten M**, Imhof-Tas M, Bult P, Karssemeijer N, Mann RM. Sonographic Phenotypes of Molecular Subtypes of Invasive Ductal Cancer in Automated 3-D Breast Ultrasound.
Ultrasound Med Biol. 2017 Sep;43(9):1820-1828. doi: 10.1016/j.ultrasmedbio.2017.03.019. Epub 2017 May 31.

Our aim was to investigate whether Breast Imaging Reporting and Data System-Ultrasound (BI-RADS-US) lexicon descriptors can be used as imaging biomarkers to differentiate molecular subtypes (MS) of invasive ductal carcinoma (IDC) in automated breast ultrasound (ABUS). We included 125 IDCs diagnosed between 2010 and 2014 and imaged with ABUS at two institutes retrospectively. IDCs were classified as luminal A or B, HER2 enriched or triple negative based on reports of histopathologic analysis of surgical specimens. Two breast radiologists characterized all IDCs using the BI-RADS-US lexicon and specific ABUS features. Univariate and multivariate analyses were performed. A multinomial logistic regression model was built to predict the MSs from the imaging characteristics. BI-RADS-US descriptor margins and the retraction phenomenon are significantly associated with MSs (both $p < 0.001$) in both univariate and multivariate analysis. Posterior acoustic features and spiculation pattern severity were only significantly associated in univariate analysis ($p < 0.001$). Luminal A IDCs tend to have more prominent retraction patterns than luminal B IDCs. HER2-enriched and triple-negative IDCs present significantly less retraction than the luminal subtypes. The mean accuracy of MS prediction was 0.406. Overall, several BI-RADS-US descriptors and the coronal retraction phenomenon and spiculation pattern are associated with MSs, but prediction of MSs on ABUS is limited.

PMID: 28579497

Ketelaars PJW, Bosgraaf RP, Siebers AG, Massuger LFAG, **van der Linden JC**, Wauters CAP, Rahamat-Langendoen JC, **van den Brule AJC**, IntHout J, Melchers WJG, Bekkers RLM. High-risk human papillomavirus detection in self-sampling compared to physician-taken smear in a responder population of the Dutch cervical screening: Results of the VERA study.
Prev Med. 2017 Aug;101:96-101. doi: 10.1016/j.ypmed.2017.05.021. Epub 2017 Jun 1.

In 2017 the cervical cancer screening program in The Netherlands will be revised. Cervical smears will primarily be tested for the presence of high-risk human papillomavirus (hrHPV) instead of cytology, and vaginal self-sampling will be offered to non-responders. This includes a potential risk that part of the women who would otherwise opt for a cervical smear will wait for self-sampling. However, self-sampling for hrHPV in a responder population has never been studied yet. The aim of this study was to investigate the applicability and accuracy of self-sampling in detecting hrHPV in a screening responder population. A total of 2049 women, aged 30-60years, participating in the screening program in The Netherlands were included from April 2013 to May 2015. After they had their cervical smear taken, women self-collected a cervicovaginal sample with a brush-based device, the Evalyn Brush. Both the cervical smear and self-sample specimen were tested with the COBAS 4800 HPV platform. The hrHPV prevalence was 8.0% (95% CI 6.9-9.2) among the physician-taken samples, and 10.0% (95% CI 8.7-11.3) among the self-samples. There was 96.8% (95% CI 96.0-97.5) concordance of hrHPV prevalence between self-samples and physician-taken samples. Women in our study evaluated self-sampling as convenient (97.1%), user-friendly (98.5%), and 62.8% preferred self-sampling over a physician-taken sampling for the next screening round. In conclusion, self-sampling showed high concordance with physician-taken

sampling for hrHPV detection in a responder screening population and highly acceptable to women. Implementation of HPV-self-sampling for the responder population as a primary screening tool may be considered.

PMID: 28585318

de Boer M, van Leeuwen K, Geissler J, van Alphen F, **de Vries E**, van der Kuip M, Terheggen SWJ, Janssen H, van den Berg TK, Meijer AB, Roos D, Kuijpers TW. Hermansky-Pudlak syndrome type 2: Aberrant pre-mRNA splicing and mislocalization of granule proteins in neutrophils.
Hum Mutat. 2017 Oct;38(10):1402-1411. doi: 10.1002/humu.23271. Epub 2017 Jun 15.

Hermansky-Pudlak syndrome type 2 (HPS2) is a syndrome caused by mutations in the beta-3A subunit of the adaptor protein (AP)-3 complex (AP3B1 gene). We describe five unreported cases with four novel mutations, one of which caused aberrant pre-mRNA splicing. A point mutation c.2702C>G in exon 23 of the AP3B1 gene caused deletion of 112 bp in the mRNA in two siblings. This mutation activates a cryptic donor splice site that overrules the wild-type donor splice site of this exon. Three other novel mutations in AP3B1 were identified, that is, a nonsense mutation c.716G>A (p.Trp239Ter), a 1-bp and a 4-bp deletion c.177delA and c.1839_1842delTAGA, respectively, both causing frameshift and premature termination of translation. Mass spectrometry in four of these HPS2 patients demonstrated the (near) absence of all AP-3 complex subunits. Immunoelectron microscopy on the neutrophils of two of these patients showed abnormal granule formation. We found clear mislocalization of myeloperoxidase in the neutrophils even though the content of this protein but not the activity seemed to be present at normal levels. In sum, HPS2 is the result of the absence of the entire AP-3 complex, which results in severe neutropenia with a defect in granule formation as the major hematological finding.

PMID: 28602525

Janssen S, Heiwegen K, van Rooij IA, Scharbatke H, Roukema J, de Blaauw I, Botden SM. Factors related to long-term surgical morbidity in congenital diaphragmatic hernia survivors.
J Pediatr Surg. 2018 Mar;53(3):508-512. doi: 10.1016/j.jpedsurg.2017.05.032. Epub 2017 Jun 3.

BACKGROUND: Patients born with a congenital diaphragmatic hernia (CDH) have a high mortality and morbidity. After discharge, complications and long-term morbidity are still encountered. This study describes the factors related to the surgical long-term outcomes in CDH survivors.
METHODS: A cohort of CDH patients born between 2000 and 2014, with a minimum of two years follow up, were included in this retrospective study. Demographics, CDH specific characteristics, treatment, and long-term surgical outcome were evaluated using multivariate logistic regression analyses.
RESULTS: 112 patients were included, with a mean follow up of 7.3 years (SD 3.8). The majority had primary repair, but 31% received patch repair. Recurrence was reported in 7% of all patients. However, recurrence risk increased for patients with extracorporeal membrane oxygenation (ECMO) treatment (ORadjusted: 6.3, 95% CI: 1.2-33.9). This risk was highest for patients needing both ECMO and patch repair (OR: 11.2, 95% CI: 2.3-54.1). Small bowel obstructions (SBO) were observed in 20% and was associated with patch repair (ORadjusted: 3.5, 95% CI: 1.2-10.0), but ECMO treatment seemed to reduce this risk (ORadjusted: 0.2, 95% CI: 0.0-1.0). Thoracic deformations (36%) was diagnosed most often after patch repair, especially when ECMO was needed (60%) as well.
CONCLUSIONS: This retrospective study shows that the incidence of surgical long-term morbidity of CDH is relatively high, with different factors accounting for this. Diaphragmatic hernia recurrence was strongest associated with ECMO treatment in combination with patch repair, while SBO's were associated with patch repair, with an unexpected protective effect of ECMO treatment.
TYPE OF STUDY: Retrospective comparative study - Level III evidence.

PMID: 28609204

van Zelst JCM, Mus RDM, Woldringh G, **Rutten MJCM**, Bult P, Vreemann S, de Jong M, Karssemeijer N, Hoogerbrugge N, Mann RM. Surveillance of Women with the BRCA1 or BRCA2 Mutation by Using Biannual Automated Breast US, MR Imaging, and Mammography.
Radiology. 2017 Nov;285(2):376-388. doi: 10.1148/radiol.2017161218. Epub 2017 Jun 13.

Purpose To evaluate a multimodal surveillance regimen including yearly full-field digital (FFD) mammography, dynamic contrast agent-enhanced (DCE) magnetic resonance (MR) imaging, and biannual automated breast (AB) ultrasonography (US) in women with BRCA1 and BRCA2 mutations. Materials and Methods This prospective multicenter trial enrolled 296 carriers of the BRCA mutation (153 BRCA1 and 128 BRCA2 carriers, and 15 women with first-degree untested relatives) between September 2010 and November 2012, with follow-up until November 2015. Participants underwent 2 years of intensified surveillance including biannual AB US, and routine yearly DCE MR imaging and FFD mammography. The surveillance performance for each modality and possible combinations were determined. Results Breast cancer was screening-detected in 16 women (age range, 33-58 years). Three interval cancers were detected by self-examination, all in carriers of the BRCA1 mutation under age 43 years. One cancer was detected in a carrier of the BRCA1 mutation with a palpable abnormality in the contralateral breast. One incidental breast cancer was detected in a prophylactic mastectomy specimen. Respectively, sensitivity of DCE MR imaging, FFD mammography, and AB US was 68.1% (14 of 21; 95% confidence interval [CI]: 42.9%, 85.8%), 37.2% (eight of 21; 95% CI: 19.8%, 58.7%), and 32.1% (seven of 21; 95% CI: 16.1%, 53.8%); specificity was 95.0% (643 of 682; 95% CI: 92.7%, 96.5%), 98.1% (638 of 652; 95% CI: 96.7%, 98.9%), and 95.1% (1030 of 1088; 95% CI: 93.5%, 96.3%); cancer detection rate was 2.0% (14 of 702), 1.2% (eight of 671), and 1.0% (seven of 711) per 100 women-years; and positive predictive value was 25.2% (14 of 54), 33.7% (nine of 23), and 9.5% (seven of 68). DCE MR imaging and FFD mammography combined yielded the highest sensitivity of 76.3% (16 of 21; 95% CI: 53.8%, 89.9%) and specificity of 93.6% (643 of 691; 95% CI: 91.3%, 95.3%). AB US did not depict additional cancers. FFD mammography yielded no additional cancers in women younger than 43 years, the mean age at diagnosis. In carriers of the BRCA2 mutation, sensitivity of FFD mammography with DCE MR imaging surveillance was 90.9% (10 of 11; 95% CI: 72.7%, 100%) and 60.0% (six of 10; 95% CI: 30.0%, 90.0%) in carriers of the BRCA1 mutation because of the high interval cancer rate in carriers of the BRCA1 mutation. Conclusion AB US may not be of added value to yearly FFD mammography and DCE MR imaging surveillance of carriers of the BRCA mutation. Study results suggest that carriers of the BRCA mutation younger than 40 years may not benefit from FFD mammography surveillance in addition to DCE MR imaging. © RSNA, 2017 Online supplemental material is available for this article.

PMID: 28625777

Gligorov J, Ataseven B, Verrill M, De Laurentiis M, Jung KH, Azim HA, Al-Sakaff N, Lauer S, Shing M, Pivot X; **SafeHer Study Group (Smilde TJ)**. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients.
Eur J Cancer. 2017 Sep;82:237-246. doi: 10.1016/j.ejca.2017.05.010. Epub 2017 Jun 16.

AIM: To assess the safety and tolerability of adjuvant subcutaneous trastuzumab (Herceptin® SC, H SC), delivered from an H SC Vial via hand-held syringe (Cohort A) or single-use injection device (Cohort B), with or without chemotherapy, for human epidermal growth factor receptor 2 (HER2)-positive stage I to IIIC early breast cancer (EBC) in the phase III SafeHer study (NCT01566721).
METHODS: Patients received 600 mg fixed-dose H SC every 3 weeks for 18 cycles. The chemotherapy partner was at the investigators' discretion (H SC monotherapy was limited to ≤10% of the population). Data from the first H SC dose until 28 days (plus a 5-day window) after the last dose are presented. Results are descriptive.
RESULTS: In the overall population, 2282/2573 patients (88.7%) experienced adverse events (AEs). Of the above, 128 (5.0%) patients experienced AEs leading to study drug discontinuation; 596 (23.2%) experienced grade ≥ 3 AEs and 326 (12.7%) experienced serious AEs. Grade ≥ 3 cardiac disorders were reported in 24 patients (0.9%), including congestive heart failure in eight (0.3%). As expected, the AE rates varied according to the timing of chemotherapy in both cohorts, with higher rates in concurrent versus sequential chemotherapy subgroups. In the concurrent chemotherapy subgroup, AEs were more common during the actual period of concurrent chemotherapy compared with the period when patients did not receive concurrent chemotherapy.
CONCLUSION: SafeHer confirms the safety and tolerability of the H SC 600 mg fixed dose for 1 year (every 3 weeks for 18 cycles) as adjuvant therapy with concurrent or sequential chemotherapy for HER2-positive EBC. These primary analysis results are consistent with the known safety profile for intravenous H and H SC.

PMID: 28654480

van Mil E, Struik A. Overweight and Obesity in Children: More Than Just the Kilos.
Pediatr Phys Ther 2017;29:S73–S75.

A new model of diagnostics and treatment for overweight in children is used for implementation of a new approach toward childhood obesity. Although based in a hospital setting, it is part of a cure and care network with other professionals. By psycho-education about the body at a 6-year-old level, parents and children become informed and competent partners. This knowledge increases their autonomy and ability to make

choices. Collaboration with the family's support group or network reduces isolation and increases the feeling of being connected and supported. Together with their support network, they can maintain this healthier lifestyle or adjust it where needed. Family workbooks and worksheets support the child and parents and increase their autonomy, self management skills, and motivation to take part in the cure and care network. The approach is a based on the three basic needs that determine motivation, namely autonomy, competence, and connectedness.

PMID: 28670734

Meuwese CL, Boulaksil M, **van Dijk J, Polad J, Meijburg HW**. Reply to "Non-ST-segment elevation myocardial infarction vs aborted myocardial infarction-triggered takotsubo syndrome?"
Echocardiography. 2017 Aug;34(8):1263. doi: 10.1111/echo.13619. Epub 2017 Jul 3.
No abstract available.

PMID: 28674765

Vriens BEPJ, Vriens IJH, Aarts MJB, van Gastel SM, van den Berkmortel FWPJ, **Smilde TJ**, van Warmerdam LJC, van Spronsen DJ, Peer PGM, de Boer M, Tjan-Heijnen VCG; Breast Cancer Trialists' Group of the Netherlands (BOOG). Improved survival for sequentially as opposed to concurrently delivered neoadjuvant chemotherapy in non-metastatic breast cancer.
Breast Cancer Res Treat. 2017 Oct;165(3):593-600.doi: 10.1007/s10549-017-4364-8. Epub 2017 Jul 3.

PURPOSE: The INTENS study was designed to determine whether delivering neoadjuvant chemotherapy at a higher dose in a shorter period of time improves outcome of breast cancer patients.
METHODS: Women with newly diagnosed breast cancer were randomly assigned to neoadjuvant chemotherapy consisting of four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel (AC 60/600-T 100 mg/m2) or six cycles of TAC as triplet chemotherapy (75/50/500 mg/m2) every 3 weeks. The primary outcome was the pathologic complete response (pCR), with disease-free and overall survival as secondary endpoints.
RESULTS: In total, 201 patients were included. The pCR rates were 28% for patients treated with AC-T and 19% for patients treated with TAC, with an odds ratio of 1.60 (95% CI 0.90-3.21). With a median follow-up of 6 years (range 0.04-8.41 years), the five-year disease-free survival was 81% for patients treated with sequentially AC-T and 71% for patients treated with concurrent triplet TAC chemotherapy with a stratified hazard ratio (HR) of 0.50 (95% CI 0.29-0.86). Five-year overall survival was 84% versus 76%, respectively, with a stratified HR of 0.55 (95% CI 0.29-1.03).
CONCLUSIONS: No differences were observed between the two treatment arms with respect to pCR rate, but the sequentially delivered chemotherapy outperformed the triplet combination chemotherapy in terms of survival, despite a lower cumulative dose per agent. GOV nr NCT00314977.

PMID: 28694305

Hartman YAW, **Jansen HJ**, Hopman MTE, Tack CJ, Thijssen DHJ. Insulin-Associated Weight Gain in Type 2 Diabetes Is Associated With Increases in Sedentary Behavior.
Diabetes Care. 2017 Sep;40(9):e120-e121. doi: 10.2337/dc17-0787. Epub 2017 Jul 10.
No abstract available.
Trefwoorden: Insuline en type 2 diabetes mellitus.

PMID: 28697123

Bouwense SA, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Bakker OJ, Banks PA, Boermeester MA, **Cappendijk VC**, Carter R, Charnley R, van Eijck CH, Freeny PC, Hermans JJ, Hough DM, Johnson CD, Laméris JS, Lerch MM, Mayerle J, Mortele KJ, Sarr MG, Stedman B, Vege SS, Werner J, Dijkgraaf MG, Gooszen HG, Horvath KD; Acute Pancreatitis Interobserver Study Group. Describing Peripancreatic Collections According to the Revised Atlanta Classification of Acute Pancreatitis: An International Interobserver Agreement Study. Pancreas. 2017 Aug;46(7):850-857. doi: 10.1097/MPA.0000000000000863.

OBJECTIVES: Severe acute pancreatitis is associated with peripancreatic morphologic changes as seen on imaging. Uniform communication regarding these morphologic findings is crucial for accurate diagnosis and treatment. For the original 1992 Atlanta classification, interobserver agreement is poor. We hypothesized that for the revised Atlanta classification, interobserver agreement will be better.
METHODS: An international, interobserver agreement study was performed among expert and nonexpert radiologists (n = 14), surgeons (n =

15), and gastroenterologists (n = 8). Representative computed tomographies of all stages of acute pancreatitis were selected from 55 patients and were assessed according to the revised Atlanta classification. The interobserver agreement was calculated among all reviewers and subgroups, that is, expert and nonexpert reviewers; interobserver agreement was defined as poor (≤0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), or very good (0.81-1.00).
RESULTS: Interobserver agreement among all reviewers was good (0.75 [standard deviation, 0.21]) for describing the type of acute pancreatitis and good (0.62 [standard deviation, 0.19]) for the type of peripancreatic collection. Expert radiologists showed the best and nonexpert clinicians the lowest interobserver agreement.
CONCLUSIONS: Interobserver agreement was good for the revised Atlanta classification, supporting the importance for widespread adaption of this revised classification for clinical and research communications.

PMID: 28698344

Timmermans MJC, van den Brink GT, van Vught AJAH, Adang E, van Berlo CLH, **Boxtel KV**, Braunius WW, Janssen L, Venema A, van den Wildenberg FJ, Wensing M, Laurant MGH. The involvement of physician assistants in inpatient care in hospitals in the Netherlands: a cost-effectiveness analysis.
BMJ Open. 2017 Jul 10;7(7):e016405. doi: 10.1136/bmjopen-2017-016405.

OBJECTIVE: To investigate the cost-effectiveness of substitution of inpatient care from medical doctors (MDs) to physician assistants (PAs).
DESIGN: Cost-effectiveness analysis embedded within a multicentre, matched-controlled study. The traditional model in which only MDs are employed for inpatient care (MD model) was compared with a mixed model in which, besides MDs, PAs are also employed (PA/MD model).
SETTING: 34 hospital wards across the Netherlands.
PARTICIPANTS: 2292 patients were followed from admission until 1 month after discharge. Patients receiving daycare, terminally ill patients and children were excluded.
PRIMARY AND SECONDARY OUTCOME MEASURES: All direct healthcare costs from day of admission until 1 month after discharge. Health outcome concerned quality-adjusted life years (QALYs), which was measured with the EuroQol five dimensions questionnaire (EQ-5D).
RESULTS: We found no significant difference for QALY gain (+0.02, 95% CI -0.01 to 0.05) when comparing the PA/MD model with the MD model. Total costs per patient did not significantly differ between the groups (+€568, 95% CI -€254 to €1391, p=0.175). Regarding the costs per item, a difference of €309 per patient (95% CI €29 to €588, p=0.030) was found in favour of the MD model regarding length of stay. Personnel costs per patient for the provider who is primarily responsible for medical care on the ward were lower on the wards in the PA/MD model (-€11, 95% CI -€16 to -€6, p<0.01).
CONCLUSIONS: This study suggests that the cost-effectiveness on wards managed by PAs, in collaboration with MDs, is similar to the care on wards with traditional house staffing. The involvement of PAs may reduce personnel costs, but not overall healthcare costs.
TRIAL REGISTRATION NUMBER: NCT01835444.

PMID: 28708268

Jolles S, Sánchez-Ramón S, Quinti I, Soler-Palacín P, Agostini C, Florkin B, Couderc LJ, Brodszki N, Jones A, Longhurst H, Warnatz K, Haerynck F, Matucci A, **de Vries E**. Screening protocols to monitor respiratory status in primary immunodeficiency disease: findings from a European survey and subclinical infection working group.
Clin Exp Immunol. 2017 Nov;190(2):226-234. doi: 10.1111/cei.13012. Epub 2017 Aug 25.

Many patients with primary immunodeficiency (PID) who have antibody deficiency develop progressive lung disease due to underlying subclinical infection and inflammation. To understand how these patients are monitored we conducted a retrospective survey based on patient records of 13 PID centres across Europe, regarding the care of 1061 adult and 178 paediatric patients with PID on immunoglobulin (Ig) G replacement. The most common diagnosis was common variable immunodeficiency in adults (75%) and hypogammaglobulinaemia in children (39%). The frequency of clinic visits varied both within and between centres: every 1-12 months for adult patients and every 3-6 months for paediatric patients. Patients diagnosed with lung diseases were more likely to receive pharmaceutical therapies and received a wider range of therapies than patients without lung disease. Variation existed between centres in the frequency with which some clinical and laboratory monitoring tests are performed, including exercise tests, laboratory testing for IgG subclass levels and specific antibodies, and lung function tests such as spirometry. Some tests were carried out more frequently in adults than in children, probably due to difficulties conducting these tests in younger children. The percentage of patients seen regularly by a chest physician, or who had microbiology tests performed following chest and sinus exacerbations, also varied widely between centres. Our survey revealed a great deal of variation across Europe in how

frequently patients with PID visit the clinic and how frequently some monitoring tests are carried out. These results highlight the urgent need for consensus guidelines on how to monitor lung complications in PID patients.

PMID: 28710053

Dahhan T, Balkenende EME, Beerendonk CCM, Fleischer K, Stoop D, Bos AME, Lambalk CB, Schats R, van Golde RJT, Schipper I, Louwé LA, Cantineau AEP, Smeenk JMJ, **de Bruin JP**, Reddy N, Kopeika Y, van der Veen F, van Wely M, Linn SC, Goddijn M. Stimulation of the ovaries in women with breast cancer undergoing fertility preservation: Alternative versus standard stimulation protocols; the study protocol of the STIM-trial.
Contemp Clin Trials. 2017 Oct;61:96-100. doi: 10.1016/j.cct.2017.07.009. Epub 2017 Jul 11.

BACKGROUND: Chemotherapy for breast cancer may have a negative impact on reproductive function due to gonadotoxicity. Fertility preservation via banking of oocytes or embryos after ovarian stimulation with FSH can increase the likelihood of a future live birth. It has been hypothesized that elevated serum estrogen levels during ovarian stimulation may induce breast tumour growth. This has led to the use of alternative stimulation protocols with addition of tamoxifen or letrozole. The effectiveness of these stimulation protocols in terms of oocyte yield is unknown.
METHODS/DESIGN: Randomized open-label trial comparing ovarian stimulation plus tamoxifen and ovarian stimulation plus letrozole with standard ovarian stimulation in the course of fertility preservation. The study population consists of women with breast cancer who opt for banking of oocytes or embryos, aged 18-43years at randomisation. Primary outcome is the number of oocytes retrieved at follicle aspiration. Secondary outcomes are number of mature oocytes retrieved, number of oocytes or embryos banked and peak E2 levels during ovarian stimulation.
DISCUSSION: Concerning the lack of evidence on which stimulation protocol should be used in women with breast cancer and the growing demand for fertility preservation, there is an urgent need to undertake this study. By performing this study, we will be able to closely monitor the effects of various stimulation protocols in women with breast cancer and pave the way for long term follow up on the safety of this procedure in terms of breast cancer prognosis.
TRIAL REGISTRATION: NTR4108.

PMID: 28711318

Stocker M, van Herk W, El Helou S, Dutta S, Fontana MS, Schuerman FABA, van den Tooren-de Groot RK, Wieringa JW, Janota J, van der Meer-Kappelle LH, Moonen R, Sie SD, **de Vries E**, Donker AE, Zimmerman U, Schlapbach LJ, de Mol AC, Hoffman-Haringsma A, Roy M, Tomaske M, Kornelisse RF, van Gijsel J, Visser EG, Willemsen SP, van Rossum AMC; NeoPInS Study Group. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns).
Lancet. 2017 Aug 26;390(10097):871-881. doi: 10.1016/S0140-6736(17)31444-7. Epub 2017 Jul 12.

BACKGROUND: Up to 7% of term and late-preterm neonates in high-income countries receive antibiotics during the first 3 days of life because of suspected early-onset sepsis. The prevalence of culture-proven early-onset sepsis is 0·1% or less in high-income countries, suggesting substantial overtreatment. We assess whether procalcitonin-guided decision making for suspected early-onset sepsis can safely reduce the duration of antibiotic treatment.
METHODS: We did this randomised controlled intervention trial in Dutch (n=11), Swiss (n=4), Canadian (n=2), and Czech (n=1) hospitals. Neonates of gestational age 34 weeks or older, with suspected early-onset sepsis requiring antibiotic treatment were stratified into four risk categories by their treating physicians and randomly assigned [1:1] using a computer-generated list stratified per centre to procalcitonin-guided decision making or standard care-based antibiotic treatment. Neonates who underwent surgery within the first week of life or had major congenital malformations that would have required hospital admission were excluded. Only principal investigators were masked for group assignment. Co-primary outcomes were non-inferiority for re-infection or death in the first month of life (margin 2·0%) and superiority for duration of antibiotic therapy. Intention-to-treat and per-protocol analyses were done. This trial was registered with ClinicalTrials.gov, number NCT00854932.
FINDINGS: Between May 21, 2009, and Feb 14, 2015, we screened 2440 neonates with suspected early-onset sepsis. 622 infants were excluded due to lack of parental consent, 93 were ineligible for reasons unknown (68), congenital malformation (22), or surgery in the first week of life (3). 14 neonates were excluded as 100% data monitoring or retrieval was not feasible, and one neonate was excluded because their procalcitonin measurements could not be taken. 1710 neonates were enrolled and randomly assigned to either procalcitonin-guided therapy (n=866) or standard therapy (n=844). 1408 neonates underwent per-protocol analysis (745 in the procalcitonin group and 663

standard group). For the procalcitonin group, the duration of antibiotic therapy was reduced (intention to treat: 55·1 vs 65·0 h, p<0·0001; per protocol: 51·8 vs 64·0 h; p<0·0001). No sepsis-related deaths occurred, and 9 (<1%) of 1710 neonates had possible re-infection. The risk difference for non-inferiority was 0·1% (95% CI -4·6 to 4·8) in the intention-to-treat analysis (5 [0·6%] of 866 neonates in the procalcitonin group vs 4 [0·5%] of 844 neonates in the standard group) and 0·1% (-5·2 to 5·3) in the per-protocol analysis (5 [0·7%] of 745 neonates in the procalcitonin group vs 4 [0·6%] of 663 neonates in the standard group).
INTERPRETATION: Procalcitonin-guided decision making was superior to standard care in reducing antibiotic therapy in neonates with suspected early-onset sepsis. Non-inferiority for re-infection or death could not be shown due to the low occurrence of re-infections and absence of study-related death.
FUNDING: The Thrasher Foundation, the NutsOhra Foundation, the Sophia Foundation for Scientific research.

PMID: 28711999

Gieselbach RJ, Muller-Hansma AH, Wijburg MT, de Bruin-Weller MS, van Oosten BW, **Nieuwkamp DJ**, Coenjaerts FE, Wattjes MP, Murk JL. Erratum to: Progressive multifocal leukoencephalopathy in patients treated with fumaric acid esters: a review of 19 cases.
J Neurol. 2017 Aug;264(8):1833-1836. doi: 10.1007/s00415-017-8557-1.
No abstract available.

PMID: 28732531

van Hoogenhuijze NE, Torrance HL, Mol F, Laven JSE, Scheenjes E, Traas MAF, Janssen C, Cohlen B, Teklenburg G, **de Bruin JP**, van Oppenraaij R, Maas JWM, Moll E, Fleischer K, van Hooff MH, de Koning C, Cantineau A, Lambalk CB, Verberg M, Nijs M, Manger AP, van Rumste M, van der Voet LF, Preys-Bosman A, Visser J, Brinkhuis E, den Hartog JE, Sluijmer A, Jansen FW, Hermes W, Bandell ML, Pelinck MJ, van Disseldorp J, van Wely M, Smeenk J, Pieterse QD, Boxmeer JC, Groenewoud ER, Eijkemans MJC, Kasius JC, Broekmans FJM. Endometrial scratching in women with implantation failure after a first IVF/ICSI cycle; does it lead to a higher live birth rate? The SCRaTCH study: a randomized controlled trial (NTR 5342).
BMC Womens Health. 2017 Jul 21;17(1):47. doi: 10.1186/s12905-017-0378-y.

BACKGROUND: Success rates of assisted reproductive techniques (ART) are approximately 30%, with the most important limiting factor being embryo implantation. Mechanical endometrial injury, also called 'scratching', has been proposed to positively affect the chance of implantation after embryo transfer, but the currently available evidence is not yet conclusive. The primary aim of this study is to determine the effect of endometrial scratching prior to a second fresh in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycle on live birth rates in women with a failed first IVF/ICSI cycle.
METHOD: Multicenter randomized controlled trial in Dutch academic and non-academic hospitals. A total of 900 women will be included of whom half will undergo an endometrial scratch in the luteal phase of the cycle prior to controlled ovarian hyperstimulation using an endometrial biopsy catheter. The primary endpoint is the live birth rate after the 2nd fresh IVF/ICSI cycle. Secondary endpoints are costs, cumulative live birth rate (after the full 2nd IVF/ICSI cycle and over 12 months of follow-up); clinical and ongoing pregnancy rate; multiple pregnancy rate; miscarriage rate and endometrial tissue parameters associated with implantation failure.
DISCUSSION: Multiple studies have been performed to investigate the effect of endometrial scratching on live birth rates in women undergoing IVF/ICSI cycles. Due to heterogeneity in both the method and population being scratched, it remains unclear which group of women will benefit from the procedure. The SCRaTCH trial proposed here aims to investigate the effect of endometrial scratching prior to controlled ovarian hyperstimulation in a large group of women undergoing a second IVF/ICSI cycle.
TRIAL REGISTRATION: NTR 5342 , registered July 31st, 2015.

PMID: 28734938

Dalton HR, **van Eijk JJJ**, Cintas P, Madden RG, Jones C, Webb GW, Norton B, Pique J, Lutgens S, Devooght-Johnson N, Woolson K, Baker J, Saunders M, Househam L, Griffiths J, Abravanel F, Izopet J, Kamar N, van Alfen N, van Engelen BGM, Hunter JG, van der Eijk AA, Bendall RP, Mclean BN, Jacobs BC. Hepatitis E virus
infection and acute non-traumatic neurological injury: A prospective multicentre study.
J Hepatol. 2017 Nov;67(5):925-932. doi: 10.1016/j.jhep.2017.07.010. Epub 2017 Jul 20.

BACKGROUND & AIMS: Hepatitis E virus (HEV) has been associated with a number of neurological syndromes, but causality has not yet been

established. The aim of this study was to explore the relationship between HEV and neurological illness by prospective HEV testing of patients presenting with acute non-traumatic neurological injury.
METHODS: Four hundred and sixty-four consecutive patients presenting to hospital with acute non-traumatic neurological illnesses were tested for HEV by serology and PCR from four centres in the UK, France and the Netherlands.
RESULTS: Eleven of 464 patients (2.4%) had evidence of current/recent HEV infection. Seven had HEV RNA identified in serum and four were diagnosed serologically. Neurological cases in which HEV infection was found included neuralgic amyotrophy (n=3, all PCR positive); cerebral ischemia or infarction (n=4); seizure (n=2); encephalitis (n=1); and an acute combined facial and vestibular neuropathy (n=1). None of these cases were clinically jaundiced and median ALT at presentation was 24IU/L (range 8-145). Cases of HEV-associated neuralgic amyotrophy were found in each of the participating countries: all were middle-aged males with bilateral involvement of the brachial plexus.
CONCLUSIONS: In this cohort of patients with non-traumatic neurological injury, 2.4% had evidence of HEV infection. Symptoms of hepatitis were mild or absent and no patients were jaundiced. The cases of HEV-associated neuralgic amyotrophy had similarities with other HEV-associated cases described in a large retrospective study. This observation supports a causal relationship between HEV and neuralgic amyotrophy. To further understand the relevance of HEV infection in patients with acute neurological illnesses, case-control studies are warranted. Lay summary: Hepatitis E virus (HEV), as its name suggests, is a hepatotropic virus, i.e. it causes damage to the liver (hepatitis). Our findings show that HEV can also be associated with a range of injury to the nervous system.

PMID: 28742991

Gunge VB, Juul KE, **van den Brule AJC**, Iftner T, Kjær SK. Sexual inactivity and occurrence of STIs in relation to weight status in women: Two large population-based studies.
Women Health. 2018 Aug;58(7):790-805. doi:10.1080/03630242.2017.1353572. Epub 2017 Aug 25.

The aim of this study was to examine sexual inactivity and occurrence of selected sexually transmitted infections in relation to body mass index. We used data from two large Danish population-based cross-sectional studies conducted in 1991-1995 (HPV study: 6869 women, aged 22-32 years) and in 2004-2005 (Liva study: 19,484 women, aged 18-45 years). Data were collected using a structured interview and measured weight, height, high-risk human papillomavirus DNA, Chlamydia DNA for the HPV study and a structured questionnaire for the Liva study. Overweight and obese women were more likely to have had no lifetime sexual partner or no sexual partner in the last year, e.g., obese women had a threefold (95 percent CI: 1.95-5.04) odds ratio of having had no sexual partner in the last year compared to normal weight women. Additionally, overweight and obese women had a lower likelihood of genital warts and high-risk human papillomavirus infection. A similar tendency was found for self-reported Chlamydia, but not with presence of Chlamydia DNA. If higher likelihood of no lifetime or recent sexual partners among overweight and obese women reflects unmet sexual needs, it could give rise to concern because quality of sexual life is associated with general quality of life.

PMID: 28753781

Gayet M, Mannaerts CK, Nieboer D, **Beerlage HP**, Wijkstra H, Mulders PFA, Roobol MJ. Prediction of Prostate Cancer: External Validation of the ERSPC Risk Calculator in a Contemporary Dutch Clinical Cohort.
Eur Urol Focus. 2018 Mar;4(2):228-234. doi: 10.1016/j.euf.2016.07.007.

BACKGROUND: The validity of prediction models needs external validation to assess their value beyond the original development setting.
OBJECTIVE: To report the diagnostic accuracy of the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator (RC)3 and RC4 in a contemporary Dutch clinical cohort.
DESIGN, SETTING, AND PARTICIPANTS: We retrospectively identified all men who underwent prostate biopsy (PBx) in the Jeroen Bosch Hospital, The Netherlands, between 2007 and 2016. Patients were included if they met ERSPC RC requirements of age (50-80 yr), prostate-specific antigen (PSA) (0.4-50 ng/ml), and prostate volume (10-150ml). The probability of a positive biopsy for prostate cancer (PCa) and significant PCa (Gleason score ≥7 and/or higher than T2b) were calculated and compared with PBx pathology results.
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Evaluation was performed by calibration, discrimination, and clinical usefulness using calibration plots, area under the receiver operating characteristic curves (AUCs), and decision curve analyses (DCAs), respectively.
RESULTS AND LIMITATIONS: A total of 2270 PBx sessions were eligible for final analysis. Discriminative ability of RC3 (AUC) was 0.78 and 0.90 for any PCa and significant PCa, respectively. For RC4 the calculated AUCs were 0.62 (any PCa) and 0.76 (significant PCa). The calibration plots of RC3 showed good results for both any PCa risk and significant PCa risk. In the repeat PBx group, RC4 tended to underestimate outcomes for PCa and showed moderate calibration for significant PCa. DCA showed an overall net benefit compared with PSA and digital rectal examination (DRE) alone. Limitations of this study are its retrospective single-institution design, retrospectively assessed DRE outcomes,

no time restrictions between the first and repeat biopsy sessions, and no anterior sampling in the repeat PBx protocol.
CONCLUSIONS: The ERSPC RCs performed well in a contemporary clinical setting. Most pronounced in the biopsy-naive group, both RCs should be favoured over a PSA plus DRE-based stratification in the decision whether or not to perform PBx.
PATIENT SUMMARY: We looked at the ability of the existing European Randomized Study of Screening for Prostate Cancer risk calculator (RC), using different clinical data to predict the presence of prostate cancer in Dutch men. The RC performed well and should be favoured in the decision of whether or not to perform prostate biopsies over the conventional diagnostic pathway.

PMID: 28753794

Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, de Wit R, van den Bergh ACM, Coenen JLLM, **Beerlage HP**, Hendriks MP, Bos MMEM, van den Berg P, van de Wouw AJ, Spermon R, Boerma MO, Geenen MM, Tick LW, Polee MB, Bloemendal HJ, Cordia I, Peters FPJ, de Vos AI, van den Bosch J, van den Eertwegh AJM, Gerritsen WR. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry.
Eur Urol Focus. 2018 Sep;4(5):694-701. doi: 10.1016/j.euf.2016.09.008.

BACKGROUND: Trials in castration-resistant prostate cancer (CRPC) treatment have shown improved outcomes, including survival. However, as trial populations are selected, results may not be representative for the real-world population. The aim of this study was to assess the differences between patients treated in a clinical trial versus standard care during the course of CRPC in a real-world CRPC population.
DESIGN, SETTING, AND PARTICIPANTS: Castration-resistant Prostate Cancer Registry is a population-based, observational, retrospective registry. CRPC patients from 20 hospitals in the Netherlands have been included from 2010 to 2013.
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Baseline characteristics, systemic treatment, and overall survival were the main outcomes. Descriptive statistics, multivariate Cox regression, and multiple imputations with the Monte Carlo Markov Chain method were used.
RESULTS AND LIMITATIONS: In total, 1524 patients were enrolled of which 203 patients had participated in trials at any time. The median follow-up period was 23 mo. Patients in the trial group were significantly younger and had less comorbidities. Docetaxel treatment was more frequently used in trial patients (85% vs 40%). Despite an observed unadjusted median overall survival difference of 35 mo versus 24 mo between the trial and standard care group, this difference was not retained after adjustment for baseline characteristics and treatment effect.
CONCLUSIONS: At CRPC diagnosis, the baseline characteristics of the patients who had been enrolled in trials notably differed from patients who received standard treatment options only. The survival difference between the trial and standard care group could be explained by baseline differences and treatment effects. These results indicate that trial results cannot easily be translated to real-world practice.
PATIENT SUMMARY: We observed that patients treated in clinical trials differed from patients who were not. We concluded that this may lead to differential treatment and survival. Caution is warranted when real-world outcomes are compared with trial results.

PMID:28754367

van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, **Bosscha K**, van Dam RM, van Eijck CH, Gerhards MF, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Klaase J, van Laarhoven CJ, Molenaar IQ, Patijn GA, Rupert CG, van Santvoort HC, Scheepers JJ, van der Schelling GP, Busch OR, Besselink MG; Dutch Pancreatic Cancer Group. Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit.
HPB (Oxford). 2017 Oct;19(10):919-926. doi: 10.1016/j.hpb.2017.06.010. Epub 2017 Jul 26.

BACKGROUND:Auditing is an important tool to identify practice variation and 'best practices'. The Dutch Pancreatic Cancer Audit is mandatory in all 18 Dutch centers for pancreatic surgery.
METHODS:Performance indicators and case-mix factors were identified by a PubMed search for randomized controlled trials (RCT's) and large series in pancreatic surgery. In addition, data dictionaries of two national audits, three institutional databases, and the Dutch national cancer registry were evaluated. Morbidity, mortality, and length of stay were analyzed of all pancreatic resections registered during the first two audit years. Case ascertainment was cross-checked with the Dutch healthcare inspectorate and key-variables validated in all centers.
RESULTS:Sixteen RCT's and three large series were found. Sixteen indicators and 20 case-mix factors were included in the audit. During 2014-2015, 1785 pancreatic resections were registered including 1345 pancreatoduodenectomies. Overall in-hospital mortality was 3.6%. Following pancreatoduodenectomy, mortality was 4.1%, Clavien-Dindo grade ≥ III morbidity was 29.9%, median (IQR) length of stay 12 (9-18) days, and readmission rate 16.0%. In total 97.2% of >40,000 variables validated were consistent with the medical charts.
CONCLUSIONS:The Dutch Pancreatic Cancer Audit, with high quality data, reports good outcomes of pancreatic surgery on a national level.

PMID: 28768475

Kip MMA, Koffijberg H, Moesker MJ, IJzerman MJ, **Kusters R**. The cost-utility of point-of-care troponin testing to diagnose acute coronary syndrome in primary care.
BMC Cardiovasc Disord. 2017 Aug 2;17(1):213. doi:10.1186/s12872-017-0647-6.

BACKGROUND: The added value of using a point-of-care (POC) troponin test in primary care to rule out acute coronary syndrome (ACS) is debated because test sensitivity is inadequate early after symptom onset. This study investigates the potential cost-utility of diagnosing ACS by a general practitioner (GP) when a POC troponin test is available versus GP assessment only.
METHODS: A patient-level simulation model was developed, representing a hypothetical cohort of the Dutch population (>35 years) consulting the GP with chest complaints. All health related consequences as well as cost consequences were included. Both symptom duration, selection of patients in whom the POC troponin test is performed, and test performance at different time points were incorporated. Health outcomes were expressed as Quality-Adjusted Life Years (QALYs). The main outcome parameters involve the effect of POC troponin testing on (in)correct hospital referrals, QALYs, and costs.
RESULTS: The POC troponin strategy decreases the referral rate in non-ACS patients from 38.46% to 31.85%. Despite a small increase in non-referral among ACS patients from 0.22% to 0.27%, the overall health effect is negligible. Costs will decrease with €77.25/patient (95% CI €-126.81 to €-33.37).
CONCLUSIONS: The POC troponin strategy is likely cost-saving, by reducing hospital referrals. The small increase in missed ACS patients can be partly explained by conservative assumptions used in the analysis. Besides, current developments in POC troponin tests will likely further improve their diagnostic performance. Therefore, future prospective studies are warranted to investigate whether those developments make the POC troponin test to a safe and cost-effective diagnostic tool for diagnosing ACS in general practices.

PMID: 28768846

van Eijk JJJ, Dalton HR, Ripellino P, Madden RG, Jones C, Fritz M, Gobbi C, Melli G, Pasi E, Herrod J, Lissmann RF, Ashraf HH, Abdelrahim M, Masri OABAL, Fraga M, Benninger D, Kuntzer T, Aubert V, Sahli R, Moradpour D, Blasco-Perrin H, Attarian S, Gérolami R, Colson P, Giordani MT, Hartl J, Pischke S, Lin NX, Mclean BN, Bendall RP, Panning M, Peron JM, Kamar N, Izopet J, Jacobs BC, van Alfen N, van Engelen BGM. Clinical phenotype and outcome of hepatitis E virus-associated neuralgic amyotrophy.
Neurology. 2017 Aug 29;89(9):909-917. doi:10.1212/WNL.0000000000004297. Epub 2017 Aug 2.

OBJECTIVE: To determine the clinical phenotype and outcome in hepatitis E virus-associated neuralgic amyotrophy (HEV-NA).
METHODS: Cases of NA were identified in 11 centers from 7 European countries, with retrospective analysis of demographics, clinical/laboratory findings, and treatment and outcome. Cases of HEV-NA were compared with NA cases without evidence of HEV infection.
RESULTS: Fifty-seven cases of HEV-NA and 61 NA cases without HEV were studied. Fifty-six of 57 HEV-NA cases were anti-HEV IgM positive; 53/57 were IgG positive. In 38 cases, HEV RNA was recovered from the serum and in 1 from the CSF (all genotype 3). Fifty-one of 57 HEV-NA cases were anicteric; median alanine aminotransferase 259 IU/L (range 12-2,961 IU/L); in 6 cases, liver function tests were normal. HEV-NA cases were more likely to have bilateral involvement (80.0% vs 8.6%, $p < 0.001$), damage outside the brachial plexus (58.5% vs 10.5%, $p < 0.01$), including phrenic nerve and lumbosacral plexus injury (25.0% vs 3.5%, $p = 0.01$, and 26.4% vs 7.0%, $p = 0.001$), reduced reflexes ($p = 0.03$), sensory symptoms ($p = 0.04$) with more extensive damage to the brachial plexus. There was no difference in outcome between the 2 groups at 12 months.
CONCLUSIONS: Patients with HEV-NA are usually anicteric and have a distinct clinical phenotype, with predominately bilateral asymmetrical involvement of, and more extensive damage to, the brachial plexus. Involvement outside the brachial plexus is more common in HEV-NA. The relationship between HEV and NA is likely to be causal, but is easily overlooked. Patients presenting with NA should be tested for HEV, irrespective of liver function test results. Prospective treatment/outcome studies of HEV-NA are warranted.

PMID: 28768850

Killestein J, Leurs CE, Hoogervorst ELJ, **van Eijk J**, Mostert JP, van den Eertwegh AJM, Uitdehaag BMJ. Five cases of malignant melanoma during fingolimod treatment in Dutch patients with MS.
Neurology. 2017 Aug 29;89(9):970-972. doi: 10.1212/WNL.0000000000004293. Epub 2017 Aug 2.
No abstract available.

PMID: 28776873

Drenth-van Maanen AC, Leendertse AJ, Jansen PAF, Knol W, Keijsers CJPW, Meulendijk MC, **van Marum RJ**. The Systematic Tool to Reduce Inappropriate Prescribing (STRIP): Combining implicit and explicit prescribing tools to improve appropriate prescribing.

J Eval Clin Pract. 2018 Apr;24(2):317-322. doi: 10.1111/jep.12787. Epub 2017 Aug 4.

Inappropriate prescribing is a major health care issue, especially regarding older patients on polypharmacy. Multiple implicit and explicit prescribing tools have been developed to improve prescribing, but these have hardly ever been used in combination. The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) combines implicit prescribing tools with the explicit Screening Tool to Alert physicians to the Right Treatment and Screening Tool of Older People's potentially inappropriate Prescriptions criteria and has shared decision-making with the patient as a critical step. This article describes the STRIP and its ability to identify potentially inappropriate prescribing. The STRIP improved general practitioners' and final-year medical students' medication review skills. The Web-application STRIP Assistant was developed to enable health care providers to use the STRIP in daily practice and will be incorporated in clinical decision support systems. It is currently being used in the European Optimizing thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) project, a multicentre randomized controlled trial involving patients aged 75 years and older using multiple medications for multiple medical conditions. In conclusion, the STRIP helps health care providers to systematically identify potentially inappropriate prescriptions and medication-related problems and to change the patient's medication regimen in accordance with the patient's needs and wishes. This article describes the STRIP and the available evidence so far. The OPERAM study is investigating the effect of STRIP use on clinical and economic outcomes.

PMID:28791679

Nelen SD, van Putten M, Lemmens VEPP, **Bosscha K**, de Wilt JHW, Verhoeven RHA. Effect of age on rates of palliative surgery and chemotherapy use in patients with locally advanced or metastatic gastric cancer.

Br J Surg. 2017 Dec;104(13):1837-1846. doi: 10.1002/bjs.10621. Epub 2017 Aug 9.

BACKGROUND: This study assessed trends in the treatment and survival of palliatively treated patients with gastric cancer, with a focus on age-related differences.

METHODS: For this retrospective, population-based, nationwide cohort study, all patients diagnosed between 1989 and 2013 with non-cardia gastric cancer with metastasized disease or invasion into adjacent structures were selected from the Netherlands Cancer Registry. Trends in treatment and 2-year overall survival were analysed and compared between younger (age less than 70 years) and older (aged 70 years or more) patients. Analyses were done for five consecutive periods of 5 years, from 1989-1993 to 2009-2013. Multivariable logistic regression analysis was used to examine the probability of undergoing surgery. Multivariable Cox regression analysis was used to identify independent risk factors for death.

RESULTS: Palliative resection rates decreased significantly in both younger and older patients, from 24·5 and 26·2 per cent to 3·0 and 5·0 per cent respectively. Compared with patients who received chemotherapy alone, both younger (21·6 versus 6·3 per cent respectively; P < 0·001) and older (14·7 versus 4·6 per cent; P < 0·001) patients who underwent surgery had better 2-year overall survival rates. Multivariable analysis demonstrated that younger and older patients who received chemotherapy alone had worse overall survival than patients who had surgery only (younger: hazard ratio (HR) 1·22, 95 per cent c.i. 1·12 to 1·33; older: HR 1·12, 1·01 to 1·24). After 2003 there was no association between period of diagnosis and overall survival in younger or older patients.

CONCLUSION: Despite changes in the use of resection and chemotherapy as palliative treatment, overall survival rates of patients with advanced and metastatic gastric cancer did not improve.

PMID: 28793317

Timmermans MJC, van Vught AJAH, Peters YAS, Meermans G, Peute JGM, Postma CT, Smit PC, **Verdaasdonk E**, de Vries Reilingh TS, Wensing M, Laurant MGH. The impact of the implementation of physician assistants in inpatient care: A multicenter matched-controlled study.

PLoS One. 2017 Aug 9;12(8):e0178212. doi: 10.1371/journal.pone.0178212. eCollection 2017.

BACKGROUND: Medical care for admitted patients in hospitals is increasingly reallocated to physician assistants (PAs). There is limited evidence about the consequences for the quality and safety of care. This study aimed to determine the effects of substitution of inpatient care from medical doctors (MDs) to PAs on patients' length of stay (LOS), quality and safety of care, and patient experiences with the provided care.

METHODS: In a multicenter matched-controlled study, the traditional model in which only MDs are employed for inpatient care (MD model)

was compared with a mixed model in which besides MDs also PAs are employed (PA/MD model). Thirty-four wards were recruited across the Netherlands. Patients were followed from admission till one month after discharge. Primary outcome measure was patients' LOS. Secondary outcomes concerned eleven indicators for quality and safety of inpatient care and patients' experiences with the provided care.
RESULTS: Data on 2,307 patients from 34 hospital wards was available. The involvement of PAs was not significantly associated with LOS (β 1.20, 95%CI 0.99-1.40, p = .062). None of the indicators for quality and safety of care were different between study arms. However, the involvement of PAs was associated with better experiences of patients (β 0.49, 95% CI 0.22-0.76, p = .001).
CONCLUSIONS: This study did not find differences regarding LOS and quality of care between wards on which PAs, in collaboration with MDs, provided medical care for the admitted patients, and wards on which only MDs provided medical care. Employing PAs seems to be safe and seems to lead to better patient experiences.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01835444.

PMID: 28793989

Grooten IJ, Koot MH, van der Post JA, Bais JM, Ris-Stalpers C, Naaktgeboren C, Bremer HA, van der Ham DP, Heidema WM, Huisjes A, Kleiverda G, Kuppens S, van Laar JO, Langenveld J, van der Made F, van Pampus MG, Papatsonis D, Pelinck MJ, Pernet PJ, van Rheenen L, **Rijnders RJ**, Scheepers HC, Vogelvang TE, Mol BW, Roseboom TJ, Painter RC. Early enteral tube feeding in optimizing treatment of hyperemesis gravidarum: the Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding (MOTHER) randomized controlled trial.
Am J Clin Nutr. 2017 Sep;106(3):812-820. doi: 10.3945/ajcn.117.158931. Epub 2017 Aug 9.

