Auraptene and Its Role in Chronic Diseases.

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Auraptene (7-geranyloxycoumarin) is the best known and most abundant prenyloxycoumarin present in nature. It is synthesized by various plant species, mainly those of the Rutaceae and Umbeliferae (Apiaceae) families, comprising many edible fruits and vegetables such as lemons, grapefruit and orange. Auraptene has shown a remarkable effect in the prevention of degenerative diseases, in particular it has been reported to be one the most promising known natural chemopreventive agents against several types of cancer. The aim of this chapter is to review the effects of auraptene in the prevention and treatment of different chronic diseases.

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Receiving the news of a diagnosis of motor neuron disease: What does it take to make it better?

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Our objectives were to identify the experiences of people with MND in receiving the diagnosis and to determine which aspects of breaking this bad news were associated with greater satisfaction with the way the diagnosis was delivered to them. An anonymous postal survey was facilitated by all MND associations in Australia, in 2014, and centred on the SPIKES protocol for communicating bad news. Of the patients (n=248, response rate 29%), 36% were dissatisfied with the delivery of the diagnosis and gave low ratings on the ability/skills of their neurologists to deliver the diagnosis. It was evident that the longer the patients spent with their neurologists during breaking such bad news, the more they were satisfied and the higher they rated the neurologists' abilities/skills. The largest significant
differences between neurologists rated as having high or low skills in delivering the diagnosis were in four domains:
1) responding empathically to the feelings of patient/family; 2) sharing the information and suggesting realistic goals;
3) exploring what patient/family are expecting or hoping for; and 4) making a plan and following through. In
conclusion, with over one-third of patients dissatisfied with their experience, there is room for improvement in the
practice of neurologists in specified areas that could form the basis for changing practice, and the development of
standards and protocols likely to have implications at the international level.

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Receiving the diagnosis of motor neurone disease (MND): Qualitative data from an Australian survey.
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Background: The diagnosis of MND is not only challenging for neurologists to give, but also for those being given
the diagnosis, and their family members. This devastating diagnosis requires great sensitivity in the manner in which it
is communicated, in order for the person and their family to come to terms with what needs to be done as well as find
support for the duration of the illness. Objective: The overall objective of this study was to identify the experiences of
people with MND and their family members in receiving the diagnosis. Method: This consisted of an anonymous
postal survey facilitated by all MND Associations across Australia, in 2014. Questions centered on the SPIKES protocol
for communicating bad news and each question contained an area for writing further responses. Results: Two
hundred and forty-eight responses were received from people with MND, estimated to be 29% of those receiving
care from all Australian MND Associations. Three themes were identified from reading and re-reading the written
responses to questions. These were: challenges in being diagnosed with MND; the emotions experienced; and links to
further information and support. Receiving an MND diagnosis requires preparation and forethought on the part of
the neurologist, including where and how the diagnosis is given; what supports should be in place so the person is
not alone; and the timing, amounts and sources of giving information. The results also showed how the emotional
reactions of the neurologist cause a lasting impression on those receiving a diagnosis of MND. Conclusion: The
diagnosis of MND requires sensitive and individualized care on the part of the neurologist. Guidelines from other
medical disciplines may provide the basis for developing disease-specific guidelines to support neurologists in giving
bad news.
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Apneic Oxygenation During Prolonged Laryngoscopy in Obese Patients: A Randomized, Controlled Trial of
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BACKGROUND:: Despite optimal preoxygenation, obese patients undergoing induction of general anesthesia exhibit
significant hypoxemia after 2 to 4 minutes of apnea. Apneic oxygenation techniques can assist airway management by
extending the safe apnea time. We hypothesized that a novel method of apneic oxygenation via the oral route would effectively prolong safe apnea in an obese surgical population. METHODS: In this open-label, parallel-arm, randomized-controlled efficacy trial, 40 ASA physical status I-II obese patients with body mass index (BMI) 30-40 were randomly assigned to standard care (n = 20) or buccal oxygenation (n = 20) during induction of total IV anesthesia. Buccal oxygen was administered via a modified 3.5-mm Ring-Adair-Elwyn (RAE) tube apposed to the left internal cheek. Prolonged laryngoscopy maintained apnea with a patent airway until SpO2 dropped below 95% or 750 seconds elapsed. The primary outcome was time to reach SpO2 < 95%. RESULTS: Patient characteristics were similar in both study arms. Recipients of buccal oxygenation were less likely to exhibit SpO2 < 95% during 750 seconds of apnea; hazard ratio 0.159 (95% confidence interval 0.044-0.226, P < .0001). Median (interquartile range [IQR]) apnea times with SpO2 > 95% were prolonged in this group: 750 (389-750) versus 296 (244-314) seconds, P < .0001. CONCLUSIONS: Clinically important prolongation of safe apnea times can be achieved delivering buccal oxygen to obese patients on induction of anesthesia. This novel use of apneic oxygenation via the oral route may improve management of the difficult airway and overcome some of the limitations of alternative techniques. Copyright © 2016 International Anesthesia Research Society

The Association of Community-Based Palliative Care With Reduced Emergency Department Visits in the Last Year of Life Varies by Patient Factors.
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Study objective: Palliative care has been shown to reduce end-of-life emergency department (ED) use. Our objective was to determine how the association of community-based palliative care with reduced ED visits in the last year of life varied by patient factors. Methods: This was a retrospective cohort study of 11,875 decedents who died with neoplasms, heart failure, renal failure, chronic obstructive pulmonary disease, or liver failure in Western Australia in 2009 to 2010. Outcome measures were adjusted hazard ratios (HRs) and daily (hazard) rates of ED visits. Results: The adjusted average rate of ED visits for the cohort was reduced 50% (HR 0.50; 95% confidence interval [CI] 0.47 to 0.53) during periods of receipt of community-based palliative care. This relative reduction in ED visits varied by patient factors, ranging from 43% (HR 0.57; 95% CI 0.45 to 0.74) for decedents aged 60 years and younger up to 71% (HR 0.29; 95% CI 0.18 to 0.46) for people aged 90 years and older. Decedents living in the most disadvantaged areas had a 44% (HR 0.56; 95% CI 0.44 to 0.72) reduction in ED visits when receiving community-based palliative care compared with a 60% (HR 0.40; 95% CI 0.31 to 0.53) reduction for decedents who lived in the least disadvantaged areas and received this care. The ED visit rates while patients were receiving palliative care also varied by ED visit history, partner status, and region of residence. Conclusion: Receipt of community-based palliative care in the last year of life was associated with a reduced rate of ED visits. The magnitude of this association was modified by patient health, as well as social and demographic factors. Copyright © 2016 American College of Emergency Physicians.

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Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic
dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial.
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Background: The majority of sudden cardiac death (SCD) in patients with heart failure occurs in those with mild-moderate left ventricular (LV) systolic dysfunction (LVEF 36-50%) who under current guidelines are ineligible for primary prevention implantable cardiac defibrillator (ICD) therapy. Recent data suggest that cardiac magnetic resonance (CMR) evidence of replacement fibrosis forms a substrate for malignant arrhythmia and therefore potentially identifies a subgroup at increased risk of SCD. Our hypothesis is that among patients with mild-moderate LV systolic dysfunction, a CMR-guided management strategy for ICD insertion based on the presence of scar or fibrosis is superior to a current strategy of standard care. Methods/Design: CMR GUIDE is a prospective, multicenter randomized control trial enrolling patients with mild-moderate LV systolic dysfunction and CMR evidence of fibrosis on optimal heart failure therapy. Participants will be randomized to receive either a primary prevention ICD or an implantable loop recorder (ILR). The primary endpoint is the time to SCD or hemodynamically significant ventricular arrhythmia (VF or VT) during an average 4-year follow-up. Secondary endpoints include quality of life assessed by Minnesota Living with Heart Failure Questionnaire, heart failure related hospitalizations, and a cost-utility analysis. Clinical trials.gov identifier NCT01918215. Discussion: CMR GUIDE trial will add substantially to our understanding of the role of myocardial fibrosis and the risk of developing life-threatening ventricular arrhythmias. If the superiority of a CMR-guided approach over standard care is proven, it may change international clinical guidelines, with the potential to considerably increase survival in this growing patient population. Copyright © 2017 European Society of Cardiology and Wiley Periodicals, Inc.

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Radiotherapy-induced right ventricular remodelling: The missing piece of the puzzle.
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The number of studies demonstrating that right ventricular structure, function and mechanics are valuable predictors of cardiovascular and total morbidity and mortality in patients with a wide range of cardiovascular conditions is constantly increasing. Most studies that evaluated the influence of radiotherapy on the heart focused on left ventricular remodelling, which is why current guidelines only recommend detailed assessment of the left ventricle. Data regarding right ventricular changes in cancer patients treated with radiotherapy are scarce. Given that radiotherapy more often induces late cardiac impairment - unlike chemotherapy-induced cardiotoxicity, which is usually acute - it is quite reasonable to follow these patients echocardiographically for a long time (even for 20. years after initiation of radiotherapy). Investigations that have followed cancer survivors for at least 10. years after radiotherapy agree that right ventricular structure, systolic/diastolic function and mechanics are significantly impaired. The mechanisms of radiation-induced right ventricular remodelling are still unclear, but it is thought that fibrosis is the dominant factor in myocardial remodelling and vascular changes. Many factors may contribute to right ventricular...
impairment during and after radiotherapy: cumulative radiation dose; dose per treatment; delivery technique; radiation target (chest and mediastinum); and co-morbidities. In this review, we aim to provide a comprehensive overview of the potential mechanisms of radiation-induced right ventricular remodelling, and to summarize clinical studies involving radiotherapy-treated cancer patients. Copyright © 2016 Elsevier Masson SAS.

Tea tree oil gel for mild to moderate acne; a 12 week uncontrolled, open-label phase II pilot study.

Malhi HK, Tu J, et al.

Background: The efficacy, tolerability and acceptability of a tea tree oil gel (200 mg/g) and face wash (7 mg/g) were evaluated for the treatment of mild to moderate facial acne. Methods: In this open-label, uncontrolled phase II pilot study, participants applied tea tree oil products to the face twice daily for 12 weeks and were assessed after 4, 8 and 12 weeks. Efficacy was determined from total numbers of facial acne lesions and the investigator global assessment (IGA) score. Tolerability was evaluated by the frequency of adverse events and the mean tolerability score determined at each visit. Product acceptability was assessed via a questionnaire at the end of the study period. Results: Altogether 18 participants were enrolled, of whom 14 completed the study. Mean total lesion counts were 23.7 at baseline, 17.2 at 4, 15.1 at 8 and 10.7 at 12 weeks. Total lesion counts differed significantly over time by repeated measures anova (P < 0.0001). The mean IGA score was 2.4 at baseline, 2.2 at 4, 2.0 at 8 and 1.9 at 12 weeks, which also differed significantly over time (P = 0.0094). No serious adverse events occurred and minor local tolerability events were limited to peeling, dryness and scaling, all of which resolved without intervention. Conclusion: This study shows that the use of the tea tree oil products significantly improved mild to moderate acne and that the products were well tolerated. Copyright © 2016 The Australasian College of Dermatologists.

Periocular Mohs micrographic surgery in Western Australia 2009–2012: A single centre retrospective review and proposal for practice benchmarks.

O'Halloran L, Smith H, et al.

Background/Objectives: Periocular skin tumours pose management challenges with literature supporting a multidisciplinary approach. This retrospective review identifies trends in multidisciplinary management, ascertaining potential benchmarks for practice review. Methods: A retrospective review of 720 patients with periocular tumours, treated with Mohs micrographic surgery (MMS) at a single free standing Day Surgery Facility between 2009 and 2012. Results: In all, 690 patients were included, with mean age 65 and slight male preponderance. Basal cell carcinoma was the most commonly excised tumour (85.4%) and lower eyelid most common tumour site (58%). Of the cases repaired by Mohs surgeons, 2% involved more than one cosmetic subunit, compared with 23% by oculoplastic surgeons. Of the cases repaired by MMS, 1% had eyelid margin involvement, compared with 64% of the cases by oculoplastic
surgeons. Mean preoperative lesion size for cases repaired by Mohs and oculoplastic surgeons was 0.5 cm<sup>2</sup>. Mean postoperative defect size was smaller for cases repaired by Mohs surgeons compared with oculoplastic surgeons (1.5 and 1.9 cm<sup>2</sup>). Mean number of stages was less for Mohs surgeon repairs (n = 1.5) compared with oculoplastic surgeon repairs (n = 1.9). Cases repaired by oculoplastic surgeons were more often combination repairs. Conclusions: This study identifies potential benchmarks for Mohs surgeons when reviewing or establishing a periocular Mohs surgery practice and for doctors referring periocular tumours for surgical removal. These include the proportion of periocular cases managed jointly and the location, size of defect and number of stages involved in tumors repaired by Mohs surgeon alone compared to those repaired by oculoplastic surgeons. Copyright © 2016 The Australasian College of Dermatologists.

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**Molecular Diagnosis and Identification of Leishmania Species in Jordan from Saved Dry Samples.**

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Diagnosis of the endemic cutaneous leishmaniasis (CL) in Jordan relies on patient clinical presentation and microscopic identification. Studies toward improved identification of the causative Leishmania species, especially in regions where multiple species exist, and the introduction of these techniques into medical diagnosis is paramount. This study looked at the current epidemiology of CL in Jordan. Clinically diagnosed 41 patients with CL were tested for the presence of Leishmania parasite using both Giemsa staining from skin scraps on glass slides and ITS1-PCR from samples blotted onto storage cards (NucleoCards). Microscopically, 28 out of the 41 (68.3%) collected samples were positive for amastigotes, whereas the molecular ITS1-PCR amplification successfully identified 30 of the 41 samples (73.2%). Furthermore, PCR-RFLP analysis allowed species identification which is impossible microscopically. Of the 30 PCR positive samples, 28 were Leishmania major positive and the other two samples were Leishmania tropica. This indicates that L. major is the most prevalent species in Jordan and the two L. tropica cases originated from Syria indicating possible future L. tropica outbreaks. Diagnosis of CL based on clinical presentation only may falsely increase its prevalence. Although PCR is more sensitive, it is still not available in our medical laboratories in Jordan.

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**Neuropsychiatric presentations and outcomes in children and adolescents with primary brain tumours: Systematic review.**


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OBJECTIVE: The purpose of this study was to systematically review the literature relating to the neuropsychiatric symptoms at presentation and outcome of childhood brain tumours.

METHODS: Seven online databases pertaining to the neuropsychiatric presentation and outcomes of childhood CNS tumours were searched and PRISMA guidelines were followed. Temporal limits were not applied to the searches.

RESULTS: There were 1879 relevant search results in total. After discovering the large body of both primary and secondary research in the field of cognitive and neuropsychological outcomes of brain tumours in children, these studies were excluded. Quality-of-life studies were excluded for the same reason. Thirty-one papers were chosen for discussion in this review.

CONCLUSION: This timely systematic review concluded that neuropsychiatric presentations are common in children with CNS tumours— with the presence of behavioural and psychological symptoms in up to 57% of cases, their frequency varies according to age of onset and is strongly associated with time since diagnosis. The findings highlight the necessity for routine psychological and psychiatric screenings of children with suspected brain tumours and at follow-up and a number of clinical recommendations to this effect are listed.

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Clinical improvement following cranioplasty.
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Objectives: To determine whether there was a measureable change in neurological function following cranioplasty.

Methods: This is a prospective single surgeon, single centre study. Fifty patients who required a cranioplasty procedure were neurologically assessed within 72 hours before and 7 days after surgery. The assessment tools were the functional independence measure (FIM) and the Cognitive assessment report (COGNISTAT). The scores for both assessments were calculated and then compared before and after surgery. Results: FIM assessment was performed on all 50 patients and a Cognistat assessment was performed on 47 patients. Most improvements were seen in the Cognistat scores; however, there appeared to be no specific areas in which there was consistent improvement. There were substantial improvements in the Cognistat assessment in nine patients. One patient had a much-improved FIM assessment (improved from 18 to 34), but a Cognistat assessment was not possible due to poor neurological function. These results suggested that improvements after cranioplasty were more likely to occur in the domain of cognitive function than motor function, although overall these results did not reach statistical significance. Multiple linear regression analysis showed that pre-operative FIM score was the most important determinant of post-operative FIM score, but occurrence of surgical complications had a predictable adverse effect on post-operative FIM scores. Bifrontal (vs unilateral) cranioplasty, timing between decompression and cranioplasty and age of the patients did not appear to affect the post-operative FIM scores, after adjusting for pre-operative FIM scores and surgical complications. Conclusions: A small but significant number of patients appear to improve clinically following cranioplasty. Neurological susceptibility to a skull defect may be more common than had been previously appreciated.

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Cost-effectiveness of primary titanium cranioplasty: A randomized controlled trial.
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Objectives: Autologous bone is usually used to reconstruct skull defects following decompressive surgery. However, it is associated with a high failure rate due to infection and resorption. The aim of this study was to see whether it would be cost-effective to use titanium as a primary reconstructive material. Methods: Sixty-four patients were enrolled and randomized to receive either their own bone or a primary titanium cranioplasty. All surgical procedures were performed by the senior surgeon. Primary and secondary outcome measures were assessed at 1 year following cranioplasty. Results: There were no primary infections in either arm of the trial. There was one secondary infection of a titanium cranioplasty that had replaced a resorbed autologous cranioplasty. In the titanium group no patients were considered to have partial or complete cranioplasty failure at 12 months follow-up (p = 0.002) and none needed revision (p = 0.053). There were two deaths unrelated to the cranioplasty, one in each arm of the trial. Amongst the 31 patients who had an autologous cranioplasty, seven patients (22%) had complete resorption of the autologous bone such that it was judged a complete failure. Partial or complete autologous bone resorption appeared to be more common among young patients than older patients (32 vs 45 years-old, p = 0.013). The total cumulative cost between the two groups was not significantly different (mean difference = A$3281, 95% confidence interval = -9869 to 3308; p = 0.327). Conclusions: Primary titanium cranioplasty should be seriously considered for young patients who require reconstruction of the skull vault following decompressive craniectomy.

Decompressive craniectomy and the disability paradox.
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Objectives: Many patients survive with severe disability following decompressive craniectomy for severe traumatic brain injury. The acceptability or otherwise of this outcome has yet to determined. The aim of this study was to assess quality-of-life and 'retrospective consent' amongst patients who had survived with severe disability following a decompressive craniectomy for severe traumatic brain injury. Methods: The patients in this study were drawn from 186 patients who had had a decompressive craniectomy for severe traumatic brain injury between the years 2004-2010. The patients who were studied were those who had been judged either severely disabled or in vegetative state at 18 months after surgery and on whom at least 3-year follow-up was available. Results: Amongst 39 eligible patients, seven had died and 20 patients or their next of kin consented to participate. Of those 20 patients, the five patients who were in vegetative state at 18 months remained so beyond 3 years and the remaining 15 patients remained severely disabled after a median follow-up period of 5 years. The patients’ average daily activity (Pearson correlation coefficient [r] = -0.661, p = 0.01) and SF-36 physical score (r = -0.543, p = 0.037) were inversely correlated with the severity of TBI. The mental SF-36 scores of the patients were, however, reasonably high (median = 46, interquartile range = 37-52). The majority of patients and their next of kin felt that they would have provided retrospective consent for surgical decompression, even if they had known their eventual outcome. Conclusion: Substantial physical recovery beyond 18-months after decompressive craniectomy for severe TBI was not observed; however, many patients appeared to have recalibrated their expectations regarding what they felt to be an acceptable quality-of-life.
Response to Letter to the Editor: 'Patient opinion of scarring is multidimensional: An investigation of the POSAS with confirmatory factor analysis'.

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Mammographic breast density as a predictor of hormone receptor positive breast cancer recurrence: A single centre longitudinal analysis.

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A.D. Redfern

Mammographic breast density as a predictor of breast cancer recurrence: a single centre longitudinal analysis of women with hormone receptor positive breast cancer Background Mammographic breast density has been associated with risk of development of breast cancer. To date clinical studies examining the use of tamoxifen and fall in mammographic breast density during this treatment have shown reduction in mammographic breast density examining change in mammographic breast density between baseline and a single follow-up mammogram to be predictive for disease recurrence. Aim To examine serial change in mammographic breast density over years to describe the changes which occur with use of aromatase inhibitors and tamoxifen, as well as changes following cessation of this treatment and to determine whether changes observed correlate with outcome. Method Eligible patients were identified from the Royal Perth Hospital breast unit database between January 1994-December 2011. Patient data was prospectively collected through the breast unit database. Additional data regarding endocrine therapy, adherence, weight, height and concomitant medications were obtained from case note review. Recurrence data was obtained from the hospital medical records system, as well as the breast unit database. Mammograms were obtained and mammographic breast density readings undertaken by a single reader using Cumulus. Percentage breast densities were obtained and statistical analysis undertaken to investigate changes in mammographic density on endocrine therapy, at switch of therapy, and cessation of therapy and correlation with disease free and overall survival. Results 1942 eligible patients were identified. 417 were premenopausal at time of diagnosis, 148 perimenopausal, 1328 postmenopausal and the remainder unknown status. 12 declined adjuvant endocrine therapy, 520 received both at least 1 aromatase inhibitor and tamoxifen during follow-up, 1189 tamoxifen only, 56 tamoxifen plus goserelin, and the remainder either aromatase inhibitor only or aromatase inhibitor with ovarian suppression. Over 10,000 mammograms were obtained for analysis. Currently results are available from 4301 mammograms from
689 patients. Mean density change between baseline scan and subsequent imaging after between 11-24 months of patient-reported endocrine adherence was -6.0%, with mean reduction of -11% in patients who were premenopausal at baseline and -4.5% in those who were postmenopausal at baseline. Kaplan Meier analysis showed late separation of overall survival curves favouring those with reduction in mammographic breast density however there was no statistically significant difference in the curves Conclusion Reduction in mammographic breast density was greatest in those who were premenopausal at baseline. Further multivariate analysis and assessment of the additional mammograms in this data set is required to assess the association between mammographic breast density and outcome in this cohort.

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http://cancerres.aacrjournals.org/content/76/4_Supplement/PD1-06.abstract?sid=d77cda97-5d53-413d-b2c7-99b052fd2f93


Interim results from the first open-label, multicenter, phase IIIb study investigating the combination of pertuzumab with subcutaneous trastuzumab and a taxane in patients with HER2-positive metastatic breast cancer (SAPPHIRE).

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N. Woodward

Background: Intravenous (IV) trastuzumab has proven clinical benefits in patients (pts) with human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC). The use of pertuzumab, which targets HER2 through an independent epitope to that of trastuzumab, in combination with IV trastuzumab and docetaxel has shown improved efficacy with acceptable toxicity in metastatic (m) BC. Subcutaneous (SC) and IV trastuzumab formulations have shown comparable efficacy. This study aimed to assess the safety, tolerability, and efficacy of combining IV pertuzumab with SC trastuzumab and a taxane, as 1st-line therapy in pts with HER2+ mBC, a combination for which results have not previously been reported. Here we present demographics and interim safety data Methods: This is an open-label, multicentre, phase IIIb study. The primary objective was the safety and tolerability of IV pertuzumab with SC trastuzumab and investigator’s choice of taxane. Pts aged ≥18 years with confirmed HER2-positive [IHC3+ or ISH+] mBC with at least one measurable lesion and/or non-measurable disease according to RECIST version 1.1 and ECOG performance status (PS) 0-2 were included. Pts received IV pertuzumab every 3 weeks (loading dose=840 mg; subsequent doses=420mg) combined with SC trastuzumab at 600mg/5mL every 3 weeks and the investigator’s choice of taxane (docetaxel, paclitaxel, or nab-paclitaxel). Treatment continued until disease progression, unacceptable toxicity, or consent was withdrawn, whichever occurred first. The incidence and severity of adverse events (AEs), serious (S) AEs and AEs leading to premature discontinuation of study treatment were analyzed Results: The planned 50 pts have been recruited from 12 centres; mean age 53 (SD-12.0) years; the majority white (84%), ECOG PS 0 (n=33) and PS 1 (n=15). 98% were females; 61% post-menopausal. Taxanes of choice were nab-paclitaxel (n=36), docetaxel (n=13) and paclitaxel (n=1). Any grade AEs (n=627) were reported in 100% pts; majority grade 1-2, the most common being diarrhoea, fatigue, peripheral neuropathy, alopecia, nausea, rash, headache and vomiting. Grade 3+ AEs (n=54) were reported in 52% pts, most commonly neutropenia (10%), febrile neutropenia (8%) and diarrhoea (6%). SAEs (n=36) were reported in 48% pts; most commonly pyrexia (14%), febrile neutropenia (8%), neutropenia (4%), pulmonary embolism (4%) and cellulitis (4%). Five AEs of suspected cardiac disorders were reported in 4 pts (atrial fibrillation, cardiomyopathy, myocardial ischemia, palpitations and ejection fraction decreased). AEs leading to study drug discontinuation (n=3) were reported in 3 pts (LVEF decreased, syncope and blister). AEs leading to chemotherapy discontinuation (n=14) were reported in 20% pts Conclusion: We report the first data on the use of pertuzumab with SC trastuzumab. The observed safety profile is consistent with that previously reported in the CLEOPATRA.

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Does adverse tumour biology contribute to inferior outcomes for Indigenous Australians diagnosed with breast cancer?

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Background: Analyses across multiple Australian states have consistently demonstrated significantly inferior breast cancer survival for Indigenous patients (IPs). Studies compensating for increased remoteness, socioeconomic disadvantage and later presentation demonstrate a residual unexplained detriment. This survival disadvantage is confined to the first five years, akin to the inferior outcomes demonstrated by higher risk biological breast cancer subtypes. We postulated that a preponderance of such higher risk subtypes could explain the disparate mortalities.

Methods: The distribution of breast cancer subtypes in Western Australian IPs diagnosed between 2001 and 2010 was assessed to explore the contribution of adverse prognostic subtypes to poorer outcome. This was a retrospective cohort study of Indigenous women (n=114) and 3:1 age and remoteness matched non-Indigenous women (n=310) diagnosed with invasive, non-metastatic, unilateral breast cancer, who underwent definitive local treatment. Subtypes were assigned as luminal A, B, HER2 enriched and triple negative by ER, PR, HER2 and tumour grade comparisons.

Differences in basic tumour demographics and biological sub-types were analysed and racial survival discrepancies explored within biological subtype cohorts. Results: Hazards for overall and breast cancer-specific mortality in IPs were 4.07 (95% CI 2.55-6.49) and 4.19 (95% CI 2.42-7.25). IPs were significantly more likely to have grade 3 tumours (41 v 25%, p<0.001), LN positive disease (39 v 27%, p<0.001) and larger tumours (median 20 v 10 mm, p<0.001). No significant differences in proportions of classical histological sub-types (ductal v lobular) or in tumours showing ER, PR or HER2 positivity were observed. There were no significant differences in biological sub-type proportions although IPs were diagnosed with numerically more non-Luminal A subtypes (56 v 44%, p=0.08), accounted for by increased Luminal B (21 v 15%) and HER2 enriched (10 v 5%) sub-types. The significant relative five-year survival deficit for IPs noted overall (94 v 73%, p<0.0001) was observed for each sub-type with the exception of HER2 positive patients. This extended from the relatively low risk luminal A sub-type where oral anti-estrogens are the mainstay of treatment (98 v 82%, p=0.0002) to the high risk triple negative sub-type where intravenous chemotherapy is the standard adjuvant therapy (94 v 50%, p=0.0014). Conclusions: The contribution of adverse tumour biological subtype to poorer outcomes for Indigenous women is modest. Indigenous women with almost all biological subtypes fare significantly worse than their non-Indigenous contemporaries. Ongoing work includes more detailed biological comparisons of RNA expression and DNA mutation between groups as well as an exploration of potentially disparate treatment patterns.

PMID:72247567


Levosimendan: New hope therapy for takotsubo syndrome.

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Impact of retinal pigment epithelium pathology on spectral-domain optical coherence tomography-derived macular thickness and volume metrics and their intersession repeatability.

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Background: To determine the impact of retinal pigment epithelium (RPE) pathology on intersession repeatability of retinal thickness and volume metrics derived from Spectralis spectral-domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany). Design: Prospective cross-sectional single centre study. Participants: A total of 56 eyes of 56 subjects were divided into three groups: (i) normal RPE band (25 eyes); (ii) RPE elevation: macular soft drusen (13 eyes); and (iii) RPE attenuation: geographic atrophy or inherited retinal diseases (18 eyes).

Methods: Each subject underwent three consecutive follow-up macular raster scans (61 B-scans at 119 μm separation) at 1-month intervals. Main outcome measures: Retinal thicknesses and volumes for each zone of the macular subfields before and after manual correction of segmentation error. Coefficients of repeatability (CR) were calculated. Results: Mean (range) age was 57 (21-88) years. Mean central subfield thickness (CST) and total macular volume were 264 and 258 μm (P = 0.62), and 8.0 and 7.8 mm<sup>3</sup> (P = 0.31), before and after manual correction. Intersession CR (95% confidence interval) for CST and total macular volume were reduced from 40 (38-41) to 8.3 (8.1-8.5) and 0.62 to 0.16 mm<sup>3</sup> after manual correction of segmentation lines. CR for CST were 7.4, 23.5 and 66.7 μm before and 7.0, 10.9 and 7.6 μm after manual correction in groups i, ii and iii. Conclusions: Segmentation error in eyes with RPE disease has a significant impact on intersession repeatability of Spectralis spectral-domain optical coherence tomography macular thickness and volume metrics. Careful examination of each B-scan and manual adjustment can enhance the utility of quantitative measurement. Improved automated segmentation algorithms are needed. Copyright © 2016 Royal Australian and New Zealand College of Ophthalmologists.

Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: A consensus definition.

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Objectives: To define standardized endpoints to aid the design of trials that compare antibiotic therapies for bloodstream infections (BSI). Methods: Prospective studies, randomized trials or registered protocols comparing antibiotic therapies for BSI, published from 2005 to 2016, were reviewed. Consensus endpoints for BSI studies were defined using a modified Delphi process. Results: Different primary and secondary endpoints were defined for pilot (small-scale studies designed to evaluate protocol design, feasibility and implementation) and definitive trials (larger-scale studies designed to test hypotheses and influence clinical practice), as well as for Staphylococcus aureus and Gram-negative BSI. For pilot studies of S. aureus BSI, a primary outcome of success at day 7 was defined by: survival, resolution of fever, stable/improved Sequential Organ Failure Assessment (SOFA) score and clearance of blood cultures, with no microbiologically confirmed failure up to 90 days. For definitive S. aureus BSI studies, a primary outcome of success at 90 days was defined by: survival and no microbiologically confirmed failure. For pilot studies of Gram-negative BSI, a primary outcome of success at day 7 was defined by: survival, resolution of fever and symptoms related to BSI source, stable or improved SOFA score and negative blood cultures. For definitive Gram-negative BSI studies, a primary outcome of survival at 90 days supported by a secondary outcome of success at day 7 (as previously defined) was agreed. Conclusions: These endpoints provide a framework to aid future trial design. Further work will be required to validate these endpoints with respect to patient-centred clinical outcomes. Copyright © 2016 European Society of Clinical Microbiology and Infectious Diseases.

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**Intersession test-retest variability of conventional and novel parameters using the MP-1 microperimeter.**

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PURPOSE: To investigate the intersession test-retest variability (TRV) of topography- and threshold-based parameters derived from the Nidek MP-1.

DESIGN: Prospective observational study.

METHODS: Sixteen participants with and without central scotoma underwent microperimetry in one eye over three sessions at 1-month intervals in a single institution. We calculated 95% coefficient of repeatability (CR) for the number of normal-suspect (NS) loci, relative scotoma (RS) and dense scotoma (DS), median macular sensitivity (MS), mean sensitivity of responding loci (RLS), perilesional loci (PLS), and extralesional loci (ELS). Topographical agreement score of mapping NS and DS loci (TASNS and TASDS) were also calculated for each patient.

RESULTS: Mean (range) age was 50 (21-86) years. The CR (95% confidence intervals) for NS, RS, and DS were 9.9 (6.5-13.3), 9.5 (6.2-12.7), and 3.0 (1.1-4.1) respectively. CR (95% CIs) for median MS, mean RLS, PLS, and ELS were 3.4 (2.3-4.5), 1.6 (1.1-2.2), 1.8 (0.9-2.6), and 2.8 (1.5-4.0) dB. We found significant change in thresholds between Test 1, and Tests 2 and 3 (both P=0.03), but not between Tests 2 and 3 (P=0.8). Medians (range) TASNS and TASDS were 74% (39%-100%) and 77% (0%-97%), respectively, between Tests 2 and 3.

CONCLUSION: We recommend the use of four DS loci (upper limit of CR) as the limit of TRV for assessing change. There was large interindividual variability in NS or DS mapping agreement. We recommend discarding the first microperimetry test and caution the use of a change in spatial distribution to determine disease progression.

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Incidence of serum sickness after the administration of Australian snake antivenom (ASP-22).
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CONTEXT: Serum sickness is a delayed immune reaction resulting from the injection of foreign protein or serum. Antivenom is known to cause serum sickness but the incidence and characteristics are poorly defined.

OBJECTIVE: To investigate the incidence and clinical features of serum sickness following the administration of Australian snake antivenoms.

MATERIALS AND METHODS: This was a prospective cohort study of patients recruited to the Australian Snakebite Project who received snake antivenom from November 2012 to March 2014. Demographics, clinical information, laboratory tests and antivenom treatment were recorded prospectively. Patients administered antivenom were followed up at 7-10 days and 6 weeks post-antivenom. The primary outcome was the proportion with serum sickness, pre-defined as three or more of: fever, erythematous rash/urticaria, myalgia/arthritis, headache, malaise, nausea/vomiting 5-20 days post-antivenom.

RESULTS: During the 16-month period, 138 patients received antivenom. 23 were not followed up (unable to contact, tourist, child, bee sting) and 6 died in hospital. Of 109 patients followed up, the commonest reason for antivenom was venom induced consumption coagulopathy in 77 patients. An acute systemic hypersensitivity reaction occurred post-antivenom in 25 (23%) and 8 (7%) were severe with hypotension. Serum sickness occurred in 32/109 (29%) patients, including 15/37 (41%) given tiger snake, 6/15 (40%) given polyvalent and 4/23 (17%) given brown snake antivenom. There was no association between the volume of antivenom and serum sickness, P = 0.18. The commonest effects were lethargy, headache, muscle/joint aches and fever.

DISCUSSION: The incidence of serum sickness after snake antivenom in Australia was higher than earlier investigations which failed to define symptoms or follow-up patients, but similar to more recent studies of antivenoms in the United States.
CONCLUSION: Serum sickness is common with Australian snake antivenom but does not appear to be predictable based on the volume of antivenom administered.

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Controversy and consensus regarding vitamin D: Recent methodological changes and the risks and benefits of vitamin D supplementation.
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A dramatic and sustained surge in vitamin D test numbers has been attributed to the extraskeletal and probable intra/paracrine effects of vitamin D and not the important role of vitamin D in the regulation of extracellular calcium homeostasis and bone metabolism. This review summarizes recent data regarding the skeletal and extraskeletal effects of vitamin D, provides an overview of current methods of 25-hydroxyvitamin D measurement and includes the beneficial and adverse effects of vitamin D replacement. The role of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, vitamin D binding protein and free hormone levels are explored and potential future developments in this area are discussed. The adoption of a reference method for the measurement of 25-hydroxyvitamin D, certified reference standards and an independent certification program administered by the Centre of Disease Control is expected to improve routine analytical performance and is a major, crucial step forward. Improvements in accuracy, precision and sensitivity of 25-hydroxyvitamin D measurement is an important prelude to accurately defining the desirable level of 25-hydroxyvitamin D that is associated with the lowest risk for falls and fractures. Finally, the results of ongoing large, prospective, randomized clinical trials such as the Australian D-Health study should clarify the role of vitamin D supplementation in the prevention and management of skeletal and nonskeletal disorders, including vitamin D effects on mortality risk.

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Paresthesia: A review of its definition, etiology and treatments in view of the traditional medicine.
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Objective: To search major Islamic Traditional Medicine (ITM) textbooks for definition, etiology and medicinal plants used to manage ‘khadar’ or ‘paresthesia’, a common sensory symptom of multiple sclerosis (MS) and peripheral neuropathies. In addition, the conformity of the efficacy of ITM-suggested plants with the findings from modern pharmacological research on MS will be discussed. Methods: Data on the medicinal plants used to treat ‘khadar’ were obtained from major ITM texts. A detailed search in PubMed, ScienceDirect, Scopus and Google Scholar databases was performed to confirm the effects of ITM-mentioned medicinal plants on MS in view of identified pharmacological actions. Results: Moringa oleifera Lam., Aloe vera (L.) Burm.f., Euphorbia species, Citrullus colocynthis (L.) Schrad., and Costus speciosus (Koen ex. Retz) Sm. are among the most effective ITM plants for the management of ‘khadar’. Recent experimental evidence confirms the effectiveness of the mentioned plants in ameliorating MS symptoms.
Moreover, according to ITM, prolonged exposure to cold and consuming foodstuff with cold temperament might be involved in the etiopathogenesis of MS. Conclusions: The use of traditional knowledge can help finding neglected risk factors as well as effective and safe therapeutic approaches, phytomedicines and dietary habits for the management of paresthesia and related disorders such as MS. Copyright © 2016 Bentham Science Publishers.


Management of Inflammatory Bowel Disease Using Stem Cell Therapy.
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Inflammatory bowel diseases (IBD) are a collection of diseases associated with chronic inflammation in the intestinal mucosa and/or transmural involvement. IBD is divided into two main categories Crohn’s disease (CD) and ulcerative colitis (UC). While there is no cure for IBD, current therapies can only reduce the inflammatory process that causes the signs and symptoms of IBD and hopefully induce long-term remission. Improved treatment modalities for the complex IBD are still evolving. The increased understanding of the underlying immunopathology has helped identify new targeted treatment options in particular the use of stem cell treatments that are capable of modulating the immune system. Haematopoietic stem cells (HSC) and mesenchymal stromal cells (MSC) therapy are both being investigated as a treatment for IBD. MSC therapy is well tolerated and associated with minimal established side-effects compared to HSC therapy, which involves ablative chemotherapy. Currently, such stem cell therapy is not a standard of care regimen for IBD. However, it may potentially become the next generation treatment of choice, especially for severe refractory IBD patients.

Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial.

Objective Non-alcoholic fatty liver disease (NAFLD) is a common liver disease characterized by excess lipid deposition in the hepatic tissue and subsequent oxidative and inflammatory damage. Curcumin is a dietary polyphenol with lipid-modifying, antioxidant and anti-inflammatory properties. This study aimed to evaluate the efficacy and safety of supplementation with phytosomal curcumin in subjects with NAFLD. Methods Patients diagnosed with NAFLD (grades 1-3 according to liver ultrasonography) were randomly assigned to the curcumin (phytosomal form; 1 000 mg/day in 2 divided doses) (n=50) or placebo group (n=52) for a period of 8 weeks. All patients received dietary and lifestyle advises before the start of trial. Anthropometric measurements, hepatic enzymes, and liver ultrasonography were assessed at baseline and after 8 weeks of follow-up. Results 87 subjects (n=44 and 43 in the curcumin and control group, respectively) completed the trial. Supplementation with curcumin was associated with a reduction in body mass index (-0.99+/-.25 vs. - 0.15+/-.31 in the curcumin and placebo groups, respectively; p=0.003) and waist circumference (-1.74+/-.58 vs. -0.23+/-.349 in the curcumin and placebo groups, respectively; p=0.024). Ultrasonographic findings were improved in 75.0% of subjects in the curcumin group, while the rate of improvement
in the control group was 4.7% (p<0.001). Serum levels of aspartate aminotransferase and alanine aminotransferase were reduced by the end of trial in the curcumin group (p<0.001) but elevated in the control group (p<0.001). Curcumin was safe and well tolerated during the course of trial. Conclusion Short-term supplementation with curcumin improves liver fat and transaminase levels in patients with NAFLD. Copyright © 2016, Georg Thieme Verlag. All rights reserved.

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Counting up the risks: How common are risk factors for morbidity and mortality in young people with psychosis?

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Background: This study examined the prevalence of risk factors for cardiovascular (CV)-related morbidity and mortality in young people with psychosis aged 18 to 24 years. Methods: The study included 132 people aged 18 to 24 who participated in the 2010 second Australian national survey of people living with psychosis. The 2009 World Health Organisation (WHO) Global Health Risks report was used as a framework to determine which specific risk factors were present in each of these young people. The risk factors assessed in this study were smoking, alcohol use, hypertension, overweight/obesity, physical inactivity, high blood glucose, high cholesterol and poor diet. Each risk factor was defined according to WHO criteria. A count of the total number of risk factors present for each participant was determined. Data for male and female participants were compared. Results: Young men had an average of 2.9 (SD 1.2) risk factors. Young women had an average of 2.4 (SD 1.2) risk factors. The most common risk factors were low fruit and vegetable intake (77.9%), cigarette smoking (67.7%), overweight/obesity (55%) and physical inactivity (39.8%). There were no significant differences between men and women in the number of risk factors present, or the prevalence of individual risk factors. Conclusion: This study demonstrated that many of the risk factors that ultimately contribute to disability and premature death are present at an early age in people with psychosis. Preventive measures need to be an integral component of early intervention services for this client population to avert progression to serious CV morbidity and early mortality. Copyright © 2016 Wiley Publishing Asia Pty Ltd.

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The relationship between serology of hepatitis E virus with liver and kidney function in kidney transplant patients.

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Although hepatitis E virus (HEV) is well known to cause acute hepatitis, there are reports showing that HEV may also be responsible for progression of acute to chronic hepatitis and liver cirrhosis in patients receiving organ transplantation. In this study, we aimed to evaluate the prevalence of HEV in patients with kidney transplantation. In this study, 110 patients with kidney transplantation were recruited, and anti-HEV IgG, creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and estimated glomerular filtration rate (eGFR) in the first, third and sixth months after renal transplantation were measured. The mean serum anti-HEV IgG titers in the study participants was 1.36 (range 0.23 to 6.3). Twenty-three patients were found to be seropositive for HEV Ab defined as anti-HEV IgG titer > 1.1. The difference in liver and renal function tests (creatinine, eGFR, AST, ALT and ALP) at different intervals was not significant between patients with HEV Ab titers higher and lower than 1.1 (p > 0.05). However, an inverse correlation was observed between HEV Ab and eGFR values in the first (p = 0.047, r = -0.21), third (p = 0.04, r = -0.20) and sixth (p = 0.04, r = -0.22) months after renal transplantation in patients with HEV Ab < 1.1 but not in the subgroup with HEV Ab > 1.1. Also, a significant correlation between age and HEV Ab levels was found in the entire study population (p = 0.001, r = 0.33). Our findings showed a high prevalence of seropositivity for anti-HEV IgG in patients receiving renal transplants. However, liver and renal functions were not found to be significantly different seropositive and seronegative patients by up to 6 months post-transplantation. 

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Efficacy of Elaeagnus Angustifolia extract in the treatment of knee osteoarthritis: a randomized controlled trial.

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Osteoarthritis (OA) is one of the most common musculoskeletal disorders all over the world. Available anti-arthritic medications have only partial efficacy and their long-term use is associated with adverse events. Elaeagnus Angustifolia (EA) is a medicinal plant with analgesic and anti-inflammatory properties. The present study evaluated the impact of two doses of EA extract compared with ibuprofen on the severity of disease in patients with knee OA. This study was designed as a randomized, double blind, active-controlled and parallel group trial. Patients with OA were randomized to receive 300 mg/day (n=33) or 600 mg/day (n=32) of EA aqueous extract, or 800 mg/day ibuprofen (n=32) for 7 weeks. EA extract contained 0.21 % (w/w) kaempferol according to HPLC. Efficacy of treatment was assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS) of pain, Lequesne’s Pain-Function Index (LPFI), and patient’s global assessment (PGA) index. The amount of kaempferol in the extract was determined by HPLC method to be 0.21 % w/w. There were significant reductions in WOMAC, VAS, LPFI and PGA scores by the end of trial with all three interventions. Comparison of the changes in
WOMAC, VAS and LPFI scores among the treatment groups did not reveal any significant difference between EA and ibuprofen, and between low and high doses of EA. EA was safe and well tolerated during the course of trial and no adverse event was reported. The present results suggest beneficial effects of aqueous EA extract in reducing the symptoms of OA with an efficacy comparable to that of ibuprofen.

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The effect of cold application and lavender oil inhalation in cardiac surgery patients undergoing chest tube removal.
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Post-surgical chest tube removal (CTR) is associated with a significant pain and discomfort for patients. Current treatment strategies for reducing CTR-associated pain and anxiety are limited and partially efficacious. To determine the effects of cold application, inhalation of lavender essential oil, and their combination on pain and anxiety during CTR was investigated. This randomized controlled open-label trial was conducted with 80 patients in the cardiac surgery intensive care unit who had a chest tube for duration of at least 24 hours after coronary artery bypass grafting (CABG). Patients were randomized (n=20 in each group) to receive cold application, aromatherapy with lavender oil, cold application in combination with lavender oil inhalation, or none of the above interventions (control group). The intensity and quality of pain and anxiety were evaluated using the visual analogue scale, short form and modified-McGill pain questionnaire (SFM-MPQ) and the Spielberger situational anxiety level inventory (STAII) scale, respectively. Patients in all treatment groups had significantly lower pain intensity and anxiety compared with the control group immediately, 5, 10 and 15 min after CTR. There was no statistically significant difference in the SFM-MPQ total scores between the intervention groups. With respect to anxiety score, there was a significantly reduced anxiety level immediately after CTR in the aromatherapy and cold-aromatherapy combination groups versus the cold application group. The present results suggested the efficacy of cold application and aromatherapy with lavender oil in reducing pain and anxiety associated with post-CABG CTR.

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Anacetrapib for the treatment of dyslipidaemia: the last bastion of the cholesteryl ester transfer protein inhibitors?
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INTRODUCTION: Inhibition of cholesteryl ester transfer protein (CETP) has emerged as a potential way to decrease cardiovascular risk by raising high density lipoprotein (HDL) cholesterol and lowering low density lipoprotein (LDL) cholesterol concentrations. However, high profile withdrawals of several CETP inhibitors have cast doubt over this hypothesis. Despite this concern, anacetrapib appears to be safe, well-tolerated and delivers a substantial increases in HDL cholesterol and reductions in LDL cholesterol as monotherapy and when combined with a statin.

AREAS COVERED: We discuss the role of CETP and HDL cholesterol as therapeutic targets, describe the pharmacokinetics and pharmacodynamics of anacetrapib, as well as report on the recent clinical trials.

EXPERT OPINION: The focus of CETP inhibition has shifted from HDL cholesterol-raising to LDL cholesterol-lowering. Although anacetrapib appears to be safe and is effective in altering lipid-related biochemical parameters of interest, its effect on cardiovascular outcomes remains unknown. Extrapolation of LDL cholesterol lowering to improved cardiovascular outcomes is not possible, because LDL and HDL functionality in the setting of anacetrapib treatment is unclear. The results of the phase III REVEAL randomised controlled trial will be critical for anacetrapib to establish a place in clinical care.

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Following a mediterranean diet for 3-months reduces home measured systolic blood pressure (SBP) in older australians; results from the mediterranean diet for cognition and cardiovascular health in the elderly (MedLey) trial.

Murphy K, Davis C, et al.

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The Mediterranean diet (MedDiet), reported to have cardiovascular health benefits, consists of a variety of foods including fruit and vegetables, wholegrain cereals, legumes, nuts, red wine, olive oil, fish, poultry and red meat delivering valuable nutrients like fibre, vitamins, minerals, omega-3 fatty acids and polyphenols. We sought to evaluate the health benefits of a Mediterranean diet in comparison with habitual diet on blood pressure (BP) in older Australians (mean age 71 +/- 5yrs) in the MedLey trial. Participants (were randomly allocated either a MedDiet (n=80) or continue their habitual diet (HabDiet) (n=72) for 6 months. Volunteers received some study foods and followed a prescribed MedDiet plan as advised by the study dietitian. All volunteers attended the clinic on a fortnightly basis to have their weight measured, discuss the intervention and receive study foods. Blood pressure was measured at home, three times daily (morning, afternoon, evening), taking 3 measures per reading for 6 days providing 54 blood pressure readings of which the average BP was obtained. Data was analysed using random effects model that included fixed effects for Diet, Visit, Diet x Visit interaction (STATA). Differences between diets were then assessed using the overall Diet x Visit interaction term and the marginally adjusted mean values. 137 volunteers completed the trial (MedDiet n=74, HabDiet n=63). Compliance to the MedDiet was maintained (92%) throughout the intervention according to 3-day weighed food records collected at each time-point. Mean SBP at baseline, 3 and 6 months, respectively, were: 124.9 +/- 1.4mmHg, 119.3 +/- 1.4mmHg and 118.9 +/- 1.6mmHg for MedDiet; and 127.8 +/- 1.5mmHg, 123.9 +/- 1.5mmHg and 122.1 +/- 1.7mmHg for Hab Diet. The MedDiet group had a significantly greater reduction in SBP than the HabDiet group at 3 months (P=0.031 for interaction) which was also significantly reduced for the afternoon measure of systolic BP alone (P=0.024 for interaction). Although both groups had clinically relevant
decreases in SBP, following the MedDiet resulted in a greater reduction in SBP than for the habitual group. This dietary pattern could be utilised in Australia as part of a diet and lifestyle intervention for the control of elevated BP. PMID:72320049
http://www.fasebj.org/content/30/1_Supplement/904.8.abstract?sid=594a653e-36ab-48ff-979d-5d94ad608b0f

**Efficacy of Antibacterial Peptides Against Peptide-Resistant MRSA Is Restored by Permeabilization of Bacteria Membranes.**
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Clinical application of antimicrobial peptides (AMPs), as with conventional antibiotics, may be compromised by the development of bacterial resistance. This study investigated AMP resistance in methicillin resistant Staphylococcus aureus, including aspects related to the resilience of the resistant bacteria toward the peptides, the stability of resistance when selection pressures are removed, and whether resistance can be overcome by using the peptides with other membrane-permeabilising agents. Genotypically variant strains of S. aureus became equally resistant to the antibacterial peptides melittin and bac8c when grown in sub-lethal concentrations. Subculture of a melittin-resistant strain without melittin for 8 days lowered the minimal lethal concentration of the peptide from 170 mug ml<sup>-1</sup> to 30 mug ml<sup>-1</sup>. Growth for 24 h in 12 mug ml<sup>-1</sup> melittin restored the MLC to 100 mug ml<sup>-1</sup>. Flow cytometry analysis of cationic fluorophore binding to melittin-naive and melittin-resistant bacteria revealed that resistance coincided with decreased binding of cationic molecules, suggesting a reduction in net negative charge on the membrane. Melittin was haemolytic at low concentrations but the truncated analog of melittin, mel12-26, was confirmed to lack haemolytic activity. Although a previous report found that mel12-26 retained full bactericidal activity, we found it to lack significant activity when added to culture medium. However, electroporation in the presence of 50 mug ml<sup>-1</sup> of mel12-26, killed 99.3% of the bacteria. Similarly, using a low concentration of the non-ionic detergent Triton X-100 to permeabilize bacteria to mel12-26 markedly increased its bactericidal activity. The observation that bactericidal activity of the non-membranolytic peptide mel12-26 was enhanced when the bacterial membrane was permeablized by detergents or electroporation, suggests that its principal mechanism in reducing bacterial survival may be through interaction with intracellular organelles or processes. Additionally, our results showed that the haemolytic peptide bac8c, had increased antibacterial activity at non-haemolytic concentrations when used with membrane-permeabilizing surfactants.
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**Risk Factors for Obstructive Sleep Apnea Are Prevalent in People with Psychosis and Correlate with Impaired Social Functioning and Poor Physical Health.**
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BACKGROUND: Obstructive sleep apnea (OSA) in the general community is associated with obesity, smoking, alcohol, and sedative medication use and contributes to depressed mood, daytime sedation, and sudden cardiovascular deaths. Poor cardiovascular health, impaired social functioning, and negative and cognitive symptoms are also among the common clinical features of psychotic disorders. People with psychosis have higher rates of sleep disturbance; however, OSA has not been extensively investigated in this population.

AIMS: This study aimed to determine the prevalence of OSA and general sleep disruption symptoms in a representative Australian sample of people with psychosis. We investigated the prevalence of potential risk factors for OSA, including obesity, psychotropic medications, and substance abuse in this population. Finally, we evaluated associations between symptoms of OSA, symptoms of general sleep disruption, and various clinical features in people with psychosis.

METHODS: Participants took part in the Second National Australian Survey of Psychosis, a population-based survey of Australians with a psychotic disorder aged 18-64years. Symptoms associated with OSA (snoring and breathing pauses during sleep) in the past year were assessed using questions from the University of Maryland Medical Centre Questionnaire and symptoms associated with general sleep disruption in the past week using the Assessment of Quality of Life Questionnaire. Data collected included psychiatric diagnosis and symptoms, education, employment, medications, smoking status, physical activity, drug and alcohol use, and cognitive function. Physical health measures included body mass index, waist circumference, blood pressure, fasting blood glucose, and lipids.

RESULTS: Snoring was reported by 41.9%; 7% stating they frequently stopped breathing (pauses) during sleep. Univariate logistic regressions show OSA symptoms (pauses and snoring) were associated with older age, female gender, lower levels of social participation or employment, cardiovascular risk factors, sedentary lifestyle, and poorer quality of life, while symptoms of general sleep disruption were more likely in people with depressive symptoms.

CONCLUSION: Australians with psychosis have high levels of sleep disturbance, including OSA. OSA symptoms were associated with cardiovascular disease risk factors, reduced social participation and employment, and poorer quality of life. Whether correction of OSA can improve these factors in people with psychosis remains to be determined.

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A Web-Based Registry for Familial Hypercholesterolaemia.

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Familial hypercholesterolaemia (FH) is the most common and serious monogenic disorder of lipoprotein metabolism that leads to premature coronary heart disease. Patients with FH are often under-treated, and many remain undiagnosed. The deployment of the FH Australasia Network Registry is a crucial component of the comprehensive model of care for FH, which aims to provide a standardised, high-quality and cost-effective system of care that is likely to have the highest impact on patient outcomes. The FH Australasia Network Registry was customised using a registry framework that is an open source, interoperable system that enables the efficient customisation and deployment of national and international web-based disease registries that can be modified dynamically as registry requirements evolve. The FH Australasia Network Registry can be employed to improve health services for FH patients across the Australasia-Pacific region, through the collation of data to facilitate clinical service planning, clinical trials, clinical audits, and to inform clinical best practice. Copyright © 2016.
Background: Familial hypercholesterolaemia (FH) is a common autosomal co-dominant condition that causes premature cardiovascular disease. Awareness of FH is poor and only 10-15% of the affected population is identified. Electronic health records provide an opportunity to increase detection and awareness in general practice. Objective: To determine whether a simple electronic extraction tool can increase detection of FH in general practice. Method: An extraction tool applied to general practice electronic health records (EHR) to screen for FH, total cholesterol and low density lipoprotein cholesterol (LDL-c) levels in association with entered diagnostic criteria and demographic data in five general practices. Results: Of 157,290 active patients examined, 0.7% (n=1081) had an LDL-c>5.0 mmol/L representing 1 in 146 of active patients. An additional 0.8% (n=1276) patients were at possible risk of FH. Of those with an LDL-c>5.0 mmol/L 43.7% of patients had no record of being prescribed statins. Twenty patients (0.013%) had a clinical diagnosis of FH entered in the EHR. Conclusions: Patients at high risk of FH can be identified by a simple electronic screening method in general practice. Clinical data entry is variable in general practice. Targeted screening enables clinical assessment of patients at risk of cardiovascular disease and using the DLCNS will enable primary care to increase identification of FH. Approximately one in five patients extracted using this method, are likely to have phenotypically probable FH, making it a useful screening tool. Copyright © 2016 Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSTCS) and the Cardiac Society of Australia and New Zealand (CSANZ). PMID:613874106 DOI:http://dx.doi.org/10.1016/j.hlc.2016.09.012

Successful endovascular management of endoleak-like phenomenon following open abdominal aortic aneurysm repair.

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INTRODUCTION: Endoleaks are a well-known complication after endovascular aortic repair. Type I endoleak-like phenomenon (also defined as a proximal pseudoaneurysm) post-open abdominal aortic aneurysm (AAA) repair is described as an anastomotic leak causing recurrent pressurization of the original aneurysm sac. It is rare but may result in aneurysmal sac rupture into the peritoneal cavity.

REPORT: A 78-year-old man presented with a progressively enlarged aneurysmal sac due to proximal anastomotic degeneration of the proximal suture line associated with an outflow through a patent large lumbar vessel following a previous emergency open AAA repair. This was successfully treated using a combination coils and ethylene-vinyl alcohol copolymer. An Endoluminal tube stent graft was successfully deployed to seal the aortic anastomotic dehiscence.

CONCLUSION: Endovascular treatment of an anastomotic dehiscence associated with a large outflow lumbar artery post-open AAA repair is feasible and safe.

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Atypical leg ulcers after sclerotherapy for treatment of varicose veins: Case reports and literature review.

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INTRODUCTION: Skin necrosis is a rare complication of foam sclerotherapy, a common form of treatment for varicose veins.

PRESENTATION OF CASE: Both patients presented to the outpatient clinic within 2-14 days after foam sclerotherapy with Aethoxysklerol® 1%, with severe soft tissue and skin necrosis. Further aggressive treatment of the ulcer was required to resolve the necrosis, resulting in marked residual scar and well granulated leg ulcer respectively.

DISCUSSION: Foam sclerotherapy is a common and usually well-tolerated treatment modality for varicose veins. The aetiology of skin necrosis is conventionally related to extravasation of sclerosant. In order to minimise the risk of necrosis, the lowest concentration and lowest volume of sclerosant necessary to achieve adequate treatment of the target vein should be used.

CONCLUSION: We would like to emphasise that whilst skin and soft tissue necrosis is a rare complication of foam sclerotherapy, it is a complication that is highly disfiguring and requires aggressive treatment. As such, it should be adequately discussed with the patient prior to obtaining informed consent.
Familial hypercholesterolemia (FH) is the most common and serious form of inherited hyperlipidaemia. Dominantly inherited with high penetrance, untreated FH leads to premature death from coronary artery disease due to accelerated atherosclerosis from birth. Despite its importance, there is still a major shortfall in awareness, detection and treatment of FH worldwide. International models of care for FH have recently been published, but their effective implementation requires the garnering of more knowledge about the condition. The "Ten Countries Study" aims to investigate diagnostic, epidemiological and service aspects, as well as physician practices and patient experiences of FH in several countries in the Asia-Pacific Region and the Southern Hemisphere. Five observational studies are being undertaken that will systematically investigate the following aspects of FH: the phenotypic predictors of low-density lipoprotein receptor mutations, the point prevalence in available community populations, current knowledge and clinical practices among primary care physicians, availability and utilisation of services and facilities, and patient perceptions and personal experiences of the condition. The information gathered will inform better clinical practice and will enable the development of country-specific models of care for FH. Copyright © 2016 Japan Atherosclerosis Society.

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MTP gene variants and response to lomitapide in patients with homozygous familial hypercholesterolemia.
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Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder, which leads to premature cardiovascular diseases. Microsomal triglyceride transport protein (MTP) inhibitors, such as lomitapide, offer a new therapeutic approach for treating these patients. We evaluated the lipid lowering (LL) efficacy of lomitapide according to several gene variants in MTP. Four clinically and/or molecularly defined HoFH patients were treated with lomitapide in addition to conventional high intensity LL therapy and regular lipoprotein apheresis. Two patients responded to the therapy, with a significant reduction of LDL cholesterol (LDL-C>50%, hyper-responders). Sequencing of all exonic and intronic flanking regions of the MTP gene in all patients revealed 36 different variants. The hyper-responders to lomitapide shared six common variants: rs17533489, rs79194015, rs745075, rs41275715, rs1491246, and rs17533517, which were not seen in hypo-responders (reduction in LDL-C<50%). We suggest that in HoFH variants in the MTP gene may impact on the therapeutic response to lomitapide, but this requires further investigation. Copyright © 2016, Japan Atherosclerosis Society. All rights reserved.

The acute effect of Bowen therapy on pressure pain thresholds and postural sway in healthy subjects.

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Objective: The purpose of the study is to determine the immediate effect of Bowen Therapy in pressure pain threshold and postural sway of healthy individuals. Design: Crossover, randomized, and double blinded study. Setting: University. Participants: Participants aged 18 years old or over, naive to Bowen therapy were recruited among university students. An a priori sample size calculation determined that 34 participants were needed. Methods: Each participant attended two sessions and received Bowen Therapy and a sham procedure. The order in which Bowen or the sham procedure were administered was randomized. All participants had their postural control and pressure pain thresholds assessed in sessions 1 and 2 both at baseline and at the end of the session. Main outcome measurements: Postural control was assessed using a force plate and centre of pressure antero-posterior and medio-lateral displacement, velocity and total sway area were calculated. Pressure pain threshold was measured at 10 different body sites on the paraspinal muscles from C1 to S1 using an electronic algometer. Result: The results showed a significant increase in the anteroposterior displacement (p = 0.04) and a significantly lower decrease in the mean velocity (p = 0.01) of the centre of pressure and a significant increase in the pressure pain thresholds of two (out of ten; p < 0.04) body sites in the group receiving Bowen Therapy compared to the group receiving the sham. No other significant differences were found. Conclusions: The findings suggest that Bowen Therapy has inconsistent immediate effects on postural control and pain threshold in healthy subjects. Further studies are needed using symptomatic participants. Copyright © 2016 Elsevier Ltd.

Curcumin: An effective adjunct in patients with statin-associated muscle symptoms?

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In spite of the unequivocal efficacy of statins in reducing primary and secondary cardiovascular events, the use of these drugs in a considerable number of patients is limited because of statin intolerance, mainly statin-associated muscle symptoms (SAMS). SAMS encompass a broad spectrum of clinical presentations, including mild muscular aching and other types of myalgias, myopathy with the significant elevation of creatine kinase, and the rare but life-threatening rhabdomyolysis. Among several pathophysiologic mechanisms of SAMS, mitochondrial dysfunction is thought to be one of the main one. Curcumin is the polyphenolic ingredient of Curcuma longa L., which has various pharmacological properties against a vast range of diseases. Curcumin has several mechanisms of actions relevant to the treatment of SAMS. These effects include the capacity to prevent and reduce delayed onset muscle soreness by blocking the nuclear factor inflammatory pathway, attenuation of muscular atrophy, enhancement of muscle fibre regeneration following injury, and analgesic and antioxidant effects. Curcumin can also increase the levels of cyclic adenosine monophosphate, which leads to an increase in the number of mitochondrial DNA duplicates in skeletal muscle cells. Finally, owing to its essential lipid-modifying properties, curcumin might serve as an adjunct to statin therapy in patients with SAMS, allowing for effective lowering of low-density lipoprotein cholesterol and possibly for statin dose reduction. Owing to the paucity of effective treatments, and the safety of curcumin in clinical practice, proof-of-concept trials are recommended to assess the potential benefit of this phytochemical in the treatment of SAMS. Copyright © 2016 John Wiley & Sons Ltd.

ETNA (Evaluating Treatment with Neoadjuvant Abraxane) randomized phase III study comparing neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) both followed by anthracycline regimens in women with HER2-negative high-risk breast cancer: A MICHELANGELO study.

Gianni L, Mansutti M, et al.

Background: Neoadjuvant chemotherapy regimens employing anthracyclines and taxanes have reported essentially doubled pCR rates with the addition of a taxane after anthracycline combinations. A reverse sequence did not reduce activity. nab-Paclitaxel (nab-P) is an albumin-bound nanoparticle of paclitaxel (P) that allows for safe infusion without premedication, and led to a significantly higher rate of pCR in the Gepar-Septo trial (Untch et al, Lancet Oncol 2016).

Methods: This multicenter open label study (NCT01822314 ) in collaboration with GEICAM and BCRC-WA randomized 695 patients with centrally-confirmed HER2-negative breast cancer to P 90 mg/m² (349 patients) or nab-P 125 mg/m² (346 patients). The two drugs were given on weeks 1, 2 and 3 followed by 1-week rest for 4 cycles before 4 cycles of an anthracycline regimen per investigator choice. Results: The ITT analysis of the
primary endpoint pCR (absence of invasive cells in breast and nodes) along with the overall objective clinical response after systemic therapy is reported below. Conclusions: The improved rate of pCR after nab-P failed to reach statistical significance. The multivariate analysis revealed that tumor subtype was the most significant factor (OR 5.11) influencing treatment outcome. Extensive collection and banking of tumor (> 90%) and blood was performed and translational studies might provide clues for more informative correlations with available results. Supported in part by an unrestricted grant from Celgene. (Table Presented).

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http://meeting.ascopubs.org/cgi/content/abstract/34/15_suppl/502?sid=1e08b08304834ea3a4032134cb375636


SIRFLOX: Differences in site of first progression between mFOLFOX6 +/- bevacizumab (bev) versus mFOLFOX6 +/- bev + selective internal radiation therapy (SIRT) in first-line patients (pts) with metastatic colorectal cancer (mCRC).

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P. Gibbs

Background: SIRFLOX, an international multi-centre open-label RCT in first-line pts with non-resectable, liver-only or liver-dominant mCRC, showed that compared to FOLFOX (+/- bev) chemotherapy alone [arm A] FOLFOX (+/- bev) plus SIRT using Y-90 resin microspheres [arm B] did not improve overall PFS (median 10.2 v 10.7 months arm A v B, HR: 0.93; 95% CI 0.77-1.12; p = 0.429). However, liver PFS by competing risk analysis was improved with the addition of SIRT (median 12.6 v 20.5 months in arm A v B, HR: 0.69; 95% CI 0.55-0.90; p = 0.002). The current analysis examines patterns of disease progression and potential impact on the primary study endpoint. Methods: Site and pattern (intra/extra-hepatic) of first progression, and whether progression was due to growth of existing lesions or the appearance of new lesions, was judged by an independent reader blinded to study arm. Results: From Oct 2006 to Apr 2013, 530 pts were randomised (arm A, n = 263; arm B, n = 267); 212 (40%) had extra-hepatic metastases at study entry; 292 (55%) were stratified to receive bev. As of 31 Jan 2015, the total number of patients with disease progression in arm A v B were 178 and 166, respectively. The site of first progression was more frequently in the liver (+/- other sites) in arm A v B (92.1% v 72.3%; p < 0.001). Conversely, site of first progression was less frequent in the lung (+/- other sites) in arm A v B (19.1% v 42.8%; p < 0.001). A higher proportion of first progression occurred in the liver alone in arm A v B (77.0% v 52.4%; p < 0.001). Conversely, a lower proportion of first progression occurred only in non-liver sites, primarily lung, in arm A v B (7.9% v 47.7%; p < 0.001). Of patients with first progression in the liver, a higher proportion occurred in existing liver lesions (+/- extrahepatic sites) in arm A v B (72.5% v48.2%; p < 0.001).

Conclusions: The addition of SIRT to FOLFOX chemotherapy alone (+/- bev) reduced the frequency at which first disease progression occurred in the liver. Where first progression did occur in the liver, the addition of SIRT led to this more frequently being due to the appearance of lesions not evident on baseline imaging.

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Antioxidant Activity of Heracleum persicum Fruit Extract: Evidence from a Randomized Controlled Trial.
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Oxidative stress is a unifying feature of several cardiometabolic risk factors, and has been suggested to be implicated in atherogenesis. This study aimed to investigate the efficacy of supplementation with Heracleum persicum fruit—a common dietary spice—in modulating systemic biomarkers of oxidative stress in subjects undergoing coronary angiography. Twenty-seven subjects with minimal coronary artery disease (CAD; defined as < 50% obstruction in the coronary arteries) were selected for this trial and were randomly allocated to Heracleum persicum hydroalcoholic fruit extract (n = 15; 300 mg/day) or placebo (n = 12) for a period of six months. Patients were visited monthly and asked to report the adverse events during the treatment period. Serum levels of malondialdehyde (MDA), reduced glutathione (GSH) and total antioxidant capacity (TAC), and enzymatic activities of glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) were determined at baseline and at the end of trial. Comparison of changes in the evaluated biomarkers of oxidative stress indicated a significantly greater effect of H. persicum extract versus placebo in reducing serum MDA (p = .001), and elevating GSH (p = .001), and TAC (p = .001) concentrations, as well as activities of GPx (p = .001) and CAT (p = .001). The groups were comparable with respect to changes in serum SOD activities during the course of trial (p = .255). The findings of the present randomized double-blind placebo-controlled trial clearly support the efficacy of H. persicum fruit extract as a safe antioxidant supplement in subjects with minimal CAD.

Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial.
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Oxidative stress is implicated in the pathogenesis of osteoarthritis. Curcuminoids are natural polyphenols with strong antioxidant capacity and may thus be helpful in the treatment of osteoarthritis. The present randomized double-blind placebo-controlled trial investigated the efficacy of curcuminoids in reducing systemic oxidative burden in patients suffering from knee osteoarthritis. Forty patients with mild-to-moderate primary knee osteoarthritis were given curcuminoid capsules (1500 mg/day in 3 divided doses; n = 19) or matched placebo capsules (n = 21) for a period of 6 weeks. Curcuminoids were co-administered with piperine (15 mg/day) in order to improve the bioavailability. Serum activities of superoxide dismutase (SOD) and concentrations of reduced glutathione (GSH) and malondialdehyde (MDA) were determined spectrophotometrically at baseline and at the end of the treatment period in both groups. Serum activities of SOD as well as GSH and MDA concentrations were comparable between the study groups at baseline (p > 0.05). There was a significant elevation in serum SOD activities (mean change: 2.94 +/- 3.73 vs. -0.38 +/- 1.33; p < 0.001), a borderline significant elevation in GSH concentrations (mean change: 1.39 +/- 2.78 vs. -0.02 +/- 1.62; p = 0.064) and a significant reduction in MDA concentrations (mean change: -5.26 +/- 4.46 vs. -2.49 +/- 3.81; p
in the curcuminoids compared with the placebo group. Changes in serum activities of SOD and concentrations of GSH and MDA during the course of trial were significantly correlated. Short-term supplementation with curcuminoids attenuates systemic oxidative stress in patients with osteoarthritis. These antioxidant effects may account for the reported therapeutic effects of curcuminoids in relieving osteoarthritis symptoms.

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A comparison of prognostic significance of strong ion gap (SIG) with other acid-base markers in the critically ill: a cohort study.

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BACKGROUND: This cohort study compared the prognostic significance of strong ion gap (SIG) with other acid-base markers in the critically ill.

METHODS: The relationships between SIG, lactate, anion gap (AG), anion gap albumin-corrected (AG-corrected), base excess or strong ion difference-effective (SIDe), all obtained within the first hour of intensive care unit (ICU) admission, and the hospital mortality of 6878 patients were analysed. The prognostic significance of each acid-base marker, both alone and in combination with the Admission Mortality Prediction Model (MPM0 III) predicted mortality, were assessed by the area under the receiver operating characteristic curve (AUROC).

RESULTS: Of the 6878 patients included in the study, 924 patients (13.4 %) died after ICU admission. Except for plasma chloride concentrations, all acid-base markers were significantly different between the survivors and non-survivors. SIG (with lactate: AUROC 0.631, confidence interval [CI] 0.611-0.652; without lactate: AUROC 0.521, 95 % CI 0.500-0.542) only had a modest ability to predict hospital mortality, and this was no better than using lactate concentration alone (AUROC 0.701, 95 % 0.682-0.721). Adding AG-corrected or SIG to a combination of lactate and MPM0 III predicted risks also did not substantially improve the latter's ability to differentiate between survivors and non-survivors. Arterial lactate concentrations explained about 11 % of the variability in the observed mortality, and it was more important than SIG (0.6 %) and SIDe (0.9 %) in predicting hospital mortality after adjusting for MPM0 III predicted risks. Lactate remained as the strongest predictor for mortality in a sensitivity multivariate analysis, allowing for non-linearity of all acid-base markers.

CONCLUSIONS: The prognostic significance of SIG was modest and inferior to arterial lactate concentration for the critically ill. Lactate concentration should always be considered regardless whether physiological, base excess or physical-chemical approach is used to interpret acid-base disturbances in critically ill patients.

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Pull-out strength comparison of a novel expanding fastener against an orthopaedic screw in an ovine vertebral body: an ex-vivo study.


Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study.

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Background Fabry disease is an X-linked lysosomal storage disorder caused by GLA mutations, resulting in a-galactosidase (a-Gal) deficiency and accumulation of lysosomal substrates. Migalastat, an oral pharmacological chaperone being developed as an alternative to intravenous enzyme replacement therapy (ERT), stabilises specific mutant (amenable) forms of a-Gal to facilitate normal lysosomal trafficking.

Methods The main objective of the 18-month, randomised, active-controlled ATTRACT study was to assess the effects of migalastat on renal function in patients with Fabry disease previously treated with ERT. Effects on heart, disease substrate, patient-reported outcomes (PROs) and safety were also assessed. Results Fifty-seven adults (56% female) receiving ERT (88% had multiorgan disease) were randomised (1.5:1), based on a preliminary cell-based assay of responsiveness to migalastat, to receive 18 months open-label migalastat or remain on ERT. Four patients had nonamenable mutant forms of a-Gal based on the validated cell-based assay conducted after treatment initiation and were excluded from primary efficacy analyses only. Migalastat and ERT had similar effects on renal function. Left ventricular mass index decreased significantly with migalastat treatment (-6.6 g/m² (-11.0 to -2.2)); there was no significant change with ERT. Predefined renal, cardiac or cerebrovascular events occurred in 29% and 44% of patients in the migalastat and ERT groups, respectively. Plasma globotriaosylsphingosine remained low and stable following the switch from ERT to migalastat. PROs were comparable between groups. Migalastat was generally safe and well tolerated. Conclusions Migalastat offers promise as a first-in-class oral monotherapy alternative treatment to intravenous ERT for patients with Fabry disease and amenable mutations. Trial registration number: NCT00925301; Preresults. Copyright © 2016 by the BMJ Publishing Group Ltd.

The role of imaging in the surveillance and diagnosis of hepatocellular cancer.

Dulku G, Dhillon R, et al.

A decision support tool has been developed as part of a suite of on-line evidence-based and consensus-based guidelines Diagnostic imaging Pathways (DIP: www.imagingpathways.health.wa.gov.au) in the form of an algorithmic flow chart with supporting evidence and consensus to inform referrers to diagnostic imaging and radiologists as to the optimum strategy for surveillance and diagnosis of primary hepatocellular cancer (HCC) in those patients with risk factors of this disease. A literature review, including reference to several international consensus-based expert guidelines, has been employed to develop this tool. Copyright © 2016 The Royal Australian and New Zealand College of Radiologists.

Interventional radiology in cancer management: The other dark art.

Hart R.

Interventional radiology in cancer management: The other dark art.
Interventional radiology (IR) has an important role to play in the management of cancer. IR techniques can be employed to attack oncological processes directly, as well as in the management of the consequences and complications of the disease. Using the full imaging armamentarium offered by diagnostic imaging, the IR team can plan interventions which best answer the clinical needs of the patient, and in their subsequent management. This presentation provides a broad-brush overview of the IR techniques employed at Royal Perth Hospital for the benefit of the cohort of patients presenting with cancer. The presentation discusses the three major areas of cancer diagnosis, cancer treatment, and management of the complications of cancer. Through a series of vignettes, a brief sample of representative cases will be presented for discussion.

Radiographer technique: Does it contribute to the question of clip migration?
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Objectives: Marker clips are commonly deployed at the site of a percutaneous breast biopsy. Studies have shown that displacement of the clip from the site of deployment is not uncommon. The objective of this study was to determine how much ‘migration’ could be seen with fixed structures within the breast tissue across three consecutive annual screening examinations, and therefore attempt to quantify how much of the reported clip migration could be due to radiographer technique. Methods: Large easily identified benign calcifications were measured by two investigators across three consecutive cycles of screening mammography. The position of the calcifications on the two standard mammographic views was measured in two planes. Other variables recorded included breast size and density, compression force used, and location of the benign calcifications within the breast. Results: In 38% of cases benign breast calcifications showed a mimicked movement of >15 mm in at least one plane. This was greatest in large breasts, those where fibroglandular tissue occupied less than 50% of the breast volume and in the upper outer quadrant of the breast where mimicked movement >10 mm was noted up to 90% in the larger breasts. Conclusion: Fixed immobile objects in the breast can appear to move a distance of >15 mm in up to 30% of cases. Clinically, some of what has previously been called marker ‘migration’ may be spurious and accounted for by differences in radiographic positioning techniques.

The pharmacogenomics of pain management: prospects for personalized medicine.
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Pain is a common symptom that can be complex to treat. Analgesic medications are the mainstay treatment, but there is wide interindividual variability in analgesic response and adverse effects. Pharmacogenomics is the study of inherited genetic traits that result in these individual responses to drugs. This narrative review will attempt to cover the current understanding of the pharmacogenomics of pain, examining common genes affecting metabolism of analgesic medications, their distribution throughout the body, and end organ effects.

Relationship between Sustained Reductions in Plasma Lipid and Lipoprotein Concentrations with Apheresis and Plasma Levels and mRNA Expression of PTX3 and Plasma Levels of hsCRP in Patients with HyperLp(a)lipoproteinemia.
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The effect of lipoprotein apheresis (Direct Adsorption of Lipids, DALI) (LA) on plasma levels of pentraxin 3 (PTX3), an inflammatory marker that reflects coronary plaque vulnerability, and expression of PTX3 mRNA was evaluated in patients with hyperLp(a)lipoproteinemia and angiographically defined atherosclerosis/coronary artery disease. Eleven patients, aged 55 +/- 9.3 years (mean +/- SD), were enrolled in the study. PTX3 soluble protein levels in plasma were unchanged by 2 sessions of LA; however, a downregulation of mRNA expression for PTX3 was observed, starting with the first session of LA (p < 0.001). The observed reduction was progressively increased in the interval between the first and second LA sessions to achieve a maximum decrease by the end of the second session. A statistically significantly greater treatment-effect correlation was observed in patients undergoing weekly treatments, compared with those undergoing treatment every 15 days. A progressive reduction in plasma levels of C-reactive protein was also seen from the first session of LA, with a statistically significant linear correlation for treatment-effect in the change in plasma levels of this established inflammatory marker (R(2) = 0.99; p < 0.001). Our findings suggest that LA has anti-inflammatory and endothelium protective effects beyond its well-established efficacy in lowering apoB100-containing lipoproteins.

Baclofen neurotoxicity: A metabolic encephalopathy susceptible to exacerbation by benzodiazepine therapy.
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Background: Baclofen, a gamma-aminobutyric acid derivative, is commonly used in the treatment of spasticity. Baclofen toxicity can produce an encephalopathy sometimes associated with myoclonus and seizures. Associated EEG abnormalities include generalized slowing, and periodic triphasic complexes and sharp waves that have been reported as non-convulsive status epilepticus (NCSE). Methods: Baclofen toxicity was defined as an encephalopathy in the setting of baclofen use and without other identifiable cause. Patients with baclofen toxicity were identified from an EEG database, and their clinical and EEG findings analysed. Results: 13 patients were identified, aged 29 to 81 years. All were receiving oral baclofen in doses ranging from 10mg to 200mg daily, most commonly for spasticity (10 patients). All patients were confused, 11 with reduced consciousness and 4 requiring intubation. 5 patients had myoclonus, 2 of whom also had tonic-clonic seizures. All patients had abnormal EEGs. 12 patients had moderate-to-severe generalized slowing. 8 patients had generalized, bisynchronous triphasic sharp waves occurring at 1-2 Hz , sometimes with an anterior to posterior phase lag. Three patients received small doses of intravenous
midazolam or diazepam, in all cases resulting in marked depression of consciousness and respiration, and without any subsequent improvement in the conscious state. Suppression of periodic complexes and all EEG activity following intravenous midazolam was confirmed in one patient, having continuous EEG monitoring. Baclofen was discontinued in all patients. Serial plasma Baclofen levels were measured in 2 patients. Falling levels mirrored clinical and electrophysiological improvement. Conclusions: Baclofen toxicity can produce an acute encephalopathy even at modest doses. When present, periodic sharp triphasic complexes on EEG are a manifestation of a toxic encephalopathy rather than NCSE. These patients exhibit a marked vulnerability to the depressant effects of benzodiazepines, even at small doses. Improvement follows a time course consistent with the period required for baclofen clearance.


**Multifocal motor neuropathy: Disease stabilisation on quinidine.**

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Objective: To describe the serendipitous effect of quinidine on intravenous immunoglobulin (IVIG) dependent multifocal motor neuropathy (MMN). Background: MMN is a rare immune-mediated demyelinating neuropathy. A consistent feature is high IVIG requirement, with latter treatment resistance. Other immunomodulatory agents have not shown consistent benefit. A putative pathological mechanism involves hyperpolarisation-depolarisation of nerve beyond areas of conduction block. We report a case of improved MMN disease control with the addition of quinidine, an anti-arrhythmic agent with membrane stabilizing and immunogenic properties. Methods: A 51 year old patient with MMN had received IVIG for over 8 years, with gradual decline in disease control after several years of therapy. Mycophenolate mofetil was not beneficial. Rituximab was added 6 years after IVIG. At 50 years, he was commenced on quinidine for an unrelated episode of ventricular fibrillation (VF). IVIG and rituximab requirements and treatment response were documented prior to, and following, treatment with quinidine. Results: Prior to quinidine therapy there was chronic mild weakness of right biceps and left finger abduction/adduction on IVIG (2g/kg/month) and regular rituximab. Disease control reproducibly deteriorated with early B-cell recovery, with increasing end of IVIG cycle weakness, prompting further re-dosing with rituximab (2g over two weeks) approximately 6 monthly. He was 4 months post-rituximab therapy at time of VF arrest. He had developed recurrence of progressive weakness, despite B-cell depletion (<1% total lymphocytes). One month following quinidine treatment, strength in previously weak muscles improved. He was maintained on monthly IVIG, and remained clinically stable for the next 12 months without requiring additional rituximab. We discuss proposed pathological mechanisms of MMN and potential mechanisms of disease stabilization induced by quinidine. Conclusions: Quinidine therapy may provide additional benefit in MMN. Further studies are needed to accurately describe treatment effect and response.

PMID:72250429


**Multifocal motor neuropathy: A single center experience.**

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Objective: To characterize a single center cohort of patients with multifocal motor neuropathy (MMN) with extended follow-up. Background: MMN is an immune-mediated demyelinating neuropathy with prevalence of 1-2/100,000. A consistent feature is high intravenous immunoglobulin (IVIG) requirement, and latter development of treatment refractoriness. Other immunomodulatory therapies have not shown consistent benefit, but reports of off-label rituximab use have suggested promise. Our experience is stabilization of disease progression may occur with concurrent rituximab therapy. Methods: A single-center cohort study was conducted involving the state quaternary neuropathy service in Western Australia, a population of just over 2.5 million. Patients with MMN, all of who received...
IVIG therapy during follow-up, were enrolled. All patients had clinical assessment by one neurologist. Results: 19 patients (12 males, 8 females) were identified. Age at symptom onset ranged from 17 to 60 years. The duration of follow up ranged from 23 to 155 months (mean 94 months). Every individual had upper limb involvement at diagnosis with 3/19 developing lower limb involvement. Sensory symptoms were reported in 8/19. Anti-ganglioside antibodies were positive in 3/19 cases. IVIG greater than 1g/kg/month was required to maintain clinical stability in most treated patients. Rituximab was used in 4 cases with disease progression despite IVIG 2g/kg/month, with improved disease control, but no reduction in IVIG requirements. A single patient with clinical response to concurrent quinidine therapy was observed. Conclusions: Our large cohort with extended follow-up demonstrates the spectrum of MMN phenotype and treatment response. Despite the slowly progressive nature of this disease, almost all treated individuals maintain functional status. IVIG monotherapy is effective in the majority of cases. There appears to be a role for rituximab in restoring IVIG responsiveness in refractory disease.

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Anterior cruciate ligament reconstruction of the knee using double bundle hamstring autograft—is the remnant preservation technique superior to the standard procedure in terms of long-term graft failure rate, the need for revision operation, and associated clinical dysfunction? : A 10 year post operative follow-up chart review from a previous prospective randomised controlled study.

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Background: Anterior cruciate remnant preservation may be beneficial in Anterior Cruciate Ligament Reconstruction (ACLR). Gohil, Annear & Breidahl (Sept, 2007) used a grade 1 randomised controlled trial to compare the two methods and at short term follow-up, the minimal debridement technique demonstrated earlier revascularisation within the ACL graft at 2 months, and suggested improved strength at 6 months based on radiological imaging. Unfortunately, this did not translate through to clinical benefits in the early 12 month post operative period. Zhang, L et al. (May, 2013) and Naylor, AJ et al. (2013) reiterated that remnant preservation may improve graft revascularization and knee proprioception. Takazawa Y et al. (Sept, 2013) demonstrated that minimal debridement may facilitate recovery of function and decreased graft rupture at two years post primary reconstruction. However, studies have yet to show consistent significant clinical advantages and follow-up has only been analysed over 1-2 years. Purpose: This current study reported results over a long-term follow-up of 10 years post operation for the same participants from the Gohil, Annear & Breidahl (2007) study. Study Design: The review was based on level 1 randomised controlled trial chart review. Methods: All 49 participants (25 standard - group 1, and 24 remnant preserving group - group 2) from the previous study have been included for investigation. The chart review recorded demographic data, graft rupture, re-operation rates, and associated clinical failures of the ACLR. The review presents comparative data between the two groups. Results At 10 year follow-up, the remnant retention ACLR group only had better outcomes for ipsilateral graft rupture (2 patients versus 3 patients). Standard ACLR group had improved outcomes for contralateral graft rupture (2 versus 3), ipsilateral other knee post operative surgery (5 versus 10), ipsilateral knee post operative complaints (7 versus 12), and other non-knee post operative issues (3 versus 4). Non of the differences were statistically significant. Conclusion: Overall our results suggested no statistically significant difference between the remnant retaining and standard technique for ACLR in these 49 subjects using chart review endpoints of graft revision and knee reoperation rates. The review is limited by a small study group and a chart only review. A larger study group with long term clinical outcome measures may offer more definitive conclusions as to the advantages of remnant sparing ACLR. In this 10 year follow-up post ACL reconstruction there has been no distinct advantage identified for either procedure.

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Muscle size explains low passive skeletal muscle force in heart failure patients.
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BACKGROUND: Alterations in skeletal muscle function and architecture have been linked to the compromised exercise capacity characterizing chronic heart failure (CHF). However, how passive skeletal muscle force is affected in CHF is not clear. Understanding passive force characteristics in CHF can help further elucidate the extent to which altered contractile properties and/or architecture might affect muscle and locomotor function. Therefore, the aim of this study was to investigate passive force in a single muscle for which non-invasive measures of muscle size and estimates of fiber force are possible, the soleus (SOL), both in CHF patients and age- and physical activity-matched control participants.

METHODS: Passive SOL muscle force and size were obtained by means of a novel approach combining experimental data (dynamometry, electromyography, ultrasound imaging) with a musculoskeletal model.

RESULTS: We found reduced passive SOL forces (~30%) (at the same relative levels of muscle stretch) in CHF vs. healthy individuals. This difference was eliminated when force was normalized by physiological cross sectional area, indicating that reduced force output may be most strongly associated with muscle size. Nevertheless, passive force was significantly higher in CHF at a given absolute muscle length (non length-normalized) and likely explained by the shorter muscle slack lengths and optimal muscle lengths measured in CHF compared to the control participants. This later factor may lead to altered performance of the SOL in functional tasks such gait.

DISCUSSION: These findings suggest introducing exercise rehabilitation targeting muscle hypertrophy and, specifically for the calf muscles, exercise that promotes muscle lengthening.

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Enhanced Visualization of Subtle Outer Retinal Pathology by En Face Optical Coherence Tomography and Correlation with Multi-Modal Imaging.
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PURPOSE: To present en face optical coherence tomography (OCT) images generated by graph-search theory algorithm-based custom software and examine correlation with other imaging modalities.

METHODS: En face OCT images derived from high density OCT volumetric scans of 3 healthy subjects and 4 patients using a custom algorithm (graph-search theory) and commercial software (Heidelberg Eye Explorer software (Heidelberg Engineering)) were compared and correlated with near infrared reflectance, fundus autofluorescence, adaptive optics flood-illumination ophthalmoscopy (AO-FIO) and microperimetry.

RESULTS: Commercial software was unable to generate accurate en face OCT images in eyes with retinal pigment epithelium (RPE) pathology due to segmentation error at the level of Bruch's membrane (BM). Accurate segmentation of the basal RPE and BM was achieved using custom software. The en face OCT images from eyes with isolated interdigitation or ellipsoid zone pathology were of similar quality between custom software and Heidelberg Eye Explorer software in the absence of any other significant outer retinal pathology. En face OCT images demonstrated angioid streaks, lesions of acute macular neuroretinopathy, hydroxychloroquine toxicity and Bietti crystalline deposits that correlated with other imaging modalities.

CONCLUSIONS: Graph-search theory algorithm helps to overcome the limitations of outer retinal segmentation inaccuracies in commercial software. En face OCT images can provide detailed topography of the reflectivity within a specific layer of the retina which correlates with other forms of fundus imaging. Our results highlight the need for standardization of image reflectivity to facilitate quantification of en face OCT images and longitudinal analysis.

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RESPECT-ED: Rates of Pulmonary Emboli (PE) and Sub-Segmental PE with Modern Computed Tomographic Pulmonary Angiograms in Emergency Departments: A Multi-Center Observational Study Finds Significant Yield Variation, Uncorrelated with Use or Small PE Rates.


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INTRODUCTION: Overuse of CT Pulmonary Angiograms (CTPA) for diagnosing pulmonary embolism (PE), particularly in Emergency Departments (ED), is considered problematic. Marked variations in positive CTPA rates are reported, with American 4-10% yields driving most concerns. Higher resolution CTPA may increase sub-segmental PE (SSPE) diagnoses, which may be up to 40% false positive. Excessive use and false positives could increase harm vs. benefit. These issues have not been systematically examined outside America.

AIMS: To describe current yield variation and CTPA utilisation in Australasian ED, exploring potential factors correlated with variation.

METHODS: A retrospective multi-centre review of consecutive ED-ordered CTPA using standard radiology reports. ED CTPA report data were inputted onto preformatted data-sheets. The primary outcome was site level yield, analysed both intra-site and against a nominated 15.3% target. Factors potentially associated with yield were assessed for correlation.

RESULTS: Fourteen radiology departments (15 ED) provided 7077 CTPA data (94% >64-slice CT); PE were reported in 1028 (yield 14.6% (95%CI 13.8-15.4%; range 9.3-25.3%; site variation p <0.0001) with four sites significantly below and one above the 15.3% target. Admissions, CTPA usage, PE diagnosis rates and size of PE were uncorrelated with yield. Large PE (>lobar) were 55% (CI: 52.1-58.2%) and SSPE 8.8% (CI: 7.1-10.5%) of positive scans. CTPA usage (0.2-1.5% adult attendances) was correlated (p<0.006) with PE diagnosis but not SSPE: large PE proportions.

DISCUSSION/CONCLUSIONS: We found significant intra-site CTPA yield variation within Australasia. Yield was not clearly correlated with CTPA usage or increased small PE rates. Both SSPE and large PE rates were similar to higher yield historical cohorts. CTPA use was considerably below USA 2.5-3% rates. Higher CTPA utilisation was positively correlated with PE diagnoses, but without evidence of increased proportions of small PE. This suggests that increased diagnoses seem to be of clinically relevant sized PE.

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BACKGROUND AND AIMS: Assessment of adiposity using dual energy x-ray absorptiometry (DXA) has been considered more advantageous in comparison to anthropometry for predicting cardio-metabolic risk in the older population, by virtue of its ability to distinguish total and regional fat. Nonetheless, there is increasing uncertainty regarding the relative superiority of DXA and little comparative data exist in young adults. This study aimed to identify which measure of adiposity determined by either DXA or anthropometry is optimal within a range of cardio-metabolic risk factors in young adults.

METHODS AND RESULTS: 1138 adults aged 20 years were assessed by DXA and standard anthropometry from the Western Australian Pregnancy Cohort (Raine) Study. Cross-sectional linear regression analyses were performed. Waist to height ratio was superior to any DXA measure with HDL-C. BMI was the superior model in relation to blood pressure than any DXA measure. Midriff fat mass (DXA) and waist circumference were comparable in relation to glucose. For all the other cardio-metabolic variables, anthropometric and DXA measures were comparable. DXA midriff fat mass compared with BMI or waist hip ratio was the superior measure for triglycerides, insulin and HOMA-IR.

CONCLUSION: Although midriff fat mass (measured by DXA) was the superior measure with insulin sensitivity and triglycerides, the anthropometric measures were better or equal with various DXA measures for majority of the cardio-metabolic risk factors. Our findings suggest, clinical anthropometry is generally as useful as DXA in the evaluation of the individual cardio-metabolic risk factors in young adults.

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Effects of the Mediterranean Diet on Cardiovascular Outcomes-A Systematic Review and Meta-Analysis.

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BACKGROUND: A Mediterranean dietary pattern is widely recommended for the prevention of chronic disease. We sought to define the most likely effects of the Mediterranean diet on vascular disease and mortality.

METHODS: We searched MEDLINE, EMBASE and the Cochrane Central Register without language restriction for
randomized controlled trials comparing Mediterranean to control diets. Data on study design, patient characteristics, interventions, follow-up duration, outcomes and adverse events were sought. Individual study relative risks (RR) were pooled to create summary estimates.

RESULTS: Six studies with a total of 10950 participants were included. Effects on major vascular events (n = 477), death (n = 693) and vascular deaths (n = 315) were reported for 3, 5 and 4 studies respectively. For one large study (n = 1000) there were serious concerns about the integrity of the data. When data for all studies were combined there was evidence of protection against major vascular events (RR 0.63, 95% confidence interval 0.53-0.75), coronary events (0.65, 0.50-0.85), stroke (0.65, 0.48-0.88) and heart failure (0.30, 0.17-0.56) but not for all-cause mortality (1.00, 0.86-1.15) or cardiovascular mortality (0.90, 0.72-1.11). After the study of concern was excluded the benefit for vascular events (0.69, 0.55-0.86) and stroke (0.66, 0.48-0.92) persisted but apparently positive findings for coronary events (0.73, 0.51-1.05) and heart failure (0.25, 0.05-1.17) disappeared.

CONCLUSION: The Mediterranean diet may protect against vascular disease. However, both the quantity and quality of the available evidence is limited and highly variable. Results must be interpreted with caution.

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Plasma CXCL10, sCD163 and sCD14 Levels Have Distinct Associations with Antiretroviral Treatment and Cardiovascular Disease Risk Factors.
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We investigate the associations of three established plasma biomarkers in the context of HIV and treatment-related variables including a comprehensive cardiovascular disease risk assessment, within a large ambulatory HIV cohort. Patients were recruited in 2010 to form the Royal Perth Hospital HIV/CVD risk cohort. Plasma sCD14, sCD163 and CXCL10 levels were measured in 475 consecutive patients with documented CVD risk (age, ethnicity, gender, smoking, blood pressure, BMI, fasting metabolic profile) and HIV treatment history including immunological/virological outcomes. The biomarkers assessed showed distinct associations with virological response: CXCL10 strongly correlated with HIV-1 RNA (p<0.001), sCD163 was significantly reduced among ‘aviraemic’ patients only (p = 0.02), while sCD14 was unaffected by virological status under 10,000 copies/mL (p>0.2). Associations between higher sCD163 and protease inhibitor therapy (p = 0.05) and lower sCD14 with integrase inhibitor therapy (p = 0.02) were observed. Levels of sCD163 were also associated with CVD risk factors (age, ethnicity, HDL, BMI), with a favourable influence of Framingham score <10% (p = 0.04). Soluble CD14 levels were higher among smokers (p = 0.002), with no effect of other CVD risk factors, except age (p = 0.045). Our findings confirm CXCL10, sCD163 and sCD14 have distinct associations with different aspects of HIV infection and treatment. Levels of CXCL10 correlated with routinely monitored variables, sCD163 levels reflect a deeper level of virological suppression and influence of CVD risk factors, while sCD14 levels were not associated with routinely monitored variables, with evidence of specific effects of smoking and integrase inhibitor therapy warranting further investigation.

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OBJECTIVES: Deprescribing has been proposed as a way to reduce polypharmacy in frail older people. We aimed to reduce the number of medicines consumed by people living in residential aged care facilities (RACF). Secondary objectives were to explore the effect of deprescribing on survival, falls, fractures, hospital admissions, cognitive, physical, and bowel function, quality of life, and sleep.

METHODS: Ninety-five people aged over 65 years living in four RACF in rural mid-west Western Australia were randomised in an open study. The intervention group (n = 47) received a deprescribing intervention, the planned cessation of non-beneficial medicines. The control group (n = 48) received usual care. Participants were monitored for twelve months from randomisation. Primary outcome was change in the mean number of unique regular medicines. All outcomes were assessed at baseline, six, and twelve months.

RESULTS: Study participants had a mean age of 84.3 +/- 6.9 years and 52% were female. Intervention group participants consumed 9.6 +/- 5.0 and control group participants consumed 9.5 +/- 3.6 unique regular medicines at baseline. Of the 348 medicines targeted for deprescribing (7.4 +/- 3.8 per person, 78% of regular medicines), 207 medicines (4.4 +/- 3.4 per person, 59% of targeted medicines) were successfully discontinued. The mean change in number of regular medicines at 12 months was -1.9 +/- 4.1 in intervention group participants and +0.1 +/- 3.5 in control group participants (estimated difference 2.0 +/- 0.9, 95%CI 0.08, 3.8, p = 0.04). Twelve intervention participants and 19 control participants died within 12 months of randomisation (26% versus 40% mortality, p = 0.16, HR 0.60, 95%CI 0.30 to 1.22) There were no significant differences between groups in other secondary outcomes. The main limitations of this study were the open design and small participant numbers.

CONCLUSIONS: Deprescribing reduced the number of regular medicines consumed by frail older people living in residential care with no significant adverse effects on survival or other clinical outcomes.

TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry ACTRN12611000370909.

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Identifying Patient-Specific Epstein-Barr Nuclear Antigen-1 Genetic Variation and Potential Autoreactive Targets Relevant to Multiple Sclerosis Pathogenesis.

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BACKGROUND: Epstein-Barr virus (EBV) infection represents a major environmental risk factor for multiple sclerosis (MS), with evidence of selective expansion of Epstein-Barr Nuclear Antigen-1 (EBNA1)-specific CD4+ T cells that cross-recognize MS-associated myelin antigens in MS patients. HLA-DRB1*15-restricted antigen presentation also appears to determine susceptibility given its role as a dominant risk allele. In this study, we have utilised standard and next-generation sequencing techniques to investigate EBNA-1 sequence variation and its relationship to HLA-DR15 binding affinity, as well as examining potential cross-reactive immune targets within the central nervous system proteome.

METHODS: Sanger sequencing was performed on DNA isolated from peripheral blood samples from 73 Western Australian MS cases, without requirement for primary culture, with additional FLX 454 Roche sequencing in 23 samples to identify low-frequency variants. Patient-derived viral sequences were used to predict HLA-DRB1*1501 epitopes (NetMHCII, NetMHCIIpan) and candidates were evaluated for cross recognition with human brain proteins. RESULTS: EBNA-1 sequence variation was limited, with no evidence of multiple viral strains and only low levels of variation identified by FLX technology (8.3% nucleotide positions at a 1% cut-off). In silico epitope mapping revealed two known HLA-DRB1*1501-restricted epitopes (‘AEG’: aa 481-496 and ‘MVF’: aa 562-577), and two putative epitopes between positions 502-543. We identified potential cross-reactive targets involving a number of major myelin antigens including experimentally confirmed HLA-DRB1*15-restricted epitopes as well as novel candidate antigens within myelin and paranodal assembly proteins that may be relevant to MS pathogenesis. CONCLUSIONS: This study demonstrates the feasibility of obtaining autologous EBNA-1 sequences directly from buffy coat samples, and confirms divergence of these sequences from standard laboratory strains. This approach has identified a number of immunogenic regions of EBNA-1 as well as known and novel targets for autoreactive HLA-DRB1*15-restricted T cells within the central nervous system that could arise as a result of cross-reactivity with EBNA-1-specific immune responses.

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Water First Aid Is Beneficial In Humans Post-Burn: Evidence from a Bi-National Cohort Study.
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INTRODUCTION: Reported first aid application, frequency and practices around the world vary greatly. Based primarily on animal and observational studies, first aid after a burn injury is considered to be integral in reducing scar and infection, and the need for surgery. The current recommendation for optimum first aid after burn is water cooling for 20 minutes within three hours. However, compliance with this guideline is reported as poor to moderate at best and evidence exists to suggest that overcooling can be detrimental. This prospective cohort study of a bi-national burn patient registry examined data collected between 2009 and 2012. The aim of the study was to quantify the magnitude of effects of water cooling first aid after burn on indicators of burn severity in a large human cohort.

METHOD: The data for the analysis was provided by the Burn Registry of Australia and New Zealand (BRANZ). The application of first aid cooling prior to admission to a dedicated burn service, was analysed for its influence on four outcomes related to injury severity. The patient related outcomes were whether graft surgery occurred, and death while the health system (cost) outcomes included total hospital length of stay and admission to ICU. Robust regression analysis using bootstrapped estimation adjusted using a propensity score was used to control for confounding and to estimate the strength of association with first aid. Dose-response relationships were examined to determine associations with duration of first aid. The influence of covariates on the impact of first aid was assessed.

RESULTS: Cooling was provided before Burn Centre admission for 68% of patients, with at least twenty minutes duration for 46%. The results indicated a reduction in burn injury severity associated with first aid. Patients probability for graft surgery fell by 0.070 from 0.537 (13% reduction) (p = 0.014). The probability for ICU admission fell by 0.084 from 0.175 (48% reduction) (p<0.001) and hospital length of stay (LOS) fell by 2.27 days from 12.9 days (18% reduction) (p = 0.001). All outcomes except death showed a dose-response relationship with the duration of first aid. The size of burn and age interacted with many of the relationships between first aid and outcome and these are described and discussed.

DISCUSSION & CONCLUSION: This study suggests that there are significant patient and health system benefits from cooling water first aid, particularly if applied for up to 20 minutes. The results of this study estimate the effect size of post-burn first aid and confirm that efforts to promote first aid knowledge are not only warranted, but provide potential cost savings.

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Improving cardiovascular outcomes among Aboriginal Australians: Lessons from research for primary care.
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BACKGROUND: The Aboriginal people of Australia have much poorer health and social indicators and a substantial life expectancy gap compared to other Australians, with premature cardiovascular disease a major contributor to poorer health. This article draws on research undertaken to examine cardiovascular disparities and focuses on ways in which primary care practitioners can contribute to reducing cardiovascular disparities and improving Aboriginal health.

METHODS: The overall research utilised mixed methods and included data analysis, interviews and group processes which included Aboriginal people, service providers and policymakers. Workshop discussions to identify barriers and what works were recorded by notes and on whiteboards, then distilled and circulated to participants and other stakeholders to refine and validate information. Additional engagement occurred through circulation of draft material and further discussions. This report distils the lessons for primary care practitioners to improve outcomes through management that is attentive to the needs of Aboriginal people.

RESULTS: Aspects of primordial, primary and secondary prevention are identified, with practical strategies for intervention summarised. The premature onset and high incidence of Aboriginal cardiovascular disease make prevention imperative and require that primary care practitioners understand and work to address the social underpinnings of poor health. Doctors are well placed to reinforce the importance of healthy lifestyle at all visits to involve the family and to reduce barriers which impede early care seeking. Ensuring better information for Aboriginal patients and better integrated care for patients who frequently have complex needs and multi-morbidities will also improve care outcomes.

CONCLUSION: Primary care practitioners have an important role in improving Aboriginal cardiovascular care outcomes. It is essential that they recognise the special needs of their Aboriginal patients and work at multiple levels both outside and inside the clinic for prevention and management of disease. A toolkit of proactive and holistic opportunities for interventions is proposed.

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The value of counting WHO-defined cardiovascular risk factors for death and disability in a national sample of adults with psychosis.
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Objective: This study explored the prevalence and associations of eight WHO-defined CVD risk factors for death and disability in people with psychosis.

Method: The study included 1156 people aged 18-64 years, diagnosed with psychosis. The 2009 World Health Organisation (WHO) Global Health Risks Report was used as a framework to determine the prevalence and number of eight key risk factors for cardiovascular disease (CVD) in men and women with psychosis. Differences in the number and type of risk factors by age and gender were investigated.

Multi-predictor analysis was performed to identify associations between demographic factors, psychiatric diagnosis and accumulative CVD risk factors. Results: Women had fewer CVD risk factors than men. The number of risk factors significantly decreased in association with single marital status, current employment and significantly increased with earning a higher income. People aged 35-49 years and 50-64 years had an average of 4 risk factors (SD 1.38 and 1.30); people aged 18-34 years had an average of 3 risk factors (SD 1.30). Mean risk factors were higher in the middle age and older age groups (35-49 years and 50-64 years) compared with the younger age group (18-34 years) (p < 0.0001). Overweight/obesity, hypertension, high blood glucose/diabetes and high cholesterol were significantly more prevalent in older men and women. Conclusion: People with psychosis have a high prevalence of individual and aggregate CVD risks. These were more common in men and rose with age, implying the necessity of close clinical monitoring. The most common risk factors should be targeted by lifestyle interventions. Copyright © 2016.

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The role of arterial elasticity and cardiovascular peripheral resistance as clinically relevant indices of health status in people with psychosis.

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Objective: Hypertension is one of the most important risk factors for cardiovascular disease (CVD). Systolic and diastolic blood pressure (BP) are higher in people with psychosis compared to the general population, but there is little research into measures of the elasticity of the arterial wall (pulse pressure; PP) and peripheral resistance (mean arterial pressure; MAP). PP and MAP can provide an additional perspective on the functioning of the circulatory system. This study investigated PP and MAP in people with psychosis, using factors known to be related to PP and MAP in the general population.

Method: Participants included 1421 people aged 18-64 years, from the second Australian national survey of psychosis, untreated with antihypertensive medication. We tested the interaction and main effects between age and gender on PP, MAP, systolic BP and diastolic BP. Odds ratios were calculated in people exceeding the at-risk thresholds for PP and MAP. Multiple linear regression was used to test whether factors
associated with at-risk PP and MAP in the general population were similarly associated in the psychosis population.

Results: The interaction effect between age and gender on PP, MAP, systolic BP and diastolic BP was not statistically significant. Variables that retained significance in the regression model in explaining higher PP and MAP were: male gender, higher age, and having a family history of hypertension. Conclusion: Clinicians monitoring and treating CV risk in this population need to ensure that they have recorded whether there is a family history of hypertension, and should be especially, more vigilant in men and in older patients. Copyright © 2016 Elsevier B.V.

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New era in genetics of early-onset muscle disease: Breakthroughs and challenges.
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Early-onset muscle disease includes three major entities that present generally at or before birth: congenital myopathies, congenital muscular dystrophies and congenital myasthenic syndromes. Almost exclusively there is weakness and hypotonia, although cases manifesting hypertonia are increasingly being recognised. These diseases display a wide phenotypic and genetic heterogeneity, with the uptake of next generation sequencing resulting in an unparalleled extension of the phenotype-genotype correlations and “diagnosis by sequencing” due to unbiased sequencing. Perhaps now more than ever, detailed clinical evaluations are necessary to guide the genetic diagnosis; with arrival at a molecular diagnosis frequently occurring following dialogue between the molecular geneticist, the referring clinician and the pathologist. There is an ever-increasing blurring of the boundaries between the congenital myopathies, dystrophies and myasthenic syndromes. In addition, many novel disease genes have been described and new insights have been gained into skeletal muscle development and function. Despite the advances made, a significant percentage of patients remain without a molecular diagnosis, suggesting that there are many more human disease genes and mechanisms to identify. It is now technically- and clinically-feasible to perform next generation sequencing for severe diseases on a population-wide scale, such that preconception-carrier screening can occur. Newborn screening for selected early-onset muscle diseases is also technically and ethically-achievable, with benefits to the patient and family from early management of these diseases and should also be implemented. The need for world-wide Reference Centres to meticulously curate polymorphisms and mutations within a particular gene is becoming increasingly apparent, particularly for interpretation of variants in the large genes which cause early-onset myopathies: NEB, RYR1 and TTN. Functional validation of candidate disease variants is crucial for accurate interpretation of next generation sequencing and appropriate genetic counseling. Many published “pathogenic” variants are too frequent in control populations and are thus likely rare polymorphisms. Mechanisms need to be put in place to systematically update the classification of variants such that accurate interpretation of variants occurs. In this review, we highlight the recent advances made and the challenges ahead for the molecular diagnosis of early-onset muscle diseases. Copyright © 2016 Elsevier Ltd.