Background: Hyperemesis gravidarum (HG) leads to dehydration, poor nutritional intake, and weight loss. HG has been associated with adverse pregnancy outcomes such as low birth weight. Information about the potential effectiveness of treatments for HG is limited.Objective: We hypothesized that in women with HG, early enteral tube feeding in addition to standard care improves birth weight.Design: We performed a multicenter, open-label randomized controlled trial [Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding (MOTHER)] in 19 hospitals in the Netherlands. A total of 116 women hospitalized for HG between 5 and 20 wk of gestation were randomly allocated to enteral tube feeding for ≥7 d in addition to standard care with intravenous rehydration and antiemetic treatment or to standard care alone. Women were encouraged to continue tube feeding at home. On the basis of our power calculation, a sample size of 120 women was anticipated. Analyses were performed according to the intention-to-treat principle.Results: Between October 2014 and March 2016 we randomly allocated 59 women to enteral tube feeding and 57 women to standard care. The mean ± SD birth weight was 3160 ± 770 g in the enteral tube feeding group compared with 3200 ± 680 g in the standard care group (mean difference: -40 g, 95% CI: -230, 310 g). Secondary outcomes, including maternal weight gain, duration of hospital stay, readmission rate, nausea and vomiting symptoms, decrease in quality of life, psychological distress, prematurity, and small-for-gestational-age, also were comparable. Of the women allocated to enteral tube feeding, 28 (47%) were treated according to protocol. Enteral tube feeding was discontinued within 7 d of placement in the remaining women, primarily because of its adverse effects (34%).Conclusions: In women with HG, early enteral tube feeding does not improve birth weight or secondary outcomes. Many women discontinued tube feeding because of discomfort, suggesting that it is poorly tolerated as an early routine treatment of HG. This trial was registered at www.trialregister.nl as NTR4197.

PMID:28797755

Busweiler LA, Henneman D, Dikken JL, Fiocco M, van Berge Henegouwen MI, Wijnhoven BP, van Hillegersberg R, Rosman C, Wouters MW, van Sandick JW; Dutch Upper GI Cancer Audit group. Collaborators: **Bosscha K**, Cats A, van Grieken NC, Hartgrink HH, Lemmens VE, Nieuwenhuijzen GA, Plukker JT, Siersema PD, Tetteroo G, Veldhuis PM, Voncken FE. Failure-to-rescue in patients undergoing surgery for esophageal or gastric cancer.
Eur J Surg Oncol. 2017 Oct;43(10):1962-1969. doi: 10.1016/j.ejso.2017.07.005. Epub 2017 Jul 29.
Trefwoorden: Esophageal neoplasms; Esophagectomy; Failure-to-rescue; Gastrectomy; Gastric neoplasms; Quality indicators

BACKGROUND:Complex surgical procedures such as esophagectomy and gastrectomy for cancer are associated with substantial morbidity and mortality. The purpose of this study was to evaluate trends in postoperative morbidity, mortality, and associated failure-to-rescue (FTR), in patients who underwent a potentially curative resection for esophageal or gastric cancer in the Netherlands, and to investigate differences between the two groups.
METHODS:All patients with esophageal or gastric cancer who underwent a potentially curative resection, registered in the Dutch Upper GI Cancer Audit (DUCA) between 2011 and 2014, were included. Primary outcomes were (major) postoperative complications, postoperative mortality and FTR. To investigate groups' effect on the outcomes of interest a mixed model was used.

RESULTS:Overall, 2644 patients with esophageal cancer and 1584 patients with gastric cancer were included in this study. In patients with gastric cancer, postoperative mortality (7.7% in 2011 vs. 3.8% in 2014) and FTR (38% in 2011 and 19% in 2014) decreased significantly over the years. The adjusted risk of developing a major postoperative complication was lower (OR 0.54; 95% CI 0.42-0.70), but the risk of FTR was higher (OR 1.85; 95% CI 1.05-3.27) in patients with gastric cancer compared to patients with esophageal cancer.
CONCLUSION:Once a postoperative complication occurred, patients with gastric cancer were more likely to die compared to patients with esophageal cancer. Underlying mechanisms like patient selection, and differences in structure and organization of care should be investigated. Next to morbidity and mortality, failure-to-rescue should be considered as an important outcome measure after esophagogastric cancer resections.

PMID: 28802945

Voskamp PWM, Dekker FW, van Diepen M, **Hoogeveen EK**; PREPARE-2 Study Group. Effect of dual compared to no or single renin-angiotensin system blockade on risk of renal replacement therapy or death in predialysis patients: PREPARE-2 study.
J Am Soc Hypertens. 2017 Oct;11(10):635-643.

Current guidelines on hypertension treatment in chronic kidney disease (CKD) patients discourage combined angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) use due to the risk of an increased kidney function decline. However, dual compared to single renin-angiotensin system (RAS) blockade may have more efficacy with regard to hypertension and proteinuria. Among incident predialysis patients (CKD 4-5), we compared dual with no or single RAS blockade regarding kidney function decline and risk of renal replacement therapy (RRT) or death. In a multicenter cohort study, 495 incident predialysis patients (>18 years) were included between 2004 and 2011 and followed until RRT, death, or October 2016. At baseline, patients were divided into four categories: nonuser, single or dual user of ACEi and/or ARB. Cox models were used to estimate the hazard ratio for the combined end point RRT or death. Differences in decline of kidney function among the four drug groups were compared with a linear mixed model. A total of 119 patients were nonusers, 164 ACEi users, 133 ARB users, and 79 dual RAS users. Compared to nonusers, the multivariable adjusted hazard ratio (95% confidence interval) for the combined end point was 0.75 (0.65 to 0.86) for ACEi users, 0.87 (0.76 to 1.00) for ARB users, and 0.79 (0.67 to 0.94) for dual RAS users. The average annual decline in kidney function did not differ among the four groups. We observed in predialysis patients that compared to no RAS blockade, both dual RAS blockade and single ACEi use were associated with about 20%-25% lower risk of RRT or death, without difference in kidney function decline.

PMID: 28820386

Mollers M, Lutgens SP, Schoffelen AF, **Schneeberger PM**, Suijkerbuijk AWM. Cost of Nosocomial Outbreak Caused by NDM-1-Containing Klebsiella pneumoniae in the Netherlands, October 2015-January 2016.
Emerg Infect Dis. 2017 Sep;23(9):1574-1576. doi: 10.3201/eid2309.161710.

During October-December 2015, 29 patients in a hospital in the Netherlands acquired nosocomial infection with a multidrug-resistant, New Delhi-metallo-β-lactamase-positive Klebsiella pneumoniae strain. Extensive infection control measures were needed to stop this outbreak. The estimated economic impact of the outbreak was $804,263; highest costs were associated with hospital bed closures.

PMID: 28837522

Nissen LHC, Pierik M, **Derikx LAAP**, de Jong E, Kievit W, van den Heuvel TRA, van Rosendael AR, Plasmeijer EI, Dewint P, Verhoeven RHA, Overbeek LIH, Nagtegaal ID, Hoentjen F, van der Meulen-de Jong AE. Risk factors and clinical outcomes in IBD patients with melanoma.
Inflamm Bowel Dis. 2017 Nov;23(11):2018-2026. doi: 10.1097/MIB.0000000000001191.

BACKGROUND: Patients with inflammatory bowel disease (IBD) are at increased risk to develop malignant melanoma and this risk may increase with use of anti-tumor necrosis factor (TNF) therapy. Impaired survival of immunosuppressed melanoma patients is reported in transplant and rheumatology patients. This study aims to (1) identify risk factors for melanoma development in patients with IBD, (2) compare clinical characteristics of melanoma in patients with IBD to the general population, and (3) assess the influence of immunosuppressive medication on survival.
METHODS: We retrospectively searched the Dutch Pathology Database to identify all Dutch patients with IBD with cutaneous melanoma

between January 1991 and December 2011. We then performed 2 case-control studies. To identify risk factors for melanoma development in IBD, we compared patients with IBD with melanoma to the general IBD population. To compare outcome and survival after melanoma diagnosis, we compared cases with non-IBD melanoma patients.
RESULTS: We included 304 patients with IBD with melanoma, 1800 IBD controls, and 8177 melanoma controls. IBD cases had more extensive IBD (ulcerative colitis: pancolitis: cases 44.5% versus IBD controls without melanoma 28.1%; P < 0.01; Crohn's disease: ileal and colonic disease: cases 57.9% versus controls 48.9%; P = 0.02). Despite a lower Nodes (N)-stage in patients with IBD (N1+ 8.3% versus 18.2%; P < 0.01) with comparable Tumor (T) and Metastasis (M) stages, survival was similar between groups, regardless of immunosuppressive or anti-TNF therapy.
CONCLUSIONS: This study showed that IBD extent is a risk factor for melanoma development. Despite the lower N-stage in patients with IBD, we could not confirm impaired survival after melanoma in patients with IBD, regardless of anti-TNF and/or thiopurine use.

PMID: 28840502

van Roeden SE, Melenotte C, **Hermans MHA, Sinnige HAM, Nooijen PTGA**, Audoly G, Hoepelman AIM, Oosterheert JJ, Raoult D, **Wever PC**. Case report: Coxiella burnetii vascular infection and lymphoma in the Netherlands.
Infection. 2018 Feb;46(1):131-134. doi: 10.1007/s15010-017-1061-9. Epub 2017 Aug 24.

OBJECTIVES AND DESIGN: Non-Hodgkin lymphoma has been linked to infection with Coxiella burnetii, potentially through overproduction of IL-10 during infection with C. burnetii.
MATERIALS AND METHODS: Description of a case report.
RESULTS: We describe a patient with retroperitoneal non-Hodgkin lymphoma and vascular infection with C. burnetii. Immunofluorescence staining and fluorescence in situ hybridization targeting specific C. burnetii 16S rRNA were performed on the retroperitoneal lymphoma tissue sample obtained at diagnosis of NHL. Both were strongly positive for the presence of C. burnetii.
CONCLUSIONS: This case provokes questions regarding a potential association between C. burnetii and NHL, and underlines the importance of further exploration of this association.

PMID: 28848182

Aarts MJ, Vriens BE, de Boer M, Peters FP, Mandigers CM, Dercksen MW, Stouthard JM, Tol J, van Warmerdam LJ, van de Wouw AJ, Jacobs EM, van der Rijt CCD, **Smilde TJ**, van der Velden AW, Peer N, Tjan-Heijnen VCG. Neutrophil Recovery in Breast Cancer Patients Receiving Docetaxel-Containing Chemotherapy with and without Granulocyte Colony-Stimulating Factor Prophylaxis.
Oncology. 2017;93(5):323-328.
Trefwoorden: neutropenie, chemotherapie

OBJECTIVE: The primary outcome of the current study is, whether there is a protective effect of prior chemotherapy or of prior granulocyte colony-stimulating factor (G-CSF) on the next cycle blood cell counts.
METHODS: Hematologic toxicity was evaluated, based on a randomized phase III study in breast cancer patients (n = 167) with >20% risk of febrile neutropenia. The primary endpoint was the nadir blood cell counts for patients treated with G-CSF given during all 6 chemotherapy cycles or limited to the first 2 chemotherapy cycles only.
RESULTS: For the present analyses, 47 patients were eligible. In the G-CSF 1-6 arm, the median white blood cell count (WBC) and absolute neutrophil count (ANC) nadir slowly decreased from 10.8 × 109/L in cycle 1 to 7.5 × 109/L in cycle 6 and from 7.1 × 109/L to 5.5 × 109/L, respectively. The median WBC nadir in the G-CSF 1-2 arm decreased from 1.2 × 109/L in cycle 3 to 0.9 × 109/L in cycle 6 and the ANC nadir showed a grade 4 neutropenia of 0.1 × 109/L in cycles 3-6. All patients had ANC recovery to normal levels (≥1.5 × 109/L) without delay on day 1 of the next cycle.
CONCLUSION: We conclude that there is no protective effect of prior G-CSF or prior chemotherapy use on nadir blood cell counts in subsequent cycles.

PMID: 28856403

Mulder FEM, Hakvoort RA, **de Bruin JP**, van der Post JAM, Roovers JWR. Comparison of clean intermittent and transurethral indwelling catheterization for the treatment of overt urinary retention after vaginal delivery: a multicentre randomized controlled clinical trial.
Int Urogynecol J. 2018 Sep;29(9):1281-1287. doi: 10.1007/s00192-017-3452-y. Epub 2017 Aug 30.

INTRODUCTION AND HYPOTHESIS: Overt postpartum urinary retention (PUR) is the inability to void after delivery and affects up to 7% of patients. Clean intermittent catheterization (CIC) and transurethral indwelling catheterization (TIC) are both standard treatments, but have not previously been compared. Clinical guidelines on postpartum bladder management are lacking.
METHODS: A total of 85 patients were randomised for TIC (n=45) and CIC (n=40). In total 68 patients (34 patients with TIC and 34 patients with CIC) completed the UDI-6 questionnaire 3 months after delivery.. Patients allocated to TIC received an indwelling catheter for 24 h and if necessary, another catheter for 48 h. Patients with CIC were intermittently catheterized or taught to self-catheterize until adequate voiding with a postvoid residual volume (PVRV) of <150 mL was achieved. The primary outcome was the presence of bothersome micturition symptoms as measured using the Dutch-validated Urogenital Distress Inventory (UDI-6).
RESULTS: Only seven patients (10%) reported bothersome micturition problems 3 months after delivery. No significant differences in the occurrence of micturition symptoms were found. Median PVRV was 800 mL in the CIC group and 650 mL in the TIC group. PVRV was ≥1,000 mL in 24% of the patients. The median duration of catheterization was significantly shorter in the CIC group than in the TIC group (12 h vs. 24 h, p < 0,01). In patients with CIC, 35% required only one catheterization before complete bladder emptying occurred. The duration of treatment was not related to the initial PVRV. Both treatments were equally well accepted by the patients.
CONCLUSIONS: In patients with overt PUR, CIC is the preferred treatment as a considerable percentage of patients appear to be over-treated when the standard duration of TIC is 24 h. The occurrence of micturition symptoms is not associated with the catheterization method used. CIC is well tolerated in patients with overt PUR.

PMID: 28859646

Oostendorp LJM, Ottevanger PB, Donders ART, van de Wouw AJ, Schoenaker IJH, **Smilde TJ**, van der Graaf WTA, Stalmeier PFM. Decision aids for second-line palliative chemotherapy: a randomised phase II multicentre trial.
BMC Med Inform Decis Mak. 2017 Aug 31;17(1):130. doi: 10.1186/s12911-017-0529-y.

BACKGROUND: There is increasing recognition of the delicate balance between the modest benefits of palliative chemotherapy and the burden of treatment. Decision aids (DAs) can potentially help patients with advanced cancer with these difficult treatment decisions, but providing detailed information could have an adverse impact on patients' well-being. The objective of this randomised phase II study was to evaluate the safety and efficacy of DAs for patients with advanced cancer considering second-line chemotherapy.
METHODS: Patients with advanced breast or colorectal cancer considering second-line treatment were randomly assigned to usual care (control group) or usual care plus a DA (intervention group) in a 1:2 ratio. A nurse offered a DA with information on adverse events, tumour response and survival. Outcome measures included patient-reported well-being (primary outcome: anxiety) and quality of the decision-making process and the resulting choice.
RESULTS: Of 128 patients randomised, 45 were assigned to the control group and 83 to the intervention group. Median age was 62 years (range 32-81), 63% were female, and 73% had colorectal cancer. The large majority of patients preferred treatment with chemotherapy (87%) and subsequently commenced treatment with chemotherapy (86%). No adverse impact on patients' well-being was found and nurses reported that consultations in which the DAs were offered went well. Being offered the DA was associated with stronger treatment preferences (3.0 vs. 2.5; p=0.030) and increased subjective knowledge (6.7 vs. 6.3; p=0.022). Objective knowledge, risk perception and perceived involvement were comparable between the groups.
CONCLUSIONS: DAs containing detailed risk information on second-line palliative treatment could be delivered to patients with advanced cancer without having an adverse impact on patient well-being. Surprisingly, the DAs only marginally improved the quality of the decision-making process. The effectiveness of DAs for palliative treatment decisions needs further exploration.
TRIAL REGISTRATION: Netherlands Trial Registry (NTR): NTR1113 (registered on 2 November 2007).

PMID: 28864963

Lorjé T, Barlo N, Reichert CLA, de Kanter W, **Sluman MA**. A 46-year-old man with recurrent embolic events.
Neth Heart J. 2017 Dec;25(12):695-696. doi: 10.1007/s12471-017-1034-8.
No abstract available.

PMID: 28870834

Malek Makan A, van Hout H, Onder G, Finne-Soveri H, van der Roest H, **van Marum R**. Prevalence of Preventive Cardiovascular Medication Use In Nursing Home Residents. Room for Deprescribing? The SHELTER Study.
J Am Med Dir Assoc. 2017 Dec 1;18(12):1037-1042. doi: 10.1016/j.jamda.2017.06.022. Epub 2017 Sep 1.

INTRODUCTION: In nursing home (NH) residents with a very short life expectancy, the benefits of preventive cardiovascular medication maintenance are questionable.
OBJECTIVE: To assess the prevalence of 4 classes of preventive cardiovascular medication (PCM) in NH residents, and to explore differences of prevalence across length of stay, mortality risk, cognitive impairment, functional disability, and across countries.
METHODS: A 12-month prospective cohort study was conducted in 57 NHs in 8 countries (Czech Republic, England, Finland, France, Germany, Italy, The Netherlands, and Israel). We assessed the prevalence at first measurement of 4 classes of PCM: oral anticoagulants (OAC), platelet aggregation inhibitor (PAI), antihypertensive (AHT), and lipid-modifying agent (LMA), in older (60+ years) residents with valid medication assessments. The PCM prevalence was compared across the length of stay (short <60 days, mid, long >12 months), health instability as defined by Changes in Health, End-Stage Disease, Signs, and Symptoms Scale (CHESS) > 3, cognitive impairment by Cognitive Performance Scale (CPS) > 2, and functional disability was measured using the Activities of Daily Living Hierarchy Scale (ADLH) ≥5.
RESULTS: Of the 3759 eligible residents, 2175 (57.9%) used at least 1 PCM. The prevalence of the 4 groups of PCM: OAC, PAI, AHT and LMA were 5.6%, 34.9%, 35.7%, and 10.4%, respectively. PCM use was lower in long-stay residents versus mid-stay: 56.0% vs. 62.7%, in cognitively impaired residents (47.1% vs. 67%), in residents with a high mortality risk (47.4% vs. 58.6%), and in residents with a high ADLH score (48.6% vs 64.0%).
CONCLUSION: Although the prevalence of PCM use was lower in long-stay, cognitively impaired residents, persons with a high mortality risk, and residents with more functional disabilities, there seems to be room for deprescribing.

PMID: 28871388

Mulder FEM, Hakvoort RA, **de Bruin JP**, Janszen EW, van der Post JAM, Roovers JWR. Long-term micturition problems of asymptomatic postpartum urinary retention: a prospective case-control study.
Int Urogynecol J. 2018 Apr;29(4):481-488. doi: 10.1007/s00192-017-3457-6. Epub 2017 Sep 4.

INTRODUCTION AND HYPOTHESIS: Covert (asymptomatic) postpartum urinary retention (PUR) is defined as post-void residual volume (PVRV) ≥150 mL. Although often supposed to be a common and harmless phenomenon, no data are available on the potential long-term micturition problems of increased PVRV after vaginal delivery.
METHODS: After the first spontaneous void post-vaginal delivery, PVRV was measured using a portable scanning device. Micturition symptoms were compared using validated questionnaires between women with PVRV < 150 mL and those with PVRV ≥150 mL until 1 year after delivery. Women with PVRV ≥ 150 mL were followed until complete bladder emptying was achieved.
RESULTS: Data of 105 patients with PVRV < 150 mL and 119 with PVRV ≥ 150 mL were available for analysis. 75% of all patients included had PVRV ≥ 250 mL. More primiparous patients had PVRV ≥ 150 mL ($p < 0.02$). 92% of women with PVRV ≥ 150 mL after delivery were able to adequately empty their bladder within 4 days. One year after delivery, no statistically significant differences were found.
CONCLUSIONS: Covert PUR according to the definition of PVRV ≥ 150 mL, is a common and transient phenomenon that does not result in more lower urinary tract symptoms 1 year after delivery. Although the current definition is not useful in identifying postpartum women with a pathological condition, we suggest that the definition of covert PUR should be change to: "PVRV≥500 mL after the first spontaneous void after (vaginal) delivery." This cut-off value is the value at which some women do need more time to normalise emptying of the bladder. The exact clinical implications of covert PUR need to be further studied in this subcategory of women.

PMID: 28873467

Hoogeveen EK, Rothman KJ, Voskamp PWM, de Mutsert R, Halbesma N, Dekker FW; PREPARE-2 Study Group. Obesity and risk of death or dialysis in younger and older patients on specialized pre-dialysis care.
PLoS One. 2017 Sep 5;12(9):e0184007.

BACKGROUND: Obesity is associated with increased mortality and accelerated decline in kidney function in the general population. Little is known about the effect of obesity in younger and older pre-dialysis patients. The aim of this study was to assess the extent to which obesity is a risk factor for death or progression to dialysis in younger and older patients on specialized pre-dialysis care.
METHOD: In a multicenter Dutch cohort study, 492 incident pre-dialysis patients (>18y) were included between 2004-2011 and followed until start of dialysis, death or October 2016. We grouped patients into four categories of baseline body mass index (BMI): <20, 20-24 (reference), 25-29, and ≥30 (obesity) kg/m2 and stratified patients into two age categories (<65y or ≥65y).
RESULTS: The study population comprised 212 patients younger than 65 years and 280 patients 65 years and older; crude cumulative risk of dialysis and mortality at the end of follow-up were 66% and 4% for patients <65y and 64% and 14%, respectively, for patients ≥65y. Among the <65y patients, the age-sex standardized combined outcome rate was 2.3 times higher in obese than those with normal BMI, corresponding

to an excess rate of 35 events/100 patient-years. After multivariable adjustment the hazard ratios (HR) (95% CI) for the combined endpoint by category of increasing BMI were, for patients <65y, 0.92 (0.41-2.09), 1 (reference), 1.76 (1.16-2.68), and 1.81 (1.17-2.81). For patients ≥65y the BMI-specific HRs were 1.73 (0.97-3.08), 1 (reference), 1.25 (0.91-1.71) and 1.30 (0.79-1.90). In the competing risk analysis, taking dialysis as the event of interest and death as a competing event, the BMI-specific multivariable adjusted subdistribution HRs (95% CI) were, for patients <65y, 0.90 (0.38-2.12), 1 (reference), 1.47 (0.96-2.24) and 1.72 (1.15-2.59). For patients ≥65y the BMI-specific SHRs (95% CI) were 1.68 (0.93-3.02), 1 (reference), 1.50 (1.05-2.14) and 1.80 (1.23-2.65).
CONCLUSION: We found that obesity in younger pre-dialysis patients and being underweight in older pre-dialysis patients are risk factors for starting dialysis and for death, compared with those with a normal BMI.

PMID: 28877022

Ramakers BP, Heijne M, Lie N, Le TN, van Vliet M, Claessen VPJ, Tolsma PJP, De Rosa M, Roest HIJ, Vanrompay D, Heddema ER, **Schneeberger P, Hermans MHA**. Zoonotic Chlamydia caviae Presenting as Community-Acquired Pneumonia.
N Engl J Med. 2017 Sep 7;377(10):992-994.
Trefwoorden: Chlamydia caviae, zoonose.
No abstract available.

PMID: 28878046

van Leijsen EMC, van Uden IWM, Ghafoorian M, Bergkamp MI, Lohner V, Kooijmans ECM, **van der Holst HM**, Tuladhar AM, Norris DG, van Dijk EJ, Rutten-Jacobs LCA, Platel B, Klijn CJM, de Leeuw FE. Nonlinear temporal dynamics of cerebral small vessel disease: The RUN DMC study.
Neurology. 2017 Oct 10;89(15):1569-1577. doi: 10.1212/WNL.0000000000004490. Epub 2017 Sep 6.

OBJECTIVE: To investigate the temporal dynamics of cerebral small vessel disease (SVD) by 3 consecutive assessments over a period of 9 years, distinguishing progression from regression.
METHODS: Changes in SVD markers of 276 participants of the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) cohort were assessed at 3 time points over 9 years. We assessed white matter hyperintensities (WMH) volume by semiautomatic segmentation and rated lacunes and microbleeds manually. We categorized baseline WMH severity as mild, moderate, or severe according to the modified Fazekas scale. We performed mixed-effects regression analysis including a quadratic term for increasing age.
RESULTS: Mean WMH progression over 9 years was 4.7 mL (0.54 mL/y; interquartile range 0.95-5.5 mL), 20.3% of patients had incident lacunes (2.3%/y), and 18.9% had incident microbleeds (2.2%/y). WMH volume declined in 9.4% of the participants during the first follow-up interval, but only for 1 participant (0.4%) throughout the whole follow-up. Lacunes disappeared in 3.6% and microbleeds in 5.7% of the participants. WMH progression accelerated over time: including a quadratic term for increasing age during follow-up significantly improved the model ($p < 0.001$). SVD progression was predominantly seen in participants with moderate to severe WMH at baseline compared to those with mild WMH (odds ratio [OR] 35.5, 95% confidence interval [CI] 15.8-80.0, $p < 0.001$ for WMH progression; OR 5.7, 95% CI 2.8-11.2, $p < 0.001$ for incident lacunes; and OR 2.9, 95% CI 1.4-5.9, $p = 0.003$ for incident microbleeds).
CONCLUSIONS: SVD progression is nonlinear, accelerating over time, and a highly dynamic process, with progression interrupted by reduction in some, in a population that on average shows progression.

PMID: 28880144

van Marum RJ. [Periodical medication review: bigger and better?].
Ned Tijdschr Geneeskd. 2017;161:D1772. Dutch.

The Netherlands' practice guideline 'Polypharmacy in older people' (2012) proposed selecting patients who would benefit from a periodical medication review. The guideline committee made it clear that firm evidence supporting selection was lacking, and recent studies evaluating the effects of medication review on relevant patient-related outcomes have failed to show a positive effect on almost any of these outcomes. Regulatory authorities have advised expanding the target population for medication review. We have to conclude, however, that rather than implementing medication reviews across a broad population of older people, many with a low risk of adverse events, it may be more cost-effective to limit this potentially useful but time-consuming intervention to a more select population who would benefit the most from it.

PMID 28881053

Eijsvoogel NB, Hollegien MI, Bok LA, Derksen-Lubsen G, Dikken FPJ, **Leenders ACAP**, Pijning A, Post EDM, Wojciechowski M, Schmitz R, **Hilbink M, de Vries E**. Lower percentage of allergic sensitization in children with Down syndrome.
Pediatr Allergy Immunol. 2017 Dec;28(8):852-857. doi: 10.1111/pai.12796. Epub 2017 Oct 3.
No abstract available.

PMID: 28890412

Roerdink RL, Dietvorst M, **van der Zwaard B**, van der Worp H, Zwerver J. Complications of extracorporeal shockwave therapy in plantar fasciitis: Systematic review.
Int J Surg. 2017 Oct;46:133-145. doi: 10.1016/j.ijsu.2017.08.587. Epub 2017 Sep 7. Review.

BACKGROUND: Extracorporeal shockwave therapy (ESWT) seems to be an effective treatment for plantar fasciitis (PF) and is assumed to be safe. No systematic reviews have been published that specifically studied the complications and side effects of ESWT in treating PF. Aim of this systematic review is therefore to evaluate the complications and side effects of ESWT in order to determine whether ESWT is a safe treatment for PF.
METHODS: For this systematic review the databases PubMed, MEDLINE, Cochrane and Embase were used to search for relevant literature between 1 January 2005 and 1 January 2017. PRISMA guidelines were followed.
RESULTS: Thirty-nine studies were included for this review, representing 2493 patients (2697 heels) who received between 6424 and 6497 ESWT treatment sessions, with an energy flux density between 0.01 mJ/mm2 and 0.64 mJ/mm2 and a frequency of 1000-3800 SWs. Average follow-up was 14.7 months (range: 24 h - 6 years). Two complications occurred: precordial pain and a superficial skin infection after regional anaesthesia. Accordingly, 225 patients reported pain during treatment and 247 reported transient red skin after treatment. Transient pain after treatment, dysesthesia, swelling, ecchymosis and/or petechiae, severe headache, bruising and a throbbing sensation were also reported.
CONCLUSION: ESWT is likely a safe treatment for PF. No complications are expected at one-year follow-up. However, according to the current literature long-term complications are unknown. Better descriptions of treatment protocols, patient characteristics and registration of complications and side effects, especially pain during treatment, are recommended.

PMID: 29891435

Strijbos RM, Hinnen JW, van den Haak RFF, Verhoeven BAN, **Koning OHJ**. Inadequate Health Literacy in Patients with Arterial Vascular Disease.
Eur J Vasc Endovasc Surg. 2018 Aug;56(2):239-245. doi: 10.1016/j.ejvs.2018.04.015.

OBJECTIVE: The aim was to identify the prevalence of inadequate health literacy in patients with arterial vascular disease. This was a cross sectional study.
METHODS: Patients with arterial vascular disease visiting the outpatient clinic between January 5, 2015 and December 28, 2016, were randomly included and screened for inadequate health literacy with the Newest Vital Sign-Dutch (NVS-D), a validated health literacy assessment measure. A score of <4 out of six identified individuals with inadequate health literacy. Age, gender, highest education level, and reason for consultation were also registered. Data analysis was performed using Student's t-test or the Mann-Whitney U test and chi-square test. Logistic regression with backward elimination was applied to identify independent predictors.
RESULTS: A total of 202 patients were included. The mean NVS-D score was 1.91 (SD ± 1.948, median 1). The prevalence of inadequate health literacy was 76.7%. A significantly higher prevalence of inadequate health literacy was found in patients ≥65 years ($p < .001$) and patients with a lower education level ($p < .001$). No significant difference was found between female/male patients ($p = .056$), nor between participants with peripheral arterial occlusive disease and abdominal aortic aneurysm ($p = .116$). Age (OR 1.060; 95% CI 1.017-1.104; $p = .005$) and education level (OR 0.164; 95% CI 0.078-0.346; $p < .001$) were identified as independent predictors of inadequate health literacy.
CONCLUSION: This study shows a prevalence of inadequate health literacy of 76.7% in patients with arterial vascular disease, with a significantly higher prevalence in patients ≥ 65 years and patients with a lower education level. The high prevalence of inadequate health literacy should be considered when information is provided, and suggests the need to further investigate the best methods to convey medical information to this group of vulnerable patients.

PMID:28892412
Lam YL, De Maeseneer M, Lawson JL, De Borst GJ, **Boersma D**. Expert review on the VenaSeal® system for endovenous cyano-acrylate adhesive ablation of incompetent saphenous trunks in patients with varicose veins. Expert Rev Med Devices. 2017 Oct;14(10):755-762. doi: 10.1080/17434440.2017.1378093.
Trefwoorden: VenaSeal; non tumescent; saphenous; varicose veins; venous

The treatment of incompetent truncal veins has been innovated by the introduction of minimally invasive non-thermal non-tumescent (NTNT) techniques. One of these consists of the use of cyanoacrylate glue to occlude the vein lumen by means of the VenaSeal device. Areas covered: This expert-review aims to evaluate NTNT ablation of incompetent saphenous trunks using the VenaSeal device. Expertcommentary: Cyanoacrylate adhesive embolization of incompetent truncal veins using the VenaSeal device is a safe and efficacious innovative technique. Further studies are needed to evaluate anatomical and clinical outcomes at long term.

PMID: 28895176
Meuwese CL, Boulaksil M, **van Dijk J, Polad J, Meijburg HW**. Reply to "Why do you not call the condition takotsubo syndrome triggered by acute coronary ischemia?"
Echocardiography. 2017 Oct;34(10):1554. doi: 10.1111/echo.13696. Epub 2017 Sep 12.
No abstract available.

PMID: 28914211
Pleunis N, Breunis WB, Merks JHM, Bouwma AE, **van der Steeg JW**. [A toddler with a vaginal mass and blood loss; the rhabdomyosarcoma].
Ned Tijdschr Geneeskd. 2017;161:D1674. Dutch.

BACKGROUND: The differential diagnosis of vaginal blood loss in childhood is broad, and includes irritation of the mucous membranes, trauma, tumours, foreign bodies and sexual abuse. Physical and additional examination is often initially difficult; however, prompt detection of a rhabdomyosarcoma, a soft-tissue tumour principally diagnosed in childhood, is vitally important.
CASE DESCRIPTION: A 3-year-old girl with a history of vaginal blood loss and an introital mass was referred to the gynaecologist. Treatment with oestriol and triamcinolone cream did not lead to healing. Pathological examination of a biopsy taken under general anaesthetic indicated an embryonic rhabdomyosarcoma. Chemotherapy, surgical resection and brachytherapy lead to persistent remission of the tumour.
CONCLUSION: Because rhabdomyosarcoma is rare and can present atypically, diagnosis can be delayed. Early recognition is, however, essential and this condition should be placed high in the differential diagnosis by vaginal blood loss or vaginal abnormality in childhood.

PMID: 28931340
Van Susante JLC, Verdonschot N, **Bom LPA**, Tomaszewski P, Campbell P, Ebramzadeh E, Schreurs BW. Lessons learnt from early failure of a patient trial with a polymer-on-polymer resurfacing hip arthroplasty.
Acta Orthop. 2018 Feb;89(1):59-65. doi: 10.1080/17453674.2017.1376526. Epub 2017 Sep 21.

Background and purpose - Hip resurfacing (HR) is a treatment option promoted for hip arthritis in young and active patients. However, adverse reactions to metal are a concern and the search for non-metallic bearing options proceeds. We present the first clinical study performed in patients using a newly developed hydrophilic polymer-on-polymer hip resurfacing device. Patients and methods - After performing extensive hip simulator tests, biocompatibility testing and animal tests (ISO 14242-1,3; 10993-3,4,5,10,11), approval was obtained from the IRB committee to enroll 15 patients in the first clinical study in humans using this experimental polymer-on-polymer hip resurfacing device. All surgeries were done by 2 experienced hip resurfacing surgeons. Clinical scores and standard radiographs as well as routine MRIs were obtained at regular intervals. Results - The surgical technique proved feasible with successful implantation of the new device using PMMA cement fixation on both sides without complications. Postoperative imaging revealed a well-positioned and well-fixed polymer resurfacing hip arthroplasty in all 4 initial cases. All 4 patients were free of pain and had good function for the first 2 months. However, in all 4 cases early cup loosening occurred between 8 and 11 weeks after surgery, necessitating immediate closure of the study. All 4 patients had a reoperation and were revised to a conventional THA. Retrieval analyses confirmed early cup loosening at the implant-cement interface in all 4 cases. The femoral components remained well attached to the cement. The periprosthetic tissues showed only small amounts of polymeric wear debris and there was only a very mild inflammatory reaction to this. Interpretation - Early cup loosening mandated a premature arrest of this study. After additional laboratory testing this failure mode was found to be the result of a small, yet measurable contraction in the cup

size after exposing these implants to biological fluid divalent ion fluctuations in vivo. Currently used preclinical tests had failed to detect this failure mechanism. Modification of the polymer is essential to overcome these problems and before the potential of a polymer-on-polymer resurfacing arthroplasty may be further evaluated in patients.

PMID: 28956088

Smit R, van Marum RJ, Péquériaux NC, Hollander DA, Bleeker MWP, Latify Y, **Hermens WA**, Derijks HJ. Prevalence of correct anti-Xa levels in renally impaired patients who are on therapeutic nadroparin. Eur J Clin Pharmacol. 2018 Jan;74(1):139-140. doi: 10.1007/s00228-017-2339-7. Epub 2017 Sep 27.
No abstract available.

PMID: 28968978

Bosch LJW, Trooskens G, Snaebjornsson P, Coupé VMH, Mongera S, Haan JC, Richman SD, Koopman M, **Tol J**, de Meyer T, Louwagie J, Dehaspe L, van Grieken NCT, Ylstra B, Verheul HMW, van Engeland M, Nagtegaal ID, Herman JG, Quirke P, Seymour MT, Punt CJA, van Criekinge W, Carvalho B, Meijer GA. Decoy receptor 1 (DCR1) promoter hypermethylation and response to irinotecan in metastatic colorectal cancer.
Oncotarget. 2017 Jun 27;8(38):63140-63154.
Trefwoorden: darmkanker, irinotecan

Diversity in colorectal cancer biology is associated with variable responses to standard chemotherapy. We aimed to identify and validate DNA hypermethylated genes as predictive biomarkers for irinotecan treatment of metastatic CRC patients. Candidate genes were selected from 389 genes involved in DNA Damage Repair by correlation analyses between gene methylation status and drug response in 32 cell lines. A large series of samples (n=818) from two phase III clinical trials was used to evaluate these candidate genes by correlating methylation status to progression-free survival after treatment with first-line single-agent fluorouracil (Capecitabine or 5-fluorouracil) or combination chemotherapy (Capecitabine or 5-fluorouracil plus irinotecan (CAPIRI/FOLFIRI)). In the discovery (n=185) and initial validation set (n=166), patients with methylated Decoy Receptor 1 (DCR1) did not benefit from CAPIRI over Capecitabine treatment (discovery set: HR=1.2 (95%CI 0.7-1.9, p=0.6), validation set: HR=0.9 (95%CI 0.6-1.4, p=0.5)), whereas patients with unmethylated DCR1 did (discovery set: HR=0.4 (95%CI 0.3-0.6, p=0.00001), validation set: HR=0.5 (95%CI 0.3-0.7, p=0.0008)). These results could not be replicated in the external data set (n=467), where a similar effect size was found in patients with methylated and unmethylated DCR1 for FOLFIRI over 5FU treatment (methylated DCR1: HR=0.7 (95%CI 0.5-0.9, p=0.01), unmethylated DCR1: HR=0.8 (95%CI 0.6-1.2, p=0.4)). In conclusion, DCR1 promoter hypermethylation status is a potential predictive biomarker for response to treatment with irinotecan, when combined with capecitabine. This finding could not be replicated in an external validation set, in which irinotecan was combined with 5FU. These results underline the challenge and importance of extensive clinical evaluation of candidate biomarkers in multiple trials.

PMID:28971733

Witte ME, Zeebregts CJ, de Borst GJ, Reijnen M, **Boersma D**. Reply to: Letter to Editor re: "Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review" - MOCA data reporting needs to be tighter and standardized!
Phlebology. 2017 Dec;32(10):682-683. doi: 10.1177/0268355517734953. Epub 2017 Oct 3.
No abstract available.

PMID: 28984901

Janssen LMA, Macken T, Creemers MCW, Pruijt JFM, Eijk JJJ, de Vries E. Truly selective primary IgM deficiency is probably very rare.
Clin Exp Immunol. 2018 Feb;191(2):203-211. doi: 10.1111/cei.13065. Epub 2017 Oct 27. Review.
Trefwoorden: IgM deficientie

Isolated decreased serum-immunoglobulin (Ig)M has been associated with severe and/or recurrent infections, atopy and autoimmunity. However, the reported high prevalence of clinical problems in IgM-deficient patients may reflect the skewed tertiary centre population studied so far. Also, many papers on IgM deficiency have included patients with more abnormalities than simply IgM-deficiency. We studied truly selective primary IgM deficiency according to the diagnostic criteria of the European Society for Immunodeficiencies (ESID) (true sIgMdef)

by reviewing the literature (261 patients with primary decreased serum-IgM in 46 papers) and analysing retrospectively all patients with decreased serum-IgM in a large teaching hospital in 's-Hertogenbosch, the Netherlands [1 July 2005-23 March 2016; n = 8049 IgM < 0·4 g/l; n = 2064 solitary (IgG+IgA normal/IgM < age-matched reference)]. A total of 359 of 2064 (17%) cases from our cohort had primary isolated decreased serum-IgM, proven persistent in 45 of 359 (13%) cases; their medical charts were reviewed. Our main finding is that true sIgMdef is probably very rare. Only six of 261 (2%) literature cases and three of 45 (7%) cases from our cohort fulfilled the ESID criteria completely; 63 of 261 (24%) literature cases also had other immunological abnormalities and fulfilled the criteria for unclassified antibody deficiencies (unPAD) instead. The diagnosis was often uncertain (possible sIgMdef): data on IgG subclasses and/or vaccination responses were lacking in 192 of 261 (74%) literature cases and 42 of 45 (93%) cases from our cohort. Our results also illustrate the clinical challenge of determining the relevance of a serum sample with decreased IgM; a larger cohort of true sIgMdef patients is needed to explore fully its clinical consequences. The ESID online Registry would be a useful tool for this.

PMID: 28985255

Schrijver EJM, de Vries OJ, van de Ven PM, Bet PM, Kamper AM, Diepeveen SHA, **van Marum RJ, van Strien AM**, Anten S, Lagaay AM, Boelaarts L, Bloemers FW, Kramer MHH, Nanayakkara PWB. Haloperidol versus placebo for delirium prevention in acutely hospitalised older at risk patients: a multi-centre double-blind randomised controlled clinical trial. Age Ageing. 2018 Jan 1;47(1):48-55. doi: 10.1093/ageing/afx124.

BACKGROUND: because the few randomised placebo-controlled trials investigating the potential role for prophylactic haloperidol in delirium prevention have focused on specific surgical populations, we investigated its efficacy and safety in acutely hospitalised older patients.
METHODS: this multi-centre, double-blind, stratified, block randomised, placebo-controlled trial was conducted at six Dutch hospitals. Patients age ≥70 years, acutely admitted through the emergency department for general medicine or surgical specialties and at risk for delirium were randomised (n = 245) to haloperidol or placebo 1 mg orally twice-daily (maximum of 14 doses) on top of standard nonpharmacological prevention strategies. The primary outcome was delirium incidence. Other endpoints included delirium severity and duration, drug safety and clinical outcomes.
RESULTS: intention-to-treat analysis included 242 participants (calculated sample size n = 390, statistical power of current sample 59%) allocated to haloperidol (n = 118) or placebo (n = 124). In the haloperidol and placebo group, delirium incidence was 19.5 versus 14.5% (OR 1.43, 95% CI 0.72 to 2.78); median (IQR) delirium duration 4 (2, 5) versus 3 (1, 6) days (P = 0.366); maximum DRS-R-98 score 16 (9.8, 19.5) versus 10 (5.5, 22.5) (P = 0.549; 53.7% missing data); hospital LOS 7 (4, 10.3) versus 7 (5, 11.8) days (P = 0.343); 3-month mortality 9.9 versus 12.5% (OR 0.77, 95% CI 0.34 to 1.75), respectively. No treatment-limiting side effects were noted.
CONCLUSIONS: prophylactic low-dose oral haloperidol did not reduce delirium incidence in acutely hospitalised older patients. Therefore, prophylactic use of haloperidol in this population is not recommended.

PMID: 28991087

van Iersel JJ, Formijne Jonkers HA, Paulides TJC, Verheijen PM, **Draaisma WA**, Consten ECJ, Broeders IAMJ. Robot-Assisted Ventral Mesh Rectopexy for Rectal Prolapse: A 5-Year Experience at a Tertiary Referral Center. Dis Colon Rectum. 2017 Nov;60(11):1215-1223. doi: 10.1097/DCR.0000000000000895.
Trefwoorden: Rectum prolaps, Robot Chirurgie

BACKGROUND: Laparoscopic ventral mesh rectopexy is being increasingly performed internationally to treat rectal prolapse syndromes. Robotic assistance appears advantageous for this procedure, but literature regarding robot-assisted ventral mesh rectopexy is limited.
OBJECTIVE: The primary objective of this study was to assess the safety and effectiveness of robot-assisted ventral mesh rectopexy in the largest consecutive series of patients to date.
DESIGN: This study is a retrospective cross-sectional analysis of prospectively collected data.
SETTINGS: The study was conducted in a tertiary referral center.
PATIENTS: All of the patients undergoing robot-assisted ventral mesh rectopexy for rectal prolapse syndromes between 2010 and 2015 were evaluated.
MAIN OUTCOME MEASURES: Preoperative and postoperative (mesh and nonmesh) morbidity and functional outcome were analyzed. The actuarial recurrence rates were calculated using the Kaplan-Meier method.
RESULTS: A total of 258 patients underwent robot-assisted ventral mesh rectopexy (mean ± SD follow-up = 23.5 ± 21.8 mo; range, 0.2 -

65.1 mo). There were no conversions and only 5 intraoperative complications (1.9%). Mortality (0.4%) and major (1.9%) and minor (<30 d) early morbidity (7.0%) were acceptably low. Only 1 (1.3%) mesh-related complication (asymptomatic vaginal mesh erosion) was observed. A significant improvement in obstructed defecation (78.6%) and fecal incontinence (63.7%) were achieved for patients (both p < 0.0005). At final follow-up, a new onset of fecal incontinence and obstructed defecation was induced or worsened in 3.9% and 0.4%. The actuarial 5-year external rectal prolapse and internal rectal prolapse recurrence rates were 12.9% and 10.4%.
LIMITATIONS: This was a retrospective study including patients with minimal follow-up. No validated scores were used to assess function. The study was monocentric, and there was no control group.
CONCLUSIONS: Robot-assisted ventral mesh rectopexy is a safe and effective technique to treat rectal prolapse syndromes, providing an acceptable recurrence rate and good symptomatic relief with minimal morbidity. See Video Abstract at http://links.lww.com/DCR/A427.

PMID:29031778

Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, Kroep JR, De Graaf H, Honkoop AH, Erdkamp FLG, van den Berkmortel FWPJ, de Boer M, de Roos WK, Linn SC, Imholz ALT, Seynaeve CM; **Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators. Collaborators**: Kitzen JJEM, Strobbe LJA, Kouwenhoven EA, van Dalen T, van Overbeeke AJ, Nuytinck JKS, Arntz IE, Blaisse RJB, Stockmann HBAC, Nijhuis PHA, Veldhuis GJ, Mastboom WJB, van Riel JMGH, van Dam JH, den Boer MO, Agterof MJ, de Roos MAJ, Roumen RMH, van der Hoeven JJM, Beeker A, Koelemij R, van Bochove A, Madretsma GS, Siemerink EJM, Guicherit OR, Vos AH, Nieuwenhuijzen GAP, Kehrer DFS, Valster FAA, Tanis BC, van Voorthuizen T, van der Velden AMT, Hellingman RA, Vree R, van Rossum-Schornagel Q, Meerum Terwogt JM, van Leeuwen-Breuk WG, Haasjes JG, Davidis-van Schoonhoven MA, Vriens EJC, Jagers M, Muller EW, Schiphorst PPJBM, van Groeningen CJ, van Dijk MA, Janssens-van Vliet E, Schepers EEM, Merkus JWS, van Diemen NGJ, van Doorn RC, **Bosscha K**, den Toom R, van der Velden PC, van Rossum CTAM, Oosterkamp HM, van Hillegersberg R, Jas B, Weernink EEM, Ketel JMA, Jansen JJ, Maring JK, Govaert MJPM, Kamm YJL, Vleugel MM, Hovenga S, de Boer J, Potthoff H, Sommeijer DW, van Dulken EJ. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol. 2017 Nov;18(11):1502-1511. doi: 10.1016/S1470-2045(17)30600-9. Epub 2017 Oct 12. Erratum in: Lancet Oncol. 2017 Nov;18(11):e642. Correction to Lancet Oncol 2017; 18: 1502-11. [Lancet Oncol. 2017]

BACKGROUND:The effect of extended adjuvant aromatase inhibition in hormone receptor-positive breast cancer after sequential endocrinetherapy of tamoxifen followed by an aromatase inhibitor for a 5-year treatment period still needs clarification. To address this issue, we began the DATA study to assess different durations of anastrozole therapy after tamoxifen.
METHODS:DATA was a prospective, randomised, open-label, multicentre, phase 3 study done in 79 hospitals in the Netherlands. We randomly assigned postmenopausal women with hormone receptor-positive early breast cancer with no signs of disease recurrence after 2-3years of adjuvant tamoxifen to either 3 or 6 years of anastrozole treatment (1 mg orally once a day) in a 1:1 ratio. We used TENALEA (Trans European Network for Clinical Trials Services) for the randomisation procedure. Stratification factors were nodal status, hormone receptor status, HER2 status, and tamoxifen treatment duration. The primary study endpoint of this analysis was disease-free survival starting beyond 3 years after randomisation (adapted disease-free survival). Here we report the final analysis from the DATA trial, which is registered with ClinicalTrials.gov, number NCT00301457.
FINDINGS:Between June 28, 2006, and Aug 10, 2009, we screened 1912 patients of whom 955 were assigned to the 3-year group and 957 to the 6-year anastrozole treatment group. 1860 patients were eligible (931 in the 6-year group and 929 in the 3-year group) and 1660 were disease free 3 years after randomisation. The 5-year adapted disease-free survival was 83·1% (95% CI 80·0-86·3) in the 6-year group and 79·4% (76·1-82·8) in the 3-year group (hazard ratio [HR] 0·79 [95% CI 0·62-1·02]; p=0·066). Patients in the 6-year treatment group had more adverse events than those in the 3-year treatment group, including all-grade arthralgia or myalgia (478 [58%] of 827 in the 6-year treatment group vs 438 [53%] of 833 in the 3-year treatment group) and osteopenia or osteoporosis (173 [21%] vs 137 [16%]).
INTERPRETATION:We cannot recommend the use of extended adjuvant aromatase inhibition after 5 years of sequential endocrine therapyin all postmenopausal women with hormone receptor-positive breast cancer.
FUNDING:AstraZeneca.

PMID: 29033560

Duenk RG, Verhagen C, Bronkhorst EM, van Mierlo P, **Broeders M**, Collard SM, Dekhuijzen P, Vissers K, Heijdra Y, Engels Y. Proactive palliative care for patients with COPD (PROLONG): a pragmatic cluster controlled trial.
Int J Chron Obstruct Pulmon Dis. 2017 Sep 28;12:2795-2806. doi: 10.2147/COPD.S141974. eCollection 2017.

BACKGROUND AND AIM: Patients with advanced chronic obstructive pulmonary disease (COPD) have poor quality of life. The aim of this study was to assess the effects of proactive palliative care on the well-being of these patients.
TRIAL REGISTRATION: This trial is registered with the Netherlands Trial Register, NTR4037.
PATIENTS AND METHODS: A pragmatic cluster controlled trial (quasi-experimental design) was performed with hospitals as cluster (three intervention and three control) and a pretrial assessment was performed. Hospitals were selected for the intervention group based on the presence of a specialized palliative care team (SPCT). To control for confounders, a pretrial assessment was performed in which hospitals were compared on baseline characteristics. Patients with COPD with poor prognosis were recruited during hospitalization for acute exacerbation. All patients received usual care while patients in the intervention group received additional proactive palliative care in monthly meetings with an SPCT. Our primary outcome was change in quality of life score after 3 months, which was measured using the St George Respiratory Questionnaire (SGRQ). Secondary outcomes were, among others, quality of life at 6, 9 and 12 months; readmissions: survival; and having made advance care planning (ACP) choices. All analyses were performed following the principle of intention to treat.
RESULTS: During the year 2014, 228 patients (90 intervention and 138 control) were recruited and at 3 months, 163 patients (67 intervention and 96 control) completed the SGRQ. There was no significant difference in change scores of the SGRQ total at 3 months between groups (-0.79 [95% CI, -4.61 to 3.34], p=0.70). However, patients who received proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months (-6.22 [-11.73 to -0.71], p=0.04) and had more often made ACP choices (adjusted odds ratio 3.26 [1.49-7.14], p=0.003). Other secondary outcomes were not significantly different.
CONCLUSION: Proactive palliative care did not improve the overall quality of life of patients with COPD. However, patients more often made ACP choices which may lead to better quality of care toward the end of life.

PMID: 29040457

van Roeden SE, Bleeker-Rovers CP, de Regt MJA, Kampschreur LM, Hoepelman AIM, **Wever PC**, Oosterheert JJ. Treatment of chronic Q fever: clinical efficacy and toxicity of antibiotic regimens. Clin Infect Dis 2018;66:719-726.

Background: Evidence on the effectiveness of first-line treatment for chronic Q fever, tetracyclines (TET) plus hydroxychloroquine (HCQ), and potential alternatives is scarce.
Methods: We performed a retrospective, observational cohort study to assess efficacy of treatment with TET plus quinolones (QNL), TET plus QNL plus HCQ, QNL monotherapy, or TET monotherapy compared to TET plus HCQ in chronic Q fever patients. We used a time-dependent Cox proportional hazards model to assess our primary (all-cause mortality) and secondary outcomes (first disease-related event and therapy failure).
Results: We assessed 322 chronic Q fever patients; 276 (86%) received antibiotics. Compared to TET plus HCQ (n = 254; 92%), treatment with TET plus QNL (n = 49; 17%), TET plus QNL plus HCQ (n = 29, 10%), QNL monotherapy (n = 93; 34%), or TET monotherapy (n = 54; 20%) were not associated with primary or secondary outcomes. QNL and TET monotherapies were frequently discontinued due to insufficient clinical response (n = 27, 29% and n = 32, 59%). TET plus HCQ, TET plus QNL, and TET plus QNL plus HCQ were most frequently discontinued due to side effects (n = 110, 43%; n = 13, 27%; and n = 12, 41%).
Conclusions: Treatment of chronic Q fever with TET plus QNL appears to be a safe alternative for TET plus HCQ, for example, if TET plus HCQ cannot be tolerated due to side effects. Treatment with TET plus QNL plus HCQ was not superior to treatment with TET plus HCQ, although this may be caused by confounding by indication. Treatment with TET or QNL monotherapy should be avoided; switches due to subjective, insufficient clinical response were frequently observed.

PMID: 29049654

Caram-Deelder C, Kreuger AL, Evers D, de Vooght KMK, van de Kerkhof D, Visser O, **Péquériaux NCV**, Hudig F, Zwaginga JJ, van der Bom JG, Middelburg RA. Association of Blood Transfusion From Female Donors With and Without a History of Pregnancy With Mortality Among Male and Female Transfusion Recipients. JAMA. 2017Oct 17;318(15):1471-1478. doi: 10.1001/jama.2017.14825. Erratum in: JAMA. 2018 Feb 20;319(7):724.

Importance: Transfusion of red blood cells from female donors has been associated with increased mortality in male recipients.
Objective: To quantify the association between red blood cell transfusion from female donors with and without a history of pregnancy and mortality of red blood cell recipients.
Design, Setting, and Participants: Retrospective cohort study of first-time transfusion recipients at 6 major Dutch hospitals enrolled from May

30, 2005, to September 1, 2015; the final follow-up date was September 1, 2015. The primary analysis was the no-donor-mixture cohort (ie, either all red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy, or all exclusively from female donors with a history of pregnancy). The association between mortality and exposure to transfusions from ever-pregnant or never-pregnant female donors was analyzed using life tables and time-varying Cox proportional hazards models.
Exposures: Red blood cell transfusions from ever-pregnant or never-pregnant female donors, compared with red blood cell transfusions from male donors.
Main Outcomes and Measures: All-cause mortality during follow-up.
Results: The cohort for the primary analyses consisted of 31 118 patients (median age, 65 [interquartile range, 42-77] years; 52% female) who received 59 320 red blood cell transfusions exclusively from 1 of 3 types of donors (88% male; 6% ever-pregnant female; and 6% never-pregnant female). The number of deaths in this cohort was 3969 (13% mortality). For male recipients of red blood cell transfusions, all-cause mortality rates after a red blood cell transfusion from an ever-pregnant female donor vs male donor were 101 vs 80 deaths per 1000 person-years (time-dependent "per transfusion" hazard ratio [HR] for death, 1.13 [95% CI, 1.01-1.26]). For receipt of transfusion from a never-pregnant female donor vs male donor, mortality rates were 78 vs 80 deaths per 1000 person-years (HR, 0.93 [95% CI, 0.81-1.06]). Among female recipients of red blood cell transfusions, mortality rates for an ever-pregnant female donor vs male donor were 74 vs 62 per 1000 person-years (HR, 0.99 [95% CI, 0.87 to 1.13]); for a never-pregnant female donor vs male donor, mortality rates were 74 vs 62 per 1000 person-years (HR, 1.01 [95% CI, 0.88-1.15]).
Conclusions and Relevance: Among patients who received red blood cell transfusions, receipt of a transfusion from an ever-pregnant female donor, compared with a male donor, was associated with increased all-cause mortality among male recipients but not among female recipients. Transfusions from never-pregnant female donors were not associated with increased mortality among male or female recipients. Further research is needed to replicate these findings, determine their clinical significance, and identify the underlying mechanism.

PMID: 29061270

van Schaik TG, Yeung KK, Verhagen HJ, de Bruin JL, van Sambeek MRHM, Balm R, Zeebregts CJ, van Herwaarden JA, Blankensteijn JD; **DREAM trial participants (Rutten MJ)**. Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms.
J Vasc Surg. 2017 Nov;66(5):1379-1389. doi: 10.1016/j.jvs.2017.05.122. Erratum in: J Vasc Surg. 2018 Feb;67(2):683.

OBJECTIVE: Randomized trials have shown an initial survival benefit of endovascular over conventional open abdominal aortic aneurysm repair but no long-term difference up to 6 years after repair. Longer follow-up may be required to demonstrate the cumulative negative impact on survival of higher reintervention rates associated with endovascular repair.
METHODS: We updated the results of the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, a multicenter, randomized controlled trial comparing open with endovascular aneurysm repair, up to 15 years of follow-up. Survival and reinterventions were analyzed on an intention-to-treat basis. Causes of death and secondary interventions were compared by use of an events per person-year analysis.
RESULTS: There were 178 patients randomized to open and 173 to endovascular repair. Twelve years after randomization, the cumulative overall survival rates were 42.2% for open and 38.5% for endovascular repair, for a difference of 3.7 percentage points (95% confidence interval, -6.7 to 14.1; P = .48). The cumulative rates of freedom from reintervention were 78.9% for open repair and 62.2% for endovascular repair, for a difference of 16.7 percentage points (95% confidence interval, 5.8-27.6; P = .01). No differences were observed in causes of death. Cardiovascular and malignant disease account for the majority of deaths after prolonged follow-up.
CONCLUSIONS: During 12 years of follow-up, there was no survival difference between patients who underwent open or endovascular abdominal aortic aneurysm repair, despite a continuously increasing number of reinterventions in the endovascular repair group. Endograft durability and the need for continued endograft surveillance remain key issues.
TRIAL REGISTRATION: ClinicalTrials.gov NCT00421330.

PMID: 29066508

Derks JL, Leblay N, Thunnissen E, **van Suylen RJ**, den Bakker M, Groen HJM, Smit EF, Damhuis R, van den Broek EC, Charbrier A, Foll M, McKay JD, Fernandez-Cuesta L, Speel EM, Dingemans AC; PALGA-Group. Molecular Subtypes of Pulmonary Large-cell Neuroendocrine Carcinoma Predict Chemotherapy Treatment Outcome.
Clin Cancer Res. 2018 Jan 1;24(1):33-42. doi: 10.1158/1078-0432.CCR-17-1921. Epub 2017 Oct 24.

Purpose: Previous genomic studies have identified two mutually exclusive molecular subtypes of large-cell neuroendocrine carcinoma (LCNEC): the RB1 mutated (mostly comutated with TP53) and the RB1 wild-type groups. We assessed whether these subtypes have a predictive value on chemotherapy outcome.Experimental Design: Clinical data and tumor specimens were retrospectively obtained from the Netherlands

Cancer Registry and Pathology Registry. Panel-consensus pathology revision confirmed the diagnosis of LCNEC in 148 of 232 cases. Next-generation sequencing (NGS) for TP53, RB1, STK11, and KEAP1 genes, as well as IHC for RB1 and P16 was performed on 79 and 109 cases, respectively, and correlated with overall survival (OS) and progression-free survival (PFS), stratifying for non-small cell lung cancer type chemotherapy including platinum + gemcitabine or taxanes (NSCLC-GEM/TAX) and platinum-etoposide (SCLC-PE).Results:RB1 mutation and protein loss were detected in 47% (n = 37) and 72% (n = 78) of the cases, respectively. Patients with RB1 wild-type LCNEC treated with NSCLC-GEM/TAX had a significantly longer OS [9.6; 95% confidence interval (CI), 7.7-11.6 months] than those treated with SCLC-PE [5.8 (5.5-6.1); P = 0.026]. Similar results were obtained for patients expressing RB1 in their tumors (P = 0.001). RB1 staining or P16 loss showed similar results. The same outcome for chemotherapy treatment was observed in LCNEC tumors harboring an RB1 mutation or lost RB1 protein.Conclusions: Patients with LCNEC tumors that carry a wild-type RB1 gene or express the RB1 protein do better with NSCLC-GEM/TAX treatment than with SCLC-PE chemotherapy. However, no difference was observed for RB1 mutated or with lost protein expression. Clin Cancer Res; 24(1); 33-42. ©2017 AACR.

PMID: 29073323

Römkens TEH, Te Morsche R, Peters W, Burger DM, Hoentjen F, Drenth JPH. Urinalysis of MMX-mesalazine as a tool to monitor 5-ASA adherence in daily IBD practice.
Br J Clin Pharmacol. 2018 Mar;84(3):477-481. doi: 10.1111/bcp.13462. Epub 2017 Dec 6.

Adherence is pivotal but challenging in ulcerative colitis (UC) treatment. Many methods to assess adherence are subjective or have limitations. (Nac-)5-aminosalicylic acid (5-ASA) urinalysis by high-performance liquid chromatography (HPLC) seems feasible and reproducible in healthy volunteers. We performed a prospective study in adult quiescent UC patients to evaluate the feasibility of spot (Nac-)5-ASA urinalysis by HPLC to assess adherence in daily inflammatory bowel disease (IBD) care. Twenty-nine patients (51.7% male, mean age 52 ± 11 years) were included (median FU 9 months) and weekly spot urine samples were collected. We found large variation in spot (Nac-)5-ASA urinary excretion that was unrelated to brand, dosing schedule or dosage of 5-ASA. In conclusion, spot (Nac-)5-ASA urinalysis is not applicable to assess 5-ASA adherence in daily IBD care.

PMID: 29074548

Derks J, **van Suylen RJ**, Thunnissen E, den Bakker M, Groen H, Smit E, Damhuis R, van den Broek E, Speel EJ, Dingemans AC. Why we should improve current practice of diagnosing and treating pulmonary large cell neuroendocrine carcinomas in patients with advanced disease.
Eur Respir J. 2017 Oct 26;50(4). pii: 1701658. doi: 10.1183/13993003.01658-2017.
No abstract available.

PMID: 29090466

Caram-Deelder C, van der Bom JG, Putter H, Leyte A, Kerkhof DV, Evers D, Beckers EA, Weerkamp F, Hudig F, Zwaginga JJ, Rondeel JMM, de Vooght KMK, **Péquériaux NCV**, Visser O, Wallis JP, Middelburg RA. Age of platelet concentrates and time to the next transfusion.
Transfusion. 2018 Jan;58(1):121-131. doi:10.1111/trf.14388. Epub 2017 Oct 31.

BACKGROUND: Storage time of platelet (PLT) concentrates has been negatively associated with clinical efficacy outcomes. The aim of this study was to quantify the association between storage time of PLT concentrates and interval to the next PLT transfusion for different types of PLT components, stored for up to 7 days and transfused to transfusion-dependent hematooncology patients with thrombocytopenia.
STUDY DESIGN AND METHODS: From a cohort of patients from 10 major Dutch hospitals, patients were selected whose transfusion patterns were compatible with PLT transfusion dependency due to hematooncologic disease. Mean time to the next transfusion and mean differences in time to the next transfusion for different storage time categories (i.e., fresh, <4 days; intermediate, 4-5 days; and old, >5 days) were estimated, per component type, using multilevel mixed-effects linear models.
RESULTS: Among a cohort of 29,761 patients who received 140,896 PLT transfusions we selected 4441 hematooncology patients who had received 12,724 PLT transfusions during periods of PLT transfusion dependency. Transfusion of fresh, compared to old, buffy coat-derived PLTs in plasma was associated with a delay to the next transfusion of 6.2 hours (95% confidence interval [CI], 4.5-8.0 hr). For buffy coat-derived PLTs in PAS-B and -C this difference was 7.7 hours (95% CI, 2.2-13.3 hr) and 3.9 hours (95% CI, -2.1 to 9.9 hr) while for apheresis PLTs in

plasma it was only 1.8 hours (95% CI, -3.5 to 7.1 hr).
CONCLUSION: Our results indicate that the time to the next transfusion shortens with increasing age of transfused buffy coat-derived PLT concentrates. This association was not observed for apheresis PLTs.

PMID: 29095051

Esmeijer K, Geleijnse JM, Giltay EJ, Stijnen T, Dekker FW, de Fijter JW, Kromhout D, **Hoogeveen EK**. Body-fat indicators and kidney function decline in older post-myocardial infarction patients: The Alpha Omega Cohort Study.
Eur J Prev Cardiol. 2018 Jan;25(1):90-99.

Background Obesity increases risk of hypertension and diabetes, the leading causes of end-stage renal disease. The effect of obesity on kidney function decline in stable post-myocardial infarction patients is poorly documented. This relation was investigated in a large cohort of older post-myocardial infarction patients. Design Data were analysed from 2410 post-myocardial infarction patients in the Alpha Omega Trial, aged 60-80 years receiving optimal pharmacotherapy treatment (79% men, 18% diabetes). Methods Cystatin C based estimated glomerular filtration rate (eGFRcysC) was calculated at baseline and after 41 months, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Obesity was defined as body mass index ≥ 30 kg/m2 and high waist circumference as ≥102 and ≥88 cm for men and women. The relation between body mass index, waist circumference and annual eGFRcysC decline was evaluated by linear regression. Results At baseline, mean (standard deviation) eGFRcysC was 81.5 (19.6) ml/min/1.73 m2, 23% of all patients were obese. After multivariable adjustment, the annual mean (95% confidence interval) eGFRcysC decline in men and women was -1.45 (-1.59 to -1.31) and -0.92 (-1.20 to -0.63) ml/min/1.73 m2, respectively (p = 0.001). Obese versus non-obese patients and patients with high versus normal waist circumference experienced greater annual eGFRcysC decline. Men and women showed an additional annual eGFRcysC decline of -0.35 (-0.56 to -0.14) and -0.21 (-0.55 to 0.14) ml/min/1.73 m2 per 5 kg/m2 body mass index increment (p for interaction 0.3). Conclusions High compared to normal body mass index or waist circumference were associated with more rapid kidney function decline in older stable post-myocardial infarction patients receiving optimal drug therapy.
TRIAL REGISTRATION: ClinicalTrials.gov NCT03192410.

PMID: 29101570

de Lacy FB, **van Laarhoven JJEM**, Pena R, Arroyave MC, Bravo R, Cuatrecasas M, Lacy AM. Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer.
Surg Endosc. 2018 May;32(5):2442-2447. doi: 10.1007/s00464-017-5944-8. Epub 2017 Nov 3.

BACKGROUND: Transanal total mesorectal excision (TaTME) seems to be a valid alternative to the open or laparoscopic TME. Quality of the TME specimen is the most important prognostic factor in rectal cancer. This study shows the pathological results of the largest single-institution series published on TaTME in patients with mid and low rectal cancer.
METHODS: We conducted a retrospective cohort study of all consecutive patients with rectal cancer, treated by TaTME between November 2011 and June 2016. Patient data were prospectively included in a standardized database. Patients with all TNM stages of mid (5-10 cm from the anal verge) and low (0-5 cm from the anal verge) rectal cancer were included.
RESULTS: A total of 186 patients were included. Tumor was in the mid and low rectum in, respectively, 62.9 and 37.1%. Neoadjuvant chemoradiotherapy was given in 62.4%, only radiotherapy in 3.2%, and only chemotherapy in 2.2%. Preoperative staging showed T1 in 3.2%, T2 in 20.4%, T3 in 67.7%, and T4 in 7.5%. Mesorectal resection quality was complete in 95.7% (n = 178), almost complete in 1.6% (n = 3), and incomplete in 1.1% (n = 2). Overall positive CRM (≤ 1 mm) and DRM (≤ 1 mm) were 8.1% (n = 15) and 3.2% (n = 6), respectively. The composite of complete mesorectal excision, negative CRM, and negative DRM was achieved in 88.1% (n = 155) of the patients. The median number of lymph nodes found per specimen was 14.0 (IQR 11-18).
CONCLUSIONS: The present study showed good rates regarding total mesorectal excision, negative circumferential, and distal resection margins. As the specimen quality is a surrogate marker for survival, TaTME can be regarded as a safe method to treat patients with rectal cancer, from an oncological point of view.

PMID:29108721

van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, **Bosscha K**, Bouwense SA, Bruno MJ, **Cappendijk VC**, Consten EC, Dejong CH, van Eijck CH, Erkelens WG, van Goor H, van Grevenstein WMU, Haveman JW, Hofker SH, Jansen JM, Laméris JS, van Lienden KP, Meijssen MA, Mulder CJ, Nieuwenhuijs VB, Poley

JW, Quispel R, de Ridder RJ, Römkens TE, Scheepers JJ, Schepers NJ, Schwartz MP, Seerden T, Spanier BWM, Straathof JWA, Strijker M, Timmer R, Venneman NG, Vleggaar FP, Voermans RP, Witteman BJ, Gooszen HG, Dijkgraaf MG, Fockens P; Dutch Pancreatitis Study Group. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial.
Lancet. 2018 Jan 6;391(10115):51-58. doi: 10.1016/S0140-6736(17)32404-2. Epub 2017 Nov 3.

BACKGROUND:Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up approach in terms of clinical and economic outcomes.
METHODS:In this multicentre, randomised, superiority trial, we recruited adult patients with infected necrotising pancreatitis and an indication for invasive intervention from 19 hospitals in the Netherlands. Patients were randomly assigned to either the endoscopic or the surgical step-up approach. The endoscopic approach consisted of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. The primary endpoint was a composite of major complications or death during 6-month follow-up. Analyses were by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN09186711.
FINDINGS:Between Sept 20, 2011, and Jan 29, 2015, we screened 418 patients with pancreatic or extrapancreatic necrosis, of which 98 patients were enrolled and randomly assigned to the endoscopic step-up approach (n=51) or the surgical step-up approach (n=47). The primary endpoint occurred in 22 (43%) of 51 patients in the endoscopy group and in 21 (45%) of 47 patients in the surgery group (risk ratio [RR] 0·97, 95% CI 0·62-1·51; p=0·88). Mortality did not differ between groups (nine [18%] patients in the endoscopy group vs six [13%] patients in the surgery group; RR 1·38, 95% CI 0·53-3·59, p=0·50), nor did any of the major complications included in the primary endpoint.
INTERPRETATION:In patients with infected necrotising pancreatitis, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The outcome of this trial will probably result in a shift to the endoscopic step-up approach as treatment preference.
FUNDING:The Dutch Digestive Disease Foundation, Fonds NutsOhra, and the Netherlands Organization for Health Research and Development.

PMID: 29121350

van Tilborg TC, Oudshoorn SC, Eijkemans MJC, Mochtar MH, van Golde RJT, Hoek A, Kuchenbecker WKH, Fleischer K, **de Bruin JP**, Groen H, van Wely M, Lambalk CB, Laven JSE, Mol BWJ, Broekmans FJM, Torrance HL; OPTIMIST study group. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis.
Hum Reprod. 2017 Dec 1;32(12):2485-2495. doi: 10.1093/humrep/dex321.

STUDY QUESTION: Is there a difference in live birth rate and/or cost-effectiveness between antral follicle count (AFC)-based individualized FSH dosing or standard FSH dosing in women starting IVF or ICSI treatment?
SUMMARY ANSWER: In women initiating IVF/ICSI, AFC-based individualized FSH dosing does not improve live birth rates or reduce costs as compared to a standard FSH dose.
WHAT IS KNOWN ALREADY: In IVF or ICSI, ovarian reserve testing is often used to adjust the FSH dose in order to normalize ovarian response and optimize live birth rates. However, no robust evidence for the (cost-)effectiveness of this practice exists.
STUDY DESIGN, SIZE, DURATION: Between May 2011 and May 2014 we performed a multicentre prospective cohort study with two embedded RCTs in women scheduled for IVF/ICSI. Based on the AFC, women entered into one of the two RCTs (RCT1: AFC < 11; RCT2: AFC > 15) or the cohort (AFC 11-15). The primary outcome was ongoing pregnancy achieved within 18 months after randomization resulting in a live birth (delivery of at least one live foetus after 24 weeks of gestation). Data from the cohort with weight 0.5 were combined with both RCTs in order to conduct a strategy analysis. Potential half-integer numbers were rounded up. Differences in costs and effects between the two treatment strategies were compared by bootstrapping.
PARTICIPANTS/MATERIALS, SETTING, METHODS: In both RCTs women were randomized to an individualized (RCT1:450/225 IU, RCT2:100 IU) or standard FSH dose (150 IU). Women in the cohort all received the standard dose (150 IU). Anti-Müllerian hormone (AMH) was measured to assess AMH post-hoc as a biomarker to individualize treatment. For RCT1 dose adjustment was allowed in subsequent cycles based on pre-specified criteria in the standard group only. For RCT2 dose adjustment was allowed in subsequent cycles in both groups. Both effectiveness and cost-effectiveness of the strategies were evaluated from an intention-to-treat perspective.
MAIN RESULTS AND THE ROLE OF CHANCE: We included 1515 women, of whom 483 (31.9%) entered the cohort, 511 (33.7%) RCT1 and 521 (34.4%) RCT2. Live births occurred in 420/747 (56.3%) women in the individualized strategy and 447/769 (58.2%) women in the standard strategy (risk difference -0.019 (95% CI, -0.06 to 0.02), P = 0.39; a total of 1516 women due to rounding up the half integer numbers). The

individualized strategy was more expensive (delta costs/woman = €275 (95% CI, 40 to 499)). Individualized dosing reduced the occurrence of mild and moderate ovarian hyperstimulation syndrome (OHSS) and subsequently the costs for management of these OHSS categories (costs saved/woman were €35). The analysis based on AMH as a tool for dose individualization suggested comparable results.
LIMITATIONS, REASONS FOR CAUTION: Despite a training programme, the AFC might have suffered from inter-observer variation. In addition, although strict cancel criteria were provided, selective cancelling in the individualized dose group (for poor response in particular) cannot be excluded as observers were not blinded for the FSH dose and small dose adjustments were allowed in subsequent cycles. However, as both first cycle live birth rates and cumulative live birth rates show no difference between strategies, the open design probably did not mask a potential benefit for the individualized group. Despite increasing consensus on using GnRH antagonist co-treatment in women predicted for a hyper response in particular, GnRH agonists were used in almost 80% of the women in this study. Hence, in those women, the AFC and bloodsampling for the post-hoc AMH analysis were performed during pituitary suppression. As the correlation between AFC and ovarian response is not compromised during GnRH agonist use, this will probably not have influenced classification of response.
WIDER IMPLICATIONS OF THE FINDINGS: Individualized FSH dosing for the IVF/ICSI population as a whole should not be pursued as it does not improve live birth rates and it increases costs. Women scheduled for IVF/ICSI with a regular menstrual cycle are therefore recommended a standard FSH starting dose of 150 IU per day. Still, safety management by individualized dosing in predicted hyper responders is open for further research.
STUDY FUNDING/COMPETING INTEREST(S): This study was funded by The Netherlands Organisation for Health Research and Development (ZonMW number 171102020). AMH measurements were performed free of charge by Roche Diagnostics. TCT, HLT and SCO received an unrestricted personal grant from Merck BV. AH declares that the department of Obstetrics and Gynecology, University Medical Centre Groningen receives an unrestricted research grant from Ferring pharmaceutics BV, The Netherlands. CBL receives grants from Merck, Ferring and Guerbet. BWJM is supported by a NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy for OvsEva, Merck and Guerbet. FJMB receives monetary compensation as a member of the external advisory board for Ferring pharmaceutics BV (the Netherlands) and Merck Serono (the Netherlands) for consultancy work for Gedeon Richter (Belgium) and Roche Diagnostics on automated AMH assay development (Switzerland) and for a research cooperation with Ansh Labs (USA). All other autors have nothing to declare.
TRIAL REGISTRATION NUMBER: Registered at the ICMJE-recognized Dutch Trial Registry (www.trialregister.nl). Registration number: NTR2657.

PMID: 29137111

de Borst MH, Baia LC, **Hoogeveen EK**, Giltay EJ, Navis G, Bakker SJL, Geleijnse JM, Kromhout D, Soedamah-Muthu SS. Effect of Omega-3 Fatty Acid Supplementation on Plasma Fibroblast Growth Factor 23 Levels in Post-Myocardial Infarction Patients with Chronic Kidney Disease: The Alpha Omega Trial.
Nutrients. 2017 Nov 11;9(11).

Fibroblast growth factor 23 (FGF23) is an independent risk factor for cardiovascular mortality in chronic kidney disease. Omega-3 (n-3) fatty acid consumption has been inversely associated with FGF23 levels and with cardiovascular risk. We examined the effect of marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and plant-derived alpha-linolenic acid (ALA) on plasma FGF23 levels in post-myocardial infarction patients with chronic kidney disease. In the randomized double-blind Alpha Omega Trial, 4837 patients with a history of myocardial infarction aged 60-80 years (81% men) were randomized to one of four trial margarines supplemented with a targeted additional intake of 400 mg/day EPA and DHA, 2 g/day ALA, EPA-DHA plus ALA, or placebo for 41 months. In a subcohort of 336 patients with an eGFR < 60 mL/min/1.73 m^2 (creatinine-cystatin C-based CKD-EPI formula), plasma C-terminal FGF23 was measured by ELISA at baseline and end of follow-up. We used analysis of covariance to examine treatment effects on FGF23 levels adjusted for baseline FGF23. Patients consumed 19.8 g margarine/day on average, providing an additional amount of 236 mg/day EPA with 158 mg/day DHA, 1.99 g/day ALA or both, in the active intervention groups. Over 79% of patients were treated with antihypertensive and antithrombotic medication and statins. At baseline, plasma FGF23 was 150 (128 to 172) RU/mL (mean (95% CI)). After 41 months, overall FGF23 levels had increased significantly ($p < 0.0001$) to 212 (183 to 241) RU/mL. Relative to the placebo, the treatment effect of EPA-DHA was indifferent, with a mean change in FGF23 (95% CI) of -17 (-97, 62) RU/mL ($p = 0.7$). Results were similar for ALA (36 (-42, 115) RU/mL) and combined EPA-DHA and ALA (34 (-44, 113) RU/mL). Multivariable adjustment, pooled analyses, and subgroup analyses yielded similar non-significant results. Long-term supplementation with modest quantities of EPA-DHA or ALA does not reduce plasma FGF23 levels when added to cardiovascular medication in post-myocardial patients with chronic kidney disease.

PMID: 29140439

Woestenberg PJ, King AJ, van Benthem BHB, Donken R, Leussink S, van der Klis FRM, de Melker HE, van der Sande MAB, Hoebe CJPA, Bogaards JA; **Medical Microbiological Laboratories and the Public Health Services (Schneeberger PM)**. Bivalent Vaccine Effectiveness Against Type-Specific HPV Positivity: Evidence for Cross-Protection Against Oncogenic Types Among Dutch STI Clinic Visitors.
J Infect Dis. 2018 Jan 4;217(2):213-222. doi: 10.1093/infdis/jix582.

Background: Observational postmarketing studies are important to assess vaccine effectiveness (VE). We estimated VE from the bivalent human papillomavirus (HPV) vaccine against HPV positivity of vaccine and nonvaccine types in a high-risk population.
Methods: We included all vaccine-eligible women from the PASSYON study, a biennial cross-sectional survey in Dutch sexually transmitted infection clinics. Vaginal swabs were analyzed using a polymerase chain reaction-based assay (SPF10-LiPA25) able to detect the 12 high-risk HPV (hrHPV) types 16/18/31/33/35/39/45/51/52/56/58/59. We compared hrHPV positivity between self-reported vaccinated (≥1 dose) and unvaccinated women, and estimated VE by a logistic mixed model.
Results: We included 1087 women of which 53% were hrHPV positive and 60% reported to be vaccinated. The adjusted pooled VE against HPV-16/18 was 89.9% (81.7%-94.4%). Moreover, we calculated significant VE against nonvaccine types HPV-45 (91%), HPV-35 (57%), HPV-31 (50%), and HPV-52 (37%). Among women who were offered vaccination 5/6 years ago, we estimated similar VE against HPV-16/18 (92%) and all hrHPV types (35%) compared to women who were offered vaccination <5 years ago (83% and 33%, respectively).
Conclusion: We demonstrated high VE of the bivalent vaccine against HPV-16/18 and cross-protection against HPV-45/35/31/52. Protection against HPV-16/18 was sustained up to 6 years postvaccination.

PMID: 29142146

Wattjes MP, Wijburg MT, **van Eijk J**, Frequin S, Uitdehaag BMJ, Barkhof F, Warnke C, Killestein J; Dutch-Belgian Natalizumab-Associated PML Study Group. Inflammatory natalizumab-associated PML: baseline characteristics, lesion evolution and relation with PML-IRIS.
J Neurol Neurosurg Psychiatry. 2018 May;89(5):535-541. doi: 10.1136/jnnp-2017-316886. Epub 2017 Nov 15.

BACKGROUND AND OBJECTIVE: Natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) patients may show imaging signs suggestive of inflammation at diagnosis ('inflammatory PML'), reminiscent of PML-immune reconstitution inflammatory syndrome (PML-IRIS). We investigated the imaging characteristics of inflammatory NTZ-PML lesions and PML-IRIS to determine differentiating and overlapping features.
METHODS: We scored the presence, localisation and pattern of imaging characteristics of inflammation on brain MRI scans of inflammatory NTZ-PML patients. The imaging characteristics were followed up until the occurrence of PML-IRIS.
RESULTS: Ten out of the 44 NTZ-PML patients included showed signs suggestive of inflammation at the time of diagnosis. The inflammation pattern at diagnosis was similar to the pattern seen at PML-IRIS, with contrast enhancement representing the most frequent sign of inflammation (90% at diagnosis, 100% at PML-IRIS). However, the severity of inflammation differed, with absence of swelling and low frequency of perilesional oedema (10%) at diagnosis, as compared with the PML-IRIS stage (40%).
CONCLUSION: Patterns of inflammation at the time of PML diagnosis and at the PML-IRIS stage overlap but differ in their severity of inflammation. This supports histopathological evidence that the inflammation seen at both stages of the same disease shares a similar underlying pathophysiology, representing the immune response to the JC virus to a variable extend.

PMID: 29159899

Lieba-Samal D, **van Eijk JJJ**, van Rosmalen MHJ, van Balken IMF, Verrips A, Mostert J, Pillen S, van Alfen N. Extremely Painful Multifocal Acquired Predominant Axonal Sensorimotor Neuropathy of the Upper Limb.
J Ultrasound Med. 2018 Jun;37(6):1565-1574. doi: 10.1002/jum.14492. Epub 2017 Nov 21.

The differential diagnosis of upper extremity mononeuritis multiplex includes neuralgic amyotrophy, vasculitic neuropathy, and Lewis-Sumner syndrome. We describe 3 patients initially suspected of neuralgic amyotrophy, who had an extremely painful, protracted, progressive disease course, not fitting one of these established diagnoses. Nerve ultrasonography showed focal caliber changes of the roots, plexus, and limb nerves. Electromyography showed predominant multifocal axonopathy. Ongoing autoimmune neuropathy was suspected. Steroid treatment

provided temporary relief, and intravenous immunoglobulin A sustained pain decrease and functional improvement. These patients appear to have extremely painful axonal inflammatory neuropathy, with a good response to immune-modulating treatment.

PMID: 29162208

Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, Vlek AL, van der Sande MA, Leenstra T; **The National Amr Surveillance Study Group** (Wielders CCH, **Renders NHM**). National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill. 2017 Nov;22(46). doi: 10.2807/1560-7917.ES.2017.22.46.17-00062.

An important cornerstone in the control of antimicrobial resistance (AMR) is a well-designed quantitative system for the surveillance of spread and temporal trends in AMR. Since 2008, the Dutch national AMR surveillance system, based on routine data from medical microbiological laboratories (MMLs), has developed into a successful tool to support the control of AMR in the Netherlands. It provides background information for policy making in public health and healthcare services, supports development of empirical antibiotic therapy guidelines and facilitates in-depth research. In addition, participation of the MMLs in the national AMR surveillance network has contributed to sharing of knowledge and quality improvement. A future improvement will be the implementation of a new semantic standard together with standardised data transfer, which will reduce errors in data handling and enable a more real-time surveillance. Furthermore, the scientific impact and the possibility of detecting outbreaks may be amplified by merging the AMR surveillance database with databases from selected pathogen-based surveillance programmes containing patient data and genotypic typing data.

PMID: 29169572

Van Lieshout LAM, **Pijlman B**, Vos MC, de Groot MJM, Houterman S, Coppus SFPJ, Harmsen MG, Vandenput I, Piek JMJ. Opportunistic salpingectomy in women undergoing hysterectomy: Results from the HYSTUB randomised controlled trial. Maturitas. 2018 Jan;107:1-6. doi: 10.1016/j.maturitas.2017.09.012. Epub 2017 Oct 3.

OBJECTIVE: To evaluate whether opportunistic salpingectomy in premenopausal women undergoing hysterectomy for benign indications is both hormonally and surgically safe, compared with hysterectomy without salpingectomy.
STUDY DESIGN: In this multicentre randomised controlled trial, women were randomised to undergo either hysterectomy with opportunistic bilateral salpingectomy (intervention group) or standard hysterectomy with preservation of the Fallopian tubes (control group).
MAIN OUTCOME MEASURES: The primary outcome was the difference in serum anti-Müllerian hormone concentration (ΔAMH), measured pre-surgery and 6 months post-surgery. Secondary outcomes were surgical outcomes and duration of hospital stay. The sample size was powered at 50 participants per group (n=100) to compare ΔAMH after hysterectomy with salpingectomy to ΔAMH after standard hysterectomy.
RESULTS: Between March 2013 and December 2016, 104 women, aged 30-55 years, were randomly allocated to hysterectomy with opportunistic bilateral salpingectomy (n=52) or standard hysterectomy (n=52). The baseline characteristics did not differ between the two groups. The median ΔAMH was -0.14pmol/L (IQR -1.47-0.95) in the intervention group and 0.00pmol/L (IQR -1.05-0.80) in the control group (p=0.49). The addition of salpingectomy did not impair surgical results and it did not affect duration of hospital stay.
CONCLUSION: Addition of opportunistic bilateral salpingectomy during hysterectomy did not result in a larger effect on ovarian reserve when compared with hysterectomy alone, neither did it affect surgical outcomes. Therefore, opportunistic salpingectomy seems to be a safe procedure in premenopausal women undergoing hysterectomy for benign gynaecological conditions.

PMID: 29199024

Oddens JR, de Reijke TM. The Current State of Predicting Response on Bacillus Calmette-Guérin Treatment for Nonmuscle Invasive Bladder Cancer is Not Yet Useful for Patients but Attributes to Understanding Its Mechanisms of Action. Eur Urol. 2018 May;73(5):749-750. doi: 10.1016/j.eururo.2017.11.021. Epub 2017 Dec 2.
No abstract available.

PMID: 29199441

Schop A, Kip MM, Stouten K, Dekker S, Riedl J, van Houten RJ, van Rosmalen J, Dinant GJ, IJzerman MJ, Koffijberg H, Bindels PJ, **Kusters R**, Levin MD. The effectiveness of a routine versus an extensive laboratory analysis in the diagnosis of anaemia in general practice.
Ann Clin Biochem. 2018 Sep;55(5):535-542. doi: 10.1177/0004563217748680. Epub 2018 Jan 30.

Background We investigated the percentage of patients diagnosed with the correct underlying cause of anaemia by general practitioners when using an extensive versus a routine laboratory work-up. Methods An online survey was distributed among 836 general practitioners. The survey consisted of six cases, selected from an existing cohort of anaemia patients (n = 3325). In three cases, general practitioners were asked to select the laboratory tests for further diagnostic examination from a list of 14 parameters (i.e. routine work-up). In the other three cases, general practitioners were presented with all 14 laboratory test results available (i.e. extensive work-up). General practitioners were asked to determine the underlying cause of anaemia in all six cases based on the test results, and these answers were compared with the answers of an expert panel. Results A total of 139 general practitioners (partly) responded to the survey (17%). The general practitioners were able to determine the underlying cause of anaemia in 53% of cases based on the routine work-up, whereas 62% of cases could be diagnosed using an extensive work-up (P = 0.007). In addition, the probability of a correct diagnosis decreased with the patient's age and was also affected by the underlying cause itself, with anaemia of chronic disease being hardest to diagnose (P = 0.003). Conclusion The use of an extensive laboratory work-up in patients with newly diagnosed anaemia is expected to increase the percentage of correct underlying causes established by general practitioners. Since the underlying cause can still not be established in 31.3% of anaemia patients, further research is necessary.

PMID: 29199442

Kip MM, Schop A, Stouten K, Dekker S, Dinant GJ, Koffijberg H, Bindels PJ, IJzerman MJ, Levin MD, **Kusters R**. Assessing the cost-effectiveness of a routine versus an extensive laboratory work-up in the diagnosis of anaemia in Dutch general practice.
Ann Clin Biochem. 2018 Nov;55(6):630-638. doi: 10.1177/0004563217748984. Epub 2018 Feb 1.

Background Establishing the underlying cause of anaemia in general practice is a diagnostic challenge. Currently, general practitioners individually determine which laboratory tests to request (routine work-up) in order to diagnose the underlying cause. However, an extensive work-up (consisting of 14 tests) increases the proportion of patients correctly diagnosed. This study investigates the cost-effectiveness of this extensive work-up. Methods A decision-analytic model was developed, incorporating all societal costs from the moment a patient presents to a general practitioner with symptoms suggestive of anaemia (aged ≥ 50 years), until the patient was (correctly) diagnosed and treated in primary care, or referred to (and diagnosed in) secondary care. Model inputs were derived from an online survey among general practitioners, expert estimates and published data. The primary outcome measure was expressed as incremental cost per additional patient diagnosed with the correct underlying cause of anaemia in either work-up. Results The probability of general practitioners diagnosing the correct underlying cause increased from 49.6% (95% CI: 44.8% to 54.5%) in the routine work-up to 56.0% (95% CI: 51.2% to 60.8%) in the extensive work-up (i.e. +6.4% [95% CI: -0.6% to 13.1%]). Costs are expected to increase slightly from €842/patient (95% CI: €704 to €994) to €845/patient (95% CI: €711 to €994), i.e. +€3/patient (95% CI: €-35 to €40) in the extensive work-up, indicating incremental costs of €43 per additional patient correctly diagnosed. Conclusions The extensive laboratory work-up is more effective for diagnosing the underlying cause of anaemia by general practitioners, at a minimal increase in costs. As accompanying benefits in terms of quality of life and reduced productivity losses could not be captured in this analysis, the extensive work-up is likely cost-effective.

PMID: 29204933

Kwakman JJM, Vink G, Vestjens JH, Beerepoot LV, de Groot JW, Jansen RL, Opdam FL, Boot H, Creemers GJ, van Rooijen JM, Los M, Vulink AJE, **Schut H**, van Meerten E, Baars A, Hamberg P, Kapiteijn E, Sommeijer DW, Punt CJA, Koopman M. Feasibility and effectiveness of trifluridine/tipiracil in metastatic colorectal cancer: real-life data from The Netherlands.
Int J Clin Oncol. 2018 Jun;23(3):482-489. doi: 10.1007/s10147-017-1220-0. Epub 2017 Dec 4.

BACKGROUND: The RECOURSE trial showed clinical efficacy for trifluridine/tipiracil for refractory metastatic colorectal cancer patients. We assessed the feasibility and effectiveness of trifluridine/tipiracil in daily clinical practice in The Netherlands.
METHODS: Medical records of patients from 17 centers treated in the trifluridine/tipiracil compassionate use program were reviewed and checked for RECOURSE eligibility criteria. Baseline characteristics, safety, and survival times were compared, and prespecified baseline characteristics were tested in multivariate analyses for prognostic significance on overall survival (OS).
RESULTS: A total of 136 patients with a median age of 62 years were analyzed. Forty-three patients (32%) did not meet the RECOURSE eligibility criteria for not having received all prior standard treatments (n = 35, 26%) and/or ECOG performance status (PS) 2 (n = 12, 9%). The

most common grade ≥3 toxicities were neutropenia (n = 44, 32%), leukopenia (n = 8, 6%), anemia (n = 7, 5%), and fatigue (n = 7, 5%). Median progression-free survival (PFS) and median OS were 2.1 (95% CI, 1.8-2.3) and 5.4 months (95% CI, 4.0-6.9), respectively. Patients with ECOG PS 2 had a worse median OS (3.2 months) compared to patients with ECOG PS 0-1 (5.9 months). ECOG PS, KRAS-mutation status, white blood cell count, serum lactate dehydrogenase, and alkaline phosphatase were prognostic factors for OS.
CONCLUSIONS: Our data show that treatment with trifluridine/tipiracil in daily clinical practice is feasible and safe. Differences in patient characteristics between our population and the RECOURSE study population should be taken into account in the interpretation of survival data. Our results argue against the use of trifluridine/tipiracil in patients with ECOG PS 2.
FUNDING: Johannes J.M. Kwakman received an unrestricted research grant from Servier.

PMID: 29210808

van Keulen K, Knol W, Schrijver EJM, **van Marum RJ, van Strien AM**, Nanayakkara PWB. Prophylactic Use of Haloperidol and Changes in Glucose Levels in Hospitalized Older Patients.
J Clin Psychopharmacol. 2018 Feb;38(1):51-54. doi: 10.1097/JCP.0000000000000812.

BACKGROUND: Treatment with antipsychotic drugs has been associated with glucose dysregulation in older outpatients, especially in the early stage of therapy. The underlying mechanism is, however, unclear. The aim of this study was to investigate changes in glucose levels during haloperidol use compared with the use of placebo among older hospitalized patients.
METHODS: This substudy was part of a larger multicenter, randomized, double blind, placebo-controlled clinical trial among hospitalized patients aged 70 years and older who had an increased risk of in-hospital delirium. Patients who were admitted to the Jeroen Bosch Hospital in 's-Hertogenbosch between June 2014 and February 2015 were invited to participate in the study. Participating patients were randomized for treatment and given 1 mg of haloperidol or a placebo twice daily for a maximum of 7 consecutive days (14 doses). Exclusion criteria for this substudy were the use of corticosteroids and changes in diabetes medication. Random blood samples to determine glucose levels were collected before day 1 and on day 6 of the study. Student independent sample t test was used to determine differences in glucose changes between both groups.
RESULTS: Twenty-nine patients were included (haloperidol, n = 14; placebo, n = 15). The mean glucose level for placebo users was 139.3 mg/dL (SD, 50.1) on day 1 and 140.8 mg/dL (SD, 45.7) on day 6, and the mean glucose level for haloperidol users was 139.9 mg/dL (SD, 71.0) on day 1 and 150.2 mg/dL (SD, 39.1) on day 6. The difference was not statistically significant (P = 0.685).
CONCLUSIONS: Short-term prophylactic use of haloperidol was not associated with changes in glucose levels in older hospitalized patients compared with those given a placebo in this small study.

PMID: 29228127

Woudt SHS, de Greeff SC, Schoffelen AF, Vlek ALM, Bonten MJM; **Infectious Diseases Surveillance Information System–Antimicrobial Resistance (ISIS-AR) Study Group (Renders NH)**. Antibiotic Resistance and the Risk of Recurrent Bacteremia.
Clin Infect Dis. 2018 May 17;66(11):1651-1657. doi: 10.1093/cid/cix1076.

Background: Direct health effects of antibiotic resistance are difficult to assess. We quantified the risk of recurrent bacteremia associated with resistance.
Methods: We extracted antimicrobial susceptibility testing data on blood isolates from the Dutch surveillance system for antimicrobial resistance between 2008 and 2017. First and first recurrent (4-30 days) bacteremia episodes were categorized as susceptible, single nonsusceptible, or co-nonsusceptible to third-generation cephalosporins without or with carbapenems (Enterobacteriaceae), ceftazidime without or with carbapenems (Pseudomonas species), aminopenicillins without or with vancomycin (Enterococcus species), or as methicillin-sensitive/-resistant S. aureus (MSSA/MRSA). We calculated risks of recurrent bacteremia after nonsusceptible vs susceptible first bacteremia, estimated the crude population attributable effect of resistance for the Netherlands, and calculated risks of nonsusceptible recurrent bacteremia after a susceptible first episode.
Results: Risk ratios for recurrent bacteremia after a single- and co-nonsusceptible first episode, respectively, vs susceptible first episode, were 1.7 (95% confidence interval [CI], 1.5-2.0) and 5.2 (95% CI, 2.1-12.4) for Enterobacteriaceae, 1.3 (95% CI, 0.5-3.1) and 5.0 (95% CI, 2.9-8.5) for Pseudomonas species, 1.4 (95% CI, 1.2-1.7) and 1.6 (95% CI, 0.6-4.2) for Enterococcus species, and 1.6 (95% CI, 1.1-2.4) for MRSA vs MSSA. The estimated population annual number of recurrent bacteremias associated with nonsusceptibility was 40. The risk of nonsusceptible recurrent bacteremia after a susceptible first episode was at most 0.4% (Pseudomonas species).
Conclusions: Although antibiotic nonsusceptibility was consistently associated with higher risks of recurrent bacteremia, the estimated annual number of additional recurrent episodes in the Netherlands (40) was rather limited.

PMID: 29234454

Scheepers PTJ, Masen-Poos L, van Rooy FGBGJ, Oerlemans A, van Daalen E, Cremers R, Lichtenbeld H, **Biesma B**, Sørli JB, Koponen IK, Larsen ST, Wolkoff P, Nørgaard AW. Pulmonary injury associated with spray of a water-based nano-sized waterproofing product: a case study.
J Occup Med Toxicol. 2017 Dec 8;12:33. doi: 10.1186/s12995-017-0180-7.

Background: In most reported cases of lung trauma with water proofing products, volatile organic compounds (VOC) have a prominent role. Here we report on a case involving ten workers exposed to a sprayed product containing nanoparticles in a water solution with only a few percent VOC.
Case presentation: Ten workers suffered from respiratory symptoms following spray impregnation of hardwood furniture using a waterproofing product that contained positively charged fluorinated acrylate copolymer solid cores with a median diameter of 70 nm (1.3 w%) in aqueous suspension with 3.3 w% VOC and 0.3 w% quaternary ammonium. The worker who applied one liter of the product in a wood workshop, using an air mix spray gun, did not report any health complaints. Another worker, who entered the workshop 3 h later and had rolled and smoked two cigarettes, was hospitalized with severe chemical pneumonitis. A chest X-ray (CXR) showed bilateral infiltrative impairment in the lower lobe regions. On the next day a second CXR showed increased patchiness marking in all fields. A high-resolution Computer Tomography (CT)-scan demonstrated extensive bilateral areas of ground-glass opacities predominantly in the lower regions of the upper lobes, the right middle lobe and the apical regions of the lower lobes, compatible with severe chemical pneumonitis. On the following morning, nine workers in an adjacent workplace in the same building, experienced dry cough, chest tightness and substernal pain upon physical exercise. Reconstruction of the spray application in a climate chamber confirmed trimethyl silanol, glycol ethers and fluoroalkenes in the gas phase. Immediately after the spray application, aerosols were observed at a maximum concentration of 6.3×104 cm-3. Mass concentrations were 0.095 and 10 mg/m3 in the size ranges 5.6-560 nm and 0.22-30 μm, respectively, decreasing to less than 10 μg/m3 in both size ranges after 15 h.
Conclusion: The hospitalized worker had smoked cigarettes contaminated with fluoropolymers which is a plausible explanation for the lung trauma. Respiratory symptoms in the nine workers may be caused by inhalation of particles that became airborne by resuspension from surfaces when workers entered the adjacent workplace the next day. A contribution from VOC appears less likely because measurements and modelling showed that concentrations in the mg/m3 range could have occurred only if the building was assumed to be completely airtight.

PMID: 29240880

Römkens TEH, Kranenburg P, Tilburg AV, Bronkhorst C, Nagtegaal ID, Drenth JPH, **Hoentjen F**. Assessment of Histological Remission in Ulcerative Colitis: Discrepancies Between Daily Practice and Expert Opinion.
J Crohns Colitis. 2018 Mar 28;12(4):425-431. doi: 10.1093/ecco-jcc/jjx165.

Background and Aims: Histological remission [HR] is a potential treatment target in ulcerative colitis [UC]. Limited 'real world' data are available on the reliability of histological scoring when assessing minimal histological inflammation. The aim of this study was to investigate the reliability of UC histological scores in colonic biopsies showing mucosal healing [MH] and limited histological inflammation, and to compare the 'daily practice' histological assessment with expert reviews by gastrointestinal [GI] pathologists.
Methods: We performed a retrospective single-centre study. Colonic biopsies from UC patients with MH [Mayo score ≤ 1] were included. All biopsies assessed in daily practice were reassessed by three blinded GI pathologists using three histological scores (Geboes score [GS], Riley score [RS], Harpaz [Gupta] Index [HGI]) and a global visual scale [GVS]. We evaluated inter- and intra-observer variation between GI pathologists and correlations between scores including the initial histological assessment using Cronbach's alpha and Spearman rho analysis.
Results: In total, 270 biopsies from 39 UC patients were included. The inter-observer concordance for all histological indexes was substantial to almost perfect [GS 0.84; HGI 0.61; GVS 0.74, RS 0.91]. Correlation between the RS and GS was almost perfect [R = 0.86], but we found no correlation between the primary histological assessment and reassessment by GI pathologists.
Conclusions: Current UC histological scores reliably assess limited histological inflammation in UC patients. The discrepancy between the initial histological assessment and the reassessment by dedicated GI pathologists suggests a gap between daily practice and academic expertise. This issue may limit the implementation of HR as a treatment target for UC in daily practice.

PMID: 29249206

Willemsen RTA, Kip MMA, Koffijberg H, **Kusters R**, Buntinx F, Glatz JFC, Dinant GJ; 'RAPIDA' – Study Team ('RAPIDA': RAPid Test for Investigating Complaints Possibly Due to Acute Coronary Syndrome). Early health technology assessment of future clinical decision rule aided triage of patients presenting with acute chest pain in primary care.
Prim Health Care Res Dev. 2018 Mar;19(2):176-188. doi: 10.1017/S146342361700069X. Epub 2017 Dec 18.

The objective of the paper is to estimate the number of patients presenting with chest pain suspected of acute coronary syndrome (ACS) in primary care and to calculate possible cost effects of a future clinical decision rule (CDR) incorporating a point-of-care test (PoCT) as compared with current practice. The annual incidence of chest pain, referrals and ACS in primary care was estimated based on a literature review and on a Dutch and Belgian registration study. A health economic model was developed to calculate the potential impact of a future CDR on costs and effects (ie, correct referral decisions), in several scenarios with varying correct referral decisions. One-way, two-way, and probabilistic sensitivity analyses were performed to test robustness of the model outcome to changes in input parameters. Annually, over one million patient contacts in primary care in the Netherlands concern chest pain. Currently, referral of eventual ACS negative patients (false positives, FPs) is estimated to cost €1,448 per FP patient, with total annual cost exceeding 165 million Euros in the Netherlands. Based on 'international data', at least a 29% reduction in FPs is required for the addition of a PoCT as part of a CDR to become cost-saving, and an additional €16 per chest pain patient (ie, 16.4 million Euros annually in the Netherlands) is saved for every further 10% relative decrease in FPs. Sensitivity analyses revealed that the model outcome was robust to changes in model inputs, with costs outcomes mainly driven by costs of FPs and costs of PoCT. If PoCT-aided triage of patients with chest pain in primary care could improve exclusion of ACS, this CDR could lead to a considerable reduction in annual healthcare costs as compared with current practice.

PMID: 29265948

Dierks J, Gaspersz MP, Belkouz A, van Vugt JLA, Coelen RJS, de Groot JWB, Ten Tije AJ, Meijer WG, **Pruijt JFM**, van Voorthuizen T, van Spronsen DJ, Rentinck M, Ten Oever D, Smit JM, Otten HM, van Gulik TM, Wilmink JW, Groot Koerkamp B, Klümpen H. Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin.

Acta Oncol. 2018 Jun;57(6):807-812. doi: 10.1080/0284186X.2017.1418532. Epub 2017 Dec 21.