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How generalizable are rehabilitation trials? The results of a large international rehabilitation trial (AVERT).
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Introduction: Generalizability of the results of randomized controlled trials (RCTs) could be compromised when recruitment is poor. We aimed to examine potential threats to generalizability of a multicenter RCT using data from A Very Early Rehabilitation Trial (AVERT). Methods: AVERT is a prospective, parallel group, assessor-blinded, randomized, clinical trial. The trial setting is acute stroke units at 44 hospitals in 8 countries. Among the first 20,000 patients screened for AVERT, 1158 were recruited and randomized. We use the Proximal Similarity Model, which considers the person, place, and setting and practice, as a framework for considering generalizability. As well as comparing the recruited patients to the target population, we performed an exploratory analysis of the demographic, clinical, site and process factors associated with recruitment. Results: The demographics and stroke characteristics of the included patients in the trial were broadly similar to population based norms, with the exception that men featured more often in those recruited (63%) than not recruited (53%, p<0.001). The most common reason for non-recruitment was late arrival to hospital (i.e. >24 hours). Overall, being older and female reduced the odds of recruitment to the trial. More women than men were excluded for most of the reasons, including refusal. The odds of exclusion due to early deterioration were particularly high for those with severe stroke (OR=10.4, p<0.001, 95%CI: 9.27-11.65). Conclusions: A model which explores person, place and setting and practice factors can provide important information about the external validity of a trial, and could be applied to other clinical trials.

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The impact of statin therapy on plasma levels of von Willebrand factor antigen: Systematic review and meta-analysis of Randomised placebo-controlled trials.

Sahebkar A, Serban C, et al.

Increased plasma levels of von Willebrand factor antigen (vWF:Ag) are associated with high risk of coronary artery disease. The effect of sta-tin therapy on vWF:Ag levels remains uncertain. Therefore the aim of this meta-analysis was to evaluate the effect of statin therapy on vWF:Ag Levels. A systematic multiple-database search was carried out to identify randomized controlled trials (RCTs) that investigated the effect of statins on plasma vWF:Ag levels. Random-effect meta-analy-sis of 21 treatment arms revealed a significant decrease in plasma vWF:Ag levels following statin therapy (SMD: -0.54, 95 %CI: -0.87, -0.21, p=0.001). In subgroup analyses, the greatest effect was ob-served with simvastatin (SMD: -1.54, 95 %>CI: -2.92, -0.17, p=0.028) and pravastatin (SMD: -0.61, 95 %>CI: -1.18, -0.04,
p=0.035), but not with fluvastatin (SMD: -0.34, 95% CI: -0.69, 0.02, p=0.065), atorvastatin (SMD: -0.23, 95% CI: -0.57, 0.11, p=0.179) and rosuvastatin (SMD: -0.20, 95% CI: -0.71, 0.30, p=0.431). The lowering effect of statins on plasma vWF:Ag levels was greater in the subset of studies lasting > 12 weeks (SMD: -0.70, 95% CI: -1.19, -0.22, p=0.005) compared with that of studies lasting < 12 weeks (SMD: -0.34, 95% CI: -0.67, 0.003, p=0.052). Finally, low-intensity statin therapy was not associated with a significant reduction in vWF:Ag levels (SMD: -0.28, 95% CI: -0.82, 0.27, p=0.320), but a significant effect was observed in high-intensity statin trials (SMD: -0.66, 95% CI: -1.07, -0.24, p=0.002). This meta-analysis of available RCTs demonstrates a significant reduction in plasma vWF:Ag levels following statin therapy. Copyright © Schattauer 2016.

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Three-year changes of prothrombotic factors in a cohort of South Africans with a high clinical suspicion of obstructive sleep apnea.

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A hypercoagulable state might be one important mechanism linking obstructive sleep apnea (OSA) with incident myocardial infarction and stroke. However, previous studies on prothrombotic factors in OSA are not uniform and cross-sectional. We longitudinally studied prothrombotic factors in relation to OSA risk, adjusting for baseline levels of prothrombotic factors, demographics, metabolic parameters, aspirin use, and life style factors. The Berlin Questionnaire and/or neck circumference were used to define high OSA risk in 329 South African teachers (48.0 % male, 44.6 % black) at baseline and at three-year followup. Von Willebrand factor (VWF), fibrinogen, D-dimer, plasminogen activator inhibitor-1, clot lysis time (CLT), and soluble urokinase-type plasminogen activator receptor (suPAR) were measured in plasma. At baseline 35.7 % of participants had a high risk of OSA. At follow-up, persistently high OSA risk, persistently low OSA risk, OSA risk remission, and new-onset OSA risk were present in 26.1 %, 53.2 %, 9.4 %, and 11.3 % of participants, respectively. New-onset OSA risk was associated with a significant and longitudinal increase in VWF, fibrinogen, CLT, and suPAR relative to persistently low OSA risk; in VWF, fibrinogen, and suPAR relative to remitted OSA risk; and in VWF relative to persistently high OSA risk. Persistently high OSA risk was associated with an increase in CLT and suPAR relative to persistently low OSA risk and in D-dimer relative to remitted OSA risk. Remitted OSA risk was associated with D-dimer decrease relative to persistently low OSA risk. In OSA, hypercoagulability is a dynamic process with a most prominent three-year increase in individuals with new-onset OSA risk. Copyright © Schattauer 2016.

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One of the major concerns in the practice of allergy is related to the safety of procedures for the diagnosis and treatment of allergic disease. Management (diagnosis and treatment) of hypersensitivity disorders involves often intentional exposure to potentially allergenic substances (during skin testing), deliberate induction in the office of allergic symptoms to offending compounds (provocation tests) or intentional application of potentially dangerous substances (allergy vaccine) to sensitized patients. These situations may be associated with a significant risk of unwanted, excessive or even dangerous reactions, which in many instances cannot be completely avoided. However, adverse reactions can be minimized or even avoided if a physician is fully aware of potential risk and is prepared to appropriately handle the situation. Information on the risk of diagnostic and therapeutic procedures in allergic diseases has been accumulated in the medical literature for decades; however, except for allergen specific immunotherapy, it has never been presented in a systematic fashion. Up to now no single document addressed the risk of the most commonly used medical procedures in the allergy office nor attempted to present general requirements necessary to assure the safety of these procedures. Following review of available literature a group of allergy experts within the World Allergy Organization (WAO), representing various continents and areas of allergy expertise, presents this report on risk associated with diagnostic and therapeutic procedures in allergology and proposes a consensus on safety requirements for performing procedures in allergy offices. Optimal safety measures including appropriate location, type and required time of supervision, availability of safety equipment, access to specialized emergency services, etc. for various procedures have been recommended. This document should be useful for allergists with already established practices and experience as well as to other specialists taking care of patients with allergies.

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Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA).

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Intra-abdominal infections (IAI) are an important cause of morbidity and are frequently associated with poor prognosis, particularly in high-risk patients. The cornerstones in the management of complicated IAIs are timely effective source control with appropriate antimicrobial therapy. Empiric antimicrobial therapy is important in the management of intra-abdominal infections and must be broad enough to cover all likely organisms because inappropriate initial antimicrobial therapy is associated with poor patient outcomes and the development of bacterial resistance. The overuse of antimicrobials is widely accepted as a major driver of some emerging infections (such as C. difficile), the selection of resistant pathogens in individual patients, and for the continued development of antimicrobial resistance globally. The growing emergence of multi-drug resistant organisms and the limited development of new agents available to counteract them have caused an impending crisis with alarming implications, especially with regards to Gram-negative bacteria. An international task force from 79 different countries has joined this project by sharing a document on the rational use of antimicrobials for patients with IAIs. The project has been termed AGORA (Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections). The authors hope that AGORA, involving many of the world’s leading experts, can actively raise awareness in health workers and can improve prescribing behavior in treating IAIs.

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2016 WSES guidelines on acute calculous cholecystitis.
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Acute calculus cholecystitis is a very common disease with several area of uncertainty. The World Society of Emergency Surgery developed extensive guidelines in order to cover grey areas. The diagnostic criteria, the antimicrobial therapy, the evaluation of associated common bile duct stones, the identification of "high risk" patients, the surgical timing, the type of surgery, and the alternatives to surgery are discussed. Moreover the algorithm is proposed: as soon as diagnosis is made and after the evaluation of choledocholithiasis risk, laparoscopic cholecystectomy should be offered to all patients exception of those with high risk of morbidity or mortality. These Guidelines must be considered as an adjunctive tool for decision but they are not substitute of the clinical judgement for the individual patient.

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WSES classification and guidelines for liver trauma.

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The severity of liver injuries has been universally classified according to the American Association for the Surgery of Trauma (AAST) grading scale. In determining the optimal treatment strategy, however, the haemodynamic status and associated injuries should be considered. Thus the management of liver trauma is ultimately based on the anatomy of the injury and the physiology of the patient. This paper presents the World Society of Emergency Surgery (WSES) classification of liver trauma and the management Guidelines.

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**WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis.**

Acute appendicitis (AA) is among the most common cause of acute abdominal pain. Diagnosis of AA is challenging; a variable combination of clinical signs and symptoms has been used together with laboratory findings in several scoring systems proposed for suggesting the probability of AA and the possible subsequent management pathway. The role of imaging in the diagnosis of AA is still debated, with variable use of US, CT and MRI in different settings worldwide. Up to date, comprehensive clinical guidelines for diagnosis and management of AA have never been issued. In July 2015, during the 3rd World Congress of the WSES, held in Jerusalem (Israel), a panel of experts including an Organizational Committee and Scientific Committee and Scientific Secretariat, participated to a Consensus Conference where eight panelists presented a number of statements developed for each of the eight main questions about diagnosis and management of AA. The statements were then voted, eventually modified and finally approved by the participants to The Consensus Conference and lately by the board of co-authors. The current paper is reporting the definitive Guidelines Statements on each of the following topics: 1) Diagnostic efficiency of clinical scoring systems, 2) Role of Imaging, 3) Non-operative treatment for uncomplicated appendicitis, 4) Timing of appendectomy and in-hospital delay, 5) Surgical treatment 6) Scoring systems for intra-operative grading of appendicitis and their clinical usefulness 7) Non-surgical treatment for complicated appendicitis: abscess or phlegmon 8) Pre-operative and post-operative antibiotics.
Phytosome: A fatty solution for efficient formulation of phytopharmaceuticals.
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Nanotechnology: A successful approach to improve oral bioavailability of phytochemicals.
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Adjunctive Therapy with Curcumin for Peptic Ulcer: A Randomized Controlled Trial.
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Background: Curcumin, the bioactive ingredient of turmeric, has been shown to improve the treatment of peptic ulcer (PU) in animal studies. However, clinical studies confirming this effect of curcumin have been scant. Objective: To assess the efficacy of adjunctive therapy with curcumin on the eradication of Helicobacter pylori infection and severity of dyspepsia in patients with PU. Methods: In this randomized double-blind placebo-controlled parallel-group trial, patients diagnosed with PU were assigned to standard H. pylori eradication triple therapy with clarithromycin (500 mg b.i.d.), amoxicillin (1 000 mg b.i.d.) and pantoprazole (40 mg b.i.d.), and randomized to receive either curcumin (500 mg/day) or placebo as adjunct to standard treatment. Severity of dyspepsia symptoms was evaluated using the Hong Kong dyspepsia index (HKDI). Eradication of H. pylori infection was assessed using the urea breath test (UBT) at 4 weeks following the end of treatment. Results: Adjunctive therapy with curcumin was associated with a greater improvement of dyspepsia symptoms according to the HKDI score (change score: -12.90+/-2.81 vs. -9.60+/-3.39 in the curcumin and control group, respectively; p<0.001). The number of subjects whose dyspepsia was resolved during
the course of treatment was significantly higher in the curcumin (27.6%) vs. placebo (6.7%) group (p=0.042). Nevertheless, the results of UBT test showed equal rate (73.3%) of H. pylori eradication in the study groups. Curcumin was safe during the course of trial. Conclusion: Addition of curcumin on top of the standard anti-helicobacter regimen in patients with PU is safe and improves dyspepsia symptoms but has no enhancing effect on the eradication of H. pylori infection. Copyright © Georg Thieme Verlag KG Stuttgart, New York.


Flap within a first dorsal metacarpal artery flap for recurrent thumb injury.

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Thumb pulp defects are commonly due to avulsion injuries. It is important to reconstruct these defects using sensate. A very good option for these defects is the islanded first dorsal metacarpal artery flap (FDMA). We present a patient, a carpenter by occupation, who had initial thumb pulp injury which was reconstructed with islanded first dorsal metacarpal artery flap. At 6-month follow-up, he had near normal sensation and two-point discrimination of 2 mm. The same patient represented after 1 year with similar injury to the same reconstructed thumb. This time, VY advancement flap was designed within the remnant of the previous FDMA flap. Flap within a flap is not a new concept. In the present scenario, it worked as a great indigenous solution as it was a simple alternative. It preserved the sensation and avoided the need of other complex reconstructions. The procedure was performed under local anaesthesia, and patient could return to his normal activities within 2 weeks post-op. This is a rare case report of making use of the concept of flap within a flap for recurrent thumb injury which was reconstructed previously with FDMA flap. VY advancement design aided the necessary movement required to cover the defect yet preserving the regained sensation making it a useful tool before embarking upon complex reconstructions. Level of Evidence: Level V, therapeutic study. Copyright © 2015, Springer-Verlag Berlin Heidelberg.

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A systematic review and meta-analysis of controlled trials on the effects of statin and fibrate therapies on plasma homocysteine lev.

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Background: Plasma homocysteine is an independent non-traditional risk factor for atherosclerotic cardiovascular disease. The impact of statin therapy on plasma homocysteine is not conclusive. Objective: To evaluate the effect of
statin therapy on plasma homocysteine concentrations in a systematic review and meta-analysis of controlled clinical trials. The secondary aim was to assess the comparative effect of statins versus fibrates on plasma homocysteine levels in head-to-head trials. Method: PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched (from the first reports to March 07, 2016) to identify controlled trials evaluating the impact of statins on plasma homocysteine concentrations. A systematic assessment of bias in the included studies was performed using the Cochrane criteria. A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of potential moderators. Results: Meta-analysis of data from 7 studies did not suggest a significant alteration in plasma homocysteine concentrations following treatment with statins compared with the control group (WMD: -0.59 mumol/L, 95% CI: -1.66, 0.48, p=0.279; I²=52.53%). However, meta-analysis of 9 studies suggested a significantly greater reduction of plasma homocysteine concentrations with statins compared with fenofibrate (WMD: -4.81 mumol/L, 95% CI: -5.39, -4.23, p<0.001; I²=0%). Results of both analyses were robust in the sensitivity analysis. Conclusion: Statin therapy is not associated with a significant alteration of plasma homocysteine levels, while fenofibrate increases the homocysteine levels when compared with statins. Copyright © 2016 Bentham Science Publishers.

Microrna-34a and its target genes: Key factors in cancer multidrug resistance.

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Following the first small non-coding RNA identification in 1993, accumulated knowledge on the biogenesis, homeostasis and functional roles of micro RNAs in different physiological and pathophysiological conditions has been discovered. Micro RNAs act through epigenetic regulation of gene expression. MiR-34a is a member of the MiR-34 family that is involved in p53 pathways, and is implicated in cell death/survival signaling. MiR-34a is associated with G1 cell cycle arrest, senescence and apoptosis, thereby possessing a tumor suppressor activity. Deregulation of MiR-34a has been reported in several types of cancers. MiR-34a down regulation has been correlated with cancer multidrug resistance (MDR), which is a major challenge for successful cancer chemotherapy. MiR-34a mimetic agents have been shown to attenuate drug resistance in different cancer cell lines. This review focuses on the in vitro, experimental and clinical findings dealing with the role of miR-34a down regulation in MDR, and potential therapeutic opportunities arising from this role of miR-34a. Copyright © 2016 Bentham Science Publishers.

Efficacy and safety of evacetrapib for modifying plasma lipids: A systematic review and meta-analysis of randomized controlled trials.

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http://www.ingentaconnect.com/content/ben/cpd


Background. Evacetrapib, a new cholesteryl ester transfer protein inhibitor, is being investigated as a potential therapeutic option for reducing cardiovascular events through increasing high-density lipoprotein cholesterol (HDL-C) concentrations. How evacetrapib affects other lipid parameters is less certain. The present study aimed to estimate the effect of evacetrapib on plasma lipid concentrations and to assess its safety through a systematic review and meta-analysis of randomized controlled trials. Methods. SCOPUS, Medline, and Google Scholar were searched to identify randomized controlled trials investigating the impact of evacetrapib on blood lipid concentrations published before December 29, 2014. A random-effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to examine the effect of evacetrapib on plasma lipid concentrations. The safety of evacetrapib was assessed by comparing the pooled incidence of adverse events (total adverse events, adverse events leading to study discontinuation, elevations in hepatic and muscular enzymes and blood pressure) between treatment and placebo groups. Sensitivity analyses were conducted using the one study remove approach. Meta-regression was performed to evaluate the association between changes plasma lipid concentrations and administered doses of evacetrapib. Results. Meta-analysis of 14 randomized treatment arms over a mean of 2 months suggested that evacetrapib significantly reduces low-density lipoprotein cholesterol (LDL-C) (weighted mean difference [WMD]: -21.11%, 95% confidence interval (CI): -24.89, -17.33, p<0.001) and elevated HDL-C (WMD: +86.00%, 95% CI: +67.63, +104.37, p<0.001) concentrations following treatment with evacetrapib. Evacetrapib had no significant effect on plasma triglycerides (WMD: -2.97%, 95% CI: -8.63, +2.69, p = 0.303) concentrations. The effects of evacetrapib on all three lipid indices (LDL-C, HDL-C and triglycerides) did not differ between subsets of trials administering evacetrapib as monotherapy or as add-on to statin therapy. Meta-regression suggested a dose-dependent effect of evacetrapib on plasma LDL-C and HDL-C, but not triglycerides concentrations. Meta-analysis suggested equivalent rates of adverse events in subjects receiving evacetrapib and placebo. Conclusion. Results of this meta-analysis suggested that evacetrapib, either as monotherapy or in combination with a statin, reduces LDL-C and increases HDL-C levels but has no effect on triglyceride concentrations. Adverse events appeared to be similar in subjects receiving evacetrapib and placebo in short-term follow-ups. Copyright © 2016 Bentham Science Publishers.

Interleukin-6: A critical cytokine in cancer multidrug resistance.
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Multidrug resistance (MDR) is a phenomenon through which tumor cells develop resistance against the cytotoxic effects of various structurally and mechanistically unrelated chemotherapeutic agents. The most consistent feature in MDR is overexpression and/or overactivity of ATP-dependent drug efflux transporters. Other mechanisms such as overexpression of drug-detoxifying enzymes and alterations in pro-survival or pro-death signaling pathways are also responsible for MDR. Inflammatory mediators including interleukin-6 (IL-6) play important roles in various events during inflammation and are also involved in development and progression of several Morteza Ghandadi types of cancers. Mounting evidence has suggested a crosstalk between IL-6 and MDR in cancer, highlighting the role of IL-6 in chemotherapy response, and the potential opportunity to control MDR through modulation of IL-6 expression. Up-regulation of IL-6 has been shown to promote MDR through activation of Janus kinases (JAK)/signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt), and Ras-MAPK (mitogen-activated protein kinase) pathways. Activation of the aforementioned pathways changes the expression...
pattern of several genes involved in proliferation, survival and cell cycle regulation, thus facilitating MDR. Conversely, IL-6 inhibition using different strategies (antibodies, siRNA, and antisense transfection) has been shown to improve tumor responsiveness and mitigate MDR in different cancer cell lines. This review focuses on the in vitro, experimental and clinical findings on the role of IL-6 in MDR, and potential therapeutic opportunities arising from this role of IL-6.


**Regulation of collagen expression using nanoparticle mediated inhibition of TGF-beta activation.**

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PXS64 is a stable mannose-6-phosphate (M6P) analogue which has been shown to be an effective anti-fibrotic agent by inhibiting the activation of latent TGF-beta1. However PXS64 is insoluble in physiological conditions. Herein, we report a multifunctional poly(glycidyl methacrylate) (PGMA) polymeric nanoparticle system for intracellular delivery of PXS64 in human primary dermal scar fibroblasts. We demonstrate the efficacy of this anti-fibrotic platform by monitoring the expression of collagen production using an in vitro scar model. Copyright © The Royal Society of Chemistry and the Centre National de la Recherche Scientifique 2016.


**Genomic characteristics of NDM-producing Enterobacteriaceae isolates in Australia and their bla<inf>NDM</inf> genetic contexts.**

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bla<inf>NDM</inf> has been reported in different Enterobacteriaceae species and on numerous plasmid replicon types (Inc). Plasmid replicon typing, in combination with genomic characteristics of the bacterial host (e.g., sequence typing), is used to infer the spread of antimicrobial resistance determinants between genetically unrelated bacterial hosts. The genetic context of bla<inf>NDM</inf> is heterogeneous. In this study, we genomically characterized 12 NDM-producing Enterobacteriaceae isolated in Australia between 2012 and 2014: Escherichia coli (n = 6), Klebsiella pneumoniae (n = 3), Enterobacter cloacae (n = 2) and Providencia rettgeri (n = 1). We describe their bla<inf>NDM</inf> genetic contexts within Tn125, providing insights into the acquisition of bla<inf>NDM</inf> into Enterobacteriaceae. IncFII-type (n = 7) and IncX3 (n = 4) plasmids were the most common plasmid types found. The IncHI1B (n = 1) plasmid was also identified. Five different bla<inf>NDM</inf> genetic contexts were identified, indicating four particular plasmids with specific bla<inf>NDM</inf> genetic contexts (NGCs), three of which were
IncFII plasmids (FII-A to -C). Of note, the bla<sub>NDM</sub>-NDM bla<sub>NDM</sub>-NDM genetic context of P. rettgeri was not conjugative. Epidemiological links between our NDM-producing Enterobacteriaceae were established by their acquisition of these five particular plasmid types. The combination of different molecular and genetic characterization methods allowed us to provide insight into the spread of plasmids transmitting bla<sub>NDM</sub>-NDM bla<sub>NDM</sub>-NDM. Copyright © 2015, American Society for Microbiology. All Rights Reserved.


**The KICA Carer: Informant information to enhance the Kimberley Indigenous Cognitive Assessment.**

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Background: A quality dementia-screening tool is required for older remote Aboriginal Australians who have high rates of dementia and limited access to appropriate medical equipment and clinicians. The Kimberley Indigenous Cognitive Assessment (KICA Cog) is a valid cognitive test for dementia in Aboriginal and Torres Strait Islander peoples. The KICA cognitive informant questionnaire (KICA Carer) had yet to be analyzed to determine validity alone or in combination with the KICA Cog. Methods: The KICA Carer was completed by nominated informants of 349 remote-living Aboriginal Australians in the Kimberley region, Western Australia. Validity was assessed by comparing KICA Carer with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Diseases (ICD-10) consensus diagnoses based on a blinded specialist review. KICA Carer and KICA Cog were then compared to determine joint validity. Results: A KICA Carer score of >3/16 gave optimum sensitivity (76.2%) and specificity (81.4%), area under curve (AUC) 0.89 (95% CI = 0.85, 0.94) with positive predictive value (PPV) of 35.8%, and negative predictive value (NPV) of 96.2%. A KICA Cog score of <33/39 gave a sensitivity of 92.9% and specificity of 89.9%, AUC 0.96 (95% CI = 0.92, 0.98), with PPV of 55.6% and NPV of 98.9%. Cut-off scores of KICA Cog < 33/39 and KICA Carer > 2/16 in series indicate possible dementia, with sensitivity of 90.5% and specificity of 93.5%. In this setting, PPV was 66.5% and NPV was 98.6%. Conclusions: The KICA Carer is an important tool to accurately screen dementia in remote Aboriginal Australians when the KICA Cog is unable to be used for a patient. It is readily accepted by caregivers. Key points: * For the best practice in the cognitive assessment of an Aboriginal Australian aged over 45 years, KICA Cog should be utilized. * In cases where Aboriginal patients are not assessed directly, KICA Carer should be conducted with an informant. A cut-off score of >3/16 should be used (these tools can be downloaded from www.wacha.org.au/kica.html). Copyright © International Psychogeriatric Association 2015.


**Changes in differential gene expression during a fatal stroke.**


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We present a young woman (with an identical twin sister) who arrived at the Emergency Department (ED) within 1 hour of her initial stroke symptoms. Previous microarray studies have demonstrated differential expression of multiple genes between stroke patients and healthy controls. However, for many of these studies there is a significant delay between the initial symptoms and collection of blood samples, potentially leaving the important early activators/regulators of the inflammatory response unrecognised. Blood samples were collected from the patient for an analysis of differential gene expression over time during the evolution of a fatal stroke. The time points for blood collection were ED arrival (T0) and 1, 3 and 24 hours post ED arrival (T1, T3 and T24). This was compared to her identical twin and an additional two age and sex-matched healthy controls. When compared to the controls, the patient had 12 mRNA that were significantly upregulated at T0, and no downregulated mRNA (with a cut off fold change value +/-1.5). Of the 12 upregulated mRNA at T0, granzyme B demonstrated the most marked upregulation on arrival, with expression steadily declining over time, whereas S100 calcium-binding protein A12 (S100A12) gene expression increased from T0 to T24, remaining >two-fold above that in the healthy controls at T24. Other genes, such as matrix metalloproteinase 9, high mobility group box 2 and interleukin-18 receptor I were not upregulated at T0, but they demonstrated clear upregulation from T1-T3, with gene expression declining by T24. A greater understanding of the underlying immunopathological mechanisms that are involved during the evolution of ischaemic stroke may help to distinguish between patients with stroke and stroke mimics. Copyright © 2015 Elsevier Ltd. All rights reserved.
Elevated plasma levels of the pro-thrombotic and pro-inflammatory factor plasminogen activator inhibitor-1 (PAI-1) may contribute to the pathogenesis of atherosclerotic cardiovascular disease. Beyond their lipid-lowering effect, statins have been shown to modulate plasma PAI-1 levels but evidence from individual randomised controlled trials (RCTs) is controversial. Therefore, we aimed to assess the potential effects of statin therapy on plasma PAI-1 concentration through a meta-analysis of RCTs. We searched Medline and SCOPUS databases (up to October 3, 2014) to identify RCTs investigating the effect of statin therapy on plasma PAI-1 concentrations. We performed random-effects meta-analysis and assessed heterogeneity (I² test, subgroup and sensitivity analyses) and publication bias (funnel plot, Egger and “trim and fill” tests). Sixteen RCTs (comprising 19 treatment arms) were included and pooled analyses showed a significant effect of statins in reducing plasma PAI-1 concentrations (weighted mean difference WMD: -15.72 ng/ml, 95 % confidence interval [CI]: -25.01, -6.43.). In subgroup analysis, this effect remained significant in with lipophilic statins (atorvastatin and simvastatin) (WMD: -21.32 ng/ml, 95 % CI: -32.73, -9.91, I²<sup>2</sup> = 99 %) and particularly atorvastatin (WMD: -20.88 ng/ml, 95 % CI: -28.79, -12.97, I²<sup>2</sup> = 97 %). In the meta-regression analysis, the impact of statins on PAI-1 did not correlate with the administered dose, duration of treatment and changes in plasma LDL-cholesterol concentrations. Finally, evidence of publication bias was observed. In conclusion, taking into account the limit of heterogeneity between studies, the present meta-analysis suggests that statin therapy (mainly atorvastatin) significantly lowers plasma PAI-1 concentrations. Copyright © Schattauer 2016.


A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU.

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Objectives: To determine if the early goal-directed mobilization intervention could be delivered to patients receiving mechanical ventilation with increased maximal levels of activity compared with standard care. Design: A pilot randomized controlled trial. Setting: Five ICUs in Australia and New Zealand. Participants: Fifty critically ill adults mechanically ventilated for greater than 24 hours. Intervention: Patients were randomly assigned to either early goal-directed mobilization (intervention) or to standard care (control). Early goal-directed mobilization comprised functional rehabilitation treatment conducted at the highest level of activity possible for that patient assessed by the ICU mobility scale while receiving mechanical ventilation. Measurements and Main Results: The ICU mobility scale, strength, ventilation duration, ICU and hospital length of stay, and total inpatient (acute and rehabilitation) stay as
well as 6-month post-ICU discharge health-related quality of life, activities of daily living, and anxiety and depression were recorded. The mean age was 61 years and 60% were men. The highest level of activity (ICU mobility scale) recorded during the ICU stay between the intervention and control groups was mean (95% CI) 7.3 (6.3-8.3) versus 5.9 (4.9-6.9), \( p = 0.05 \). The proportion of patients who walked in ICU was almost doubled with early goal-directed mobilization (intervention \( n = 19 \) [66%] vs control \( n = 8 \) [38%]; \( p = 0.05 \)). There was no difference in total inpatient stay (d) between the intervention versus control groups (20 [15-35] vs 34 [18-43]; \( p = 0.37 \)). There were no adverse events. Conclusions: Key Practice Points: Delivery of early goal-directed mobilization within a randomized controlled trial was feasible, safe and resulted in increased duration and level of active exercises. Copyright © 2016 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc.

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**Immunology of chronic obstructive pulmonary disease and Sulfur mustard induced airway injuries: Implications for immunotherapeutic interventions.**

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Background: Sulfur mustard (SM)-induced airway injuries and chronic obstructive pulmonary disease (COPD) are characterized by chronic inflammation of the respiratory tract and share some similarities regarding the cellular and molecular mechanisms orchestrating airway destruction. Since available data regarding the immunobiology of COPD is much more known compared with SM-mediated injuries, and considering the similarities in the immunopathogenesis of these diseases, comparison of the immunopathogenesis of COPD and SM-induced respiratory complications can help designing new therapeutic approaches for treatment of SM-induced injuries. Methods: A multi-database search was performed to identify articles dealing with the role of immune system function in the pathogenesis of COPD and mustard mustard-induced respiratory complications. Results: This review outlines the role of different components of the immune system in the pathogenesis of COPD and mustard-induced respiratory complications, and suggests therapeutic implication for improving the management of the latter condition as the most common chronic complication of sulfur mustard exposure. Conclusion: Although COPD and mustard lung are overlapping phenotypes and have shared pathophysiologic features, there are certain differences between these two diseases that necessitate further scrutiny. Combination therapies to counterbalance inflammation, oxidative stress and immune imbalance hold promise for the management of SM-induced respiratory complications but the success of such combined treatments need to be confirmed in proof-of-concept trials. Copyright © 2016 Bentham Science Publishers.

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**A novel individual reconstruction of a medial orbital wall blow-out fracture using a bone graft molded intraoperatively using a 3-D model: a case report.**
This report describes the surgical reconstruction of a traumatic medial orbital wall blow-out fracture using an autologous calvarial bone graft modeled intraoperatively using a three-dimensional (3-D) fused deposition model of the fracture defect. Previous case reports have demonstrated the use of 3-D models in planning the surgical approach, selecting and fashioning the desired implant in the perioperative period, and even using models with sterile coverings intraoperatively to mold synthetic implants. This is an individually unique application of 3-D printing for the surgical repair of pure medical wall blow-out fracture. Copyright © 2016 The Author(s)

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Background: Despite the effectiveness of adjuvant endocrine therapy in preventing breast cancer recurrence, breast cancer events continue at a high rate for at least 10 years after completion of therapy. Patients and methods: This randomised open label phase III trial recruited postmenopausal women from 29 Australian and New Zealand sites, with hormone receptor-positive early breast cancer, who had completed >4 years of endocrine therapy [aromatase inhibitor (AI), tamoxifen, ovarian suppression, or sequential combination] >1 year prior, to oral letrozole 2.5 mg daily for 5 years, or observation. Treatment allocation was by central computerised randomisation, stratified by institution, axillary node status and prior endocrine therapy. The primary outcome was invasive breast cancer events (new invasive primary, local, regional or distant recurrence, or contralateral breast cancer), analysed by intention to treat. The secondary outcomes were disease-free survival (DFS), overall survival, and safety. Results: Between 16 May 2007 and 14 March 2012, 181 patients were randomised to letrozole and 179 to observation (median age 64.3 years). Endocrine therapy was completed at a median of 2.6 years before randomisation, and 47.5% had tumours of >2 cm and/or node positive. At 3.9 years median follow-up (interquartile range 3.1- 4.8), 2 patients assigned letrozole (1.1%) and 17 patients assigned observation (9.5%) had experienced an invasive breast cancer event (difference 8.4%, 95% confidence interval 3.8% to 13.0%, log-rank test P = 0.0004). Twenty-four patients (13.4%) in the observation and 14 (7.7%) in the letrozole arm experienced a DFS event (log-rank P = 0.067). Adverse events linked to oestrogen depletion, but not serious adverse events, were more common with letrozole. Conclusion: These results should be considered exploratory, but lend weight to emerging data supporting longer duration endocrine therapy for hormone receptor-positive breast cancer, and offer insight into reintroduction of AI therapy. Copyright © The Author 2016.

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Second Cancer Risk and Late Mortality in Adult Australians Receiving Allogeneic Hematopoietic Stem Cell Transplantation: A Population-Based Cohort Study.

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We quantified the risk of second cancer activities targeted at high-risk subgroups and late mortality in a population-based Australian cohort of 3273 adult (>15 years) allogeneic hematopoietic stem cell transplant recipients (1992 to 2007). Most recipients received nonradiation-based conditioning and a peripheral blood graft from a matched related donor. Using record linkage with death and cancer registries, 79 second cancers were identified a median of 3.5 years after transplantation. The competing-risk adjusted cumulative incidence of second cancers was 3.35% (95% CI, 2.59 to 4.24) at 10 years, and the cancer risk relative to the matched general population was 2.10 (95% CI, 1.65 to 2.56). We observed an excess risk of melanoma and lip, tongue, esophagus, and soft tissue cancers. Cancer risk relative to the general population was elevated for those transplanted for lymphoma, some leukemia subtypes, and severe aplastic anemia, recipients who developed chronic graft-versus-host disease (cGVHD) and irrespective of radiation-based conditioning or stem cell source. In those alive 2 years after transplantation (n = 1463), the cumulative incidence of late mortality was 22.2% (95% CI, 19.7 to 24.9) at 10 years, and the risk of death relative to the matched general population was 13.8 (95% CI, 12.2 to 15.6). In multivariable modeling, risk of late death was reduced for females compared with males and those transplanted for chronic myeloid leukemia compared with acute myeloid leukemia; risk was increased for recipients with discordant sex donors, cGVHD, those undergoing second transplants, and disease relapse. Adults undergoing allogeneic transplantation have unique cancer and mortality risk profiles that continue to warrant prevention and surveillance activities targeted at high-risk subgroups. Copyright © 2016 American Society for Blood and Marrow Transplantation.

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The Prognostic Value of Percentage Total Plaque Score Adjusted to Age: A Potential Marker of Coronary Vascular Age.

Ayoub C, Yam Y, et al.
Background: Total plaque score (TPS) on coronary computed tomography angiography (CCTA) has been validated as a surrogate measure of coronary artery disease (CAD) burden and is prognostic. We propose a novel measure, percentage TPS adjusted to age (%TPS/age), that may reflect vascular age and potentially more rapidly progressive atherosclerosis and evaluate its potential prognostic value. Methods: %TPS/age was calculated for consecutive patients prospectively enrolled into our institutional CCTA registry and evaluated for primary composite outcome of cardiac death, nonfatal myocardial infarction, and late revascularization. Results: Of 1896 patients identified (mean age 57.7 +/- 11.4 years, 50.1% male, median follow-up 18.6 months [interquartile range: 15.3, 32.4]), 552 (29%) had %TPS/age = 0 (no atherosclerosis), with 1 (0.2%) primary outcome observed (annual event rate [AER] = 0.1%). Two events (0.4%, AER = 0.3%) were observed in %TPS/age < 0.314 category, 22 (5.0%, AER = 2.2%) in %TPS/age 0.314 to 0.699 category, and 54 (12.0%, AER = 5.7%) in %TPS/age > 0.700 category. After adjusting for clinical predictors and obstructive CAD, higher %TPS/age category was associated with hazard ratio 1.95 (1.31-2.88, P <.001) for primary outcome on multivariable analysis, Harrell-C-Statistic 0.87 (confidence interval 95%: 0.84-0.90), and net reclassification improvement of 0.71 (P <.001). Conclusion: %TPS/Age has incremental prognostic value to traditional risk factors and CCTA measures of CAD and improves evaluation of burden of coronary atherosclerosis and clinical risk. Copyright © 2016 SAGE Publications.


Does bipolar disorder have a benign course?
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Probiotic fermented milk or isolated probiotic bacteria for primary prevention of cardiovascular disease in adults.
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This is the protocol for a review and there is no abstract. The objectives are as follows: To assess the effects of probiotic fermented milk or isolated probiotic bacteria for primary prevention of cardiovascular disease in adults.

Management of familial hypercholesterolemia in Hong Kong.


Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disease characterized by elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature atherosclerotic coronary heart disease (CHD). Patients with FH in Hong Kong were found by the identification of potential probands with primary hypercholesterolemia manifesting total cholesterol levels greater than 7.5 mmol/L or LDL-C levels greater than 4.9 mmol/L and undertaking cascade screening of available relatives in the Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong since the early 1990s. Our previous study in a group of 252 subjects from 87 pedigrees clinically diagnosed as having heterozygous FH reported the mean plasma LDL-C level as 7.2±1.5 mmol/L. Xanthomata were present in 40.6% of males and 54.8% of females. The prevalence of known CHD was relatively low at 9.9% in males and 8.5% in females. All FH patients were offered treatment with statins and many of them reached the LDL-C goal with a moderate or high dose of potent statin alone. Ezetimibe is usually added for patients who have not achieved target LDL-C levels on statin alone, particularly in patients with established CHD. Some FH patients who have not achieved the LDL-C targets with this combination have entered into clinical trials with new cholesterol-modifying agents such as the monoclonal antibodies to proprotein convertase subtilisin-kexin type 9. Increased awareness, early identification, and optimal treatment are essential to reduce the risk of CHD, increase life expectancy, and improve the quality of life of patients with FH.

International developments in the care of familial hypercholesterolemia: Where now and where to next?


Several international guidelines and consensus statements have recently been published on the care of familial hypercholesterolemia (FH). They agree on approaches to case detection and cascade testing,
protocols in children, lifestyle and drug treatment strategies, and indications for lipoprotein apheresis. However, most countries in the world still do not have integrated, systematic FH screening programs to adequately detect and treat cases in the community. This study provides a comprehensive overview of recent and future international initiatives for closing the gaps in the care of FH. Copyright © 2016, Japan Atherosclerosis Society. All rights reserved.

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**Constraint-induced aphasia therapy (CIAT): a randomised controlled trial in very early stroke rehabilitation.**

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Background: Communication outcomes following stroke are improved when treatments for aphasia are administered early, within the first 3 months after stroke, and provided for more than 2 hours per week. However, uncertainty remains about the optimal type of aphasia therapy. Aims: We compared constraint-induced aphasia therapy (CIAT) with individual, impairment-based intervention, both administered early and daily after acute stroke.

Methods&Procedures: This prospective, single-blinded, randomised, controlled trial recruited participants with mild to severe aphasia within 10 days of an acute stroke from acute/subacute Perth metropolitan hospitals (n = 20). Participants were allocated by computer-generated block randomisation method to either the CIAT (n = 12) or individual, impairment-based intervention group (n = 8) delivered at the same intensity (45-60 min, 5 days a week) for 20 sessions over 5 weeks (15-20 hours total). The primary outcome, measured after completing the intervention, was the Aphasia Quotient (AQ) from the Western Aphasia Battery. Secondary outcomes were the AQ at 12 and 26 weeks post-stroke, a Discourse Analysis (DA) score and the Stroke and Aphasia Quality of Life Scale (SAQoL), measured at therapy completion, 12 and 26 weeks post-stroke. There was a 10% (n = 2) dropout at the primary end point, both participants were in the CIAT group. The estimates for each treatment group were compared using repeated measures ANOVAs. Data from the 26-week follow-up assessment are presented, however, were not included in the between-group comparisons due to the low number of data points in each group. Outcomes & Results: Within groups analyses comparing performance at baseline, therapy completion, and 12 weeks post stroke revealed a statistically significant treatment effect for the AQ (p < .001), DA (p = .002), and SAQoL (p < .001). Between groups analysis found there was no significant difference between the CIAT and individual therapy groups on any outcome measure. Conclusions: CIAT and individual therapy produced comparable amounts of change in the very early phase of recovery suggesting a standard, intensive daily dose of therapy within this period of recovery is feasible and beneficial. There were no significant differences between the two groups demonstrating that CIAT, which is provided in a group format, may be a viable option in the very early phase of aphasia recovery. The study highlights the need for further research into the impact of therapy type in very early aphasia therapy. Copyright © 2015 Taylor & Francis.

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**Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials.**

Dinca M, Serban MC, et al.
We aimed to elucidate the role of vitamin D supplementation on adipokines through a systematic review and a meta-analysis of randomized placebo-controlled trials (RCTs). The search included PubMed, Scopus, Web of Science and Google Scholar through July 1st, 2015. Finally we identified 9 RCTs and 484 participants. Meta-analysis of data from 7 studies did not find a significant change in plasma adiponectin concentrations following vitamin D supplementation (mean difference [MD]: 4.45%, 95%CI: -3.04, 11.93, p=0.244; Q=2.18, I(2)=0%). In meta-regression, changes in plasma adiponectin concentrations following vitamin D supplementation were found to be independent of treatment duration (slope: 0.25; 95%CI: -0.69, 1.19; p=0.603) and changes in serum 25-hydroxy vitamin D [25(OH)D] levels (slope: -0.02; 95%CI: -0.15, 0.12; p=0.780). Meta-analysis of data from 6 studies did not find a significant change in plasma leptin concentrations following vitamin D supplementation (MD: -4.51%, 95%CI: -25.13, 16.11, p=0.668; Q=6.41, I(2)=21.97%). Sensitivity analysis showed that this effect size is sensitive to one of the studies; removing it resulted in a significant reduction in plasma leptin levels (MD: -12.81%, 95%CI: -24.33, -1.30, p=0.029). In meta-regression, changes in plasma leptin concentrations following vitamin D supplementation were found to be independent of treatment duration (slope: -1.93; 95%CI: -4.08, 0.23; p=0.080). However, changes in serum 25(OH)D were found to be significantly associated with changes in plasma leptin levels following vitamin D supplementation (slope: 1.05; 95%CI: 0.08, 2.02; p=0.033). In conclusion, current data did not indicate a significant effect of vitamin D supplementation on adiponectin and leptin levels.

Curcumin downregulates human tumor necrosis factor-alpha levels: A systematic review and meta-analysis of randomized controlled trials.
Sahebkar A, Cicero AF, et al.

Curcumin downregulates human tumor necrosis factor-alpha levels: A systematic review and meta-analysis of randomized controlled trials.
Sahebkar A, Cicero AF, et al.


Curcumin downregulates human tumor necrosis factor-alpha levels: A systematic review and meta-analysis of randomized controlled trials.
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BACKGROUND: Tumor necrosis factor-alpha (TNF-alpha) is a key inflammatory mediator and its reduction is a therapeutic target in several inflammatory diseases. Curcumin, a bioactive polyphenol from turmeric, has been shown in several preclinical studies to block TNF-alpha effectively. However, clinical evidence has not been fully conclusive.

OBJECTIVE: The aim of the present meta-analysis was to evaluate the efficacy of curcumin supplementation on circulating levels of TNF-alpha in randomized controlled trials (RCTs).

METHODS: The search included PubMed-Medline, Scopus, Web of Science and Google Scholar databases by up to September 21, 2015, to identify RCTs investigating the impact of curcumin on circulating TNF-alpha concentration. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. Meta-regression and leave-one-out sensitivity analyses were performed to assess the modifiers of treatment response.

RESULTS: Eight RCTs comprising nine treatment arms were finally selected for the meta-analysis. There was a significant reduction of circulating TNF-alpha concentrations following curcumin supplementation (WMD: -4.69 pg/mL, 95% CI: -7.10, -2.28, p<0.001). This effect size was robust in sensitivity analysis. Meta-regression did not suggest any significant association between the circulating TNF-alpha-lowering effects of curcumin with either dose or duration (slope: 0.197; 95% CI: -1.73, 2.12; p=0.841) of treatment.

CONCLUSION: This meta-analysis of RCTs suggested a significant effect of curcumin in lowering circulating TNF-alpha concentration.

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Familial hypercholesterolaemia (FH) is the most common autosomal dominant condition, with a prevalence of between one in 200 and 350 people in the general population. Untreated FH is associated with premature atherosclerotic cardiovascular disease (CVD). The prevalence of homozygous or compound heterozygous FH is now considered to be about one in 300000 people. Treating children with FH reduces progression of atherosclerotic CVD and future CVD events. Most individuals with FH are undiagnosed, which together with the recent frequency data in the population and in individuals with premature coronary disease creates a public health challenge and mandates a key role for primary care. Childhood is the optimal period for detecting FH, since lowdensity lipoprotein cholesterol (LDL-c) concentrations better differentiate affected from unaffected individuals. In an Australian community setting, over 70% of adults with an LDL-c level > 6.5mmol/L have clinical FH; of these, 30% have a detectable mutation. The community laboratory has an important role in identifying FH, with interpretive comments leading to additional reductions in LDL-c concentrations, and a phone call from the pathologist to the general practitioner improving detection of cases. Cascade screening using DNA testing is cost-effective and acceptable to screenees. Next generation genetic sequencing may differentiate people with polygenic hypercholesterolaemia alone from those with FH. Smoking, hypertension, elevated lipoprotein(a) levels, chronic kidney disease and diabetes are additional atherosclerotic CVD risk factors in FH. Equations for assessing absolute risk of CVD in primary prevention underestimate risk in FH. The adult LDL-c goal is a greater than 50% reduction in LDL-c levels, followed by a target of <2.5 mmol/L, or <1.8mmol/L for individuals with CVD or other CVD risk factors. Proprotein convertase subtilisin/kexin type 9 inhibitors significantly reduce LDL-c and lipoprotein(a) levels in people with FH. Registries are essential for improving the care of people with FH. Copyright © 2016 AMPCo Pty Ltd. Produced with Elsevier B.V. All rights reserved.
Sexual transmission of HIV and the law: An Australian medical consensus statement.
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Introduction: Criminal cases involving human immunodeficiency virus transmission or exposure require that courts correctly comprehend the rapidly evolving science of HIV transmission and the impact of an HIV diagnosis. This consensus statement, written by leading HIV clinicians and scientists, provides current scientific evidence to facilitate just outcomes in Australian criminal cases involving HIV. Main recommendations: Caution should be exercised when considering charges or prosecutions regarding HIV transmission or exposure because:

* Scientific evidence shows that the risk of HIV transmission during sex between partners of different HIV serostatus can be low, negligible or too low to quantify, even when the HIV-positive partner is not taking effective antiretroviral therapy, depending on the nature of the sexual act, the viral load of the partner with HIV, and whether a condom or pre-exposure prophylaxis is employed to reduce risk.
* The use of phylogenetic analysis in cases of suspected HIV transmission requires careful consideration of its limited probative value as evidence of causation of HIV infection, although such an approach may provide valuable information, particularly in relation to excluding HIV transmission between individuals.

* Most people recently infected with HIV are able to commence simple treatment providing them a normal and healthy life expectancy, largely comparable with their HIV-negative peers. Among people who have been diagnosed and are receiving treatment, HIV is rarely life threatening. People with HIV can conceive children with negligible risk to their partner and low risk to their child. Changes in management as result of the consensus statement: Given the limited risk of HIV transmission per sexual act and the limited long term harms experienced by most people recently diagnosed with HIV, appropriate care should be taken before HIV prosecutions are pursued. Careful attention should be paid to the best scientific evidence on HIV risk and harms, with consideration given to alternatives to prosecution, including public health management. Copyright © 2016 AMPCo Pty Ltd. Produced with Elsevier B.V. All rights reserved.

Alternatives to the baseline KUB for CTKUB-detected calculi: evaluation of CT scout and average and maximum intensity projection images.
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Purpose: A CT of the kidneys, ureters, and bladder (CTKUB) is the investigation of choice in suspected renal colic. Plain kidney, ureter, and bladder radiographs (KUB) can be used to monitor the progress of a stone if radiographically visible on a baseline KUB. This study aims to determine if a low-dose CT Scout, thick-slab average intensity projection
(AIP), or maximum intensity projection (MIP) images are suitable as substitutes for a baseline KUB. Method: A retrospective review of patients from a tertiary adult institute that had a positive CTKUB and a KUB within 4 h of the CT was performed. Two consultant radiologists independently reviewed the KUB, CT Scout, AIP, and MIP for stone visibility and their sensitivities and agreement values were compared. Stone characteristics (size, location, and peak Hounsfield units) and patient thickness were recorded and examined for any association with discordant results. Results: 74 stones were evaluated for the study. KUB had a sensitivity of 66.2% (95% CI 54.3-76.8), CT Scout 47.3% (95% CI 35.6-59.3), AIP 55.4% (95% CI 43.4-67.0), and MIP 83.8% (95% CI 73.4-91.3). Fair agreement was found between the KUB and both CT Scout (kappa=0.363, 95% CI 0.167-0.558) and AIP (kappa=0.384, 95% CI 0.175-0.592). Moderate agreement was found between the KUB and MIP (kappa=0.412, 95% CI 0.198-0.625). Neither any stone characteristic nor patient thickness had a significant association with discordant results. Conclusion: None of the possible substitutes for a baseline KUB showed strong agreement with the KUB. Low-dose CT Scouts have a similar sensitivity to the published literature for higher dose CT Scouts. Copyright © 2016 Springer Science+Business Media New York

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Of a different age.

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Effects of intensive induction and consolidation chemotherapy with idarubicin and high dose cytarabine on minimal residual disease levels in newly diagnosed adult precursor-B acute lymphoblastic leukemia.
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An intensive induction regimen, consisting of idarubicin and high dose cytarabine, was assessed in 19 adult patients, median age 44 years, with newly diagnosed precursor-B acute lymphoblastic leukemia (ALL). Patients achieving a complete response (CR) were given an attenuated consolidation course. The primary endpoints were induction death rate and incidence of serious non-hematological toxicity. Grades 3-4 diarrhoea occurred in 47% of patients during induction. Two patients (11%) died during induction therapy, and 2 were withdrawn due to resistant disease or prolonged marrow hypoplasia. Fifteen patients achieved CR (79%), but levels of minimal residual disease (MRD) after induction were comparable with those previously observed using a modified pediatric protocol. Overall survival at 5 years was 36.8% while leukemia-free survival was 44.1%. An intensive AML protocol used in adults with ALL resulted in substantial toxicity and provided similar levels of cytoreduction to conventional ALL protocols, without improving long-term outcomes. Copyright © 2016 The Authors.
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X-ray protection, surface chemistry and rheology of ball-milled submicron $\text{Gd}_2\text{O}_3$ aqueous suspension.

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X-ray protective garments are typically comprised of lead-based materials, which are toxic to both people and the environment. Developing alternative lightweight radiation shielding materials is a priority for protecting people working with radiation. Gadolinium, with an electron configuration typical of radiation shielding elements, is proposed as a non-toxic replacement for lead. This study provides new insights into the potential for a gadolinium suspension for replacing lead and proposes an inexpensive and effective preparation method. Submicron gadolinium oxide ($\text{Gd}_2\text{O}_3$) was generated using a cost effective ball milling method involving addition of NaCl. Then, the dispersed-flocculated behaviour of $\text{Gd}_2\text{O}_3$ aqueous slurries was studied via yield stress and zeta potential techniques to stabilise the dispersion. The relationship of the transmission-volume fraction at different kVp from an interventional radiology source was established to investigate radiation attenuation performance of the suspension. At a low volume fraction (0.082), the gadolinium slurry attenuated more than 95% of the X-ray load from a 50-100 kVp source. The equivalent weight-thickness at the same attenuation of 95% (5% transmission) of the $\text{Gd}_2\text{O}_3$ suspension was 1.5 g/cm$^2$, which is comparable to that of equivalent commercial lead-based materials (>1 g/cm$^2$). This research is significant for developing a non-lead-based material, $\text{Gd}_2\text{O}_3$ aqueous slurry, which offers effective radiation attenuation with weight-thickness minimisation and safe use and disposal. Copyright © 2016 Elsevier B.V.


**Stapled Mesh stomA Reinforcement Technique (SMART) in the prevention of parastomal hernia: a single-centre experience.**

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Purpose: Parastomal hernia remains a frequent complication following creation of an abdominal stoma. Previous interests have centred around the exploration of methods to repair; however, prophylactic mesh placement has demonstrated its efficacy in reduction of parastomal hernia. The aim of this retrospective analysis was to evaluate the outcomes of Stapled Mesh stomA Reinforcement Technique (SMART) in terms of parastomal hernia occurrence rate and mesh-related complications. Methods and materials: All patients operated with an abdominal perineal resection or Hartmann’s procedure with SMART from November 2013 to March 2016 were included. Patient demographics, operative details and stoma-related symptoms were collected. Patients were examined clinically by the medical team and also reviewed independently by a specialist stoma care nurse for signs of stoma-related complications. As part of oncological follow-up, CT scans were available for review for evidence of parastomal herniation. Results: 14 patients (mean age 76 years) were included in the analysis. All the SMART cases were successfully completed with no intraoperative or immediate post-operative complications. No cases of mesh-related complications such as infection, immediate stoma prolapse, stenosis, retraction, stoma obstruction, mesh erosion or fistulation were observed. No mesh removal was required. There were two cases of parastomal hernia detected on CT scan. Both cases have


Compliance with reporting guidelines by Australian pathologists: An audit of the quality of histopathology reporting in high-grade glioma.