Trefwoorden: Galwegkanker, chemotherapie

BACKGROUND: Biliary tract cancer (BTC) is an uncommon cancer with an unfavorable prognosis. Since 2010, the standard of care for patients with unresectable BTC is palliative treatment with gemcitabine plus cisplatin, based on the landmark phase III ABC-02 trial. This current study aims to evaluate the efficacy and safety of gemcitabine and cisplatin in patients with unresectable cholangiocarcinoma and gallbladder cancer in daily practice that meet the criteria for the ABC-02 trial in comparison to patients who did not.
METHODS: Patients diagnosed with unresectable BTC between 2010 and 2015 with an indication for gemcitabine and cisplatin were included. We divided these patients into three groups: (I) patients who received chemotherapy and met the criteria of the ABC-02 trial, (II) patients who received chemotherapy and did not meet these criteria and (III) patients who had an indication for chemotherapy, but received best supportive care without chemotherapy. Primary outcome was overall survival (OS) and secondary outcome was progression-free survival (PFS).
RESULTS: We collected data of 208 patients, of which 138 (66.3%) patients received first line chemotherapy with gemcitabine and cisplatin. Median OS of 69 patients in group I, 63 patients in group II and 65 patients in group III was 9.6 months (95%CI = 6.7-12.5), 9.5 months (95%CI = 7.7-11.3) and 7.6 months (95%CI = 5.0-10.2), respectively. Median PFS was 6.0 months (95%CI = 4.4-7.6) in group I and 5.1 months (95%CI = 3.7-6.5) in group II. Toxicity and number of dose reductions (p = .974) were comparable between the two chemotherapy groups.
CONCLUSION: First-line gemcitabine and cisplatin is an effective and safe treatment for patients with unresectable BTC who do not meet the eligibility criteria for the ABC-02 trial. Median OS, PFS and treatment side effects were comparable between the patients who received chemotherapy (group I vs. group II).

PMID: 29270357

van der Holst HM, Tuladhar AM, Zerbi V, van Uden IWM, de Laat KF, van Leijsen EMC, Ghafoorian M, Platel B, Bergkamp MI, van Norden AGW, Norris DG, van Dijk EJ, Kiliaan AJ, de Leeuw FE. White matter changes and gait decline in cerebral small vessel disease.

Neuroimage Clin. 2017 Dec 7;17:731-738. doi:10.1016/j.nicl.2017.12.007. eCollection 2018.

The relation between progression of cerebral small vessel disease (SVD) and gait decline is uncertain, and diffusion tensor imaging (DTI) studies on gait decline are lacking. We therefore investigated the longitudinal associations between (micro) structural brain changes and gait decline in SVD using DTI. 275 participants were included from the Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUN DMC), a prospective cohort of participants with cerebral small vessel disease aged 50-85 years. Gait (using GAITRite) and magnetic resonance imaging measures were assessed during baseline (2006-2007) and follow-up (2011 - 2012). Linear regression analysis was used to investigate the association between changes in conventional magnetic resonance and diffusion tensor imaging measures and gait decline. Tract-based spatial statistics analysis was used to investigate region-specific associations between changes in white matter integrity and gait decline. 56.2% were male, mean age was 62.9 years (SD8.2), mean follow-up duration was 5.4 years (SD0.2) and mean

gait speed decline was 0.2 m/s (SD0.2). Stride length decline was associated with white matter atrophy (β = 0.16, p = 0.007), and increase in mean white matter radial diffusivity and mean diffusivity, and decrease in mean fractional anisotropy (respectively, β = - 0.14, p = 0.009; β = - 0.12, p = 0.018; β = 0.10, p = 0.049), independent of age, sex, height, follow-up duration and baseline stride length. Tract-based spatial statistics analysis showed significant associations between stride length decline and fractional anisotropy decrease and mean diffusivity increase (primarily explained by radial diffusivity increase) in multiple white matter tracts, with the strongest associations found in the corpus callosum and corona radiata, independent of traditional small vessel disease markers. White matter atrophy and loss of white matter integrity are associated with gait decline in older adults with small vessel disease after 5 years of follow-up. These findings suggest that progression of SVD might play an important role in gait decline.

PMID:29273212

Beck N, Busweiler LAD, Schouwenburg MG, Fiocco M, Cats A, Voncken FEM, Wijnhoven BPL, van Berge Henegouwen MI, Wouters MWJM, van Sandick JW; **Dutch Upper GI Cancer Audit (DUCA) Group and the Dutch Gastric Cancer Perioperative Therapy Study group. Collaborators: Bosscha K**, Dikken JL, van Duijvendijk P, van Grieken NCT, Gisbertz SS, Hartgrink HH, Hartemink KJ, Van Hillegersberg R, Hulsewé K, Kouwenhoven E, Lemmens VEPP, Nieuwenhuijzen GAP, Ooijen B, Plukker JT, Rosman C, Scheepers J, Siersema PD, de Steur WO, Tetteroo G, Veldhuis PMJF. Factors contributing to variation in the use of multimodality treatment in patients with gastric cancer: A Dutch population based study.
Eur J Surg Oncol. 2018 Feb;44(2):260-267. doi: 10.1016/j.ejso.2017.11.023. Epub 2017 Dec 13.
Trefwoorden: Combined modality therapy; Quality assurance; Stomach neoplasms

BACKGROUND:Substantial variation in the use of (neo) adjuvant treatment in patients with gastric cancer exists. The aim of this study was to identify underlying (organizational and process) factors associated with the use of perioperative therapy.
PATIENTS AND METHODS:Patients with resectable gastric cancer who underwent surgery between 2012 and 2014 were selected from the Dutch Upper gastrointestinal Cancer Audit (DUCA). The proportion of perioperatively treated patients was defined per hospital. Five hospitals with the lowest percentage (LP group) and 5 hospitals with the highest percentage (HP group) of perioperative therapy were identified. In the selected hospitals additional information was obtained from patients' medical records using a structured list with predefined variables.
RESULTS:In total, 429 patients (231 in LP group, 198 in HP group) from 9 different hospitals were included. Perioperative therapy was given in 16.0% of patients in the LP group compared to 40.4% in the HP group. In the LP group, patients were enrolled in a clinical trial less frequently (10.8% versus 26.8%, P<.001), and a higher percentage grade III-IV toxicity was observed during neoadjuvant treatment (25.7% versus 46.3%, P=.007). Multivariable analysis showed that, besides known casemix factors, consultation with ≥3 upper GI specialists prior to treatment decision was positively associated with initiating perioperative therapy (OR 2.08, 95% CI 1.19-3.66).
CONCLUSION:Results of this study confirm considerable hospital variation in the use of perioperative therapy in patients with gastric cancer. Besides known casemix factors, use of perioperative therapy was associated with the level of involvement of multidisciplinary care.

PMID: 29273245

Weiss NS, Nahuis MJ, Bordewijk E, Oosterhuis JE, Smeenk JM, Hoek A, Broekmans FJ, Fleischer K, **de Bruin JP**, Kaaijk EM, Laven JS, Hendriks DJ, Gerards MH, van Rooij IA, Bourdrez P, Gianotten J, Koks C, Lambalk CB, Hompes PG, van der Veen F, Mol BWJ, van Wely M. Gonadotrophins versus clomifene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomifene failure (M-OVIN): a randomised, two-by-two factorial trial.
Lancet. 2018 Feb 24;391(10122):758-765. doi: 10.1016/S0140-6736(17)33308-1. Epub 2017 Dec 19.

OBJECTIVE: To evaluate whether opportunistic salpingectomy in premenopausal women undergoing hysterectomy for benign indications is both hormonally and surgically safe, compared with hysterectomy without salpingectomy.
STUDY DESIGN: In this multicentre randomised controlled trial, women were randomised to undergo either hysterectomy with opportunistic bilateral salpingectomy (intervention group) or standard hysterectomy with preservation of the Fallopian tubes (control group).
MAIN OUTCOME MEASURES: The primary outcome was the difference in serum anti-Müllerian hormone concentration (ΔAMH), measured pre-surgery and 6 months post-surgery. Secondary outcomes were surgical outcomes and duration of hospital stay. The sample size was powered at 50 participants per group (n=100) to compare ΔAMH after hysterectomy with salpingectomy to ΔAMH after standard hysterectomy.
RESULTS: Between March 2013 and December 2016, 104 women, aged 30-55 years, were randomly allocated to hysterectomy with opportunistic bilateral salpingectomy (n=52) or standard hysterectomy (n=52). The baseline characteristics did not differ between the two groups. The median ΔAMH was -0.14pmol/L (IQR -1.47-0.95) in the intervention group and 0.00pmol/L (IQR -1.05-0.80) in the control group (p=0.49). The addition of salpingectomy did not impair surgical results and it did not affect duration of hospital stay.

CONCLUSION: Addition of opportunistic bilateral salpingectomy during hysterectomy did not result in a larger effect on ovarian reserve when compared with hysterectomy alone, neither did it affect surgical outcomes. Therefore, opportunistic salpingectomy seems to be a safe procedure in premenopausal women undergoing hysterectomy for benign gynaecological conditions.

PMID: 29279164

Schulz J, P Marques J, Ter Telgte A, **van Dorst A**, de Leeuw FE, Meijer FJA, Norris DG. Clinical application of Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) imaging accelerated by simultaneous multi-slice acquisition.
Eur J Radiol. 2018 Jan;98:200-206. doi: 10.1016/j.ejrad.2017.11.022. Epub 2017 Dec 2.

As a single-shot sequence with a long train of refocusing pulses, Half-Fourier Acquisition Single-Shot Turbo-Spin-Echo (HASTE) suffers from high power deposition limiting use at high resolutions and high field strengths, particularly if combined with acceleration techniques such as simultaneous multi-slice (SMS) imaging. Using a combination of multiband (MB)-excitation and PINS-refocusing pulses will effectively accelerate the acquisition time while staying within the SAR limitations. In particular, uncooperative and young patients will profit from the speed of the MB-PINS HASTE sequence, as clinical diagnosis can be possible without sedation. Materials and MethodsMB-excitation and PINS-refocusing pulses were incorporated into a HASTE-sequence with blipped CAIPIRINHA and TRAPS including an internal FLASH reference scan for online reconstruction. Whole brain MB-PINS HASTE data were acquired on a Siemens 3T-Prisma system from 10 individuals and compared to a clinical HASTE protocol. ResultsThe proposed MB-PINS HASTE protocol accelerates the acquisition by about a factor 2 compared to the clinical HASTE. The diagnostic image quality proved to be comparable for both sequences for the evaluation of the overall aspect of the brain, the detection of white matter changes and areas of tissue loss, and for the evaluation of the CSF spaces although artifacts were more frequently encountered with MB-PINS HASTE. ConclusionsMB-PINS HASTE enables acquisition of slice accelerated highly T2-weighted images and provides good diagnostic image quality while reducing acquisition time.

PMID: 29297513

Dinmohamed AG, **Issa DE**, van der Poel MWM, Schouten HC, Lugtenburg PJ, Chamuleau MED, Zweegman S, Visser O. Treatment and relative survival in very elderly patients with DLBCL in The Netherlands: a population-based study, 1989 to 2015.
Blood Adv. 2017 Sep 22;1(21):1839-1841. doi: 10.1182/bloodadvances.2017011031. eCollection 2017 Sep 26.
No abstract available.

PMID:29298706

de Rooij T, van Hilst J, **Bosscha K**, Dijkgraaf MG, Gerhards MF, Groot Koerkamp B, Hagendoorn J, de Hingh IH, Karsten TM, Lips DJ, Luyer MD, Molenaar IQ, van Santvoort HC, Tran TCK, Busch OR, Festen S, Besselink MG; Dutch Pancreatic Cancer Group. Minimally invasive versus open pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial.
Trials. 2018 Jan 3;19(1):1. doi: 10.1186/s13063-017-2423-4.
Trefwoorden: Laparoscopic; Minimally invasive; Pancreatoduodenectomy; Robot-assisted; Whipple

BACKGROUND:Data from observational studies suggest that minimally invasive pancreatoduodenectomy (MIPD) is superior to openpancreatoduodenectomy regarding intraoperative blood loss, postoperative morbidity, and length of hospital stay, without increasing total costs. However, several case-matched studies failed to demonstrate superiority of MIPD, and large registry studies from the USA even suggested increased mortality for MIPDs performed in low-volume (<10 MIPDs annually) centers. Randomized controlled multicenter trials are lacking but clearly required. We hypothesize that time to functional recovery is shorter after MIPD compared with openpancreatoduodenectomy, even in an enhanced recovery setting.
METHODS/DESIGN:LEOPARD-2 is a randomized controlled, parallel-group, patient-blinded, multicenter, phase 2/3, superiority trial in centers that completed the Dutch Pancreatic Cancer Group LAELAPS-2 training program for laparoscopic pancreatoduodenectomy or LAELAPS-3 training program for robot-assisted pancreatoduodenectomy and have performed ≥ 20 MIPDs. A total of 136 patients with symptomatic benign, premalignant, or malignant disease will be randomly assigned to undergo minimally invasive or openpancreatoduodenectomy in an enhanced recovery setting. After the first 40 patients (phase 2), the data safety monitoring board will assess safety outcomes (not blinded for treatment allocation) and decide on continuation to phase 3. Patients from phase 2 will then be included in phase 3. The primary outcome measure is time (days) to functional recovery. All patients will be blinded for the surgical approach, at least until postoperative day 5, but preferably until

functional recovery has been attained. Secondary outcome measures are operative and postoperative outcomes, including clinically relevant complications, mortality, quality of life, and costs.
DISCUSSION:The LEOPARD-2 trial is designed to assess whether MIPD reduces time to functional recovery, as compared with openpancreatoduodenectomy in an enhanced recovery setting.
TRIAL REGISTRATION:Netherlands Trial Register, NTR5689 . Registered on 2 March 2016.

PMID: 29303089

Mertens BJ, Kwint HF, Bouvy ML, **van Marum RJ**. [Multidose drug dispensing: what does it really involve?].
Ned Tijdschr Geneeskd. 2017;161:D1770. Dutch.

Multidose drug dispensing (MDD) systems are individualised forms of distribution that give structure to medication use. - Starting to use a multidose drug dispensing system must be initiated in joint discussion with the patient, once alternatives such as dosing schemes or automatic repeat-prescription services have been considered. The patient's autonomy and self-management are central.- Studies have shown positive effects of individualised forms of distribution on intermediary outcome measures such as HbA1c, LDL cholesterol, blood pressure and adherence. - Changes in medication should preferably be implemented when the pharmacist orders a new multidose drug dispensing system. It is difficult for the pharmacist to determine whether an immediate change is necessary if the indication and other possible reasons for change are not known. - The prescriber should preferably enquire whether the patient has a multidose dispensing system and should state the moment or the reason for the change on the prescription.- Pharmacotherapy in patients using a multidose drug dispensing system should be reviewed annually.

PMID: 29325142

van Roeden SE, Bleeker-Rovers CP, Kampschreur LM, de Regt MJA, **Vermeulen Windsant A**, Hoepelman AIM, **Wever PC**, Oosterheert JJ. The effect of measuring serum doxycycline concentrations on clinical outcomes during treatment of chronic Q fever.
J Antimicrob Chemother 2018;73:1068-1076.

Background: First choice treatment for chronic Q fever is doxycycline plus hydroxychloroquine. Serum doxycycline concentration (SDC) >5 µg/mL has been associated with a favourable serological response, but the effect on clinical outcomes is unknown.
Objectives: To assess the effect of measuring SDC during treatment of chronic Q fever on clinical outcomes.
Methods: We performed a retrospective cohort study, to assess the effect of measuring SDC on clinical outcomes in patients treated with doxycycline and hydroxychloroquine for chronic Q fever. Primary outcome was the first disease-related event (new complication or chronic Q fever-related mortality); secondary outcomes were all-cause mortality and PCR-positivity. Multivariable analysis was performed with a Cox proportional hazards model, with shared-frailty terms for different hospitals included.
Results: We included 201 patients (mean age 68 years, 83% male): in 167 patients (83%) SDC was measured, 34 patients (17%) were treated without SDC measurement. First SDC was >5 µg/mL in 106 patients (63%), all with 200 mg doxycycline daily. In patients with SDC measured, dosage was adjusted in 41% (n = 68), concerning an increase in 64 patients. Mean SDC was 4.1 µg/mL before dosage increase, and 5.9 µg/mL afterwards. SDC measurement was associated with a lower risk for disease-related events (HR 0.51, 95% CI 0.26-0.97, P = 0.04), but not with all-cause mortality or PCR-positivity.
Conclusions: SDC measurement decreases the risk for disease-related events, potentially through more optimal dosing or improved compliance. We recommend measurement of SDC and striving for SDC >5 µg/mL and <10 µg/mL during treatment of chronic Q fever.

PMID: 29343467

van Vliet J, Tieleman AA, van Engelen BGM, Bassez G, Servais L, Béhin A, Stojkovic T, Meulstee J, Engel JAM, Lamas G, Eymard B, Verhagen WIM, Mamelle E. Hearing impairment in patients with myotonic dystrophy type 2.
Neurology. 2018 Feb 13;90(7):e615-e622. doi: 10.1212/WNL.0000000000004963. Epub 2018 Jan 17.

OBJECTIVE: To systematically assess auditory characteristics of a large cohort of patients with genetically confirmed myotonic dystrophy type 2 (DM2).
METHODS: Patients with DM2 were included prospectively in an international cross-sectional study. A structured interview about hearing symptoms was held. Thereafter, standardized otologic examination, pure tone audiometry (PTA; 0.25, 0.5, 1, 2, 4, and 8 kHz), speech audiometry, tympanometry, acoustic middle ear muscle reflexes, and brainstem auditory evoked potentials (BAEP) were performed. The ISO

7029 standard was used to compare the PTA results with established hearing thresholds of the general population according to sex and age.
RESULTS: Thirty-one Dutch and 25 French patients with DM2 (61% female) were included with a mean age of 57 years (range 31-78). The median hearing threshold of the DM2 cohort was higher for all measured frequencies, compared to the 50th percentile of normal ($p < 0.001$). Hearing impairment was mild in 39%, moderate in 21%, and severe in 2% of patients with DM2. The absence of an air-bone gap with PTA, concordant results of speech audiometry with PTA, and normal findings of BAEP suggest that the sensorineural hearing impairment is located in the cochlea. A significant correlation was found between hearing impairment and age, even when corrected for presbycusis.
CONCLUSIONS: Cochlear sensorineural hearing impairment is a frequent symptom in patients with DM2, suggesting an early presbycusis. Therefore, we recommend informing about hearing impairment and readily performing audiometry when hearing impairment is suspected in order to propose early hearing rehabilitation with hearing aids when indicated.

PMID:29353163

van der Werf LR, Dikken JL, van der Willik EM, van Berge Henegouwen MI, Nieuwenhuijzen GAP, Wijnhoven BPL; **Dutch Upper Gastrointestinal Cancer Audit (DUCA) group.** Collaborators **Bosscha K**, van Grieken NCT, Hartgrink HH, van Hillegersberg R, Lemmens VEPP, Plukker JT, Rosman C, van Sandick JW, Siersema PD, Tetteroo G, Veldhuis PMJF, Voncken FEM. Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study.
Eur J Cancer. 2018 Mar;91:76-85. doi: 10.1016/j.ejca.2017.12.009. Epub 2018 Jan 30.
Trefwoorden: Neoadjuvant chemoradiotherapy; Oesophageal carcinoma; Oesophageal surgery; Pathological complete response; Time-to-treatment; Treatment outcome

INTRODUCTION:The optimal time between end of neoadjuvant chemoradiotherapy (nCRT) and oesophagectomy is unknown. The aim of this study was to assess the association between this interval and pathologic complete response rate (pCR), morbidity and 30-day/in-hospital mortality.
METHODS:Patients with oesophageal cancer treated with nCRT and surgery between 2011 and 2016 were selected from a national database: the Dutch Upper Gastrointestinal Cancer Audit (DUCA). The interval between end of nCRT and surgery was divided into six periods: 0-5 weeks (n = 157;A), 6-7 weeks (n = 878;B), 8-9 weeks (n = 972;C), 10-12 weeks (n = 720;D), 13-14 weeks (n = 195;E) and 15 or more weeks (n = 180;F). The association between these interval groups and outcomes was investigated using univariable and multivariable analysis with group C (8-9 weeks) as reference.
RESULTS:In total, 3102 patients were included. The pCR rate for the groups A to F was 31%, 28%, 26%, 31%, 40% and 37%, respectively. A longer interval was associated with a higher probability of pCR (≥10 weeks for adenocarcinoma: odds ratio [95% confidence interval]: 1.35 [1.00-1.83], 1.95 [1.24-3.07], 1.64 [0.99-2.71] and ≥13 weeks for squamous cell carcinoma: 2.86 [1.23-6.65], 2.67 [1.29-5.55]. Patients operated ≥10 weeks after nCRT had the same probability for intraoperative/postoperative complications. Patients from groups D and F had a higher 30-day/in-hospital mortality (1.80 [1.08-3.00], 3.19 [1.66-6.14]).
CONCLUSION:An interval of ≥10 weeks for adenocarcinoma and ≥13 weeks for squamous cell carcinoma between nCRT and oesophagectomy was associated with a higher probability of having a pCR. Longer intervals were not associated with intraoperative/postoperative complications. The 30-day/in-hospital mortality was higher in patients with extended intervals (10-12 and ≥15 weeks); however, this might have been due to residual confounding.

PMID: 29383223

Haverals L, **Mattheij M**, Hoppenreijs E, Bergé S, van der Weij A. A boy with recurrent swelling of the jaw. Pediatr Rep. 2018 Jan 4;9(4):7489. doi: 10.4081/pr.2017.7489. eCollection 2017 Nov 21.
No abstract available.

PMID: 29385240

Aalders J, Hartman E, Nefs G, Nieuwesteeg A, Hendrieckx C, Aanstoot HJ, Winterdijk P, **van Mil E**, Speight J, Pouwer F. Mindfulness and fear of hypoglycaemia in parents of children with Type 1 diabetes.
Diabet Med. 2018 May;35(5):650-657.

AIMS: To identify the sociodemographic and clinical correlates of fear of hypoglycaemia among parents of children (aged 4-18 years) with Type 1 diabetes and to examine the relationships between parental fear of hypoglycaemia, mindfulness and mindful parenting.
METHODS: Sociodemographic, self-reported clinical and psychological data were extracted from the cross-sectional Diabetes MILES Youth

- The Netherlands dataset. Questionnaires included the Hypoglycaemia Fear Survey - Parent Worry (parental fear of hypoglycaemia), the Freiburg Mindfulness Inventory - Short version (mindfulness) and the Interpersonal Mindfulness in Parenting Scale (mindful parenting).
RESULTS: A total of 421 parents (359 mothers) participated. Hierarchical linear regression analyses showed that greater parental fear of hypoglycaemia was related to younger parental age, low educational level, non-Dutch nationality, more frequent blood glucose monitoring, and less general mindfulness. Adding mindful parenting to the model negated the previous contribution of general mindfulness. In this model, lower mindful parenting was related to greater parental fear of hypoglycaemia. In particular, parents with an increased ability to be less judgemental of themselves as parents and less reactive to emotions within parenting interactions reported less fear of hypoglycaemia. In total, 21% of the variance in parental fear of hypoglycaemia was explained.
CONCLUSION: Parental fear of hypoglycaemia was associated largely with parental characteristics, including non-modifiable sociodemographics (i.e. age, education, nationality) and modifiable psychological factors (i.e. mindful parenting). These findings suggest that it is important to further explore mindfulness-based interventions for parents to reduce fear of hypoglycaemia next to interventions to reduce hypoglycaemia.

PMID: 29385437

Schols AMR, Dinant GJ, Hopstaken R, Price CP, **Kusters R**, Cals JWL. International definition of a point-of-care test in family practice: a modified e-Delphi procedure.
Fam Pract. 2018 Jul 23;35(4):475-480. doi: 10.1093/fampra/cmx134.

Background: The use of point-of-care tests (POCTs) in family practice is increasing, and the term POCT is often used in medical literature and clinical practice. Yet, no widely supported definition by several professional fields exists.
Objective: To reach consensus on an international definition of a POCT in family practice.
Methods: We performed a modified international e-Delphi procedure of four rounds among expert panel members from different professional backgrounds-family practitioners, laboratory specialists, policymakers, researchers and manufacturers.
Results: Of 27 panel members from seven different countries, 26 participated in all rounds. Most panel members were active in POCT research or policymaking and 70% worked in family medicine. After choosing important components, structuring of answers and feedback, the following definition was chosen as the best or second best definition by 81% of panel members: a point-of-care test in family practice is a test to support clinical decision making, which is performed by a qualified member of the practice staff nearby the patient and on any part of the patient's body or its derivatives, during or very close to the time of consultation, to help the patient and physician to decide upon the best suited approach, and of which the results should be known at the time of the clinical decision making.
Conclusion: The definition emerging from this study can inform family practitioners, laboratory specialists, policymakers and manufacturers on the most widely supported and recognized definition and could act as a clear starting point for the organization and execution of professional point-of-care testing in family practice worldwide.

PMID: 29386053

Dingemans SA, Birnie MFN, Sanders FRK, van den Bekerom MPJ, Backes M, van Beeck E, Bloemers FW, van Dijkman B, Flikweert E, Haverkamp D, Holtslag HR, Hoogendoorn JM, Joosse P, Parkkinen M, Roukema G, Sosef N, Twigt BA, van Veen RN, van der Veen AH, Vermeulen J, Winkelhagen J, **van der Zwaard BC**, van Dieren S, Goslings JC, Schepers T. Routine versus on demand removal of the syndesmotic screw; a protocol for an international randomised controlled trial (RODEO-trial).
BMC Musculoskelet Disord. 2018 Jan 31;19(1):35. doi: 10.1186/s12891-018-1946-5.

BACKGROUND: Syndesmotic injuries are common and their incidence is rising. In case of surgical fixation of the syndesmosis a metal syndesmotic screw is used most often. It is however unclear whether this screw needs to be removed routinely after the syndesmosis has healed. Traditionally the screw is removed after six to 12 weeks as it is thought to hamper ankle functional and to be a source of pain. Some studies however suggest this is only the case in a minority of patients. We therefore aim to investigate the effect of retaining the syndesmotic screw on functional outcome.
DESIGN: This is a pragmatic international multicentre randomised controlled trial in patients with an acute syndesmotic injury for which a metallic syndesmotic screw was placed. Patients will be randomised to either routine removal of the syndesmotic screw or removal on demand. Primary outcome is functional recovery at 12 months measured with the Olerud-Molander Score. Secondary outcomes are quality of life, pain and costs. In total 194 patients will be needed to demonstrate non-inferiority between the two interventions at 80% power and a significance level of 0.025 including 15% loss to follow-up.
DISCUSSION: If removal on demand of the syndesmotic screw is non-inferior to routine removal in terms of functional outcome, this will offer a strong argument to adopt this as standard practice of care. This means that patients will not have to undergo a secondary procedure, leading

to less complications and subsequent lower costs.
TRIAL REGISTRATION: This study was registered at the Netherlands Trial Register (NTR5965), Clinicaltrials.gov (NCT02896998) on July 15th 2016.

PMID: 29387957

de Groot JJA, Maessen JMC, Dejong CHC, Winkens B, Kruitwagen RFPM, Slangen BFM, van der Weijden T; **all the members of the study group (Pijlman BM)**. Interdepartmental Spread of Innovations: A Multicentre Study of the Enhanced Recovery After Surgery Programme.
World J Surg. 2018 Aug;42(8):2348-2355. doi: 10.1007/s00268-018-4495-z.

BACKGROUND: Spread of evidence-based innovations beyond pioneering settings is essential to improve quality of care. This study aimed to evaluate the influence of a national project to implement 'Enhanced Recovery After Surgery' (ERAS) among colorectal teams on the spread of this innovation to gynaecological procedures.
METHODS: A retrospective observational multicentre study was performed of a consecutive sample of patients who underwent major elective gynaecological surgery in 2012-2013. Ten Dutch hospitals (294 patients) had participated in a colorectal breakthrough project implementing ERAS on a nationwide basis and were assigned to the intervention group. Thirteen hospitals (390 patients) that had not participated in this project acted as controls. Outcome measures were time to functional recovery and total length of postoperative hospital stay. Multilevel models adjusted for clustering and baseline demographics were used for analysis. The uptake of ten selected perioperative care elements was evaluated for each hospital.
RESULTS: The estimated mean difference (95% confidence interval) between the intervention and control hospitals was -0.3 (-0.9 to 0.3) days in the time to recovery and 0.2 (-0.8 to 1.3) days in the total length of hospital stay. The mean (± standard deviation) absolute rate of implemented perioperative care elements per hospital was 28.9 ± 14.9% in the control, versus 29.3 ± 11.1% in the intervention group (p = 0.934).
CONCLUSION: Initial implementation effects seem to be restricted to the participating teams and do not automatically spread to other surgical teams in the same hospital.

PMID: 29392409

van der Aa AAMA, Mannaerts CK, **van der Linden H, Gayet M, Schrier BP**, Mischi M, **Beerlage HP**, Wijkstra H. Concordance of Gleason grading with three-dimensional ultrasound systematic biopsy and biopsy core pre-embedding.
World J Urol. 2018 Jun;36(6):863-869. doi: 10.1007/s00345-018-2209-7.

PURPOSE: To determine the value of a three-dimensional (3D) greyscale transrectal ultrasound (TRUS)-guided prostate biopsy system and biopsy core pre-embedding method on concordance between Gleason scores of needle biopsies and radical prostatectomy (RP) specimens.
METHODS: Retrospective analysis of prostate biopsies and subsequent RP for PCa in the Jeroen Bosch Hospital, the Netherlands, from 2007 to 2016. Two cohorts were analysed: conventional 2D TRUS-guided biopsies and RP (2007-2013, n = 266) versus 3D TRUS-guided biopsies with pre-embedding (2013-2016, n = 129). The impact of 3D TRUS-guidance with pre-embedding on Gleason score (GS) concordance between biopsy and RP was evaluated using the κ-coefficient. Predictors of biopsy GS 6 upgrading were assessed using logistic regression models.
RESULTS: Gleason concordance was comparable between the two cohorts with a $\kappa = 0.44$ for the 3D cohort, compared to $\kappa = 0.42$ for the 2D cohort. 3D TRUS-guidance with pre-embedding, did not significantly affect the risk of biopsy GS 6 upgrading in univariate and multivariate analysis.
CONCLUSIONS: 3D TRUS-guidance with biopsy core pre-embedding did not improve Gleason concordance. Improved detection techniques are needed for recognition of low-grade disease upgrading.

PMID: 29417251

van Zelst JCM, Tan T, Clauser P, Domingo A, Dorrius MD, Drieling D, Golatta M, Gras F, de Jong M, Pijnappel R, **Rutten MJCM**, Karssemeijer N, Mann RM. Dedicated computer-aided detection software for automated 3D breast ultrasound; an efficient tool for the radiologist in supplemental screening of women with dense
breasts.
Eur Radiol. 2018 Jul;28(7):2996-3006. doi: 10.1007/s00330-017-5280-3. Epub 2018 Feb 7.

OBJECTIVES: To determine the effect of computer-aided-detection (CAD) software for automated breast ultrasound (ABUS) on reading time (RT) and performance in screening for breast cancer.
MATERIAL AND METHODS: Unilateral ABUS examinations of 120 women with dense breasts were randomly selected from a multi-institutional archive of cases including 30 malignant (20/30 mammography-occult), 30 benign, and 60 normal cases with histopathological verification or ≥ 2 years of negative follow-up. Eight radiologists read once with (CAD-ABUS) and once without CAD (ABUS) with > 8 weeks between reading sessions. Readers provided a BI-RADS score and a level of suspiciousness (0-100). RT, sensitivity, specificity, PPV and area under the curve (AUC) were compared.
RESULTS: Average RT was significantly shorter using CAD-ABUS (133.4 s/case, 95% CI 129.2-137.6) compared with ABUS (158.3 s/case, 95% CI 153.0-163.3) ($p < 0.001$). Sensitivity was 0.84 for CAD-ABUS (95% CI 0.79-0.89) and ABUS (95% CI 0.78-0.88) ($p = 0.90$). Three out of eight readers showed significantly higher specificity using CAD. Pooled specificity (0.71, 95% CI 0.68-0.75 vs. 0.67, 95% CI 0.64-0.70, $p = 0.08$) and PPV (0.50, 95% CI 0.45-0.55 vs. 0.44, 95% CI 0.39-0.49, $p = 0.07$) were higher in CAD-ABUS vs. ABUS, respectively, albeit not significantly. Pooled AUC for CAD-ABUS was comparable with ABUS (0.82 vs. 0.83, $p = 0.53$, respectively).
CONCLUSION: CAD software for ABUS may decrease the time needed to screen for breast cancer without compromising the screening performance of radiologists.
KEY POINTS: • ABUS with CAD software may speed up reading time without compromising radiologists' accuracy. • CAD software for ABUS might prevent non-detection of malignant breast lesions by radiologists. • Radiologists reading ABUS with CAD software might improve their specificity without losing sensitivity.

PMID: 29449581

Voskamp PWM, van Diepen M, Dekker FW, **Hoogeveen EK**. Dyslipidemia and risk of renal replacement therapy or death in incident pre-dialysis patients.
Sci Rep. 2018 Feb 15;8(1):3130.

Globally the number of patients on renal replacement therapy (RRT) is rising. Dyslipidemia is a potential modifiable cardiovascular risk factor, but its effect on risk of RRT or death in pre-dialysis patients is unclear. The aim of this study was to assess the association between dyslipidemia and risk of RRT or death among patients with CKD stage 4-5 receiving specialized pre-dialysis care, an often under represented group in clinical trials. Of the 502 incident pre-dialysis patients (>18 y) in the Dutch PREPARE-2 study, lipid levels were available in 284 patients and imputed for the other patients. During follow up 376 (75%) patients started RRT and 47 (9%) patients died. Dyslipidemia was defined as total cholesterol ≥5.00 mmol/L, LDL cholesterol ≥2.50 mmol/L, HDL cholesterol <1.00 mmol/L, HDL/LDL ratio <0.4, or triglycerides (TG) ≥2.25 mmol/L, and was present in 181 patients and absent in 93 patients. After multivariable adjustment Cox regression analyses showed a HR (95% CI) for the combined endpoint for dyslipidemia of 1.12 (0.85-1.47), and for high LDL of 1.20 (0.89-1.61). All other HRs were smaller. In conclusion, we did not find an association between dyslipidemia or the separate lipid levels and RRT or death in CKD patients on specialized pre-dialysis care.

PMID: 29466257

de Rooij BH, Ikiz H, Boll D, Pijnenborg JMA, **Pijlman BM**, Kruitwagen RFPM, van de Poll-Franse LV, Vos MC, Ezendam NPM. Recurrent Cancer Is Associated With Dissatisfaction With Care-A Longitudinal Analysis Among Ovarian and Endometrial Cancer Patients.
Int J Gynecol Cancer. 2018 Mar;28(3):614-622. doi: 10.1097/IGC.0000000000001204.

OBJECTIVE: The primary aim of this study was to assess the longitudinal impact of a recurrence of gynecological cancer on satisfaction with information provision and care. The secondary aim was to assess the impact of a recurrence on illness perceptions, anxiety, and depression and health-related quality of life.
METHODS: This study is a longitudinal analysis from the ROGY Care trial, conducted between 2011 and 2014, including patients with endometrial (n = 215) and ovarian (n = 149) cancer. Patients were invited to complete questionnaires directly after initial treatment and after 6, 12, and 24 months. Satisfaction with information provision and care, illness perceptions, anxiety, and depression were compared before and after the recurrence. Linear mixed-model analyses were conducted to assess the differences in outcomes of patients with a recurrence compared with patients without a recurrence.
RESULTS: During 2-year follow-up, 25 patients with endometrial cancer (12%) and 64 patients with ovarian cancer (43%) had recurrent disease, of whom 9 endometrial and 26 ovarian cancer patients completed at least 1 questionnaire after their recurrence was determined. Patients reported lower satisfaction with care after the diagnosis of a recurrence (doctor interpersonal skills, exchange of information between caregivers, and general satisfaction with care) compared with patients without recurrence. In addition, patients reported lower health-related

quality of life, more anxiety and depression, and more threatening illness perceptions after diagnosis of a recurrence.
CONCLUSIONS: After diagnosis of recurrent disease, endometrial and ovarian cancer patients were less satisfied with care compared with patients without a recurrence. Our findings suggest that patients with recurrent cancer are in need of care that is better tailored to their needs.

PMID: 29466591

van den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, **Simons KS**, Dennesen PJW, Van der Voort PHJ, Houterman S, van der Hoeven JG, Pickkers P; REDUCE Study Investigators. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial JAMA. 2018 Feb 20;319(7):680-690
Trefwoorden; Haloperidolprofylaxe, delier

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

PMID: 29471496

de Lange MMA, Gijsen LEV, Wielders CCH, van der Hoek W, Scheepmaker A, **Schneeberger PM**. Should Acute Q-Fever Patients be Screened for Valvulopathy to Prevent Endocarditis?
Clin Infect Dis. 2018 Jul 18;67(3):360-366. doi: 10.1093/cid/ciy128.

Background: Echocardiographic screening of acute Q-fever patients and antibiotic prophylaxis for patients with cardiac valvulopathy is considered an important approach to prevent chronic Q-fever-related endocarditis. During a large Q-fever epidemic in the Netherlands, routine screening echocardiography was discontinued, raising controversy in the international literature. We followed a cohort of acute Q-fever patients to estimate the risk for developing chronic Q-fever, and we evaluated the impact of screening in patients who were not yet known to have a valvulopathy.
Methods: The study population consisted of patients diagnosed with acute Q-fever in 2007 and 2008. We retrospectively reviewed all screening echocardiographs and checked for development of chronic Q-fever 8 years after the acute episode. Risks of developing chronic Q-fever in relation to the presence or absence of valvulopathy were analyzed with logistic regression.
Results: The cohort included 509 patients, of whom 306 received echocardiographic screening. There was no significant difference (P-value = .22) in occurrence of chronic Q-fever between patients with a newly detected valvulopathy (2/84, 2.4%) and those with no valvulopathy (12/202, 5.9%). Two patients with a newly detected valvulopathy, who did not receive antibiotic prophylaxis, developed chronic Q-fever at a later stage.

Conclusions: We found no difference in outcome between patients with and without a valvulopathy newly detected by echocardiographic screening. In retrospect, the 2 above-mentioned patients could have benefitted from antibiotic prophylaxis, but its omission must be weighed against the unnecessary large-scale and long-term use of antibiotics that would have resulted from universal echocardiographic screening.

PMID: 29472225

de Vries E, Fransen L, **van den Aker M**, Meijboom BR. Preventing gatekeeping delays in the diagnosis of rare diseases. Br J Gen Pract. 2018 Mar;68(668):145-146. doi: 10.3399/bjgp18X695225.
No abstract available.

PMID: 29478249

Parren LJMT, Baron JM, Joussen S, Marquardt Y, Hanneken S, van Steensel MAM, Steijlen PM, van Geel M, Frank J. CYLD mutations differentially affect splicing and mRNA decay in Brooke-Spiegler syndrome.
J Eur Acad Dermatol Venereol. 2018 Aug;32(8):e331-e333.
Trefwoorden: CYLD en Brooke-Spiegler syndroom
No abstract available.

PMID: 29482957

Dijksterhuis A, Friedeman E, van der Heijden B. Squamous Cell Carcinoma of the Nail Unit: Review of the Literature. J Hand Surg Am. 2018 Apr;43(4):374-379.e2. doi: 10.1016/j.jhsa.2018.01.010. Review.

Squamous cell carcinoma of the nail unit (SCCNU) is often misdiagnosed and improperly treated because it mimics a number of other conditions. This review details current knowledge of anatomy, pathophysiology, clinical presentation, diagnosis, and treatment of SCCNU. A heightened clinical awareness is critical to treating SCCNU and preventing development of advanced disease at which time amputation is needed and metastasis may occur. Physicians should consider SCCNU in each case of a nail abnormality unresponsive to topical treatment. For adequate diagnosis and excision of SCCNU, timely and appropriate specialist referral is necessary.

PMID: 29486136

Ripellino P, Norton B, **van Eijk J**, Dalton HR. Non-traumatic neurological injury and hepatitis E infection.
Expert Rev Anti Infect Ther. 2018 Apr;16(4):255-257. doi: 10.1080/14787210.2018.1446827. Epub 2018 Mar 7.
No abstract available.

PMID: 29510717

de Lange N, Schol P, Lancé M, Woiski M, Langenveld J, **Rijnders R**, Smits L, Wassen M, Henskens Y, Scheepers H. Restrictive Versus Massive Fluid Resuscitation Strategy (REFILL study), influence on blood loss and hemostatic parameters in obstetric hemorrhage: study protocol for a randomized controlled trial.
Trials. 2018 Mar 6;19(1):166. doi: 10.1186/s13063-018-2512-z.

BACKGROUND: Postpartum hemorrhage (PPH) is associated with maternal morbidity and mortality and has an increasing incidence in high-resource countries, despite dissemination of guidelines, introduction of skills training, and correction for risk factors. Current guidelines advise the administration, as fluid resuscitation, of almost twice the amount of blood lost. This advice is not evidence-based and could potentially harm patients.
METHODS: All women attending the outpatient clinic who are eligible will be informed of the study; oral and written informed consent will be obtained. Where there is more than 500 ml blood loss and ongoing bleeding, patients will be randomized to care as usual, fluid resuscitation with 1.5-2 times the amount of blood loss or fluid resuscitation with 0.75-1.0 times the blood loss. Blood loss will be assessed by weighing all draping. A blood sample, for determining hemoglobin concentration, hematocrit, thrombocyte concentration, and conventional coagulation parameters will be taken at the start of the study, after 60 min, and 12-18 h after delivery. In a subgroup of women, additional thromboelastometric parameters will be obtained.
DISCUSSION: Our hypothesis is that massive fluid administration might lead to a progression of bleeding due to secondary coagulation

disorders. In non-pregnant individuals with massive blood loss, restrictive fluid management has been shown to prevent a progression to dilution coagulopathy. These data, however, cannot be extrapolated to women in labor. Our objective is to compare both resuscitation protocols in women with early, mild PPH (blood loss 500-750 ml) and ongoing bleeding, taking as primary outcome measure the progression to severe PPH (blood loss >1000 ml).
TRIAL REGISTRATION: Netherlands Trial Register, NTR 3789 . Registered on 11 January 2013.

PMID: 29510782

Rondy M, Kissling E, Emborg HD, Gherasim A, Pebody R, Trebbien R, Pozo F, Larrauri A, McMenamin J, Valenciano M; **I-MOVE/I-MOVE+ group (Schneeberger PM)**. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies.
Euro Surveill. 2018 Mar;23(9). doi: 10.2807/1560-7917.ES.2018.23.9.18-00086.

Between September 2017 and February 2018, influenza A(H1N1)pdm09, A(H3N2) and B viruses (mainly B/Yamagata, not included in 2017/18 trivalent vaccines) co-circulated in Europe. Interim results from five European studies indicate that, in all age groups, 2017/18 influenza vaccine effectiveness was 25 to 52% against any influenza, 55 to 68% against influenza A(H1N1)pdm09, -42 to 7% against influenza A(H3N2) and 36 to 54% against influenza B. 2017/18 influenza vaccine should be promoted where influenza still circulates.

PMID:29524046

van der Werf LR, Dikken JL, van Berge Henegouwen MI, Lemmens VEPP, Nieuwenhuijzen GAP, Wijnhoven BPL; Dutch Upper GI Cancer Audit group. Collaborators **Bosscha K**, van Grieken NCT, Hartgrink HH, van Hillegersberg R, Lemmens VEPP, Plukker JT, Rosman C, van Sandick JW, Siersema PD, Tetteroo G, Veldhuis PMJF, Voncken FEM. A Population-based Study on Lymph Node Retrieval in Patients with Esophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit.
Ann Surg Oncol. 2018 May;25(5):1211-1220. doi: 10.1245/s10434-018-6396-7. Epub 2018 Mar 9.

BACKGROUND:For esophageal cancer, the number of retrieved lymph nodes (LNs) is often used as a quality indicator. The aim of this studyis to analyze the number of retrieved LNs in The Netherlands, assess factors associated with LN yield, and explore the association with short-term outcomes. This is a population-based study on lymph node retrieval in patients with esophageal cancer, presenting results from the Dutch Upper Gastrointestinal Cancer Audit.
STUDY DESIGN:For this retrospective national cohort study, patients with esophageal carcinoma who underwent esophagectomy between 2011 and 2016 were included. The primary outcome was the number of retrieved LNs. Univariable and multivariable regression analyses were used to test for association with ≥ 15 LNs.
PATIENTS AND RESULTS:3970 patients were included. Between 2011 and 2016, the median number of LNs increased from 15 to 20. Factors independently associated with ≥ 15 LNs were: 0-10 kg preoperative weight loss (versus: unknown weight loss, odds ratio [95% confidence interval]: 0.71 [0.57-0.88]), Charlson score 0 (versus: Charlson score 2: 0.76 [0.63-0.92]), cN2 category (reference: cN0, 1.32 [1.05-1.65]), no neoadjuvant therapy and neoadjuvant chemotherapy (reference: neoadjuvant chemoradiotherapy, 1.73 [1.29-2.32] and 2.15 [1.54-3.01]), minimally invasive transthoracic (reference: open transthoracic, 1.46 [1.15-1.85]), open transthoracic (versus open and minimally invasive transhiatal, 0.29 [0.23-0.36] and 0.43 [0.32-0.59]), hospital volume of 26-50 or > 50 resections/year (reference: 0-25, 1.94 [1.55-2.42] and 3.01 [2.36-3.83]), and year of surgery [reference: 2011, odds ratios (ORs) 1.48, 1.53, 2.28, 2.44, 2.54]. There was no association of ≥ 15 LNs with short-term outcomes.
CONCLUSIONS:The number of LNs retrieved increased between 2011 and 2016. Weight loss, Charlson score, cN category, neoadjuvant therapy, surgical approach, year of resection, and hospital volume were all associated with increased LN yield. Retrieval of ≥ 15 LNs was not associated with increased postoperative morbidity/mortality.

PMID: 29568254

Wollinga T, Ezendam NPM, Eggink FA, Smink M, van Hamont D, **Pijlman B**, Boss E, Robbe EJ, Ngo H, Boll D, Mom CH, van der Aa MA, Kruitwagen RFLP, Nijman HW, Pijnenborg JMA. Implementation of laparoscopic hysterectomy for endometrial cancer over the past decade.
Gynecol Surg. 2018;15(1):7. doi: 10.1186/s10397-018-1040-x. Epub 2018 Feb 27.

Background: Laparoscopic hysterectomy (LH) for the treatment of early-stage endometrial carcinoma/cancer (EC) has demonstrated to be safe in several randomized controlled trials. Yet, data on implementation of LH in clinical practice are limited. In the present study, implementation

of LH for EC was evaluated in a large oncology network in the Netherlands.
Results: Retrospectively, a total of 556 EC patients with FIGO stage I-II were registered in the selected years. The proportion of LH gradually increased from 11% in 2006 to 85% in 2015. LH was more often performed in patients with low-grade EC and was not related to the studied patient characteristics. The introduction of TLH was frequently preceded by LAVH. Patients treated in teaching hospitals were more likely to undergo a LH compared to patients in non-teaching hospitals. The conversion rate was 7.7%, and the overall complication rates between LH and AH were comparable, but less postoperative complications in LH.
Conclusions: Implementation of laparoscopic hysterectomy for early-stage EC increased from 11 to 85% in 10 years. Implementation of TLH was often preceded by LAVH and was faster in teaching hospitals.

PMID:29571615

van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, **Bosscha K**, van Dam RM, van Eijck CH, Gerhards MF, Gerritsen JJ, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Klaase J, van der Kolk BM, van Laarhoven CJ, Luyer MD, Molenaar IQ, Patijn GA, Rupert CG, Scheepers JJ, van der Schelling GP, Vahrmeijer AL, Busch ORC, van Santvoort HC, Groot Koerkamp B, Besselink MG; Dutch Pancreatic Cancer Group. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit.
HPB (Oxford). 2018 Aug;20(8):759-767. doi: 10.1016/j.hpb.2018.02.640. Epub 2018 Mar 21.

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

PMID: 29575519

Siebers AG, **van der Linden H**, Vedder JEM, Bekkers RLM, Melchers WLG, Bulten J. Presence of koilocytosis in low-grade smears of high-risk HPV-positive women is a negative predictor for cervical intraepithelial neoplasia grade 3 or more.
Cytopathology. 2018 Jun;29(3):275-280. doi: 10.1111/cyt.12536. Epub 2018 Mar 25.

OBJECTIVE: The Netherlands converted to high-risk (hr)HPV-based screening in 2017. An increase in referral of hrHPV-positive women with low risk for cervical intraepithelial neoplasia grade 3 or more (CIN3+) is anticipated and reduction of unjustified referrals will have priority. The relevance of koilocytosis in relation to the underlying risk of high-grade CIN in a primary HPV screening setting is unclear. The aim was to investigate whether the risk for CIN3+ differs between hrHPV-positive atypical squamous cells of undetermined significance (ASC-US)/low-grade squamous intraepithelial lesion (LSIL) with or without koilocytosis.
METHODS: Retrospective cohort study, using data from the Dutch national pathology database (PALGA). The population was 1201 hrHPV-positive women with cytological diagnosis of ASC-US/LSIL. Reporting of koilocytosis was assessed as well as detection rates of CIN1 or less, CIN2 and CIN3+ for ASC-US/LSIL cytology stratified by presence or absence of koilocytosis. Crude and adjusted odds ratios were determined.
RESULTS: Koilocytosis was present in 40.1% of ASC-US and 45.9% of LSIL cases. CIN3+ is significantly less often found when koilocytosis is present (7.8% for hrHPV-positive ASC-US with- vs 15.8% without koilocytosis). For hrHPV-positive LSIL this was 11.7% vs 20.2%. The crude and adjusted odds ratios for CIN3+ was 0.45 for hrHPV-positive ASC-US and 0.52 for hrHPV-positive LSIL.
CONCLUSIONS: The presence of koilocytosis is a negative predictor of CIN3+. The risk of hrHPV-positive ASC-US with koilocytosis is in the same range as hrHPV-positive/cytology negative cases and in a setting of primary hrHPV screening these cases could be followed conservatively by repeat cytology. The results should be confirmed by the first data from the Dutch HPV-based screening programme.

PMID: 29582411

Groenewoud ER, Cohlen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJM, **de Bruin JP**, van Dool G, Fleisher K, Friederich J, Goddijn M, Hoek A, Hoozemans DA, Kaaijk EM, Koks CAM, Laven JSE, van der Linden PJQ, Manger AP, van Rumste M, Spinder T, Macklon NS. Influence of endometrial thickness on pregnancy rates in modified natural cycle frozen-thawed embryo transfer. Acta Obstet Gynecol Scand. 2018 Jul;97(7):808-815. doi: 10.1111/aogs.13349. Epub 2018 Apr 24.

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

PMID: 29590118

van Oers AM, Mutsaerts MAQ, Burggraaff JM, Kuchenbecker WKH, Perquin DAM, Koks CAM, van Golde R, Kaaijk EM, Broekmans FJ, **de Bruin JP**, van der Veen F, Nap AW, Gondrie ETCM, Mol BWJ, Groen H, Hoek A; LIFEstyle study group. Association between periconceptional weight loss and maternal and neonatal outcomes in obese infertile women. PLoS One. 2018 Mar 28;13(3):e0192670. doi: 10.1371/journal.pone.0192670. eCollection 2018.

BACKGROUND: Obesity in women of reproductive age has deleterious effects on reproductive and offspring health. In this study, we aimed to evaluate the association between the magnitude of periconceptional body-mass index (BMI) change and maternal and neonatal outcomes in obese infertile women who participated in the LIFEstyle study. The LIFEstyle study was a randomized controlled trial, evaluating if a six-month lifestyle intervention program prior to infertility treatment in obese infertile women improved birth rates, compared to prompt infertility treatment.
METHODS AND FINDINGS: This is an exploratory post hoc analysis of the LIFEstyle study. We recorded periconceptional BMI change in women with an ongoing pregnancy, pooling data of all women, regardless of randomization arm. Periconceptional BMI change was calculated using weight at randomization and the periconceptional weight (measured in kilograms 12 weeks before or after conception and expressed as BMI change in units BMI (kg/m2)). Subsequently, women were categorized into quartiles according to the magnitude of their periconceptional change in BMI. The odds of maternal and neonatal outcomes were calculated using logistic regression analysis, comparing women in each of the first three weight change quartiles separately, and combined, to women in the fourth quartile. The fourth quartile was chosen as reference group, since these women had the least weight loss. We adjusted for periconceptional BMI, nulliparity and smoking status. In addition, we performed a subgroup analysis for singleton pregnancies. In the LIFEstyle study, 321 obese infertile women achieved an ongoing pregnancy which was conceived within 24 months after randomization. Periconceptional BMI change was available in 244 of these women (76%). Median BMI at randomization was 35.9 kg/m2. Women in the first quartile (Q1) had a periconceptional BMI change of <-2.1 kg/m2, women in the second quartile (Q2) -2.1 to -0.9 kg/m2, women in the third quartile (Q3) -0.9 to 0.1 kg/m2 and women in the fourth quartile (Q4) gained ≥0.1 kg/m2. There were no significant differences between women in the quartiles regarding rates of excessive gestational weight gain (in term pregnancies), gestational diabetes, preterm birth, induction of labor, spontaneous vaginal birth and Caesarean section. Compared to women in Q4, the adjusted odds ratios, aOR, and 95% confidence interval for a hypertensive complication were; 0.55 (0.22-1.42) for women in Q1, 0.30 (0.12-0.78) for women in Q2, 0.39 (0.16-0.96) for women in Q3 and 0.39 (0.19-0.82) for women in Q1 to Q3 combined. In the subgroup analysis, investigating singleton pregnancies only, the statistically significant decreased rate of a hypertensive complication remained in women in Q2 (aOR 0.27, 95% CI 0.10-0.72) and Q3 (aOR 0.39, 95%CI 0.16-0.98) and when comparing women in Q1 to Q3 together to women in Q4 (aOR 0.38, 95%CI 0.18-0.80). Furthermore, there was a significantly decreased aOR (95%CI) of preterm birth in women in Q2 (0.24, 0.06-

0.98) and when combining women in Q1 to Q3 (0.37, 0.14-0.97) compared to women in Q4.
CONCLUSIONS: These results suggest that a periconceptional decrease in BMI in obese infertile women could lead to a decrease of the rates of hypertensive pregnancy complications and preterm birth. The results are limited by the exploratory nature of the analyses and further evidence is necessary to provide more definitive conclusions.

PMID: 29601898

van Vliet J, Tieleman AA, Verrips A, Timmerman H, van Dongen RTM, van Engelen BGM, Wilder-Smith OHG. Qualitative and Quantitative Aspects of Pain in Patients With Myotonic Dystrophy Type 2.
J Pain. 2018 Aug;19(8):920-930. doi: 10.1016/j.jpain.2018.03.006. Epub 2018 Mar 27.

Pain is a common but often ignored symptom in patients with myotonic dystrophy type 2 (DM2). In this explorative study, we assessed qualitative and quantitative aspects of pain in DM2 using 4 questionnaires and quantitative sensory testing. A disease control group (fibromyalgia [FMS]) as well as healthy controls were used to compare the results, because pain in DM2 shows many clinical similarities to pain in FMS. Thirty-four patients with genetically confirmed DM2 (71% female, mean age 54 years), 28 patients with FMS, and 33 healthy controls were included, age- as well as sex-matched. Pain prevalence was 65% in DM2, 100% in FMS ($P < .001$), and 15% in healthy controls ($P < .001$). The mean of the pressure pain thresholds was lower in DM2 than in healthy controls ($P = .016$), with the largest differences in the rectus femoris, trapezius, and thenar muscles. Mechanical and electric pain thresholds were significantly higher in DM2 than in FMS, and no differences were found in electric pain thresholds between DM2 and healthy controls. These results confirm that pain is a frequent and important symptom in patients with DM2, affecting quality of life. Peripheral mechanisms of pain seem to play a role in DM2. The widespreadness of the hyperalgesia suggests central sensitization, but this finding was not supported by the other results. This study opens new avenues for further research and eventually novel treatment strategies, in DM2 as well as in other muscular disorders.
PERSPECTIVE: This article presents qualitative as well as quantitative aspects of pain in patients with DM2. Pain is a frequent and important symptom in patients with DM2, affecting quality of life. We found mechanical hyperalgesia, indicative of a peripheral mechanism of pain. The widespreadness of hyperalgesia may suggest central sensitization, but this finding was not supported by other results and needs further exploration.

PMID: 29603547

Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, van Loon AJ, Hoogenberg K, Bekedam DJ, Brouwer TCB, Porath M, Erdtsieck RJ, NijBijvank B, Kip H, van der Heijden OWH, Elving LD, Hermsen BB, Potter van Loon BJ, **Rijnders RJP, Jansen HJ**, Langenveld J, Akerboom BMC, Kiewiet RM, Naaktgeboren CA, Mol BWJ, Franx A, Evers IM. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial.
Diabetes Obes Metab. 2018 Aug;20(8):1894-1902. doi: 10.1111/dom.13310. Epub 2018 May 8.

AIM: Diabetes is associated with a high risk of adverse pregnancy outcomes. Optimal glycaemic control is fundamental and is traditionally monitored with self-measured glucose profiles and periodic HbA1c measurements. We investigated the effectiveness of additional use of retrospective continuous glucose monitoring (CGM) in diabetic pregnancies.
MATERIAL AND METHODS: We performed a nationwide multicentre, open label, randomized, controlled trial to study pregnant women with type 1 or type 2 diabetes who were undergoing insulin therapy at gestational age < 16 weeks, or women who were undergoing insulin treatment for gestational diabetes at gestational age < 30 weeks. Women were randomly allocated (1:1) to intermittent use of retrospective CGM or to standard treatment. Glycaemic control was assessed by CGM for 5-7 days every 6 weeks in the CGM group, while self-monitoring of blood glucose and HbA1c measurements were applied in both groups. Primary outcome was macrosomia, defined as birth weight above the 90th percentile. Secondary outcomes were glycaemic control and maternal and neonatal complications.
RESULTS: Between July 2011 and September 2015, we randomized 300 pregnant women with type 1 (n = 109), type 2 (n = 82) or with gestational (n = 109) diabetes to either CGM (n = 147) or standard treatment (n = 153). The incidence of macrosomia was 31.0% in the CGM group and 28.4% in the standard treatment group (relative risk [RR], 1.06; 95% CI, 0.83-1.37). HbA1c levels were similar between treatment groups.
CONCLUSIONS: In diabetic pregnancy, use of intermittent retrospective CGM did not reduce the risk of macrosomia. CGM provides detailed information concerning glycaemic fluctuations but, as a treatment strategy, does not translate into improved pregnancy outcome.

PMID: 29606135

Smeets XJNM, da Costa DW, Fockens P, Mulder CJJ, Timmer R, Kievit W, Zegers M, Bruno MJ, Besselink MGH, Vleggaar FP, van der Hulst RWM, Poen AC, Heine GDN, Venneman NG, Kolkman JJ, Baak LC, **Römkens TEH**, van Dijk SM, Hallensleben NDL, van de Vrie W, Seerden TCJ, Tan ACITL, Voorburg AMCJ, Poley JW, Witteman BJ, Bhalla A, Hadithi M, Thijs WJ, Schwartz MP, Vrolijk JM, Verdonk RC, van Delft F, Keulemans Y, van Goor H, Drenth JPH, van Geenen EJM; Dutch Pancreatitis Study Group.
Fluid hydration to prevent post-ERCP pancreatitis in average- to high-risk patients receiving prophylactic rectal NSAIDs (FLUYT trial): study protocol for a randomized controlled trial.
Trials. 2018 Apr 2;19(1):207. doi: 10.1186/s13063-018-2583-x.

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

PMID: 29627773

van den Berg B, Storm EF, **Garssen MJP**, Blomkwist-Markens PH, Jacobs BC. Clinical outcome of Guillain-Barré syndrome after prolonged mechanical ventilation.
J Neurol Neurosurg Psychiatry. 2018 Sep;89(9):949-954. doi:
10.1136/jnnp-2018-317968. Epub 2018 Apr 7.

BACKGROUND: Patients with Guillain-Barré syndrome (GBS) may suffer from respiratory failure for months or longer. The aim of this study was to determine the frequency, clinical course and outcome of patients with GBS requiring prolonged mechanical ventilation (MV).
METHODS: Prospectively collected data from 526 patients with GBS participating in previous trials were analysed to determine the frequency and duration of prolonged MV (longer than 2 months). In addition, a cross-sectional study was conducted in patients with GBS requiring MV to determine the clinical course and long-term outcome with the ability to walk unaided as primary endpoint.
RESULTS: In the cohort study, 145 of 526 patients with GBS (28%) required MV, including 33 (6%) patients with prolonged MV. Patients requiring prolonged MV had a lower Medical Research Council sum score and more frequent bulbar involvement and inexcitable nerves compared with shorter ventilated patients. At 6 months, 18% of patients with prolonged MV were able to walk unaided compared with 76% of patients requiring shorter MV (P<0.001). In the cross-sectional study, 63 patients requiring MV were included with a median follow-up of 11 years (range 2-44 years). Twenty-six (41%) of these patients needed prolonged MV (median 93 days, range 62-261). Fifteen (58%) of these patients were able to walk unaided at maximum follow-up and eight (31%) reached this endpoint more than 1 year after diagnosis.
CONCLUSIONS: Prolonged ventilation in GBS is associated with poor prognosis, yet patients requiring prolonged ventilation may show slow but persistent recovery for years and even reach the ability to walk and live independently.

PMID: 29637664

Albers MEWA, **Buisman ETIA**, Kahn RS, Franx A, Onland-Moret NC, de Heus R. Intra- and interobserver agreement for fetal cerebral measurements in 3D-ultrasonography.
Hum Brain Mapp. 2018 Aug;39(8):3277-3284. doi: 10.1002/hbm.24076.

The aim of this study is to evaluate intra- and interobserver agreement for measurement of intracranial, cerebellar, and thalamic volume with the Virtual Organ Computer-aided AnaLysis (VOCAL) technique in three-dimensional ultrasound images, in comparison to two-dimensional measurements of these brain structures. Three-dimensional ultrasound images of the brains of 80 fetuses at 20-24 weeks' gestational age were obtained from YOUth, a Dutch prospective cohort study. Two observers performed offline measurement of the occipitofrontal diameter, intracranial volume, transcerebellar diameter, cerebellar volume, and thalamic width, area, and volume, independently. VOCAL was used for calculation of the volumes. The two-way random, single measures intraclass correlation coefficient (ICC) was used for analysis of agreement and Bland-Altman plots were configured. Intra- and interobserver agreement was almost perfect for occipitofrontal diameter (intra ICC 0.88, 95% CI 0.82-0.92; inter ICC 0.91, 95% CI 0.85-0.94), intracranial volume (intra ICC 0.96, 95% CI 0.91-0.98; inter ICC 0.97, 95% CI 0.96-0.98) and transcerebellar diameter (intra ICC 0.91, 95% CI 0.86-0.94; inter ICC 0.86, 95% CI 0.78-0.910). For cerebellar volume, the intraobserver agreement was almost perfect (0.85, 95% CI 0.76-0.90), whereas the interobserver agreement was substantial (0.75, 95% CI 0.44-0.88). Agreement was only moderate for thalamic measurements. Bland-Altman plots for the volume measurements are normally distributed with acceptable mean differences and 95% limits of agreement. The intra- and interobserver agreement of the measurement of intracranial and cerebellar volume with VOCAL was almost perfect. These measurements are therefore reliable, and can be used to investigate fetal brain development. Thalamic measurements are not reliable enough.

PMID: 29650493

van Roeden SE, van Houwelingen F, Donkers CMJ, Hogewoning SJ, de Lange MMA, van der Hoek W, Kampschreur LM, Bonten MJM, Hoepelman AIM, Bleeker-Rovers CP, **Wever PC**, Oosterheert JJ.
Exposure to Coxiella burnetii and risk of non-Hodgkin lymphoma: a retrospective population-based analysis in the Netherlands.
Lancet Haematol 2018;5:e211-e219.

BACKGROUND: An association between Coxiella burnetii and non-Hodgkin lymphoma has been suggested. After a large Q fever epidemic in the Netherlands (2007-10), we postulated that the incidence of non-Hodgkin lymphoma would be increased during and after the epidemic in areas with a high endemicity of Q fever compared with those with low endemicity.
METHODS: We did a retrospective population-based analysis and calculated relative risks (RRs) of non-Hodgkin lymphoma during 1-year periods before, during, and after the Q fever epidemic, for areas with intermediate and high endemicity of Q fever compared with low endemic areas. We also calculated the RR of non-Hodgkin lymphoma in people with chronic Q fever compared with the general population.
FINDINGS: Between Jan 1, 2002, and Dec 31, 2013, 48 760 cases of non-Hodgkin lymphoma were diagnosed. The incidence of non-Hodgkin lymphoma ranged from 21·4 per 100 000 per year in 2002 to 26·7 per 100 000 per year in 2010. A significant association with non-Hodgkin lymphoma was noted in 2009 for areas with a high endemicity of Q fever compared with low endemic areas (RR 1·16, 95% CI 1·02-1·33; p=0·029); no further associations were noted in any other year or for areas with intermediate Q fever endemicity. Among 439 individuals with chronic Q fever, five developed non-Hodgkin lymphoma, yielding a crude absolute risk of 301·0 cases per 100 000 per year (RR 4·99, 95% CI 2·07-11·98; p=0·0003) compared with the general population in the Netherlands.
INTERPRETATION: These findings do not support the hypothesis that Q fever has a relevant causal role in the development of non-Hodgkin lymphoma. Several limitations, inherent to the design of this study, might lead to both underestimation and overestimation of the studied association.
FUNDING: Foundation Q-support and Institut Mérieux.

PMID: 29661729

Bekers EM, Eijkelenboom A, Grünberg K, Roverts RC, de Rooy JWJ, van der Geest ICM, van Gorp JM, Creytens D, Flucke U.
Myositis ossificans - Another condition with USP6 rearrangement, providing evidence of a relationship with nodular fasciitis and aneurysmal bone cyst.
Ann Diagn Pathol. 2018 Jun;34:56-59. doi: 10.1016/j.anndiagpath.2018.01.006.

Myositis ossificans is defined as a self-limiting pseudotumor composed of reactive hypercellular fibrous tissue and bone. USP6 rearrangements have been identified as a consistent genetic driving event in aneurysmal bone cyst and nodular fasciitis. It is therefore an integral part of the diagnostic workup when dealing with (myo)fibroblastic lesions of soft tissue and bone. Two cases of myositis ossificans with USP6 rearrangement were published so far. We determine herein the incidence of USP6 rearrangement in myositis ossificans using USP6 fluorescence in situ hybridization analysis (FISH). Of the 11 cases included, seven patients were female and four were male. Age ranged from 6 to 56 years (mean 27 years). Lesions were located in the thigh (n = 5), knee (n = 1), lower leg (n = 1), lower arm (n = 1), perineum (n = 1),

gluteal (n = 1) and thoracic wall (n = 1). All assessable cases except one (8/9) showed rearrangement of USP6 providing evidence that myositis ossificans is genetically related to nodular fasciitis and aneurysmal bone cyst.

PMID: 29679152

Bolkenstein HE, **Draaisma WA**, van de Wall B, Consten E, Broeders I. Treatment of acute uncomplicated diverticulitis without antibiotics: risk factors for treatment failure.
Int J Colorectal Dis. 2018 Jul;33(7):863-869. doi: 10.1007/s00384-018-3055-1. Epub 2018 Apr 21.

PURPOSE: Conservative treatment strategy without antibiotics in patients with uncomplicated diverticulitis (UD) has proven to be safe. The aim of the current study is to assess the clinical course of UD patients who were initially treated without antibiotics and to identify risk factors for treatment failure.
METHODS: A retrospective cohort study was performed including all patients with a CT-proven episode of UD (defined as modified Hinchey 1A). Only non-immunocompromised patients who presented without signs of sepsis were included. Patients that received antibiotics within 24 h after or 2 weeks prior to presentation were excluded from analysis. Patient characteristics, clinical signs, and laboratory parameters were collected. Treatment failure was defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotics, operative intervention, or percutaneous abscess drainage within 30 days after initial presentation. Multivariable logistic regression analyses were used to quantify which variables are independently related to treatment failure.
RESULTS: Between January 2005 and January 2017, 751 patients presented at the emergency department with a CT-proven UD. Of these, 186 (25%) patients were excluded from analysis because of antibiotic treatment. A total of 565 patients with UD were included. Forty-six (8%) patients experienced treatment failure. In the multivariable analysis, a high CRP level (>170 mg/L) was a significant predictive factor for treatment failure.
CONCLUSION: UD patients with a CRP level >170 mg/L are at higher risk for non-antibiotic treatment failure. Clinical physicians should take this finding in consideration when selecting patients for non-antibiotic treatment.

PMID: 29679158

Mengerink BB, Nelen WLDM, **van Leijsen SAL**, Heesakkers JPFA, Kluivers KB. De-implementation of urodynamics in The Netherlands after the VALUE/VUSIS-2 results: a nationwide survey.
Int Urogynecol J. 2018 Sep;29(9):1261-1277. doi: 10.1007/s00192-018-3648-9.

INTRODUCTION AND HYPOTHESIS: We aimed to estimate the level of de-implementation of preoperative routine urodynamics (UDS) before stress urinary incontinence (SUI) surgery in The Netherlands and to analyze facilitators and barriers. Routine UDS was performed by 37% of the medical specialists in 2010. We hypothesized that the recommendations from the recent Value of Urodynamics prior to Stress Incontinence Surgery (VUSIS) and Value of Urodynamic Evaluation (ValUE) studies would have been followed by a reduction of routine UDS.
METHODS: A national survey was performed among all Dutch gynecologists and urologists dealing with SUI in daily practice. The questionnaire contained two parts: (1) respondents' characteristics and their actual care concerning preoperative UDS, and (2) facilitators and barriers.
RESULTS: The response rate was 41% (127/308). Of the respondents, 93% (n = 118) did not perform routine UDS in the preoperative workup for women in this group. Professional characteristics associated with not following the recommendations were profession urologist, academic hospital, and a lower number of midurethral sling (MUS) placed yearly. Facilitators to follow the recommendation not to perform routine UDS were adequate design of the VUSIS-II study and outcome and recommendations from the studies. Barriers not to follow the recommendation were believe in the additional value of UDS, especially the pressure transmission ratio, and the presence of detrusor overactivity.
CONCLUSION: According to respondents to this questionnaire, VUSIS-II and ValUE study results are well implemented in The Netherlands. The vast majority of respondents replied as not performing routine preoperative UDS in women with primary, uncomplicated (predominant) SUI. Therefore, there is no need for a further de-implementation strategy.

PMID: 29680465

Braam SC, **de Bruin JP**, Buisman ETIA, Brandes M, Nelen WLDM, Smeenk JMJ, **van der Steeg JW**, Mol BWJ, Hamilton CJCM. Treatment strategies and cumulative live birth rates in WHO-II ovulation disorders.
Eur J Obstet Gynecol Reprod Biol. 2018 Jun;225:84-89. doi: 10.1016/j.ejogrb.2018.04.006. Epub 2018 Apr 10.

OBJECTIVE: To assess the live birth rate in women with WHO II anovulation and the proportion of women that need second or third line treatments if the initial therapy fails.
STUDY DESIGN: In this multicenter cohort study we included couples with unfulfilled child wish who were referred to three fertility clinics in the Netherlands and selected women with a WHO II ovulation disorder as the only final infertility diagnosis (n = 468).
RESULTS: The cumulative live birth rate of the total group was 82% (383/468). The majority started with clomiphene-citrate as first-line treatment (n = 378) resulting in 180 (48%) live births. There were 153 couples (40%) who underwent a second-line treatment (recombinant-FSH or laparoscopic electrocoagulation of the ovaries, LEO) and 52 couples (14%) a third-line treatment (IVF/ICSI), resulting in 44% and 63% treatment dependent live births rates, respectively. Of all couples, 92 (20%) conceived naturally, 186 (40%) after clomiphene-citrate, 60 (13%) after recombinant-FSH, nine (2%) after LEO and 36 (8%) after IVF.
CONCLUSION: Subfertile women with a WHO II ovulation disorder have a good prognosis on live birth, and most did so after ovulation induction with clomiphene-citrate. If first-line ovulation induction has failed ovulation induction with gonadotrophins or IVF still result in a live birth in about half of the cases.

PMID:29683186

Nelen SD, **Bosscha K**, Lemmens VEPP, Hartgrink HH, Verhoeven RHA, de Wilt JHW; Dutch Upper Gastrointestinal Cancer Audit group. Morbidity and mortality according to age following gastrectomy for gastric cancer.
Br J Surg. 2018 Aug;105(9):1163-1170. doi: 10.1002/bjs.10836. Epub 2018 Apr 23.

BACKGROUND:This study investigated age-related differences in surgically treated patients with gastric cancer, and aimed to identify factors associated with outcome.
METHODS:Data from the Dutch Upper Gastrointestinal Cancer Audit were used. All patients with non-cardia gastric cancer registered between 2011 and 2015 who underwent surgery were selected. Patients were analysed by age group (less than 70 years versus 70 years or more). Multivariable logistic regression was used to assess the influence of clinicopathological factors on morbidity and mortality.
RESULTS:A total of 1109 patients younger than 70 years and 1206 aged 70 years or more were included. Patients aged at least 70 years had more perioperative or postoperative complications (41·2 versus 32·5 per cent; P < 0·001) and a higher 30-day mortality rate (7·9 versus 3·2 per cent; P < 0·001) than those younger than 70 years. In multivariable analysis, age 70 years or more was associated with a higher risk of complications (odds ratio 1·29, 95 per cent c.i. 1·05 to 1·59). Postoperative mortality was not significantly associated with age. In the entire cohort, morbidity and mortality were influenced most by ASA grade, neoadjuvant chemotherapy and type of resection.
CONCLUSION:ASA grade, neoadjuvant chemotherapy and type of resection are independent predictors of morbidity and death in patients with gastric cancer, irrespective of age.

PMID: 29685511

Karhof S, van Roeden SE, Oosterheert JJ, Bleeker-Rovers CP, **Renders NHM**, de Borst GJ, Kampschreur LM, Hoepelman AIM, **Koning OHJ, Wever PC** . Primary and secondary arterial fistulas during chronic Q fever.
J Vasc Surg. 2018 Dec;68(6):1906-1913.e1. doi: 10.1016/j.jvs.2018.01.044

OBJECTIVE: After primary infection with Coxiella burnetii, patients may develop acute Q fever, which is a relatively mild disease. A small proportion of patients (1%-5%) develop chronic Q fever, which is accompanied by high mortality and can be manifested as infected arterial or aortic aneurysms or infected vascular prostheses. The disease can be complicated by arterial fistulas, which are often fatal if they are left untreated. We aimed to assess the cumulative incidence of arterial fistulas and mortality in patients with proven chronic Q fever.
METHODS: In a retrospective, observational study, the cumulative incidence of arterial fistulas (aortoenteric, aortobronchial, aortovenous, or arteriocutaneous) in patients with proven chronic Q fever (according to the Dutch Chronic Q Fever Consensus Group criteria) was assessed. Proven chronic Q fever with a vascular focus of infection was defined as a confirmed mycotic aneurysm or infected prosthesis on imaging studies or positive result of serum polymerase chain reaction for C. burnetii in the presence of an arterial aneurysm or vascular prosthesis.
RESULTS: Of 253 patients with proven chronic Q fever, 169 patients (67%) were diagnosed with a vascular focus of infection (42 of whom had a combined vascular focus and endocarditis). In total, 26 arterial fistulas were diagnosed in 25 patients (15% of patients with a vascular focus): aortoenteric (15), aortobronchial (2), aortocaval (4), and arteriocutaneous (5) fistulas (1 patient presented with both an aortocaval and an arteriocutaneous fistula). Chronic Q fever-related mortality was 60% for patients with and 21% for patients without arterial fistula (P < .0001). Primary fistulas accounted for 42% and secondary fistulas for 58%. Of patients who underwent surgical intervention for chronic Q fever-related fistula (n = 17), nine died of chronic Q fever-related causes (53%). Of patients who did not undergo any surgical intervention (n = 8), six died of

chronic Q fever-related causes (75%).
CONCLUSIONS: The proportion of patients with proven chronic Q fever developing primary or secondary arterial fistulas is high; 15% of patients with a vascular focus of infection develop an arterial fistula. This observation suggests that C. burnetii, the causative agent of Q fever, plays a role in the development of fistulas in these patients. Chronic Q fever-related mortality in patients with arterial fistula is very high, in both patients who undergo surgical intervention and patients who do not.

PMID: 29685877

Carvalho B, Diosdado B, **Terhaar Sive Droste JS**, Bolijn AS, Komor MA, de Wit M, Bosch LJW, van Burink M, Dekker E, Kuipers EJ, Coupé VMH, van Grieken NCT, Fijneman RJA, Meijer GA. Evaluation of Cancer-Associated DNA Copy Number Events in Colorectal (Advanced) Adenomas.
Cancer Prev Res (Phila). 2018 Jul;11(7):403-412. doi: 10.1158/1940-6207.CAPR-17-0317.

About 5% of colorectal adenomas are estimated to progress to colorectal cancer. However, it is important to identify which adenomas actually carry a high risk of progression, because these serve as intermediate endpoints, for example, in screening programs. In clinical practice, adenomas with a size of ≥10 mm, villous component and/or high-grade dysplasia, called advanced adenomas, are considered high risk, although solid evidence for this classification is lacking. Specific DNA copy number changes are associated with adenoma-to-carcinoma progression. We set out to determine the prevalence of cancer-associated events (CAE) in advanced and nonadvanced adenomas. DNA copy number analysis was performed on archival tissues from three independent series of, in total, 297 adenomas (120 nonadvanced and 177 advanced) using multiplex ligation-dependent probe amplification or low-coverage whole-genome DNA sequencing. Alterations in two or more CAEs were considered to mark adenomas as high risk. Two or more CAEs were overall present in 25% (95% CI, 19.0-31.8) of advanced adenomas; 23% (11/48), 36% (12/33), and 23% (22/96) of the advanced adenomas in series 1, 2, and 3, respectively, and 1.7% (1/58) and 4.8% (3/62) of the nonadvanced adenomas, in series 1 and 2, respectively. The majority of advanced adenomas do not show CAEs, indicating that only a subset of these lesions is to be considered high risk. Nonadvanced adenomas have very low prevalence of CAEs, although those with CAEs should be considered high risk as well. Specific DNA copy number alterations may better reflect the true progression risk than the advanced adenoma phenotype. Cancer Prev Res; 11(7); 403-12. ©2018 AACR.

PMID: 29705714

Bekers EM, van Broekhoven DLM, van Dalen T, Bonenkamp JJ, van der Geest ICM, de Rooy JWJ, van Gorp JM, Creytens DH, de Leng WWJ, Scheijen B, Eijkelenboom A, Flucke U. Multifocal occurrence of extra-abdominal desmoid type fibromatosis - A rare manifestation. A clinicopathological study of 6 sporadic cases and 1 hereditary case.
Ann Diagn Pathol. 2018 Aug;35:38-41. doi: 10.1016/j.anndiagpath.2018.04.001.

Desmoid-type fibromatosis, also called desmoid tumor, is a locally aggressive myofibroblastic neoplasm that usually arises in deep soft tissue with significant potential for local recurrence. It displays an unpredictable clinical course. β-Catenin, the genetic key player of desmoid tumors shows nuclear accumulation due to mutations that prevent its degradation leading to activation of Wnt signaling and myofibroblastic cell proliferation. The corresponding hot spot mutations are located in exon 3 of the CTNNB1 gene or alternatively, in the APC tumor suppressor gene, most often as a germline mutation. Multifocal desmoid tumors are very rare and clinical characteristics are poorly understood. Here we present six sporadic and one familial case of multifocal desmoid tumors. Four female and three male patients, aged between 7 and 30 years (mean 18.4 years) were identified in a cohort of 1392 cases. Tumors were located in (distal) extremities, thorax, breast, abdominal wall, shoulder, and neck. Four cases showed a CTNNB1 mutation and one an APC germline mutation. In two sporadic cases no CTNNB1 mutation was identified. Four patients showed (multiple) recurrences and one patient was lost to follow-up. In conclusion, multifocal desmoid tumors are a very rare disease and may occur in sporadic cases that are characterized by recurrent CTNNB1 mutations. However, the underlying pathogenesis of multifocal desmoid tumors remains poorly understood with often aggressive clinical behavior and challenging therapeutical management.

PMID: 29709394

Baysal Ö, Hamilton JAM, **Hamilton CJCM**, Braat DDM, Beerendonk CCM, Nelen WLDM. Clinical practice guidelines for fertility preservation in young women undergoing gonadotoxic treatment: an overview and critical appraisal of methodological quality and content.

Reprod Biomed Online. 2018 Jul;37(1):60-70. doi: 10.1016/j.rbmo.2018.03.022. Review.

RESEARCH QUESTION: What is the methodological quality and content of internationally available clinical practice guidelines (CPGs) on fertility preservation (FP) care in adult women?

DESIGN: Internationally available CPGs on FP care in adult women were identified after conducting an extensive literature search and consulting (inter)national key experts. The methodological quality of the CPGs was appraised by an (inter)national panel of experts using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The content of the best CPGs, scoring ≥60% for the domain 'Rigour of development' of the AGREE II instrument, was extracted and categorized according to their topic.

RESULTS: Thirty of the 1808 documents found were included. After consulting (inter)national key experts, 30 CPGs were included, six of which scored ≥60% for their 'Rigour of development'. The number of FP-related topics discussed by these six CPGs ranged from 4 to 12. The number of recommendations provided by the CPGs on these topics varied. The number of topics to which ≥5 recommendations were dedicated ranged from 0 to 4 between CPGs.

CONCLUSION: CPGs on the subject of FP care are available, but there is room for improvement in quality and content. Although written for use in daily practice, the CPGs can also be used to develop quality indicators to monitor the quality of current FP care or to evaluate future improvement initiatives.

PMID: 29716912

Simons KS, Boeijen ERK, Mertens MC, Rood P, **de Jager CPC**, van den Boogaard M. Effect of Dynamic Light Application on Cognitive Performance and Well-being of Intensive care Nurses. Am J Crit Care. 2018 May;27(3):245-248. doi: 10.4037/ajcc2018908.

BACKGROUND: Exposure to bright light has alerting effects. In nurses, alertness may be decreased because of shift work and high work pressure, potentially reducing work performance and increasing the risk for medical errors.

OBJECTIVES: To determine whether high-intensity dynamic light improves cognitive performance, self-reported depressive signs and symptoms, fatigue, alertness, and well-being in intensive care unit nurses.

METHODS: In a single-center crossover study in an intensive care unit of a teaching hospital in the Netherlands, 10 registered nurses were randomly divided into 2 groups. Each group worked alternately for 3 to 4 days in patients' rooms with dynamic light and 3 to 4 days in control lighting settings. High-intensity dynamic light was administered through ceiling-mounted fluorescent tubes that delivered bluish white light up to 1700 lux during the daytime, versus 300 lux in control settings. Cognitive performance, self-reported depressive signs and symptoms, fatigue, and well-being before and after each period were assessed by using validated cognitive tests and questionnaires.

RESULTS: Cognitive performance, self-reported depressive signs and symptoms, and fatigue did not differ significantly between the 2 light settings. Scores of subjective well-being were significantly lower after a period of working in dynamic light.

CONCLUSIONS: Daytime lighting conditions did not affect intensive care unit nurses' cognitive performance, perceived depressive signs and symptoms, or fatigue. Perceived quality of life, predominantly in the psychological and environmental domains, was lower for nurses working in dynamic light.

PMID: 29724890

van Leijsen EMC, Bergkamp MI, van Uden IWM, Ghafoorian M, **van der Holst HM**, Norris DG, Platel B, Tuladhar AM, de Leeuw FE. Progression of White Matter Hyperintensities Preceded by Heterogeneous Decline of Microstructural Integrity. Stroke. 2018 Jun;49(6):1386-1393. doi: 10.1161/STROKEAHA.118.020980. Epub 2018 May 3.

BACKGROUND AND PURPOSE: White matter hyperintensities (WMH) are frequently seen on neuroimaging of elderly and are associated with cognitive decline and the development of dementia. Yet, the temporal dynamics of conversion of normal-appearing white matter (NAWM) into WMH remains unknown. We examined whether and when progression of WMH was preceded by changes in fluid-attenuated inversion recovery and diffusion tensor imaging values, thereby taking into account differences between participants with mild versus severe baseline

WMH.
METHODS: From 266 participants of the RUN DMC study (Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort), we semiautomatically segmented WMH at 3 time points for 9 years. Images were registered to standard space through a subject template. We analyzed differences in baseline fluid-attenuated inversion recovery, fractional anisotropy, and mean diffusivity (MD) values and changes in MD values over time between 4 regions: (1) remaining NAWM, (2) NAWM converting into WMH in the second follow-up period, (3) NAWM converting into WMH in the first follow-up period, and (4) WMH.
RESULTS: NAWM converting into WMH in the first or second time interval showed higher fluid-attenuated inversion recovery and MD values than remaining NAWM. MD values in NAWM converting into WMH in the first time interval were similar to MD values in WMH. When stratified by baseline WMH severity, participants with severe WMH had higher fluid-attenuated inversion recovery and MD and lower fractional anisotropy values than participants with mild WMH, in all areas including the NAWM. MD values in WMH and in NAWM that converted into WMH continuously increased over time.
CONCLUSIONS: Impaired microstructural integrity preceded conversion into WMH and continuously declined over time, suggesting a continuous disease process of white matter integrity loss that can be detected using diffusion tensor imaging even years before WMH become visible on conventional neuroimaging. Differences in microstructural integrity between participants with mild versus severe WMH suggest heterogeneity of both NAWM and WMH, which might explain the clinical variability observed in patients with similar small vessel disease severity.

PMID: 29727373

Maher CF, Baessler KK, Barber MD, Cheon C, Consten ECJ, Cooper KG, Deffieux X, Dietz V, Gutman RE, **van Iersel JJ**, Nager CW, Sung VW, de Tayrac R. Summary: 2017 International Consultation on Incontinence Evidence-Based Surgical Pathway for Pelvic Organ Prolapse.
Female Pelvic Med Reconstr Surg. 2018 Apr 28. doi: 10.1097/SPV.0000000000000591
Trefwoorden: internationale richtlijn bekkenbodemverzakkingen

OBJECTIVE: The aim of this article is to summarize the relevant findings that inform the 2017 International Consultation on Incontinence pathway for surgical treatment of pelvic organ prolapse (POP).
METHODS: We conducted an evidence-based review of the English-language peer-reviewed literature relating to POP surgery published prior to December 2016. Level 1 evidence (randomized controlled trials [RCTs] or systematic reviews of RCTs) was preferred; however, level 2 (poor-quality RCT, prospective cohort studies) or 3 evidence (case series or retrospective studies) has been included if level 1 data were lacking. The committee evaluated the literature and made recommendations based on the Oxford grading system summarized as follows: grade A recommendation usually depends on consistent level 1 evidence; grade B recommendation usually depends on consistent level 2 and/or 3 studies, or "majority evidence" from RCTs; grade C recommendation usually depends on level 3 studies or "majority evidence" from level 2/3 studies or Delphi-processed expert opinion; grade D, "no recommendation possible," would be used where the evidence is inadequate or conflicting.
RESULTS: The recommendations from each chapter of the review are presented and serve to inform an evidence-based pathway for the surgical treatment of prolapse. A Web-based interactive application of the pathway is presented.
CONCLUSIONS: The 2017 International Consultation on Incontinence pathway on surgery for POP is designed as an adjunct to transparent consultation and consent relating to POP surgery. The final decision regarding surgical intervention can be made only after a shared decision-making process between the patient and the clinician that will evaluate a variety of individual factors that cannot be assessed in the pathway.

PMID: 29728150

Wassenaar A, Schoonhoven L, Devlin JW, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, **Simons KS**, Egerod I, Burry LD, Beishuizen A, Matos J, Donders ART, Pickkers P, van den Boogaard M.; Delirium prediction in the intensive care unit: comparison of two delirium prediction models.
Crit Care. 2018 May 5;22(1):114

BACKGROUND: Accurate prediction of delirium in the intensive care unit (ICU) may facilitate efficient use of early preventive strategies and stratification of ICU patients by delirium risk in clinical research, but the optimal delirium prediction model to use is unclear. We compared the predictive performance and user convenience of the prediction model for delirium (PRE-DELIRIC) and early prediction model for delirium (E-PRE-DELIRIC) in ICU patients and determined the value of a two-stage calculation.
METHODS: This 7-country, 11-hospital, prospective cohort study evaluated consecutive adults admitted to the ICU who could be reliably

assessed for delirium using the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist. The predictive performance of the models was measured using the area under the receiver operating characteristic curve. Calibration was assessed graphically. A physician questionnaire evaluated user convenience. For the two-stage calculation we used E-PRE-DELIRIC immediately after ICU admission and updated the prediction using PRE-DELIRIC after 24 h.
RESULTS: In total 2178 patients were included. The area under the receiver operating characteristic curve was significantly greater for PRE-DELIRIC (0.74 (95% confidence interval 0.71-0.76)) compared to E-PRE-DELIRIC (0.68 (95% confidence interval 0.66-0.71)) (z score of -2.73 ($p < 0.01$)). Both models were well-calibrated. The sensitivity improved when using the two-stage calculation in low-risk patients. Compared to PRE-DELIRIC, ICU physicians (n = 68) rated the E-PRE-DELIRIC model more feasible.
CONCLUSIONS: While both ICU delirium prediction models have moderate-to-good performance, the PRE-DELIRIC model predicts delirium better. However, ICU physicians rated the user convenience of E-PRE-DELIRIC superior to PRE-DELIRIC. In low-risk patients the delirium prediction further improves after an update with the PRE-DELIRIC model after 24 h.
TRIAL REGISTRATION: ClinicalTrials.gov, NCT02518646 . Registered on 21 July 2015.

PMID: 29729143

Janssens PMW, **van der Horst A**. Improved prospective risk analysis for clinical laboratories compensated for the throughput in processes.
Clin Chem Lab Med. 2018 Oct 25;56(11):1878-1885. doi: 10.1515/cclm-2018-0109.

BACKGROUND: Practical application of prospective risk analysis (PRA) in clinical laboratories should reflect processes as they are carried out, while making the PRA results obtained from different processes comparable. This means that not only STAT and standard testing and testing for critical and less critical parameters should be distinguished (as published), but also that the throughput in processes and process steps should be taken into account.
METHODS: Building on our previously published PRA, a method was developed to compensate for the throughput in processes and process steps. A factor T, related to the actually observed throughput, was introduced in the risk score calculation. Introduction of this compensation factor leads to different overall risk scores. The criteria by which the risk scores are evaluated were modified accordingly.
RESULTS: Introduction of a factor in the PRA to compensate for throughput leads to a change in the risk score for various conceivable failures in process steps. As compared to the PRA in which no compensation for throughput is made, in a process with low throughput the risk score for various conceivable failures in process steps comes out higher after introduction of the compensation factor, while in a process with high throughput various risk scores come out lower.
CONCLUSIONS: Introduction of a factor to account for the throughput in a process (and process steps) leads to an improved, more realistic PRA, the results of which makes the risk scores of different processes (and process steps) better comparable to each other.

PMID: 29738783

Schuurmans J, **Lutgens SP**, Groen L, **Schneeberger PM**. Do safety engineered devices reduce needlestick injuries?
J Hosp Infect. 2018 Sep;100(1):99-104. doi: 10.1016/j.jhin.2018.04.026. Epub 2018 May 5.

BACKGROUND: Needlestick injuries (NSIs) are one of the most common health hazards facing healthcare workers (HCWs) across the globe. Needles with safety engineered devices (SEDs) have been developed to minimize the risk of exposure to blood-borne infections, such as hepatitis B virus, hepatitis C virus and human immunodeficiency virus, associated with NSIs.
AIM: To assess the effect of the introduction of SEDs in preventing NSIs among HCWs at Jeroen Bosch Hospital, the Netherlands.
METHODS: The incidence rates of reported NSIs before and after the introduction of SEDs were compared. All HCWs who reported an NSI with an SED were interviewed in order to understand the underlying causes of the NSIs.
FINDINGS: Despite the introduction of SEDs, the incidence of NSIs increased from 1.9 per 100 HCWs before the introduction of SEDs to 2.2 per 100 HCWs after the introduction of SEDs. The registration of reported SED-related NSIs showed a significant decrease in the number of NSIs related to injection needles and blood sugar needles, while an unexpected significant increase in NSIs with nadroparin calcium needles and infusion needles was found. The most common causes reported for NSIs were unsafe disposal of the needles and problems with the safety feature.
CONCLUSION: The application of SEDs has not led to a reduction in NSIs. The majority of NSIs caused by a needle with an SED can be prevented by stimulation of safe needle disposal, proper use of SEDs, and provision of feedback to manufacturers to keep improving product design.

PMID: 29743106

van Rijswijk J, van Welie N, Dreyer K, van Hooff MHA, **de Bruin JP**, Verhoeve HR, Mol F, Kleiman-Broeze KA, Traas MAF, Muijsers GJJM, Manger AP, Gianotten J, de Koning CH, Koning AMH, Bayram N, van der Ham DP, Vrouenraets FPJM, Kalafusova M, van de Laar BIG, Kaijser J, van Oostwaard MF, Meijer WJ, Broekmans FJM, Valkenburg O, van der Voet LF, van Disseldorp J, Lambers MJ, Peters HE, Lier MCI, Lambalk CB, van Wely M, Bossuyt PMM, Stoker J, van der Veen F, Mol BWJ, Mijatovic V.
The FOAM study: is Hysterosalpingo foam sonography (HyFoSy) a cost-effective alternative for hysterosalpingography (HSG) in assessing tubal patency in subfertile women? Study protocol for a randomized controlled trial.
BMC Womens Health. 2018 May 9;18(1):64. doi: 10.1186/s12905-018-0556-6.

BACKGROUND: Tubal pathology is a causative factor in 20% of subfertile couples. Traditionally, tubal testing during fertility work-up is performed by hysterosalpingography (HSG). Hysterosalpingo-foam sonography (HyFoSy) is a new technique that is thought to have comparable accuracy as HSG, while it is less expensive and more patient friendly. HyFoSy would be an acceptable alternative for HSG, provided it has similar effectiveness in terms of patient outcomes.
METHODS/DESIGN: We aim to compare the effectiveness and costs of management guided by HyFoSy or by HSG. Consenting women will undergo tubal testing by both HyFoSy and HSG in a randomized order during fertility work-up. The study group will consist of 1163 subfertile women between 18 and 41 years old who are scheduled for tubal patency testing during their fertility work-up. Women with anovulatory cycles not responding to ovulation induction, endometriosis, severe male subfertility or a known contrast (iodine) allergy will be excluded.
We anticipate that 7 % (N = 82) of the participants will have discordant test results for HyFoSy and HSG. These participants will be randomly allocated to either a management strategy based on HyFoSy or a management strategy based on HSG, resulting in either a diagnostic laparoscopy with chromopertubation or a strategy that assumes tubal patency (intrauterine insemination or expectant management).
The primary outcome is ongoing pregnancy leading to live birth within 12 months after randomization. Secondary outcomes are patient pain scores, time to pregnancy, clinical pregnancy, miscarriage rate, multiple pregnancy rate, preterm birth rate and number of additional treatments. Costs will be estimated by counting resource use and calculating unit prices.
DISCUSSION: This trial will compare the effectiveness and costs of HyFoSy versus HSG in assessing tubal patency in subfertile women.
TRIAL REGISTRATION: Dutch Trial Register (NTR 4746, http://www.trialregister.nl). Date of registration: 19 August 2014.

PMID: 29759590

de Lange SV, Bakker MF, Monninkhof EM, Peeters PHM, de Koekkoek-Doll PK, Mann RM, **Rutten MJCM**, Bisschops RHC, Veltman J, Duvivier KM, Lobbes MBI, de Koning HJ, Karssemeijer N, Pijnappel RM, Veldhuis WB, van Gils CH. Reasons for (non) participation in supplemental population-based MRI breast screening for
women with extremely dense breasts.
Clin Radiol. 2018 Aug;73(8):759.e1-759.e9. doi: 10.1016/j.crad.2018.04.002. Epub 2018 Jun 18.

AIM: To determine the willingness of women with extremely dense breasts to undergo breast cancer screening with magnetic resonance imaging (MRI) in a research setting, and to examine reasons for women to participate or not.
MATERIALS AND METHODS: Between 2011 and 2015, 8,061 women (50-75 years) were invited for supplemental MRI as part of the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial (ClinicalTrials.gov Identifier: NCT01315015), after a negative screening mammography in the national population-based mammography screening programme. Demographics of participants and non-participants were compared. All invitees were asked to report reasons for (non)participation. Ethical approval was obtained. Participants provided written informed consent.
RESULTS: Of the 8,061 invitees, 66% answered that they were interested, and 59% eventually participated. Participants were on average 54-years old (interquartile range: 51-59 years), comparable to women with extremely dense breasts in the population-based screening programme (55 years). Women with higher socio-economic status (SES) were more often interested in participation than women with lower SES (68% versus 59%, p<0.001). The most frequently stated reasons for non-participation were "MRI-related inconveniences and/or self-reported contraindications to MRI" (27%) and "anxiety regarding the result of supplemental screening" (21%). "Expected personal health benefit" (68%) and "contribution to science" (43%) were the most frequent reasons for participation.
CONCLUSION: Of women invited for MRI because of extremely dense breasts, 59% participated. Common reasons for non-participation were "MRI-related inconveniences" and "anxiety regarding the result of supplemental screening". In case of future implementation, availability of precise evidence on benefits and harms might reduce this anxiety.

PMID: 29767323

Collet MO, Caballero J, Sonneville R, Bozza FA, Nydahl P, Schandl A, Wøien H, Citerio G, van den Boogaard M, Hästbacka J, Haenggi M, Colpaert K, Rose L, Barbateskovic M, Lange T, Jensen A, Krog MB, Egerod I, Nibro HL, Wetterslev J, Perner A; **AID-ICU cohort study co-authors (Simons KS)**. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. Intensive Care Med. 2018 Jul;44(7):1081-1089
Trefwoorden; Risicofactoren delier

PURPOSE: We assessed the prevalence and variables associated with haloperidol use for delirium in ICU patients and explored any associations of haloperidol use with 90-day mortality.
METHODS: All acutely admitted, adult ICU patients were screened during a 2-week inception period. We followed the patient throughout their ICU stay and assessed 90-day mortality. We assessed patients and their variables in the first 24 and 72 h in ICU and studied their association together with that of ICU characteristics with haloperidol use.
RESULTS: We included 1260 patients from 99 ICUs in 13 countries. Delirium occurred in 314/1260 patients [25% (95% confidence interval 23-27)] of whom 145 received haloperidol [46% (41-52)]. Other interventions for delirium were benzodiazepines in 36% (31-42), dexmedetomidine in 21% (17-26), quetiapine in 19% (14-23) and olanzapine in 9% (6-12) of the patients with delirium. In the first 24 h in the ICU, all subtypes of delirium [hyperactive, adjusted odds ratio (aOR) 29.7 (12.9-74.5); mixed 10.0 (5.0-20.2); hypoactive 3.0 (1.2-6.7)] and circulatory support 2.7 (1.7-4.3) were associated with haloperidol use. At 72 h after ICU admission, circulatory support remained associated with subsequent use of haloperidol, aOR 2.6 (1.1-6.9). Haloperidol use within 0-24 h and within 0-72 h of ICU admission was not associated with 90-day mortality [aOR 1.2 (0.5-2.5); p = 0.66] and [aOR 1.9 (1.0-3.9); p = 0.07], respectively.
CONCLUSIONS: In our study, haloperidol was the main pharmacological agent used for delirium in adult patients regardless of delirium subtype. Benzodiazepines, other anti-psychotics and dexmedetomidine were other frequently used agents. Haloperidol use was not statistically significantly associated with increased 90-day mortality.

PMID: 29770839

Mertens BJ, Kwint HF, **van Marum RJ**, Bouvy ML. Are multidose drug dispensing systems initiated for the appropriate patients?
Eur J Clin Pharmacol. 2018 Sep;74(9):1159-1164. doi: 10.1007/s00228-018-2478-5.

PURPOSE: It is unknown if multidose drug dispensing (MDD) systems are initiated for the appropriate patients. Therefore, the objective of this study was to compare the medication management problems of patients who were about to start with a MDD system (MDD patients) and patients who continued manually dispensed medication (non-MDD users) in order to identify if the appropriate patients receive a MDD system.
METHODS: Patient interviews (semi-structured) were conducted by 44 community pharmacists at the patient's home. Patients over 65 years of age, home dwelling and using at least five chronic drugs, were eligible for the study. An assessment tool was developed including 22 potential medication management problems, covering four domains: functional (7), organizational (7), medication adherence (6), and medication knowledge (2). Median scores were calculated with the interquartile range. Additionally, cognitive function was assessed with the Mini-Cog and frailty using the Groningen Frailty Indicator.
RESULTS: One hundred eighty-eight MDD users and 230 non-MDD users were interviewed. MDD users were older, more often female, and using more drugs. Forty-two percent of the MDD users were possibly cognitively impaired and 63% were assessed as frail compared to 20 and 27% respectively of the non-MDD users. MDD users had more potential organizational problems (3 vs. 1; p < 0.01), functional problems (2 vs. 1; p < 0.01), medication adherence problems (1 vs. 0; p < 0.01), and medication knowledge problems (1 vs. 0; p < 0.01) compared to non-MDD users. Seventy percent of the MDD users scored six or more potential medication management problems while this was 22% among non-MDD users.
CONCLUSIONS: The majority of MDD systems were initiated for patients who experienced multiple potential medication management problems suggesting a decreased medication management capacity.

PMID: 29772837

van Steenhoven JEC, Kuijer A, van Diest PJ, van Gorp JM, Straver M, Elias SG, Wesseling J, Rutgers E, Timmer-Bonte JNH, Nieboer P, **Smilde TJ**, Imholz A, Blanken CFJM, Siesling S, van Dalen T. Conventional Pathology Versus Gene Signatures for Assessing Luminal A and B Type Breast Cancers: Results of a Prospective Cohort
Study.
Genes (Basel). 2018 May 17;9(5). pii: E261. doi: 10.3390/genes9050261.

In this study, in estrogen receptor positive (ER+) early stage breast cancer patients who were considered candidates for 70-gene signature (70-GS, "MammaPrint") use, we compared molecular subtyping (MS) based on the previously validated 80-gene signature (80-GS, "BluePrint") versus surrogate pathological subtyping (PS). Between 1 January 2013 and 31 December 2015, 595 clinical intermediate risk ER+ early stage breast cancer patients were enrolled. Hormone receptor (HR) and HER2 receptor status were determined by conventional pathology using immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). Ki67 was assessed in a subset of patients. The overall concordance between PS and MS for luminal type cancers (A and B together) was 98%. The concordance between PS and MS for luminal A and luminal B type cancers based on the Bloom Richardson histological grade (BR) (n = 586) or Ki67 (n = 185) was low: 64% (Kappa 0.20 [95% CI 0.11-0.28]) and 65% (Kappa 0.22 [95% CI 0.062-0.37]), respectively. In this prospective study (NCT02209857) of a selection of ER+ and predominantly HER2- early-stage breast cancer patients, the additional ability of the 80-GS to distinguish between luminal, HER2-type and basal-like cancers was inherently very limited. The distinction of luminal-type tumors into A and B according to Ki67 status or BR grade versus the 70-GS revealed poor concordance.

PMID: 29776554

van Eijk JJJ, Cintas P, Jacobs BC, Kamar N, Dalton HR. Reply to: "Association of hepatitis E virus infection and myasthenia gravis: A pilot study".
J Hepatol. 2018 Jun;68(6):1321-1322. doi: 10.1016/j.jhep.2018.02.017.
No abstract available.

PMID: 29781837

Derikx LAAP, de Jong ME, Hoentjen F. Short article: Recommendations on rectal surveillance for colorectal cancer after subtotal colectomy in patients with inflammatory bowel disease.
Eur J Gastroenterol Hepatol. 2018 Aug;30(8):843-846. doi: 10.1097/MEG.0000000000001171.

Approximately 30% of patients with ulcerative colitis require a colectomy during their disease course. This substantially reduces colorectal cancer risk, although it is still possible to develop colorectal neoplasia in the remaining rectum. Although clear and well-accepted surveillance guidelines exist for patients with inflammatory bowel disease with an intact colon, specific surveillance recommendations following colectomy are less clear. Here, we aim to summarize the prevalence, incidence, and risk factors for developing colorectal cancer in patients with inflammatory bowel disease who underwent subtotal colectomy with a permanent end ileostomy and rectal stump, or with ileorectal anastomosis. Subsequently, gained insights are integrated into a proposed endoscopic surveillance strategy of the residual rectum.