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Background. Diagnostic pathology reports inform management plans for patients with glioma, and there is an increasing clinical need for molecular testing. We assessed the quality of histopathology reports of grade III/IV gliomas. Methods. Reports were obtained as part of a tumor biobank. From 720 pathology reports, 594 eligible reports were assessed for 28 elements derived from published checklists. A summary quality score incorporated 9 critical parameters for clinical decision making: diagnosis using World Health Organization 2007 criteria; cell type; grade; narrative supporting cell type and grade; absence of equivocal language; conclusion reporting cell type and grade; and conclusion aligned with report narrative. Results. Of 594 eligible reports, the final conclusion was not supported by the report narrative in 122 (21%). Tumor classification and grade were not supported by the narrative in 105 (18%) and 36 (6%) reports, respectively. Only 145 (24%) reports fulfilled all 9 quality criteria, while 25% contained 6 or fewer key quality indices. Report quality was higher when pathologists had neuropathology subspecialization, when a grade IV tumor was reported, and when the specimen was from an initial resection or grade-progressed tumor rather than recurrent high-grade glioma. Use of molecular testing increased over time, from 29% to 48% over four quartiles of the study. Molecular testing was more frequently done where oligodendroglial elements were reported. Conclusion. A significant proportion of reports failed to meet key indicators of report quality. Pathology reporting is critical in communicating between pathologists and treating clinicians. Clinicians should be aware of reporting quality and seek clarification when required. Copyright © The Author(s) 2015. PMID:610606014 DOI:http://dx.doi.org/10.1093/nop/npv033 http://nop.oxfordjournals.org/ http://smhslibresources.health.wa.gov.au/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18a&AN=610606014


False-positive uptake of 18F-FDG in hypoglossal nerve palsy following chemoradiotherapy for tongue base cancer.

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PMID:24845760
Later life transitions and changes in psychiatry.

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OBJECTIVE: The objective of this study was to discuss some concerns that today's psychiatrists are likely to experience in the later stages of their careers.

CONCLUSIONS: When changes associated with ageing begin to make their presence felt, there is a need to come to terms with them. For many psychiatrists this may generate a surprising creativity. Psychiatrists also need to come to terms with a paradigm change that has taken place in psychiatric practice. This paper, one of a series that captures a broad perspective on ageing, was solicited (by the Members Engagement Committee) to specifically capture the psychotherapist's view of later life transitions.

Statin impact on disease activity and C-reactive protein concentrations in systemic lupus erythematosus patients: A systematic review and meta-analysis of controlled trials.

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BACKGROUND AND PURPOSE: Efficacy and safety of statin therapy in patients with systemic lupus erythematosus (SLE) is controversial. The aim of this meta-analysis was to evaluate whether statin therapy affects SLE disease activity and systemic inflammation (C-reactive protein, CRP) according to the evidence from controlled clinical trials.

EXPERIMENTAL APPROACH: A systematic review followed by a bibliographic search in Medline and SCOPUS (up to March 2015) was performed. Quantitative data synthesis was performed using a random-effects model and the generic inverse variance weighting method. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

KEY RESULTS: Meta-analysis of five controlled trials reporting statin impact on SLE disease activity did not suggest any significant effect of statin therapy on SLEDAI. Evaluation of seven controlled trials with reported effects on CRP levels suggested a significant reduction of plasma CRP concentrations in patients with SLE independent of the treatment duration. The effect size on plasma CRP concentrations was significant with lipophilic (atorvastatin) but not hydrophilic (pravastatin and rosuvastatin) statins.

CONCLUSION AND IMPLICATIONS: The present results suggest that statin therapy is likely to be safe in patients with SLE. In addition, statin-treated SLE patients may benefit from CRP reduction in terms of managing severe
cardiovascular complications associated with the disease.


Structure-function correlation and natural history of accidental juxtafoveal injury from a 250milliwatt recreational hand-held green laser device.

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A randomized controlled trial of the effects of n-3 fatty acids on resolvins in chronic kidney disease.

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BACKGROUND AND OBJECTIVE: The high incidence of cardiovascular disease (CVD) in chronic kidney disease (CKD) is related partially to chronic inflammation. n-3 Fatty acids have been shown to have anti-inflammatory effects and to reduce the risk of CVD. Specialized Proresolving Lipid Mediators (SPMs) derived from the n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) actively promote the resolution of inflammation. This study evaluates the effects of n-3 fatty acid supplementation on plasma SPMs in patients with CKD.

METHODS: In a double-blind, placebo-controlled intervention of factorial design, 85 patients were randomized to either n-3 fatty acids (4 g), Coenzyme Q10 (CoQ) (200 mg), both supplements, or control (4 g olive oil), daily for 8 weeks. The SPMs 18-HEPE, 17-HDHA, RvD1, 17R-RvD1, and RvD2, were measured in plasma by liquid chromatography-tandem mass spectrometry before and after intervention.

RESULTS: Seventy four patients completed the 8 weeks intervention. n-3 Fatty acids but not CoQ significantly increased (P < 0.0001) plasma levels of 18-HEPE and 17-HDHA, the upstream precursors to the E- and D-series resolvins, respectively. RvD1 was significantly increased (P = 0.036) after n-3 fatty acids, but no change was seen in other SPMs. In regression analysis the increase in 18-HEPE and 17-HDHA after n-3 fatty acids was significantly predicted by the change in platelet EPA and DHA, respectively.
CONCLUSION: SPMs are increased after 8 weeks n-3 fatty acid supplementation in patients with CKD. This may have important implications for limiting ongoing low grade inflammation in CKD.


Developing role of microRNA-33 in lipid metabolism and atherosclerosis.
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Use of serum lactate levels to predict survival for patients with out-of-hospital cardiac arrest: A cohort study.
Williams TA, Martin R, et al.

OBJECTIVES: We examined the association of serum lactate levels and early lactate clearance with survival to hospital discharge for patients suffering an out-of-hospital cardiac arrest (OHCA).

METHODS: A retrospective cohort analysis was performed of patients with OHCA transported by ambulance to two adult tertiary hospitals in Perth, Western Australia. Exclusion criteria were traumatic cardiac arrest, return of spontaneous circulation prior to the arrival of the ambulance, age less than 18 years and no serum lactate levels recorded. Serum lactate levels recorded for up to 48 h post-arrest were obtained from the hospital clinical information system, and lactate clearance over 48 h was calculated. Descriptive and logistic regression analyses were
conducted.
RESULTS: There were 518 patients with lactate values, of whom 126 (24.3%) survived to hospital discharge. Survivors and non-survivors had different mean initial lactate levels (mean +/- SD 6.9 +/- 4.7 and 12.2 +/- 5.5 mmol/L, respectively; P < 0.001). Lactate clearance was higher in survivors. Lactate levels for non-survivors did not decrease below 2 mmol/L until at least 30 h after the ambulance call.
CONCLUSION: In OHCA patients who had serum lactate levels measured, both lower initial serum lactate and early lactate clearance in the first 48 h following OHCA were associated with increased likelihood of survival. However, the use of lactate in isolation as a predictor of survival or neurological outcome is not recommended. Prospective studies that minimise selection bias are required to determine the clinical utility of serum lactate levels in OHCA patients.

Traumatic facet joint dislocation in Western Australia.
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INTRODUCTION: Facet joint dislocation is a traumatic injury, which frequently results in devastating clinical outcomes. In Western Australia (WA), Royal Perth Hospital (RPH) provides a statewide Spinal Trauma Service and accepts all referrals from the entirety of the state. The economics of distance in WA mean that there is often a considerable delay between initial presentation at the peripheral hospital and enrolment of the dislocation in Perth. This study aims to identify any prejudicial clinical outcomes as a consequence of this delay.
METHODS: This study retrospectively examines all facet joint dislocations that presented to RPH between in a 46-month period. Data were collected on the demographics of patients, mechanism of injury, neurological assessment at presentation of injury based on the American spinal injury association (ASIA), initial presentation to RPH, post-surgical reduction and post rehabilitation.
RESULTS: Over this time there were 23 urban patients and 28 rural patients. In the urban group, 18 patients had a final ASIA score of D or E while 5 patients had a final ASIA score of A, B or C. In the rural group, 17 patients had a final ASIA score of A, B or C while 11 patients had a final ASIA score of D or E.
CONCLUSION: This study confirms the challenges of management of these injuries in a large geographical area, with a centralised spinal trauma service. Generally, facet joint dislocations that had delayed reductions had a poorer outcome. We hope that the proposed protocol would deliver better management of these injuries.

Evidence-Based Nursing. 2016; 19(2): 47.
Intermittent pneumatic compression is effective in reducing proximal DVT.
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DOI:https://dx.doi.org/10.1136/eb-2015-102265
RESPOND: a patient-centred programme to prevent secondary falls in older people presenting to the emergency department with a fall-protocol for a mixed methods programme evaluation.

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BACKGROUND: Programme evaluations conducted alongside randomised controlled trials (RCTs) have potential to enhance understanding of trial outcomes. This paper describes a multi-level programme evaluation to be conducted alongside an RCT of a falls prevention programme (RESPOND).

OBJECTIVES: (1) To conduct a process evaluation in order to identify the degree of implementation fidelity and associated barriers and facilitators. (2) To evaluate the primary intended impact of the programme: participation in fall prevention strategies and the factors influencing participation. (3) To identify the factors influencing RESPOND RCT outcomes: falls, fall injuries and emergency department (ED) re-presentations.

METHODS/DESIGN: 528 community-dwelling adults aged 60-90 years presenting to two EDs with a fall will be recruited and randomly assigned to the intervention or standard care group. All RESPOND participants and RESPOND clinicians will be included in the evaluation. A mixed methods design will be used and a programme logic model will frame the evaluation. Data will be sourced from interviews, focus groups, questionnaires, clinician case notes, recruitment records, participant-completed calendars, hospital administrative datasets and audio-recordings of intervention contacts. Quantitative data will be analysed via descriptive and inferential statistics and qualitative data will be interpreted using thematic analysis.

DISCUSSION: The RESPOND programme evaluation will provide information about contextual and influencing factors related to the RESPOND RCT outcomes. The results will assist researchers, clinicians and policy makers regarding decisions about future falls prevention interventions. Insights gained may be applicable to a range of chronic conditions where similar preventive intervention approaches are indicated.

TRIAL REGISTRATION NUMBER: This programme evaluation is linked to the RESPOND RCT which is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000336684).

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**Integrated multidisciplinary community service for chronic obstructive pulmonary disease reduces hospitalisations.**
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**BACKGROUND:** Hospitalisations for chronic obstructive pulmonary disease (COPD) exacerbation affect patient outcomes and healthcare costs. The long-term impact of an integrated COPD disease-management approach on hospitalisation remains controversial.

**AIM:** The aim of this study was to evaluate whether a multidisciplinary community service reduces respiratory hospitalisations for COPD patients.

**METHODS:** A total of 346 patients was followed for a mean duration of 27.3 months. The number of admissions, total bed days for respiratory (COPD exacerbation or pneumonia) or general medical causes and length of stay (LOS) per respiratory admission was compared before and after referral with the service. A secondary multivariate analysis examined which clinical parameters best predict benefit from such service.

**RESULTS:** The total respiratory admission and hospital bed days after referral were reduced by 31% (288 vs 417, \( P<0.001 \)) and 40.4% (1637 vs 2746, \( P<0.0001 \)) respectively, compared with the equivalent duration prior. The average LOS for each respiratory admission was also significantly reduced after referral (6.61 vs 5.70, \( P=0.02 \)). Overall, 55% patients experienced a reduction in admission frequency and hospital days. The impact on admission frequency and hospital days was the greatest in those with an at least moderate disease (GOLD >2, odds ratio (OR): 3.2, 95% confidence interval (CI): 1.2, 8.9; \( P=0.019 \)) and those who completed pulmonary rehabilitation (PR) (OR: 1.7, 95% CI: 1.1, 2.8; \( P=0.04 \)). In contrast, general medical admissions increased, one-third attributable to a cardiovascular cause both before and after referral.

**CONCLUSIONS:** The implementation of COPD multidisciplinary community service was associated with reduced respiratory hospitalisations in the long term. Patients with moderate or severe disease and who are able to complete PR are much more likely to benefit.

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**Epidemiology and antimicrobial susceptibility profiles of pathogens causing urinary tract infections in the Asia-Pacific region: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2010-2013.**
A total of 9599 isolates of Gram-negative bacteria (GNB) causing urinary tract infections (UTIs) were collected from 60 centres in 13 countries in the Asia-Pacific region from 2010-2013. These isolates comprised Enterobacteriaceae species (mainly Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Klebsiella oxytoca, Enterobacter cloacae and Morganella morganii) and non-fermentative GNB species (predominantly Pseudomonas aeruginosa and Acinetobacter baumannii). In vitro susceptibilities were determined by the agar dilution method and susceptibility profiles were determined using the minimum inhibitory concentration (MIC) interpretive breakpoints recommended by the Clinical and Laboratory Standards Institute in 2015. Production of extended-spectrum beta-lactamases (ESBLs) amongst E. coli, K. pneumoniae, P. mirabilis and K. oxytoca isolates was determined by the double-disk synergy test. China, Vietnam, India, Thailand and the Philippines had the highest rates of GNB species producing ESBLs and the highest rates of cephalosporin resistance. ESBL production and hospital-acquired infection (isolates obtained >48 h after admission) significantly compromised the susceptibility of isolates of E. coli and K. pneumoniae to ciprofloxacin, levofloxacin and most beta-lactams, with the exception of imipenem and ertapenem. However, >87% of ESBL-producing E. coli strains were susceptible to amikacin and piperacillin/tazobactam, indicating that these antibiotics might be appropriate alternatives for treating UTIs due to ESBL-producing E. coli. Fluoroquinolones were shown to be inappropriate as empirical therapy for UTIs. Antibiotic resistance is a serious problem in the Asia-Pacific region. Therefore, continuous monitoring of evolutionary trends in the susceptibility profiles of GNB causing UTIs in Asia is crucial.


**Depression as a risk factor for cognitive impairment in later life: the Health In Men cohort study.**

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BACKGROUND: Depression is an established risk factor for dementia in later life, but it is unclear if this relationship is causal. This study aimed to determine if clinically significant depressive symptoms are likely to be causally related to cognitive impairment in later life.

METHODS: Observational cohort study of 4568 men aged 70-89 years living in Perth, Western Australia, who were free of cognitive impairment at the beginning of follow-up. Current clinically significant depressive symptoms were defined by a score of 7 or more on the Geriatric Depression Scale 15 items. Past depression was ascertained via electronic medical records, by self-report or use of antidepressants. A score of 27 or less on the Telephone Interview for Cognitive Status modified or a recorded diagnosis of dementia in electronic medical records established the presence of cognitive impairment.

RESULTS: During the 5-year follow-up, 534 men developed cognitive impairment, 811 died and 1455 were lost. The presence of clinically significant depressive symptoms at study entry was associated with increased risk rate (RR) of cognitive impairment (RR = 2.59, 95% confidence interval: 95%CI = 1.57-4.27), death (RR = 5.07, 95%CI = 3.32-7.75) and loss to follow-up (RR = 2.03, 95%CI = 1.32-3.13). These associations remained statistically significant after adjustment for age, country of birth, education, smoking history, and prevalence hypertension, diabetes, coronary heart disease and stroke. History of past clinically significant depressive symptoms was not associated with incident cognitive impairment (RR = 1.09, 95%CI = 0.78-1.52).

CONCLUSIONS: The lack of association between past depression and cognitive impairment suggests that the link between depression and cognitive impairment is not causal and that the presence of clinically significant depressive symptoms in later life may herald the onset of cognitive impairment in at least some people.
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We study the associations between apoA-II fractional catabolic rate (FCR) and the kinetics of VLDL subspecies and apoA-1 and show that, in abdominally obese individuals, apoA-II FCR is positively and independently associated with both apoA-I FCR and VLDL1-TG indirect FCR.

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Microalbuminuria--an important marker of residual risk: evidence from a primary care setting.
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Screen-detected breast carcinoma with macroscopic dystrophic calcification: A pictorial essay with radiological pathological correlation.
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Breast calcifications are among the most common abnormal radiographic findings detected at screening mammography. This essay illustrates the clinico-pathological features of nine screen-detected breast carcinomas, which had benign-appearing macrocalcifications, as a radiographically dominant presenting feature. We aimed to demonstrate that benign-appearing calcifications within a breast lesion are not diagnostic of a benign process if the other imaging characteristics of the lesion are suspicious of malignancy.
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Duration of diabetes and its association with depression in later life: The Health In Men Study (HIMS).
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OBJECTIVE: To examine if diabetes and duration of diabetes are direct or indirect causes of depression in later life.

RESEARCH DESIGN AND METHODS: Cross-sectional study of a community-derived sample of 5462 men aged 70-89 years. Men with ‘current depression’ scored 7 or more on the abbreviated Geriatric Depression Scale (GDS-15), whereas men with ‘ever depression’ were either currently depressed or reported history or treatment for past depression. The presence of diabetes was established by self-reported history, fasting glucose >7 mmol/L (126 mg/dL), or use of insulin or hypoglycemic drugs. Duration of diabetes relied on self-report. Other measured factors included age, place of birth, education, smoking history, and the FRAIL scale.

RESULTS: Diabetes was associated with increased odds ratio (OR) of ever (OR=1.49, 95%CI=1.25, 1.76) and current depression (OR=1.94, 95%CI=1.15, 2.48). The association between duration of diabetes and risk of current depression was ‘J-shaped’ with odds ratios of 1.92 (95%CI=1.44, 2.54), 1.56 (95%CI=0.89, 2.75), 2.49 (95%CI=1.16, 5.32) and 3.13 (95%CI=1.28, 7.63) for <10, 10-19.9, 20-29.9 and >30 years of diabetes history compared with older men without diabetes. The strength of these associations was attenuated after the analyses were adjusted for other measured factors, but the shape of the curve did not change. Structural equation modeling showed that frailty mediated some of the association between diabetes duration and depression (about 15%) and was a strong predictor of depression in the sample.

CONCLUSIONS: In older men, the association between time lived with the diagnosis of diabetes and the risk of depression is ‘J-shaped’. Frailty mediates some of the association between diabetes and depression, although other unmeasured factors are also likely to play a role. The introduction of strategies that are effective at decreasing diabetes-related complications may also contribute to decrease the risk of depression among older men.

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Is it time to think about the sodium glucose co-transporter 2 sympathetically?

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Disturbances in glucose homeostasis are a key feature of the metabolic syndrome and type 2 diabetes. Renal glucose reabsorption is an important factor in glycaemic control. Glucose reabsorption in the proximal tubules is mediated by the sodium glucose co-transporter 2. The capacity for glucose reabsorption is increased in type 2 diabetes and contributes significantly to hyperglycaemia and impaired glucose control. Understanding the mechanisms underpinning the regulation of the sodium glucose co-transporter 2 is therefore of high clinical relevance. However, despite recent advances in the field and the availability of pharmacological inhibitors of this glucose transporter for the treatment of type 2 diabetes, the mechanisms that regulate sodium glucose co-transporter 2 expression are not fully understood. The sympathetic nervous system is an important modulator of glucose homeostasis, and sympathetic hyperactivity is a characteristic feature of obesity, the metabolic syndrome and type 2 diabetes. Sympathetic inhibition either achieved pharmacologically or by renal sympathetic denervation has been associated with improved glucose control. Importantly, sympathetic nerves innervate the proximal tubules of the kidney where they have been shown to regulate the expression of other transporters such as the sodium hydrogen exchanger 3. This review aims to explore the evidence for the regulation of sodium glucose co-transporter 2-mediated glucose reabsorption by the sympathetic nervous system.

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Nigella sativa (black seed) effects on plasma lipid concentrations in humans: A systematic review and meta-analysis of randomized placebo-controlled trials.


The effects of Nigella sativa (NS) on plasma lipid concentrations are controversial. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to obtain a conclusive result in humans. PubMed-Medline, SCOPUS, Web of Science, and Google Scholar databases were searched (up to August 2015) to identify RCTs investigating the impact of NS on total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglycerides concentrations. A random-effects model and the generic inverse variance weighting method were used for quantitative data synthesis. Meta-regression, sensitivity analysis, and publication bias assessments were performed using standard methods. A total of 17 RCTs examining the effects of NS on plasma lipid concentrations were included. Meta-analysis suggested a significant association between NS supplementation and a reduction in total cholesterol (weighed-mean-difference [WMD]: -15.65mg/dL, 95% CI: -24.67, -6.63, p=0.001), LDL-C (WMD: -14.10mg/dL, 95% CI: -19.32, -8.88, p<0.001), and triglyceride levels (WMD: -20.64mg/dL, 95% CI: -30.29, -11.00, p<0.001). No significant effect on HDL-C concentrations (WMD: 0.28mg/dL, 95% CI: -1.96, 2.53, p=0.804) was found. A greater effect of NS seed oil versus seed powder was observed on serum total cholesterol and LDL-C levels, and an increase in HDL-C levels was found only after NS seed powder supplementation. NS has a significant impact on plasma lipid concentrations, leading to lower total cholesterol, LDL-C, and TG levels while increased HDL-C is associated with NS powder only. Further RCTs are needed to explore the NS benefits on cardiovascular outcomes.


Specialised pro-resolving mediators of inflammation in inflammatory arthritis.

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INTRODUCTION: Specialised pro-resolving mediators (SPM) are derived from n-3 long chain polyunsaturated fatty acids (n-3FA). They promote resolution of inflammation and may contribute to the beneficial effects of n-3FA in patients with arthritis. This study compared SPM in knee effusions and plasma of patients with arthritis taking n-3FA, and plasma of healthy volunteers taking n-3FA.

METHODS: Thirty six patients taking n-3FA undergoing arthrocentesis for an inflammatory knee effusion and 36 healthy volunteers who had taken n-3FA (2.4g/day) for 4 weeks were studied. SPM in synovial fluid and plasma were
measured by liquid chromatography-tandem mass spectrometry included 18-hydroxyeicosapentaenoic acid (18-HEPE), the precursor of the E-series SPM (RvE1, RvE2, RvE3, 18R-RvE3), and 17-hydroxydocosahexaenoic acid (17-HDHA), the precursor of the D-series SPM (RvD1, 17R-RvD1, RvD2). Other SPM included protectin D1 (PD1), 10S,17S-dihydroxydocosahexaenoic acid (10,17S-DHDHA), maresin-1 (MaR-1) and 14-hydroxydocosahexaenoic acid (14-HDHA) derived from docosahexaenoic acid (DHA).

RESULTS: E- and D-series SPM and the precursors 18-HEPE and 17-HDHA were present in synovial fluid and plasma of the patients with inflammatory arthritis. Plasma SPM were negatively related to erythrocyte sedimentation rate in arthritis patients (P<0.01) and synovial fluid RvE2 was negatively associated with pain score (P=0.02). Conversion from 18-HEPE and 17-HDHA to E- and D-series SPM was greater in synovial fluid (P<0.01). Most plasma SPM in arthritis patients were elevated (P<0.05) compared with healthy volunteers, and conversion to E- and D-series SPM was greater (P<0.01).

CONCLUSIONS: SPM are present in chronic knee effusions and although the levels are lower than in plasma, the association between synovial fluid RvE2 and reduced pain scores suggests that synthesis of SPM at the site of inflammation is a relevant mechanism by which n-3FA alleviate the symptoms of arthritis.

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Differences in Frame Geometry Between Balloon-expandable and Self-expanding Transcatheter Heart Valves and Association With Aortic Regurgitation.

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INTRODUCTION AND OBJECTIVES: Patient- and procedure-related factors are known to be associated with aortic regurgitation after transcatheter aortic valve implantation. Nevertheless, this entity may also be caused by a specific device-host interaction due to the biomechanical properties of the valves, independently of clinical factors. We sought to elucidate the role of frame geometry in the occurrence of aortic regurgitation after Medtronic CoreValve and Edwards SAPIEN valve implantation.

METHODS: We conducted an observational study encompassing 134 patients undergoing transcatheter aortic valve implantation with the Medtronic CoreValve and Edwards SAPIEN valve. Frame analysis was performed at 3 predefined levels of both valves by rotational angiography using dedicated motion compensation software. A distinction was made between patients with no-to-mild and moderate-to-severe aortic regurgitation by echocardiography.

RESULTS: Baseline characteristics were similar between the 2 valves. Despite greater use of predilation in the CoreValve (95.2% vs 82.0%; P= 0.012), more oversizing (perimeter, 114+/-7% vs 103+/-7%; P<.001), and the same depth of implantation (noncoronary sinus, 7+/-4 vs 8+/-2mm; left coronary sinus, 8+/-4 vs 8+/-2mm), it was less expanded and more eccentric than the Edwards SAPIEN (83+/-7% vs 92+/-4%; P<.001 and 82+/-8% vs 95+/-3%; P<.001, respectively) and when eccentricity was adjusted for the patient’s annulus eccentricity (4+/-13% vs 21+/-11%; P<.001). Eccentricity and adjusted eccentricity were associated with moderate-to-severe aortic regurgitation.

CONCLUSIONS: Independently of patient- and procedure-related factors, there is a device-specific device-host interaction that explains aortic regurgitation after transcatheter aortic valve implantation.

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Red blood cell transfusion is associated with further bleeding and fresh-frozen plasma with mortality in nonvariceal upper gastrointestinal bleeding.

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BACKGROUND: Blood products are commonly transfused for patients with nonvariceal upper gastrointestinal bleeding (NVUGIB). While concerns exist about further bleeding and mortality in subsets of patients receiving red blood cell (RBC) transfusion, the impact of non-RBC blood products has not previously been systematically investigated. The aim of the study was to investigate the associations between blood products transfusion, further bleeding, and mortality after acute NVUGIB.

STUDY DESIGN AND METHODS: A retrospective cohort study examined further bleeding and 30-day and 1-year mortality in adult patients who underwent gastroscopy for suspected acute NVUGIB between 2008 and 2010 in three tertiary hospitals in Western Australia. Survival analysis was performed.

RESULTS: A total of 2228 adults (63% male) with 2360 hospital admissions for NVUGIB met the inclusion criteria. Median age at presentation was 70 years (range, 19-99 years). Thirty-day mortality was 4.9% and 1-year mortality was 13.9%. Transfusion of 4 or more units of RBCs was associated with greater than 10 times the odds of further bleeding in patients with a hemoglobin level of more than 90 g/L (odds ratio, 11.9; 95% confidence interval [CI], 3.1-45.7; p < 0.001), but was not associated with mortality. Administration of 5 or more units of fresh-frozen plasma (FFP) was associated with increased 30-day (hazard ratio, 2.8; 95% CI, 1.3-5.9; p = 0.008) and 1-year (hazard ratio, 2.6; 95% CI, 1.3-5.0; p = 0.005) mortality after adjusting for coagulopathy, comorbidity, Rockall score, and other covariates.

CONCLUSION: In this large, multicenter study of NVUGIB, RBC transfusion was associated with further bleeding but not mortality, while FFP transfusion was associated with increased mortality in a subset of patients.
OBJECTIVE: To compare the biomechanical properties of dual bone fixation (DBF) constructs to radial locking compression plating (LCP) in an ex vivo feline antebrachial fracture gap model.

STUDY DESIGN: Ex vivo study.

SAMPLE POPULATION: Cadaveric feline antebrachii (n=12 pairs).

METHODS: Antebrachii were radiographed to confirm normal skeletal appearance and maturity. After creation of a 5 mm radial and ulnar ostectomy, each antebrachium received 1 of 3 constructs using an incomplete randomized block design (n=8 per group). All groups received a 10 hole 2.0 mm radial LCP. DBF groups received either a 1.2 mm ulnar intramedullary pin (LCP with pin) or an 8 hole 2.0 mm ulnar LCP in addition to the radial LCP. Biomechanical testing was performed in axial compression and caudocranial and mediolateral 4-point bending before destruction in axial compression.

RESULTS: DBF constructs (LCP with pin and dual LCP) were significantly stiffer than radial LCP alone in axial compression and caudocranial bending. There were no differences between LCP with pin and dual LCP constructs in axial compression and caudocranial bending or between any constructs in mediolateral bending. Failure load was significantly greater for dual LCP than LCP with pin or LCP alone constructs. Failure loads were not different between LCP with pin and LCP alone.

CONCLUSION: DBF significantly increased construct stiffness and strength. Given the high complication rate reported in cat antebrachial fractures when only the radius is stabilized, surgeons should consider DBF.

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Trends in incidence and prevalence of hospitalization for atrial fibrillation and associated mortality in Western Australia, 1995-2010.

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OBJECTIVE: Hospitalization for atrial fibrillation (AF) is a large and growing public health problem. We examined current trends in the incidence, prevalence, and associated mortality of first-ever hospitalization for AF.

METHODS: Linked hospital admission data were used to identify all Western Australia residents aged 35-84 years with prevalent AF and incident (first-ever) hospitalization for AF as a principal or secondary diagnosis during 1995-2010.

RESULTS: There were 57,552 incident hospitalizations, mean age 69.8 years, with 41.4% women. Over the calendar periods, age- and sex-standardized incidence of hospitalization for AF as any diagnosis declined annually by 1.1% (95% CI; 0.93, 1.29), while incident AF as a principal diagnosis increased annually by 1.2% (95% CI; 0.84, 1.50). Incident AF hospitalization was higher among men than women, and 15-fold higher in the 75-84 compared with 35-64 year age group. The age- and sex-standardized prevalence of AF increased annually by 2.0% (95% CI; 1.88, 2.03) over the same period. Comorbidity trends were mixed with diabetes and valvular heart disease increasing, and hypertension, coronary artery disease, heart failure, cerebrovascular disease, and chronic kidney disease decreasing. The 1-year all-cause mortality after incident AF hospitalization declined from 17.6% to 14.6% (trend P<0.001), with an adjusted hazard ratio of 0.86 (95% CI; 0.81, 0.91).

CONCLUSION: This contemporary study shows that incident AF hospitalization is not increasing except for AF as a principal diagnosis, while population prevalence of hospitalized AF has risen substantially. The high 1-year mortality following incident AF hospitalization has improved only modestly over the recent period.

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Chronic HIV-1 Infection Induces B-Cell Dysfunction That Is Incompletely Resolved by Long-Term Antiretroviral Therapy.

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OBJECTIVES: To determine the effect of long-term antiretroviral therapy (ART) on HIV-1-induced B-cell dysfunction.

DESIGN: Comparative study of ART-naive and ART-treated HIV-infected patients with non-HIV controls.

METHODS: B-cell dysfunction was examined in patients with HIV-1 infection (n = 30) who had received ART for a median time of 9.25 years (range: 1.3-21.7) by assessing proportions of CD21 B cells (a marker of B-cell exhaustion) and proportions of tumor necrosis factor-related apoptosis-inducing ligand or B and T lymphocyte attenuator B cells, and serum levels of immunoglobulin free light chains (markers of B-cell hyperactivation). The association of these markers with serum levels of IgG1 and IgG2, and production of IgG antibodies after vaccination with pneumococcal polysaccharides were also examined. ART-naive patients with HIV (n = 20) and controls (n = 20) were also assessed for comparison.

RESULTS: ART-treated patients had increased proportions of CD21 and tumor necrosis factor-related apoptosis-inducing ligand B cells and, furthermore, although proportions of B and T lymphocyte attenuator B cells were not significantly different from controls, they correlated negatively with CD21 B cells. Proportions of CD21 B cells also correlated negatively with current CD4 T-cell counts. In ART-naive patients with HIV, free light chains correlated with CD21 B cells and IgG1, but not IgG2. Serum IgG2:IgG1 ratios were substantially lower than normal in patients with HIV and did not resolve on ART. In ART-treated patients, IgG antibody responses to pneumococcal polysaccharides after vaccination were not associated with markers of B-cell dysfunction.

CONCLUSIONS: B-cell dysfunction persists in patients with HIV receiving long-term ART. The causes and consequences of this require further investigation.

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Regulation of sarcoma cell migration, invasion and invadopodia formation by AFAP1L1 through a phosphotyrosine-dependent pathway.

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Regulation of sarcoma cell migration, invasion and invadopodia formation by AFAP1L1 through a phosphotyrosine-dependent pathway.

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Invasion and metastasis are controlled by the invadopodia, which delivers matrix-degrading enzymes to the invasion interface permitting cancer cell penetration and spread into healthy tissue. We have identified a novel pathway that directs Lyn/Src family tyrosine kinase signals to the invadopodia to regulate sarcoma cell invasion via the molecule AFAP-1-like-1 (AFAP1L1), a new member of the AFAP (actin filament-associated protein) family. We show that AFAP1L1 can transform cells, promote migration and co-expression with active Lyn profoundly influences cell morphology and movement. AFAP1L1 intersects several invadopodia pathway components through its multiple domains and motifs, including the following (i) pleckstrin homology domains that bind phospholipids generated at the plasma membrane by phosphoinositide 3-kinase, (ii) a direct filamentous-actin binding domain and (iii) phospho-tyrosine motifs (pY136 and pY566) that specifically bind Vav2 and Nck2 SH2 domains, respectively. These phosphotyrosine motifs are essential for AFAP1L1-mediated cytoskeleton regulation. Through its interaction with Vav2, AFAP1L1 regulates Rac activity and downstream control of PAK1/2/3 (p21-activated kinases) phosphorylation of myosin light chain (MLC) kinase and MLC2. AFAP1L1 interaction with Nck2 recruits actin-nucleating complexes. Significantly, in osteosarcoma cell lines, knockdown of AFAP1L1 inhibits phosphorylated MLC2 recruitment to filamentous-actin structures, disrupts invadopodia formation, cell attachment, migration and invasion. These data define a novel pathway that directs Lyn/Src family tyrosine kinase signals to sarcoma cell invadopodia through specific recruitment of Vav2 and Nck2 to phosphorylated AFAP1L1, to control cell migration and invasion.

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Quality of health information on the Internet for prostate cancer.

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Introduction and Objectives: To compare the quality of health information on the Internet for keywords related to prostate cancer and to compare the source of sponsorship in these websites. Methods: Health On the Net (HON) Foundation principles were utilised to determine quality information. We used a search engine (www.google.com) on an Internet browser equipped with an automated HON toolbar function. Ten keywords related to prostate cancer were searched for, and the first 150 websites in English were assessed against the HON principles and the source of sponsorship determined. Results: A total of 1500 websites were analysed. Six out of 10 search terms had <10% of HON-accredited websites (Table 1). Proportion of HON-accredited websites for individual search terms range between 3.3% (robotic prostatectomy) and 15.3% (prostate cancer and prostate specific antigen). The first 50 websites searched were less likely to be HON-negative compared to websites 51-100 (OR 2.041; 95% CI 1.359-3.066) and 101-150 (OR 3.215; 95% CI 2.025-5.106). The three main website sponsors were from educational/journal sources (30.33%), followed by physician/surgeon (27.40%) and commercial sources (27.33%). Conclusions: A majority of health information on prostate cancer websites were not validated. More than one-quarter of websites in this study have commercial sponsorship. Doctors should recognise the need to develop informative, ethical and reliable health websites and direct their patients to them.

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Local anaesthetic transperineal biopsy correlates strongly with final prostatectomy histology.
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Introduction and Objectives: Transperineal (TP) and transrectal(TRUS) biopsies are two methods used to diagnose prostate cancer. TP biopsies have two main advantages over TRUS biopsies; a reduced incidence of post-biopsy sepsis(1), and an improved detection rate for anterior tumours(2). The main disadvantage of TP biopsies is that they are usually performed under general anaesthesia. Performing TP biopsies under local anaesthesia solves this problem; however fewer biopsies may be taken and the pathological reliability of this technique has not been well reported. The objective of this study was to assess the correlation between TP biopsies performed under local anaesthesia and radical prostatectomy histology. Method: All TP biopsies were performed by a single experienced radiologist under rectal ultrasound guidance. After instillation of approximately 20 ml of 0.7% lignocaine local anaesthetic, 11-13 core biopsies were taken circumferentially from around the prostate with targeting of suspicious areas. Biopsies were taken by passing the biopsy needle through the lumen of a larger static needle using aseptic technique. Retrospective Analysis was conducted of 100 men who underwent TP biopsies and subsequent radical prostatectomy. TP prostatectomy results were compared to determine the accuracy of TP biopsies taken under local anaesthesia. Results: Hundred patients with a mean age of 73 were evaluated. Median PSA was 7.5 (range 1.4-18). Median positive biopsy cores was 4 (range 1-10). Gleason score was upgraded between TP biopsies and radical prostatectomy in 28% of patients, and downgraded in 8% of patients. The laterality of malignant tissue correlated in 90% of samples. No procedure was abandoned due to pain Conclusions: Transperineal biopsy is feasible as an outpatient procedure under local anaesthetic. It is safer in terms of anaesthetic and infection risk, and has economic benefits in avoiding theatre lists, day case admissions and general anaesthetic. The final biopsy grade and laterality of disease corresponded strongly with the final prostatectomy histology (3,4). It has advantages in terms of sepsis rates and sampling of the prostate and given these distinct advantages, this approach should be considered for more widespread implementation.

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Quality of health information on the internet for urolithiasis.
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Introduction and Objectives: To compare the quality of health information on the Internet for keywords related to urolithiasis, to assess for difference in information quality across four main Western languages and to compare the source of sponsorship in these websites.

Methods: Health On the Net (HON) Foundation principles were utilised to determine quality information.1 We used a search engine (www.google.com) on an Internet browser equipped with an automated HON toolbar function. Fifteen keywords related to urolithiasis were searched for, and the first 150 websites in each language were assessed against the HON principles and the source of sponsorship determined.

Results: A total of 9000 websites were analysed. Eleven out of 15 search terms had <10% of HON-accredited websites. Proportion of HON-accredited websites for individual search terms range between 2.5% (litholapaxy) and 12.0% (renal colic). The first 50 websites searched were less likely to be HON-negative compared to websites 51-100 (OR 2.160; 95% CI 1.794-2.602) and 101-150 (OR 2.696; 95% CI 2.211-3.287). French websites searched were less likely to be HON-negative (OR 0.596, 95% CI 0.491-0.724) compared to English websites whereas German (OR 2.766, 95% CI 2.097-3.650) and Spanish (OR 1.326; 95% CI 1.058-1.661) websites were more likely to be HON-negative. The three main website sponsors were from government/educational sources (40.22%), followed by commercial (29.87%) and physician/surgeon sources (18.58%).

Conclusions: Health information on most urolithiasis websites was not validated. Nearly one-third of websites in this study have commercial sponsorship. Doctors should recognise the need to develop informative, ethical and reliable health websites and direct their patients to them.

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Characteristics of various categories of controlled donors after circulatory death do not affect outcome after lung transplantation; an analysis of ISHLT DCD registry data.


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Purpose: Lung transplantation (LTX) from donors after circulatory death (DCD) has become routine with reported similar survival compared to brain-dead donor (BDD). However, it remains unknown whether possible differences in donor and recipient characteristics between various DCD categories affect outcome. Methods: Between 01/2003 and 07/2015, 516 LTX from 12 participating institutions were reported to the ISHLT DCD Registry. No uncontrolled DCDs (I and II) have yet been recorded. Ten cases after euthanasia (DCD-V) were excluded from analysis, leaving 486 DCD-III (withdrawal from life support) and 20 DCD-IV (unexpected cardiac arrest in BDD) LTX recipients. Results: Donor age tended to be higher in DCD-III. Ante-mortem heparin was administered more frequently while steroids were given less often in DCD-IV. Time interval from cardiac arrest to cold flush was longer in DCD-III. Indication for LTX varied significantly. Total ischemic time and length of hospital stay were similar. 1, 3, and 5-year survival was 89.2%, 71.2%, 60.3% vs 94.7%, 73.7%, 49.1% in DCD-III and DCD-IV recipients, respectively (p= 0.95, log rank). Conclusion: DCD-III is the most frequent category (94%) in the Registry. Despite older donor age, less heparinization, and longer warm ischemic time interval from arrest to flush in DCD-III, early and late outcome were comparable. DCD-III do not carry an increased risk for successful LTx compared to DCD-IV. (Table presented).
Donation after circulatory death (DCD) versus donation after brain death (DBD): Contrasting donor and recipient characteristics in the ISHLT DCD lung transplant (LTX) registry.

Purpose: The features and outcomes of DCD LTx have been previously described in small case series. The ISHLT DCD LTx Registry is an international, multi-center collaboration between 12 LTx centers, established in 2012. Methods: This report compared donor and recipient characteristics and survival outcomes of DCD Category 3 versus contemporaneous DBD LTx utilizing data obtained from the ISHLT DCD Registry, using Chi-square or Kruskal Wallis analyses as appropriate. Results: Between 2005 and 2015, 483 DCD LTx were compared with 4750 DBD LTx reported from the same institutions over the same time period (Table 1). DCD LTx donors were older, anoxia was a more frequent cause of cause of donor death, while CVA and trauma were less frequent. DCD LTx were more commonly bilateral. Recipient lung disease diagnosis was similar between the 2 groups. Importantly, survival of DCD versus DBD LTx was not different at 1yr (89 vs 88%), 3yr (71 vs 73%) or 5yr (60 vs 63%) (p= 0.57). Conclusion: Our analysis suggests that the intermediate-term DCD LTx survival rates are excellent. The ISHLT DCD LTx Registry confirms that controlled DCD is a valuable lung donor source and provides vital pooled data enabling further study of DCD LTx outcomes. (Table Presented).

Warm ischemic time (WIT) measurements do not correlate with early lung allograft function: Analysis from the Australian donation after circulatory death (DCD) lung transplant (LTX) collaborative.

Purpose: The impact and clinical definitions of agonal warm ischemia in controlled DCD LTx are not well described. The lung has unique properties that may protect it from ischemic damage. The relative importance of monitoring agonal, hemodynamic and subsequent ventilatory parameters during the DCD donation process remains unclear. The limits of LTx DCD WIT have been implied from other solid organ DCD transplants. Methods: Since 2006, the Australian DCD LTx Collaborative has recorded DCD donor and recipient data from all 4 LTx centers. WIT measures have been defined as intervals (mean & SD) between multiple time points: Withdrawal (WD), BP systolic 50mmHg (BPs50), asystole (BP0), donor lung ventilation (Vent) and pulmonary artery flush (PAfl). Early allograft function is reported as the PO2/FiO2 value closest to 24hrs post-LTx (PF24). WIT measures were correlated with PF24 using Pearsons Coefficient. Post BP0 stand-off time (2-10mins) and onset of ventilation (2-15mins) varied according to local DCD guidelines and EVLP was not utilized in this cohort. Results: Between May 2006-Oct 2015, WIT data on 227 DCD LTx were reported and analyzed. (see Table 1). Mean PF24 was 314+/− 87.9 and there were no significant WIT correlations with PF24 (reported as R2, p= ns for all WIT time intervals). Conclusion: Surprisingly, conventional agonal,
hemodynamic and ventilatory measures of warm ischemia do not correlate with early LTx allograft function in our large DCD LTx cohort. Either the clinical timings recorded during controlled LTx DCD donation are significantly short of the tolerable WIT limits, or these parameters do not truly reflect the risk of allograft ischemic damage. These data cautiously encourage the extension of WIT limits for clinical DCD LTx. (Table Presented).

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Results of a first-in-man study of mesenchymal stem cell therapy for bronchiolitis obliterans syndrome.

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Purpose: Bone marrow derived mesenchymal stem cells (MSC) represent an attractive cellular therapeutic target given their immunosuppressive and tolerogenic properties and relative immune privilege. Preclinical studies and human trials in graft versus host disease suggest potential efficacy in bronchiolitis obliterans syndrome (BOS). The purpose of this dual centre, phase 1 study (www.clinicaltrials.gov NCT01175655) was to explore the feasibility and safety of delivery of allogeneic MSC in patients with BOS complicating lung transplantation. Methods: MSC from unrelated donors were isolated, expanded and cryopreserved in DMSO according to GMP principles in an accredited manufacturing facility. Patients had BOS grade >2 or 1 with risk factors for rapid progression. Patients with >3 infective exacerbations in the preceding year or a history of CMV pneumonitis were excluded. MSC (2 x106 cells/kg patient weight) were infused via a peripheral vein twice weekly for two weeks, with 52 weeks follow-up. Results: 10 Patients (5 male, 4 CF, 2 COPD, 2 IPF, 8 BSSLTx, median (IQR) age 40 (30-59) years, 3 BOS2, 7 BOS3) participated. MSC treatment was well tolerated with all patients receiving the full dosing schedule without any procedure-related serious adverse events. Most patients experienced stabilisation of lung function (Figure). Two patients died at 152 and 270 days post-MSC treatment, both from progressive BOS. Conclusion: Infusion of allogeneic bone marrow-derived MSC is feasible and appears safe in patients with BOS. As a result of this study, the Australian Lung Transplant Collaborative will be commencing a phase 2 randomised controlled trial to assess the efficacy of MSC therapy in patients with new-onset BOS (total n= 82) in 2016. (Figure Presented).

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Realworld evaluation of viekira pak (ritonavir boosted paritaprevir, ombitasvir and dasabuvir +/-ribavirin) in HCV genotype 1 targeting advanced liver disease (the rev1tal study).

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Background and Aims: Combination therapy with ritonavir boosted paritaprevir, ombitasvir and dasabuvir (PrOD) +/-ribavirin in phase III registration trials has been shown to be safe, well tolerated and to have excellent efficacy with SVR12 rates >95% in subjects with HCV genotype 1 infection including those with cirrhosis. However, data is limited
on whether the excellent safety and efficacy profile of PrOD therapy in subjects with cirrhosis translates into real-world clinical practice. The aim of this study was to determine the efficacy and safety of treatment with PrOD in patients with genotype 1 hepatitis C and advanced liver disease treated in a real-world setting. Methods: Between October 2014 and July 2015, a compassionate access program supported by AbbVie Pty Ltd was conducted in Australia across 47 viral hepatitis treatment centers most of which were affiliated with the Australian Liver Association Clinical Research Network (ALA CRN). Preliminary data is presented in this abstract although data collection is ongoing. Patients were included if they received at least one dose of PrOD. The primary end-points were SVR12 (defined as HCV viral load below level of quantification at 12 weeks post-treatment) and drug discontinuation rates due to adverse events. Frequency and nature of adverse events were reported by local physicians with particular focus on death, hepatic decompensation and grade 3/4 elevations in serum bilirubin and ALT levels. Results: 623 subjects with HCV genotype 1 (n = 582) or 4 (n = 41) received treatment with PrOD. The top 20 ALA CRN treating sites recruited 500 patients. Patients with genotype 1 were predominantly cirrhotic (82%) and subgenotype 1a (67%). Baseline features of the fully characterized patients to date (n = 172) are shown in Table 1. In this interim analysis of 172 patients (82.6% cirrhotic, 10.3% CPB, 70.7% G1a) the overall SVR12 rate was 93.8%. Early cessation of therapy occurred in 4.5% of patients. Hepatic decompensation resulting in early discontinuation occurred infrequently (<1%). Elevations in bilirubin were common (Table 1). In 14% of patients there was an increase of >51 mumol/L from baseline. Conclusions: In a real-world setting, treatment with PrOD in genotype 1 HCV infection appears safe and achieves high SVR12 rates including those with cirrhosis. Hyperbilirubinaemia is a frequent on-treatment finding but hepatic decompensation resulting in early cessation of therapy appears rare. (Table Presented).

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Postherpetic neuralgia How to prevent it, how to treat it.

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Postherpetic neuralgia (PHN) is a common late complication of acute shingles. This neuropathic pain is often severe and accompanied by sensitivity to touch. It significantly impairs the quality of life of affected patients. The difficulties in treating PHN justify preventive measures such as vaccination and early aggressive management of the acute shingles episode. Copyright © MedicineToday 2016.

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Structural abnormalities do not result in reduced exercise capacity in preterm children.

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Introduction/Aim: Children born preterm have been shown to have a reduced exercise capacity and structural lung disease. The aim of this study was to identify the effect of structural lung disease on the exercise response in children aged 9-11, who were born preterm. Methods: Pre-term children (<32-week gestational age) performed spirometry, incremental treadmill exercise to volitional exhaustion and underwent a high resolution CT (HRCT) scan of the chest. Results: Children (n = 78) performed an exercise test and HRCT. AbnormalCTwas noted in 68 (87%) children. The most common abnormalitieswere linear subpleural triangular opacities (82%), decreased pulmonary attenuation on expiration (40%) and peribronchial thickening (38%). Peak V'O2 was not associated with any CT abnormality. The presence of sub pleural linear and triangular opacities was associated with an increased peak VE/VCO2 at peak
exercise. The presence of any other abnormality was not associated with any other exercise parameter. The extent of subpleural linear and triangular opacites was associated with increased VE/VO2 slope (P = 0.007). The extent of decreased pulmonary attenuation was associated with an increase in end inspiratory lung volume as a percentage of total lung capacity at peak exercise (P = 0.026). No other CT outcomes were significantly associated with changes in exercise response. The presence of sub-pleural linear triangular opacities was associated with increased ventilatory inefficiency.

Conclusion: In this study, structural lung disease was common in preterm children. While these abnormalities did not contribute to a reduced exercise response, the presence of sub-pleural linear triangular opacities was associated with increased ventilatory inefficiency.

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**Community acquired pneumonia requiring in hospital management - A regional experience.**

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Introduction/Aim: Community acquired pneumonia (CAP) is the commonest infection requiring hospital admission. Early empirical antibiotic therapy based on local epidemiology and disease severity improves patient outcomes. We aim to describe patient characteristics and assess the adherence to national therapeutic guidelines on initial antibiotic selection for CAP. Method: We retrospectively surveyed medical records of all patients admitted to Armadale Kelmscott Memorial Hospital with CAP from 1st August to 31st October 2014. We extracted data on demographic characteristics, evaluation of disease severity on admission, initial antibiotic treatment and length of stay. CORP score was recalculated for each patient based on admission documentation to assess adherence to antibiotic guidelines. Results: Sixty-one patients (51% men, mean age 67 years) with CAP were identified. Pneumonia severity score was documented in only 10 patients on admission. However, based on calculated CORP score, 57 patients (93%) had moderate and four (7%) had severe pneumonia. Forty-nine patients with moderate and all four patients with severe pneumonia were treated according to guidelines. Commonest protocol violation in patients with moderate CAP was using intravenous Ceftriaxone and Azithromycin instead of intravenous Benzylpenicillin and Doxycycline. When protocol specific treatment was given, the average length of hospital stay in patients with moderate CAP was 3.9 days [95% CI 3.5 to 4.3] compared to 4.1 [95% CI 3.6 to 4.6] in patients who received intravenous Ceftriaxone and Azithromycin. Conclusion: We identified deficiencies in following national therapeutic guidelines in treatment of CAP at Armadale Kelmscott Memorial Hospital. Use of antibiotics specified for more severe CAP in patients with moderate CAP does not appear to have an additional benefit. Prescriber education and continuous encouragement is required to improve adherence.

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**Infective exacerbation of bronchiectasis due to Pasteurella multocida.**

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Case Report: A 25 year old Burmese man presented with a 3 year history of productive cough, mild hemoptysis and wheeze. He denied shortness of breath, fever, night sweats, weight loss and nasal symptoms. He described recurrent childhood chest infections but had no history of whooping cough, measles or tuberculosis. He was not on any medication, had never smoked and did not have any contact with animals. Chest auscultation revealed coarse bi-basal crackles. There was no clubbing or lymphadenopathy. Full blood picture, electrolytes, renal function, liver function test and vasculitic screen were normal. Total IgE was 737 ku/L but Aspergillus-specific IgE was not elevated. Pasteurella...
multocida was cultured repeatedly from expectorated sputum. CT chest showed significant widespread bronchial wall thickening and cystic bronchiectasis. Treatment with amoxicillin 1g BD for four weeks led to significant improvement of cough and wheeze and complete resolution of hemoptysis. Discussion: Pasteurella multocida is a Gram-negative cocacobacillus commonly found in the oral flora of domestic animals and livestock. It is often associated with soft tissue infections following animal bites. Pulmonary involvement can occur in the elderly, patients with impaired host defences and those with underlying lung disease. The spectrum of pulmonary involvement includes airway colonization, bronchitis, pneumonia, lung abscess and empyema. Treatment with penicillins is usually effective.

Conclusion: We report an infective exacerbation of bronchiectasis caused by Pasteurella multocida, an uncommon respiratory pathogen associated with animals which usually responds favourably to treatment.

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Skin cancer prevalence in lung transplant recipients in Western Australia.
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Introduction/Aim: Skin cancers are the most common malignancies in solid organ transplantation.1 A Swedish study in 2013 reported a total number of 251 skin cancers in 6,227 patient years (rate of 0.04 cancers/patient year) in a cohort of 1,012 heart and/or lung transplant recipients. There was a calculated 83-fold increase in total number of skin cancers compared to the general population.2 Our aim was to calculate the rate and point prevalence of skin cancer in lung transplant recipients in Western Australia, which we hypothesised would be significantly higher given the climate here. Methods: We conducted a retrospective cohort study on lung transplant recipients aged > 18 years who were followed up at the state lung transplantation centre as at 31st December 2014. Patients who had not been followed up by our service for 12 months or had not survived past 12 months posttransplant were excluded. Data was collected from medical records and patient databases. Ethics approval was granted by the institution’s Human Research Ethics Committee. Results: 105 patients and 110 transplants (5 redo lung transplants) were included in the data analysis. There were 72 bilateral lung transplants, 28 single lung transplants and 10 heart-lung transplants. The median age at time of transplant was 48 years (mean = 44.6 years). We identified a total of 314 individual skin cancers over 614 patient years (rate of 0.51 cancers/patient year). 46 out of the 105 (43.8%) patients had at least one skin cancer. Of these 46, 29 (63.0%) had at least 3 skin cancers. The point prevalence (percentage of patients living with a current/previous diagnosis of skin cancer) was 39.4%. Median time to first cancer was 21 months (mean = 40 months). Conclusion: Skin cancers occur frequently in lung transplant recipients in Western Australia. Further research on risk factors and preventative interventions is indicated.
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Safe discharge of acute asthma patients: A clinical audit.
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Introduction/Aim: Asthma is a common disease that affects almost 10% of all Australians. There remains significant mortality, with 449 deaths in Australia in 2008 (2 per 10000 cases).1 Data from the Centre of Disease on Control and Prevention shows similar mortality rates from the United States.2 We aimed to assess discharge planning of acute asthma patients in accordance with Australian and International guidelines. We set a minimum standard target for the audit parameters at 70%, with an ideal target of 90%. Methods: We conducted a retrospective audit on patients admitted to Royal Perth Hospital with a diagnosis of acute asthma over 12 months. Data were collected from medical records and electronic patient databases. Our audit parameters included: 1) Documentation of peak expiratory flow
during inpatient stay 2) Receiving of asthma education 3) Review of inhaler technique 4) Arrangement of appropriate follow-up. These parameters were retrieved from the Australian Asthma (2014), National Institute for health and Care Excellence (NICE) (2013), British Thoracic Society (2014) and National Heart, Lung and Blood Institute (NHLBI) guidelines (2007). Results: Results for 108 patients were analysed. The median and mean length of stay were 3 days and 3.56 days respectively. Of the 108 patients, 36 were current smokers (33.3%) and 13 were ex-smokers. 69 patients (63.9%) reported adherence to prescribed preventer therapy. During their admission, 63 patients (58.3%) had documented evidence of peak expiratory flow measurement. 53 patients (49.1%) received asthma education. 53 patients (49.1%) had documentation that inhaler technique was checked. 87 (80.5%) of patients had follow-up arranged - of these, 24.1% had GP follow-up and 75.9% specialist follow-up. Conclusion: Our findings show that discharge safety audit parameters have not met our pre-set minimum targets, with the exception of arrangement of appropriate follow-up. We plan to perform systems analysis to investigate reasons behind this, and repeat the audit after implementation of practice-improving change.