PMID: 29786516

Mertens BJ, Kwint HF, **van Marum RJ**, Bouvy ML. Immediate or deferred adjustment of drug regimens in multidose drug dispensing systems.
Res Social Adm Pharm. 2019 Mar;15(3):303-309. doi: 10.1016/j.sapharm.2018.05.008. Epub 2018 May 18.

BACKGROUND: Multidose drug dispensing (MDD) is used to help patients take their medicines appropriately. Little is known about drug regimen changes within these MDD systems and how they are effectuated by the community pharmacist. Manual immediate adjustments of the MDD system could introduce dispensing errors. MDD guidelines therefore recommend to effectuate drug regimen changes at the start of a new MDD system.
OBJECTIVE: The aim of this study was to investigate the frequency, type, procedure followed, immediate necessity, and time taken to make MDD adjustments.
METHODS: This was a cross-sectional study in eight community pharmacies in the Netherlands. All adjustments to MDD systems were systematically documented for 3 weeks by the community pharmacist.
RESULTS: Overall, 261 MDD adjustments involving 364 drug changes were documented for 250 patients: 127 (35%) drug changes involved the addition of a new drug, 124 (34%) a change in dosage, and 95 (26%) drug discontinuation. Of the MDD adjustments, 135 (52%) were effectuated immediately: 81 (31%) by adjusting the MDD system manually, 49 (19%) by temporarily dispensing the drug separately from the MDD system, and 5 (2%) by ordering a new MDD system. Pharmacists considered that 36 (27%) of the immediate MDD adjustments could have been deferred until the next MDD system was produced. Immediate adjustment took significantly longer than deferred adjustment ($p < 0.001$).

CONCLUSIONS: This study shows that in patients using MDD systems, over half of the drug regimen changes are adjusted immediately. The necessity of these immediate changes should be critically evaluated.

PMID: 29787930

Flucke U, Shepard SJ, **Bekers EM**, Tirabosco R, van Diest PJ, Creytens D, van Gorp JM. Fibro-osseous pseudotumor of digits - Expanding the spectrum of clonal transient neoplasms harboring USP6 rearrangement.
Ann Diagn Pathol. 2018 Aug;35:53-55. doi: 10.1016/j.anndiagpath.2018.05.003.

Fibro-osseous pseudotumors of the digits (FOPD) is a rare self-limiting lesion composed of bland looking hypercellular fibrous tissue and bone. USP6 rearrangement is a consistent genetic finding in aneurysmal bone cyst, nodular fasciitis, myositis ossificans and giant cell lesions of small bones. We report herein the occurrence of USP6 rearrangement in fibro-osseous pseudotumors of the digits using fluorescence in situ hybridization analysis (FISH). Of the five patients included, three were female and two were male. The age ranged from 33 to 72 years (mean 48 years). Lesions arose in the palm (n = 2), thenar (n = 1), middle finger (n = 1) and great toe (n = 1). All patients underwent resection. Four cases (80%) harbored USP6 rearrangements showing that fibro-osseous pseudotumors of digits belongs to the spectrum of clonal transient neoplasms including aneurysmal bone cyst, nodular fasciitis, myositis ossificans and giant cell lesion of small bones.

PMID: 29801516

Simons KS, van den Boogaard M, Hendriksen E, Gerretsen J, van der Hoeven JG, Pickkers P, **de Jager CPC**. Temporal biomarker profiles and their association with ICU acquired delirium: a cohort study.
Crit Care. 2018 May 25;22(1):137. doi: 10.1186/s13054-018-2054-5.
Trefwoorden; Biomarkers, delierpredictie

BACKGROUND: Neuroinflammation is thought to play an important role in the pathogenesis of ICU-acquired delirium, but the association between inflammatory and brain-specific proteins and ICU delirium is poor. We investigated whether or not serial determinations of markers may improve this association.
METHODS: Critically ill patients with a high risk of ICU delirium and with an ICU length of stay of at least 6 days were included in the study. Blood was drawn on days 1, 2, 4 and 6 after ICU admission and analyzed for different markers of inflammation and several brain proteins. Differences in courses over time prior to and following the onset of delirium and absolute differences over time were analyzed in patients with and without delirium using repeated measurement analysis of variance. In addition, a cross-sectional analysis of levels of these markers before the first onset of delirium was performed.
RESULTS: Fifty patients were included in this study. In the longitudinal analysis, there were no differences in the levels of any of the markers immediately prior to and following the onset of delirium, but overall, median levels of adiponectin (9019 (IQR 5776-15,442) vs. 6148 (IQR 4447-8742) ng/ml, p = 0.05) were significantly higher in patients with delirium compared to patients without delirium. In the cross-sectional analysis, median levels of the brain protein Tau (90 (IQR 46-224) vs. 31 (IQR 31-52) pg/ml, p = 0.009) and the ratio Tau/amyloid β1-42 (1.42 ((IQR 0.9-2.57) vs. 0.68 (IQR 0.54-0.96), p = 0.003) were significantly higher in patients with hypoactive delirium compared to patients without. Levels of neopterin (111 (IQR 37-111) vs. 29 (IQR 16-64) mmol/l, p = 0.004) and IL-10 (28 (IQR 12-39) vs. 9 (IQR 4-12) pg/ml, p = 0.001) were significantly higher in patients with hypoactive delirium compared to patients with mixed-type delirium.
CONCLUSIONS: While there are differences in markers (adiponectin and several brain proteins) between patients with and without delirium, the development of delirium is not preceded by a change in the biomarker profile of inflammatory markers or brain proteins. Patients with hypoactive delirium account for the observed differences in biomarkers.
TRIAL REGISTRATION: ClinicalTrials.gov, NCT 01274819 . Registered on 12 January 2011.

PMID: 29858927

Kerckhoffs APM, Hartong EGTM, Grootens KP. The perspectives of patients with lithium-induced end-stage renal disease.
Int J Bipolar Disord. 2018 Jun2;6(1):13. doi: 10.1186/s40345-018-0121-0.

BACKGROUND: Lithium is the treatment of choice for patients suffering from bipolar disorder (BD) but prolonged use induces renal dysfunction in at least 20% of patient. Intensive monitoring of kidney functioning helps to reveal early decline in renal failure. This study investigates the views and experiences of BD patients who have developed end-stage renal disease and were receiving renal replacement therapy.

RESULTS: The patients overall reported not to have been offered alternative treatment options at the start of lithium therapy or when renal functions deteriorated. All indicated to have lacked sound information and dialogue in accordance with shared decision making. Kidney monitoring was inadequate in many cases and decision making rushed.
CONCLUSIONS: Retrospectively, the treatment and monitoring of lithium and the information process were inadequate in many cases. We give suggestions on how to inform patients taking lithium for their BD timely and adequately on the course of renal function loss in the various stages of their treatment.

PMID: 29859113

van Gorp DAM, van der Klink JJL, Abma FI, Jongen PJ, van Lieshout I, Arnoldus EPJ, Beenakker EAC, Bos HM, **van Eijk JJJ**, Fermont J, Frequin STFM, de Gans K, Hengstman GJD, Hupperts RMM, Mostert JP, Pop PHM, Verhagen WIM, Zemel D, Heerings MAP, Reneman MF, Middelkoop HAM, Visser LH, van der Hiele K. The capability set for work - correlates of sustainable employability in workers with multiple sclerosis. Health Qual Life Outcomes. 2018 Jun 1;16(1):113. doi: 10.1186/s12955-018-0942-7.

BACKGROUND: The aim of this study was to examine whether work capabilities differ between workers with Multiple Sclerosis (MS) and workers from the general population. The second aim was to investigate whether the capability set was related to work and health outcomes.
METHODS: A total of 163 workers with MS from the MS@Work study and 163 workers from the general population were matched for gender, age, educational level and working hours. All participants completed online questionnaires on demographics, health and work functioning. The Capability Set for Work Questionnaire was used to explore whether a set of seven work values is considered valuable (A), is enabled in the work context (B), and can be achieved by the individual (C). When all three criteria are met a work value can be considered part of the individual's 'capability set'.
RESULTS: Group differences and relationships with work and health outcomes were examined. Despite lower physical work functioning ($U = 4250$, $p = 0.001$), lower work ability ($U = 10591$, $p = 0.006$) and worse self-reported health ($U = 9091$, $p \leq 0.001$) workers with MS had a larger capability set ($U = 9649$, $p \leq 0.001$) than the general population. In workers with MS, a larger capability set was associated with better flexible work functioning ($r = 0.30$), work ability ($r = 0.25$), self-rated health ($r = 0.25$); and with less absenteeism ($r = -0.26$), presenteeism ($r = -0.31$), cognitive/neuropsychiatric impairment ($r = -0.35$), depression ($r = -0.43$), anxiety ($r = -0.31$) and fatigue ($r = -0.34$).
CONCLUSIONS: Workers with MS have a larger capability set than workers from the general population. In workers with MS a larger capability set was associated with better work and health outcomes.
TRIAL REGISTRATION: This observational study is registered under NL43098.008.12: 'Voorspellers van arbeidsparticipatie bij mensen met relapsing-remitting Multiple Sclerose'. The study is registered at the Dutch CCMO register (https://www.toetsingonline.nl). This study is approved by the METC Brabant, 12 February 2014. First participants are enrolled 1st of March 2014.

PMID: 29863955

Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Kelsch C, Lee A, Coleman S, Deng Y, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A, Reck M; IMpower150 Study Group (**Biesma B**). tezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-2301. doi: 10.1056/NEJMoa1716948.

BACKGROUND: The cancer-cell-killing property of atezolizumab may be enhanced by the blockade of vascular endothelial growth factor-mediated immunosuppression with bevacizumab. This open-label, phase 3 study evaluated atezolizumab plus bevacizumab plus chemotherapy in patients with metastatic nonsquamous non-small-cell lung cancer (NSCLC) who had not previously received chemotherapy.
METHODS: We randomly assigned patients to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The two primary end points were investigator-assessed progression-free survival both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with EGFR or ALK genetic alterations were excluded) and among patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population) and overall survival in the WT population. The ABCP group was compared with the BCP group before the ACP group was compared with the BCP group.
RESULTS: In the WT population, 356 patients were assigned to the ABCP group, and 336 to the BCP group. The median progression-free survival was longer in the ABCP group than in the BCP group (8.3 months vs. 6.8 months; hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.52 to 0.74; $P<0.001$); the corresponding values in the Teff-high WT population were 11.3 months and 6.8 months (hazard ratio, 0.51 [95% CI, 0.38 to 0.68]; $P<0.001$). Progression-free survival was also longer in the ABCP group than in the

BCP group in the entire intention-to-treat population (including those with EGFR or ALK genetic alterations) and among patients with low or negative programmed death ligand 1 (PD-L1) expression, those with low Teff gene-signature expression, and those with liver metastases. Median overall survival among the patients in the WT population was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; hazard ratio for death, 0.78; 95% CI, 0.64 to 0.96; P=0.02). The safety profile of ABCP was consistent with previously reported safety risks of the individual medicines.
CONCLUSIONS: The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status. (Funded by F. Hoffmann-La Roche/Genentech; IMpower150 ClinicalTrials.gov number, NCT02366143 .).

PMID:29870855

van der Does Y, Limper M, **Jie KE**, Schuit SCE, **Jansen H**, Pernot N, van Rosmalen J, Poley MJ, Ramakers C, Patka P, van Gorp ECM, Rood PPM. Procalcitonin-guided antibiotic therapy in patients with fever in a general emergency department population: a multicenter noninferiority randomized clinical trial (HiTEMP study).
Clinical Microbiol Infect. 2018. 1282-1289.
Trefwoorden: Koorts en spoedeisende hulp.

OBJECTIVES: Overuse of broad-spectrum antibiotics in emergency departments (EDs) results in antibiotic resistance. We determined whether procalcitonin (PCT) -guided therapy can be used to reduce antibiotic regimens in EDs by investigating efficacy, safety and accuracy.
METHODS: This was a non-inferiority multicentre randomized clinical trial, performed in two Dutch hospitals. Adult patients with fever ≥38.2°C (100.8°F) in triage were randomized between standard diagnostic workup (control group) and PCT-guided therapy, defined as standard workup with the addition of one single PCT measurement. The treatment algorithm encouraged withholding antibiotic regimens with PCT <0.5 μg/L, and starting antibiotic regimens at PCT ≥0.5 μg/L. Exclusion criteria were immunocompromised conditions, pregnancy, moribund patients, patients <72 h after surgery or requiring primary surgical intervention. Primary outcomes were efficacy, defined as number of prescribed antibiotic regimens; safety, defined as combined safety end point consisting of 30 days mortality, intensive-care unit admission, ED return visit within 2 weeks; accuracy, defined as sensitivity, specificity and area-under-the-curve (AUC) of PCT for bacterial infections. Non-inferiority margin for safety outcome was 7.5%.
RESULTS: Between August 2014 and January 2017, 551 individuals were included. In the PCT-guided group (n = 275) 200 (73%) patients were prescribed antibiotic regimens, in the control group (n = 276) 212 (77%) patients were prescribed antibiotics (p 0.28). There was no significant difference in combined safety end point between the PCT-guided group, 29 (11%), and control group, 46 (16%) (p 0.16), with a non-inferiority margin of 0.46% (n = 526). AUC for confirmed bacterial infections for PCT was 0.681 (95% CI 0.633-0.730), and for CRP was 0.619 (95% CI 0.569-0.669).
CONCLUSIONS: PCT-guided therapy was non-inferior in terms of safety, but did not reduce prescription of antibiotic regimens in an ED population with fever. In this heterogeneous population, the accuracy of PCT in diagnosing bacterial infections was poor. TRIAL REGISTRATION IN NETHERLANDS TRIAL REGISTER: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4949.

PMID: 29876710

van Velzen MHN, Stolker RJ, Loeve AJ, Niehof SP, Mik EG. Comparison between pulse wave velocities measured using Complior and measured using Biopac.

Abstract
Arterial stiffness is a reliable prognostic parameter for cardiovascular diseases. The effect of change in arterial stiffness can be measured by the change of the pulse wave velocity (PWV). The Complior system is widely used to measure PWV between the carotid and radial arteries by means of piezoelectric clips placed around the neck and the wrist. The Biopac system is an easier to use alternative that uses ECG and simple optical sensors to measure the PWV between the heart and the fingertips, and thus extends a bit more to the peripheral vasculature compared to the Complior system. The goal of this study was to test under various conditions to what extent these systems provide comparable and correlating values. 25 Healthy volunteers, 20-30 years old, were measured in four sequential position: sitting, lying, standing and sitting. The results showed that the Biopac system measured consistently and significantly lower PWV values than the Complior system, for all positions. Correlation values and Bland-Altman plots showed that despite the difference in PWV magnitudes obtained by the two systems the measurements did agree well. Which implies that as long as the differences in PWV magnitudes are taken into account, either system could be used to measure PWV changes over time. However, when basing diagnosis on absolute PWV values, one should be very much aware of how the PWV was measured and with what system

PMID: 29880095

Blenke AA, van Marum RJ, Vermeulen Windsant-van den Tweel AM, Hermens WA, Derijks HJ. Deprescribing in Newly Admitted Psychogeriatric Nursing Facility Patients.
Consult Pharm. 2018 Jun 1;33(6):331-338. doi: 10.4140/TCP.n.2018.331.

OBJECTIVE: To determine whether advised changes as a result of structured medication reviews in psychogeriatric patients were implemented and if the implemented changes were maintained.
DESIGN: Prospective cohort study.
SETTING: Three nursing facilities in The Netherlands.
PATIENTS, PARTICIPANTS: Newly admitted psychogeriatric residents.
INTERVENTION: After admission, a structured medication review was performed by a pharmacist and physician resulting in a treatment plan that was approved by the patient's legal representative and implemented.
MAIN OUTCOME MEASURE(S): The percentage of advised changes approved (= approval rate) and the percentage of implemented medication changes still present 90 days after approval (= 90-day implementation rate).
RESULTS: A total of 45 patients were included who used a total number of 333 drugs (mean ± standard deviation 7.4 ± 3.3 drugs). Changes were advised to 159 medications used by 42 patients. Of these changes, 150 were approved (approval rate 94.3%). Finally, 105 were implemented, and 89 were still implemented after 90 days (90-day implementation rate 84.8%). Overall, 59.7% of the advised changes concerned deprescribing (stopping or dose reduction). The proportion of advised changes implemented was similar for symptommodifying and risk-modifying drugs, namely, almost 85%. Overall, 55.3% of the recommended changes to deprescribe concerned 10 drug groups.
CONCLUSION: Medication could be successfully deprescribed from psychogeriatric patients after structured medication reviews performed by pharmacists and nursing facility physicians. More than 50% of the advised changes to deprescribe involved 10 drug groups, which raises the question whether the structured medication review can be performed more efficiently by focusing on the most common problems.

PMID: 29894393

van Strien AM, Souverein PC, **Keijsers CJPW**, Heerdink ER, **Derijks HJ, van Marum RJ**. Association Between Urinary Tract Infections and Antipsychotic Drug Use in Older Adults.
J Clin Psychopharmacol. 2018 Aug;38(4):296-301. doi:10.1097/JCP.0000000000000895.

Antipsychotic drugs are frequently prescribed to older adults, but they may be associated with serious adverse effects. The objective was to investigate the association between use of antipsychotics in older adults and the risk of urinary tract infections (UTIs).This study was designed as a cohort study.Data were obtained from the Clinical Practice Research Datalink from January 1, 2000, to September 29, 2016.Primary care patients 65 years or older in the United Kingdom with a first prescription for an oral antipsychotic were included in the study.Incidence of UTIs was calculated for periods with and without exposure to antipsychotic drugs in one cohort. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate hazard ratios (HRs) with 95% confidence interval (CI).During the study period, 191,827 individuals with a first prescription for an oral antipsychotic drug were identified. Current use of antipsychotics was associated with an increased risk of UTI compared with past use (adjusted HR, 1.31; 95% CI, 1.28-1.34). This effect was strongest in the first 14 days of use (adjusted HR, 1.83; 95% CI, 1.73-1.95) and in individuals who used more than one antipsychotic drug concomitantly (adjusted HR, 1.64; 95% CI, 1.45-1.87). The risk was slightly higher for typical antipsychotics than for atypical antipsychotics. Stratification by sex showed that risk estimates were slightly higher in men than in women.Use of antipsychotics was associated with an increased risk of UTIs in both men and women, particularly in the first weeks after the start of treatment.

PMID: 29945042

van den Brink MJ, Beelen P, Herman MC, Claassen NJJ, Bongers MY, Geomini PM, **van der Steeg JW**, van den Wijngaard L, van Wely M. Women's preferences for the levonorgestrel intrauterine system versus endometrial ablation for heavy menstrual bleeding.
Eur J Obstet Gynecol Reprod Biol. 2018 Sep;228:143-147. doi: 10.1016/j.ejogrb.2018.06.020. Epub 2018 Jun 12.

OBJECTIVES: Women's preferences for treatment of heavy menstrual bleeding (HMB) are important in clinical decision-making. Our aim was to investigate whether women with HMB have a preference for treatment characteristics of the levonorgestrel intrauterine system (LNG-IUS) or endometrial ablation and to assess the relative importance of these characteristics.
STUDY DESIGN: A discrete choice experiment was performed in general practices and gynaecology outpatient clinics in the Netherlands. Women with HMB were asked to choose between hypothetical profiles containing characteristics of LNG-IUS or endometrial ablation.

Characteristics included procedure performed by gynaecologist or general practitioner; reversibility of the procedure; probability of dysmenorrhea; probability of irregular bleeding; additional use of contraception; need to repeat the procedure after five years; and treatment containing hormones. Data were analysed using panel mixed logit models. The main outcome measures were the relative importance of the characteristics and willingness to make trade-offs.
RESULTS: 165 women completed the questionnaire; 36 (22%) patients were recruited from general practices and 129 (78%) patients were recruited from gynaecology outpatient clinics. The characteristic found most important was whether a treatment contains hormones. Women preferred a treatment without hormones, a treatment with the least side effects, and no need for a repeat procedure or additional contraception. Women completing the questionnaire at the gynaecology outpatient clinic differed from women in primary care in their preference for a definitive treatment to be performed by a gynaecologist.
CONCLUSIONS: Whether or not a treatment contains hormones was the most important characteristic influencing patient treatment choice for HMB. Participants preferred characteristics that were mostly related to endometrial ablation, but were willing to trade-off between characteristics.

PMID: 29973187

Baijens SWE, **Huppelschoten AG**, Van Dillen J, Aarts JWM. Improving shared decision-making in a clinical obstetric ward by using the three questions intervention, a pilot study.
BMC Pregnancy Childbirth. 2018 Jul 4;18(1):283. doi: 10.1186/s12884-018-1921-z.

BACKGROUND: Shared decision-making (SDM) is an important aspect of modern health care. Many studies evaluated different interventions to improve SDM, however, none in an inpatient clinical setting. A tool that has been proven effective in an outpatient department is the three questions intervention. These questions are created for patients to get optimal information from their medical team and to make an informed medical decision. In this study, we evaluated the feasibility and effectiveness of this simple intervention on SDM in the obstetric inpatient department of a university hospital in the Netherlands.
METHOD: This is a clinical pilot before and after study, using mixed methods with quantitative and qualitative data collection. The three questions were stated on a card; (i.e. 1) What are my options; 2) What are the possible benefits and harms of those options; 3) How likely are each of those benefits and harms to happen to me?). The study period lasted 6 weeks in which all patients admitted to the obstetric ward were asked to participate in the study. In the first 3 weeks patients did not receive the three questions intervention (pre-intervention group). In the final 3 weeks all patients included received the intervention (intervention group). The main quantitative outcome measure was the level of SDM measured using the SDM-Q9 questionnaire at discharge (range 0-100). In addition, interviews with four patients of the intervention group were conducted and qualitatively analyzed.
RESULTS: Thirty-three patients were included in the pre-intervention group, 29 patients in the intervention group. The mean score of the SDM-Q9 in the pre-intervention group was 65.5 (SD 22.83) and in the intervention group 63.2 (SD 20.21), a not statistically significant difference. In the interviews, patients reported the three questions to be very useful. They used the questions mainly as a prompt and encouragement to ask more specific questions.
DISCUSSION: No difference in SDM was found between the two groups, possibly because of a small sample size. Yet the intervention appeared to be feasible and simple to use in an inpatient department. Further studies are needed to evaluate the impact of implementation of these three questions on a larger scale.

PMID: 29974194

Parren LJMT, Giehl K, van Geel M, Frank J. Phenotype variability in tumor disorders of the skin appendages associated with mutations in the CYLD gene.
Arch Dermatol Res. 2018 Sep;310(7):599-606.
Trefwoorden: CYLD en huidadnextumoren

Mutations in the tumor suppressor gene CYLD underlie phenotypically heterogeneous hereditary tumor disorders of the skin appendages. These diseases are inherited autosomal dominantly and include Brooke-Spiegler syndrome (BSS; OMIM 605041), familial cylindromatosis (FC; OMIM 132700) and multiple familial trichoepithelioma (MFT; OMIM 601606). Clinically, cylindromas, trichoepitheliomas and spiradenomas can be found in affected individuals. We sought to elucidate the molecular genetic basis in individuals with newly diagnosed cylindromas, trichoepitheliomas and/or spiradenomas. Mutation analysis using polymerase chain reaction (PCR)-based techniques was performed in seven German patients and one Turkish patient. We detected two missense, two nonsense, two deletions and two duplication mutations in the CYLD gene, of which seven have not yet been reported. No genotype-phenotype correlation was detected amongst the patients. Our data provide additional information on the clinical and molecular genetic heterogeneity of disorders associated with CYLD mutations.

PMID: 29980413
Flucke U, **Bekers EM**, Creytens D, van Gorp JM. COL1A1 is a fusionpartner of USP6 in myositis ossificans - FISH analysis of six cases.
Ann Diagn Pathol. 2018 Oct;36:61-62. doi: 10.1016/j.anndiagpath.2018.06.009.
No abstract available.

PMID: 29982408
van der Have M, Oldenburg B, Kaptein AA, Jansen JM, **Scheffer RCH**, van Tuyl BA, van der Meulen-de Jong AE, Pierik M, Siersema PD, van Oijen MGH, Fidder HH. Corrigendum: Non-adherence to Anti-TNF Therapy is Associated with Illness Perceptions and Clinical Outcomes in Outpatients with Inflammatory Bowel Disease: Results from a Prospective Multicentre Study.
J Crohns Colitis. 2018 Nov 15;12(11):1381. doi: 10.1093/ecco-jcc/jjy083.
No abstract available.

PMID: 29985990
de Lange MMA, Gijsen LEV, Wielders CCH, van der Hoek W, Scheepmaker A, **Schneeberger PM**. Reply to Million and Raoult.
Clin Infect Dis. 2019 Jan 1;68(1):170-171. doi: 10.1093/cid/ciy536.
No abstract available.

PMID: 29989031
Esmeijer K, Geleijnse JM, de Fijter JW, Giltay EJ, Kromhout D, **Hoogeveen EK**. Cardiovascular Risk Factors Accelerate Kidney Function Decline in Post-Myocardial Infarction Patients: The Alpha Omega Cohort Study. Kidney Int Rep. 2018 Mar 16;3(4):879-888.

Introduction: Impaired kidney function is a robust risk factor for cardiovascular mortality. Age-related annual kidney function decline of 1.0 ml/min per 1.73 m2 after age 40 years is doubled in post-myocardial infarction (MI) patients.
Methods: We investigated the impact of the number of cardiovascular risk factors (including unhealthy lifestyle) on annual kidney function decline, in 2426 post-MI patients (60-80 years) of the prospective Alpha Omega Cohort study. Glomerular filtration rate was estimated by serum cystatin C (eGFRcysC) and combined creatinine-cystatin C (eGFRcr-cysC), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012. Data were analyzed by multivariable linear and logistic regression.
Results: At baseline, mean (SD) eGFRcysC and eGFRcr-cysC were 81.5 (19.6) and 78.5 (18.7) ml/min per 1.73 m2, respectively. Of all patients, 79% were men, 19% had diabetes, 56% had high blood pressure (≥140/90 mm Hg), 16% were current smokers, 56% had high serum low-density lipoprotein (LDL of ≥2.5 mmol/l), and 23% were obese (body mass index of ≥30.0 kg/m2). After multivariable adjustment, the additional annual eGFRcysC decline (95% confidence interval) was as follows: in patients with versus without diabetes, -0.90 (-1.23 to -0.57) ml/min per 1.73 m2; in patients with high versus normal blood pressure, -0.50 (-0.76 to -0.24) ml/min per 1.73 m2; in obese versus nonobese patients, -0.31 (-0.61 to 0.01) ml/min per 1.73 m2; and in current smokers versus nonsmokers, -0.19 (-0.54 to 0.16) ml/min per 1.73 m2. High LDL was not associated with accelerated eGFRcysC decline. Similar results were obtained with eGFRcr-cysC.
Conclusion: In older, stable post-MI patients without cardiovascular risk factors, the annual kidney function decline was -0.90 (-1.16 to -0.65) ml/min per 1.73 m2. In contrast, in post-MI patients with ≥3 cardiovascular risk factors, the annual kidney function decline was 2.5-fold faster, at -2.37 (-2.85 to -1.89) ml/min per 1.73 m2.

PMID: 29989856
Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Klümpen HJ, van den Berg HA, **Smilde TJ**, Vanneste BGL, Aarts MJ, Incrocci L, van den Bergh ACM, Jóźwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M.
Risk of Solid Cancer After Treatment of Testicular Germ Cell Cancer in the Platinum Era.
J Clin Oncol. 2018 Aug 20;36(24):2504-2513. doi: 10.1200/JCO.2017.77.4174. Epub 2018 Jul 10.

Purpose Testicular cancer (TC) treatment increases risk of subsequent malignant neoplasms (SMNs). It is unknown whether changes in TC treatment over time have affected SMN risk. Methods Solid SMN risk was evaluated in a multicenter cohort comprising 5,848 1-year

survivors treated for TC before age 50 years between 1976 and 2007. SMN incidence was compared with cancer incidence in the general population. Treatment-specific risks were assessed using multivariable regression in a case-cohort design. Results After a median follow-up of 14.1 years, 350 solid SMNs were observed, translating into a 1.8-fold (95% CI, 1.6-2.0) increased risk compared with general population rates. Solid SMN risk was increased in patients with seminoma and those with nonseminoma (standardized incidence ratio, 1.52 and 2.21, respectively). Patients with nonseminoma experienced increased risk of SMNs of the thyroid, lung, stomach, pancreas, colon, and bladder and of melanoma and soft tissue sarcoma, whereas those with seminoma experienced increased risk of SMNs of the small intestine, pancreas, and urinary bladder. The 25-year cumulative incidence of solid SMNs was 10.3% (95% CI, 9.0% to 11.6%). In multivariable analysis, platinum-based chemotherapy was associated with increased risk of a solid SMN (hazard ratio [HR], 2.40; 95% CI, 1.58 to 3.62), colorectal SMN (HR, 3.85; 95% CI, 1.67 to 8.92), and noncolorectal GI SMN (HR, 5.00; 95% CI, 2.28 to 10.95). Receipt of platinum 400 to 499 and ≥ 500 mg/m2 increased solid SMN risk compared with surgery only (HR, 2.43; 95% CI, 1.40 to 4.23 and HR, 2.42; 95% CI, 1.50 to 3.90, respectively), whereas risk was not significantly increased with lower doses (HR, 1.75; 95% CI, 0.90 to 3.43). The HR of a GI SMN increased by 53% (95% CI, 26% to 80%) per 100 mg/m2 of platinum-containing chemotherapy. The HR of an infradiaphragmatic SMN increased by 8% per Gray of radiation dose administered (95% CI, 6% to 9%; P < .001). Conclusion Radiotherapy and platinum-containing chemotherapy are associated with increased solid SMN risk, specifically with GI SMNs.

PMID: 29993539

Wildeboer RR, Van Sloun RJG, Schalk SG, Mannaerts CK, **Van Der Linden JC**, Huang P, Wijkstra H, Mischi M. Convective-Dispersion Modeling in 3D Contrast-Ultrasound Imaging for the Localization of Prostate Cancer. IEEE Trans Med Imaging. 2018 Dec;37(12):2593-2602. doi: 10.1109/TMI.2018.2843396. Epub 2018 Jun 4.

Despite being the solid tumor with the highest incidence in western men, prostate cancer (PCa) still lacks reliable imaging solutions that can overcome the need for systematic biopsies. Dynamic contrast-enhanced ultrasound imaging (DCE-US) allows us to quantitatively characterize the vascular bed in the prostate, due to its ability to visualize an intravenously administered bolus of contrast agents. Previous research has demonstrated that DCE-US parameters related to the vascular architecture are useful markers for the localization of PCa lesions. In this paper, we propose a novel method to assess the convective dispersion (D) and velocity (v) of the contrast bolus spreading through the prostate from three-dimensional (3D) DCE-US recordings. By assuming that D and v are locally constant, we solve the convective-dispersion equation by minimizing the corresponding regularized least-squares problem. 3D multiparametric maps of D and v were compared with 3D histopathology retrieved from the radical prostatectomy specimens of six patients. With a pixel-wise area under the receiver operating characteristic curve of 0.72 and 0.80, respectively, the method shows diagnostic value for the localization of PCa.

PMID: 30037794

Jansen AFM, Dinkla A, Roest H-J, Bleeker-Rovers CP, Schoffelen T, Joosten LAB, **Wever PC**, van Deuren M, Koets AP. Viable Coxiella burnetii induces differential cytokine responses in chronic Q fever patients compared to heat-killed Coxiella burnetii. Infect Immun 2018;86:e00333-18.

Cytokine responses of chronic Q fever patients to the intracellular bacterium Coxiella burnetii have mostly been studied using ex vivo stimulation of immune cells with heat-killed C. burnetii due to the extensive measures needed to work with viable biosafety level 3 agents. Whether research with heat-killed C. burnetii can be translated to immune responses to viable C. burnetii is imperative for the interpretation of previous and future studies with heat-killed C. burnetii Peripheral blood mononuclear cells (PBMCs) of chronic Q fever patients (n = 10) and healthy controls (n = 10) were stimulated with heat-killed or viable C. burnetii of two strains, Nine Mile and the Dutch outbreak strain 3262, for 24 h, 48 h, and 7 days in the absence or presence of serum containing anti-C. burnetii antibodies. When stimulated with viable C. burnetii, PBMCs of chronic Q fever patients and controls produced fewer proinflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor alpha, and IL-1β) after 24 h than after stimulation with heat-killed C. burnetii In the presence of Q fever seronegative serum, IL-10 production was higher after stimulation with viable rather than heat-killed C. burnetii; however, when incubating with anti-C. burnetii antibody serum, the effect on IL-10 production was reduced. Levels of adaptive, merely T-cell-derived cytokine (gamma interferon, IL-17, and IL-22) and CXCL9 production were not different between heat-killed and viable C. burnetii stimulatory conditions. Results from previous and future research with heat-killed C. burnetii should be interpreted with caution for innate cytokines, but heat-killed C. burnetii-induced adaptive cytokine production is representative of stimulation with viable bacteria.

PMID: 30040272

Zeldenrust MJG, **van Suylen RJ**, Ramakers BPC. [The Waterhouse-Friderichsen syndrome].
Ned Tijdschr Geneeskd. 2018 May 25;162. pii: D2344. Dutch.

BACKGROUND: The Waterhouse-Friderichsen syndrome (WFS) is a serious illness associated with a high mortality rate and characterized by septic shock and signs of adrenocortical insufficiency.
CASE DESCRIPTION: A 33-year-old male was seen in the emergency department with severe abdominal and back pain with diffuse mottled skin and rapidly progressive petechiae all over his body. Laboratory results showed severe lactate acidosis with renal dysfunction and indications of diffuse intravascular coagulation. Because he had signs of progressive septic shock, the patient was admitted to the ICU. There he subsequently developed hypoglycaemia (glucose < 0.1 mmol/l) and CPR had to be performed twice - the patient died shortly afterwards. Autopsy showed bilateral necrosis and haemorrhage of the adrenal glands, indicative of the diagnosis of WFS. Streptococcus pneumoniae was identified.
CONCLUSION: In case of sepsis, with fever, rapidly expanding petechiae and purpura the Waterhouse-Friderichsen syndrome should be considered. Intensive therapy with antibiotics, fluids, vasopressors, and corticosteroids should be initiated immediately.

PMID: 30054437

van Alfen N, Doorduin J, van Rosmalen MHJ, **van Eijk JJJ**, Heijdra Y, Boon AJ, Gaytant MA, van den Biggelaar RJM, Sprooten RTM, Wijkstra PJ, Groothuis JT. Phrenic neuropathy and diaphragm dysfunction in neuralgic amyotrophy.
Neurology. 2018 Aug 28;91(9):e843-e849. doi: 10.1212/WNL.0000000000006076.

OBJECTIVE: To describe the clinical phenotype and recovery of diaphragm dysfunction caused by neuralgic amyotrophy in a large cohort of patients, to improve accurate awareness of this entity, and to encourage adoption of a standardized approach for diagnosis and treatment.
METHODS: This observational cohort study recruited adult patients with neuralgic amyotrophy and symptoms of idiopathic phrenic neuropathy from the database of the Dutch expert center for neuralgic amyotrophy and the Dutch centers for home mechanical ventilation. Demographic and clinical information on diagnosis, symptoms, and recovery was obtained from chart review. We attempted to contact all patients for a follow-up interview.
RESULTS: Phrenic neuropathy occurs in 7.6% of patients with neuralgic amyotrophy. Unilateral diaphragmatic dysfunction and bilateral diaphragmatic dysfunction are frequently symptomatic, causing exertional dyspnea, orthopnea, disturbed sleep, and excessive fatigue. Diagnostic practices varied widely and were often not optimally targeted. The majority of patients experienced at least moderate recovery within 2 years.
CONCLUSION: We recommend screening every patient with neuralgic amyotrophy for diaphragm dysfunction by asking about orthopnea and by performing upright and supine vital capacity screening and diaphragm ultrasound in cases of suspected phrenic neuropathy to optimize diagnosis and care.

PMID: 30062440

Wildeboer RR, van Sloun RJG, Postema AW, Mannaerts CK, Gayet M, **Beerlage HP**, Wijkstra H, Mischi M. Accurate validation of ultrasound imaging of prostate cancer: a review of challenges in registration of imaging and histopathology.
J Ultrasound. 2018 Sep;21(3):197-207. doi: 10.1007/s40477-018-0311-8. Review.

As the development of modalities for prostate cancer (PCa) imaging advances, the challenge of accurate registration between images and histopathologic ground truth becomes more pressing. Localization of PCa, rather than detection, requires a pixel-to-pixel validation of imaging based on histopathology after radical prostatectomy. Such a registration procedure is challenging for ultrasound modalities; not only the deformations of the prostate after resection have to be taken into account, but also the deformation due to the employed transrectal probe and the mismatch in orientation between imaging planes and pathology slices. In this work, we review the latest techniques to facilitate accurate validation of PCa localization in ultrasound imaging studies and extrapolate a general strategy for implementation of a registration procedure.

PMID: 30076459

Karsten MDA, van Oers AM, Groen H, Mutsaerts MAQ, van Poppel MNM, Geelen A, van de Beek C, Painter RC, Mol BWJ, Roseboom TJ, Hoek A; **LIFEstyle study group (de Bruin JP)**. Determinants of successful lifestyle change during a 6-month preconception lifestyle intervention in women with obesity and infertility. Eur J Nutr. 2018 Aug 3. doi: 10.1007/s00394-018-1798-7.

PURPOSE: To identify demographic, (bio)physical, behavioral, and psychological determinants of successful lifestyle change and program completion by performing a secondary analysis of the intervention arm of a randomized-controlled trial, investigating a preconception lifestyle intervention.
METHODS: The 6-month lifestyle intervention consisted of dietary counseling, physical activity, and behavioral modification, and was aimed at 5-10% weight loss. We operationalized successful lifestyle change as successful weight loss (≥ 5% weight/BMI ≤ 29 kg/m2), weight loss in kilograms, a reduction in energy intake, and an increase in physical activity during the intervention program. We performed logistic and mixed-effect regression analyses to identify baseline factors that were associated with successful change or program completion.
RESULTS: Women with higher external eating behavior scores had higher odds of successful weight loss (OR 1.10, 95% CI 1.05-1.16). Women with the previous dietetic support lost 0.94 kg less during the intervention period (95% CI 0.01-1.87 kg). Women with higher self-efficacy reduced energy intake more than women with lower self-efficacy ($p < 0.01$). Women with an older partner had an increased energy intake (6 kcal/year older, 95% CI 3-13). A high stage of change towards physical activity was associated with a higher number of daily steps ($p = 0.03$). A high stage of change towards weight loss was associated with completion of the intervention ($p = 0.04$).
CONCLUSIONS: Determinants of lifestyle change and program completion were: higher external eating behavior, not having received previous dietetic support, high stage of change. This knowledge can be used to identify women likely to benefit from lifestyle interventions and develop new interventions for women requiring alternative support.
TRIAL REGISTRATION: The LIFEstyle study was registered at the Dutch trial registry (NTR 1530; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1530).

PMID: 30076631

Jansen BHE, Disselhorst GW, Schutte T, Jansen B, Rissmann R, Richir MC, **Keijsers CJPW**, Vanmolkot FHM, van den Brink AM, Kramers C, Vondeling AM, Dumont GJH, de Waard-Siebinga I, Van Agtmael MA, Tichelaar J. Essential diseases in prescribing: A national Delphi study towards a core curriculum in pharmacotherapy education.
Br J Clin Pharmacol. 2018 Nov;84(11):2645-2650. doi: 10.1111/bcp.13730. Epub 2018 Sep 6.
Trefwoorden: medical education; pharmacotherapy; prescribing

AIMS: Prescribing is a core skill for junior doctors, yet 8-10% of their prescriptions contain errors. To ensure adequate training in prescribing, it is important to define the diseases for which junior doctors should be competent to prescribe. The aim of the present study was therefore to identify the essential diseases in prescribing for junior doctors.
METHODS: A two-round Delphi consensus study was conducted among medical specialists, general practitioners, junior doctors, pharmacists and pharmacotherapy teachers from all eight academic hospitals in the Netherlands. Using a five-point Likert scale, the participants indicated for each item on an initial questionnaire whether it should be considered an essential disease for junior doctors. The items for which ≥80% of all respondents agreed or strongly agreed were accepted as essential diseases.
RESULTS: Sixty-two participants completed the Delphi survey. In total, 63 of 220 items were considered to be essential diseases.
CONCLUSION: This is the first Delphi consensus study identifying exact conditions that junior doctors must be able to prescribe for. The essential diseases can be used for training in prescribing and assessment of junior doctors' prescribing competence.

PMID: 30078408

Federico M, Caballero Barrigón MD, Marcheselli L, Tarantino V, Manni M, Sarkozy C, Alonso-Álvarez S, Wondergem M, Cartron G, Lopez-Guillermo A, **Issa D**, Morschhauser F, Alcoceba M, Kimby E, Rusconi C, Chamuleau M, Holte H, Lockmer S, Montoto S, Gomes da Silva M, Aurer I, Zucca E, Paszkiewicz-Kozik E, Minoia C, Skrypets T, Blaker YN, Salles G, Coiffier B; Aristotle Consortium. Rituximab and the risk of transformation of follicular lymphoma: a retrospective pooled analysis.
Lancet Haematol. 2018 Aug;5(8):e359-e367. doi: 10.1016/S2352-3026(18)30090-5.

BACKGROUND: Histological transformation of follicular lymphoma to aggressive lymphoma is a serious event with a substantial effect on patient outcome. The aim of the Aristotle study was to assess the effect of rituximab on the risk of histological transformation and its outcome.
METHODS: 11 cooperative groups or institutions across Europe contributed data to this study. Eligible patients (≥18 years) had histologically confirmed follicular lymphoma grade 1, 2, or 3a, diagnosed between Jan 2, 1997, and Dec 20, 2013. Histological transformation was defined as a biopsy-proven aggressive lymphoma that occurred as a first event after first-line therapy. The primary endpoints were the cumulative hazard of histological transformation and survival after transformation.
FINDINGS: Information was available for 10 001 patients with follicular lymphoma, 8116 of whom were eligible for analysis. 509 histological transformations were reported. After a median follow-up of 87 months (range 1-221; 2·5-97·5th percentile 5-160), the 10-year cumulative hazard of histological transformation was 7·7% (95% CI 6·9-8·5). The 10-year cumulative hazard of histological transformation was 5·2% (95% CI 4·5-6·2) in patients who received rituximab and 8·7% (7·2-10·6) in those who did not (hazard ratio [HR] 0·73, 95% CI 0·58-0·90; p=0·004). The 10-year cumulative hazard of histological transformation was 5·9% (95% CI 5·0-7·0) for patients who received induction rituximab only and 3·6% (95% CI 2·3-5·5) for those treated with induction and maintenance rituximab (HR 0·55, 95% CI 0·37-0·81; p=0·003). This finding was confirmed in a multivariate analysis (p=0·016). 287 deaths were recorded in 509 patients with histological transformation, resulting in a 10-year survival after transformation of 32% (95% CI 26-38). Survival after transformation did not differ between patients not exposed to rituximab and those who received rituximab in induction only (HR 0·94, 95% CI 0·69-1·28; p=0·70), and those who received rituximab in induction and maintenance (0·96, 0·58-1·61; p=0·88).
INTERPRETATION: The risk of histological transformation as a first event can be significantly reduced by the use of rituximab. These findings support the need to inform patients using rituximab nowadays that the risk of transformation is lower than it was before the introduction of rituxumab.
FUNDING: Associazione Angela Serra per la Ricerca sul Cancro, European Lymphoma Institute, European Hematology Association Lymphoma Group, Fondazione Italiana Linfomi, Spanish Group of Lymphoma and Bone Marrow Transplantation.

PMID: 30088117

Sijtsma LC, Keijsers CJPW, Kerckhoffs APM, Agema WRP, **Bootsma JEM**. Metoclopramide: A Safe Alternative to Domperidone? A Case Report on Severe Cardiac Adverse Effects in an Older Patient.
Drug Saf Case Rep. 2018 Aug 7;5(1):24. doi: 10.1007/s40800-018-0090-3.

Peripheral antidopaminergic medication is frequently prescribed to treat nausea. However, domperidone is ill-famed for its severe cardiac adverse effects. Metoclopramide has been suggested as a relatively safe alternative because it has long been considered to have less significant cardiovascular adverse effects. We present an older patient who developed severe bradycardia and hypotension shortly after receiving intravenous metoclopramide. Cardiac adverse effects of metoclopramide in elderly are not frequently described in the literature, especially not in patients without a major history of cardiac disease. We recommend caution with intravenous administered metoclopramide in older patients.

PMID: 30095761

Woiski M, de Visser S, van Vugt H, Dijkman A, Schuitemaker N, van Meir C, Middeldorp J, Huisjes A, Mol BW, Molkenboer J, Moonen-Delarue D, Oudijk M, van Rheenen-Flach L, **Rijnders R**, Pernet P, Porath M, de Wit S, Grol R, Scheepers H, Hermens R. Evaluating Adherence to Guideline-Based Quality Indicators for Postpartum Hemorrhage Care in the Netherlands Using Video Analysis.
Obstet Gynecol. 2018 Sep;132(3):656-667. doi: 10.1097/AOG.0000000000002781.

OBJECTIVE: To assess adherence to the national postpartum hemorrhage guideline and Managing Obstetric Emergencies and Trauma course instructions and its determinants in the Netherlands.
METHODS: A prospective observational multicenter study in 16 Dutch hospitals analyzing data from medical records of 398 women at high risk for postpartum hemorrhage, of which 293 were supplemented with data from prospective video recordings. Adherence to guideline-based quality indicators for prevention, management, and organization of postpartum hemorrhage care was measured. Indicators for prevention and management of postpartum hemorrhage were categorized according to the amount of blood loss (less than 500, greater than 500, greater than 1,000, and greater than 2,000 mL).
RESULTS: Overall, a lack of adherence was observed, particularly for the actions to be undertaken with blood loss greater than 1,000 mL (69 patients). Actions were not or only taken in a later stage when the blood loss had already increased to greater than 2,000 mL (21 patients). In almost 41% (n=119/293) of the deliveries, no active management was performed, and in almost 80% (n=89/112), vital signs were not monitored (blood loss greater than 500 mL) or monitored too late with respect to blood loss. The video recordings showed that in general the

actual care given was considerably underreported in medical records. Postpartum hemorrhage care in the hospitals was well organized. Fifteen hospitals had a local postpartum hemorrhage protocol, and in 12 hospitals, team trainings were organized. Regarding the determinants, high-risk patient identification and type of hospital (university vs nonuniversity hospital) were mostly associated with better adherence.
CONCLUSION: This study showed low adherence to the guideline-based quality indicators, indicating a problem with Dutch quality care. The unique video observations provided additional, valuable information at which level improvement can be made. A tailor-made implementation strategy to improve quality of postpartum hemorrhage care has been developed.
CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT00928863.

PMID: 30102400

van Roeden SE, Reukers DFM, van Jaarsveld CHM, Kampschreur LM, Hoepelman IM, **Wever PC**, Bleeker-Rovers CP, Oosterheert JJ. Chronic Q fever: patient and treatment-related factors influencing long-term quality of life.
QJM 2018;111:791-797.

Background: Chronic Q fever is accompanied by high mortality and morbidity, and requires prolonged antibiotic treatment. Little is known on long-term quality of life (LQOL) in chronic Q fever patients treated with antibiotics.
Aim: To identify patient and treatment-related factors associated with impaired LQOL in chronic Q fever patients treated with antibiotics, and to assess patients' perception on treatment.
Design: Cross-sectional study.
Methods: LQOL was assessed with a validated questionnaire from the Nijmegen Clinical Screening Instrument. Patients' perception on treatment was measured with three newly developed questions.
Results: We included 64 patients: LQOL was impaired in 55% (n = 35) after a median follow-up of 5 years. Median treatment duration was 27 months. In multivariable analysis, treatment duration was significantly associated with impaired LQOL (OR 1.07; 95%CI 1.02-1.12, P < 0.01 per month increase). Age, gender, number of antibiotic regimens, surgical intervention, complications, diagnostic classification, focus of infection or registration of side effects during treatment were not associated with impaired LQOL. After start of treatment, 17 patients (27%) perceived improvement of their condition. Disadvantages of treatment were experienced on a daily basis by 24 patients (69%) with impaired LQOL and 13 patients (46%) without impaired LQOL (P = 0.04).
Conclusions: LQOL in chronic Q fever patients treated with antibiotics is impaired in more than half of patients 5 years after diagnosis. Antibiotic treatment duration was the only variable associated with impaired LQOL. The majority of patients experienced disadvantages on a daily basis, highlighting the high burden of disease and treatment.

PMID: 30108611

Schrijver EJ, Verstraaten M, van de Ven PM, Bet PM, **van Strien AM**, de Cock C, Nanayakkara PW. Low dose oral haloperidol does not prolong QTc interval in older acutely hospitalised adults: a subanalysis of a randomised double-blind placebo-controlled study.
J Geriatr Cardiol. 2018 Jun;15(6):401-407. doi: 10.11909/j.issn.1671-5411.2018.06.003.
Trefwoorden: Haloperidol; Prolongation; QTc interval; The aged

Background: Haloperidol is the most frequently prescribed antipsychotic for delirium symptoms. The risk of QTc prolongation often raises concerns, although the effect of haloperidol on QTc interval has not yet been investigated in a randomised placebo-controlled fixed-dose study.
Methods: A subanalysis of a randomised double-blind placebo-controlled study was conducted to evaluate the effect of prophylactic haloperidol 1 mg or placebo 1 mg orally twice-daily (maximum of 14 doses) on QTc interval in patients aged 70 years and over. Bedside, 12-lead ECGs were recorded before, during and after the one-week intervention period. Automatic QTc measurements were obtained in addition to manual measurements of QT and RR intervals, blinded for treatment status. Manual measurements were corrected (QTc) using Bazett (QTc-B), Framingham (QTc-Fa), Fridericia (QTc-Fi) and Hodges (QTc-H) methods. Mixed model analyses were used to test for differences in longitudinal course of QTc between patients receiving haloperidol and placebo.
Results: ECG recordings of 72 patients (haloperidol n = 38) were analysed, 45.8% male. Median (range) haloperidol serum concentration on day 4 was 0.71 (0.32-1.82) µg/L (n = 23). Longitudinal course of mean QTc did not significantly differ between treatment arms for any of the automatic or manually derived QTc values.
Conclusions: Low dose oral haloperidol did not result in QTc prolongation in older acutely hospitalised patients. Results may not be generalizable to patients with existing ECG abnormalities such as atrial fibrillation.

PMID: 30120542

van Baar H, Beijer S, Bours MJL, Weijenberg MP, van Zutphen M, van Duijnhoven FJB, Slooter GD, **Pruijt JFM**, Dronkers JJ, Haringhuizen A, Spillenaar Bilgen EJ, Hansson BME, de Wilt JHW, Kampman E, Winkels RM. Low radiographic muscle density is associated with lower overall and disease-free survival in early-stage colorectal cancer patients.
J Cancer Res Clin Oncol. 2018 Nov;144(11):2139-2147. doi: 10.1007/s00432-018-2736-z. Epub 2018 Aug 17.
Trefwoorden: Dikkedarmkanker en spiermassa

BACKGROUND: In cancer patients with a poor prognosis, low skeletal muscle radiographic density is associated with higher mortality. Whether this association also holds for early-stage cancer is not very clear. We aimed to study the association between skeletal muscle density and overall mortality among early-stage (stage I-III) colorectal cancer (CRC) patients. Furthermore, we investigated the association between skeletal muscle density and both CRC-specific mortality and disease-free survival in a subset of the study population.
METHODS: Skeletal muscle density was assessed in 1681 early-stage CRC patients, diagnosed between 2006 and 2015, using pre-operative computed tomography images. Adjusted Cox proportional hazard models were used to evaluate the association between muscle density and overall mortality, CRC-specific mortality and disease-free survival.
RESULTS: The median follow-up time was 48 months (range 0-119 months). Low muscle density was detected in 39% of CRC patients. Low muscle density was significantly associated with higher mortality (low vs. normal: adjusted HR 1.91, 95% CI 1.53-2.38). After stratification for comorbidities, the association was highest in patients with ≥2 comorbidities (HR 2.11, 95% CI 1.55-2.87). Furthermore, low skeletal muscle density was significantly associated with poorer disease-free survival (HR 1.68, 95% CI 1.14-2.47), but not with CRC-specific mortality (HR 1.68, 95% CI 0.89-3.17) in a subset of the study population.
CONCLUSION: In early-stage CRC patients, low muscle density was significantly associated with higher overall mortality, and worse disease-free survival.

PMID: 30123220

Tel-Karthaus N, Kers-Rebel ED, Looman MW, Ichinose H, de Vries CJ, Ansems M. Nuclear Receptor Nur77 Deficiency Alters Dendritic Cell Function.
Front Immunol. 2018 Aug 3;9:1797. doi: 10.3389/fimmu.2018.01797. eCollection 2018.

Dendritic cells (DCs) are the professional antigen-presenting cells of the immune system. Proper function of DCs is crucial to elicit an effective immune response against pathogens and to induce antitumor immunity. Different members of the nuclear receptor (NR) family of transcription factors have been reported to affect proper function of immune cells. Nur77 is a member of the NR4A subfamily of orphan NRs that is expressed and has a function within the immune system. We now show that Nur77 is expressed in different murine DCs subsets in vitro and ex vivo, in human monocyte-derived DCs (moDCs) and in freshly isolated human BDCA1+ DCs, but its expression is dispensable for DC development in the spleen and lymph nodes. We show, by siRNA-mediated knockdown of Nur77 in human moDCs and by using Nur77-/- murine DCs, that Nur77-deficient DCs have enhanced inflammatory responses leading to increased T cell proliferation. Treatment of human moDCs with 6-mercaptopurine, an activator of Nur77, leads to diminished DC activation resulting in an impaired capacity to induce IFNγ production by allogeneic T cells. Altogether, our data show a yet unexplored role for Nur77 in modifying the activation status of murine and human DCs. Ultimately, targeting Nur77 may prove to be efficacious in boosting or diminishing the activation status of DCs and may lead to the development of improved DC-based immunotherapies in, respectively, cancer treatment or treatment of autoimmune diseases.

PMID: 30124386

Osterthun R, Tjalma TA, Spijkerman DCM, Faber WXM, van Asbeck FWA, Adriaansen JJE, Post MWM. Functional independence of persons with long-standing motor complete spinal cord injury in the Netherlands.
J Spinal Cord Med. 2018 Aug 20:1-8. doi: 10.1080/10790268.2018.1504427.

CONTEXT/OBJECTIVE: Since life expectancy of persons with spinal cord injury (SCI) has improved, it is relevant to know whether this group is able to maintain functional abilities many years after onset of SCI. Objectives of this study were (1) to examine associations between time since injury (TSI) and functional independence in persons with long-standing SCI and (2) to explore associations between functional independence and level of injury, comorbidities, mental health, waist circumference and secondary health conditions (SHCs).
DESIGN: TSI-stratified cross-sectional study. Strata were 10-19, 20-29 and 30+ years.
SETTING: Community.
PARTICIPANTS: 226 persons with long-standing SCI.
INCLUSION CRITERIA: motor complete SCI; age at injury 18-35 years; TSI ≥10 years; current age 28-65 years; wheelchair dependency.

INTERVENTIONS: Not applicable.
OUTCOME MEASURES: The Spinal Cord Independence Measure III (SCIM) was administered by a trained research assistant. Level of injury, comorbidities, mental health, waist circumference and SHCs were assessed by a rehabilitation physician.
RESULTS: Mean TSI was 23.6 (SD 9.1) years. No significant differences in SCIM scores were found between TSI strata. SCIM scores were lower for persons with tetraplegia, autonomic dysreflexia, hypotension, more than four SHCs and a high waist circumference. In linear regression analyses, TSI nor age was associated with the SCIM total score. Only level of injury (β = -0.7; P < .001) and waist circumference (β = -0.1; P = .042) were independent determinants (explained variance 55%).
CONCLUSION: We found no association between TSI and functional independence in persons with long-standing motor complete SCI. This study confirms the possible effect of overweight on functional independence.

PMID: 30130623

Pedunculated Morphology of T1 Colorectal Tumors Associates With Reduced Risk of Adverse Outcome.
Kessels K, Backes Y, Elias SG, van den Blink A, Offerhaus GJA, van Bergeijk JD, Groen JN, Seerden TCJ, Schwartz MP, de Vos Tot Nederveen Cappel WH, Spanier BWM, Geesing JMJ, Kerkhof M, Siersema PD, Didden P, Boonstra JJ, Herrero LA, Wolfhagen FHJ, Ter Borg F, van Lent AU, **Terhaar Sive Droste JS**, Hazen WL, Schrauwen RWM, Vleggaar FP, Laclé MM, Moons LMG; Dutch T1 Colorectal Cancer Working Group.
Clin Gastroenterol Hepatol. 2019 May;17(6):1112-1120.e1. doi: 10.1016/j.cgh.2018.08.041.

BACKGROUND & AIMS: Risk stratification for adverse events, such as metastasis to lymph nodes, is based only on histologic features of tumors. We aimed to compare adverse outcomes of pedunculated vs nonpedunculated T1 colorectal cancers (CRC).
METHODS: We performed a retrospective study of 1656 patients diagnosed with T1CRC from 2000 through 2014 at 14 hospitals in The Netherlands. The median follow-up time of patients was 42.5 months (interquartile range, 18.5-77.5 mo). We evaluated the association between tumor morphology and the primary composite end point, adverse outcome, adjusted for clinical variables, histologic variables, resection margins, and treatment approach. Adverse outcome was defined as metastasis to lymph nodes, distant metastases, local recurrence, or residual tissue. Secondary end points were tumor metastasis, recurrence, and incomplete resection.
RESULTS: Adverse outcome occurred in 67 of 723 patients (9.3%) with pedunculated T1CRCs vs 155 of 933 patients (16.6%) with nonpedunculated T1CRCs. Pedunculated morphology was independently associated with decreased risk of adverse outcome (adjusted odds ratio [OR], 0.59; 95% CI, 0.42-0.83; P = .003). Metastasis, incomplete resection, and recurrence were observed in 5.8%, 4.6%, and 3.9% of pedunculated T1CRCs vs 10.6%, 8.0%, and 6.6% of nonpedunculated T1CRCs, respectively. Pedunculated morphology was independently associated with a reduced risk of metastasis (adjusted OR, 0.62; 95% CI, 0.41-0.94; P = .03), incomplete resection (adjusted OR, 0.57; 95% CI, 0.36-0.91; P = .02), and recurrence (adjusted hazard ratio, 0.52; 95% CI, 0.32-0.85; P = .009). Metastasis, incomplete resection, and recurrence did not differ significantly between low-risk pedunculated vs nonpedunculated T1CRCs (0.8% vs 2.9%, P = .38; 1.5% vs 0%, P = .99; 1.5% vs 0%; P = .99). However, incomplete resection and recurrence were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs (6.5% vs 12.5%; P = .007; 4.4% vs 8.6%; P = .03).
CONCLUSIONS: In a retrospective study of patients with T1CRC, we found pedunculated morphology to be associated independently with a decreased risk of adverse outcome in a T1CRC population at high risk of adverse outcome. Incorporating morphologic features of tumors in risk assessment could help predict outcomes of patients with T1CRC and help identify the best candidates for surgery.

PMID: 30137325

Danhof NA, van Wely M, Repping S, Koks C, Verhoeve HR, **de Bruin JP**, Verberg MFG, van Hooff MHA, Cohlen BJ, van Heteren CF, Fleischer K, Gianotten J, van Disseldorp J, Visser J, Broekmans FJM, Mol BWJ, van der Veen F, Mochtar MH; SUPER study group. Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial.
Hum Reprod. 2018 Oct 1;33(10):1866-1874. doi: 10.1093/humrep/dey268.

STUDY QUESTION: Is FSH or clomiphene citrate (CC) the most effective stimulation regimen in terms of ongoing pregnancies in couples with unexplained subfertility undergoing IUI with adherence to strict cancellation criteria as a measure to reduce the number of multiple pregnancies?
SUMMARY ANSWER: In IUI with adherence to strict cancellation criteria, ovarian stimulation with FSH is not superior to CC in terms of the cumulative ongoing pregnancy rate, and yields a similar, low multiple pregnancy rate.
WHAT IS ALREADY KNOWN: FSH has been shown to result in higher pregnancy rates compared to CC, but at the cost of high multiple

pregnancy rates. To reduce the risk of multiple pregnancy, new ovarian stimulation regimens have been suggested, these include strict cancellation criteria to limit the number of dominant follicles per cycle i.e. withholding insemination when more than three dominant follicles develop. With such a strategy, it is unclear whether the ovarian stimulation should be done with FSH or with CC.
STUDY DESIGN, SIZE, DURATION: We performed an open-label multicenter randomized superiority controlled trial in the Netherlands (NTR 4057).
PARTICIPANTS/MATERIALS, SETTING, METHODS: We randomized couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation with 75 IU FSH or 100 mg CC. Cycles were cancelled when more then three dominant follicles developed. The primary outcome was cumulative ongoing pregnancy rate. Multiple pregnancy was a secondary outcome. We analysed the data on intention to treat basis. We calculated relative risks and absolute risk difference with 95% CI.
MAIN RESULTS AND THE ROLE OF CHANCE: Between July 2013 and March 2016, we allocated 369 women to ovarian stimulation with FSH and 369 women to ovarian stimulation with CC. A total of 113 women (31%) had an ongoing pregnancy following ovarian stimulation with FSH and 97 women (26%) had an ongoing pregnancy following ovarian stimulation with CC (RR = 1.16, 95% CI: 0.93-1.47, ARD = 0.04, 95% CI: -0.02 to 0.11). Five women (1.4%) had a multiple pregnancy following ovarian stimulation with FSH and eight women (2.2%) had a multiple pregnancy following ovarian stimulation with CC (RR = 0.63, 95% CI: 0.21-1.89, ARD = -0.01, 95% CI: -0.03 to 0.01).
LIMITATIONS, REASONS FOR CAUTION: We were not able to blind this study due to the nature of the interventions. We consider it unlikely that this has introduced performance bias, since pregnancy outcomes are objective outcome measures.
WIDER IMPLICATIONS OF THE FINDINGS: We revealed that adherence to strict cancellation criteria is a successful solution to reduce the number of multiple pregnancies in IUI. To decide whether ovarian stimulation with FSH or with CC should be the regimen of choice, costs and patients' preferences should be taken into account.
STUDY FUNDING/COMPETING INTEREST(S): This trial received funding from the Dutch Organization for Health Research and Development (ZonMw). Prof. Dr B.W.J. Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for Merck, ObsEva and Guerbet. The other authors declare that they have no competing interests.
TRIAL REGISTRATION NUMBER: Nederlands Trial Register NTR4057.

PMID: 30143521

Foks KA, van den Brand CL, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, den Boogert HF, Sir Ö, Patka P, Polinder S, Gaakeer MI, Schutte CE, **Jie KE, Visee HF**, Hunink MGM, Reijners E, Braaksma M, Schoonman GG, Steyerberg EW, Jellema K, Dippel DWJ. External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands.
BMJ. 2018 Aug 24;362:k3527. doi: 10.1136/bmj.k3527.

OBJECTIVE: To externally validate four commonly used rules in computed tomography (CT) for minor head injury.
DESIGN: Prospective, multicentre cohort study.
SETTING: Three university and six non-university hospitals in the Netherlands.
PARTICIPANTS: Consecutive adult patients aged 16 years and over who presented with minor head injury at the emergency department with a Glasgow coma scale score of 13-15 between March 2015 and December 2016.
MAIN OUTCOME MEASURES: The primary outcome was any intracranial traumatic finding on CT; the secondary outcome was a potential neurosurgical lesion on CT, which was defined as an intracranial traumatic finding on CT that could lead to a neurosurgical intervention or death. The sensitivity, specificity, and clinical usefulness (defined as net proportional benefit, a weighted sum of true positive classifications) of the four CT decision rules. The rules included the CT in head injury patients (CHIP) rule, New Orleans criteria (NOC), Canadian CT head rule (CCHR), and National Institute for Health and Care Excellence (NICE) guideline for head injury.
RESULTS: For the primary analysis, only six centres that included patients with and without CT were selected. Of 4557 eligible patients who presented with minor head injury, 3742 (82%) received a CT scan; 384 (8%) had a intracranial traumatic finding on CT, and 74 (2%) had a potential neurosurgical lesion. The sensitivity for any intracranial traumatic finding on CT ranged from 73% (NICE) to 99% (NOC); specificity ranged from 4% (NOC) to 61% (NICE). Sensitivity for a potential neurosurgical lesion ranged between 85% (NICE) and 100% (NOC); specificity from 4% (NOC) to 59% (NICE). Clinical usefulness depended on thresholds for performing CT scanning: the NOC rule was preferable at a low threshold, the NICE rule was preferable at a higher threshold, whereas the CHIP rule was preferable for an intermediate threshold.
CONCLUSIONS: Application of the CHIP, NOC, CCHR, or NICE decision rules can lead to a wide variation in CT scanning among patients with minor head injury, resulting in many unnecessary CT scans and some missed intracranial traumatic findings. Until an existing decision rule has been updated, any of the four rules can be used for patients presenting minor head injuries at the emergency department. Use of the CHIP rule is recommended because it leads to a substantial reduction in CT scans while missing few potential neurosurgical lesions.

PMID: 30150623

Polinder-Bos HA, Diepen MV, Dekker FW, **Hoogeveen EK**, Franssen CFM, Gansevoort RT, Gaillard CAJM. Lower body mass index and mortality in older adults starting dialysis.
Sci Rep. 2018 Aug 27;8(1):12858. doi: 10.1038/s41598-018-30952-2. Erratum in: Sci Rep. 2018 Sep 18;8(1):14231.

Lower body mass index (BMI) has consistently been associated with mortality in elderly in the general and chronic disease populations. Remarkably, in older incident dialysis patients no association of BMI with mortality was found. We performed an in-depth analysis and explored possible time-stratified effects of BMI. 908 incident dialysis patients aged ≥65 years of the NECOSAD study were included, and divided into tertiles by baseline BMI (<23.1 (lower), 23.1-26.0 (reference), ≥26.0 (higher) kg/m2). Because the hazards changed significantly during follow-up, the effect of BMI was modeled for the short-term (<1 year) and longer-term (≥1 year after dialysis initiation). During follow-up (median 3.8 years) 567 deaths occurred. Lower BMI was associated with higher short-term mortality risk (adjusted-HR 1.63 [1.14-2.32] P = 0.007), and lower longer-term mortality risk (adjusted-HR 0.81 [0.63-1.04] P = 0.1). Patients with lower BMI who died during the first year had significantly more comorbidity, and worse self-reported physical functioning compared with those who survived the first year. Thus, lower BMI is associated with increased 1-year mortality, but conditional on surviving the first year, lower BMI yielded a similar or lower mortality risk compared with the reference. Those patients with lower BMI, who had limited comorbidity and better physical functioning, had better survival.

PMID: 30151941

Walgaard C, Jacobs BC, Lingsma HF, Steyerberg EW, Cornblath DR, van Doorn PA; **Dutch GBS Study Group (Garssen MJP)**. Second IVIg course in Guillain-Barré syndrome patients with poor prognosis (SID-GBS trial): Protocol for a double-blind randomized, placebo-controlled clinical trial. J Peripher Nerv Syst. 2018 Dec;23(4):210-215. doi: 10.1111/jns.12286. Epub 2018 Sep 24.

One course of intravenous immunoglobulins (IVIg) of 2 g/kg is standard treatment in Guillain-Barré syndrome (GBS) patients unable to walk independently. Despite treatment some patients recover poorly, in part related to rapid consumption of IVIg, indicating that they may benefit from a second course of IVIg. The aim of the study is to determine whether a second course of IVIg, administered 1 week after start of the first course in patients with GBS and predicted poor outcome improves functional outcome on the GBS disability scale after 4 weeks. Secondary outcome measures include adverse events (AEs), Medical Research Council sumscore and GBS disability score after 8, 12, and 26 weeks, length of hospital and ICU admission, mortality, and changes in serum IgG levels. GBS patients of 12 years and older with a poor prognosis, based on the modified Erasmus GBS outcome score (mEGOS) at 1 week after start of the first IVIg course are eligible for randomization in this double-blind, placebo-controlled (IVIg or albumin) clinical trial. This study will determine if a second course of IVIg administered in the acute phase of the disease is safe, feasible, and effective in patients with GBS and a poor prognosis. This Dutch trial is registered prospectively as NTR 2224 in the Netherlands National Trial Register (NTR) which is the Primary Registry in the WHO Registry Network for the Netherlands.

PMID: 30159720

Steures P, Milani AL, van Rumpt-van de Geest DA, Kluivers KB, Withagen MIJ. Partially absorbable mesh or native tissue repair for pelvic organ prolapse: a randomized controlled trial. Int Urogynecol J. 2019 Apr;30(4):565-573. doi: 10.1007/s00192-018-3757-5. Epub 2018 Aug 29.

INTRODUCTION AND HYPOTHESIS: The objective was to compare medium-term efficacy and safety of a partially absorbable mesh kit and native tissue repair in pelvic organ prolapse (POP).
MATERIALS AND METHODS: Women with primary POP stage ≥ II were randomized to transvaginal trocar-guided partially absorbable mesh (81 women) or native tissue repair (82 women). Primary outcome was overall anatomical success (POP < stage II) at 24 months. Secondary outcomes were composite success, global improvement, and adverse events.
RESULTS: Sixty-nine (85%) of the women allocated to partially absorbable mesh underwent mesh surgery; 8 (10%) crossed over to native tissue repair and 4 women (5%) withdrew from the study. Eighty (98%) of the women allocated to native tissue repair underwent the assigned treatment and 2 (2%) withdrew. Twenty-four months later, 140 surgically treated women (89%) demonstrated an overall anatomical success of 39%; 45% (32 out of 71 women) for mesh, and 32% (22 out of 69) for native tissue repair (RR 1.4, 95% CI 0.92 to 2.2). Composite success was 88 and 73% respectively (RR: 1.1, 95% CI 0.93 to 1.4). There was global improvement in 86% (48 out of 56 women) in the mesh group and in 77% (47 out of 60 women) in the native tissue group (RR: 1.1, 95% CI 0.92 to 1.3). Four women were diagnosed with mesh exposure at 2 years (6%).
CONCLUSION: At 24 months, no significant anatomical or composite benefit of partially absorbable mesh over native tissue repair could be demonstrated in women who had been surgically treated for primary POP.

PMID: 30169885

van Eerden L, **Gaugler-Senden I**, de Vries RJ, Zeeman GG, de Groot CJM, Bolte AC. Mode of Delivery in Severe Preeclampsia Before 28 Weeks' Gestation: A Systematic Review.
Obstet Gynecol Surv. 2018 Aug;73(8):469-474. doi: 10.1097/OGX.0000000000000589. Review.

Importance: Preeclampsia with an onset before 28 weeks' gestation poses dilemmas for the obstetrician with regard to the mode of delivery.
Objective: The aim of this study was to analyze the success rate of attempted vaginal delivery and the maternal and neonatal outcome according to the mode of delivery in women with preeclampsia and an indicated delivery before 28 weeks' gestation.
Evidence Acquisition: A comprehensive search was performed in the bibliographic databases PubMed, Embase.com, and Wiley Cochrane Library. The main outcome was success rate of attempted vaginal delivery. Secondary outcomes were maternal and neonatal outcomes.
Results: Eight studies describing a total of 800 women were included. Success rates of vaginal delivery varied from 1.8% to 80%, and rates for cesarean delivery after induction of labor varied from 13% to 51%. The rates for planned cesarean delivery varied from 0% to 73%. Two studies (n = 53) described no statistical significant differences in maternal outcomes. Two other studies (n = 107) report no statistical difference in neonatal outcome.
Conclusions: Studies that report the success rate of attempted vaginal delivery are limited in size. However, giving the available evidence in the reported studies a trial of labor is a considerable option in counseling women with a pregnancy complicated by preeclampsia before 28 weeks' gestation due to the similar maternal and neonatal outcome. No differences in maternal or neonatal outcome were attributed to the mode of delivery, however, numbers are small.

PMID: 30196973

van Rijswijk J, Pham CT, Dreyer K, Verhoeve HR, Hoek A, **de Bruin JP**, Nap AW, Wang R, Lambalk CB, Hompes PGA, Mijatovic V, Karnon JD, Mol BW. Oil-based or water-based contrast for hysterosalpingography in infertile women: a cost-effective analysis of a randomized controlled trial.
Fertil Steril. 2018 Sep;110(4):754-760. doi: 10.1016/j.fertnstert.2018.05.001.

OBJECTIVE: To determine the cost effectiveness of the use of oil-based versus water-based contrast in infertile women undergoing hysterosalpingography (HSG).
DESIGN: Economic evaluation alongside a multicenter randomized trial.
SETTING: Hospitals.
PATIENT(S): Infertile women with an ovulatory cycle, 18-39 years of age, low risk of tubal pathology.
INTERVENTION(S): Use of oil-based versus water-based contrast during HSG.
MAIN OUTCOME MEASURE(S): Costs per additional ongoing pregnancy and per live birth within 6 months of randomization, incremental cost-effective ratios (ICERs).
RESULT(S): A total of 1,119 women were randomized to HSG (oil-based contrast, n = 557; water-based contrast, n = 562). After HSG, most women had no additional treatment; a minority had IUI or IVF. In the oil group, 39.7% women had an ongoing pregnancy within 6 months of randomization versus 29.1% women in the water group. There was a 10.7% increase in the live birth rate in the oil group. For ongoing pregnancy, the mean costs per couple were US$2,014 in the oil group and US$1,144 in the water group, with a corresponding ICER of US$8,198 per additional ongoing pregnancy. For live birth, the mean costs per couple were US$11,532 in the oil group and US$8,310 in the water group, with a corresponding ICER of US$30,112 per additional live birth.
CONCLUSION(S): Hysterosalpingography with oil-based contrast results in higher 6-month ongoing pregnancy and live birth rate. If society is willing to pay US$8,198 for an additional ongoing pregnancy, HSG with oil-based contrast is a cost-effective strategy compared with HSG with water-based contrast for infertile, ovulatory women at low risk for tubal pathology.
CLINICAL TRIAL REGISTRATION NUMBER: Dutch Trial Register, NTR 6577 (www.trialregister.nl).

PMID: 30197416

Lentferink YE, van der Aa MP, **van Mil EGAH**, Knibbe CAJ, van der Vorst MMJ; Long-term metformin treatment in adolescents with obesity and insulin resistance, results of an open label extension study.
Nutr Diabetes. 2018 Sep 10;8(1):47.

BACKGROUND/OBJECTIVES: Off-label metformin is nowadays frequently used for the treatment of obesity in adolescents. However, studies on long-term metformin treatment in adolescents with obesity are scarce. Therefore, an 18 month open label extension study following an 18 months randomized placebo-controlled trial (RCT) on the efficacy, safety, and tolerability of metformin in adolescents with obesity and insulin resistance was performed.
SUBJECTS/METHODS: After completion of the RCT, metformin was offered to all participants with a body mass index standard deviation score (BMI-sds) > 2.3 and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) ≥ 3.4. Endpoints were change in BMI and HOMA-IR.
RESULTS: Overall, 31/42 participants completed the extension study (74% girls, median age 14.8 (11.6 - 17.9), BMI 31.2 (22.3 - 45.1), HOMA-IR 3.4 (0.2 - 8.8)). At start, 22/42 (52.4%) participants were eligible for metformin of which 13 (59.0%) agreed with treatment. In participants who continued metformin, an increase was observed in BMI (+2.2 (+0.2 to +9.0)) and HOMA-IR (+13.7 (+1.6 to +48.3)). In metformin naive participants, BMI stabilized after an initial decrease (+0.5 (-2.1 to +5.1)). For HOMA-IR, a decrease was observed (-1.1 (-4.6 to +1.4)).
CONCLUSION: While metformin treatment in metformin naive participants seems to result in an initial decrease in BMI and HOMA-IR, there is no evidence for sustained effect after prolonged use in adolescents. Limited compliance and/or insufficient dose may explain the differences in long-term effects between adolescents and adults.

PMID: 30228289

Polinder-Bos HA, Diepen MV, Dekker FW, **Hoogeveen EK**, Franssen CFM, Gansevoort RT, Gaillard CAJM, de Jonge I. Lower body mass index and mortality in older adults starting dialysis.
Sci Rep. 2018 Aug 27;8(1):12858.
No abstract available.

PMID: 30245797

Pavlov K, Koehestanie P, **Beutler JJ, Römkens TEH, Hoogeveen EK, Nissen LHC**. Thoracic and abdominal pain in a 28-year-old woman with a failing kidney transplant.
Frontline Gastroenterol. 2018 Oct;9(4):323-324.

This case report describes a young, immunocompromised patient who presented with thoracic pain. After an extensive workup, she was diagnosed with a varicella zoster virus infection with involvement of the gastric mucosa, pancreas and lungs for which she was treated with acyclovir. Although the viral load decreased significantly, the patient had persistent postherpetic neuralgia and nausea.

PMID: 30247567

Doets AY, Verboon C, van den Berg B, Harbo T, Cornblath DR, Willison HJ, Islam Z, Attarian S, Barroso FA, Bateman K, Benedetti L, van den Bergh P, Casasnovas C, Cavaletti G, Chavada G, Claeys KG, Dardiotis E, Davidson A, van Doorn PA, Feasby TE, Galassi G, Gorson KC, Hartung HP, Hsieh ST, Hughes RAC, Illa I, Islam B, Kusunoki S, Kuwabara S, Lehmann HC, Miller JAL, Mohammad QD, Monges S, Nobile Orazio E, Pardo J, Pereon Y, Rinaldi S, Querol L, Reddel SW, Reisin RC, Shahrizaila N, Sindrup SH, Waqar W, Jacobs BC; **IGOS Consortium (Garssen MJP)**. Regional variation of Guillain-Barré syndrome.
Brain. 2018 Oct 1;141(10):2866-2877. doi: 10.1093/brain/awy232.

Guillain-Barré syndrome is a heterogeneous disorder regarding the clinical presentation, electrophysiological subtype and outcome. Previous single country reports indicate that Guillain-Barré syndrome may differ among regions, but no systematic comparative studies have been conducted. Comparative studies are required to identify factors determining disease susceptibility, variation and prognosis, and to improve diagnostic criteria. The International Guillain-Barré Syndrome Outcome Study is a prospective, observational cohort study including all patients within the diagnostic spectrum, aiming to describe the heterogeneity of Guillain-Barré syndrome worldwide. The current study was based on the first 1000 inclusions with a follow-up of at least 1 year and confirmed the variation in clinical presentation, course and outcome between patients. The full clinical spectrum of Guillain-Barré syndrome was observed in patients from all countries participating in the International Guillain-Barré Syndrome Outcome Study, but the frequency of variants differed between regions. We compared three regions based on geography, income and previous reports of Guillain-Barré syndrome subtypes: 'Europe/Americas', 'Asia' (without Bangladesh), and 'Bangladesh'. We excluded 75 (8%) patients because of alternative diagnoses, protocol violations, or missing data. The predominant clinical variant was sensorimotor in Europe/Americas (n = 387/562, 69%) and Asia (n = 27/63, 43%), and pure motor in Bangladesh (n = 74/107, 69%). Miller Fisher syndrome and Miller Fisher-Guillain-Barré overlap syndrome were more common in Asia (n = 14/63, 22%) than in the other two regions (Europe/Americas: n = 64/562, 11%; Bangladesh: n = 1/107, 1%) (P < 0.001). The predominant electrophysiological subtype was

demyelinating in all regions (Europe/Americas: n = 312/573, 55%; Asia: n = 29/65, 45%; Bangladesh: n = 38/94, 40%). The axonal subtype occurred more often in Bangladesh (n = 34/94, 36%) than in Europe/Americas (n = 33/573, 6%) and other Asian countries (n = 4/65, 6%) (P < 0.001). In all regions, patients with the axonal subtype were younger, had fewer sensory deficits, and showed a trend towards poorer recovery compared to patients with the demyelinating subtype. The proportion of patients able to walk unaided after 1 year varied between Asia (n = 31/34, 91%), Europe/Americas (n = 334/404, 83%) and Bangladesh (n = 67/97, 69%) (P = 0.003). A similar variation was seen for mortality, being higher in Bangladesh (n = 19/114, 17%) than in Europe/Americas (n = 23/486, 5%) and Asia (n = 1/45, 2%) (P < 0.001). This study showed that factors related to geography have a major influence on clinical phenotype, disease severity, electrophysiological subtype, and outcome of Guillain-Barré syndrome.

PMID: 30259313

Willemsen AECAB, de Geus-Oei LF, de Boer M, **Tol J**, Kamm Y, de Jong PC, Jonker MA, Vos AH, Grootjans W, de Groot JWB, Mulder SF, Aarntzen EHJG, Gerritsen WR, van Herpen CML, van Erp NP. Everolimus Exposure and Early Metabolic Response as Predictors of Treatment Outcomes in Breast Cancer Patients Treated with Everolimus and Exemestane.
Target Oncol. 2018 Oct;13(5):641-648
Trefwoorden: everolimus, voorspeller van respons

BACKGROUND: Treating breast cancer patients with everolimus and exemestane can be challenging due to toxicity and suboptimal treatment responses.
OBJECTIVE: We investigated whether everolimus exposure and early metabolic response are predictors for toxicity and effectiveness in these patients.
PATIENTS AND METHODS: We performed pharmacokinetic assessments 14 and 35 days after starting treatment. [18F]fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) was performed at baseline, and 14 and 35 days after the start of the therapy. We recorded toxicity, defined as dose interventions within 3 months, and progression-free survival (PFS).
RESULTS: Among 44 evaluable patients, the geometric mean (GM) Ctrough was higher in patients with toxicity compared to patients without (17.4 versus 12.3 μg/L (p = 0.02)). The optimal cut-off value to predict toxicity was Ctrough > 19.2 μg/L. GM Ctrough of patients with and without progressive disease (PD) within 3 months was not significantly different (12.0 versus 15.2 μg/L (p = 0.118)). In 28 evaluable patients, PD within 3 months could best be predicted using the percentage decrease in peak standardized uptake value normalized by lean body mass of the lesion with highest FDG uptake (SULpeak high) at day 14. Patients with <11% versus >11% decrease in SULpeak high at day 14 had a median PFS of 90 days versus 411 days, respectively (p = 0.0013) and more frequently had PD within 3 months: 70 vs 11%, respectively.
CONCLUSIONS: Our results show that everolimus toxicity is related to everolimus Ctrough. No relation was observed between everolimus exposure and treatment effectiveness. An early FDG-PET can identify patients at high risk of nonresponse. These results warrant further validation. Clinicaltrials.gov identifier: NCT01948960.

PMID: 30266833

Zhang X, Rimbert A, **Balder W**, Zwinderman AH, Kuivenhoven JA, Dallinga-Thie GM, Groen AK. Use of plasma metabolomics to analyze phenotype-genotype relationships in young hypercholesterolemic females.
J Lipid Res. 2018 Nov;59(11):2174-2180. doi: 10.1194/jlr.M088930.

Hypercholesterolemia is characterized by high plasma LDL cholesterol and often caused by genetic mutations in LDL receptor (LDLR), APOB, or proprotein convertase subtilisin/kexin type 9 (PCSK9). However, a substantial proportion of hypercholesterolemic subjects do not have any mutations in these canonical genes, leaving the underlying pathobiology to be determined. In this study, we investigated to determine whether combining plasma metabolomics with genetic information increases insight in the biology of hypercholesterolemia. For this proof of concept study, we combined plasma metabolites from 119 hypercholesterolemic females with genetic information on the LDL canonical genes. Using hierarchical clustering, we identified four subtypes of hypercholesterolemia, which could be distinguished along two axes represented by triglyceride and large LDL particle concentration. Subjects with mutations in LDLR or APOB preferentially clustered together, suggesting that patients with defects in the LDLR pathway show a distinctive metabolomics profile. In conclusion, we show the potential of using metabolomics to segregate hypercholesterolemic subjects into different clusters, which may help in targeting genetic analysis.

PMID: 30276525

Jansen R, van Klarenbosch BR, Cramer MJ, Meijer RCA, Westendorp PHM, **Meijburg HWJ**, Bucx JJJ, Chamuleau SAJ, Kluin J. Longitudinal echocardiographic and clinical follow-up of patients undergoing mitral valve surgery without concomitant tricuspid valve repair.
Neth Heart J. 2018 Nov;26(11):552-561. doi: 10.1007/s12471-018-1159-4.

BACKGROUND: In patients with mild to moderate functional tricuspid regurgitation (TR) and absence of right ventricular dysfunction or tricuspid annulus (TA) dilatation, there is currently no indication for concomitant tricuspid valve (TV) repair during elective mitral valve (MV) surgery. However, long-term results are conflicting. Here, we sought to determine the clinical outcome of this cohort, the rate of TR progression after MV surgery and the role of MV aetiology.
METHODS: Patients for elective MV surgery without concomitant TV repair were retrospectively analysed with longitudinal echocardiographic and clinical follow-up, focusing on TR progression and MV aetiology. Linear regression analysis was performed for change in TR at follow-up, using pre-determined variables and confounders.
RESULTS: In total 204 patients without TV repair were analysed. Development of more than moderate TR after a median of 3.1 [1.6-4.6] years was rarely seen: only in 2 out of 161 patients (1.2%) with known TR grade at follow-up. Overall, median preoperative and late postoperative TR grade were equal (p = 0.116). Subanalysis showed no significant difference in MV aetiology subgroups. Preoperative TR grade and male gender were inversely correlated to change in TR. Mortality was not influenced by the 1 year postoperative TR severity.
CONCLUSION: Our data showed that in a study population of patients with mild to moderate TR undergoing MV surgery without concomitant TV repair, significant late TR was rarely seen. Based on our study, it is safe to waive concomitant TV repair in this specific patient cohort.

PMID: 30279545

van Sloun RJG, Demi L, Schalk SG, Caresio C, Mannaerts C, Postema AW, Molinari F, **van der Linden HC**, Huang P, Wijkstra H, Mischi M. Contrast-enhanced ultrasound tractography for 3D vascular imaging of the prostate.
Sci Rep. 2018 Oct 2;8(1):14640. doi: 10.1038/s41598-018-32982-2.

Diffusion tensor tractography (DTT) enables visualization of fiber trajectories in soft tissue using magnetic resonance imaging. DTT exploits the anisotropic nature of water diffusion in fibrous structures to identify diffusion pathways by generating streamlines based on the principal diffusion vector. Anomalies in these pathways can be linked to neural deficits. In a different field, contrast-enhanced ultrasound is used to assess anomalies in blood flow with the aim of locating cancer-induced angiogenesis. Like water diffusion, blood flow and transport of contrast agents also shows a principal direction; however, this is now determined by the local vasculature. Here we show how the tractographic techniques developed for magnetic resonance imaging DTT can be translated to contrast-enhanced ultrasound, by first estimating contrast flow velocity fields from contrast-enhanced ultrasound acquisitions, and then applying tractography. We performed 4D in-vivo contrast-enhanced ultrasound of three human prostates, proving the feasibility of the proposed approach with clinically acquired datasets. By comparing the results to histopathology after prostate resection, we observed qualitative agreement between the contrast flow tracts and typical markers of cancer angiogenic microvasculature: higher densities and tortuous geometries in tumor areas. The method can be used in-vivo using a standard contrast-enhanced ultrasound protocol, opening up new possibilities in the area of vascular characterization for cancer diagnostics.

PMID: 30280635

Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM; KEYNOTE-407 Investigators (**Biesma B**). Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer.
N Engl J Med. 2018 Nov 22;379(21):2040-2051. doi: 10.1056/NEJMoa1810865.

BACKGROUND: Standard first-line therapy for metastatic, squamous non-small-cell lung cancer (NSCLC) is platinum-based chemotherapy or pembrolizumab (for patients with programmed death ligand 1 [PD-L1] expression on ≥50% of tumor cells). More recently, pembrolizumab plus chemotherapy was shown to significantly prolong overall survival among patients with nonsquamous NSCLC.
METHODS: In this double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, 559 patients with untreated metastatic, squamous NSCLC to receive 200 mg of pembrolizumab or saline placebo for up to 35 cycles; all the patients also received carboplatin and either paclitaxel or nanoparticle albumin-bound [nab]-paclitaxel for the first 4 cycles. Primary end points were overall survival and progression-free survival.
RESULTS: After a median follow-up of 7.8 months, the median overall survival was 15.9 months (95% confidence interval [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001). The overall survival benefit was consistent regardless of the level of PD-L1 expression. The

median progression-free survival was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab-combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group (hazard ratio for disease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001). Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group. Discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs. 6.4%).
CONCLUSIONS: In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck Sharp & Dohme; KEYNOTE-407 ClinicalTrials.gov number, NCT02775435 .).

PMID: 30290829

Simons KS, Verweij E, Lemmens PMC, Jelfs S, Park M, Spronk PE, Sonneveld JPC, Feijen HM, van der Steen MS, Kohlrausch AG, van den Boogaard M, **de Jager CPC**. Noise in the intensive care unit and its influence on sleep quality: a multicenter observational study in Dutch intensive care units.
Crit Care. 2018 Oct 5;22(1):250.
Trefwoorden: Geluidsoverlast Intensive Care

BACKGROUND: High noise levels in the intensive care unit (ICU) are a well-known problem. Little is known about the effect of noise on sleep quality in ICU patients. The study aim is to determine the effect of noise on subjective sleep quality.
METHODS: This was a multicenter observational study in six Dutch ICUs. Noise recording equipment was installed in 2-4 rooms per ICU. Adult patients were eligible for the study 48 h after ICU admission and were followed up to maximum of five nights in the ICU. Exclusion criteria were presence of delirium and/or inability to be assessed for sleep quality. Sleep was evaluated using the Richards Campbell Sleep Questionnaire (range 0-100 mm). Noise recordings were used for analysis of various auditory parameters, including the number and duration of restorative periods. Hierarchical mixed model regression analysis was used to determine associations between noise and sleep.
RESULTS: In total, 64 patients (68% male), mean age 63.9 (± 11.7) years and mean Acute Physiology And Chronic Health Evaluation (APACHE) II score 21.1 (± 7.1) were included. Average sleep quality score was 56 ± 24 mm. The mean of the 24-h average sound pressure levels (LAeq, 24h) was 54.0 dBA (± 2.4). Mixed-effects regression analyses showed that background noise ($\beta = -0.51$, $p < 0.05$) had a negative impact on sleep quality, whereas number of restorative periods ($\beta = 0.53$, $p < 0.01$) and female sex ($\beta = 1.25$, $p < 0.01$) were weakly but significantly correlated with sleep.
CONCLUSIONS: Noise levels are negatively associated and restorative periods and female gender are positively associated with subjective sleep quality in ICU patients.
TRIAL REGISTRATION: www.ClinicalTrials.gov, NCT01826799 . Registered on 9 April 2013.

PMID: 30290905

van de Donk NW, van der Holt B, Minnema MC, Vellenga E, Croockewit S, Kersten MJ, von dem Borne PA, Ypma P, Schaafsma R, de Weerdt O, Klein SK, Delforge M, Levin MD, Bos GM, Jie KG, **Sinnige H**, Coenen JL, de Waal EG, Zweegman S, Sonneveld P, Lokhorst HM. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial.
Lancet Haematol. 2018 Oct;5(10):e479-e492. doi: 10.1016/S2352-3026(18)30149-2.

BACKGROUND: In patients with recently diagnosed multiple myeloma, the HOVON-50 phase 3 trial showed improved event-free survival for thalidomide-containing induction and maintenance regimens (in conjunction with high-dose melphalan and autologous stem cell transplantation [auto-SCT]) after a median of 52 months of follow-up, by comparison with regimens containing classical cytotoxic drugs. In this follow-up analysis, we aimed to determine the long-term effects of thalidomide in induction and maintenance therapy in multiple myeloma.
METHODS: In this open-label, phase 3 randomised controlled trial, patients with recently diagnosed multiple myeloma were recruited from 44 Dutch and Belgian hospitals. Participants had been diagnosed with multiple myeloma of Durie-Salmon stage II or III and were aged 18-65 years. Patients were randomly assigned (1:1) either to receive three 28-day cycles of vincristine (0·4 mg, intravenous rapid infusion on days 1-4), doxorubicin (9 mg/m2, intravenous rapid infusion on days 1-4) and dexamethasone (40 mg, orally on days 1-4, 9-12, and 17-20; control group); or to receive the same regimen, but with thalidomide (200-400 mg, orally on days 1-28) instead of vincristine (thalidomide group). No masking after assignment to intervention was used. Patients were randomly assigned to groups, stratified by centre and treatment policy (one vs two courses of high-dose melphalan and auto-SCT). After stem cell harvest, patients received one or two courses of 200 mg/m2 melphalan intravenously with auto-SCT. Patients with at least a partial response to high-dose melphalan and auto-SCT were eligible for maintenance therapy, starting 2-3 months after high-dose melphalan. Patients in the control group received maintenance therapy with

interferon alfa (3 × 106 international units, subcutaneously, three times weekly). Patients in the thalidomide group received thalidomide as maintenance therapy (50 mg, orally, daily). Maintenance therapy was given until relapse, progression, or the occurrence of adverse events. The primary endpoint of the study was event-free survival (EFSc; censored at allogeneic stem cell transplantation), analysed by intention to treat. The study is closed for enrolment and this Article represents the final analysis. This trial was registered with the Netherlands Trial Register, number NTR238.

FINDINGS: Between Nov 27, 2001 and May 31, 2005, 556 patients were enrolled in the study, of whom 536 (96%) were eligible for evaluation and were randomly allocated (268 [50%] to the control group and 268 [50%] to the thalidomide group). These 536 patients were assessed for the primary endpoint of EFSc. At an extended median follow-up of 129 months (IQR 123-136), EFSc was significantly longer in the thalidomide group compared with the control group (multivariate analysis hazard ratio [HR] 0·62, 95% CI 0·50-0·77; p<0·0001). Thalidomide maintenance was stopped because of toxicity in 65 (42%) of 155 patients in the thalidomide group (neuropathy in 49 [75%] patients, skin reactions in four [6%] patients, fatigue in two [3%] patients, and as other symptoms [such as abdominal pain, pancreatitis, and dyspnoea] in ten [15%] patients). 24 (27%) of 90 patients in the control group discontinued protocol treatment during maintenance therapy with interferon alfa because of toxicity (five [21%] patients with psychiatric side-effects, five [21%] patients with flu-like symptoms, four [17%] patients with haematological toxicity [thrombocytopenia and leucocytopenia], three [13%] patients with skin reactions, and seven [29%] patients with other symptoms [such as infections, cardiomyopathy, and headache]). The frequency of second primary malignancies was similar in both groups. There were 23 second primary malignancies in 17 patients in the control group and 29 second primary malignancies in 24 patients in the thalidomide group. There were 19 treatment-related deaths in the control group, and 16 treatment-related deaths in the thalidomide group.

INTERPRETATION: Our data indicate that thalidomide-based treatment could be a treatment option for patients with multiple myeloma who are eligible for auto-SCT who live in countries without access to proteasome inhibitors or lenalidomide. However, careful follow-up and timely dose adjustments are important to prevent the development of thalidomide-induced neurotoxicity.

FUNDING: The Dutch Cancer Foundation.

PMID: 30297773

Groot HJ, Gietema JA, Aleman BMP, Incrocci L, de Wit R, Witjes JA, Groenewegen G, de Brouwer P, Meijer OWM, Hulshof MCCM, van den Berg HA, **Smilde TJ**, Vanneste BGL, Aarts MJ, van den Bergh ACM, Kerst JM, van den Belt-Dusebout AW, Lubberts S, Jóźwiak K, Horenblas S, van Leeuwen FE, Schaapveld M. Risk of diabetes after para-aortic radiation for testicular cancer.

Br J Cancer. 2018 Oct;119(7):901-907. doi: 10.1038/s41416-018-0248-x. Epub 2018 Oct 9.

BACKGROUND: While the risk of diabetes is increased following radiation exposure to the pancreas among childhood cancer survivors, its association among testicular cancer (TC) survivors has not been investigated.

METHODS: Diabetes risk was studied in 2998 1-year TC survivors treated before 50 years of age with orchidectomy with/without radiotherapy between 1976 and 2007. Diabetes incidence was compared with general population rates. Treatment-specific risk of diabetes was assessed using a case-cohort design.

RESULTS: With a median follow-up of 13.4 years, 161 TC survivors were diagnosed with diabetes. Diabetes risk was not increased compared to general population rates (standardised incidence ratios (SIR): 0.9; 95% confidence interval (95% CI): 0.7-1.1). Adjusted for age, para-aortic radiotherapy was associated with a 1.66-fold (95% CI: 1.05-2.62) increased diabetes risk compared to no radiotherapy. The excess hazard increased with 0.31 with every 10 Gy increase in the prescribed radiation dose (95% CI: 0.11-0.51, P = 0.003, adjusted for age and BMI); restricted to irradiated patients the excess hazard increased with 0.33 (95% CI: -0.14 to 0.81, P = 0.169) with every 10 Gy increase in radiation dose.

CONCLUSION: Compared to surgery only, para-aortic irradiation is associated with increased diabetes risk among TC survivors.

PMID: 30307080

van Leijsen EMC, Tay J, van Uden IWM, Kooijmans ECM, Bergkamp MI, **van der Holst HM**, Ghafoorian M, Platel B, Norris DG, Kessels RPC, Markus HS, Tuladhar AM, de Leeuw FE. Memory decline in elderly with cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy.

Hippocampus. 2019 Jun;29(6):500-510. doi: 10.1002/hipo.23039. Epub 2018 Nov 23.

White matter hyperintensities (WMH) constitute the visible spectrum of cerebral small vessel disease (SVD) markers and are associated with cognitive decline, although they do not fully account for memory decline observed in individuals with SVD. We hypothesize that WMH might

exert their effect on memory decline indirectly by affecting remote brain structures such as the hippocampus. We investigated the temporal interactions between WMH, hippocampal atrophy and memory decline in older adults with SVD. Five hundred and three participants of the RUNDMC study underwent neuroimaging and cognitive assessments up to 3 times over 8.7 years. We assessed WMH volumes semi-automatically and calculated hippocampal volumes (HV) using FreeSurfer. We used linear mixed effects models and causal mediation analyses to assess both interaction and mediation effects of hippocampal atrophy in the associations between WMH and memory decline, separately for working memory (WM) and episodic memory (EM). Linear mixed effect models revealed that the interaction between WMH and hippocampal volumes explained memory decline (WM: β = .067; 95%CI[.024-0.111]; p < .01; EM: β = .061; 95%CI[.025-.098]; p < .01), with better model fit when the WMH*HV interaction term was added to the model, for both WM (likelihood ratio test, $\chi 2$ [1] = 9.3, p < .01) and for EM (likelihood ratio test, $\chi 2$ [1] = 10.7, p < .01). Mediation models showed that both baseline WMH volume (β = -.170; p = .001) and hippocampal atrophy (β = 0.126; p = .009) were independently related to EM decline, but the effect of baseline WMH on EM decline was not mediated by hippocampal atrophy (p value indirect effect: 0.572). Memory decline in elderly with SVD was best explained by the interaction of WMH and hippocampal volumes. The relationship between WMH and memory was not causally mediated by hippocampal atrophy, suggesting that memory decline during aging is a heterogeneous condition in which different pathologies contribute to the memory decline observed in elderly with SVD.

PMID: 30309835

Ferwerda M, van Beugen S, van Middendorp H, Visser H, Vonkeman H, **Creemers M**, van Riel P, Kievit W, Evers A. Tailored, Therapist-Guided Internet-Based Cognitive Behavioral Therapy Compared to Care as Usual for Patients With Rheumatoid Arthritis: Economic Evaluation of a Randomized Controlled Trial.
J Med Internet Res. 2018 Oct 11;20(10):e260. doi: 10.2196/jmir.9997.

BACKGROUND: Internet-based cognitive behavioral therapy can aid patients with rheumatoid arthritis with elevated levels of distress to enhance their quality of life. However, implementation is currently lacking and there is little evidence available on the (cost-) effectiveness of different treatment strategies.
OBJECTIVE: Cost-benefit ratios are necessary for informing stakeholders and motivating them to implement effective treatment strategies for improving health-related quality of life (HRQoL) of patients with rheumatoid arthritis. A cost-effectiveness study from a societal perspective was conducted alongside a randomized controlled trial on a tailored, therapist-guided internet-based cognitive behavioral therapy (ICBT) intervention for patients with rheumatoid arthritis with elevated levels of distress as an addition to care as usual (CAU).
METHODS: Data were collected at baseline or preintervention, 6 months or postintervention, and every 3 months thereafter during the 1-year follow-up. Effects were measured in terms of quality-adjusted life years (QALYs) and costs from a societal perspective, including health care sector costs (health care use, medication, and intervention costs), patient travel costs for health care use, and costs associated with loss of labor.
RESULTS: The intervention improved the quality of life compared with only CAU (Δ QALYs=0.059), but at a higher cost (Δ=€4211). However, this increased cost substantially reduced when medication costs were left out of the equation (Δ=€1863). Of all, 93% (930/1000) of the simulated incremental cost-effectiveness ratios were in the north-east quadrant, indicating a high probability that the intervention was effective in improving HRQoL, but at a greater monetary cost for society compared with only CAU.
CONCLUSIONS: A tailored and guided ICBT intervention as an addition to CAU for patients with rheumatoid arthritis with elevated levels of distress was effective in improving quality of life. Consequently, implementation of ICBT into standard health care for patients with rheumatoid arthritis is recommended. However, further studies on cost reductions in this population are warranted.
TRIAL REGISTRATION: Nederlands Trial Register NTR2100; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2100 (Archived by WebCite at http://www.webcitation.org/724t9pvr2).

PMID: 30324287

Aleva FE, **de Jager CPC**. Shaking and tremors in Thyroid Storm.
Intensive Care Medicine. 2019 Jul;45(7):1021. doi: 10.1007/s00134-018-5410-7. Epub 2018 Oct 15.
No abstract available.

PMID: 30332390

van Balveren JA, Verboeket-van de Venne WPHG, Erdem-Eraslan L, de Graaf AJ, Loot AE, Musson REA, Oosterhuis WP, Schuijt MP, van der Sijs H, Verheul RJ, de Wolf HK, **Kusters R, Hoedemakers RMJ**; Dutch Society for Clinical Chemistry and Laboratory Medicine, task group 'SMILE': Signaling Medication Interactions and Laboratory test Expert system. Impact of interactions between drugs and laboratory test results on diagnostic test interpretation - a systematic review.
Clin Chem Lab Med. 2018 Nov 27;56(12):2004-2009. doi: 10.1515/cclm-2018-0900.

Intake of drugs may influence the interpretation of laboratory test results. Knowledge and correct interpretation of possible drug-laboratory test interactions (DLTIs) is important for physicians, pharmacists and laboratory specialists. Laboratory results may be affected by analytical or physiological effects of medication. Failure to take into account the possible unintended influence of drug use on a laboratory test result may lead to incorrect diagnosis, incorrect treatment and unnecessary follow-up. The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support systems on laboratory test interpretation. Particular interactions were reported in a large number of articles, but they were fragmentarily described and some papers even reported contradictory findings. To provide an overview of information that clinicians and laboratory staff need to interpret test results, DLTI databases have been made by several groups. In a literature search, only four relevant studies have been found on DLTI decision support applications for laboratory test interpretation in clinical practice. These studies show a potential benefit of automated DLTI messages to physicians for the correct interpretation of laboratory test results. Physicians reported 30-100% usefulness of DLTI messages. In one study 74% of physicians sometimes even refrained from further additional examination. The benefit of decision support increases when a refined set of clinical rules is determined in cooperation with health care professionals. The prevalence of DLTIs is high in a broad range of combinations of laboratory tests and drugs and these frequently remain unrecognized.

PMID: 30350001

Joustra R, van Dijk APJ, **Meijburg HWJ**, Boulaksil M. A freaky artery.
Neth Heart J. 2018 Nov;26(11):572. doi: 10.1007/s12471-018-1188-z.
No abstract available.

PMID: 30350002

Joustra R, van Dijk APJ, **Meijburg HWJ**, Boulaksil M. A freaky artery.
Neth Heart J. 2018 Nov;26(11):577-578. doi: 10.1007/s12471-018-1189-y.
No abstract available.