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Correlation of low dose chest CT findings with physiologic measures of asbestosis.
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Introduction/Aim: Low dose computed tomography (LDCT) technology enables image acquisition at very low radiation doses. LDCT is increasingly being used in asbestos-exposed populations, but the correlation between LDCT-detected parenchymal lung changes and pulmonary function abnormalities is not known. The aim of this study was to determine the relationship between LDCT-detected interstitial lung disease (ILD) and measures of pulmonary function. Methods: LDCT readings and pulmonary function tests of former miners and township residents exposed to blue asbestos at Wittenoom were analysed. Two thoracic radiologists independently categorized LDCT ILD appearances as absent (score 0), probable (1) or definite (2) without knowledge of asbestos exposure or level of lung function. Inter-observer agreement was evaluated with Cohen's kappa test. Pulmonary function measures included spirometry and diffusing capacity to carbon monoxide (DLCO). The correlation between variables was determined by Spearman's correlation coefficient. Results: One hundred forty-three participants (130 (93%) males) of median (IQR) age 73.0 (69.8-76.9) years were included. Mean cumulative asbestos exposure was 11.5 +/- 29.9 (SD) fibres/mL/year, and mean DLCO was 21.6 +/- 6.5 (SD) mL/min/mmHg. Mean effective radiation dose estimate was 0.8 (range 0.3-1.8) mSv. 63/143 (44.1%) of participants had probable or definite ILD scores. Inter-observer agreement was high (k = 0.613, p < 0.001). There was a statistically significant correlation between ILD score and both cumulative asbestos exposure (r = 0.194, p = 0.01) and DLCO (r = -0.335, p < 0.0001) but no correlation between ILD score and FEV1/FVC ratio (r = 0.048, p = 0.571). Conclusions: Changes consistent with interstitial fibrosis on LDCT correlate well with cumulative asbestos exposure and corresponding reductions in gas transfer, similar to HRCT. In asbestos-exposed populations, LDCT may be used in lieu of HRCT to reliably detect asbestosis.
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Baseline pulmonary function test predicts survival: Analysis from the Australian IPF registry.
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal lung disease characterized by progressive loss of lung function. The natural history for an individual with IPF is variable. We aimed to identify baseline physiological variables predictive of disease progression and/or mortality in Australian IPF patients. Methods: The Australian IPF Registry (AIPFR) recruits IPF patients across Australia. State-based co-ordinators collate patient questionnaires, physiological data and vital status every 6 months, providing a real world, longitudinal cohort. Disease progression is defined as a sustained relative fall in FVC > 10% or DLCO > 15% from baseline. The predictive capacity of baseline variables for mortality and disease progression was assessed by Cox survival analysis. Results: There were 625 participants (68.8% male; mean age 71.7 ± 9.2 years) enrolled in the AIPFR in September 2015. Most had a history of smoking (71.2%), and a significant number reported co-morbidities including COPD (30.1%) and GORD (35.5%). Most participants had mild to moderate impairment with FVC 80.6 ± 21.4% and DLco 48.6 ± 16.7%. On univariate Cox regression, the following variables predicted mortality: age, BMI, smoking status, FVC%, DLco%, composite physiological index (CPI) and 6-min walk distance. On multivariate analysis, FVC (HR 0.09; p < 0.0001; 95% CI 0.02-0.34), DLco% (HR 0.01; p < 0.0001; 95% CI 0.001-0.07), age (HR 1.04; p = 0.001; 95% CI 1.02-1.08) and BMI (HR 0.95; p = 0.04; 95% CI 0.90-0.998) independently predicted mortality. Progression free survival was independently associated with FVC and DLco, but not with age. Patients with mild disease (FVC > 80%) had a decreased risk of death or progression (HR 1.9; p < 0.0001; 95% CI 1.47-2.48). Conclusions: Mortality and disease progression are associated with lower baseline FVC and DLco in Australian IPF patients. While older age was a significant predictor of mortality, it was not significant for progression free survival suggesting that older participants may die from causes other than IPF.

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DOI:http://dx.doi.org/10.1111/resp.12754


Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel: Systematic review and meta-analysis of individual patient data.


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Prior studies have shown an association between high on-clopidogrel platelet reactivity (PR) and the risk of major adverse cardiovascular events (MACE). However, large intervention trials on PR-tailored treatments have been neutral.
The role and usefulness of PR with regard to levels of cardiovascular risk are unclear. We undertook a systematic review and meta-analysis of individual patient data on MACE outcomes (acute coronary syndromes (ACS), ischaemic strokes, and vascular deaths) in relation to PR and its interaction with cardiovascular risk levels. PR was determined using ADP-induced light transmission aggregometry with a primary concentration of 20 micro M ADP. Thirteen prospective studies totaled 6,478 clopidogrel-treated patients who experienced 421 MACE (6.5 %) during a median follow-up of 12 months. The strength of the association between the risk of MACE and PR increased significantly (p=0.04) with the number of risk factors present (age > 75 years, ACS at inclusion, diabetes, and hypertension). No association was detected in patients with no risk factor (p=0.48). In patients presenting one risk factor, only high-PR was associated with an increased risk of MACE (HR 3.2, p=0.001). In patients presenting > 2 risk factors, the increase of risk started from medium-PR (medium-PR: HR=2.9, p=0.0004; high-PR: HR=3.7, p=0.0003). PR allowed the re-classification of 44 % of the total population to a different risk level for the outcome of MACE, mostly in intermediate or high risk patients. In conclusion, the magnitude of the association between PR and MACE risk is strongly dependent on the level of cardiovascular risk faced by patients on clopidogrel. Copyright © Schattauer 2016. PMID:610147440
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Do the generalised cognitive deficits observed in schizophrenia indicate a rapidly-ageing brain?
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Background and Objectives: The nature and pattern of cognitive deficits (CD) in schizophrenia and whether the deficits are generalised or domain specific continues to be debated vigorously. We ascertained the pattern of CD in schizophrenia using a novel statistical approach by comparing the similarity of cognitive profiles of patients and healthy individuals. Methods: In a consecutive sample of 78 patients with schizophrenia, performance on six cognitive domains (verbal memory, working memory, motor speed, processing speed, verbal fluency and executive functions) was measured using the Brief Assessment of Cognition in Schizophrenia (BACS). The similarity of cognitive profile between patients and two groups of healthy controls (age-matched and older adults who were in the age group of 70-79) was evaluated using a special purpose-built macro. Results: Cognitive performance profiles in various domains of patients with schizophrenia and age-matched controls were markedly similar in shape, but differed in the overall performance, with patients performing significantly below the healthy controls. However, when the cognitive profiles of patients with schizophrenia were compared to those of older adult controls, the profiles remained similar whilst the overall difference in performance vanished. Conclusions: Cognitive deficit in schizophrenia appears to be generalised. Resemblance of cognitive profiles between patients with schizophrenia and older adult controls provides some support for the accelerated ageing hypothesis of schizophrenia. Copyright © 2016, University of Zaragoza. All rights reserved. PMID:613155399
http://scielo.isciii.es/pdf/ejpen/v30n2/original05.pdf

Expanding the Caring Lens: Nursing and Medical Students Reflecting on Images of Older People.
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In changing higher education environments, health profession’s educators have been increasingly challenged to prepare future health professionals to care for aging populations. This article reports on an exploratory, mixed-method research study that used an innovative photo-elicitation technique and interprofessional small-group work in the classroom to enhance the reflective learning experience of medical and nursing students. Data were collected from pre- and postquestionnaires and focus groups to explore shifts in perceptions toward older persons following the reflective learning session. The qualitative data revealed how using visual images of older persons provides a valuable learning space for reflection. Students found meaning in their own learning by creating shared storylines that challenged their perceptions of older people and themselves as future health professionals. These data support the use of visual methodologies to enhance engagement, reflection, and challenge students to explore and deepen their understanding in gerontology.

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**Correlates of physical activity in people living with psychotic illness.**

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OBJECTIVE: In the light of the high prevalence of physical comorbidities in people with psychotic illness, there is a need to explore modifiable risk factors that may contribute to this disease burden. The benefits of physical activity to both physical and mental health have been well established. We aimed to examine the prevalence and correlates of physical activity in a national sample of adults living with psychotic illness.

METHODS: Physical activity was assessed in 1801 people using the International Physical Activity Questionnaire. Participants were dichotomised into low and moderate-high physical activity groups and associations between physical activity and a range of sociodemographic, clinical and physical comorbidity variables were examined using logistic regression.

RESULTS: More than half the participants were categorised in the moderate-high physical activity group with nearly half of the sample engaged in physical activity every day. There were significant associations between low physical activity and older age, unemployment, educational non-participation, antipsychotic medication use, social dysfunction, self-reported loneliness and obesity. However, there was no significant association between physical activity and sex, psychosis type, illness duration, physical comorbidity or negative symptoms.

CONCLUSION: The findings from this study may inform future interventions designed to increase physical activity in people with psychotic illness.


An international, multicenter, prospective, observational study of neutropenia in patients being treated with lenalidomide+dexamethasone for relapsed or relapsed/refractory multiple myeloma (RR-MM).

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Neutropenia is a well-known dose-limiting toxicity associated with lenalidomide plus dexamethasone treatment in patients with multiple myeloma; however, little is known about its management and associated outcomes in the real world setting. The present prospective, multicenter, observational study evaluated the incidence, management, and outcomes of grade 3/4 neutropenia in patients with relapsed or relapsed/refractory multiple myeloma who initiated treatment with lenalidomide plus dexamethasone. Of 198 patients, 62 (31%, 95% CI: 25, 38) experienced grade 3/4 neutropenia, and half of these patients experienced 3 or more events during the 12-month observational period. Grade 3/4 neutropenia occurred throughout lenalidomide treatment, with a median time to first event of 8.8 weeks (Q1, Q3: 5.9, 17.3). In a multivariate analysis, diagnosis of relapsed and refractory disease was associated with grade 3/4 neutropenia. Lenalidomide exposure reduction, use of G-CSF, unplanned hospitalization, and outpatient clinic visits were more common in patients who experienced grade 3/4 neutropenia than in those who did not. In conclusion, grade 3/4 neutropenia is a common toxicity and patients are at continued risk throughout treatment with lenalidomide and dexamethasone. Further efforts should be made to improve the recommendations for neutropenia...
Preeclampsia does not share common risk alleles in 9p21 with coronary artery disease and type 2 diabetes.

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INTRODUCTION: Preeclampsia is a common and partially genetic pregnancy complication characterized by hypertension and proteinuria. Association with cardiovascular disease and type 2 diabetes has been reported in 9p21 by several genome-wide association studies. It has been hypothesized that cardiometabolic diseases may share common etiology with preeclampsia.
MATERIALS AND METHODS: We tested association with the 9p21 region to preeclampsia in the Finnish population by genotyping 23 tagging single nucleotide polymorphisms (SNPs) in 15 extended preeclampsia families and in a nationwide cohort consisting of 281 cases and 349 matched controls. Replication was conducted in additional datasets.

RESULTS: Four SNPs (rs7044859, rs496892, rs564398 and rs7865618) showed nominal association (p<0.024 uncorrected) with preeclampsia in the case-control cohort. To increase power, we genotyped two SNPs in additional 388 cases and 341 controls from the Finnish Genetics of Preeclampsia Consortium (FINNPEC) cohort. Partial replication was also attempted in a UK cohort (237 cases and 199 controls) and in 74 preeclamptic families from Australia/New Zealand. We were unable to replicate the initial association in the extended Finnish dataset or in the two international cohorts.

CONCLUSIONS: Our study did not find evidence for the involvement of the 9p21 region in the risk of preeclampsia. Key Message Chromosome 9p21 is not associated with preeclampsia.

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Swelling, mechanical strength, and release properties of probucol microcapsules with and without a bile acid, and their potential oral delivery in diabetes.


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We have demonstrated a permeation-enhancing effect of deoxycholic acid (DCA), the bile acid, in diabetic rats. In this study, we designed DCA-based microcapsules for the oral delivery of the antilipidemic drug probucol (PB), which has potential antidiabetic effects. We aimed to further characterize these microcapsules and examine their pH-dependent release properties, as well as the effects of DCA on their stability and mechanical strength at various pH and temperature values. Using the polymer sodium alginate (SA), we prepared PB-SA (control) and PB-DCA-SA (test) microcapsules. The microencapsulation efficiency and production yield were also examined. The addition of DCA resulted in microcapsules with a greater density and with reduced swelling at a pH of 7.8 and at temperatures of 25°C and 37°C. The size, surface composition, production yield, and microencapsulation efficiency of the microcapsules remained similar after DCA addition. PB-SA microcapsules produced multiphasic PB release, while PB-DCA-SA microcapsules produced monophasic PB release, suggesting more controlled PB release in the presence of DCA. The PB-DCA-SA microcapsules showed good stability and a pH-sensitive uniphasic release.
pattern, which may suggest potential applications in the oral delivery of PB in diabetes.

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**Plasma ferritin concentrations are not associated with abdominal aortic aneurysm diagnosis, size or growth.**

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**BACKGROUND AND AIMS:** Experimental studies using a rodent model have suggested that iron overload may contribute to abdominal aortic aneurysm (AAA) pathogenesis.

**METHODS:** We assessed the association of total body iron, as measured by plasma ferritin, with AAA diagnosis, size and growth in 4024 community-dwelling older men screened for AAA, using logistic regression and linear mixed effects models.

**RESULTS:** Plasma ferritin concentrations were similar in men who did (n = 293) and did not (n = 3731) have an AAA (median [inter-quartile range] concentrations 115.4 [63.0–203.1] and 128.5 [66.1–229.1] ng/mL respectively, p = 0.124). There was no association between plasma ferritin concentration and AAA diagnosis in unadjusted logistic regression (odds ratio (OR) for a 1 standard deviation increase: 0.880 [95%CI: 0.764–1.015]; p = 0.078), or when adjusting for AAA risk factors and factors known to influence circulating ferritin (OR for a 1 standard deviation increase: 0.898 [95% CI: 0.778–1.035]; p = 0.138). Iron overload prevalence (plasma ferritin concentrations >200 ng/mL) was lower in men with an AAA (25.3%) than those without (30.8%; p = 0.048), but was not associated with AAA diagnosis after adjusting as above (OR: 0.781 [95% CI:0.589–1.035]; p = 0.086). The association of iron overload with AAA growth was investigated in 265 men with small AAAs who received at least 1 repeat ultrasound scan in the 3 years following screening. We saw no difference in AAA growth between men who did and did not have iron overload (n = 65 and 185 respectively, p = 0.164).

**CONCLUSIONS:** Our data suggest that iron overload is unlikely to be important in AAA pathogenesis.

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**Cyclical Inguinal Keratoderma: A New Clinical Entity or a Variant of Pityriasis Rubra Pilaris?**
Successful evaluation of cognitive function and the nature of cognitive deficits among people with schizophrenia in clinical rehabilitation settings.

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OBJECTIVES: Despite possessing considerable relevance for planning and delivery of effective rehabilitation interventions, systematic evaluation of cognitive function is often ignored in clinical practice. This paper describes a successful method for measuring cognitive function and the nature of cognitive deficits (CD) in people with schizophrenia admitted to psychiatric rehabilitation services.

METHODS: Data on the cognitive functioning of consecutive patients with schizophrenia / schizoaffective disorder admitted during a 5-year period to a public in-patient rehabilitation facility was collated retrospectively and analysed. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate cognitive function.

RESULTS: It was possible to administer the BACS to 122 of 135 consecutive admissions. The mean composite score on the BACS was 1.8 standard deviations below the norm, and 43% had moderate or severe CD. The BACS sub-tests of list learning and symbol coding revealed more severe deficits.

CONCLUSIONS: The study indicates that evaluation of cognitive function using brief instruments is feasible in psychiatric rehabilitation settings. Global and domain-specific CD were prevalent among people with schizophrenia. In view of the strong association of cognitive functioning with community functioning and rehabilitation outcomes, further studies exploring the feasibility and utility of routinely evaluating cognitive function are warranted. Copyright © The Royal Australian and New Zealand College of Psychiatrists 2016.

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Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial.

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BACKGROUND: Cytokines are involved in the development of metabolic abnormalities that may result in metabolic syndrome (MetS). Since curcumin has shown anti-inflammatory properties, the aim of this study was to evaluate the effect of curcumin supplementation on serum cytokines concentrations in subjects with MetS.

METHODS: This study was a post-hoc analysis of a randomized controlled trial in which males and females with diagnosis of MetS, according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines, were studied. Subjects who met the inclusion criteria were randomly assigned to either curcumin (daily dose of 1g/day) or a matched placebo for a period of 8 weeks.

RESULTS: One hundred and seventeen subjects were assigned to either curcumin (n=59) or placebo (n=58) groups. Within-group analysis revealed significant reductions in serum concentrations of TNF-alpha, IL-6, TGF-beta and MCP-1 following curcumin supplementation (p<0.001). In the placebo group, serum levels of TGF-beta were decreased (p=0.003) but those of IL-6 (p=0.735), TNF-alpha (p=0.138) and MCP-1 (p=0.832) remained unaltered by the end of study. Between-group comparison suggested significantly greater reductions in serum concentrations of TNF-alpha, IL-6, TGF-beta and MCP-1 in the curcumin versus placebo group (p<0.001). Apart from IL-6, changes in other parameters remained statistically significant after adjustment for potential confounders including changes in serum lipids and glucose levels, and baseline serum concentration of the cytokines.

CONCLUSION: Results of the present study suggest that curcumin supplementation significantly decreases serum concentrations of pro-inflammatory cytokines in subjects with MetS.

Risk of dementia and death in community-dwelling older men with bipolar disorder.

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**Background:** Bipolar disorder has been associated with cognitive decline, but confirmatory evidence from a community-derived sample of older people is lacking.

**Aims:** To investigate the 13-year risk of dementia and death in older adults with bipolar disorder.

**Method:** Cohort study of 37,768 men aged 65–85 years. Dementia (primary) and death (secondary), as recorded by...
RESULTS: Bipolar disorder was associated with increased adjusted hazard ratio (HR) of dementia (HR = 2.30, 95% CI 1.80-2.94). The risk of dementia was greatest among those with <5 years of history of bipolar disorder or who had had illness onset after 70 years of age. Bipolar disorder was also associated with increased mortality (HR = 1.51, 95% CI 1.28-1.77). Competing risk regression showed that bipolar disorder was associated with increased hazard of death by suicide, accidents, pneumonia or influenza, and diseases of the liver and digestive system.

CONCLUSIONS: Bipolar disorder in later life is associated with increased risk of dementia and premature death.

Discriminant validity of the Hospital Anxiety and Depression Scale, Beck Depression Inventory (II) and Beck Anxiety Inventory to confirmed clinical diagnosis of depression and anxiety in patients with chronic obstructive pulmonary disease.

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The objective of this study was to investigate the discriminant validity of commonly used depression and anxiety screening tools in order to determine the most suitable tool for patients with chronic obstructive pulmonary disease (COPD). COPD patients (n = 56) completed the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). These scores were compared to confirmed clinical diagnoses of depression and anxiety using the Mini Neuropsychiatric Interview. HADS depression subscale (HADS-D) sensitivity/specificity was 78/81%; BDI-II 89/77%; HADS anxiety subscale (HADS-A) 71/81%; and BAI 89/62%. HADS-D sensitivity/specificity was improved (100/83%) with the removal of Q4 ‘I feel as if I am slowed down’ and adjusted cut-off (>5). Removal of BDI-II Q21 ‘Loss of interest in sex’ with adjusted cut-off >12 resulted in similar improvement (100/79%). No problematic items were identified for HADS-A or BAI. Previously reported low sensitivity/specificity of the HADS for COPD patients was not replicated. Furthermore, simple modifications of the HADS-D markedly improved sensitivity/specificity for depression.BDI-II, HADS-A and BAI produced acceptable sensitivity/specificity unmodified. Pending further research for COPD patients we recommend continued use of the HADS-A with standard cut-off (>8) and removal of Q4 of the HADS-D with lower cut-off >5.

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A systematic review and meta-analysis of the impact of Spirulina supplementation on plasma lipid concentrations.


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BACKGROUND & AIMS: The impact of Spirulina supplementation on plasma lipid concentrations has not been conclusively studied. Therefore the aim of the meta-analysis was to assess the effect of Spirulina supplementation on plasma lipid concentrations.

METHODS: We searched PubMed and Scopus (up to July 03, 2015) to identify randomized controlled trials (RCTs) that investigate the effect Spirulina supplementation on plasma lipid concentrations. Meta-analysis and meta-regression were performed using random-effects models.

RESULTS: Random-effect meta-analysis of data from 7 RCTs showed a significant effect of supplementation with spirulina in reducing plasma concentrations of total cholesterol (WMD: -46.76 mg/dL, 95% CI: -67.31 to -26.22, p < 0.001), LDL-C (WMD: -41.32 mg/dL, 95% CI: -60.62 to -22.03, p < 0.001) and triglycerides (WMD: -44.23 mg/dL, 95% CI: -50.22 to -38.24, p < 0.001), and elevating those of HDL-C (WMD: 6.06 mg/dL, 95% CI: 2.37-9.76, p = 0.001). The impact of spirulina on plasma concentrations of total cholesterol (slope: -1.32; 95% CI: -8.58 to 5.93; p = 0.720), LDL-C (slope: -1.01; 95% CI: -8.03 to 6.02; p = 0.778), triglycerides (slope: -1.39; 95% CI: -4.26 to 1.48; p = 0.342) and HDL-C (slope: 1.79, 95% CI: -0.48 to 4.05; p = 0.122) was independent of administered dose. Regarding duration of supplementation with Spirulina, significant associations were found with changes in plasma concentrations of total cholesterol (slope: -1.77, 95% CI: -3.48 to -0.07; p = 0.042), LDL-C (slope: -1.73, 95% CI: -3.40 to -0.06; p = 0.042) HDL-C (slope: 0.91, 95% CI: 0.68-1.14; p < 0.001) and triglycerides (slope: -1.39, 95% CI: -2.28 to -0.50; p = 0.002).

CONCLUSIONS: This meta-analysis showed a significant effect of supplementation with Spirulina in reducing plasma concentrations of total cholesterol, LDL-C, triglycerides and elevating those of HDL-C.

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BACKGROUND: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that is causally linked to dysregulation of the serotonergic system. The aim of this study is to investigate the efficacy of Withania somnifera (W. somnifera) root extract as an adjunct therapy to standard OCD treatment.

METHODS: Thirty patients with a confirmed diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria participated in this randomized double-blind placebo-controlled trial and were randomly assigned to the treatment group (W. somnifera extract, 120mg/day; n=15) or the placebo group (n=15). All patients were under treatment with Selective Serotonin Re-uptake Inhibitors (SSRIs), and were instructed to take 4 capsules of the extract or placebo per day, preferably after meals, for a period of six weeks. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was used in order to assess the severity of OCD symptoms at baseline and at the end of the trial. Statistical analyses were performed using SPSS software and Y-BOCS values were presented as median and range (Min-Max).

RESULTS: Comparison of the change in Y-BOCS score during the course of the trial revealed a significantly greater effect of W. somnifera (26 (14-40) [pre-treatment] versus 14 (4-40) [post-treatment]; change: -8 (-23 to 0)) versus placebo (18 (11-33) [pre-treatment] versus 16 (10-31) [post-treatment]; change: -2 (-4 to 0)) (P<0.001). The extract was safe and no adverse event was reported during the trial.

CONCLUSION: W. somnifera extract may be beneficial as a safe and effective adjunct to SSRIs in the treatment of OCD.

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Assessing a doctor you’ve rarely worked with: The use of workplace-based assessments in a busy inner city emergency department.

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OBJECTIVE: Historically, end-of-term assessments for Junior Medical Officers in our ED have been completed by nominated Consultants based on varying amounts of observation in addition to feedback from other health professionals. Our hypothesis is that this system of assessment is both inconsistent and unreliable. Our objective was to increase the validity of our assessment process using workplace-based assessments linked specifically to the domains set out in the Australian Medical Council intern assessment form.

METHODS: Current practice was established using an online survey. Workplace-based assessments were then performed on each junior doctor throughout the course of a term. A repeat survey at the end of term was used to audit the use of the workplace-based assessments and their effect on the adequacy of the assessments.

RESULTS: Almost three quarters of our Consultants used workplace-based assessments as part of their end-of-term assessment. Overall, 80% of Consultants agreed that the Junior Medical Officers assessment process was improved when using workplace-based assessments as an adjunct.

CONCLUSION: Workplace-based assessments improve the validity of end-of-term assessments for junior doctors in an ED as perceived by those performing the assessment.

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The inverted U curve and emergency medicine: Overdiagnosis and the law of unintended consequences.

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We all think and assume that more is better, but unintended consequences can arise in a complex system. However, in our complex world, everything of consequence follows an inverted U curve. The inverted U curve helps us challenge our natural assumption that more is better. This leads us to the issue of overdiagnosis and the harms that result.

Journals are now publishing lists of studies where more medical care caused harm. Changing diagnostic thresholds together with the fear of uncertainty by both patients and doctors has a synergistic and costly effect on the health system. The over-reliance on technology tends to supplant clinical judgement. This intervention bias promotes the overutilisation of diagnostic testing. What patients actually value is thinking doctors who talk to them. Promoting clinical judgement reinforces the mantra that less is more, resulting in positively intended consequences. This essay aims to be a thought-provoking commentary of our practice.

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Sepsis Early Alert Tool: Early recognition and timely management in the emergency department.

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INTRODUCTION: The Surviving Sepsis Campaign guidelines recommend administration of appropriate antibiotics within 1h in patients with severe sepsis, with two sets of blood cultures taken prior to administration.

OBJECTIVE: We evaluated the effect of introducing a Sepsis Early Alert Tool (SEAT) in the ED. Outcomes were antibiotic timing, antibiotic choice and obtaining adequate blood cultures.

METHODS: A retrospective chart review compared consecutive severe sepsis presentations admitted to ICU via the ED during two equivalent 6month periods before and after SEAT introduction.

RESULTS: The analyses included 55 patients before and 45 following SEAT introduction. The groups were similar in age, sex, triage category, sepsis source, Acute Physiology and Chronic Health Evaluation III scores and hospital mortality. The percentage receiving antibiotics within 60min of triage increased from 24% (95% CI 13-37%) to 44% (95% CI 30-60%), P=0.03. Median time from triage to first antibiotic was 105 (IQR 65-170)min and 85 (IQR 50-140)min before and after SEAT introduction, respectively, P=0.15. Percentages receiving antibiotics within 60min of first recognition of severe sepsis were 67% (95% CI 53-79%) and 71% (95% CI 56-84%) before and after SEAT introduction, P=0.83. The percentage having two sets of blood cultures drawn prior to antibiotic administration increased from 18% (95% CI 9-34%) to 44% (95% CI 27-60%), P=0.008. Appropriateness of antibiotics was 58% (95% CI 44-71%) and 75% (95% CI 60-87%) before and after SEAT implementation, P=0.09.

CONCLUSION: The introduction of a SEAT in the ED is associated with earlier recognition of severe sepsis and improvements in quality of care.

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Triglyceride-rich lipoprotein metabolism in women: roles of apoC-II and apoC-III.
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BACKGROUND: Experimental data suggest that apolipoprotein (apo) C-II and C-III regulate triglyceride-rich lipoprotein (TRL) metabolism, but there are limited studies in humans. We investigated the metabolic associations of TRLs with apoC-II and apoC-III concentrations and kinetics in women.

MATERIAL AND METHODS: The kinetics of plasma apoC-II, apoC-III and very low-density lipoprotein (VLDL) apoB-100 and triglycerides were measured in the postabsorptive state using stable isotopic techniques and compartmental modelling in 60 women with wide-ranging body mass index (19.5-32.9 kg/m(2) ).

RESULTS: Plasma apoC-II and apoC-III concentrations were positively associated with the concentrations of plasma triglycerides, VLDL1 - and VLDL2 -apoB-100 and triglyceride (all P < 0.05). ApoC-II production rate (PR) was positively associated with VLDL1 -apoB-100 concentration, VLDL1 triglyceride concentration and VLDL1 triglyceride PR, while apoC-II fractional catabolic rate (FCR) was positively associated with VLDL1 triglyceride FCR (all P < 0.05). No significant associations were observed between apoC-II and VLDL2 apoB-100 or triglyceride kinetics. ApoC-III PR, but not FCR, was positively associated with VLDL1 triglyceride, and VLDL2 -apoB-100 and triglyceride concentrations (all P < 0.05). No significant associations were observed between apoC-III and VLDL-apoB-100 and triglyceride kinetics. In multivariable analysis, including homoeostasis model assessment score, menopausal status and obesity, apoC-II concentration was significantly associated with plasma triglyceride, VLDL1 -apoB-100 and VLDL1 triglyceride concentrations and PR. Using the same multivariable analysis, apoC-III was significantly associated with plasma triglyceride and VLDL1 - and VLDL2 -apoB-100 and triglyceride concentrations and FCR.

CONCLUSIONS: In women, plasma apoC-II and apoC-III concentrations are regulated by their respective PR and are significant, independent determinants of the kinetics and plasma concentrations of TRLs.

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Congenital Heart Disease Requires a Lifetime Continuum of Care: A Call for a Regional Registry.
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Determined of residual viraemia during combination HIV treatment: Impacts of baseline HIV RNA levels and treatment choice.

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OBJECTIVES: Effective HIV therapy reflects suppression of plasma HIV RNA levels below assay detection thresholds, although lower levels of “residual viraemia” have also been demonstrated over extended periods of effective antiretroviral treatment. Here we examine the determinants of HIV RNA suppression below the standard assay threshold (40 HIV-1 RNA copies/mL) as well as factors associated with detectable HIV RNA below this reported detection limit.

METHODS: Between 2007 and 2010, 11 575 consecutive viral load (VL) tests were obtained from 1540 patients, including 356 on effective antiretroviral therapy followed since initiation (1996-2001: n = 165; 2002-2009: n = 191). Analyses modelled the probability of an undetectable VL given successful suppression to < 200 copies/mL, and the probability of residual viraemia given an undetectable result.

RESULTS: Detectable HIV RNA amplification was demonstrated in 20% of samples with a VL result < 40 copies/mL. Longitudinal analyses from 356 patients revealed that the likelihood of achieving results < 40 copies/mL was increased with current nonnucleoside reverse transcriptase inhibitor (NNRTI) therapy [odds ratio (OR) 2.0; P < 0.05] and reduced with prior virological rebound (OR 0.5; P < 0.05). In contrast, the presence of detectable HIV RNA < 40 copies/mL was strongly associated with pretreatment HIV RNA levels among those on current protease inhibitor (PI) treatment (OR 1.5 per log10 copies/mL increase; P = 0.02) as well as those on NNRTIs (OR 1.7; P = 0.002).

CONCLUSIONS: While HIV treatment history was associated with plasma HIV RNA levels below the detection limit, residual viraemia results were dominantly determined by pretreatment VL. These findings support the concept of a stable, long-lived reservoir of latently infected cells as a source of residual viraemia despite effective HIV treatment. Copyright © 2015 British HIV Association.

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End-of-life care in the intensive care unit (ICU) was identified as an objective in a series of Task Forces developed by the World Federation of Societies of Intensive and Critical Care Medicine Council in 2014. The objective was to develop a generic statement about current knowledge and to identify challenges relevant to the global community that may inform regional and local initiatives. An updated summary of published statements on end-of-life care in the ICU from national Societies is presented, highlighting commonalities and differences within and between international
regions. The complexity of end-of-life care in the ICU, particularly relating to withholding and withdrawing life-sustaining treatment while ensuring the alleviation of suffering, within different ethical and cultural environments is recognized. Although no single statement can therefore be regarded as a criterion standard applicable to all countries and societies, the World Federation of Societies of Intensive and Critical Care Medicine endorses and encourages the role of Member Societies to lead the debate regarding end-of-life care in the ICU within each country and to take a leading role in developing national guidelines and recommendations within each country.

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Characteristics and outcomes of patients treated with airway pressure release ventilation for acute respiratory distress syndrome: A retrospective observational study.

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BACKGROUND: The optimal mode of ventilation in acute respiratory distress syndrome (ARDS) remains uncertain. Airway pressure release ventilation (APRV) is a recognized treatment for mechanically-ventilated patients with severe hypoxaemia. However, contemporary data on its role as a rescue modality in ARDS is lacking. The goal of this study was to describe the clinical and physiological effects of APRV in patients with established ARDS.

METHODS: This retrospective observational study was performed in a 23-bed adult intensive care unit in a tertiary extracorporeal membrane oxygenation (ECMO) referral centre. Patients with ARDS based on Berlin criteria were included through a prospectively-collected APRV database. Patients receiving APRV for less than six hours were excluded.

RESULTS: Fifty patients fulfilled the eligibility criteria. Prior to APRV initiation, median Murray Lung Injury Score was 3.5 (interquartile range (IQR) 2.5-3.9) and PaO2/FiO2 was 99mmHg (IQR 73-137). PaO2/FiO2 significantly improved within twenty-four hours post-APRV initiation (ANOVA F(1, 27)=24.34, P<.005). Two patients (4%) required intercostal catheter insertion for barotrauma. Only one patient (2%) required ECMO after APRV initiation, despite a majority (68%) fulfilling previously established criteria for ECMO at baseline. Hospital mortality rate was 38%.

CONCLUSIONS: In patients with ARDS-related refractory hypoxaemia treated with APRV, an early and sustained improvement in oxygenation, low incidence of clinically significant barotrauma and progression to ECMO was observed. The safety and efficacy of APRV requires further consideration.

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Renal denervation for resistant hypertension: closing in on potential confounders.

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Malignant hyperechoic breast lesions at ultrasound: A pictorial essay.

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Malignant breast lesions are typically hypoechoic at sonography. However, a small subgroup of hyperechoic malignant breast lesions is encountered in clinical practice. We present a pictorial essay of a number of different hyperechoic breast malignancies with mammographic, sonographic and histopathologic correlation. Suspicious sonographic features in a hyperechoic lesion include inhomogeneity in echogenic pattern, an irregular margin, posterior acoustic shadowing and internal vascularity. A hyperechoic lesion at ultrasound does not discount the need to undertake histological assessment of a mammographically suspicious lesion.

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Role of microRNAs in the Therapeutic Effects of Curcumin in Non-Cancer Diseases.

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Curcumin is a bioactive polyphenol occurring in the rhizomes of Curcuma longa. It is well-reputed for its chemopreventive and anticancer properties; however, recent evidence has revealed numerous biological and pharmacological effects of curcumin that are relevant to the treatment of non-cancer diseases. Mechanistically, curcumin exerts its pharmacological effects through anti-inflammatory and antioxidant mechanisms via interaction with different signaling molecules and transcription factors. In addition, epigenetic modulators such as microRNAs (miRs) have emerged as novel targets of curcumin. Curcumin was found to modulate the expression of several pathogenic miRs in brain, ocular, renal, and liver diseases. The present systematic review was conducted to identify miRs that are regulated by curcumin in non-cancer diseases.

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Progress in the care of common inherited atherogenic disorders of apolipoprotein B metabolism.
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Familial hypercholesterolaemia, familial combined hyperlipidaemia (FCH) and elevated lipoprotein(a) are common, inherited disorders of apolipoprotein B metabolism that markedly accelerate the onset of atherosclerotic cardiovascular disease (ASCVD). These disorders are frequently encountered in clinical lipidology and need to be accurately identified and treated in both index patients and their family members, to prevent the development of premature ASCVD. The optimal screening strategies depend on the patterns of heritability for each condition. Established therapies are widely used along with lifestyle interventions to regulate levels of circulating lipoproteins. New therapeutic strategies are becoming available, and could supplement traditional approaches in the most severe cases, but their long-term cost-effectiveness and safety have yet to be confirmed. We review contemporary developments in the understanding, detection and care of these highly atherogenic disorders of apolipoprotein B metabolism.
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CAV3 mutations causing exercise intolerance, myalgia and rhabdomyolysis: Expanding the phenotypic spectrum of caveolinopathies.
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Rhabdomyolysis is often due to a combination of environmental trigger(s) and genetic predisposition; however, the underlying genetic cause remains elusive in many cases. Mutations in CAV3 lead to various neuromuscular phenotypes with partial overlap, including limb girdle muscular dystrophy type 1C (LGMD1C), rippling muscle disease, distal myopathy and isolated hyperCKemia. Here we present a series of eight patients from seven families presenting with exercise intolerance and rhabdomyolysis caused by mutations in CAV3 diagnosed by next generation sequencing (NGS) (n=6). Symptoms included myalgia (n=7), exercise intolerance (n=7) and episodes of rhabdomyolysis (n=2). Percussion-induced rapid muscle contractions (PIRCs) were seen in five out of six patients examined. A previously reported heterozygous mutation in CAV3 (p.T78M) and three novel variants (p.V14I, p.F41S, p.F54V) were identified. Caveolin-3 immunolabeling in muscle was normal in 3/4 patients; however, immunoblotting showed more than 50% reduction of caveolin-3 in five patients compared with controls. This case series demonstrates that exercise intolerance, myalgia and rhabdomyolysis may be caused by CAV3 mutations and broadens the phenotypic spectrum of caveolinopathies. In our series, immunoblotting was a more sensitive method to detect reduced caveolin-3 levels than immunohistochemistry in skeletal muscle. Patients presenting with muscle pain, exercise intolerance and rhabdomyolysis should be routinely tested for PIRCs as this may be an important clinical clue for caveolinopathies, even in the absence of other "typical" features. The use of NGS may expand current knowledge concerning inherited diseases, and unexpected/atypical phenotypes may be attributed to well-known human disease genes.


ORACLE Stroke Study: Opinion Regarding Acceptable Outcome Following Decompressive Hemicraniectomy for Ischemic Stroke.
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BACKGROUND: There continues to be considerable interest in the use of decompressive hemicraniectomy in the management of malignant cerebral artery infarction; however, concerns remain about long-term outcome.
OBJECTIVE: To assess opinion on consent and acceptable outcome among a wide range of healthcare workers.
METHODS: Seven hundred seventy-three healthcare workers at the 2 major public neurosurgical centers in Western Australia participated. Participants were asked to record their opinion on consent and acceptable outcome based on the modified Rankin Score (mRS). The evidence for clinical efficacy of the procedure was presented, and participants were then asked to reconsider their initial responses.
RESULTS: Of the 773 participants included in the study, 407 (52.7%) initially felt that they would provide consent for a decompressive craniectomy as a lifesaving procedure, but only a minority of them considered an mRS score of 4 or 5 an acceptable outcome (for mRS score <4, n = 67, 8.7%; for mRS score = 4, n = 57, 7.4%). After the introduction of the concept of the disability paradox and the evidence for the clinical efficacy of decompressive craniectomy, more participants were unwilling to accept decompressive craniectomy (18.1% vs 37.8%), but at the same time, more were willing to accept an mRS score <4 as an acceptable outcome (for mRS score <4, n = 92, 11.9%; for mRS score = 4, n = 79, 10.2%).
CONCLUSION: Most participants felt survival with dependency to be unacceptable. However, many would be willing to provide consent for surgery in the hopes that they may survive with some degree of independence.

ABBREVIATIONS: DESTINY, Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral ArterymRS, modified Rankin Scale.
Interpretative comments specifically suggesting specialist referral increase the detection of familial hypercholesterolaemia.

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Familial hypercholesterolaemia (FH) is an under-diagnosed inherited condition characterised by elevated low density lipoprotein (LDL)-cholesterol and premature coronary artery disease. The requesting general practitioner of individuals with extremely elevated LDL-cholesterol measured by St John of God Pathology receives an interpretative comment on the lipid results highlighting possible FH. We sought to determine whether specifically recommending referral to the regional Lipid Disorders Clinic (LDC) increased referral and FH detection rates. A prospective case-control study of individuals with LDL-cholesterol >6.5 mmol/L was conducted. All individuals received an interpretative comment highlighting the possibility of FH. The cases comment also suggested LDC referral, and a subset of cases received the LDC’s fax number (fax-cases) in addition. There were 231 individuals with an LDL-cholesterol >6.5 mmol/L; 96 (42%) controls and 135 (58%) cases, of which 99 were fax-cases. Twenty-four (18%) cases were referred to clinic compared with eight (8%) controls (p = 0.035). After specialist review and genetic testing, four probable and four definite FH individuals were detected amongst controls, compared with seven possible, eight probable and nine definite FH amongst cases. Genetic testing was performed in 31 (94%) individuals, 13 (42%) had a causative mutation identified. Interpretative commenting specifically recommending specialist review augments the detection of FH in the community.


The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials.

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Dyslipidemia and hyperglycemia are associated with an increased risk of ischemic cardiovascular disease. Positive effects of a nutraceutical combination comprising red yeast rice, berberine, policosanol, astaxanthin, coenzyme Q10 and folic acid (NComb) on plasma lipid and glucose levels have been reported in some but not all clinical trials. To address this inconsistency, we tried to estimate the size of lipid- and glucose-lowering effects of NComb through a systematic review and meta-analysis of randomized controlled trials. A systematic literature search in PubMed-Medline, SCOPUS and Google Scholar databases was conducted to identify randomized controlled trials investigating the effects of NComb on plasma lipids and glucose levels. Inverse variance-weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in lipid and glucose levels using a random-effects model. Random-effects meta-regression was performed to assess the effect of putative confounders on plasma lipid and glucose levels. Fourteen trials (1670 subjects in the NComb arm and 1489 subjects in the control arm) met the eligibility criteria for lipid analysis and 10 trials (1014 subjects in the NComb arm and 962 subjects in the control arm) for glucose analysis. Overall, WMDs were significant for the impact of NComb supplementation on plasma levels of total cholesterol (-26.15mg/dL, p<0.001), LDL-cholesterol (-23.85mg/dL, p<0.001), HDL-cholesterol (2.53mg/dL, p<0.001), triglycerides (-13.83mg/dL, p<0.001) and glucose (-2.59mg/dL, p=0.010). NComb-induced amelioration of lipid profile was not affected by duration of supplementation nor by baseline lipid levels; conversely, a greater glucose-lowering effect of NComb was found with higher baseline glucose levels and longer durations of supplementation. In conclusion, the present results suggest that NComb supplementation is associated with improvement of lipid and glucose profile. Short-term beneficial effects of NComb supplementation appear to be maintained in the long term.

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**Patient selection essential for computed tomography coronary angiography.**

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**OBJECTIVE:** Computed tomography coronary angiography (CTCA) has become a commonly used imaging modality in patients with suspected anginal symptoms but also in asymptomatic populations. This practice has raised concerns due to potential high radiation exposure in terms of adequate benefit to risk profile.

**DESIGN:** Demographics and CTCA scan details were collected from a consecutive series of 586 patients referred to a single community radiology practice for a CTCA.

**RESULTS:** Of the 586 patients, 271 (46.2%) were women. Mean age was 58.3 standard deviation (SD) 12.2, range 15-90 years, body mass index (BMI) 28.6 SD 5.9kg/m(2), and heart rate 60 SD 10 beats per minute. Mean total radiation was 4.79 SD 3.45 mSv (range 0.64-31.34). The mean radiation exposure in the lowest quartile of BMI and heart rate were
3.01 SD 1.84 mSv and 3.95 SD 2.72 mSv, compared to the highest 7.32 SD 3.51 mSv and 6.20 SD 4.38 mSv (p for trend <0.0001 in both).

CONCLUSION: The radiation exposure in this consecutive series of patients is low in general but patient selection for CTCA imaging appears to be paramount. Patients with a high BMI and especially with high heart rate receive a higher dose of radiation.

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**Control Measures for Human Respiratory Viral Infection.**

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New viral respiratory pathogens are emerging with increasing frequency and have potentially devastating impacts on the population worldwide. Recent examples of newly emerged threats include severe acute respiratory syndrome coronavirus, the 2009 H1N1 influenza pandemic, and Middle East respiratory syndrome coronavirus. Experiences with these pathogens have shown up major deficiencies in how we deal globally with emerging pathogens and taught us salient lessons in what needs to be addressed for future pandemics. This article reviews the lessons learnt from past experience and current knowledge on the range of measures required to limit the impact of emerging respiratory infections from public health responses down to individual patient management. Key areas of interest are surveillance programs, political limitations on our ability to respond quickly enough to emerging threats, media management, public information dissemination, infection control, prophylaxis, and individual patient management. Respiratory physicians have a crucial role to play in many of these areas and need to be aware of how to respond as new viral pathogens emerge.

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**Are Medical Students Who Want to Become Surgeons Different? An International Cross-Sectional Study: Reply.**

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**Sympathetic nervous response to ischemia-reperfusion injury in humans is altered with remote ischemic preconditioning.**

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Sympathetic neural activation may be detrimentally involved in tissue injury caused by ischemia-reperfusion (IR). We examined the effects of experimental IR in the forearm on sympathetic nerve response, finger reactive hyperemia, and oxidative stress, and the protection afforded by applying remote ischemic preconditioning (RIPC). Ischemia was induced in the forearm for 20 min in healthy volunteers. RIPC was induced by applying two cycles, 5 min each, of ischemia and reperfusion to the upper leg immediately before IR. We examined muscle sympathetic nerve activity (MSNA) in the contralateral leg using microneurography, finger reactive hyperemia [ischemic reactive hyperemia index (RHI)], erythrocyte production of reduced glutathione (GSH), and plasma nitric oxide (NO) concentration. In controls (no RIPC; n = 15), IR increased MSNA in the early and late phase of ischemia (70% at 5 min; 101% at 15 min). In subjects who underwent RIPC (n = 15), the increase in MSNA was delayed to the late phase of ischemia and increased only by 40%. GSH increased during ischemia in the control group (P = 0.05), but not in those who underwent RIPC. Nitrate and nitrite concentration, taken as an index of NO availability, decreased during the reperfusion period in control individuals (P < 0.05), while no change was observed in those who underwent RIPC. Experimental IR did not affect RHI in the control condition, but a significant vasodilatory response occurred in the RIPC group (P < 0.05). RIPC attenuated ischemia-induced sympathetic activation, prevented the production of an erythrocyte marker of oxidative stress and the reduction of NO availability, and ameliorated RHI.

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Neglecting legumes has compromised human health and sustainable food production.

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The United Nations declared 2016 as the International Year of Pulses (grain legumes) under the banner 'nutritious seeds for a sustainable future'. A second green revolution is required to ensure food and nutritional security in the face of global climate change. Grain legumes provide an unparalleled solution to this problem because of their inherent capacity for symbiotic atmospheric nitrogen fixation, which provides economically sustainable advantages for farming. In addition, a legume-rich diet has health benefits for humans and livestock alike. However, grain legumes form only a minor part of most current human diets, and legume crops are greatly under-used. Food security and soil fertility could be significantly improved by greater grain legume usage and increased improvement of a range of grain legumes. The current lack of coordinated focus on grain legumes has compromised human health, nutritional security and sustainable food production.
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Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A.
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Recombinant VIII (rVIII)-SingleChain is a novel B-domain-truncated recombinant factor VIII (rFVIII), comprised of covalently bonded factor VIII (FVIII) heavy and light chains. It was designed to have a higher binding affinity for von Willebrand factor (VWF). This phase 1/3 study investigated the efficacy and safety of rVIII-SingleChain in the treatment of bleeding episodes, routine prophylaxis, and surgical prophylaxis. Participants were >12 years of age, with severe hemophilia A (endogenous FVIII <1%). The participants were allocated by the investigator to receive rVIII-SingleChain in either an on-demand or prophylaxis regimen. Of the 175 patients meeting study eligibility criteria, 173 were treated with rVIII-SingleChain, prophylactically (N = 146) or on-demand (N = 27). The total cumulative exposure was 14306 exposure days (EDs), with 120 participants reaching >50 EDs and 52 participants having >100 EDs. Hemostatic efficacy was rated by the investigator as excellent or good in 93.8% of the 835 bleeds treated and assessed. Across all prophylaxis regimens, the median annualized spontaneous bleeding rate was 0.00 (Q1: 0.0, Q3: 2.4) and the median overall annualized bleeding rate (ABR) was 1.14 (Q1: 0.0, Q3: 4.2). Surgical hemostasis was rated as excellent/good in 100% of major surgeries by the investigator. No participant developed FVIII inhibitors. In conclusion, rVIII-SingleChain is a novel rFVIII molecule showing excellent hemostatic efficacy in surgery and in the control of bleeding events, low ABR in patients on prophylaxis, and a favorable safety profile in this large clinical study. This trial was registered at www.clinicaltrials.gov as #NCT01486927.

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Back pain beliefs in adolescents and adults in Australasia: A cross-sectional pilot study of selected psychometric properties of paper-based and web-based questionnaires in two diverse countries.

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BACKGROUND: It is unknown whether questionnaires measuring psychosocial constructs related to low back pain (LBP) that were originally designed for adults are suitable for adolescents, and if paper and web-versions have similar measurement properties.

OBJECTIVES: To examine selected psychometric properties for the paper- and web-based Back-Beliefs Questionnaire (BBQ) and the Fear Avoidance Beliefs Questionnaire (FABQ-phys) among adults and adolescents in two diverse countries and to determine whether differences existed between countries and pain groups.

METHODS: A sample of 156 adults (Hong Kong, n= 75; Australia, n= 81) and 96 adolescents (Hong Kong, n= 61; Australia, n= 35) participated in this cross-sectional study.

RESULTS: Main effects for country and administration mode were observed in adult BBQ scores, where Australian adults reported significantly higher BBQ scores than Hong Kong adults (mean difference (MD); 95% CI: 2.85; 0.96-4.74) and significantly higher scores were recorded on the web mode compared to the paper mode (MD 0.74; 0.10-1.38). Similarly, Hong Kong adults and adolescents reported higher FABQ-phys scores than Australian adults and adolescents (MD; 95% CI: 3.40; 1.37-5.43 and 4.88; 0.53-9.23, respectively). Internal consistency values were mostly acceptable (alpha > 0.7).

CONCLUSION: Differences exist between cultures for LBP-related beliefs. The BBQ and FABQ-phys have acceptable measurement properties in both administration modes.

Emerging Infectious Diseases. 2016; 22(8): 1420-1427.

Cutaneous melioidosis cluster caused by contaminated wound irrigation fluid.


Emerging Infectious Diseases. 2016; 22(8): 1420-1427.


Maintenance of IgG tetanus toxoid (TT) antibodies in humans is associated with TT-specific IgG<sup>+</sup>, but not IgD<sup>+</sup>IgM<sup>+</sup> memory B cells.

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Immunoglobulin (Ig) G antibodies play a central role in vaccine-induced immunity against pathogens. Circulating IgG antibodies are secreted by plasma cells, however long-term vaccine-induced memory is retained by memory B cells, of which IgG<sup>+</sup> and IgD<sup>+</sup>IgM<sup>+</sup> are the major subsets. The contribution of these memory B cell subsets to the maintenance of plasma IgG antibody levels in humans is unclear. We adapted a flow cytometry-based method to enumerate antigen-specific memory B cell subsets using tetanus toxoid (TT) as a model antigen. Plasma TT-specific IgG antibodies and TT-specific memory B cells were assayed in 4 healthy adults before and at weeks 1, 2, 3 and 4 after a booster vaccination with TT and in 30 adults with latent or active tuberculosis (TB) and unknown TT vaccination histories. B cells were enriched from PBMC via negative bead selection, stained with CD3-PerCP-Cy5.5, IgG-FITC, IgM-APC, CD20-APC-H7, CD27-V450, IgD-BV510 and a multimeric TT-PE probe, and assessed by flow cytometry. Plasma TT-specific IgG antibody levels and TT<sup>+</sup>IgG<sup>+</sup> memory B cell proportions increased following booster vaccination and were strongly correlated (p=0.81, p<0.0001). Proportions of TT<sup>+</sup>IgD<sup>+</sup>IgM<sup>+</sup> memory B cells exhibited no change following booster vaccination. Similarly, in the adults with TB and unknown TT vaccination history, plasma TT-specific IgG antibody levels correlated with the proportions of TT<sup>+</sup>IgG<sup>+</sup> (p=0.70, p<0.0001), but not TT<sup>+</sup>IgD<sup>+</sup>IgM<sup>+</sup> memory B cells. These results suggest that TT<sup>+</sup>IgG<sup>+</sup>, but not TT<sup>+</sup>IgD<sup>+</sup>IgM<sup>+</sup>, memory B cells contribute to the maintenance of circulating TT-specific IgG antibody levels.

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**Ultraviolet-B irradiation of the skin for alteration of immunophenotype and functional responses in clinically isolated syndrome.**

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Multiple sclerosis (MS) is an autoimmune disease characterised by demyelination in the CNS. T cells play a crucial role in the development of MS, with evidence of a T helper (Th)1/Th17 skewed phenotype, impaired regulatory T cell (Treg) function, and increased circulating follicular helper T cells (Tfh). Low exposure to ultraviolet-B radiation (UVB) is a strong MS environmental risk factor. UVB is immunosuppressive; inducing Treg and downregulating Th1/Th17 pathways. Due to the therapeutic use of UVB in psoriasis we are investigating its efficacy as a therapy in a neurological autoimmune condition. We have a world first, NHMRC-funded, randomised controlled trial of narrowband UVB phototherapy for Clinically Isolated Syndrome - a first and single demyelinating event suggestive of MS. The hypothesis is that UVB phototherapy will slow or prevent the progression to MS via immunosuppression. Participants are randomised to receive, or not, 24 sessions of UVB phototherapy over 8 weeks. In addition, all participants receive vitamin D supplementation to control for the independent effects of vitamin D. Blood is collected at seven time points over the 12 month follow-up for measurement of serum 25(OH)D3 and bio-banking of peripheral blood mononuclear cells. Neurological examination and MRI scans are conducted to monitor clinical progression. Here we present longitudinal analysis of Th, Treg and Tfh phenotypes in n=12 participants and an equivalent number of age- and sex-matched controls. This study will inform on the biomarkers of progression of disease from a pre-MS condition, as well as the mechanisms by which UVB may be immunoregulatory.