PMID: 30350095

Mertens AC, Tolboom RC, Zavrtanik H, **Draaisma WA**, Broeders IAMJ. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center.
Surg Endosc. 2019 Jul;33(7):2152-2161. doi: 10.1007/s00464-018-6494-4. Epub 2018 Oct 22.

INTRODUCTION: Published data regarding robot-assisted hiatal hernia repair are mainly limited to small cohorts. This study aimed to provide information on the morbidity and mortality of robot-assisted complex hiatal hernia repair and redo anti-reflux surgery in a high-volume center.
MATERIALS AND METHODS: All patients that underwent robot-assisted hiatal hernia repair, redo hiatal hernia repair, and anti-reflux surgery between 2011 and 2017 at the Meander Medical Centre, Amersfoort, the Netherlands were evaluated. Primary endpoints were 30-day morbidity and mortality. Major complications were defined as Clavien-Dindo ≥ IIIb.
RESULTS: Primary surgery 211 primary surgeries were performed by two surgeons. The median age was 67 (IQR 58-73) years. 84.4% of patients had a type III or IV hernia (10.9% Type I; 1.4% Type II; 45.5% Type III; 38.9% Type IV, 1.4% no herniation). In 3.3% of procedures, conversion was required. 17.1% of patients experienced complications. The incidence of major complications was 5.2%. Ten patients (4.7%) were readmitted within 30 days. Symptomatic early recurrence occurred in two patients (0.9%). The 30-day mortality was 0.9%. Redo surgery 151 redo procedures were performed by two surgeons. The median age was 60 (IQR 51-68) years. In 2.0%, the procedure was converted. The overall incidence of complications was 10.6%, while the incidence of major complications was 2.6%. Three patients (2.0%) were readmitted within 30 days. One patient (0.7%) experienced symptomatic early recurrence. No patients died in the 30-day postoperative period.
CONCLUSIONS: This study provides valuable information on robot-assisted laparoscopic repair of primary or recurrent hiatal hernia and anti-reflux surgery for both patient and surgeon. Serious morbidity of 5.2% in primary surgery and 2.6% in redo surgery, in this large series with a high surgeon caseload, has to be outweighed by the gain in quality of life or relief of serious medical implications of hiatal hernia when counseling for surgical intervention.

PMID: 30357272

Pickkers P, Mehta RL, Murray PT, Joannidis M, Molitoris BA, Kellum JA, Bachler M, Hoste EAJ, Hoiting O, Krell K, Ostermann M, **Rozendaal W**, Valkonen M, Brealey D, Beishuizen A, Meziani F, Murugan R, de Geus H, Payen D, van den Berg E, Arend J; STOP-AKI Investigators. Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial.
JAMA. 2018 Nov 20;320(19):1998-2009. doi: 10.1001/jama.2018.14283.

Importance: Sepsis-associated acute kidney injury (AKI) adversely affects long-term kidney outcomes and survival. Administration of the detoxifying enzyme alkaline phosphatase may improve kidney function and survival.
Objective: To determine the optimal therapeutic dose, effect on kidney function, and adverse effects of a human recombinant alkaline phosphatase in patients who are critically ill with sepsis-associated AKI.
Design, Setting, and Participants: The STOP-AKI trial was an international (53 recruiting sites), randomized, double-blind, placebo-controlled, dose-finding, adaptive phase 2a/2b study in 301 adult patients admitted to the intensive care unit with a diagnosis of sepsis and AKI. Patients were enrolled between December 2014 and May 2017, and follow-up was conducted for 90 days. The final date of follow-up was August 14, 2017.
Interventions: In the intention-to-treat analysis, in part 1 of the trial, patients were randomized to receive recombinant alkaline phosphatase in a dosage of 0.4 mg/kg (n = 31), 0.8 mg/kg (n = 32), or 1.6 mg/kg (n = 29) or placebo (n = 30), once daily for 3 days, to establish the optimal dose. The optimal dose was identified as 1.6 mg/kg based on modeling approaches and adverse events. In part 2, 1.6 mg/kg (n = 82) was compared with placebo (n = 86).
Main Outcomes and Measures: The primary end point was the time-corrected area under the curve of the endogenous creatinine clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC1-7 ECC). Incidence of fatal and nonfatal (serious) adverse events ([S]AEs) was also determined.
Results: Overall, 301 patients were enrolled (men, 70.7%; median age, 67 years [interquartile range {IQR}, 59-73]). From day 1 to day 7, median ECC increased from 26.0 mL/min (IQR, 8.8 to 59.5) to 65.4 mL/min (IQR, 26.7 to 115.4) in the recombinant alkaline phosphatase 1.6-mg/kg group vs from 35.9 mL/min (IQR, 12.2 to 82.9) to 61.9 mL/min (IQR, 22.7 to 115.2) in the placebo group (absolute difference, 9.5 mL/min [95% CI, -23.9 to 25.5]; P = .47). Fatal adverse events occurred in 26.3% of patients in the 0.4-mg/kg recombinant alkaline phosphatase group; 17.1% in the 0.8-mg/kg group, 17.4% in the 1.6-mg/kg group, and 29.5% in the placebo group. Rates of nonfatal SAEs were 21.0% for the 0.4-mg/kg recombinant alkaline phosphatase group, 14.3% for the 0.8-mg/kg group, 25.7% for the 1.6-mg/kg group, and 20.5% for the placebo group.
Conclusions and Relevance: Among patients who were critically ill with sepsis-associated acute kidney injury, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. Further research is necessary to assess other clinical outcomes.
Trial Registration: ClinicalTrials.gov Identifier: NCT02182440.

PMID: 30371636

Beex-Oosterhuis MM, Heerdink ERR, Van Gool AR, **van Marum RJ**. Predicting Unsuccessful Clozapine Treatment After First Use in Adult Patients With Psychotic Disorders.
J Clin Psychopharmacol. 2018 Dec;38(6):604-608. doi: 10.1097/JCP.0000000000000977.

PURPOSE/BACKGROUND: Cessation of clozapine therapy and insufficient response may result in relapse of psychotic symptoms and in clinical admissions. However, discontinuation rates are high. Identifying patients at risk for unsuccessful clozapine use might enable clinicians to direct specific attention to them.
METHODS/PROCEDURES: Routinely collected data from a large insurance company were used to develop a simple prediction model for unsuccessful clozapine treatment in psychiatric patients 1 year after clozapine was first dispensed by a community pharmacy in the Netherlands. Multivariate logistic regression analyses were performed with the Nagelkerke R statistic as a measure of the predictive value of the model.
FINDINGS/RESULTS: A total of 937 patients were dispensed clozapine for the first time by their community pharmacy between January 1, 2011, and December 31, 2015 (index date). Of these, 741 patients had started their clozapine treatment in hospital before the index date (inpatient starters); the remaining 196 patients started clozapine as outpatients on the index date (outpatient starters). In 191 patients (20.4%), clozapine treatment was unsuccessful 1 year after the index date. Unsuccessful treatment was more common among outpatient starters than among inpatient starters (32.1% vs 17.3%). Using backward selection of the variables, a model consisting of 61 variables had the best predictive value overall (Nagelkerke R = 0.301), whereas a model consisting of 52 variables had the best predictive value in outpatient starters (Nagelkerke R = 0.676).

IMPLICATIONS/CONCLUSIONS: The likelihood of unsuccessful clozapine treatment after 1 year was higher among patients who started clozapine as outpatients. Despite the use of a diversity of variables and different statistical approaches, it was not possible to make a simple prediction model for unsuccessful clozapine treatment using relatively easily accessible data.

PMID: 30374358

Janssen LMA, Bassett P, **Macken T**, van Esch J, Pruijt H, Knoops A, Sköld M, Parker A, de Vries J, de Vries E. Mild Hypogammaglobulinemia Can Be a Serious Condition.
Front Immunol. 2018 Oct 15;9:2384. doi: 10.3389/fimmu.2018.02384. eCollection 2018.
Trefwoorden: Hypogammaglobulinemie en infecties

Background: Most patients with primary antibody deficiency (PAD) suffer from less well-described and understood forms of hypogammaglobulinemia (unclassified primary antibody deficiency, unPAD). Because of the moderately decreased immunoglobulin levels compared to CVID, unPAD is generally considered to be clinically mild and not very relevant. Objective: To describe our cohort of-mainly-unPAD patients, and to analyze whether subgroups can be identified. Methods: Data were prospectively collected (February-2012 to June-2016) as part of a standardized, 1-day Care Pathway for suspected primary immunodeficiency. The TNO-AZL Questionnaire for Health-Related Quality of Life (HRQoL) was part of the pre-first-visit intake procedure. Results: Three hundred and twenty patients were referred to the Care Pathway. Data from 23/27 children and 99/113 adults who were diagnosed with PAD and gave informed consent were available for analysis. 89/99 adults had unPAD, the majority (74%) were female and 44% already showed bronchiectasis. HRQoL was significantly decreased in all domains, meaning that a lot of unPAD patients had to cope simultaneously with pain, negative feelings and impairments in cognition, home management tasks, sleep, social interaction, and work. The most prominently impaired HRQoL domain was vitality, indicating these patients feel extremely tired and worn out. Conclusion: These results highlight the need for more attention to the potential patient burden of unPADs. A larger cohort is needed to increase our understanding of unPADs and to analyze whether distinct subgroups can be identified. For now, it is important for the clinician to acknowledge the existence of unPAD and be aware of its potential consequences, in order to timely and appropriately manage its effects and complications.

PMID: 30394135

Bolkenstein HE, van de Wall BJ, Consten EC, van der Palen J, Broeders IA, **Draaisma WA**. Development and validation of a diagnostic prediction model distinguishing complicated from uncomplicated diverticulitis.
Scand J Gastroenterol. 2018 Oct - Nov;53(10-11):1291-1297. doi: 10.1080/00365521.2018.1517188. Epub 2018 Nov 5.

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

PMID: 30406175

Willemse EAJ, van Maurik IS, Tijms BM, Bouwman FH, Franke A, Hubeek I, Boelaarts L, Claus JJ, Korf ESC, **van Marum RJ**, Roks G, Schoonenboom N, Verwey N, Zwan MD, Wahl S, van der Flier WM, Teunissen CE. Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: The ABIDE project.
Alzheimers Dement (Amst). 2018 Sep 12;10:563-572. doi: 10.1016/j.dadm.2018.08.006. eCollection 2018.

INTRODUCTION: We compared the automated Elecsys and manual Innotest immunoassays for cerebrospinal fluid (CSF) Alzheimer's disease biomarkers in a multicenter diagnostic setting.
METHODS: We collected CSF samples from 137 participants in eight local memory clinics. Amyloid β(1-42) (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) were centrally analyzed with Innotest and Elecsys assays. Concordances between methods were assessed.
RESULTS: Biomarker results strongly correlated between assays with Spearman's ρ 0.94 for Aβ42, 0.98 for t-tau, and 0.98 for p-tau. Using Gaussian mixture modeling, cohort-specific cut-points were estimated at 1092 pg/mL for Aβ42, 235 pg/mL for t-tau, and 24 pg/mL for p-tau. We found an excellent concordance of biomarker abnormality between assays of 97% for Aβ42 and 96% for both t-tau and p-tau.
DISCUSSION: The high concordances between Elecsys and Innotest in this nonacademic, multicenter cohort support the use of Elecsys for CSF Alzheimer's disease diagnostics and allow conversion of results between methods.

PMID: 30424796

Kip MMA, van Oers JA, Shajiei A, Beishuizen A, Berghuis AMS, Girbes AR, de Jong E, de Lange DW, Nijsten MWN, IJzerman MJ, Koffijberg H, **Kusters R**. Cost-effectiveness of procalcitonin testing to guide antibiotic treatment duration in critically ill patients: results from a randomised controlled multicentre trial in the Netherlands.
Crit Care. 2018 Nov 13;22(1):293. doi: 10.1186/s13054-018-2234-3.

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

PMID: 30446574

Van Lieshout EM, Van Yperen DT, Van Baar ME, Polinder S, **Boersma D**, Cardon AY, De Rijcke PA, Guijt M, Klem TM, Lansink KW, Ringburg AN, Staarink M, Van de Schoot L, Van der Veen AH, Van Eijck FC, Van Eerten PV, Vegt PA, Vos DI, Waleboer M, Verhofstad MH, Van der Vlies CH. Epidemiology of injuries, treatment (costs) and outcome in burn patients admitted to a hospital with or without dedicated burn centre (Burn-Pro): protocol for a multicentre prospective observational study.
BMJ Open. 2018 Nov 15;8(11):e023709. doi: 10.1136/bmjopen-2018-023709.

INTRODUCTION: The Emergency Management of Severe Burns (EMSB) referral criteria have been implemented for optimal triaging of burn patients. Admission to a burn centre is indicated for patients with severe burns or with specific characteristics like older age or comorbidities. Patients not meeting these criteria can also be treated in a hospital without burn centre. Limited information is available about the organisation of care and referral of these patients. The aims of this study are to determine the burn injury characteristics, treatment (costs), quality of life and scar quality of burn patients admitted to a hospital without dedicated burn centre. These data will subsequently be compared with data from patients with<10% total bodysurface area (TBSA) burned who are admitted (or secondarily referred) to a burn centre. If admissions were in agreement with the EMSB, referral criteria will also be determined.
METHODS AND ANALYSIS: In this multicentre, prospective, observational study (cohort study), the following two groups of patients will be

followed: 1) all patients (no age limit) admitted with burn-related injuries to a hospital without a dedicated burn centre in the Southwest Netherlands or Brabant Trauma Region and 2) all patients (no age limit) with<10%TBSA burned who are primarily admitted (or secondarily referred) to the burn centre of Maasstad Hospital. Data on the burn injury characteristics (primary outcome), EMSB compliance, treatment, treatment costs and outcome will be collected from the patients' medical files. At 3 weeks and at 3, 6 and 12 months after trauma, patients will be asked to complete the quality of life questionnaire (EuroQoL-5D), and the patient-reported part of the Patient and Observer Scar Assessment Scale (POSAS). At those time visits, the coordinating investigator or research assistant will complete the observer-reported part of the POSAS.

ETHICS AND DISSEMINATION: This study has been exempted by the medical research ethics committee Erasmus MC (Rotterdam, The Netherlands). Each participant will provide written consent to participate and remain encoded during the study. The results of the study are planned to be published in an international, peer-reviewed journal.

TRIAL REGISTRATION NUMBER: NTR6565.

PMID: 30448096

Bergkamp MI, Tuladhar AM, **van der Holst HM**, van Leijsen EMC, Ghafoorian M, van Uden IWM, van Dijk EJ, Norris DG, Platel B, Esselink RAJ, Leeuw FE. Brain atrophy and strategic lesion location increases risk of parkinsonism in cerebral small vessel disease.

Parkinsonism Relat Disord. 2019 Apr;61:94-100. doi: 10.1016/j.parkreldis.2018.11.010. Epub 2018 Nov 8.

INTRODUCTION: Incident parkinsonism in patients with comparable cerebral small vessel disease (SVD) burden is not fully explained by presence of SVD alone. We therefore investigated if severity of SVD, SVD location, incidence of SVD and/or brain atrophy plays a role in this distinct development of parkinsonism.

METHODS: Participants were from the RUN DMC study, a prospective cohort of 503 individuals with SVD. Parkinsonism was diagnosed according to the UKPDS brain bank criteria. Fine and Gray method was used to assess the association between SVD and incident parkinsonism. Differences in white matter hyperintensities (WMH) progression and brain atrophy were calculated with a linear mixed effect analysis.

RESULTS: After a median follow-up of 8.6 years, 32 of 501 participants developed parkinsonism (6.4%). The highest WMH load was found in the frontal lobe for both groups. Presence of more than one lacune at baseline was higher in the group who developed parkinsonism, especially in the frontal lobe (22% versus 3%, p < 0.001) and basal ganglia (12.5% versus 1%, p-value <0.001). The annual rate of total brain atrophy was significantly higher for those who developed parkinsonism compared to those who did not (8.7 ml [95%CI 7.1-10.3] and 4.9 ml [95%CI 4.5-5.3], respectively). While WMH progression was not different, incidence of lacunes and microbleeds was higher in the group with parkinsonism.

CONCLUSION: The risk of parkinsonism in patients with SVD is especially increased when WMH and lacunes are present in the frontal lobe. A higher brain atrophy rate might further increase this risk.

PMID: 30477432

Legdeur N, Badissi M, Carter SF, de Crom S, van de Kreeke A, Vreeswijk R, Trappenburg MC, Oudega ML, Koek HL, van Campen JP, **Keijsers CJPW**, Amadi C, Hinz R, Gordon MF, Novak G, Podhorna J, Serné E, Verbraak F, Yaqub M, Hillebrand A, Griffa A, Pendleton N, Kramer SE, Teunissen CE, Lammertsma A, Barkhof F, van Berckel BNM, Scheltens P, Muller M, Maier AB, Herholz K, Visser PJ. Resilience to cognitive impairment in the oldest-old: design of the EMIF-AD 90+ study.

BMC Geriatr. 2018 Nov 26;18(1):289. doi: 10.1186/s12877-018-0984-z.

BACKGROUND: The oldest-old (subjects aged 90 years and older) population represents the fastest growing segment of society and shows a high dementia prevalence rate of up to 40%. Only a few studies have investigated protective factors for cognitive impairment in the oldest-old. The EMIF-AD 90+ Study aims to identify factors associated with resilience to cognitive impairment in the oldest-old. In this paper we reviewed previous studies on cognitive resilience in the oldest-old and described the design of the EMIF-AD 90+ Study.

METHODS: The EMIF-AD 90+ Study aimed to enroll 80 cognitively normal subjects and 40 subjects with cognitive impairment aged 90 years or older. Cognitive impairment was operationalized as amnestic mild cognitive impairment (aMCI), or possible or probable Alzheimer's Disease (AD). The study was part of the European Medical Information Framework for AD (EMIF-AD) and was conducted at the Amsterdam University Medical Centers (UMC) and at the University of Manchester. We will test whether cognitive resilience is associated with cognitive reserve, vascular comorbidities, mood, sleep, sensory system capacity, physical performance and capacity, genetic risk factors, hallmarks of ageing,

and markers of neurodegeneration. Markers of neurodegeneration included an amyloid positron emission tomography, amyloid β and tau in cerebrospinal fluid/blood and neurophysiological measures.
DISCUSSION: The EMIF-AD 90+ Study will extend our knowledge on resilience to cognitive impairment in the oldest-old by extensive phenotyping of the subjects and the measurement of a wide range of potential protective factors, hallmarks of aging and markers of neurodegeneration.
TRIAL REGISTRATION: Nederlands Trial Register NTR5867 . Registered 20 May 2016.

PMID: 30478494

Mertens BJ, Kwint HF, **van Marum RJ**, Bouvy ML. Patients' experiences with multidose drug dispensing: a cross sectional study.
Int J Clin Pharm. 2019 Feb;41(1):104-112. doi: 10.1007/s11096-018-0749-y. Epub 2018 Nov 26.

Background Automated multidose drug dispensing is used to support patients with their medication management. Though multidose drug dispensing systems are frequently used, little is known about patients' experiences with multidose drug dispensing systems. Objective
To explore patients' experiences with the initiation and use of multidose drug dispensing systems. Setting A survey was carried out with patients using multidose drug dispensing systems through three community pharmacies. Method A semi-structured interview protocol was designed based on existing literature and a pilot study. Main outcome measures The main outcome measures were (1) patients' experiences with initiating multidose drug dispensing systems and (2) patients' experienced advantages and disadvantages of multidose drug dispensing systems. Results The start of multidose drug dispensing was discussed with 76% of the patients (n = 62). Ninety percent of patients expressed the opinion that the multidose drug dispensing system supported them with their medication management. Sixty patients reported 110 advantages, which can be organized into the following categories: improved medication adherence and medication safety (59%); patient's convenience (40%); and other (1%). Sixty-nine percent of patients reported no disadvantages, 24% had problems opening the bags or outer packaging and 13% had problems with the legibility of the printed text on the bag. Conclusion In concordance with the Dutch guideline, patients are generally involved in the decision to initiate an multidose drug dispensing system. Patients are very satisfied using the system and report multiple advantages. Multidose drug dispensing systems may be further improved by simplifying the manual opening of the bags and improving the legibility of the text on the bags.

PMID: 30507314

Kouwijzer I, Valent L, **Osterthun R**, van der Woude L, de Groot S; HandbikeBattle group. Peak power output in handcycling of individuals with a chronic spinal cord injury: predictive modeling, validation and reference values.
Disabil Rehabil. 2018 Dec 3:1-10. doi: 10.1080/09638288.2018.1501097.

Purpose: To develop and validate predictive models for peak power output to provide guidelines for individualized handcycling graded exercise test protocols for people with spinal cord injury (SCI); and to define reference values.Materials and methods: Power output was measured in 128 handcyclists with SCI during a synchronous handcycling exercise test. Eighty percent of the data was used to develop four linear regression models: two theoretical and two statistical models with peak power output (in W and W/kg) as dependent variable. The other 20% of the data was used to determine agreement between predicted versus measured power output. Reference values were based on percentiles for the whole group.Results: Lesion level, handcycling training hours and sex or body mass index were significant determinants of peak power output. Theoretical models (R2 = 42%) were superior to statistical models (R2=39% for power output in W, R2 = 30% for power output in W/kg). The intraclass correlation coefficients varied between 0.35 and 0.60, depending on the model. Absolute agreement was low. Conclusions: Both models and reference values provide insight in physical capacity of people with SCI in handcycling. However, due to the large part of unexplained variance and low absolute agreement, they should be used with caution. Implications for rehabilitationIndividualization of the graded exercise test protocol is very important to attain the true peak physical capacity in individuals with spinal cord injury.The main determinants to predict peak power output during a handcycling graded exercise test for individuals with a spinal cord injury are lesion level, handcycling training hours and sex or body mass index.The predictive models for peak power output should be used with caution and should not replace a graded exercise test.

PMID: 30515540

Vermeulen CKM, **Coolen ALWM**, Spaans WA, Roovers JPWR, Bongers MY. Treatment of vaginal vault prolapse in The Netherlands: a clinical practice survey.
Int Urogynecol J. 2019 Apr;30(4):581-587. doi: 10.1007/s00192-018-3832-y. Epub 2018 Dec 4.

INTRODUCTION AND HYPOTHESIS: A great variety of conservative and surgical procedures to correct vaginal vault prolapse have been reported. The aim of this study was to describe practice pattern variation-the difference in care that cannot be explained by the underlying medical condition-among Dutch gynecologists regarding treatment of vaginal vault prolapse.
METHODS: A clinical practice survey was conducted from March to April 2017. The questionnaire was developed to evaluate treatment of vaginal vault prolapse. All members of the Dutch Society for Urogynaecology were invited to participate in a web-based survey.
RESULTS: One hundred four Dutch gynecologists with special interest in urogynecology responded to the survey (response rate, 44%). As first-choice therapy for vaginal vault prolapse, 78% of the respondents chose pessary treatment, whereas sacrospinous fixation was the second most common therapy choice according to 64% of the respondents. Preferences on how to approach vaginal vault prolapse surgically are conflicting. Overall, the most performed surgery for vaginal vault prolapse is sacrospinous fixation, followed by laparoscopic and robotic sacrocolpopexy.
CONCLUSIONS: Gynecologists in The Netherlands manage vaginal vault prolapse very differently. No standardized method could be determined for the treatment of vaginal vault prolapse in The Netherlands, and we observed practice pattern variations.

PMID: 30518401

den Toom ML, Grinwis G, **van Suylen RJ**, Boroffka SA, de Jong P, van Steenbeek FG, Szatmári V. Pulmonary veno-occlusive disease as a cause of severe pulmonary hypertension in a dog.
Acta Vet Scand. 2018 Dec 5;60(1):78. doi: 10.1186/s13028-018-0433-1.

BACKGROUND: Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary arterial hypertension (PAH) in humans and can be classified in idiopathic, heritable, drug and radiation-induced, and associated with connective tissue disease or human immunodeficiency virus infection. Recently, biallelic mutations of the EIF2AK4 gene have been discovered as a cause for an autosomal recessive form of PVOD in humans. In dogs, PAH is poorly characterized and is generally considered to be idiopathic or secondary to (for example) congenital left-to right cardiovascular shunts or heartworm disease. However, recently, the pathologic features resembling human PVOD were retrospectively described in post-mortem lung samples of dogs presenting with respiratory distress and idiopathic pulmonary hypertension (PH), which suggests that PVOD contributes to an unknown percentage of cases with unexplained PH. In dogs, information on the clinical presentation of PVOD is scarce and the cause and pathogenesis of this disease is still unknown.
CASE PRESENTATION: An 11-year-old, intact male German Shepherd dog (GSD) was presented with a 2-day history of acute-onset dyspnea and generalized weakness. Physical examination, laboratory analysis, thoracic radiography, echocardiography, a computed tomography scan and an ante mortem lung biopsy demonstrated severe arterial hypoxemia and severe PH but were not diagnostic for a known disease syndrome. Based on the poor reaction to therapy with oxygen, sildenafil, pimobendan and dexamethasone the dog was euthanized. Histopathology of the lungs showed venous and arterial remodelling, segmental congestion of alveolar capillaries and foci of vascular changes similar to human pulmonary capillary hemangiomatosis, indicating that the dog suffered from PVOD. Whole genome sequencing analysis was performed on the case and a healthy GSD. Validation was performed by Sanger sequencing of five additional GSD's unknown for any form of respiratory stress and aged ≥10 years. No causal variants were found in the genes that are known to be involved in human PVOD and PAH.
CONCLUSIONS: This case report confirms that PVOD should be a diagnostic consideration in dogs presenting with dyspnea and unexplained PH. In the present case, no casual genetic mutations known to be involved in humans with PVOD and PAH were found.

PMID: 30521839

Loonen AJM, Leijtens S, Serin O, **Hilbink M, Wever PC, van den Brule AJC**, Toonen EJM. Soluble mannose receptor levels in blood correlate to disease severity in patients with community-acquired pneumonia.
Immunol Lett. 2019 Feb;206:28-32. doi: 10.1016/j.imlet.2018.12.001. Epub 2018 Dec 4.

PURPOSE: Community-acquired pneumonia (CAP) is the most common form of pneumonia and is a leading infectious cause worldwide. Identification of patients that are at risk to develop severe disease has proven to be a major challenge. Soluble mannose receptor (sMR; sCD206) is a new serum marker for macrophage activation. Recent studies showed that sMR levels are increased in patients suffering from severe infections making it a potential biomarker for improved discrimination of disease severity. For measuring sMR, no standardized assay is available. Aim of this study is to develop an assay for standardized measurement of sMR. Next, this assay was used to assess sMR plasma levels for its ability to predict severe disease development in a patient cohort for community-acquired pneumonia.
METHODS: We developed a well-validated sandwich ELISA that enables standardized measurement of sMR in plasma and serum samples. Repeatability was tested by calculating the percentage coefficient of variation (%CV) within and between runs and within and between operators. sMR levels were assessed in a cohort of 100 patients with community-acquired pneumonia.
RESULTS: All %CV values were <10%, indicating low variation. Higher sMR levels were observed in patients with severe disease when compared to patients without severe disease development ($p = 0.004$). Patients with sMR levels between 100-430 ng/ml had 22.7% chance to develop

severe disease whereas patients with levels between 430-1000 ng/ml had 33.3% chance to develop severe disease.
CONCLUSIONS: We suggest that sMR has potential as a new biomarker for the prediction of disease severity in patients with community-acquired pneumonia.

PMID: 30528277

van Hilst J, de Rooij T, van den Boezem PB, **Bosscha K**, Busch OR, van Duijvendijk P, Festen S, Gerhards MF, de Hingh IH, Karsten TM, Kazemier G, Lips DJ, Luyer MD, Nieuwenhuijs VB, Patijn GA, Stommel MW, Zonderhuis BM, Daams F, Besselink MG; Dutch Pancreatic Cancer Group. Laparoscopic pancreatoduodenectomy with open or laparoscopic reconstruction during the learning curve: a multicenter propensity score matched study.
HPB (Oxford). 2019 Jul;21(7):857-864. doi: 10.1016/j.hpb.2018.11.003. Epub 2018 Dec 5.

BACKGROUND: Laparoscopic pancreatoduodenectomy with open reconstruction (LPD-OR) has been suggested to lower the rate of postoperative pancreatic fistula reported after laparoscopic pancreatoduodenectomy with laparoscopic reconstruction (LPD). Propensity score matched studies are, lacking.
METHODS: This is a multicenter prospective cohort study including patients from 7 Dutch centers between 2014-2018. Patients undergoing LPD-OR were matched LPD patients in a 1:1 ratio based on propensity scores. Main outcomes were postoperative pancreatic fistulas (POPF) grade B/C and Clavien-Dindo grade ≥3 complications.
RESULTS: A total of 172 patients were included, involving the first procedure for all centers. All 56 patients after LPD-OR could be matched to a patient undergoing LPD. With LPD-OR, the unplanned conversion rate was 21% vs. 9% with LPD (P < 0.001). Median blood loss (300 vs. 400 mL, P = 0.85), operative time (401 vs. 378 min, P = 0.62) and hospital stay (10 vs. 12 days, P = 0.31) were comparable for LPD-OR vs. LPD, as were Clavien-Dindo grade ≥3 complications (38% vs. 52%, P = 0.13), POPF grade B/C (23% vs. 21%, P = 0.82), and 90-day mortality (4% vs. 4%, P > 0.99).
CONCLUSION: In this propensity matched cohort performed early in the learning curve, no benefit was found for LPD-OR, as compared to LPD.

PMID: 30528371

van Prehn J, van Triest MI, Altorf-van der Kuil W, van Dijk K; Third-generation cephalosporin and carbapenem resistance in Streptococcus mitis/oralis. Results from a nationwide registry in the Netherlands. **Dutch National AMR Surveillance Study Group (Renders NH)**. Clin Microbiol Infect. 2019 Apr;25(4):518-520. doi: 10.1016/j.cmi.2018.11.021. Epub 2018 Dec 4.
No abstract available.

PMID: 30578185

Timmers T, Janssen L, Pronk Y, **van der Zwaard BC**, Koëter S, van Oostveen D, de Boer S, Kremers K, Rutten S, Das D, van Geenen RC, Koenraadt KL, Kusters R, van der Weegen W. Assessing the Efficacy of an Educational Smartphone or Tablet App With Subdivided and Interactive Content to Increase Patients' Medical Knowledge: Randomized Controlled Trial.
JMIR Mhealth Uhealth. 2018 Dec 21;6(12):e10742. doi: 10.2196/10742.

BACKGROUND: Modern health care focuses on shared decision making (SDM) because of its positive effects on patient satisfaction, therapy compliance, and outcomes. Patients' knowledge about their illness and available treatment options, gained through medical education, is one of the key drivers for SDM. Current patient education relies heavily on medical consultation and is known to be ineffective.
OBJECTIVE: This study aimed to determine whether providing patients with information in a subdivided, categorized, and interactive manner via an educational app for smartphone or tablet might increase the knowledge of their illness.
METHODS: A surgeon-blinded randomized controlled trial was conducted with 213 patients who were referred to 1 of the 6 Dutch hospitals by their general practitioner owing to knee complaints that were indicative of knee osteoarthritis. An interactive app that, in addition to standard care, actively sends informative and pertinent content to patients about their illness on a daily basis by means of push notifications in the week before their consultation. The primary outcome was the level of perceived and actual knowledge that patients had about their knee complaints and the relevant treatment options after the intervention.
RESULTS: In total, 122 patients were enrolled in the control group and 91 in the intervention group. After the intervention, the level of actual knowledge (measured on a 0-36 scale) was 52% higher in the app group (26.4 vs 17.4, P<.001). Moreover, within the app group, the level of perceived knowledge (measured on a 0-25 scale) increased by 22% during the week within the app group (from 13.5 to 16.5, P<.001), compared with no gain in the control group.

CONCLUSIONS: Actively offering patients information in a subdivided (per day), categorized (per theme), and interactive (video and quiz questions) manner significantly increases the level of perceived knowledge and demonstrates a higher level of actual knowledge, compared with standard care educational practices.
TRIAL REGISTRATION: International Standard Randomized Controlled Trial Number ISRCTN98629372; http://www.isrctn.com/ISRCTN98629372 (Archived by WebCite at http://www.webcitation.org/73F5trZbb).

PMID: 30579407

Numan T, van den Boogaard M, Kamper AM, Rood PJT, Peelen LM, Slooter AJC; **Dutch Delirium Detection Study Group.** Delirium detection using relative delta power based on 1-minute single-channel EEG: a multicentre study.
Br J Anaesth. 2019 Jan;122(1):60-68. doi: 10.1016/j.bja.2018.08.021. Epub 2018 Oct 2.

BACKGROUND: Delirium is frequently unrecognised. EEG shows slower frequencies (i.e. below 4 Hz) during delirium, which might be useful in improving delirium recognition. We studied the discriminative performance of a brief single-channel EEG recording for delirium detection in an independent cohort of patients.
METHODS: In this prospective, multicentre study, postoperative patients aged ≥60 yr were included (n=159). Before operation and during the first 3 postoperative days, patients underwent a 5-min EEG recording, followed by a video-recorded standardised cognitive assessment. Two or, in case of disagreement, three delirium experts classified each postoperative day based on the video and chart review. Relative delta power (1-4 Hz) was based on 1-min artifact-free EEG. The diagnostic value of the relative delta power was evaluated by the area under the receiver operating characteristic curve (AUROC), using the expert classification as the gold standard.
RESULTS: Experts classified 84 (23.3%) postoperative days as either delirium or possible delirium, and 276 (76.7%) non-delirium days. The AUROC of the relative EEG delta power was 0.75 [95% confidence interval (CI) 0.69-0.82]. Exploratory analysis showed that relative power from 1 to 6 Hz had significantly higher AUROC (0.78, 95% CI 0.72-0.84, P=0.014).
CONCLUSIONS: Delirium/possible delirium can be detected in older postoperative patients based on a single-channel EEG recording that can be automatically analysed. This objective detection method with a continuous scale instead of a dichotomised outcome is a promising approach for routine detection of delirium.
CLINICAL TRIAL REGISTRATION: NCT02404181.

PMID: 30579824

Dreyer K, van Eekelen R, Tjon-Kon-Fat RI, **van der Steeg JW, Steures P**, Eijkemans M, van der Veen F, Hompes P, Mol B, van Geloven N. The therapeutic effect of hysterosalpingography in couples with unexplained subfertility: a post-hoc analysis of a prospective multi-centre cohort study.
Reprod Biomed Online. 2019 Feb;38(2):233-239. doi: 10.1016/j.rbmo.2018.11.005. Epub 2018 Dec 7.

RESEARCH QUESTION: Hysterosalpingography (HSG) with an oil-based contrast has been shown to increase ongoing pregnancy rates compared with HSG with water-based contrast, but it remains unclear if an effect of HSG occurs compared with no HSG.
DESIGN: A secondary data-analysis of a prospective cohort study among 4556 couples that presented with unexplained subfertility in 38 clinics in the Netherlands between January 2002 and December 2004. A time-varying Cox regression with inverse probability of treatment weighing was used to analyse ongoing pregnancy rates in women after undergoing the HSG procedure (with the use of either water- or oil-based contrast media) compared with women who did not undergo HSG.
RESULTS: The probability of natural conception within 24 months after first presentation at the fertility clinic was increased after HSG, regardless of the type of contrast medium used, compared with no HSG (adjusted hazard ratio 1.48, 95% CI 1.26 to 1.73, corresponding to an absolute increase in 6-month pregnancy rate of +6%). When this analysis was limited to HSGs that were made with water-contrast, the treatment effect remained (adjusted hazard ratio 1.40, 95% CI 1.16 to 1.70).
CONCLUSIONS: HSG increases the ongoing pregnancy rate of couples with unexplained subfertility compared with no HSG, regardless of the contrast medium used. Results need to be validated in future, preferably randomized, studies.

PMID: 30594169

Bui BN, Torrance HL, Janssen C, Cohlen B, **de Bruin JP,** den Hartog JE, van der Linden PJQ, Deurloo KL, Maas JWM, van Oppenraaij R, Cantineau A, Lambalk CB, Visser H, Brinkhuis E, van Disseldorp J, Schoot BC, Lardenoije C, van Wely M, Eijkemans MJC, Broekmans FJM. Does endometrial scratching increase the rate of spontaneous conception in couples with unexplained infertility and a good prognosis (Hunault > 30%)? Study protocol of the SCRaTCH-OFO trial: a randomized controlled trial. BMC Pregnancy Childbirth. 2018 Dec 29;18(1):511. doi: 10.1186/s12884-018-2160-z.

BACKGROUND: In the Netherlands, couples with unexplained infertility and a good prognosis to conceive spontaneously (i.e. Hunault > 30%) are advised to perform timed intercourse for at least another 6 months. If couples fail to conceive within this period, they will usually start assisted reproductive technology (ART). However, treatment of unexplained infertility by ART is empirical and can involve significant burdens. Intentional endometrial injury, also called 'endometrial scratching', has been proposed to positively affect the chance of embryo implantation in patients undergoing in vitro fertilization (IVF). It might also be beneficial for couples with unexplained infertility as defective endometrial receptivity may play a role in these women. The primary aim of this study is to determine whether endometrial scratching increases live birth rates in women with unexplained infertility.
METHOD: A multicentre randomized controlled trial will be conducted in Dutch academic and non-academic hospitals starting from November 2017. A total of 792 women with unexplained infertility and a good prognosis for spontaneous conception < 12 months (Hunault > 30%) will be included, of whom half will undergo endometrial scratching in the luteal phase of the natural cycle. The women in the control group will not undergo endometrial scratching. According to Dutch guidelines, both groups will subsequently perform timed intercourse for at least 6 months. The primary endpoint is cumulative live birth rate. Secondary endpoints are clinical and ongoing pregnancy rate; miscarriage rate; biochemical pregnancy loss; multiple pregnancy rate; time to pregnancy; progression to intrauterine insemination (IUI) or IVF; pregnancy complications; complications of endometrial scratching; costs and endometrial tissue parameters associated with reproductive success or failure. The follow-up duration is 12 months.
DISCUSSION: Several small studies show a possible beneficial effect of endometrial scratching in women with unexplained infertility trying to conceive naturally or through IUI. However, the quality of this evidence is very low, making it unclear whether these women will truly benefit from this procedure. The SCRaTCH-OFO trial aims to investigate the effect of endometrial scratching on live birth rate in women with unexplained infertility and a good prognosis for spontaneous conception < 12 months.
TRIAL REGISTRATION: NTR6687 , registered August 31st, 2017.

PMID: 30759216

Nissen LHC, Derikx LAAP, Jacobs AME, van Herpen CM, Kievit W, Verhoeven R, van den Broek E, Bekers E, van den Heuvel T, Pierik M, Rahamat-Langendoen J, Takes RP, Melchers WJG, Nagtegaal ID, Hoentjen F; Dutch Initiative on Crohn and Colitis (ICC); Dutch Head and Neck Society, PALGA group; IBD/HNC group. Risk Factors and Clinical Outcomes of Head and Neck Cancer in Inflammatory Bowel Disease: A Nationwide Cohort Study.
Inflamm Bowel Dis. 2018 Aug 16;24(9):2015-2026. doi: 10.1093/ibd/izy096

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

PMID: 30775391

van de Ven SE, Pavlov KV, **Beutler JJ, Scheffer RC**. Bile Cast Nephropathy Caused by Obstructive Pancreatic Carcinoma and Failed ERCP.

ACG Case Rep J. 2018 Dec 5;5:e88. doi: 10.14309/crj.2018.88. eCollection 2018.

Bile cast nephropathy is an often overlooked condition of acute renal injury in the setting of high serum bilirubin. While the exact pathophysiology remains unknown, possible mechanisms of renal injury are tubular obstruction from bile casts, direct toxicity from bile acids, and decreased renal perfusion due to hemodynamic changes. We present a patient with hyperbilirubinemia as a result of common bile duct obstruction due to pancreatic adenocarcinoma who developed anuric acute renal injury. Urine analysis showed bile casts that were highly suggestive for bile cast nephropathy. The patient underwent hemodialysis and bile drainage with full restoration of renal function.

PMID: 31100233

Mannaerts CK, **Gayet M**, Verbeek JF, Engelbrecht MRW, Savci-Heijink CD, **Jager GJ, Gielens MPM, van der Linden H, Beerlage HP**, de Reijke TM, Wijkstra H, Roobol MJ. Prostate Cancer Risk Assessment in Biopsy-naïve Patients: The Rotterdam Prostate Cancer Risk Calculator in Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound (TRUS) Fusion Biopsy and Systematic TRUS Biopsy.

Eur Urol Oncol. 2018 Jun;1(2):109-117. doi: 10.1016/j.euo.2018.02.010. Epub 2018 May 15.

BACKGROUND: The value of multiparametric magnetic resonance imaging (mpMRI) and targeted biopsy (TBx) remains controversial for biopsy-naïve men when compared to transrectal ultrasound (TRUS)-guided systematic biopsy (SBx). Risk-based patient selection could help to selectively identify men with significant prostate cancer (PCa) and thus reduce unnecessary mpMRI and biopsies.
OBJECTIVES: To compare PCa detection rates for mpMRI TBx with SBx and to determine the rate of potentially avoided mpMRI and biopsies through risk-based selection using the Rotterdam Prostate Cancer Risk Calculator (RPCRC).
DESIGN, SETTING, AND PARTICIPANTS: Two-hundred consecutive biopsy-naïve men in two centres underwent mpMRI scanning, 12-core SBx, and subsequent MRI-TRUS TBx in the case of suspicious lesion(s) (Prostate Imaging-Reporting and Data System v.2 score ≥3).
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: We measured the detection rate for high-grade (Gleason score ≥ 3+4) PCa for TBx and SBx. We carried out a retrospective stratification according to RPCRC biopsy advice to determine the rate of mpMRI and biopsies that could potentially be avoided by RPCRC-based patient selection in relation to the rate of high-grade PCa missed.
RESULTS AND LIMITATIONS: TBx yielded high-grade PCa in 51 men (26%) and low-grade PCa in 14 men (7%), while SBx yielded high-grade PCa in 63 men (32%) and low-grade PCa in 41 men (21%). Four out of 73 men (5%) with negative RPCRC advice and 63 out of 127 men (50%) with positive advice had high-grade PCa. Upfront RPCRC-based patient selection for mpMRI and TBx would have avoided 73 out of 200 (37%) mpMRI scans, missing two out of 51 (4%) high-grade PCas. Limitations include the RPCRC definition of high- and low-grade PCa and different mpMRI techniques.
CONCLUSIONS: mpMRI with TBx detected PCa with high Gleason score and avoided biopsy in low-grade PCa, but failed to detect all high-grade PCa when compared to SBx among biopsy-naïve men. Risk-based patient selection using the RPCRC can avoid one-third of mpMRI scans and SBx in biopsy-naïve men.
PATIENT SUMMARY: Men with a suspicion of prostate cancer are increasingly undergoing a magnetic resonance imaging (MRI) scan. Although promising, MRI-targeted biopsy is not accurate enough to safely replace systematic prostate biopsy for now. Individualised assessment of prostate cancer risk using the Rotterdam Prostate Cancer Risk Calculator could avoid one-third of MRI scans and systematic prostate biopsies.

PMID: 31035740

Hermens WAJJ, Wever PC. John McCrae, arts en dichter van In Flanders Fields.

Ned Tijdschr Geneeskd 2018;162:D3215.

During the Second Battle at Ypres (1915), the Canadian medical officer John McCrae was situated in an Advanced Dressing Station in Boezinge, Belgium. Heavily influenced by the suffering of the war he wrote the poem “In Flanders Fields” in May 1915. In this poem he writes about the fallen soldiers who will not rest, until others have taken over the torch of the battle. The poem has become particularly well known in the United Kingdom, Canada and the United States. For army administration, soldiers and their families this poem meant a call for more financial support and material goods to win the war. The poppy, which takes centre stage in the poem, became a worldwide symbol of the sacrifice of soldiers on the battlefield, but more recently has itself become the subject of controversy.

PMID: 31080602

van Dijk LJ, van Noord D, de Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJ, Moelker A, Bruno MJ. Clinical management of chronic mesenteric ischemia.
United European Gastroenterol J. 2019 Mar;7(2):179-188. doi: 10.1177/2050640618817698. Epub 2018 Dec 4. Review.

This **This Dutch Mesenteric Ischemia Study group consists of**: Ron Balm, Academic Medical Center, Amsterdam Gert Jan de Borst, University Medical Center Utrecht, Utrecht Juliette T Blauw, Medisch Spectrum Twente, Enschede Marco J Bruno, Erasmus MC University Medical Center, Rotterdam Olaf J Bakker, St Antonius Hospital, Nieuwegein Louisa JD van Dijk, Erasmus MC University Medical Center, Rotterdam Hessel CJL Buscher, Gelre Hospitals, Apeldoorn Bram Fioole, Maasstad Hospital, Rotterdam Robert H Geelkerken, Medisch Spectrum Twente, Enschede Jaap F Hamming, Leiden University Medical Center, Leiden Jihan Harki, Erasmus MC University Medical Center, Rotterdam Daniel AF van den Heuvel, St Antonius Hospital, Nieuwegein Eline S van Hattum, University Medical Center Utrecht, Utrecht **Jan Willem Hinnen, Jeroen Bosch Hospital, 's-Hertogenbosch** Jeroen J Kolkman, Medisch Spectrum Twente, Enschede Maarten J van der Laan, University Medical Center Groningen, Groningen Kaatje Lenaerts, Maastricht University Medical Center, Maastricht Adriaan Moelker, Erasmus MC University Medical Center, Rotterdam Desirée van Noord, Franciscus Gasthuis & Vlietland, Rotterdam Maikel P Peppelenbosch, Erasmus MC University Medical Center, Rotterdam André S van Petersen, Bernhoven Hospital, Uden Pepijn Rijnja, Medisch Spectrum Twente, Enschede Peter J van der Schaar, St Antonius Hospital, Nieuwegein Luke G Terlouw, Erasmus MC University Medical Center, Rotterdam Hence JM Verhagen, Erasmus MC University Medical Center, Rotterdam Jean Paul PM de Vries, University Medical Center Groningen, Groningen Dammis Vroegindeweij, Maasstad Hospital, Rotterdam review provides an overview on the clinical management of chronic mesenteric ischemia (CMI). CMI is defined as insufficient blood supply to the gastrointestinal tract, most often caused by atherosclerotic stenosis of one or more mesenteric arteries. Patients classically present with postprandial abdominal pain and weight loss. However, patients may present with, atypically, symptoms such as abdominal discomfort, nausea, vomiting, diarrhea or constipation. Early consideration and diagnosis of CMI is important to timely treat, to improve quality of life and to prevent acute-on-chronic mesenteric ischemia. The diagnosis of CMI is based on the triad of clinical symptoms, radiological evaluation of the mesenteric vasculature and if available, functional assessment of mucosal ischemia. Multidisciplinary consensus on the diagnosis of CMI is of paramount importance to adequately select patients for treatment. Patients with a consensus diagnosis of single-vessel or multi-vessel atherosclerotic CMI are preferably treated with endovascular revascularization.

PMID: 31152741

De Lil HS, Lantinga MA, Sinnige HAM. An unusual cause of colonic ulceration.
Gastroenterology. 2019 May 29. pii: S0016-5085(19)40972-4. doi: 10.1053/j.gastro.2019.05.054
No abstract available.

PMID: 31165098

van Leijsen EM, Bergkamp MI, van Uden IW, Cooijmans S, Ghafoorian M, **van der Holst HM**, Norris DG, Kessels RP, Platel B, Tuladhar AM, de Leeuw FE. Cognitive consequences of regression of cerebral small vessel disease. Eur Stroke J. 2019 Mar;4(1):85-89. doi: 10.1177/2396987318820790. Epub 2018 Dec 21.

Introduction: Recent studies have shown that neuroimaging markers of cerebral small vessel disease can also regress over time. We investigated the cognitive consequences of regression of small vessel disease markers.
Patients and methods: Two hundred and seventy-six participants of the RUNDMC study underwent neuroimaging and cognitive assessments at three time-points over 8.7 years. We semi-automatically assessed white matter hyperintensities volumes and manually rated lacunes and microbleeds. We analysed differences in cognitive decline and accompanying brain atrophy between participants with regression, progression and stable small vessel disease by analysis of variance.
Results: Fifty-six participants (20.3%) showed regression of small vessel disease markers: 31 (11.2%) white matter hyperintensities regression, 10 (3.6%) vanishing lacunes and 27 (9.8%) vanishing microbleeds. Participants with regression showed a decline in overall cognition, memory, psychomotor speed and executive function similar to stable small vessel disease. Participants with small vessel disease progression showed more cognitive decline compared with stable small vessel disease ($p < 0.001$ for cognitive index and memory; $p < 0.01$ for executive function), although significance disappeared after adjusting for age and sex. Loss of total brain, gray matter and white matter volume did not differ between participants with small vessel disease regression and stable small vessel disease, while participants with small vessel disease progression showed more volume loss of total brain and gray matter compared to those with stable small vessel disease ($p < 0.05$), although significance disappeared after adjustments.
Discussion: Regression of small vessel disease markers was associated with similar cognitive decline compared to stable small vessel disease and did not accompany brain atrophy, suggesting that small vessel disease regression follows a relatively benign clinical course. Future studies

are required to validate these findings and to assess the role of vascular risk factor control on small vessel disease regression and possible recovery of clinical symptoms.
Conclusion: Our findings of comparable cognitive decline between participants with regression and stable small vessel disease might suggest that small vessel disease regression has a relative benign cognitive outcome.

PMID: 31214345

Laan C, van de Vrugt M, **Olsman J**, Boucherie RJ. Static and dynamic appointment scheduling to improve patient access time. Health Syst (Basingstoke). 2017 Nov 28;7(2):148-159. doi: 10.1080/20476965.2017.1403675. eCollection 2018.

Appointment schedules for outpatient clinics have great influence on efficiency and timely access to health care services. The number of new patients per week fluctuates, and capacity at the clinic varies because physicians have other obligations. However, most outpatient clinics use static appointment schedules, which reserve capacity for each patient type. In this paper, we aim to optimise appointment scheduling with respect to access time, taking fluctuating patient arrivals and unavailabilities of physicians into account. To this end, we formulate a stochastic mixed integer programming problem, and approximate its solution invoking two different approaches: (1) a mixed integer programming approach that results in a static appointment schedule, and (2) Markov decision theory, which results in a dynamic scheduling strategy. We apply the methodologies to a case study of the surgical outpatient clinic of the Jeroen Bosch Hospital. We evaluate the effectiveness and limitations of both approaches by discrete event simulation; it appears that allocating only 2% of the capacity flexibly already increases the performance of the clinic significantly.

PMID: 31639761

van Balveren JA, Gemen EFA, Kusters R. Recentrifugation of Lithium Heparin Gel Separator Tubes up to 8 h after Blood Collection Has No Relevant Influence on the Stability of 30 Routine Biochemical Analytes.
J Appl Lab Med. 2019 Mar;3(5):864-869. doi: 10.1373/jalm.2018.026567. Epub 2018 May 24.

BACKGROUND: Venipuncture for the purpose of blood analysis is often performed at remote locations, and samples may be centrifuged locally to preserve the integrity of analytes. At the central laboratory, these tubes may be centrifuged again in the routine process. However, limited research shows that >1 centrifugation cycle of gel separator tubes causes significant changes in analytes, in particular troponin I and potassium. These preanalytical test changes are undesirable and may lead to errors in diagnosis and treatment of patients.
METHODS: Ten volunteers donated blood in 10 lithium heparin gel tubes. Per volunteer, 5 tubes were centrifuged with Becton Dickinson centrifugation settings and 5 tubes with our local centrifugation settings. For each centrifugation setting, 1 tube was centrifuged directly after venipuncture; the second tube, directly after venipuncture and again after 4 h; the third tube, directly after venipuncture and again after 8 h; the fourth tube, 4 h after venipuncture; the last tube, 8 h after venipuncture. Thirty routine chemistry analyses were performed in plasma directly after the last centrifugation cycle. All tubes were kept at room temperature. Analytes were considered unstable when the mean percentage deviation exceeded the total allowable error.
RESULTS: Except for calcium, which slightly exceeded the predefined total allowable error limit, all the investigated analytes remained stable up to 8 h after a second centrifugation cycle with both centrifugation settings.
CONCLUSION: This study shows that recentrifugation up to 8 h after blood collection does not cause relevant deviations in test results and may be applied safely.