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Serial mast cell tryptase measurements: Sensitivity and specificity for a diagnosis of anaphylaxis in patients with shock and/or hypoxemia.

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Background: Anaphylaxis is difficult to identify in cases presenting with atypical symptoms. Serial measurements of mast cell tryptase (MCT), looking for changes in MCT levels (delta-MCT) may increase the sensitivity of current diagnostic methods. The usefulness of this approach depends on the ability of delta-MCT to distinguish anaphylaxis from other critical illnesses, which is investigated in this study. Methods: MCT was measured (ImmunoCAP) in serum samples from patients with anaphylaxis (n=85) and non-anaphylactic critical illness (n=120) on at least three occasions: ED arrival, 1-2 hours, 3-4 hours, and 12-24 hours post-arrival where possible. Delta-MCT was calculated as the difference between the highest and lowest values regardless of time point, and analyzed using Receiver Operating Characteristic Curves. A positive delta-MCT was defined as >2.0 ng/mL. Results: 48 (56%) of 85 anaphylaxis cases were positive, compared to 31 (25%) of 120 cases of critical illness (including sepsis, cardiac arrest, trauma and toxicology). Non-anaphylaxis cases had delta-MCT values ranging from 0-22 ng/mL (2 cases had delta-MCT >10), whereas anaphylaxis cases had delta MCT values ranging from 0-114 ng/mL (22 cases had delta-MCT >10). The diagnostic specificity was 0.74 with a sensitivity of 0.56. Higher cutoff values provided higher specificity but lower sensitivity. Conclusion: The specificity and sensitivity observed in this study indicate that delta-MCT measurements do not perform well in cases where anaphylactic shock has to be differentiated from other critical illnesses, which may also involve some mast cell degranulation. In this situation higher cut-offs are required, however this results in poor sensitivity.

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B-cell abnormalities in HIV disease are associated with increased interferon-alpha activity.

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B-cell dysfunction, such as increased frequencies of exhausted CD21<sup>lo/-</sup> B-cells and decreased isotype diversification of IgG antibody responses, is observed in HIV-1 infection. Understanding more about these defects may lead to novel therapies for enhancing antibody responses, including those induced by therapeutic HIV vaccines. Here, we have investigated the role of interferon-alpha (IFN-alpha). In antiretroviral therapy (ART)-naive (n=19) and ART-treated (n=30) HIV patients, levels of plasma IP-10 and soluble (s) IFNAR2 were examined by ELISA as indicators of IFN-alpha activity and B-cell activation and exhaustion was assessed by enumeration of CD21<sup>lo/-</sup> B-cells and serum levels of kappa and lambda free light chains (FLCs), IgG1 and IgG2. In ART-naive patients, plasma IP-10 and sIFNAR2 levels correlated with frequencies of CD21<sup>lo/-</sup> B-cells, FLCs and serum IgG1 levels (r>0.5, p<0.03 and r>0.6, p<0.01, respectively). In contrast, IP-10 and sIFNAR2 were inversely correlated with serum IgG2 (r=-0.4, p=0.09 and r=-0.6, p=0.007, respectively). To assess the effect of IFN-alpha on B cell differentiation in vitro, B cells from non-HIV donors (n=25) were stimulated for 5 days with interleukin- 21 and CD40 ligand in the absence or presence of IFN-alpha2b. Addition of IFN-alpha2b to cultures did not alter the induction of plasmablasts (CD27<sup>hi</sup>) but decreased the production of all IgG subclasses (p<0.002) in culture supernatants, particularly IgG2 (p< 0.0001). Thus, increased IFN-alpha activity is associated with B cell activation and
exhaustion in HIV patients and IFN-alpha exerts an inhibitory effect on IgG production which may limit isotype diversification of IgG antibody responses. 

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Characterisation of the antibody response to hepatitis C virus by infected individuals.
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Hepatitis C virus (HCV) is a blood borne pathogen which is responsible for life long, chronic infection of the liver. It is expected that the optimal HCV vaccine will contain both cell mediated immunity and antibody stimulating epitopes. Our aim is to characterise antibodies against HCV elicited by infection that are genotype cross-reactive and infection neutralising in vitro. Previously we have reported that 98% of a cohort of 100 chronic hepatitis C patients responded by ELISA to g2 (JFH-1) HCV prior to treatment. Analysis by denaturing western blot in a subset of this cohort revealed that each person recognised HCV core antigens but this was not found for the viral envelope glycoprotein, E2, which is the target of many infection neutralising antibody responses. Neutralisation of JFH-1 HCV infection of Huh7 cells in vitro was also common amongst the entire cohort irrespective of whether patients were infected with genotype 1, 2, 3 or 4 HCV. The presence of antibody to E2 has been tested by ELISA in a subset of patients using recombinant E2 for genotypes 1, 2, 3 and 4 produced in mammalian cells. Cross-reactivity of the antibody response between genotypes was common while the strength of the response to E2 was not directly related to the infecting HCV genotype. This information has been used to select donors whose HCV reactive B cells are captured in a modified ELISPOT for isolation of immunoglobulin sequences for diagnostic and vaccine development purposes.

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Vaccination induced ICOS<sup>+</sup> circulating memory T<inf>FH</inf> cells share similar characteristics to T<inf>FH</inf> cells but are dysfunctional and Th2 skewed in chronic HIV-1 infection.
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HIV infection increases the risk of pneumococcal disease, probably related to B-cell and/or T follicular helper (T<inf>FH</inf>) cell dysfunction. We have shown that decreased production of pneumococcal polysaccharide (PcP)-specific IgG2<sup>+</sup> antibody secreting cells (ASC) in HIV patients 7 days after vaccination with unconjugated PcPs is associated with impaired expansion of ICOS<sup>+</sup> cells. Here, we sought to further characterise these cells in antiretroviral therapy (ART)-treated (n=27) and ART-naive (n=11) HIV patients and non-HIV subjects (n=20). Intracellular expression of Bcl-6, Blimp-1 and BATF, and surface expression of CCR6, CCR7, CXCXR3, BTLA and IL-6Ralpha were examined in unstimulated cells while production of IL-21 and IFN-gamma were assessed following in vitro stimulation. After vaccination, ICOS<sup>+</sup> cmT<inf>FH</inf> cells in HIV patients and non-HIV subjects displayed characteristics of canonical T<inf>FH</inf> cells, with BTLA, IL-6Ralpha and Bcl-6 expression and IL-21 production all observed. However, IL-21 production by
ICOS<sup>+</sup> cmT<inf>FH</inf> cells was decreased in ART-naive (p=0.02) and ART-treated (p=0.03) patients compared to non-HIV subjects. Furthermore, production of IgG2 ASCs specific for Pcp serotypes 4, 68, 9V and 14 correlated with ICOS<sup>+</sup> cmT<inf>FH</inf> cells that displayed a Th1 phenotype (CXCR3<sup>+</sup> CCR6<sup>-</sup>) in non-HIV subjects (R=0.42, p<0.06) but a Th2 phenotype (CXCR3<sup>-</sup> CCR6<sup>-</sup>) in ART-treated HIV patients (R=0.44, p=0.02). Thus, after vaccination with Pcs, ICOS<sup>+</sup> cmT<inf>FH</inf> cells were skewed from Th1 to Th2 and displayed impaired production of IL-21 in ART-treated HIV patients. These findings provide new evidence that impaired antibody responses to Pcs, and possibly other antigens, in HIV patients receiving ART may result from residual T<sup>+</sup> cell dysfunction.


Sympathetic nervous response to ischaemia-reperfusion is altered in remote ischaemic preconditioning.

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Background: Sympathetic activation may be implicated in tissue injury caused by ischaemia-reperfusion (IR). Prior remote ischaemic preconditioning (RIPC) can reduce tissue injury during IR. We examined the effects of experimental IR in the human forearm on limb muscle sympathetic nerve response, endothelial function and oxidative stress, and the protection afforded by applying RIPC. Method: IR was achieved by BP cuff inflation (to 200mmHg) and deflation, each for 20 min, using the forearm of healthy volunteers. RIPC was achieved by 2x5 min I-R of the leg by BP cuff. We examined muscle sympathetic nerve activity (MSNA) in the contralateral leg by microneurography, post-ischaemic reactive hyperaemia (RHI) using an EndoPAT device and erythrocyte glutathione content and plasma nitrate+nitrite.

Results: In control individuals (no RIPC; n=8), IR increased MSNA from baseline in both the early and late phase of ischaemia (by 70% after first 5 min; by 101% after 15 min). In subjects who underwent RIPC (n=10), the MSNA rise was delayed to the late phase of ischaemia and increased only by 40%, a significantly smaller effect GSH significantly increased during ischaemia in the control group (77.6+/-1.1 vs 73.4+/-1.0 mg/100 ml RBC), while no changes were observed in those individuals underwent RIPC. Endothelial function remained unchanged in controls, whereas it significantly increased in the RIPC group (RHI: 2.33+/-0.12 vs 1.74+/-0.12). RIPC prevented a fall in NO concentration during the reperfusion period, compared to baseline, unlike in control individuals. Conclusion: RIPC attenuated ischaemia-induced sympathetic activation, prevented the production of an erythrocyte marker of oxidant stress and ameliorated endothelial function.


Left atrial appendage closure in patients with contra-indications to anticoagulants.

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Background: In patients with contraindications to oral anticoagulation (OAC), left atrial appendage (LAA) closure is a novel therapy to prevent stroke. This study sought to evaluate the utility of LAA device occlusion alone without OAC in patients at high risk of stroke but at serious risk of bleeding. Methods: 94 consecutive patients with CHA2DS2Vasc score 4.3+/-1.7,HASBLED score 2.7+/-1 and definite contraindications to OAC underwent LAA closure under fluoroscopy and trans-oesophageal echocardiography (TOE) guidance. Post procedure, anti-platelet drugs (ASA+/-Clopidogrel) were prescribed for maximum of 3 months. The patients were reviewed clinically at 7 days, 3
months and 6 monthly intervals. A TOE was performed at 3 months. Results: All 94 patients with age 75.5 +/- 8.4 years underwent successful LAA closure and followed up for 8.3 +/- 9.8 months. Table 1 shows the baseline characteristics of the patients. Contra-indications to anticoagulation were intracranial bleeds and AV malformations 43/94 (45.7%), GI bleeds in 22/94 (23.4%) and intolerance to OAC in 18/94 (19.2%). Mean device size was 25.6 +/- 3.6 mm. Acute procedural complications consisted of one stroke, six pericardial effusions without tamponade, six femoral access complications and one nonfatal oesophageal perforation secondary to TEE. There was no device embolism. Minor peri-device leak (1-3 mm) was noted in 11 patients at device implant and persisted at 3 months follow up. Although a single device thrombus was noted at three months, no strokes were observed during follow up. Conclusions: Standalone LAA closure is a safe alternative to prevent AF-related stroke in patients with serious contraindications to OAC.

Contrast induced nephropathy in patients undergoing coronary angiography and intervention: The cincai study.

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Introduction: Contrast induced nephropathy (CIN) complicating coronary angiography +/- intervention is associated with risk of morbidity and mortality. The primary aim of this study was to identify the incidence of contrast nephropathy in our patient population. The secondary aims were to identify the prevalence of CIN risk and to determine whether appropriate prophylactic strategies were used. Methods: A retrospective review was done on 310 patients. Patients were stratified into low, medium and high risk groups based on modified version of the Mehran score. CIN is defined as absolute (> 44 umol/L) or relative (>25%) increase in serum creatinine within 48-72 hours. Appropriateness of prophylactic strategies were compared with standards of care. Results: Overall incidence of CIN was 4.8%, however direct correlation was seen with level of risk with 9.2% in medium/high risk group and 1.2% in low risk group. In terms of risk prevalence, 12.6% were at high risk preprocedure, and 18.7% were at medium risk. Documentation of CIN risk was found in 30% of cases. Prophylactic strategies used in medium/high risk groups: nephrotoxic medications withheld (ACE/ARB 37%, Diuretics 30.2%, NSAIDS 80%); metformin withheld in 71.7%; prehydration given in 63.9%; post procedural hydration in 18.6%. High risk group patients had lower average contrast volume (137.1 mls) than medium (157.8 mls) or low (153.6 mls) risk groups. Conclusion: CIN is a significant complication with increasing incidence in those at higher levels of risk. Management of our at risk patients could be further optimised to further minimise the risk of CIN. Measures taken, and subsequent reaudit of patient outcomes, will be presented in the future.

Uptake of novel oral anticoagulant use in regional Western Australia.

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The availability of Novel Oral Anticoagulants (NOACs) has seen an increase in prescription of these medications over Warfarin. In regional Australia, managing anticoagulation therapy could be more challenging than in metropolitan areas. We collected retrospective data from consecutive patients on NOACs, attending a private physician’s practice in Bunbury, in South-West Western Australia. Our aim was to assess the proportion of Atrial Fibrillation/Flutter (AF) patients being treated with NOACs, the physician’s compliance with anticoagulation guidelines and to discuss trends in anticoagulation use in regional Western Australia. Of a total of 126 patients, 52% of patients lived in Bunbury, 36%...
112 patients had AF and 8 patients had DVT/PE. Other indications for therapy are addressed. For patients with pre-existing non-valvular AF, Rivaroxaban was used as often as warfarin (24%). Among 18 patients with newly-diagnosed non-valvular AF that commenced anticoagulation, 17% (3) were commenced on Warfarin as opposed to 72% (13) commenced on Rivaroxaban. 2 patients (11%) were commenced on Apixaban. The average age for patients on Warfarin was 76 years whilst the average for patients on Rivaroxaban was 72 years. There was no NOAC specific serious complications noted over the two-year period. These results are preliminary findings from a larger collection of data planned to evaluate the management atrial fibrillation in regional WA. Uptake of NOAC use in regional WA as first line anticoagulation in thromboprophylaxis has been safe and successful. We expect a further upwards trend in NOAC use in regional WA.


An article on early changes in lipoproteins following elective cardiac surgery.
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Background: Changes in lipoproteins occur following an acute myocardial infarction (AMI). There are limited reliable models to detect these changes within the first 24 hours of ischaemia due to the difficulty in predicting the onset of spontaneous AML. This study assessed the changes in concentrations of lipoproteins in the first 24 hours of induced myocardial ischaemia following cardiac surgery and investigated the correlation between change in serum lipoproteins and troponin elevation. Methods: Blood samples were collected from 45 patients undergoing elective cardiac surgery pre-procedure (Time 1), post operatively (Time 2 median = 43 minutes) and within 24 hours post procedure (Time 3 median = 16.6 hours). Change in lipoprotein (Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C) and Triglyceride (TG)) concentrations were analysed in relation to peak postoperative troponin after adjustment for haemodilution with albumin change ratio.

Results: TC and LDL-C decreased significantly (12.35% and 29.15%, respectively) between Time 2 and Time 3, F(1.66,68.13) =8.32, p=.001 and -2(2) =33.76, p=.001, respectively. Postoperative reductions in LDL-C were negatively correlated with troponin elevation (rs(40) =-0.4, p=.01) Median High Sensitivity Troponin T elevation was 652 ng/L (range 114-8084 ng/L). Conclusions: We have demonstrated that TC and LDL-C levels decrease within the 24 hours post myocardial ischaemia using a cardiac surgery model and that the postoperative change in LDL-C negatively correlates with rise in troponin. Current guidance that lipoprotein assessment is accurate in the first 24 hours of an AMI may need review.


Radiation dose for transfemoral and transradial access in cardiac catheterisation procedures.
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Objectives: Transradial cardiac catheterisation procedures are associated with improved outcomes compared to the transfemoral approach. However, previous studies have suggested this approach is associated with increased procedure time and radiation dose. With increasing experience in transradial access, we examined radiation dosage between the two techniques in the contemporary era of experienced radial operators. Methods: Consecutive coronary diagnostic and interventional procedures over the past 18 months at our institution were analysed. Radial operators were experienced with more than 500 total transradial interventional procedures performed each, and greater than 150 cases performed per year. Mean fluoroscopy time (mins), dose area product (uGym2), and skin dose (mGy) were
compared between transradial and transfemoral procedures using an unpaired t-test. Results: Of the 2372 cases, 908 were performed via transfemoral access, with 1464 utilising transradial access. There were 68% male in the femoral group with an average age of 63.5 years and 72% male in the radial group with an average age of 61.9 years. There were no significant differences between the access site approaches in fluoroscopy time (femoral 13.3+/−12.3mins, radial 13.6+/−10.2mins; p=0.54), dose area product (femoral 8166+/−6856.0 uGym2, radial 8081.9+/−5836.2 uGym2; p=0.75), although skin dose was lower in the radial group (femoral 2135.7+/−1895.8 mGy, radial 1839.8+/−1537.1 mGy; p<0.001). Conclusions: Transradial diagnostic coronary and interventional procedures, when performed by experienced operators, are not associated with increased radiation dose compared to the transfemoral approach. Given the association with improved outcomes, the transradial approach should be the preferred arterial access route in invasive coronary catheterisation procedures.

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Comparison of radiation dose between bioresorbable vascular scaffolds and drug-eluting stents.
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Introduction: Bioresorbable vascular scaffolds (BVS) resorb naturally into the body leaving no permanent scaffold, with recent evidence suggesting short-term equivalence to current generation drug-eluting stents (DES). However, the implantation of BVS can be technically more demanding, requiring meticulous attention to lesion preparation and adequate post-dilatation. Accurate positioning can be particularly challenging when deploying overlapping BVS. There is a concern that the deployment of BVS may be associated with an increased radiation dose compared to drug-eluting stents. Methods: Consecutive coronary interventional procedures over the past 12 months at our institution were analysed, stratified into BVS and DES implantation. Mean fluoroscopy time (mins), dose area product (uGym2), and skin dose (mGy) were compared between BVS and DES implantation using an unpaired t-test. Results: A total of 987 patients underwent DES implantation with 48 patients having BVS deployed. There was no significant difference between the groups in terms of fluoroscopy time (DES 19.84 +/- 12.01 mins vs. BVS 18.46 +/- 7.99 mins; P=0.43), skin dose (DES 2913 +/- 1812 mGy vs. BVS 3052 +/- 2243 mGy; P=0.61), and dose-area product (DES 11317 +/- 6627 uGym2 vs. BVS 12053 +/- 8340 uGym2; P=0.46). Conclusions: Although the implantation of BVS can be technicallymore demanding thanDESdeployment, therewas no significant difference in radiation doses noted between the two groups.

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Novel oral anticoagulants (NOACS) versus warfarin - How do they compare for safety and efficacy in real world -regional WA experience.
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Since the introduction of NOACs, the pattern of OAC use for thromboprophylaxis in patients with Atrial Fibrillation/Flutter (AF) and other approved indications in Australia has significantly changed in favour of NOACs. To date, there is limited data evaluating the safety of anticoagulation therapy in patients living in regional Australia. We have retrospectively collected data from 90 consecutive patients attending a private Physician’s practice in Bunbury, in the South-West region of Western Australia. Patients on any type of oral anticoagulation therapy were included and followed over a two-year period. TheOACindications included; AF, DVT/PE, SLE, Metallic heart valves and LV thrombus. Our aims were to assess the adverse events and complication rates of NOAC therapy and Warfarin. This is part of a
larger study with plans to evaluate overall quality of AF management in patients in Regional WA. (Table Presented)
The table (above) lists the number of patients (N) on each anticoagulant and the total number of adverse events (AE).
Eight per cent of patients on anticoagulation experienced an adverse event. In this group, patients on warfarin
therapy experienced a higher rate of adverse events without any additional protective benefit over NOACs from
thromboembolic complications. Further data collection is taking place in order to make more accurate conclusions on
anticoagulation safety in Regional WA.
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A rare cause for coronary sinus dilation.
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A 29-year-old lady of Indian ethnicity presented with intermittent palpitations. She had an abnormal
electrocardiogram with deep asymmetric anteroseptal T wave inversion. Subsequent exercise stress test was negative
for ischaemia. A 24-hour Holter monitor had no significant arrhythmias. Transthoracic echocardiography revealed
moderate right ventricular dilatation with preserved systolic function, normal pulmonary pressures (26mmHg) and
severe dilatation of the right atrium (RA). Cardiac Computed Tomography (CT) revealed partial anomalous pulmonary
venous connection (PAPVC) with left superior (LS) and left inferior (LI) pulmonary veins (PV) draining into a dilated
coronary sinus (CS) (Figure) with an intact interatrial septum. Given her paucity of symptoms and desire for
pregnancy, cardiac surgery was deferred. (Figure presented) PAPVC is a congenital anomaly involving drainage of
some of the PVs into the systemic venous circulation, with an estimated incidence at autopsy of 0.6-0.7% (Healy et al.,
1952). The left PV is less commonly involved (16%) (Ammash et al., 1997). Anomalous left PVs drain into superior vena
cava (SVC) (59%), RA (12%), RA-SVC (9%) and CS (3%) (Ammash et al., 1997). This case highlights the role of cardiac
CT in diagnosis of PAPVC and specifying anatomy for surgical planning.
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A new technique for improving standardisation and image quality in contrast aortography.
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Aims: Contrast aortography has been used for more than 50 years however this method remains semi-subjective with
high inter-observer variability. We developed a method to determine an Overlap-Free projection which enables
standardisation of contrast aortography and improves quantification of aortic regurgitation, particularly useful for
para-valvular regurgitation in TAVI. Methods and results: In patients referred for TAVI, a total of 65 computed
tomography angiogram (CTA) scans and 19 prospectively collected aortograms were analysed. Using volume
rendered three-dimensional reconstruction the Overlap-Free Projection (OFP)-defined as the C-arm angulation with
no overprojection of the descending aorta on the aortic root or left ventricle was determined in both right anterior
oblique and left anterior oblique orientation. From this data a method was developed to predict the optimal
angulation for OFP using information readily available during femoral contrast aortography. In the prospectively
collected aortograms there were no cases of overlap when the OFP rule was correctly applied. Conclusions: The OFP
rule is an easy to use method to reliably determine a patient specific projection for standardised contrast aortography
and will allow for improvements in quantification of aortic regurgitation. Further validation of this method in a larger
cohort is currently in progress.
PMID:612750375

Catastrophic ventricular failure secondary to phaeochromocytoma requiring extra-corpooreal membrane oxygenation.
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A normally healthy 58 year old male presented with increasing headache, abdominal and chest pain, with rapidly worsening dyspnœa. His background included longstanding systemic hypertension which had been well controlled. On arrival, he was hypertensive, tachycardic and markedly dyspnoeic. ECG showed sinus tachycardia with 2mm upsloping ST-segment depression, chest X-ray demonstrating bilateral diffuse airspace changes. An urgent CT aortogram showed no aortic dissection. Transthoracic echocardiography revealed severe global left ventricular impairment with no valvular or pericardial pathology, and subsequent urgent coronary angiography showed no obstructive disease. Within an hour of presentation his respiratory condition rapidly deteriorated requiring ventilatory support. Progressive haemodynamic collapse followed despite increasing inotropic support and intra-aortic balloon pump insertion. Veno-arterial extra-corpooreal membranous oxygenation (VA-ECMO) was commenced, maintaining adequate perfusion and oxygenation. Over the next 24-hours the patient remained haemodynamically stable, left ventricular function normalised on repeat echocardiography and VA-ECMO and inotropes were weaned. Within 48-hours the patient was extubated with no neurological deficit. Cardiac MRI performed 10 days after initial presentation showed no myocardial abnormality, normal perfusion and calculated left ventricular ejection fraction of 66%. The initial CT aortogram was reviewed in further detail, demonstrating a 23x20mm left-sided adrenal lesion, intensely active on Iodine-123 meta-iodobenzylguanidine scan. Urine and plasma metanephrine levels were consistent with a phaeochromocytoma. The patient was started on phenoxybenzamine, underwent uncomplicated adrenalectomy and remains well at 6 month follow-up. This case demonstrates the importance of prompt escalation of resuscitation measures in patients with undifferentiated cardiogenic shock, and the importance of considering rarer causes.

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Use of the guideliner catheter to support complex coronary intervention using transradial access.
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Background: The GuideLiner catheter (Vascular Solutions, Inc.) is a rapid exchange guide catheter extension system, designed to facilitate delivery of interventional equipment in difficult coronary anatomy by improving support and co-axial alignment. In the transradial era, improving guide support in complex intervention is increasingly relevant.

Methods: All coronary interventional procedures utilising the GuideLiner catheter over the previous twelve months at our institution were reviewed. Demographic, procedural, and lesion data were collected. Results: There were 27 patients identified in whom the GuideLiner catheter was used. The average patient age was 69 years, with 82% male. Transradial access was utilised in 20 (74%) of cases, with a 6Fr sheath used in the majority (93%). The right coronary artery (11 cases) was the predominant vessel requiring GuideLiner support, followed by the circumflex artery (8), the left anterior descending artery (7), and the LAD via the LIMA on a single occasion. Of the included lesions, 13 (48%) were AHA Type C lesions, including 5 chronic total occlusion (CTO) cases, with the remainder being Type B2. Successful GuideLiner delivery with PCI success were achieved in 23 (85%) of cases. There were no complications related to either the GuideLiner catheter or the interventional procedure in our series. Discussion: The GuideLiner catheter adds valuable support to complex coronary intervention particularly in transradial cases, with a high-success rate and low complications. Its use allows for smaller sheath and guide size, which is favourable in the transradial...

Transulnar unprotected left main coronary artery percutaneous coronary intervention in a high risk individual with absent bilateral radial pulses.

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Background: Radial access for PCI consistently offers more favourable results, when compared with femoral access. However, among patients with absent bilateral radial pulses it remains unclear whether the clinical benefits observed with transradial intervention are transferrable to ulnar access. The Case: A 65-year-old man with severe peripheral vascular disease, bilateral aorto-iliac bypass grafting, severe LV dysfunction (EF 33%) and progressive crescendo angina came forward for invasive assessment. In the absence of bilateral radial pulses, access was gained into his right ulnar artery using a standard 5-in-6F Terumo radial Glidesheath. Forearm angiography demonstrated an occluded radial artery, with the ulnar artery being the dominant forearm vessel (image available). Coronary angiography demonstrated angiographically equivocal LMCA and proximal LAD disease, an unobstructed circumflex and a chronically occluded dominant RCA. Using a 6F IL3.5 guide a pressure wire study of the LAD and LMCA was performed; at steady state FFR measured 0.55 in the mid LAD. PCI was performed; 2.75 x 24 Promus Element (LAD), 3.5 x 18 Xience Xpedition (LADLMCA). OCT confirmed an excellent intravascular result (images available). Despite accurate placement of a Terumo Radial band, 'turned around' to cover the ulnar puncture site, a small haematoma developed. He recovered well and was discharged home the following day. Conclusion: Among patients with absent bilateral radial pulses, the ulnar artery may represent a suitable alternative. Further studies are required to fully understand the role of transulnar intervention. Finally, given the current lack of specifically designed ulnar closure bands, ulnar haematoma remains a significant problem.

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Cardiac arrest in early pregnancy due to left main coronary artery obstruction; Emergency percutaneous coronary intervention with subsequent successful term delivery.

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Background: Cardiovascular disease remains the leading cause of indirect maternal mortality in developed countries. The relative risk of myocardial infarction is reportedly 3-4 times greater among pregnant versus non-pregnant women of childbearing potential, and carries an associated mortality of approximately 5-7%. Furthermore, due to later parity and increasing prevalence of diabetes and obesity, ischaemic heart disease within pregnancy is likely to become increasingly prevalent. The Case: A previously well 40 year old pregnant female (G2P0, 7 weeks gestation) experienced chest pain, followed by out-of-hospital cardiac arrest. She was a current smoker with history of hypertension but not diabetes. Following cardiopulmonary resuscitation, including defibrillation, ECG demonstrated ST-segment elevation in aVR with widespread deep ST-depression. She was immediately transferred, intubated and ventilated, to the cardiac catheter laboratory. Coronary angiography demonstrated a critical stenosis of her LMCA (figure available). Intravascular ultrasound (IVUS) confirmed the presence of coronary atheroma, with significant LMCA intramural haematoma most likely secondary to atherosclerotic plaque rupture (figure available). Emergency trans-radial PCI was performed (3.5x23mm Xience Xpedition drug-eluting stent) with an excellent result on IVUS. She was transferred to intensive care, recovered well and discharged home day nine with good higher cerebral function. Despite the profound circulatory collapse during cardiac arrest, the patient’s pregnancy remained viable. Conclusion: Cardiovascular disease remains an important indirect driver of maternal mortality. Coronary atherosclerosis among
women of childbearing age is becoming increasingly prevalent and problematic. Thorough pre-pregnancy assessment may help identify high risk individuals who should be assessed and ideally managed within a joint cardio-obstetric service.

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Patterns of primary care, specialist consultations, ED attendances and hospitalisations for aboriginal and non-aboriginal patients following first admission for ischaemic heart disease in Western Australia.
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T. Teng, National Heart Centre, Singapore
Aim: We investigated differences in general practice (GP), specialist and emergency department (ED) consultations, readmissions and death in Aboriginal and non-Aboriginal people after hospitalisation for ischaemic heart disease (IHD) in Western Australia. Methods: Linked data were used to identify the first IHD admission in 2002-2007, and readmissions and death in patients aged 25-74 years. GP, specialist and ED consultations were identified from person-linked Medicare Benefits Scheme (MBS) and ED records in the two years post-discharge. Multivariable regression models assessed readmissions. Results: Aboriginal people (4.7% of 27,230) were on average 10 years younger, more commonly women (45% vs 28%, p<0.001), rural, and more likely to have acute forms of IHD (64% vs 52%, p<0.001). Two year all-cause mortality was higher in Aboriginal patients (7.9% vs 4.3%, p<0.001). 2,184,877 relevant MBS claims were identified 2 years postdischarge (3.0% Aboriginal). 62% of Aboriginal MBS claims were for GP services (vs 38.7% in non-Aboriginals). Only 5.4% of claims were for specialists (vs 19.5%, all p<0.001). Median interval to first specialist and GP consultation post-discharge was longer in Aboriginal people (specialists, 70 days vs 9 days; GP, 9 days vs 5 days; all p<0.001). More Aboriginal patients visited ED within 90 days post-discharge (44% vs 18%), with higher rates of emergency hospitalisation (adjusted rate ratio 1.78, 95% CI 1.71-1.85). Conclusions: Aboriginal people visit ED more often than non-Aboriginals, and have higher rates of emergency hospitalisation and death within two years following an IHD admission. They have fewer MBS-reimbursed specialist visits and longer times to first consultation post-discharge.
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The Szabo technique to assist geo-positioning of ostial bifurcation percutaneous coronary intervention.
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Background: Ostial coronary artery lesions represent a significant interventional challenge, due in part to the risk of geographic miss when deploying the stent. The Szabo technique, originally described to treat aorto-ostial disease, may play an additional role when treating downstream epicardial bifurcation ostial disease (Medina 0,1,0 or 0,0,1). In particular, the Szabo technique may help limit excessive stent protrusion, important when treating ostial LAD and circumflex lesions. The Szabo technique involves twin guidewires, with the second (non-target vessel) wire back-loaded through the most proximal stent cell prior to the stent being advanced into the guide (bench-top photographs available). Once the stent is advanced into the target vessel, this second wire acts to hold the stent at the ostium during deployment. The Cases: The Szabo technique was employed in three consecutive cases with ostial lesions. Case 1: 66-year-old female, transradial approach, RCA treated with 4x18mm Xience Xpedition (Abbott
Vascular). Case 2: 55-year-old female, transfemoral approach, LAD (Medina 0,1,0) treated with 3.5x24mm Promus Element (Boston Scientific). Case 3: 49-year-old female, transfemoral approach, circumflex (Medina 0,0,1) treated with 2.75x20mm Promus Element (Boston Scientific) drug eluting stent (images available). In all cases a balanced middleweight wire was used as the second ‘geo-locating’ wire. All cases were uncomplicated and excellent angiographic results were achieved. Conclusion: The Szabo technique may assist with accurate stent placement, minimise excessive stent protrusion and prevent geographic miss when treating epicardial bifurcation ostial disease. However, further studies are required in order to better understand the long-term results of this technique.

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Myocardial infarction post Kawasaki’s disease: An unfortunate legacy of a childhood disease.
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A 26 year old female presented with chest pain for 3 hours with ST elevation in infero-posterior leads and peak hstroponin I of 33100. The patient had a delayed diagnosis of Kawasaki’s disease at age two and despite intravenous immunoglobulin developed giant coronary artery aneurysms (CAA). She was managed with warfarin and aspirin, which were discontinued at ages 19 and 23. ST elevation myocardial infarction complicating known giant CAA was diagnosed. Coronary angiography showed proximal occlusion of right coronary artery (RCA) and severe proximal left anterior descending artery (LAD) stenosis with extensive calcification. CT coronary angiography (effective dose 1.0mSv) demonstrated a giant aneurysm (20x19x15mm)of the proximal RCA with thrombotic occlusion of lumen (arrow) and 2 calcified aneurysms in the mid RCA and proximal LAD. Cardiac MRI showed transmural myocardial infarction in RCA territory with viability in other territories. She had coronary artery bypass grafting with LIMA to the LAD and SVG to the PDA with observed functional recovery. Giant CAA (internal diameter >8mm) is associated with poorer prognosis and lower likelihood of regression compared to smaller size aneurysms. Persistent aneurysms result in progressive myointimal proliferation and calcification, increasing risk of stenosis and thrombotic occlusion, which persist into adulthood. Recommended management of giant CAA consist of life-long aspirin and anticoagulation. This raises difficult management challenges, particularly in young female patients wishing to start families.
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Successful snare and retrieval of a free intra-coronary rotawire during complex unprotected left main coronary artery bifurcation percutaneous coronary intervention in a high-risk individual.
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A 46-year-old female with longstanding haemodialysisdependent ESRF, presented with NSTE-ACS, decompensated biventricular heart failure and significant ascites. Coronary angiography demonstrated severe, calcified distal LMCA bifurcation disease (Medina 1,1,1). Echocardiography revealed moderate LV dysfunction and severe RV dysfunction. Surgical intervention was declined due to excessive risk (EuroSCORE 45%; STS 9% mortality, 57% morbidity/mortality). Following intensive haemodialysis for volume optimisation, she came forward for LMCA PCI. 7Fr femoral access was gained using an ultrasoundguided micro-puncture technique. Using a 7Fr X83.5 guiding catheter, rotational atherectomy (1.75mm burr) was performed sequentially from LMCA to LAD; then LMCA to circumflex.Whilst burring into the angulated ostium of the circumflex, the burr sheared through the rota-wire. Following predilatation of the ostial circumflex, the free rota-wire was snared using a2mmGoseneck snare. TheLMCAbifurcation was then treated using a conventional Culotte technique; 4 x 28mm (LMCA-LAD) and 4 x 32mm (LMCA-circumflex) Promus Premier drug-eluting stents; with final kissing balloon inflation using 3.5mm NC balloons at 12atm. Upon return to the ward,
the patient rapidly deteriorated secondary to pericardial tamponade requiring urgent pericardiocentesis and heparin reversal. Review of angiography revealed evidence of a coronary perforation within the distal circumflex, presumably related to snaring. The patient subsequently recovered well and was discharged on day seventeen. Rotational atherectomy within heavily calcified, angulated lesions may be extremely challenging. Snare retrieval of a free rota wire may be possible in the unlikely event of wire shear, however this is not without significant risk of further complications.

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**Subclavian-to-subclavian bypass graft access via transradial approach for percutaneous coronary intervention.**

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Arterial access for invasive coronary procedures in patients with severe peripheral vascular disease can be technically difficult. We describe a challenging case of peripheral arterial access, requiring use of a pre-existing subclavian-to-subclavian bypass graft to access the aortic arch and subsequently image and intervene on the circumflex coronary artery. An 80-year-old female presented with a non-ST elevation myocardial infarction. Her past medical history is significant for ischaemic heart disease with a right coronary artery (RCA) stent in 1997; as well as peripheral vascular disease with previous stenting to the brachio-cephalic trunk, and subsequent subclavian-to-subclavian arterial vascular bypass graft following subclavian stent occlusion. Her cardiovascular risk factors include hypertension, ongoing smoking, type 2 diabetes mellitus and chronic renal impairment. Planned coronary angiography was undertaken with arterial access unattainable via either femoral artery or the left radial artery. Computed tomography (CT) angiography previously had demonstrated a patent subclavian-to-subclavian bypass graft with reflux of contrast from the distal right brachio-cephalic trunk into the common carotid artery (figure A). A decision was made to perform coronary angiography via the right radial artery approach, through the subclavian-to-subclavian artery conduit, into the ascending aorta via the left subclavian artery (figure B). Angiography showed a new severe obtuse marginal lesion, which was successfully treated with a 2.75 x 26 mm drug eluting stent (Resolute Integrity, Medtronic) via a 6 French guiding catheter (Cordis Vista Brite Tip). Primary success was achieved and patient was discharged on dual anti-platelet therapy.

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**Impact of optical coherence tomography on physician decision making during coronary intervention: A single centre experience.**


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Optical coherence tomography (OCT) is a novel imaging modality that uses infrared light to provide very high resolution images of intra-coronary structures and deployed stents. We studied the use and utility of OCT since it’s introduction at our centre to assess the impact of OCT on interventional cardiologist decision making during percutaneous coronary intervention (PCI). All patients who underwent OCT at the time of coronary angiography/angioplasty between September 2013 and January 2016 were identified from the OCT database. Baseline demographic data was collected from the electronic record of patients including discharge letters with review of angiography and OCT images and any record of the OCT findings. These data were used to determine the reason OCT was used, the image quality and need for repeated acquisitions due to non-diagnostic images, the impact of OCT on clinical decision making during PCI and any complications related to OCT. A total of 115 patients were identified from the OCT database. Clinical data were missing on 7 patients who were excluded from subsequent analyses. The mean
The age of patients was 58.8 years (SD+/-12.8), with typical risk factors (smokers 19.4%, Diabetes 32.4%, arterial hypertension 60.1% and documented hyperlipidaemia 46.2%). The clinical presentation was ST segment myocardial infarction in 22.2%, acute coronary syndrome in 53.7%, angina with inducible ischaemia in 12% and others in 10.1%. The target vessel imaged was the Left main stem (8%), Left anterior descending (53%), left circumflex (7%), and right coronary artery (7%). Preliminary data indicate that OCT was used pre PCI in 26% in, 52% post PCI and in 22% case both pre and post PCI. In 70% of pre PCI cases plan was changed. In 52% of post PCI cases further optimisation was performed following the availability of OCT. In our case series OCT was safe and had an impact on clinical decision making during coronary intervention the majority of cases where it was used.

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**Systemic mastocytosis as a rare cause of pulseless electrical activity (PEA) cardiac arrest and recurrent syncope.**
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Systemic mastocytosis is a rare disorder of mast cell proliferation and accumulation in various tissues. The clinical presentation is variable with cutaneous signs, symptoms of mediator release, and organ infiltration. We describe a rare case of indolent systemic mastocytosis presenting initially as pulseless electrical activity (PEA) cardiac arrest. Sudden onset of lightheadedness preceded witnessed loss of consciousness. Following successful cardiopulmonary resuscitation, cardiac investigations were unremarkable and he was discharged home with an implantable loop recorder. There were three further re-admissions over two months for presyncope with hypotension but no documented arrhythmia. Further history revealed that preceding each episode, diclofenac (NSAID) for chronic back pain was taken. Systemic mastocytosis was suspected with serum tryptase elevated at multiple time intervals. A bone marrow biopsy confirmed the diagnosis with clusters of spindle-shaped mast cells expressing CD 117, CD25, CD2 and mast cell tryptase. PCR revealed D816V mutation of c-kit (the most common mutation). The patient was successfully managed with regular H1 and H2 antagonist, with an adrenaline autoinjector pen. This case highlights two lessons; Firstly, detailed history taking is essential in the assessment of patients with unexplained illness including the use of agents such as NSAIDs which in this case helped with diagnosis of the disorder avoiding further catastrophic presentations. Our case is unique as the patient had no obvious preceding mediator-release related symptoms and therefore his diagnosis was delayed. Secondly, systemic mastocytosis should be suspected in patients with unexplained “cardiac arrest” and recurrent presyncope with symptoms suggestive of mediator release.

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**Recurrent myocardial infarction in erdheim-chester disease: A rare complication from a rarer disease.**
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Erdheim-Chester Disease is a rare non-Langerhans histiocytosis affecting mostly middle-aged males which is characterised by multisystem tissue infiltration of foamy CD68 positive/CD1a negative histiocytes. Almost any tissue type can be involved, but nearly all patients will have the pathognomonic feature of osteosclerosis of meta-diaphysis of long bones. Cardiac involvement occurs in 45% of cases which portends a poorer prognosis. More common cardiac manifestations include pericardial disease, pseudo-tumoural lesions and cardiac failure. Here we describe a rare case of a man with previously diagnosed Erdheim-Chester Disease who presents with increasing frequency of recurrent myocardial infarction secondary to coronary artery infiltration, requiring repeated percutaneous coronary intervention. The patient has a history of classical manifestations of Erdheim-Chester Disease, which provides a framework for
describing this rare condition. Despite the significant morbidity and mortality involved, treatment options for this disease remain limited with no definitive consensus regarding management. Recent identification of BRAF V600E gene mutation in 50% cases of Erdheim-Chester Disease could have significant therapeutic implications, especially for patients with a history of interferon intolerance.

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SOLACE AU registry: Interim results at one year of the Edwards SAPIEN XT TM transcatheter heart valve in intermediate risk patients with severe aortic stenosis in Australia.

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Background: We report the clinical outcomes of intermediate-risk patients at one year from the SOLACE AU Registry who received the Edwards SAPIEN XT TM Transcatheter Heart Valve (THV). Methods: This is a single arm multi-centre study in 11 centres throughout Australia of select symptomatic patients with severe aortic stenosis (mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of < 0.8 cm² or indexed EOA < 0.5 cm²/m²) of at least intermediate risk (STS>4), undergoing transcatheter valve implantation (TAVI) with Heart Team agreement. This study will also evaluate cost utilisation and will ultimately be case controlled with the PARTNERS 2 study in the USA. Results: The total enrolment for the study was 200 patients, the mean ages: 85.5 +/- 4.5 years, female: 55.1%, STS score: 7.0 +/- 5.18, Logistic Euroscore: 18.6 +/- 12.17, with insertion of 23mm (24%), 26 mm (54%) and 29 mm (22%) valves. At 1 year the primary outcomes according to VARC definitions included all-cause mortality 10.2%, major vascular complications 3.0%, acute kidney injury 1%, life-threatening or disabling bleeding 1.1% and reintervention 1%. There were no major strokes or peri-procedural myocardial infarction. The valve was deployed in the optimal position in 98.5%of cases. In this cohort of intermediate risk patients undergoing TAVI with the SAPIEN XT THV we demonstrated excellent one year outcomes with high rates of optimal deployment and low rates of morbidity and mortality.

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Improving clinical efficiency, timeliness of revascularisation and cost effectiveness among patients with new onset angina; The royal perth hospital experience.

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Background: Managing patients with new onset chest pain continues to place a significant burden on healthcare services. Streamlined pathways, such as a Rapid Access Chest Pain Clinic (RACPC), may improve clinical efficiency, timeliness of revascularisation and provide cost-savings. Methods: We studied patients referred to Royal Perth Hospital, with new onset chest pain, 6-months before and 4-months after the introduction of a RACPC. Comparisons were made between groups; time from referral to (i) clinic assessment, (ii) investigation, (iii) revascularisation as well as unplanned ED presentations. Data expressed as mean (SD) if normally distributed or median (IQR) if skewed. Results: 159 patients (92 pre-RACPC, 67 RACPC) were studied. The cohorts were of similar age (58+/-13.5 vs 58+/-13.5, p=0.85). Compared to pre-RACPC, patients managed in RACPC had a higher incidence of high risk characteristics (diabetes, smoking, hypercholesterolaemia); 81% vs 64%, p<0.05. Among patients managed within the RACPC, time from referral to (i) clinic assessment (5 (3-6) vs 83 (53-111) days, p<0.001), (ii) investigation (14 (5-29) vs 107 (80-147)
days, p<0.001) and (iii) revascularisation (12 (8-41) vs 76 (48-104) days, p<0.05) was significantly shorter compared to patients referred in the prior 6-months. Between the time of referral to time seen in clinic, 15 patients from the pre-RACPC group presented to ED compared to none managed within the RACPC. Prevention of unnecessary ED presentations translated to an estimated annual cost-saving of $41,790 (based on ABF costing). Conclusion: Introduction of the RACPC dramatically reduced delays in patients being seen, investigated and revascularised and offered significant cost-savings.

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Safety of rotational atherectomy without on-site cardiac surgery support.
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Introduction: Coronary rotational atherectomy is associated with an infrequent but significant risk of complications, in particular coronary artery perforation. Following the recent loss of on-site cardiac surgery support at our centre, this procedure continues to be performed. Our aim was to assess the safety profile of rotational atherectomy performed in our institution. Methods: A retrospective review of patients undergoing PCI with rotational atherectomy over 12 months from February 2015 through February 2016 was performed. The focus of the audit was the safety profile of the procedure. Results: 16 patients were identified as undergoing rotational atherectomy. The mean age was 70.3 (+/-13) years, with 56% being female. Vascular site access utilised was femoral artery in 56% of cases with radial artery used 44%. The commonest artery treated was the left anterior descending (63%), with transvenous temporary pacing used in 38% of cases. There were two complications. The first was a coronary perforation in the setting of an anterior STEMI, due to stent thrombosis following a recent under-deployed stent in a calcified mid LAD, also in the context of an anterior STEMI. This was successfully treated with prolonged balloon inflation, however the patient subsequently passed away due to cardiac failure. The second was a fractured Rota-floppy wire in a tortuous circumflex artery requiring snare retrieval, complicated by vessel perforation, requiring urgent pericardiocentesis. Patient recovery was uneventful following successful completion of PCI. Conclusion: Coronary rotational atherectomy was performed safely in our centre without the need for on-site cardiac surgery back up.

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Left atrial appendage closure: CT sizing is associated with highly favourable procedural outcomes.
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Background: Percutaneous left atrial appendage (LAA) closure affords stroke prophylaxis in atrial fibrillation where the risks of anticoagulation are prohibitive. Accurate sizing of the LAA orifice is a key consideration in reducing procedural hazard. CT may be superior to 2D-TOE alone, but there are currently no published outcome data for this strategy to LAA closure workup. Methods: Contrast CT was routinely conducted for LAA sizing workup in all cases undertaken by our group. Doubleoblique CT imaging of the LAA orifice was used to determine maximum and mean diameters and eccentricity index, and thus to guide closure device sizing. Procedural complications, embolic events, major bleeding and death were prospectively documented. Results: In our LAA closure program of 69 consecutive cases there were no device-related procedural complications. On retrospective blinded comparison, LAA sizing by TOE versus CT were frequently divergent (bias -2.9mm versus maximum diameter on CT diameter; bias -1.1mm versus perimeter-derived mean diameter on CT). CT influenced device size selection in 51% of cases. Of particular note, gross sizing error by
TOE as compared to CT was detected in 5.5% of cases. Magnitude of discrepancy between modalities was correlated with the degree of eccentricity of the orifice. Conclusions: Multi-modality imaging of the LAA that incorporated CT was associated with a zero device-associated procedural hazard during percutaneous closure in this single-centre registry. A particular value of CT may be the detection and avoidance of gross sizing error by 2D-TOE that occurs in a small but important proportion of cases.

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Teaching neuroimages: ‘Blind drunk’: neuroimaging findings in methanol poisoning.
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DOI: https://dx.doi.org/10.1007/s13760-015-0594-x

Short Communication: Few Liver-Infiltrating Cells Express CXCR3 in HIV/HCV Patients Commencing Antiretroviral Therapy.
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Coinfections with Hepatitis C virus and human immunodeficiency virus accelerate the progression of both conditions and hamper effective treatment. Here we describe expression of CXCR3 on liver-infiltrating cells and peripheral T cells from coinfected patients commencing antiretroviral therapy (ART) in Indonesia. CXCR3 was expressed by small number of intrahepatic inflammatory cells, mostly in the portal areas. The number of cells did not change on ART and was markedly lower than the number of CD4<sup>+</sup> and CD8<sup>+</sup> cells in the liver. Data suggest that CXCR3 may contribute to liver infiltration but demonstrate a dynamic situation, changing as the immune system recovers on ART.
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Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: Rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration.


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BACKGROUND: The potential for global collaborations to better inform public health policy regarding major non-communicable diseases has been successfully demonstrated by several large-scale international consortia. However, the true public health impact of familial hypercholesterolaemia (FH), a common genetic disorder associated with premature cardiovascular disease, is yet to be reliably ascertained using similar approaches. The European Atherosclerosis Society FH Studies Collaboration (EAS FHSC) is a new initiative of international stakeholders which will help establish a global FH registry to generate large-scale, robust data on the burden of FH worldwide.

METHODS: The EAS FHSC will maximise the potential exploitation of currently available and future FH data (retrospective and prospective) by bringing together regional/national/international data sources with access to individuals with a clinical and/or genetic diagnosis of heterozygous or homozygous FH. A novel bespoke electronic platform and FH Data Warehouse will be developed to allow secure data sharing, validation, cleaning, pooling, harmonisation and analysis irrespective of the source or format. Standard statistical procedures will allow us to investigate cross-sectional associations, patterns of real-world practice, trends over time, and analyse risk and outcomes (e.g. cardiovascular outcomes, all-cause death), accounting for potential confounders and subgroup effects.

CONCLUSIONS: The EAS FHSC represents an excellent opportunity to integrate individual efforts across the world to tackle the global burden of FH. The information garnered from the registry will help reduce gaps in knowledge, inform best practices, assist in clinical trials design, support clinical guidelines and policies development, and ultimately improve the care of FH patients.

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Falls risk assessment outcomes and factors associated with falls for older Indigenous Australians.

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OBJECTIVE: To describe the prevalence of falls and associated risk factors in older Indigenous Australians, and compare the accuracy of validated falls risk screening and assessment tools in this population in classifying fall status.

METHOD: Cross-sectional study of 289 Indigenous Australians aged >45 years from the Kimberley region of Western Australia who had a detailed assessment including self-reported falls in the past year (n=289), the adapted Elderly Falls Screening Tool (EFST; n=255), and the Falls Risk for Older People-Community (FROP-Com) screening tool (3 items, n=74) and FROP-Com falls assessment tool (n=74).

RESULTS: 32% of participants had >1 fall in the preceding year, and 37.3% were classified high falls risk using the EFST (cut-off >2). In contrast, for the 74 participants assessed with the FROP-Com, only 14.9% were rated high risk, 35.8% moderate risk, and 49.3% low risk. The FROP-Com screen and assessment tools had the highest classification accuracy for identifying fallers in the preceding year (area under curve >0.85), with sensitivity/specificity highest for the FROP-Com assessment (cut-off >12), sensitivity=0.84 and specificity=0.73.

CONCLUSIONS: Falls are common in older Indigenous Australians. The FROP-Com falls risk assessment tool appears useful in this population, and this research suggests changes that may improve its utility further.

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A case report of clozapine continuation after pulmonary embolism in the context of other risk factors for thromboembolism.
Goh JG, John AP.

Presents a case report of a 31-year-old woman with diagnosis of treatment-resistant schizophrenia (TRS) with previous sub-optimal response to multiple antipsychotics and electro-convulsive therapy was initiated on clozapine. Elevated troponin and postural hypotension were observed 18 days later. Pathology tests revealed raised d-dimer and ventilation/ perfusion scan uncovered bilateral segmental pulmonary embolism (PE) in lower lobes. She was commenced on enoxaparin sodium initially, which was converted to warfarin. Coagulopathy screen was negative. Clozapine treatment was continued at 300 mg without interruption, and over the next few weeks, the patient’s mental state improved significantly. Until her discharge from the psychiatry ward 3 months later, there was no further episode of thromboembolism. (PsycINFO Database Record (c) 2017 APA, all rights reserved)

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Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial.
Chan MT, Peyton PJ, et al.

Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial.
Chan MT, Peyton PJ, et al.

BACKGROUND: Previous animal and clinical studies showed that nitrous oxide may produce long-term analgesia. The aim of this study was to evaluate the effect of nitrous oxide in preventing chronic postsurgical pain. We also explored whether methylenetetrahydrofolate reductase gene polymorphisms (1298A>C, 667C>T) would enhance nitrous oxide analgesia.

METHODS: We conducted a telephone interview at 12 months after surgery on 2924 (41.1%) patients enrolled in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia-II trial. Pain at the wound site was recorded using the modified brief pain inventory and the neuropathic pain questionnaire. General health status was measured using the EQ-5D questionnaire. Genotyping was performed in a subset of 674 Asian patients in Hong Kong.

RESULTS: At 12 months after surgery, 356 (12.2%) patients reported chronic postsurgical pain at the wound site and 112 (3.8%) patients had severe pain and required regular analgesic interventions. Nitrous oxide did not affect the rate of chronic postsurgical pain (11.8% nitrous oxide group; 12.5% no nitrous oxide group), relative risk (95% confidence intervals): 0.94 (0.75-1.17), P=0.57. However, in a planned subgroup analysis, nitrous oxide reduced the risk of chronic postsurgical pain in Asian patients, relative risk (95% confidence intervals): 0.70 (0.50-0.98), P=0.031. Patients who were homozygous for either gene polymorphism and who received nitrous oxide during surgery were less likely to report chronic postsurgical pain.

CONCLUSIONS: Nitrous oxide administration had no impact on chronic postsurgical pain, but benefits may still be possible in Asian patients and patients with variants in methylenetetrahydrofolate reductase gene.

Clinical trial registration: nct00430989.
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Impact of statin therapy on plasma leptin concentrations: a systematic review and meta-analysis of randomized placebo-controlled trials.


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OBJECTIVES: The effects of statins on insulin sensitivity, metabolic homeostasis and adipokines in humans are controversial. Several studies have investigated the impact of statin therapy on plasma leptin concentrations but the results have been inconsistent. The aim of the present study was to conduct a systematic review and meta-analysis of available evidence to calculate the effect size of statin therapy in changing serum leptin concentrations.

METHODS: A systematic search in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases was performed to identify randomized placebo-controlled trials investigating the effect of statins on plasma leptin concentrations. A random-effects model and generic inverse variance method were used for meta-analysis. Sensitivity analysis, risk-of-bias evaluation and publication bias assessment were carried out using standard methods. Random-effects meta-regression was used to evaluate the impact of treatment duration on the estimated effect size.

RESULTS: Six trials, with a total of 425 subjects, met the eligibility criteria. Overall, statin therapy had no significant effect on leptin levels (weighted mean difference -0.32 ng ml<sup>-1</sup> , 95% confidence interval: -2.94, 2.30, P
This effect was robust in the sensitivity analysis and in subgroup analyses of trials with <12 or >12 weeks' duration. There was no association between the duration of statin therapy and changes in plasma leptin levels. Furthermore, there was no differential effect of hydrophilic and lipophilic statins on plasma leptin concentrations.

CONCLUSION: Unless more consistent evidence becomes available in the future, the hypothesis of a relationship between statin use and serum leptin concentrations seem to be unfounded.

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**Xbox KinectTM based rehabilitation as a feasible adjunct for minor upper limb burns rehabilitation: A pilot RCT.**

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**INTRODUCTION:** Rehabilitation following burns is integral to improving physical and psychological outcomes. Interactive video game consoles are emerging as therapeutic adjuncts due to their ease of use, affordability, and interactive gameplay. The Xbox KinectTM has advantage over similar consoles, with controller free interaction utilising three dimensional motion capture software. Player movements during gameplay have been shown to be comparable to completing daily tasks and therefore the Xbox KinectTM has potential for use as a rehabilitation tool.

**AIM:** The objectives of this pilot study were to compare the efficacy of the Xbox KinectTM with conventional physiotherapy as an adjunctive tool to promote activity and, to explore their efficacy in influencing functionality and pain.

**METHOD:** A randomised controlled clinical trial design was used. Intervention group participants were asked to complete two daily 30min exercise sessions consisting of 15min of self-directed physiotherapy exercise followed by 15min of Xbox KinectTM activities, based on location of burn. Control group participants were asked to complete two daily 30min exercise sessions of self-directed physiotherapy exercises involving two 15min sets of exercises, standardised for location of burn. Participants were recruited for a maximum of 7 days. Outcomes assessed included daily activity time, treatment satisfaction, upper limb disability, pain, and self-reported fear of movement (kinesiophobia).

**RESULTS:** A sample of 30 burn patients admitted to Royal Perth Hospital was randomised into intervention and control groups. The intervention group demonstrated significantly greater total activity time compared to control group (median 49.4 and 26.7min respectively, p<0.0001), irrespective of total burns surface area (TBSA). Significantly greater satisfaction scores were also demonstrated in the intervention group compared to controls (median 8.53 vs 7.8 respectively, p<0.0001). There was no evidence to support differences between group measures for upper limb disability, pain and fear avoidance of movement.

**CONCLUSION:** The Xbox KinectTM is a useful tool in increasing rehabilitation exercise time and patient satisfaction compared to conventional physiotherapy without indication of concurrent negative effects on patient recovery.

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**Pleural Infections in Intensive Care.**

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DOI:https://dx.doi.org/10.1016/j.chest.2016.09.032


**Pregabalin for the Treatment of Drug and Alcohol Withdrawal Symptoms: A Comprehensive Review.**


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Treatments for physical dependence and associated withdrawal symptoms following the abrupt discontinuation of prescription drugs (such as opioids and benzodiazepines), nicotine, alcohol, and cannabinoids are available, but there is still a need for new and more effective therapies. This review examines evidence supporting the potential use of pregabalin, an alpha2delta voltage-gated calcium channel subunit ligand, for the treatment of physical dependence and associated withdrawal symptoms. A literature search of the MEDLINE and Cochrane Library databases up to and including 11 December 2015 was conducted. The search term used was ‘(dependence OR withdrawal) AND pregabalin’. No other date limits were set and no language restrictions were applied. Works cited in identified articles were cross-referenced and personal archives of references also searched. Articles were included based on the expert opinions of the authors. There is limited evidence supporting the role of pregabalin for the treatment of physical dependence and accompanying withdrawal symptoms associated with opioids, benzodiazepines, nicotine, cannabinoids, and alcohol, although data from randomized controlled studies are sparse. However, the current evidence is promising and provides a platform for future studies, including appropriate randomized, placebo- and/or comparator-controlled studies, to further explore the efficacy and safety of pregabalin for the treatment of withdrawal symptoms. Given the potential for pregabalin misuse or abuse, particularly in individuals with a previous history of substance abuse, clinicians should exercise caution when using pregabalin in this patient population.

PMID:27848217
PURPOSE OF REVIEW: Implementation of effective interventions often requires evidence regarding value, that is, whether they are worth what we pay for them. This review explores recent evidence concerning cost-effectiveness in familial hypercholesterolemia, and discusses the cause of, and likelihood of solutions to, the paucity of such evidence.

RECENT FINDINGS: Cost-effectiveness analysis in familial hypercholesterolemia has been limited almost exclusively to adult populations. However, there is growing evidence that childhood intervention offers substantial benefit in terms of downstream health gains. Statin therapy in adults has been demonstrated to be cost-effective, but the range of novel agents that might be used will require de novo economic evaluation alongside exploration of their effect and safety profile.

SUMMARY: The familial hypercholesterolemia field has limited evidence regarding cost-effectiveness, which limits optimum allocation of resources. Economic evaluations are necessary to appraise new agents and optimal timing of management approaches. Evaluations often have substantial data demands; consequentially, their applicability to medical decision-making or policy will be partly determined by the availability of data, particularly those providing information about the long-term trajectory of health benefit from familial hypercholesterolemia treatment.

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Endothelial adhesion molecules and multiple organ failure in patients with severe sepsis.

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OBJECTIVE: To determine if serum levels of endothelial adhesion molecules were associated with the development of multiple organ failure (MOF) and in-hospital mortality in adult patients with severe sepsis.

DESIGN: This study was a secondary data analysis of a prospective cohort study.

SETTING: Patients were admitted to two tertiary intensive care units in San Antonio, TX, between 2007 and 2012.

PATIENTS: Patients with severe sepsis at the time of intensive care unit (ICU) admission were enrolled. Inclusion criteria were consistent with previously published criteria for severe sepsis or septic shock in adults. Exclusion criteria included immunosuppressive medications or conditions.

INTERVENTIONS: None.

MEASUREMENTS: Baseline serum levels of the following endothelial cell adhesion molecules were measured within the first 72h of ICU admission: Intracellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), and Vascular Endothelial Growth Factor (VEGF). The primary and secondary outcomes were development of MOF (2 organ dysfunction) and in-hospital mortality, respectively.

MAIN RESULTS: Forty-eight patients were enrolled in this study, of which 29 (60%) developed MOF. Patients that developed MOF had higher levels of VCAM-1 (p=0.01) and ICAM-1 (p=0.01), but not VEGF (p=0.70) compared with patients without MOF (single organ failure only). The area under the curve (AUC) to predict MOF according to VCAM-1, ICAM-1 and VEGF was 0.71, 0.73, and 0.54, respectively. Only increased VCAM-1 levels were associated with in-hospital mortality (p=0.03). These associations were maintained even after adjusting for APACHE and SOFA scores using logistic regression.

CONCLUSIONS: High levels of serum ICAM-1 was associated with the development of MOF. High levels of VCAM-1 was associated with both MOF and in-hospital mortality.

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The VHOT (Vindaloo Hastens Outpouring of Troponins) Study.
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BACKGROUND: Multiple cardiac and non-cardiac processes may cause an elevated highly sensitive troponin (hsTn). We postulated that the consumption of a seriously hot vindaloo could cause an increase in hsTn levels in seemingly healthy volunteers.

OBJECTIVE: To determine whether eating a very hot curry can cause elevated hsTn.

METHODS: This was a prospective observational cohort study. Participants had blood drawn for hsTn pre-ingestion and at 2 and 4 h post-ingestion of, first, a rather mild butter chicken and, 2 weeks later, a seriously hot lamb vindaloo. We assessed pre-curry tolerance and perception of curry hotness for both curries using the VHOT scale.

RESULTS: Although no participant had a troponin above the reference range at any point in time, we found dramatic relative increases in troponin in many of our participants. In the vindaloo phase, 8/22 (36%) had a relative change >20%, whereas 5/22 (23%) had a relative change >50% at 4h. However, these changes were not significantly different to those in the butter chicken phase. Based on biological variability alone, 15/22 (68%) had a relative change of >20%, and 11/22 (50%) had a relative change of >50% between the two sessions (pre-ingestion).

CONCLUSIONS: Eating a seriously hot vindaloo does not appear to be a risk factor for troponitis, and people may consume vindaloo safely with the knowledge that this is unlikely to result in significant damage to their myocardium. However, clinicians should be aware of the biological variability of hsTn and exercise caution when interpreting apparent changes within the normal range.

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Which patients should be transported to the emergency department? A perpetual prehospital dilemma.
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OBJECTIVE: To examine the ability of paramedics to identify patients who could be managed in the community and to identify predictors that could be used to accurately identify patients who should be transported to EDs.

METHODS: Lower acuity patients who were assessed by paramedics in the Perth metropolitan area in 2013 were studied. Paramedics prospectively indicated on the patient care record if they considered that the patient could be treated in the community. The paramedic decisions were compared with actual disposition from the ED (discharge and admission), and the occurrence of subsequent events (ambulance request, ED visit, admission and death) for discharged patients at the scene was investigated. Decision tree analysis was used to identify predictors that were associated with hospital admission.

RESULTS: In total, 57183 patients were transported to the ED, and 10204 patients were discharged at the scene by paramedics. Paramedics identified 2717 patients who could potentially be treated in the community among those who were transported to the ED. Of these, 1455 patients (53.6%) were admitted to hospital. For patients discharged at the scene, those who were indicated as suitable for community care were more likely to experience subsequent events than those who were not. The decision tree found that two predictors (age and aetiology) were associated with hospital admission. Overall discriminative power of the decision tree was poor; the area under the receiver operating characteristic curve was 0.686.

CONCLUSION: Lower acuity patients who could be treated in the community were not accurately identified by paramedics. This process requires further evaluation.

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Association between ambulance dispatch priority and patient condition.
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OBJECTIVE: To compare chief complaints of the Medical Priority Dispatch System in terms of the match between dispatch priority and patient condition.

METHODS: This was a retrospective whole-of-population study of emergency ambulance dispatch in Perth, Western Australia, 1 January 2014 to 30 June 2015. Dispatch priority was categorised as either Priority 1 (high priority), or Priority 2 or 3. Patient condition was categorised as time-critical for patient(s) transported as Priority 1 to hospital or who died (and resuscitation was attempted by paramedics); else, patient condition was categorised as less time-critical. The chi-square statistic was used to compare chief complaints by false omission rate (percentage of Priority 2 or 3 dispatches that were time-critical) and positive predictive value (percentage of Priority 1 dispatches that were time-critical). We also reported sensitivity and specificity.

RESULTS: There were 211473 cases of dispatch. Of 99988 cases with Priority 2 or 3 dispatch, 467 (0.5%) were time-critical. Convulsions/seizures and breathing problems were highlighted as having more false negatives (time-critical despite Priority 2 or 3 dispatch) than expected from the overall false omission rate. Of 111485 cases with Priority 1 dispatch, 6520 (5.8%) were time-critical. Our analysis highlighted chest pain, heart problems/automatic implanted cardiac defibrillator, unknown problem/collapse, and headache as having fewer true positives (time-critical and Priority 1 dispatch) than expected from the overall positive predictive value.

CONCLUSION: Scope for reducing under-triage and over-triage of ambulance dispatch varies between chief complaints of the Medical Priority Dispatch System. The highlighted chief complaints should be considered for future research into improving ambulance dispatch system performance.

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**Comparison of preoperative continuation and discontinuation of aspirin in patients undergoing total hip or knee arthroplasty.**

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**INTRODUCTION:** Preoperative discontinuation of aspirin (acetylsalicylic acid) can reduce bleeding risk but may increase the risk of perioperative cardiovascular events.

**MATERIALS AND METHODS:** We retrospectively assessed the impact of preoperative continuation versus discontinuation of aspirin compared with a control group in a cohort of 739 consecutive patients undergoing total hip (THA) (n = 396) or knee arthroplasty (TKA) (n = 343) at a tertiary hospital. Bleeding risk, local complications, orthopaedic outcome, and cardiac and cerebral complications were assessed.

**RESULTS:** Four hundred and sixty-five patients did not receive antithrombotic or full-dose anticoagulant medication, 175 patients were taking low-dose aspirin, 99 vitamin K antagonists, clopidogrel, or a combination of these drugs. Of the patients taking aspirin, 139 discontinued and 36 continued aspirin. Blood loss and local bleeding complications were comparable in these two groups. TKA patients who continued aspirin more frequently showed marked knee swelling after 1 week than those discontinuing aspirin (35.1 vs. 81.3 %; p = 0.001). However, orthopaedic outcome did not differ significantly between the two groups. There was a trend towards an increased risk of cardiac complications in patients who discontinued aspirin (6.5 vs. 0.0 %; p = 0.107).

**CONCLUSIONS:** Continuation or discontinuation of aspirin did not show a statistically significant difference in the risk of relevant perioperative bleeding complications in our study. Continuation of aspirin was associated with a transitory increase in knee swelling, but had no effect on orthopaedic outcome. Continuation of aspirin may be associated with a favourable perioperative cardiac outcome. Our data support perioperative continuation of aspirin intake in patients undergoing THA or TKA.

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**A comparison of kneeling ability after lateral or midline incisions in total knee arthroplasty.**

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Kneeling is often impaired following total knee replacement. There is no clinical study comparing a lateral to a midline skin incision with regard to kneeling. Patients with a well-functioning total knee replacement enrolled in the trial. The participants with a lateral skin incision were matched with those with a standard midline incision. Twenty-two patients were enrolled in the study: 10 had a lateral skin incision, and 12 had a midline incision. Those with a lateral skin incision had a significantly higher Forgotten Joint Score than with a midline skin incision (Difference of Means Lateral
vs Midline = 10.9 [p value 0.0098]), and an improved ability to kneel at 110 degrees of flexion (Kneeling Ability Test; Difference of Means Lateral vs Midline = 41.7 [p value 0.020]). These results suggest that a lateral skin incision may provide reduced joint awareness and improved kneeling ability. Further investigation with a randomised controlled trial is needed.

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F<sub>2</sub>-Isoprostanes in HDL are bound to neutral lipids and phospholipids.

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Low HDL cholesterol (HDL-C) is a risk factor for coronary artery disease (CAD). However, interventions that raise HDL-C have failed to reduce cardiovascular events. We previously reported that HDL is the main carrier of plasma F<sub>2</sub>-isoprostanes (F<sub>2</sub>-IsoPs) that are markers of oxidative stress formed upon oxidation of arachidonic acid. F<sub>2</sub>-IsoPs are predominantly associated with phospholipids. However, there is evidence that F<sub>2</sub>-IsoPs in the liver of rats treated with carbon tetrachloride associate with the neutral lipids. To date it is not known whether F<sub>2</sub>-IsoPs are found in the neutral lipids in HDL in humans. Possible candidate neutral lipids include cholesteryl esters, triglycerides, diglycerides, and monoglycerides. This study aimed to identify the lipid classes within native and oxidized HDL that contain F<sub>2</sub>-IsoPs. We showed that F<sub>2</sub>-IsoPs in HDL are bound to neutral lipids as well as phospholipids. HDL-3 contained the highest concentration of F<sub>2</sub>-IsoPs in all lipid classes before and after in vitro oxidation. Using targeted LC/MS and high resolution MS, we were unable to provide conclusive evidence for the presence of the synthesized standards 15(R)-15-F<sub>2</sub>-isoprostane cholesterol and 1-ent-15(RS)-15-F<sub>2</sub>-isoprostanoylethanolamine in the neutral lipids of HDL. Our findings show that oxidized lipids such as F<sub>2</sub>-IsoPs are found in the core and surface of HDL. However, the exact molecular species remain to be definitively characterized. Future studies are required to determine whether the presence of F<sub>2</sub>-IsoPs in neutral lipids alters HDL function.

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HLA Class I and II alleles, heterozygosity and HLA-KIR interactions are associated with rates of genital HSV shedding and lesions.

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Variation at HLA and KIR loci is associated with the severity of viral infections. To assess associations of genital HSV-2 infection with human HLA and KIR genetic loci, we measured the frequencies of genital herpes simplex virus (HSV) DNA detection and of genital lesions in HSV-2 seropositive persons. We followed 267 HSV-2 seropositive persons who collected daily genital swabs and recorded lesions for 30 days. All persons were laboratory-documented as HIV-seronegative, and all were Caucasian by self-report. HSV detection rate and lesion frequency were compared by genotype using Poisson regression. Overall, HSV was detected on 19.1% of days and lesions on 11.6% of days. The presence of HLA-A*01 was directly associated with HSV detection frequency, whereas the presence of HLA-C*12 was inversely associated with HSV detection frequency. The presence of HLA-A*01 was directly associated with lesion rate, while HLA-A*26, -C*01 and -DQB1*0106 were associated with decreased lesions. We observed an interaction between the absence of both 2DS4del and HLA-Bw4 and higher lesion rate. Heterozygosity of HLA was also associated with reduced lesion frequency. Immune control of genital HSV infection relies on multiple interacting immunogenetic elements, including epistatic interactions between HLA and KIR.

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Characterization of a novel staphylococcal cassette chromosome composite island from community-associated MRSA isolated in aged care facilities in Western Australia.

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BACKGROUND: In Western Australia (WA), clonal complex 5, ST835, community-associated (CA) MRSA is isolated almost exclusively from aged care facilities. In WA four different staphylococcal cassette chromosome (SCC) mec (SCCmec) elements have been identified in this ST, indicating high genetic activity in the SCCmec region.

OBJECTIVES: To investigate the SCC region of ST835 CA-MRSA WA MRSA-40 and determine the distribution of an SCCsorbitol element found within the region.

RESULTS: The SCC region contained a composite island, SCCmec<sub>WA MRSA-40</sub>-CI, that was composed of three elements, PSISCCpIs, SCCsorbitol and SCCmecV<sub>T</sub> (5C2&5). This is the first time that a sorbitol operon has been reported in an SCC element.

CONCLUSIONS: Generation of SCCmec<sub>WA MRSA-40</sub>-CI has involved multiple genetic events and recombination with CoNS has occurred during evolution of the SCC elements. While Staphylococcus aureus is renowned for its ability to utilize mobile genetic elements to disseminate antimicrobial resistance, the SCC region of WA MRSA-40 shows that this clone has also utilized SCC elements to acquire extra virulence and possibly adapt to a niche environment.

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**Plate Positioning in Periprosthetic or Interprosthetic Femur Fractures With Stable Implants-A Biomechanical Study.**

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BACKGROUND: Angular stable plate fixation is a widely accepted treatment option for interprosthetic or periprosthetic femoral fractures with stable implants. This biomechanical study tries to establish a safe distance of the plate from the tip of a femoral prosthesis.

METHODS: A total of 38 composite femurs were reamed to an inner diameter of 23 mm to create an osteoporotic bone model. A Weber hip stem was cemented into each and a distal femoral NCB plate applied with the distance to the stem varying from 8 cm apart to 6 cm overlap in 2-cm steps. Each specimen was tested in cyclic axial loading (400 N-1500 N) and then cyclic torsion (0.6 Nm-50 Nm). Peak strain on the femur around the tip of the plate was measured with a 3D image correlation system and averaged over 26 cycles (excluding the first 3 and the last cycles). Finally, each femur was axially loaded to failure.

RESULTS: Strain increased with decreasing overlap or gap. Seven specimens failed early between 2-cm overlap and 2-cm gap. Results were divided into a far group with a distance of >4 cm and a close group of <4 cm. Strain was significantly higher in the close group for axial (P < .001) and torsional (P < .001) loading. Failure load was significantly lower in the close group (P = .002).

CONCLUSION: A minimal gap and/or overlap of at least 6 cm is recommended in osteoporotic bone to avoid stress.
Determinants of 6-month survival of critically ill patients with an active hematologic malignancy.

Richards, S; Wibrow, B; et al.

PURPOSE: This study assessed the determinants of 6-month survival of critically ill patients with an active hematologic malignancy (HM).

METHODS: All patients with an active HM defined by either receiving ongoing or due to receive antineoplastic therapy, admitted to 2 tertiary intensive care units between 2010 and 2015, were included in this retrospective cohort study.

RESULTS: Of the 273 patients included in the study (median age, 63[interquartile range, 54-71] years; 40.7% female), 116 (42.5%; 95% confidence interval, 36.8-48.4) died in hospital. The 6-month mortality was 56.4% (95% confidence interval, 50.5-62.2). Mechanical ventilation, intensive care unit admission source, and the type of active HM were significantly associated with hospital mortality and 6-month survival, after adjusting for severity of acute illness. The type of active HM was the most important prognostic factor, with over a 10-fold difference in 6-month survival between HM with the best and worst prognosis. In addition, recent hematopoietic stem cell transplant (<30 days) was associated with a better 6-month survival.

CONCLUSION: Differences in 6-month survival between critically ill patients with different types of active HM were substantial. Recent hematopoietic stem cell transplant, severity of illness, and use of mechanical ventilation were additional important determinants of 6-month survival in patients with an active HM.

Use and limitations of prognostic models for the critically ill.

Ho, K.M.

PURPOSE: This study assessed the use and limitations of prognostic models for the critically ill patients with an active hematologic malignancy (HM).

METHODS: All patients with an active HM defined by either receiving ongoing or due to receive antineoplastic therapy, admitted to 2 tertiary intensive care units between 2010 and 2015, were included in this retrospective cohort study.

RESULTS: Of the 273 patients included in the study (median age, 63[interquartile range, 54-71] years; 40.7% female), 116 (42.5%; 95% confidence interval, 36.8-48.4) died in hospital. The 6-month mortality was 56.4% (95% confidence interval, 50.5-62.2). Mechanical ventilation, intensive care unit admission source, and the type of active HM were significantly associated with hospital mortality and 6-month survival, after adjusting for severity of acute illness. The type of active HM was the most important prognostic factor, with over a 10-fold difference in 6-month survival between HM with the best and worst prognosis. In addition, recent hematopoietic stem cell transplant (<30 days) was associated with a better 6-month survival.

CONCLUSION: Differences in 6-month survival between critically ill patients with different types of active HM were substantial. Recent hematopoietic stem cell transplant, severity of illness, and use of mechanical ventilation were additional important determinants of 6-month survival in patients with an active HM.

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Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry.

Bohm M, Ukena C, et al.

OBJECTIVES: Renal denervation (RDN) can reduce sympathetic activity and blood pressure (BP) in patients with hypertension. The effects on resting and ambulatory heart rate (HR), also regulated by the sympathetic nervous system, are not established.

METHODS: Herein, we report 12-month outcomes from the Global SYMPLICITY Registry on office and ambulatory HR and BP in patients with uncontrolled hypertension (n = 846).

RESULTS: HR declined in correlation with the HR at baseline and at 12 months, in particular, in patients in the upper tertile of HR (>74 bpm). BP reduction was similar in the tertiles of HR at baseline. Similar effects were observed when 24-h ambulatory HR and SBP were determined. Office HR was similarly decreased when patients were on a beta-blocker or not. Antihypertensive treatment remained unchanged during the 12-month period of the Global SYMPLICITY Registry.

CONCLUSION: RDN reduces BP independent from HR. A HR reduction is dependent on baseline HR and unchanged by beta-blocker treatment. The effects of RDN on SBP and HR are durable up to 1 year. HR reduction might be a target for RDN in patients with high HR at baseline, which needs to be scrutinized in prospective trials.

Effects of muscle strength and endurance on blood pressure and related cardiometabolic risk factors from childhood to adolescence.


OBJECTIVE: This study aimed to examine the evolution of relationships between measures of muscle strength and endurance with individual cardiometabolic risk factors from childhood to late adolescence in a prospective population-based cohort.

METHODS: Participants from the Western Australian Pregnancy Cohort (Raine) Study at ages 10, 14 and 17 were analysed, using longitudinal linear mixed model analyses.

RESULTS: Handgrip strength after adjusting for the confounding effects of BMI was positively associated with SBP, but not DBP. The association between handgrip strength and SBP was stronger in men than women at all time points (coefficient [women]: 0.18, P < 0.001; sex x handgrip strength coefficient: 0.09, P = 0.002). The association was strongest at 10 years and significantly attenuated over time (year x handgrip coefficient from 10 to 14 years: -0.11, P = 0.003; year x handgrip coefficient from 10 to 17 years: -0.19, P < 0.001). After the inclusion of BMI as a confounder, handgrip strength was significantly negatively associated with homeostatic model assessment of insulin resistance and high-sensitivity C-reactive protein over time in both sexes. Back muscle endurance was positively associated with SBP, but not DBP, after adjustment for the confounding effects of BMI (coefficient: 0.01, P = 0.002). There were small, albeit significant, inverse associations between back muscle endurance and log homeostatic model assessment of insulin resistance and log high-sensitivity C-reactive protein.
CONCLUSION: The positive association between handgrip strength and back muscle endurance with SBP throughout childhood and adolescence contrasts with beneficial effects on other related traditional cardiometabolic risk factors. Mechanisms underlying these paradoxical effects on SBP warrant further investigation.

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Effects of pentoxifylline on inflammatory markers and blood pressure: a systematic review and meta-analysis of randomized controlled trials.


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INTRODUCTION: Pentoxifylline is a xanthine derivative with potential cardiovascular benefits.

AIM: To evaluate the impact of pentoxifylline on blood pressure (BP) and plasma TNF-alpha, C-reactive protein (CRP) and IL-6 through a systematic review and meta-analysis of randomized controlled trials.

METHODS: The protocol was registered (PROSPERO: CRD42016035988). The search included PUBMED, ProQuest, Scopus and EMBASE until 1 September 2015 to identify trials reporting BP or inflammatory markers during pentoxifylline therapy. Quantitative data synthesis was performed using a random-effects model, with weighted mean difference (WDF) and 95% confidence intervals (CIs) as summary statistics.

RESULTS: Fifteen studies (16 treatment arms) were found to be eligible for inclusion. Meta-analysis did not suggest any effect of pentoxifylline on either SBP or DBP. Pentoxifylline treatment was associated with a significant reduction in plasma concentrations of TNF-alpha (WDF: -1.03 pg/ml, 95% CI: -1.54, -0.51; P < 0.001, 11 treatment arms) and CRP (WDF: -1.39 mg/l, 95% CI: -2.68, -0.10; P = 0.034, five treatment arms). No alteration in plasma IL-6 concentration was observed. The impact of pentoxifylline on plasma TNF-alpha levels was found to be positively associated with treatment duration (slope: 0.031; 95% CI: 0.004, 0.057; P = 0.023) but independent of pentoxifylline dose (slope: -0.0003; 95% CI: -0.002, 0.001; P = 0.687).

CONCLUSION: Pentoxifylline did not alter BP or plasma IL-6 concentration, but significantly reduced circulating TNF-alpha and CRP concentrations.

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Effect of omega-3 fatty acid supplementation on arterial elasticity in patients with familial hypercholesterolaemia on statin therapy.

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BACKGROUND AND AIMS: Increased arterial stiffness is closely linked with raised blood pressure that contributes substantially to enhanced risk of coronary heart disease in high risk individuals with familial hypercholesterolaemia (FH). Omega-3 fatty acid (omega3-FA) supplementation has been demonstrated to lower blood pressure in subjects with a high cardiovascular disease risk. Whether omega3-FA supplementation improves arterial stiffness in FH subjects, on background statin therapy, has yet to be investigated.

METHOD AND RESULTS: We carried out an 8-week randomized, crossover intervention trial to test the effect of 4 g/d omega3-FA supplementation (46% eicosapentaenoic acid and 38% docosahexaenoic acid) on arterial elasticity in 20 adults with FH on optimal cholesterol-lowering therapy. Large and small artery elasticity were measured by pulse contour analysis of the radial artery. omega3-FA supplementation significantly (P < 0.05 in all) increased large artery elasticity (+9%) and reduced systolic blood pressure (-6%) and diastolic blood pressure (-6%), plasma triglycerides (-20%), apoB concentration (-8%). In contrast, omega3-FAs had no significant effect on small artery elasticity. The change in large artery elasticity was not significantly associated with changes in systolic blood pressure or plasma triglyceride concentration.

CONCLUSIONS: omega3-FA supplementation improves large arterial elasticity and arterial blood pressure independent of statin therapy in adults with FH.

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Suicide in older men: The health in men cohort study (HIMS).
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Suicide rates are high in later life, particularly among older men. Mood disorders are known risk factors, but the risk of suicide associated with poor physical health remains unclear. We completed a cohort study of a community
A representative sample of 38,170 men aged 65-85 in 1996 who were followed for up to 16 years. Data on suicide attempts and completion were obtained from the Western Australia Data Linkage System, as was information about medical and mental health diagnoses. 240 (0.6%) participants had a recorded history of past suicide attempt, most commonly by poisoning (85%). Sixty-nine men died by suicide during follow up (0.3% of all deaths), most often by hanging (50.7%). Age-adjusted competing risk regression showed that past suicide attempt was not a robust predictor of future suicide completion (sub-hazard ratio, SHR=1.58, 95% CI=0.39, 6.42), but bipolar (SHR=7.82, 95% CI=3.08, 19.90), depressive disorders (SHR=2.26, 95% CI=1.14, 4.51) and the number of health systems affected by disease (SHR for 3-4 health systems=6.02, 95% CI=2.69, 13.47; SHR for >5 health systems=11.18, 95% CI=4.89, 25.53) were. The population fraction of suicides attributable to having 5 or more health systems affected by disease was 79% (95% CI=57%, 90%), and for any mood disorder (bipolar or depression) it was 17% (95% CI=3%, 28%). Older Australian men with multiple health morbidities have the highest risk of death by suicide, even after taking into account the presence of mood disorders. Improving the overall health of the population may be the most effective way of decreasing the rates of suicide in later life.

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**Pushing the envelope: laparoscopy and primary anastomosis are technically feasible in stable patients with Hinchey IV perforated acute diverticulitis and gross faeculent peritonitis.**

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**INTRODUCTION:** Modern management of severe acute complicated diverticulitis continues to evolve towards more conservative and minimally invasive strategies. Although open sigmoid colectomy with end colostomy remains the most commonly used procedure for the treatment of perforated diverticulitis with purulent/faeculent peritonitis, recent major advances challenged this traditional approach, including the increasing attitude towards primary anastomosis as an alternative to end colostomy and use of laparoscopic approach for urgent colectomy.

**TECHNIQUE:** Provided an accurate patients selection, having the necessary haemodynamic stability, pneumoperitoneum is established with open Hasson technique and diagnostic laparoscopy is performed. If faeculent peritonitis (Hinchey IV perforated diverticulitis) is found, laparoscopy can be continued and a further three working ports are placed using bladeless trocars, as in traditional laparoscopic sigmoidectomy, with the addition of fourth trocar in left flank. The fecal matter is aspirated either with large-size suction devices or, in case of free solid stools, these can be removed with novel application of tight sealing endobags, which can be used for scooping the fecal content out and for its protected retrieval. After decontamination, a sigmoid colectomy is performed in the traditional laparoscopic fashion. The sigmoid is fully mobilised from the retroperitoneum, and mesocolon is divided up to the origin of left colic vessels. Whenever mesentery has extremely inflamed and thickened oedematous tissues, an endostapler with vascular load can be used to avoid vascular selective ligatures. Splenic flexure should be appropriately mobilised. The specimen is extracted through mini-Pfannenstiel incision with muscle splitting technique. Transanal colo-rectal anastomosis is fashioned. Air-leak test must be performed and drains placed where appropriate.
RESULTS: The video shows operative technique for a single-stage, entirely laparoscopic, washout and sigmoid colectomy with primary colorectal anastomosis in a 35-year-old male patient with severe and diffuse free faeculent diverticular peritonitis (Hinchey IV). The patient was managed post-operatively according to enhanced recovery protocol and discharged home after 9 days, following an uneventful recovery.

CONCLUSIONS: This case documents the technical feasibility of a minimally invasive single-stage procedure in a patient with Hinchey IV perforated diverticulitis with diffuse fecal peritonitis. The laparoscopic approach facilitated an effective decontamination of the peritoneal cavity, with a combination of large suction devices and aid of protected retrieval by closed endobags for effectively and completely laparoscopic removal of the solid fecal matter, offering clear advantages and excellent results even in such challenging cases. With necessary expertise, the sigmoid resection can be thereafter safely and entirely performed laparoscopically, the specimen extracted through mini-Pfannenstiel incision, and a laparoscopic intracorporeal transanal circular primary anastomosis performed.

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Interactive patient blood management dashboards used in Western Australia.
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Relationship Between 'Immediate' Resistive Index Measurement After Renal Transplantation and Renal Allograft Outcomes.
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BACKGROUND: The arterial resistive index, also referred to as the resistive index (RI) or Pourcelot Index, is a measure of pulsatile blood flow. Previous studies have demonstrated the usefulness of the RI as a predictor of allograft outcomes based on RI measurement in the later stages after transplantation. However, there is little evidence of the predictive value of “immediate” RI measurement within 24 hours after transplantation.

METHODS: We performed a retrospective cohort study of 305 adult renal transplants carried out between 2003 and 2013. The associations between immediate RI measurement (within 24 hours after transplantation) and donor,
recipient, and surgical factors were analyzed. In addition, the correlations between immediate RI measurement and renal allograft outcomes, including delayed graft function (DGF) and transplant failure (TF), also were evaluated.

RESULTS: From a cohort of 305 patients, 52 were excluded on the basis of confounding factors. Of the remaining 253 patients, the mean age was 48.4 years, 57.5% were male, and approximately one-third had diabetes. Two hundred twenty-six patients had an RI < 0.8, whereas only 27 had an RI > 0.8. Significant associations were found between elevated RI (>0.8) and both DGF (odds ratio = 3.22, P = .006) and TF (odds ratio = 3.54, P = .008).

CONCLUSIONS: Immediate RI measurement after renal transplantation is a strong predictor of both DGF and TF.

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What we need to know about renal nerve ablation for treatment of hypertension and other states of sympathetic overactivity.
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Renal nerves are key players in the regulation of kidney function and blood pressure control. Targeting the neurogenic mechanisms underlying hypertension and cardiac and renal disease has been attempted by means of surgical and pharmacologic approaches and most recently by catheter-based interventions aimed at disrupting renal sympathetic nerve traffic. The recent developments in the area and the relevant questions that need to be addressed to advance the field further are briefly reviewed in this article.

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In vivo label-free lymphangiography of cutaneous lymphatic vessels in human burn scars using optical coherence tomography.
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in vivo using optical coherence tomography (OCT). This method corrects for the variation in OCT signal due to the confocal function and sensitivity fall-off of a spectral-domain OCT system and utilizes a single-scattering model to compensate for A-scan signal attenuation to enable reliable thresholding of lymphatic vessels. A segment-joining algorithm is then incorporated into the method to mitigate partial-volume effects with small vessels. The lymphatic vessel images are augmented with images of the blood vessel network, acquired from the speckle decorrelation with additional weighting to differentiate blood vessels from the observed high decorrelation in lymphatic vessels. We demonstrate the method with longitudinal scans of human burn scar patients undergoing ablative fractional laser treatment, showing the visualization of the cutaneous lymphatic and blood vessel networks.

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BACKGROUND: Antimicrobial resistance (AMR) by Neisseria gonorrhoeae is considered a serious global threat.

METHODS: In this nationwide study, we used MassARRAY iPLEX genotyping technology to examine the epidemiology of N. gonorrhoeae and associated AMR in the Australian population. All available N. gonorrhoeae isolates (n = 2452) received from Australian reference laboratories from January to June 2012 were included in the study. Genotypic data were combined with phenotypic AMR information to define strain types.

RESULTS: A total of 270 distinct strain types were observed. The 40 most common strain types accounted for over 80% of isolates, and the 10 most common strain types accounted for almost half of all isolates. The high male to female ratios (>94% male) suggested that at least 22 of the top 40 strain types were primarily circulating within
networks of men who have sex with men (MSM). Particular strain types were also concentrated among females: two strain types accounted for 37.5% of all isolates from females. Isolates harbouring the mosaic penicillin binding protein 2 (PBP2)-considered a key mechanism for cephalosporin resistance-comprised 8.9% of all N. gonorrhoeae isolates and were primarily observed in males (95%).

CONCLUSIONS: This large scale epidemiological investigation demonstrated that N. gonorrhoeae infections are dominated by relatively few strain types. The commonest strain types were concentrated in MSM in urban areas and Indigenous heterosexuals in remote areas, and we were able to confirm a resurgent epidemic in heterosexual networks in urban areas. The prevalence of mosaic PBP2 harboring N. gonorrhoeae strains highlight the ability for new N. gonorrhoeae strains to spread and become established across populations.

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'It promoted a positive culture around falls prevention': staff response to a patient education programme-a qualitative evaluation.

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OBJECTIVES: The purpose of this study was to understand how staff responded to individualised patient falls prevention education delivered as part of a cluster randomised trial, including how they perceived the education contributed to falls prevention on their wards.

DESIGN: A qualitative explanatory study.

METHODS: 5 focus groups were conducted at participatory hospital sites. The purposive sample of clinical staff (including nurses, physiotherapists and quality improvement staff) worked on aged care rehabilitation wards when a cluster randomised trial evaluating a patient education programme was conducted. During the intervention period, an educator, who was a trained health professional and not a member of staff, provided individualised falls prevention education to patients with good levels of cognition (Mini-Mental State Examination > 23/30). Clinical staff were provided with training to support the programme and their feedback was sought after the trial concluded, to
understand how they perceived the programme impacted on falls prevention. Data were thematically analysed using NVivo qualitative data analysis software.

RESULTS: 5 focus groups were conducted at different hospitals (n=30 participants). Staff perceived that the education created a positive culture around falls prevention and further, facilitated teamwork, whereby patients and staff worked together to address falls prevention. The educator was perceived to be a valuable member of the team. Staff reported that they developed increased knowledge and awareness about creating a safe ward environment. Patients being proactive and empowered to engage in falls prevention strategies, such as ringing the bell for assistance, was viewed as supporting staff falls prevention efforts and motivating staff to change practice.

CONCLUSIONS: Staff responded positively to patient falls prevention education being delivered on their wards. Providing individualised patient education to older patients with good levels of cognition can empower staff and patients to work as a team to address falls prevention on hospital rehabilitation wards.

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ODYSSEY ESCAPE: is PCSK9 inhibition the Trojan Horse for the use of lipoprotein apheresis in familial hypercholesterolaemia?
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Influenza epidemiology in patients admitted to sentinel Australian hospitals in 2015: the Influenza Complications Alert Network.
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The Influenza Complications Alert Network (FluCAN) is a sentinel hospital-based surveillance program that operates at sites in all states and territories in Australia. This report summarises the epidemiology of hospitalisations with laboratory-confirmed influenza during the 2015 influenza season. In this observational study, cases were defined as patients admitted to one of the sentinel hospitals with an acute respiratory illness with influenza confirmed by nucleic acid detection. During the period 1 April to 30 October 2015 (the 2015 influenza season), 2,070 patients were admitted with confirmed influenza to one of 17 FluCAN sentinel hospitals. Of these, 46% were elderly (> 65 years), 15% were children (< 16 years), 5% were Indigenous Australians, 2.1% were pregnant and 75% had chronic co-morbidities. A high proportion were due to influenza B (51%). There were a large number of hospital admissions detected with confirmed influenza in this national observational surveillance system in 2015 with case numbers similar to that reported in 2014. The national immunisation program is estimated to avert 46% of admissions from confirmed influenza across all at-risk groups, but more complete vaccination coverage in target groups could further reduce influenza admissions by as much as 14%.

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Intercostal artery pseudoaneurysm with spontaneous resolution in the setting of an artery of Adamkiewicz.

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We report an extremely unique and previously unreported case of a pseudoaneurysm arising from an intercostal artery that also gave origin to the artery of Adamkiewicz. Due to the potential risk of losing the artery of Adamkiewicz, a conservative approach was indicated. On short interval follow-up imaging, the pseudoaneurysm and associated hematoma spontaneously resolved with preservation of the intercostal artery. We performed a literature review of the natural course of pseudoaneurysm as well as their occurrence in the intercostal arteries.

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Challenges during long-term follow-up of ICU patients with and without chronic disease.
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INTRODUCTION: Reflecting on researchers’ experiences during follow-up of patients enrolled in research may lead to improved understanding of the challenges faced in maintaining contact when patients leave hospital.

AIMS: (1) Describe the challenges researchers face when following-up patients who survive ICU. (2) Identify issues that influenced our ability to follow-up patients.

METHODS: This sub-study was part of a larger “case-control” study investigating the quality of life of ICU survivors with and without pre-existing chronic disease. Patients completed self-assessment QLQ and symptom assessment before hospital discharge and at six months, plus they were asked to keep a paper diary of healthcare services used. Patient contact was maintained by monthly telephone calls. Each telephone call was logged and summaries of conversations documented. Our experience of conducting the study was reviewed by the identification of common issues which arose from the follow-up of patients.

RESULTS: Thirty patients with a history of chronic disease and 30 patients without underlying chronic disease were followed-up. A total of 582 telephone calls were made for 60 patients discharged from hospital of which 261 (45%) calls led to a telephone interview. Only 19 (30%) of diaries were completed and returned. We identified six challenges associated with issues that arose from the follow-up of patients.

CONCLUSION: We underestimated the number of telephone calls required for follow-up after discharge. Diaries were unreliable sources of data suggesting strategies are needed to improve compliance. How patients respond to follow-up is not always predictable. Processes are needed to deal with unexpected information provided during telephone follow-up.

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Interactive gaming consoles reduced pain during acute minor burn rehabilitation: A randomized, pilot trial.

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INTRODUCTION: Interactive gaming consoles (IGCs) have been used successfully in rehabilitation settings as an adjunct to conventional exercise for restoring or maintaining active function and augmenting pharmacological analgesia.

AIM: The objective of this pilot study was to assess if adjunctive use of the Nintendo Wii IGC was of benefit to acute burn patients.

METHOD: This was a randomized, controlled trial. The intervention group received routine rehabilitation in addition to up to 5 days of twice daily, 20-30 min of exercise using the Nintendo Wii IGC. The control group received routine rehabilitation exercise therapy.

RESULTS: A total of 22 subjects were recruited and randomized by location of burn to intervention and control
groups. Pain scores were significantly improved in the intervention group ($r(2)=1.18; 95\%CI -0.584 to -0.298, p=0.019$) as indicated by a 17% greater drop in the pre-post-study pain compared to controls. Fear avoidance and ROM measurements were not statistically different between the groups.

CONCLUSION: The Nintendo Wii IGC was associated with a greater reduction in pain, particularly in those with higher levels of pain at baseline.

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**Patterns of sedentary behaviour and physical activity in people following curative intent treatment for non-small cell lung cancer.**

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This study aimed to compare patterns of sedentary behaviour (SB) and physical activity (PA) in people following curative intent treatment for non-small cell lung cancer (NSCLC) with healthy controls. Participants 6-10 weeks following lobectomy for NSCLC and healthy controls wore two activity monitors for 7 days. Waking hours were divided into time spent in SB (<1.5 metabolic equivalent of tasks (METs)), light intensity PA (LIPA > 1.5 to <3.0METs) and moderate-to-vigorous intensity PA (>3.0METs). Daily steps were also recorded. Data were available in 20 participants with NSCLC (13 females; 68 +/- 10 years) and 20 healthy controls (13 females; 69 +/- 5 years). The NSCLC group accumulated a greater percentage of time in SB in uninterrupted bouts >30 minutes (49% vs. 42%; $p = 0.048$). Further, the NSCLC group spent a lower percentage of waking hours in LIPA (21 +/- 9% vs. 26 +/- 8%; $p = 0.04$) and accumulated a lower percentage of time in this domain in uninterrupted bouts >10 minutes (49% vs. 42%; $p = 0.048$) and moderate-to-vigorous intensity PA (56% vs. 67%; $p = 0.048$). The NSCLC group also had a lower daily step count (8863 +/- 3737 vs. 11,856 +/- 3024 steps/day; $p = 0.009$). Time spent in moderate-to-vigorous intensity PA was similar in both groups ($p = 0.92$). People following curative intent treatment for NSCLC spend more time in prolonged bouts of SB at the expense of LIPA.

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**Evaluation of the efficacy of a polyherbal mouthwash containing Zingiber officinale, Rosmarinus officinalis and Calendula officinalis extracts in patients with gingivitis: A randomized double-blind placebo-controlled trial.**
BACKGROUND: Gingivitis is a highly prevalent periodontal disease resulting from microbial infection and subsequent inflammation. The efficacy of herbal preparations in subjects with gingivitis has been reported in some previous studies.

OBJECTIVE: To investigate the efficacy of a polyherbal mouthwash containing hydroalcoholic extracts of Zingiber officinale, Rosmarinus officinalis and Calendula officinalis (5% v/w) compared with chlorhexidine and placebo mouthwashes in subjects with gingivitis.

METHODS: Sixty patients participated in this randomized double-blind placebo-controlled trial and were randomly assigned to the polyherbal mouthwash (n = 20), chlorhexidine mouthwash (n = 20) or placebo mouthwash (n = 20). Participants were instructed to use the mouthwash twice a day (after breakfast and dinner) for 30 s for a period of two weeks. Gingival and plaque indices were assessed using MGI, GBI and MQH scales at baseline, day 7 and day 14 of the trial.

RESULTS: There were significant improvements in all assessed efficacy measures i.e. MGI, GBI and MQH scores from baseline to the end of trial in both polyherbal and chlorhexidine mouthwash groups; however, the scores remained statistically unchanged in the placebo group. MGI, BGI and MQH scores in the treatment groups were significantly lower compared with those of the control group at both day 7 and day 14 of the trial. However, there was no significant difference between the polyherbal and chlorhexidine groups, neither at day 7 nor day 14 of the trial. Polyherbal mouthwash was safe and there was neither report of adverse reactions, nor any drop-out during the course of study.

CONCLUSION: Polyherbal mouthwash containing hydroalcoholic extracts of Z. officinale, R. officinalis and C. officinalis (5%) was effective in the treatment of gingivitis and its efficacy was comparable to that of chlorhexidine mouthwash. Copyright © 2015 Elsevier Ltd. All rights reserved. PMID:26850813 DOI:https://dx.doi.org/10.1016/j.ctcp.2015.12.001


Central Sympathetic Inhibition: a Neglected Approach for Treatment of Cardiac Arrhythmias?
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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Overactivation of the sympathetic nervous system (SNS) plays an important role in the pathogenesis of comorbidities related to AF such as hypertension, congestive heart failure, obesity, insulin resistance, and obstructive sleep apnea. Methods that reduce sympathetic drive, such as centrally acting sympatho-inhibitory agents, have been shown to reduce the incidence of spontaneous or induced atrial arrhythmias, suggesting that neuromodulation may be helpful in controlling AF. Moxonidine acts centrally to reduce activity of the SNS, and clinical trials indicate that this is associated with a decreased AF burden in hypertensive patients with paroxysmal AF and reduced post-ablation recurrence of AF in patients with hypertension who underwent pulmonary vein isolation (PVI). Furthermore, device-based approaches to reduce sympathetic drive, such as renal denervation, have yielded promising results in the prevention and treatment of cardiac arrhythmias. In light of these recent findings, targeting elevated sympathetic drive with either pharmacological or device-based approaches has become a focus of clinical research. Here, we review the data currently available to explore the potential utility of sympatho-inhibitory therapies in the prevention and treatment of cardiac arrhythmias.


**n-3 Fatty acid supplementation and proresolving mediators of inflammation.**

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PURPOSE OF REVIEW: The review presents recent developments in the identification of specialized proresolving mediators (SPMs) of inflammation following supplementation with n-3 fatty acids in humans.

RECENT FINDINGS: A number of reports have measured SPMs in human plasma after n-3 fatty acid supplementation. Although studies have shown some variability in plasma SPM levels, there is strong evidence that a number of resolvins are increased after n-3 fatty acids to concentrations that have been shown to have biological activity. SPM concentrations at the inflammatory site would be expected to be higher than that in blood. SPMs derived from docosapentaenoic acid require further investigation.

SUMMARY: Resolution of inflammation is an active process with SPM playing a vital role in maintaining homeostasis. Studies in humans are providing evidence to suggest that this may be a relevant mechanism that can be stimulated by n-3 fatty acid supplementation. Further research is now required to determine SPM profiles in patients with different chronic conditions and to examine whether supplementation with n-3 fatty acids affects SPMs in relation to their clinical outcome.

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**Mesenchymoangioblast-derived mesenchymal stromal cells inhibit cell damage, tissue damage and improve peripheral blood flow following hindlimb ischemic injury in mice.**

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BACKGROUND AIMS: Existing treatments have limited success in modifying the course of peripheral artery disease, which may eventually lead to limb-threatening ulcers and amputation. Cellular therapies have the potential to provide a new treatment option for this condition, but isolation of cells by conventional means has limitations with respect to reproducibility and scalability.

METHODS: Induced pluripotent stem cells (iPSCs) were differentiated into precursor cells known as mesenchymoangioblasts (MCAs) and subsequently into mesenchymal stromal cells (MSCs). Hindlimb ischemia in mice was created by ligating both the iliac and femoral arteries of one hindlimb. Immediately after surgery, each animal received intramuscular injections of 5x10(6) cells or media in the ischemic limb. Toe necrosis was assessed visually, and hindlimb blood flow was measured by laser Doppler using a set region of interest (ROI) and by tracing the entire foot. Myofiber heterogeneity, nuclear centralization, fatty degeneration, fibrosis and capillary angiogenesis in the gastrocnemius muscle were assessed histologically.

RESULTS: Blood flow in the MCA-derived MSC-treated animals was higher at each day (P<0.006), and these mice recovered faster than control animals (3.6 vs. 2.5 for set ROI; 7.5 vs. 4.1 foot tracing; slope; P<0.001). There was significantly less myofiber heterogeneity, nuclear centralization, fatty degeneration and fibrosis in MCA-derived MSC-treated animals, indicating less tissue damage.

DISCUSSION: MCA-derived MSCs improved limb blood flow, reduced necrosis and maintained muscle mass and gross muscle appearance. We conclude that MCA-derived MSCs have a significant and protective effect against ischemic insults.


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Sustaining a fall during hospitalization reduces a patient’s ability to return home following discharge. It is well accepted that factors, such as alteration in balance, functional mobility, muscle strength, and fear of falling, are all factors that impact on the quality of life of elderly people following a fall. However, the impact that falls have on mental health outcomes in older adult mental health patients remains unexplored. The present study reports Health of the Nation Outcome Scale scores for people over the age of 65 (HoNOS65+), which were examined in a cohort of 65 patients who sustained a fall and 73 non-fallers admitted to an older adult mental health service (OAMHS). Results were compared with state and national HoNOS65+ data recorded in Australian National Outcome Casemix Collection data to explore the effect that sustaining a fall while hospitalized has on mental health outcomes. Australian state and national HoNOS65+ data indicate that older adults generally experience improved HoNOS65+ scores from admission to discharge. Mental health outcomes for patients who sustained a fall while admitted to an OAMHS did not follow this trend. Sustaining a fall while admitted to an OAMHS negatively affects discharge mental health outcomes.

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Is Pulmonary non-Tuberculous Mycobacterial Disease Linked with a High Burden of Latent Cytomegalovirus?


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Cytomegalovirus (CMV) establishes lifelong infections with episodes of active replication. We hypothesized that recurrent CMV replication in older individuals may suppress protective immune responses to non-tuberculous mycobacteria (NTM) and so potentiate pulmonary disease. Accordingly, levels of antibodies to three CMV antigen preparations were higher in NTM patients than in age-matched controls. This did not reflect broad-spectrum B cell activation as total immunoglobulin levels were not equivalently increased.

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PURPOSE: This study compared the performance of 3 admission prognostic scores in predicting hospital mortality.

MATERIALS AND METHODS: Patient admission characteristics and hospital outcome of 9549 patients were recorded prospectively. The discrimination and calibration of the predicted risks of death derived from the Simplified Acute Physiology Score (SAPS III), Admission Mortality Prediction Model (MPM0 III), and admission Acute Physiology and Chronic Health Evaluation (APACHE) II were assessed by the area under the receiver operating characteristic curve and a calibration plot, respectively.

MEASUREMENTS AND MAIN RESULTS: Of the 9549 patients included in the study, 1276 patients (13.3%) died after intensive care unit admission. Patient admission characteristics were significantly different between the survivors and nonsurvivors. All 3 prognostic scores had a reasonable ability to discriminate between the survivors and nonsurvivors (area under the receiver operating characteristic curve for SAPS III, 0.836; MPM0 III, 0.807; admission APACHE, 0.845), with best discrimination in emergency admissions. The SAPS III model had a slightly better calibration and overall performance (slope of calibration curve, 1.03; Brier score, 0.09; Nagelkerke R(2), 0.297) compared to the MPM0 III and admission APACHE II model.

CONCLUSIONS: All 3 intensive care unit admission prognostic scores had a good ability to predict hospital mortality of critically ill patients, with best discrimination in emergency admissions.

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ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients.


BACKGROUND: Respiratory syncytial virus (RSV) infection in lung transplant (LTx) patients is associated with an increased incidence of bronchiolitis obliterans syndrome (BOS). ALN-RSV01 is a small interfering RNA targeting RSV replication that was shown in an earlier Phase 2a trial to be safe and to reduce the incidence of BOS when compared with placebo.

METHODS: We performed a Phase 2b randomized, double-blind, placebo-controlled trial in RSV-infected LTx patients to examine the impact of ALN-RSV01 on the incidence of new or progressive BOS. Subjects were randomized (1:1) to receive aerosolized ALN-RSV01 or placebo daily for 5 days.

RESULTS: Of 3,985 symptomatic patients screened, 218 were RSV-positive locally, of whom 87 were randomized to receive ALN-RSV01 or placebo (modified intention-to-treat [mITT] cohort). RSV infection was confirmed by central laboratory in 77 patients (ALN-RSV01, n = 44; placebo, n = 33), which comprised the primary analysis cohort (central mITT [mITTc]). ALN-RSV01 was found to be safe and well-tolerated. At Day 180, in ALN-RSV01-treated patients, compared with placebo, in the mITTc cohort there was a trend toward a decrease in new or progressive BOS (13.6% vs 30.3%, p = 0.058), which was significant in the per-protocol cohort (p = 0.025). Treatment effect was enhanced when ALN-RSV01 was started <5 days from symptom onset, and was observed even without ribavirin treatment. There was no significant impact on viral parameters or symptom scores.

CONCLUSIONS: These results confirm findings of the earlier Phase 2a trial and provide further support that ALN-RSV01 reduces the risk of BOS after RSV in LTx recipients.

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FibroGENE: A gene-based model for staging liver fibrosis.

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BACKGROUND & AIMS: The extent of liver fibrosis predicts long-term outcomes, and hence impacts management and therapy. We developed a non-invasive algorithm to stage fibrosis using non-parametric, machine learning methods designed for predictive modeling, and incorporated an invariant genetic marker of liver fibrosis risk.

METHODS: Of 4277 patients with chronic liver disease, 1992 with chronic hepatitis C (derivation cohort) were analyzed to develop the model, and subsequently validated in an independent cohort of 1242 patients. The model was assessed in cohorts with chronic hepatitis B (CHB) (n=555) and non-alcoholic fatty liver disease (NAFLD) (n=488). Model performance was compared to FIB-4 and APRI, and also to the NAFLD fibrosis score (NFS) and Forns’ index, in those with NAFLD.

RESULTS: Significant fibrosis (F2) was similar in the derivation (48.4%) and validation (47.4%) cohorts. The FibroGENE-DT yielded the area under the receiver operating characteristic curve (AUROCs) of 0.87, 0.85 and 0.804 for the prediction of fast fibrosis progression, cirrhosis and significant fibrosis risk, respectively, with comparable results in the validation cohort. The model performed well in NAFLD and CHB with AUROCs of 0.791, and 0.726, respectively. The negative predictive value to exclude cirrhosis was >0.96 in all three liver diseases. The AUROC of the FibroGENE-DT performed better than FIB-4, APRI, and NFS and Forns’ index in most comparisons.

CONCLUSION: A non-invasive decision tree model can predict liver fibrosis risk and aid decision making.
BACKGROUND: Two meticillin-resistant Staphylococcus aureus (MRSA) clones, sequence type (ST) 22 and ST239, have successfully spread globally. Across Australia, ST22 has supplanted ST239 as the main healthcare-associated MRSA. To understand the reasons underlying this shift, the epidemiology and clinical features of infections due to ST22 and ST239 MRSA isolates from a tertiary hospital in Melbourne, Australia were compared.

METHODS: Over six months, consecutive MRSA isolates with clinical data were collected from specimens referred to Alfred Health Pathology (AHP). Isolates were genotyped by a multi-locus-sequence-typing-based high-resolution melting method.

FINDINGS: Three hundred and twenty-eight of 1079 (30%) S. aureus isolated by AHP were MRSA. Of these, 313 were genotyped; 78 (25%) were clonal complex (CC) 22 (representing ST22) and 142 (45%) were CC239 (representing ST239). Common clinical syndromes included skin or soft tissue, respiratory tract and osteo-articular infections. On multi-variate logistic regression, compared with CC239, CC22 was associated with older patients [adjusted odds ratio (aOR) 1.04 for each year increase, 95% confidence interval (CI) 1.02-1.07], and patients from subacute hospitals (aOR 2.7, 95% CI 1.2-5.8) or long-term care facilities (LTCFs; aOR 5.5, 95% CI 2.0-14.5). Median time from patient admission to MRSA isolation was nine days for CC239 and one day for CC22 (P < 0.01). MRSA strain epidemiology varied according to hospital unit.

CONCLUSIONS: CC22 and CC239 MRSA have differing ecological niches. CC22 is associated with elderly patients in LTCFs, and CC239 is associated with nosocomial acquisition. Infection control strategies involving LTCFs and their residents will likely be required to achieve continued MRSA control.

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Inflammatory breast cancer (IBC) is a rare malignancy accounting for 1-2% of breast cancers. It has an aggressive clinical presentation and poor prognosis. The sonographic findings in 41 patients with a clinical diagnosis of IBC and biopsy-proven breast malignancy are presented in this study. The most common finding was the presence of skin thickening (92%). Multiple small anechoic spaces within the dermis, correlating with the presence of dermal lymphatic invasion by tumour emboli on histopathology were noted in approximately one-third of cases. Other sonographic findings included single or multiple masses, parenchymal oedema, axillary lymphadenopathy, echogenic foci consistent with microcalcifications and increased vascularity.
Novel CT and scintigraphic findings of bone metastasis from invasive lobular breast cancer.
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INTRODUCTION: The aim of this study is to identify and describe the computed tomography and scintigraphic imaging patterns of osseous metastasis from invasive lobular breast cancer (ILC).

MATERIALS AND METHODS: CT and skeletal scintigraphy (SS) studies of 23 patients with diagnosis of ILC and osseous metastasis on their initial presentation were reviewed.

RESULTS: Osseous metastases in 14 patients (60.8%) appear as uniform small sclerotic lesions (USSL) on CT scan. The SS in these patients were interpreted as negative for metastasis (either normal or with some equivocal findings not typical for metastasis).

CONCLUSION: Osseous metastasis from ILC can have a characteristic imaging pattern on CT and SS. The pattern of USSL on CT scan with negative SS is highly suggestive of osseous metastasis from ILC.

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A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants.

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Advanced age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with limited therapeutic options. Here we report on a study of >12 million variants, including 163,714 directly genotyped, mostly rare, protein-altering variants. Analyzing 16,144 patients and 17,832 controls, we identify 52 independently associated common and rare variants (P < 5 x 10(-8)) distributed across 34 loci. Although wet and dry AMD subtypes exhibit predominantly shared genetics, we identify the first genetic association signal specific to wet AMD, near MMP9 (difference P value = 4.1 x 10(-10)). Very rare coding variants (frequency <0.1%) in CFH, CFI and TIMP3 suggest causal roles for these genes, as does a splice variant in SLC16A8. Our results support the hypothesis that rare coding variants can pinpoint causal genes within known genetic loci and illustrate that applying the approach systematically to detect new loci requires extremely large sample sizes.

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Suprachiasmatic cystic lesion. Incidental vs pathological?
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DOI:https://dx.doi.org/10.1016/j.pathol.2015.12.256

Subarachnoid haemorrhage due to aneurysmal rupture secondary to fibromuscular dysplasia.
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PMID:27773191
DOI:https://dx.doi.org/10.1016/j.pathol.2015.12.255

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West Australian experience with adrenal venous sampling studies in the diagnosis of primary aldosteronism.
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Tanyctic ependymoma vs pilocytic astrocytoma? Pitfalls in diagnosis.
Dyke JM, Junckerstoff RC, et al.
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Triple threats: Tracking antigen-specific T cells in a case of concurrent autoimmunity, infectious disease and possible malignancy.
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With 'complements' to occam's razor.
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Prospective longitudinal study of testosterone and incident depression in older men: The Health In Men Study.
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BACKGROUND: Depression in older men has been associated with low circulating testosterone concentration but data from prospective studies are limited.

METHODS: We conducted a prospective longitudinal study in a community representative cohort of 3179 older men free of clinically significant depressive symptoms at baseline. The main objective of this study was to determine if low serum testosterone, dihydrotestosterone and estradiol concentrations are associated with the development of depressive symptoms. Incident depression was assessed with the Patient Health Questionnaire and via an electronic health record database (The West Australian Data Linkage System). The main exposures of interest were serum testosterone, dihydrotestosterone and estradiol measured by liquid chromatography-mass spectrometry and calculated free testosterone in baseline blood samples (collected between 2001 and 2004).

RESULTS: One hundred and thirty five men (4.2%) developed depression over a median follow up time of 9.4 years (range 8.4-10.9). Men with incident depression were older (median age 77.7 vs 76.1 years, z=-3.82, p<0.001) and were more likely to have cardiovascular disease (43.0% vs 32.6%, chi(2)=6.32, p=0.012) and diabetes (22.2% vs 13.2%, chi(2)=8.95, p=0.003). Low serum total testosterone (<6.4 nmol/L) was associated with incident depression (HR 2.07, 95%CI 1.17-3.68) and this remained significant after adjustment for relevant potential confounding factors (HR 1.86, 95%CI 1.05-3.31). Low serum dihydrotestosterone, estradiol and calculated free testosterone were not associated with risk of depression.

CONCLUSIONS: Low serum total testosterone, but not calculated free testosterone, was associated with incident depression in this sample of older men.
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OBJECTIVE: Despite Level 1b evidence and international consensus that exercise is beneficial in ankylosing spondylitis (AS), there is a paucity of detailed information to guide exercise prescription, including the type and dosage of exercise required for the most benefit. This collaborative project, combining evidence with clinical expertise, was established to develop practical recommendations to guide sustainable exercise prescription for individuals with AS.

METHODS: Using a modified Delphi technique, 10 clinical questions were generated and a systematic literature review was conducted for each. Draft recommendations were developed at a 2-day meeting, based on the integration of evidence summaries and expert opinion. Feedback was obtained from patient and health professional groups prior to finalisation.

RESULTS: Recommendations and practice points were developed for the following areas: assessment; monitoring; safety; disease management; AS-specific exercise; physical activity; dosage, adherence and setting. A framework was developed that could also be adapted for exercise in other chronic musculoskeletal conditions. Feedback suggests that the final consensus statement provides useful information for those seeking to provide best practice exercise prescription for people with AS.

CONCLUSION: The recommendations provide an up-to-date, evidence-based approach to the full range of issues related to the use of exercise in AS, as well as identifying evidence gaps for further research. Most importantly, this includes investigation of aspects of exercise programme design required to produce the largest effect, long-term adherence with exercise programs and the specific exercise requirements of sub-groups of people with AS. Widespread dissemination and implementation of the guidelines will be required to optimise exercise outcomes.

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Concentration-dependent effect of hypocalcaemia on in vitro clot strength in patients at risk of bleeding: a retrospective cohort study.

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AIM: It is uncertain whether hypocalcaemia is associated with an increased risk of bleeding. This study assessed the dose-related relationship between ionised calcium concentrations and in vitro clot strength measured by maximum amplitude (MA) on the thromboelastograph (TEG).

METHODS: A total of 610 patients who were at risk of bleeding or had active bleeding between 2010 and 2014 were considered in this retrospective cohort study. A scatter plot with Pearson correlation coefficient (r) and multiple linear regression was used to assess the dose-related relationship between ionised calcium concentrations and MA on the TEG.

RESULTS: The mean ionised calcium of the patients was 1.10 mmol L(-1) (interquartile range: 1.04-1.17) and 235 (38.5%) of them had hypocalcaemia (<1.1 mmol L(-1)). Hypocalcaemia was more common in patients with significant coexisting coagulopathy. Ionised calcium concentrations (r = 0.285, 95% confidence interval (CI) 0.211-0.356, P = 0.001), as well as fibrinogen concentrations, platelet counts, international normalised ratio (INR) and activated Partial Thromboplastin Time (aPTT), had a significant linear correlation with the MA on the TEG. Ionised calcium concentrations and its interaction term with platelet count were both significantly associated with the MA on the TEG (slope of the regression line 1.1 per 0.1 mmol L(-1) increment, 95%CI 0.3 to 1.9, P = 0.011), after adjusting for fibrinogen concentrations, platelet counts, INR and aPTT.

CONCLUSIONS: Ionised calcium concentrations had a concentration-dependent association with in vitro clot strength after adjusting for other coagulation abnormalities in patients with coexisting coagulopathy. Maintaining a normal ionised calcium concentration, >1 mmol L(-1), during critical bleeding is recommended.

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Safety of gluten in gluten-free foods.

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Discovery and characterisation of a new insect-specific bunyavirus from Culex mosquitoes captured in northern Australia.
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Insect-specific viruses belonging to significant arboviral families have recently been discovered. These viruses appear to be maintained within the insect population without the requirement for replication in a vertebrate host. Mosquitoes collected from Badu Island in the Torres Strait in 2003 were analysed for insect-specific viruses. A novel bunyavirus was isolated in high prevalence from Culex spp. The new virus, provisionally called Badu virus (BADUV), replicated in mosquito cells of both Culex and Aedes origin, but failed to replicate in vertebrate cells. Genomic sequencing revealed that the virus was distinct from sequenced bunyavirus isolates reported to date, but
phylogenetically clustered most closely with recently discovered mosquito-borne, insect-specific bunyaviruses in the newly proposed Goukovirus genus. The detection of a functional furin cleavage motif upstream of the two glycoproteins in the M segment-encoded polyprotein suggests that BADUV may employ a unique strategy to process the virion glycoproteins.

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The Incidence of Neurologic Susceptibility to a Skull Defect.
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OBJECTIVE: To determine whether there is a measurable change in neurologic function after cranioplasty.

METHODS: This is a prospective single-surgeon, single-center study. Fifty patients who required a cranioplasty procedure were assessed neurologically within 72 hours before and 7 days after surgery. The assessment tools were the Functional Independence Measure (FIM) and the Cognitive assessment report (Cognistat). The scores for both assessments were calculated and then compared before and after surgery.

RESULTS: FIM assessment was performed on all fifty patients, and a Cognistat assessment was performed on 47 patients. Most improvements were seen in the Cognistat scores; however, there appeared to be no specific areas in which there was consistent improvement. There were substantial improvements in the Cognistat assessment in 9 patients. One patient had a much-improved FIM assessment (improved from 18 to 34), but a Cognistat assessment was not possible because of poor neurologic function. These results suggested that improvements after cranioplasty were more likely to occur in the domain of cognitive function than motor function, although overall these results did not reach statistically significance. Bifrontal (vs. unilateral) cranioplasty, timing between decompression and cranioplasty, and age of the patients did not appear to affect the postoperative FIM scores, after we adjusted for preoperative FIM scores and surgical complications.

CONCLUSIONS: A small but significant number of patients appear to improve clinically after cranioplasty. Neurologic susceptibility to a skull defect may be more common than had been appreciated previously.

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Abatacept experience in steroid and rituximab-resistant focal segmental glomerulosclerosis.
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Primary focal segmental glomerular sclerosis (FSGS), one of the major causes of nephrotic syndrome, eventually results in end-stage renal disease. Currently, FSGS is treated with immunosuppressive therapies, which include calcineurin inhibitors (cyclosporine), glucocorticoids, B-cell depleting agents (rituximab) and, recently, a T-cell co-stimulatory inhibitor (abatacept). Until recently, there had been no cases reporting resistance to all current therapies. We report a case of a 62-year-old Caucasian man with biopsy-proven FSGS, who responded well to oral prednisolone therapy. However, 2 years later, he had a relapse and failed to respond to prednisolone. Subsequent treatments then included cyclosporine, rituximab and cyclophosphamide, which were not successful. The patient was
then administered abatacept, a novel T-cell co-stimulatory inhibitor—though he did not experience any side effects, there was no change in proteinuria nor in creatinine.

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Genetic and cellular studies highlight that A Disintegrin and Metalloproteinase 19 is a protective biomarker in human prostate cancer.

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BACKGROUND: Prostate cancer is the second most frequently diagnosed cancer in men worldwide. Current treatments include surgery, androgen ablation and radiation. Introduction of more targeted therapies in prostate cancer, based on a detailed knowledge of the signalling pathways, aims to reduce side effects, leading to better clinical outcomes for the patient. ADAM19 (A Disintegrin And Metalloproteinase 19) is a transmembrane and soluble protein which can regulate cell phenotype through cell adhesion and proteolysis. ADAM19 has been positively associated with numerous diseases, but has not been shown to be a tumor suppressor in the pathogenesis of any human cancers. Our group sought to investigate the role of ADAM19 in human prostate cancer.

METHODS: ADAM19 mRNA and protein levels were assessed in well characterised human prostate cancer cohorts. ADAM19 expression was assessed in normal prostate epithelial cells (RWPE-1) and prostate cancer cells (LNCaP, PC3) using western blotting and immunocytochemistry. Proliferation assays were conducted in LNCaP cells in which ADAM19 was over-expressed. In vitro scratch assays were performed in PC3 cells over-expressing ADAM19.

RESULTS: Immunohistochemical studies highlighted that ADAM19 protein levels were elevated in normal prostate tissue compared to prostate cancer biopsies. Results from the clinical cohorts demonstrated that high levels of ADAM19 in microarrays are positively associated with lower stage (p = 0.02591) and reduced relapse (p = 0.00277) of human prostate cancer. In vitro, ADAM19 expression was higher in RWPE-1 cells compared to LNCaP cells. In addition, human ADAM19 over-expression reduced LNCaP cell proliferation and PC3 cell migration.

CONCLUSIONS: Taken together, our immunohistochemical and microarray results and cellular studies have shown for
the first time that ADAM19 is a protective factor for human prostate cancer. Further, this study suggests that upregulation of ADAM19 expression could be of therapeutic potential in human prostate cancer.


Pitfalls in haemodynamic monitoring in the postoperative and critical care setting.
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Haemodynamic monitoring is a vital part of daily practice in anaesthesia and intensive care. Although there is evidence to suggest that goal-directed therapy may improve outcomes in the perioperative period, which haemodynamic targets we should aim at to optimise patient outcomes remain elusive and controversial. This review highlights the pitfalls in commonly used haemodynamic targets, including arterial blood pressure, central venous pressure, cardiac output, central venous oxygen saturation and dynamic haemodynamic indices. Evidence suggests that autoregulation in regional organ circulation may change either due to chronic hypertension or different disease processes such as traumatic brain injury, cerebrovascular ischaemia or haemorrhage; this will influence the preferred blood pressure target. Central venous pressure can be influenced by multiple pathophysiological factors and, unless central venous pressure is very low, it is rarely useful as a predictor for fluid responsiveness. Central venous oxygen saturation can be easily increased by a high arterial oxygen tension, making it useless as a surrogate marker of good cardiac output or systemic oxygen delivery in the presence of hyperoxaemia. Many dynamic haemodynamic indices have been reported to predict fluid responsiveness, but they all have their own limitations. There is also insufficient evidence to support that giving fluid until the patient is no longer fluid responsive can improve patient-centred outcomes. With the exception in the context of preventing contrast-induced nephropathy, large randomised controlled studies suggest that excessive fluid treatment may prolong duration of mechanical ventilation without preventing acute kidney injury in the critically ill.

Viscoelastic point-of-care testing to guide transfusion and antithrombotic therapy in perioperative and critically ill patients: are all parameters created equal?
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Clinical Outcomes of Patients Treated With Pulmonary Vasodilators Early and in High Dose After Left Ventricular Assist Device Implantation.
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Right ventricular failure (RVF) is common after left ventricular assist device (LVAD) implantation and a major determinant of adverse outcomes. Optimal perioperative right ventricular (RV) management is not well defined. We evaluated the use of pulmonary vasodilator therapy during LVAD implantation. We performed a retrospective analysis of continuous-flow LVAD implants and pulmonary vasodilator use at our institution between September 2004 and June 2013. Preoperative RVF risk was assessed using recognized variables. Sixty-five patients (80% men, 50±/−14 years) were included: 52% HeartWare ventricular assist device (HVAD), 11% HeartMate II (HMII), 17% VentrAssist, 20% Jarvik. Predicted RVF risk was comparable with contemporary LVAD populations: 8% ventilated, 14% mechanical support, 86% inotropes, 25% BUN >39mg/dL, 23% bilirubin >2mg/dL, 31% RV : LV (left ventricular) diameter >0.75, 27% RA : PCWP (right atrium : pulmonary capillary wedge pressure) >0.63, 36% RV stroke work index

The majority (91%) received pulmonary vasodilators early and in high dose: 72% nitric oxide, 77% sildenafil (max 200+/−79mg/day), 66% iloprost (max 126+/−37mug/day). Median hospital stay was 26 (21) days. No patient required RV mechanical support. Of six (9%) patients meeting RVF criteria based on prolonged need for inotropes, four were transplanted, one is alive with an LVAD at 3 years, and one died on day 35 of intracranial hemorrhage. Two-year survival was 77% (92% for HMII/HVAD): transplanted 54%, alive with LVAD 21%, recovery/explanted 2%. A low incidence of RVF and excellent outcomes were observed for patients treated early during LVAD implantation with combination, high-dose pulmonary vasodilators. The results warrant further investigation in a randomized controlled study.
Simple accurate mathematical models of blood HbO2 and HbCO2 dissociation curves at varied physiological conditions: evaluation and comparison with other models.

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PURPOSE: Equations for blood oxyhemoglobin (HbO2) and carbaminohemoglobin (HbCO2) dissociation curves that incorporate nonlinear biochemical interactions of oxygen and carbon dioxide with hemoglobin (Hb), covering a wide range of physiological conditions, are crucial for a number of practical applications. These include the development of physiologically-based computational models of alveolar-blood and blood-tissue O2-CO2 transport, exchange, and metabolism, and the analysis of clinical and in vitro data.

METHODS AND RESULTS: To this end, we have revisited, simplified, and extended our previous models of blood HbO2 and HbCO2 dissociation curves (Dash and Bassingthwaighte, Ann Biomed Eng 38:1683-1701, 2010), validated wherever possible by available experimental data, so that the models now accurately fit the low HbO2 saturation (SHbO2) range over a wide range of values of PCO2, pH, 2,3-DPG, and temperature. Our new equations incorporate a novel PO2-dependent variable cooperativity hypothesis for the binding of O2 to Hb, and a new equation for P50 of O2 that provides accurate shifts in the HbO2 and HbCO2 dissociation curves over a wide range of physiological conditions. The accuracy and efficiency of these equations in computing PO2 and PCO2 from the SHbO2 and SHbCO2 levels using simple iterative numerical schemes that give rapid convergence is a significant advantage over alternative SHbO2 and SHbCO2 models.

CONCLUSION: The new SHbO2 and SHbCO2 models have significant computational modeling implications as they provide high accuracy under non-physiological conditions, such as ischemia and reperfusion, extremes in gas concentrations, high altitudes, and extreme temperatures.

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Soleus Muscle as a Surrogate for Health Status in Human Heart Failure.

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We propose the hypothesis that soleus muscle function may provide a surrogate measure of functional capacity in patients with heart failure. We summarize literature pertaining to skeletal muscle as a locus of fatigue and present our recent findings, using in vivo imaging in combination with biomechanical experimentation and modeling, to reveal novel structure-function relationships in chronic heart failure skeletal muscle and gait.

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Increased proportions of dendritic cells and recovery of IFNgamma responses in HIV/HCV co-infected patients receiving ART.
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Dendritic cell (DC) numbers and functions can be affected by HIV and HCV disease, but the effects of antiretroviral therapy (ART) on DC and the implications of these changes are unclear. We examined circulating DC in samples from Indonesian patients beginning ART with advanced HIV disease and documented mild/moderate HCV hepatitis. Frequencies of myeloid and plasmacytoid DC increased after 6 months on ART, but frequencies of DC producing IL-12 or IFNalpha following stimulation with TLR agonists (CL075, CpG) did not change. IFNgamma responses to CL075, HCV and other antigens rose over this period. Hence increased IFNgamma responses during ART may be associated with increased DC frequencies rather than changes in their functional capacity.

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The association between chronic hepatitis C infection and cardiovascular risk.
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BACKGROUND: Vascular disease is a common cause of death in patients with chronic hepatitis C (CHC) infection; however, the association between CHC and atherosclerosis is unclear.
AIMS: To determine whether patients with CHC have increased subclinical vascular disease and whether genotype or antiviral treatment modifies this risk.
METHODS: Fifty CHC patients and 22 age-matched and sex-matched healthy controls underwent clinical and biochemical assessment for vascular risk factors. In addition, vascular risk was assessed by measuring arterial stiffness (aortic augmentation index and carotid-femoral pulse wave velocity (PWV)), endothelial dysfunction (brachial artery flow-mediated dilatation (FMD) and dilatation post-glycerol trinitrate administration) and carotid intima-media thickness (CIMT). Assessment was repeated in subset of CHC patients (n=12) undergoing antiviral treatment 18months after initiation of treatment.
RESULTS: Baseline vascular risk factors and measures of arterial stiffness, endothelial dysfunction and CIMT were not different between cases and controls (P > 0.2 for all). Genotype 1 CHC patients had greater endothelial dysfunction with lower FMD (8.2 +/- 3.5% vs 10.9 +/- 5.2%, P = 0.03) and higher right CIMT (0.6 +/- 0.1mm vs 0.5 +/- 0.07mm, P =
0.04) compared with non-genotype 1. Patients who achieved sustained virological response (7/12) showed significant improvement in insulin resistance (homeostasis model of assessment of insulin resistance 2.3 +/- 1.2 vs 1.8 +/- 0.8, P = 0.02) and arterial stiffness (PWV 7.4 +/- 1.1m/s vs 6.5 +/- 0.6m/s, P = 0.04).

CONCLUSIONS: Subclinical vascular disease is not greater in CHC subjects compared with controls. However, among CHC subjects, genotype 1 infection is associated with greater endothelial dysfunction and increased carotid-intima medial thickness compared with non-genotype 1 infection. Successful viral eradication may improve insulin resistance and arterial stiffness.

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Complementary medicine use by people living with HIV in Australia - a national survey.
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Little is known about the use of complementary medicines by people living with HIV in Australia since the advent of more effective combination antiretroviral therapy. We conducted an anonymous survey of 1211 adult patients receiving combination antiretroviral therapy from one of eight specialist HIV clinics across Australia, aiming to identify the current patterns of use of ingestible complementary medicines. Data collected included reasons for use, information sources and rates of disclosure of use of complementary medicines to medical practitioners and pharmacists. Ingestible complementary medicine was used by up to 53% of the 1037 patients returning a survey. Complementary medicine was commonly used for general health, to boost immune function and, to a lesser extent, to address co-morbidities. Disclosure of complementary medicines use to doctors was far higher than to pharmacists. Given the potential for interactions, pharmacists should be more aware of patients' complementary medicines use.
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Autophagic activation: A key piece of the puzzle for the curcumin-associated cognitive enhancement?
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Effect of garlic on plasma lipoprotein(a) concentrations: A systematic review and meta-analysis of randomized controlled clinical trials.
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OBJECTIVES: Garlic can play an essential role in the prevention of atherosclerosis, but the research addressing the effect of garlic on the concentration of lipoprotein(a) [Lp(a)] has not been fully demonstrated. The aim of this study was to assess the effect of garlic on plasma Lp(a) concentrations through systematic review of literature and meta-analysis of available randomized controlled trials.

METHODS: The literature search included SCOPUS, PubMed-Medline, ISI Web of Science, and Google Scholar databases up to March 10, 2015 to identify randomized controlled trials investigating the effect of garlic on plasma Lp(a) concentrations. Two independent reviewers extracted data on study characteristics, methods, and outcomes. Overall, the effect of garlic on plasma Lp(a) levels was reported in six trials.

RESULTS: Meta-analysis did not suggest a significant alteration in plasma Lp(a) levels after garlic consumption (weighted mean difference [WMD] = 16.86%; 95% confidence interval, -4.59 to 38.31; P = 0.124). This result was robust in the leave-one-out sensitivity analysis. When the studies were categorized according to the duration of supplementation, there was no effect in the subgroup of trials lasting <12 wk (WMD = 2.01%; 95% CI, -14.67 to 18.68; P = 0.813) but a significant elevation of plasma Lp(a) concentrations was found in trials lasting >12 wk (WMD = 54.59%; 95% CI, 30.47-78.71; P < 0.001). Random-effects meta-regression suggested an inverse association between the changes in plasma concentrations of Lp(a) and duration of supplementation (slope 1.71; 95% CI, 0.46-2.97; P = 0.007).

CONCLUSIONS: The present meta-analysis did not suggest a significant effect of garlic supplementation on the reduction of Lp(a) levels.
selected. Random-effects meta-analysis suggested a significant increase in plasma cortisol concentrations following statin therapy (WMD: 6.34%, 95% CI: 1.80, 10.87, p=0.006). Subgroup analysis confirmed the significance of the effect with lipophilic statins comprising atorvastatin, simvastatin, and lovastatin (WMD: 7.00%, 95% CI: 2.21, 11.79, p=0.004) but not with hydrophilic statins (rosuvastatin and pravastatin) (WMD: 0.60%, 95% CI: -13.46, 14.66, p=0.933). In the meta-regression analysis, changes in plasma cortisol concentrations following statin therapy were found to be independent of treatment duration. Results of this meta-analysis of RCTs suggest a significant elevation in plasma cortisol levels following statin therapy.

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**Head-to-head comparison of statins versus fibrates in reducing plasma fibrinogen concentrations: A systematic review and meta-analysis.**
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**BACKGROUND:** Several studies suggest differences between fibrates and statins in lowering plasma fibrinogen (Fib) concentrations, but the evidence is not definitive. Therefore, the aim of this meta-analysis of head-to-head randomized trials was to compare the efficacy of statins and fibrates on plasma Fib concentrations.

**METHODS:** The literature search included Medline, Scopus, and Web of Science up to February 1st, 2015, to identify head-to-head comparative randomized trials investigating the efficacy of fibrates vs statins on plasma Fib concentrations.
RESULTS: In total 22 trials with 2762 participants were included to the meta-analysis. Random-effect meta-analysis suggested a significantly greater effect of fibrates vs statins in lowering plasma Fib concentrations (weighted mean difference [WMD]: -40.7mg/dL, 95% confidence interval [CI]: -55.2, -26.3, p<0.001). When the analysis was stratified according to the type of fibrate administered, there were significant Fib-lowering effects with both bezafibrate (n=8 treatment arms; WMD: -23.7mg/dL, 95% CI: -41.8, -5.7, p=0.01) and fenofibrate (n=15 treatment arms; WMD: -43.7mg/dL, 95% CI: -61.3, -26.2, p<0.001). Overall, there was a numerically greater effect in the subgroup of trials with >12 weeks duration (n=17 treatment arms; WMD: -42.7mg/dL, 95% CI: -60.3, -25.1, p<0.001) compared with the subgroup of trials lasting <12 weeks (n=7 treatment arms; WMD: -36.7mg/dL, 95% CI: -52.0, -21.4, p<0.001).

CONCLUSIONS: Monotherapy with either fibrates or statins suggested a significantly greater effect of fibrates in lowering plasma Fib concentrations. According to these findings, mechanisms associated with fibrinogen metabolism might be responsible for the distinct effects of statins and fibrates in reducing cardiovascular endpoints.

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Healthcare-associated pneumonia: Can we salvage anything from the wreckage?

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Blunt Traumatic Abdominal Wall Hernias: A Surgeon's Dilemma.

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BACKGROUND: Traumatic abdominal wall hernias (TAWH) have been recognized for more than a century since they were first reported by Selby (JAMA 47:1485-1486, 1906). They continue to be a rare diagnosis, encountered in approximately 1% blunt trauma admissions. The present study is a 10-year retrospective review of patients presenting with TAWH to a State Major Trauma Unit in Western Australia. We hypothesized that the timing of the repair of TAWH was dependent on the severity of the abdominal wall injury, as well as associated injuries, and in turn, this may affect patient outcomes.

MATERIALS AND METHODS: The Trauma Registry at Royal Perth Hospital (the only Level I Trauma Centre for adults in Western Australia) was scrutinized for TAWH, between 2003 and 2013. The injuries were graded by the classification system of Dennis et al. (Am J Surg 197:413-417, 2009). Patients with TAWH following penetrating trauma were excluded.

RESULTS: During the study period, 44 patients were diagnosed to have TAWH accounting for 0.08% of admissions. Thirty (68%) of the patients were male and the median age was 36 years (IQR 24-54). The median BMI was between 25 and 30. The majority of the patients sustained trauma secondary to motor vehicle crashes and the commonest associated injury was a pelvic fracture. Grades 3 and 4 injuries were found to have an association with a pelvic fracture (p < 0.001). No association was seen in the present study between seat belt use and the development of TAWH or between the location of TAWH and seat belt pattern. The median time of diagnosis of TAWH following arrival to hospital was 18 hours while the median time of surgery from diagnosis was 15.5 hours. Forty-one (93%) of the patients underwent surgery. Of these, 8 (20%) were emergent due to a simultaneous bowel perforation and another
five had primary mesh repairs. Three of the patients suffered superficial complications (7.5%) and there were 3 (7%) recurrences at a mean time of 7.25 months from the first repair. The follow-up period ranged from 1 to 51 months with an average time of 16 months.

CONCLUSION: This series is the largest single institution study conducted on TAWH to date. Despite its retrospective nature and small numbers, it has generated some important questions. A larger prospective study with a longer follow-up period is required to generate reliable treatment algorithms as well as to standardize the management of TAWH.

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Renal artery anatomy affects the blood pressure response to renal denervation in patients with resistant hypertension.
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BACKGROUND: Renal denervation (RDN) has been shown to reduce blood pressure (BP), muscle sympathetic nerve activity (MSNA) and target organ damage in patients with resistant hypertension (RH) and bilateral single renal arteries. The safety and efficacy of RDN in patients with multiple renal arteries remains unclear.

METHODS: We measured office and 24-hour BP at baseline, 3 and 6 months following RDN in 91 patients with RH, including 65 patients with single renal arteries bilaterally (group 1), 16 patients with dual renal arteries on either one or both sides (group 2) and 10 patients with other anatomical constellations or structural abnormalities (group 3). Thirty nine out of 91 patients completed MSNA at baseline and follow-up.

RESULTS: RDN significantly reduced office and daytime SBP in group 1 at both 3 and 6 months follow-up (P<0.001) but not in groups 2 and 3. Similarly, a significant reduction in resting baseline MSNA was only observed in group 1.
There was no deterioration in kidney function in any group.

CONCLUSION: While RDN can be performed safely irrespective of the underlying renal anatomy, the presence of single renal arteries with or without structural abnormalities is associated with a more pronounced BP and MSNA lowering effect than the presence of dual renal arteries in patients with RH. However, when patients with dual renal arteries received renal nerve ablation in all arteries there was trend towards a greater BP reduction. Insufficient renal sympathetic nerve ablation may account for these differences.


Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study.


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BACKGROUND: It is uncertain whether a diagnostic strategy supplemented by early coronary computed tomography angiography (CCTA) is superior to contemporary standard optimal care (SOC) encompassing high-sensitivity troponin assays (hs-troponins) for patients suspected of acute coronary syndrome (ACS) in the emergency department (ED).

OBJECTIVES: This study assessed whether a diagnostic strategy supplemented by early CCTA improves clinical effectiveness compared with contemporary SOC.

METHODS: In a prospective, open-label, multicenter, randomized trial, we enrolled patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary revascularization. The primary endpoint was the number of patients identified with significant coronary artery disease requiring revascularization within 30 days.

RESULTS: The study population consisted of 500 patients, of whom 236 (47%) were women (mean age 54 +/- 10 years). There was no difference in the primary endpoint (22 [9%] patients underwent coronary revascularization within 30 days in the CCTA group and 17 [7%] in the SOC group [p = 0.40]). Discharge from the ED was not more frequent after CCTA (65% vs. 59%, p = 0.16), and length of stay was similar (6.3 h in both groups; p = 0.80). The CCTA group...
had lower direct medical costs (337 vs. 511, p < 0.01) and less outpatient testing after the index ED visit (10 [4%] vs. 26 [10%], p < 0.01). There was no difference in incidence of undetected ACS.

CONCLUSIONS: CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. However, in the era of hs-troponins, CCTA does not identify more patients with significant CAD requiring coronary revascularization, shorten hospital stay, or allow for more direct discharge from the ED. (Better Evaluation of Acute Chest Pain with Computed Tomography Angiography [BEACON]; NCT01413282). Copyright © 2016 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved. PMID:26764061

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Impact of L-carnitine on plasma lipoprotein(a) concentrations: A systematic review and meta-analysis of randomized controlled trials.
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We aimed to assess the impact of L-carnitine on plasma Lp(a) concentrations through systematic review and meta-analysis of available RCTs. The literature search included selected databases up to 31(st) January 2015. Meta-analysis was performed using fixed-effects or random-effect model according to I(2) statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The meta-analysis showed a significant reduction of Lp(a) levels following L-carnitine supplementation (WMD: -8.82mg/dL, 95% CI: -10.09, -7.55, p<0.001). When the studies were categorized according to the route of administration, a significant reduction in plasma Lp(a) concentration was observed with oral (WMD: -9.00mg/dL, 95% CI: -10.29, -7.72, p<0.001) but not intravenous L-carnitine (WMD: -2.91mg/dL, 95% CI: -10.22, 4.41, p=0.436). The results of the meta-regression analysis showed that the pooled estimate is independent of L-carnitine dose (slope: -0.30; 95% CI: -4.19, 3.59; p=0.878) and duration of therapy (slope: 0.18; 95% CI: -0.22, 0.59; p=0.374). In conclusion, the meta-analysis suggests a significant Lp(a) lowering by oral L-carnitine supplementation. Taking into account the limited number of available Lp(a)-targeted drugs, L-carnitine might be an effective alternative to effectively reduce Lp(a). Prospective outcome trials will be required to fully elucidate the clinical value and safety of oral L-carnitine supplementation.

**Combination of Vancomycin and beta-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial.**

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**BACKGROUND:** In vitro laboratory and animal studies demonstrate a synergistic role for the combination of vancomycin and antistaphylococcal beta-lactams for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. Prospective clinical data are lacking.

**METHODS:** In this open-label, multicenter, clinical trial, adults with MRSA bacteremia received vancomycin 1.5 g intravenously twice daily and were randomly assigned (1:1) to receive intravenous flucloxacillin 2 g every 6 hours for 7 days (combination group) or no additional therapy (standard therapy group). Participants were stratified by hospital and randomized in permuted blocks of variable size. Randomization codes were kept in sealed, sequentially numbered, opaque envelopes. The primary outcome was the duration of MRSA bacteremia in days.

**RESULTS:** We randomly assigned 60 patients to receive vancomycin (n = 29), or vancomycin plus flucloxacillin (n = 31).

The mean duration of bacteremia was 3.00 days in the standard therapy group and 1.94 days in the combination group. According to a negative binomial model, the mean time to resolution of bacteremia in the combination group was 65% (95% confidence interval, 41%-102%; P = .06) that in the standard therapy group. There was no difference in the secondary end points of 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity.

**CONCLUSIONS:** Combining an antistaphylococcal beta-lactam with vancomycin may shorten the duration of MRSA bacteremia. Further trials with a larger sample size and objective clinically relevant end points are warranted.


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**Diabetes, statins and FH.**

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**Deep sequencing of uveal melanoma identifies a recurrent mutation in PLCB4.**


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Next generation sequencing of uveal melanoma (UM) samples has identified a number of recurrent oncogenic or loss-of-function mutations in key driver genes including: GNAQ, GNA11, EIF1AX, SF3B1 and BAP1. To search for additional driver mutations in this tumor type we carried out whole-genome or whole-exome sequencing of 28 tumors or primary cell lines. These samples have a low mutation burden, with a mean of 10.6 protein changing mutations per sample (range 0 to 53). As expected for these sun-shielded melanomas the mutation spectrum was not consistent with an ultraviolet radiation signature, instead, a BRCA mutation signature predominated. In addition to mutations in the known UM driver genes, we found a recurrent mutation in PLCB4 (c.G1888T, p.D630Y, NM_000933), which was validated using Sanger sequencing. The identical mutation was also found in published UM sequence data (1 of 56 tumors), supporting its role as a novel driver mutation in UM. PLCB4 p.D630Y mutations are mutually exclusive with mutations in GNA11 and GNAQ, consistent with PLCB4 being the canonical downstream target of the
former gene products. Taken together these data suggest that the PLCB4 hotspot mutation is similarly a gain-of-function mutation leading to activation of the same signaling pathway, promoting UM tumorigenesis. PMID:26683228
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**Lipoprotein lipase deficiency presenting with neonatal perianal abscesses.**
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Lipoprotein lipase (LPL), a member of the triglyceride lipase gene family, is synthesised by parenchymal cells of the heart, skeletal muscle and adipose tissues before being transported to luminal surfaces of vascular endothelial cells to exert its main physiological function to hydrolyse plasma lipoproteins. LPL deficiency is a rare autosomal recessive disorder, resulting in severe hypertriglyceridaemia from birth. The effect of marked hypertriglyceridaemia on the immune function in children has not been described. We present a case of a neonate with LPL deficiency and grossly elevated plasma triglyceride levels, presenting with recurrent and recalcitrant perianal abscesses suggestive of underlying immunodeficiency. With reduced levels of plasma triglycerides, the recurrent perianal infections resolved. This case report reviews evidence for potential deleterious effects of hypertriglyceridaemia on immune function, however, underlying mechanisms are poorly understood. Whether hypertriglyceridaemia contributes to immune dysfunction in this context is unknown. If there is a pathophysiological link, this may have implications for hypertriglyceridaemia management.

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**Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis.**
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BACKGROUND: Recent hypertension guidelines have reversed previous recommendations for lower blood pressure targets in high-risk patients, such as those with cardiovascular disease, renal disease, or diabetes. This change represents uncertainty about whether more intensive blood pressure-lowering strategies are associated with greater reductions in risk of major cardiovascular and renal events. We aimed to assess the efficacy and safety of intensive blood pressure-lowering strategies.

METHODS: For this updated systematic review and meta-analysis, we systematically searched MEDLINE, Embase, and the Cochrane Library for trials published between Jan 1, 1950, and Nov 3, 2015. We included randomised controlled trials with at least 6 months’ follow-up that randomly assigned participants to more intensive versus less intensive blood pressure-lowering treatment, with different blood pressure targets or different blood pressure changes from baseline. We did not use any age or language restrictions. We did a meta-analysis of blood pressure reductions on relative risk (RR) of major cardiovascular events (myocardial infarction, stroke, heart failure, or cardiovascular death, separately and combined), and non-vascular and all-cause mortality, end-stage kidney disease, and adverse events, as well as albuminuria and progression of retinopathy in trials done in patients with diabetes.

FINDINGS: We identified 19 trials including 44,989 participants, in whom 2496 major cardiovascular events were recorded during a mean 3.8 years of follow-up (range 1.0-8.4 years). Our meta-analysis showed that after randomisation, patients in the more intensive blood pressure-lowering treatment group had mean blood pressure levels of 133/76 mm Hg, compared with 140/81 mm Hg in the less intensive treatment group. Intensive blood pressure-lowering treatment achieved RR reductions for major cardiovascular events (14% [95% CI 4-22]), myocardial infarction (13% [0-24]), stroke (22% [10-32]), albuminuria (10% [3-16]), and retinopathy progression (19% [0-34]). However, more intensive treatment had no clear effects on heart failure (15% [95% CI 1-11 to 34]), cardiovascular death (9% [-11 to 26]), total mortality (9% [-3 to 19]), or end-stage kidney disease (10% [-6 to 23]). The reduction in major cardiovascular events was consistent across patient groups, and additional blood pressure lowering had a clear benefit even in patients with systolic blood pressure lower than 140 mm Hg. The absolute benefits were greatest in trials in which all enrolled patients had vascular disease, renal disease, or diabetes. Serious adverse events associated with blood pressure lowering were only reported by six trials and had an event rate of 1.2% per year in intensive blood pressure-lowering treatment group participants, compared with 0.9% in the less intensive treatment group (RR 1.35 [95% CI 0.93-1.97]). Severe hypotension was more frequent in the more intensive treatment regimen (RR 2.68 [1.21-5.89], p=0.015), but the absolute excess was small (0.3% vs 0.1% per person-year for the duration of follow-up).

INTERPRETATION: Intensive blood pressure lowering provided greater vascular protection than standard regimens. In high-risk patients, there are additional benefits from more intensive blood pressure lowering, including for those with systolic blood pressure below 140 mmHg. The net absolute benefits of intensive blood pressure lowering in high-risk individuals are large.

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Recurrence in patients with stage I colorectal cancer.
BACKGROUND: Outcomes of patients with stage I colorectal cancer submitted to surgery with curative intent have not been thoroughly explored in contemporary series.

METHODS: All patients with colon or rectal adenocarcinoma who underwent resection from the St John of God Hospital (1996-2013) and BioGrid (1991-2013) databases were identified. Patients submitted to local excision, polypectomies or neoadjuvant treatment were excluded. Outcomes included recurrence (combined local and systemic), recurrence-free and overall survival, and survival after recurrence.

RESULTS: A total of 1193 patients with stage I disease were included. Median age was 67 (interquartile range 59-75) and median follow-up was 3.2 years (interquartile range 1.4-5.8). Five-year recurrence rate was 7.1% (95% confidence interval (CI) 5.4-9.4%; 5.0% for colon and 11.1% for rectal cancer). Rectal location was an independent predictor of recurrence (hazard ratio (HR) 1.97, 95% CI 1.09-3.55; P=0.024). Lymphovascular invasion was an independent predictor of recurrence only in patients with rectal cancer (HR 3.0, 95% CI 1.2-7.6; P=0.018). Five-year recurrence-free survival was 83.2% (95% CI 80.3-85.4%). Age (HR 1.05, 95% CI 1.03-1.07; P<0.001), elective surgery (HR 0.41, 95% CI 0.21-0.80; P=0.011) and the American Society of Anesthesiologists (ASA) score (HR 3.08, 95% CI 1.51-6.31; P<0.001) were independently associated with recurrence-free survival. Median survival after recurrence was 41 months. Resection of recurrence was attempted in 39% of patients.

CONCLUSION: Patients with stage I colorectal cancers still have a clinically significant risk of recurrence. Rectal location is independently associated with higher recurrence. Age, elective surgery and ASA are independently associated with recurrence-free survival. A significant proportion of patients with recurrence underwent further resection.

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**Inter-device comparison of retinal sensitivity measurements: the CenterVue MAIA and the Nidek MP-1.**

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BACKGROUND: Our aim is to compare retinal sensitivity measurements obtained on two microperimeters: the CenterVue MAIA and the Nidek MP-1.

DESIGN: A prospective study was conducted in a private ophthalmology clinic.

PARTICIPANTS: Seventeen individuals with a range of stable macular function were recruited as participants.

METHODS: Microperimetry in one eye with identical test strategy in both devices, with randomized testing order, is used.

MAIN OUTCOME MEASURES: The main outcome measures include differences in mean sensitivity (MS), point-wise sensitivity (PWS) and duration. Limits of agreement (LoA) in MS and pooled PWS were calculated. Concordance in
scotoma assessment was analysed by kappa (kappa) agreement of local defect classification (LDC), LoA in number of scotomatous loci detected and congruence in scotoma localization (CSL).

RESULTS: Median (interquartile range) MS of the MP-1 and MAIA was 13.3 (5.6-18.1) and 21.2 (14.5-27.0) dB, (P<0.05). Mean difference in PWS was 7.3dB (MAIA>MP-1). Median (interquartile range) duration for the MP-1 and MAIA was 10’28 (7’17-11’53) and 8’46 (8’30-9’06), (P=0.21). LoA for MS and pooled PWS was 1.4 to 13.3dB and -3.9 to 18.5dB. There was moderate agreement between the devices for LDC (weighted kappa=0.55, P<0.05). LoA in number of scotomatous loci detected was -13 to 18. CSL varied from 0 to 100% and correlated strongly with increasing scotoma size.

CONCLUSIONS: The large LoA and variation in scotoma mapping concordance suggest that the same microperimeter should be used for follow-up examination. We recommend caution in comparing results derived from different types of microperimeters.

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Uncertainty, conflict and consent: revisiting the futility debate in neurotrauma.
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The concept of futility has been debated for many years, and a precise definition remains elusive. This is not entirely unsurprising given the increasingly complex and evolving nature of modern medicine. Progressively more complex decisions are required when considering increasingly sophisticated diagnostic and therapeutic interventions. Allocating resources appropriately amongst a population whose expectations continue to increase raises a number of ethical issues not least of which are the difficulties encountered when consideration is being given to withholding "life-preserving" treatment. In this discussion we have used decompressive craniectomy for severe traumatic brain injury as a clinical example with which to frame an approach to the concept. We have defined those issues that initially lead us to consider futility and thereafter actually provoke a significant discussion. We contend that these issues are uncertainty, conflict and consent. We then examine recent scientific advances in outcome prediction that may address some of the uncertainty and perhaps help achieve consensus amongst stakeholders. Whilst we do not anticipate that this re-framing of the idea of futility is applicable to all medical situations, the approach to specify patient-centred benefit may assist those making such decisions when patients are incompetent to participate.

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Acute effects of quercetin-3-O-glucoside on endothelial function and blood pressure: a randomized dose-response study.
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BACKGROUND: Epidemiologic studies have suggested that a flavonoid-rich diet can reduce the risk of developing cardiovascular disease. Certain flavonoids, in particular quercetin, have been shown to ameliorate endothelial dysfunction and reduce blood pressure (BP), possibly by increasing the bioavailability of the potent vasodilator nitric oxide (NO). Several studies have indicated that improvements in measures of cardiovascular health do not occur linearly, but rather, plateau or decrease with an increasing dose of flavonoids.

OBJECTIVES: We determined whether the acute administration of increasing doses of a common quercetin glycoside (quercetin-3-O-glucoside) improves endothelial function and reduces BP in a dose-dependent manner. We also explored whether any effects were correlated with changes in plasma NO production.

DESIGN: A randomized, controlled, crossover study was performed in 15 healthy volunteers who each completed 5 visits with a minimum washout period of 1 wk between testing days. Participants received each of the following 5 interventions in a random order: 1) 0, 2) 50, 3) 100, 4) 200, or 5) 400 mg quercetin-3-O-glucoside. Endothelial function and BP were assessed before and 60 min after intervention. A blood sample was taken before and 90 min after intervention for the analysis of plasma nitrate and nitrite as markers of NO production as well as of plasma quercetin metabolites.

RESULTS: Although we observed a significant correlation between the dose of quercetin-3-O-glucoside and plasma concentrations of total quercetin (R(2) = 0.52, P < 0.001) and isorhamnetin (R(2) = 0.12, P = 0.005), we showed no improvements in endothelial function or BP and no changes in NO production after any dose.

CONCLUSION: From these results, we conclude that there are no acute changes in BP or the NO-mediated endothelium-dependent relaxation of the brachial artery with doses of quercetin ranging from 50 to 400 mg in healthy men and women. This trial was registered at www.anzctr.org.au as ACTRN12615001338550.

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Surgical Results and Outcomes After Reimplantation for the Management of Anomalous Aortic Origin of the Right Coronary Artery.

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BACKGROUND: Anomalous aortic origin of the right coronary artery (AAORCA) has been reported to cause myocardial ischemia, leading to angina, dyspnea, and decreased exercise tolerance. Reimplantation is a repair technique devised to exclude the abnormal intramural portion of the anomalous artery and avoid the known late attrition of saphenous vein grafts. Our study aims to evaluate the medium-term clinical outcomes with this technique.

METHODS: A retrospective review was made of patients who underwent repair of AAORCA by reimplantation between 2002 and 2014 in two institutions in Western Australia. Follow-up computed tomography coronary
angiography was used to assess the status of the reimplanted right coronary artery (RCA). Data on survival, freedom from symptoms, cardiac events, and cardiac interventions were also analyzed.

RESULTS: Of the 16 patients (aged 17 to 70 years old), 14 (88%) were symptomatic before surgery, with angina (50%) and exertional dyspnea (56%) being the most common symptoms. Surgical reimplantation was successful in 15 patients (94%) without operative mortality. One patient required saphenous vein bypass grafting of the RCA intraoperatively after presumed failed repair and difficulty weaning from cardiopulmonary bypass. All patients who had successful reimplantation of AAORCA were symptom-free after surgery, and none had subsequent cardiac events attributable to the RCA or required further interventions. Ten patients (67%) had computed tomography coronary angiography after surgery; none had stenosis, kinking, or compression of the RCA by the pulmonary artery. Two further patients (including the patient who underwent saphenous vein grafting for presumed failed reimplantation) underwent conventional angiography, which demonstrated patent reimplantations.

CONCLUSIONS: To the best of our knowledge, this is the largest reported series of anomalous RCA managed by surgical reimplantation. Our results suggest that this technique is safe and has excellent medium to long-term results regarding symptom-free survival.

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The effect of killer cell immunoglobulin-like receptor (KIR)-ligand matching on outcomes after unrelated cord blood (CB) transplantation was studied in 461 patients with acute myeloid leukemia, categorizing KIR ligand for HLA-C groups C1 and C2 and Bw4. Donor-recipient HLA matching considered allele-level matching at HLA-A, -B, -C, and -DRB1. Separate analyses were conducted for 6-7/8 HLA-matched and 3-5/8 HLA-matched transplants because HLA matching confounded KIR-ligand matching (ie, KIR-ligand mismatching was less likely with better HLA matching). All patients received single CB unit and myeloablative conditioning. There were no significant differences in nonrelapse mortality (NRM), relapse, and overall mortality by KIR-ligand match status. However, among recipients of 3-5/8 HLA-matched transplants, NRM (HR, 2.26; P = .008) and overall mortality (HR, 1.78; P = .008) but not relapse were higher with KIR-ligand mismatched (host-versus-graft direction) compared with KIR-ligand matched transplants. These data do not support selecting CB units based on KIR-ligand match status for transplants mismatched at 1 or 2 HLA loci. Although transplants mismatched at 3 or more HLA loci are not recommended, avoiding KIR-ligand
mismatching in this setting lowers mortality risks.


Levels of CMV-reactive antibodies correlate with the induction of CD28(null) T cells and systemic inflammation in chronic obstructive pulmonary disease (COPD).

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Classification of image artefacts in optical coherence tomography angiography of the choroid in macular diseases.

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BACKGROUND: To evaluate and classify image artefacts in optical coherence tomography (OCT) angiography (OCTA) of the choroid in a group of patients with macular diseases.

DESIGN: Retrospective observational study.

PARTICIPANTS: Five patients with age-related macular degeneration, three with central serous retinopathy, one with polypoidal choroidal vasculopathy and one with multiple evanescent white dot syndrome.

METHODS: OCTA and OCT reflectivity (OCTR) maps were reviewed along with their fluorescein angiography and indocyanine green angiography. Sixty OCTA images (20 outer retina, 20 Sattler and 20 Haller layers) were graded for image artefacts by two examiners independently.

MAIN OUTCOME MEASURES: OCTA artefacts and their correlation with OCTR maps, angiography and OCT B-scans.

RESULTS: Artefacts (frequency) were classified into (i) motion (70–100%), (ii) fringe washout (100%), (iii) decorrelation projection (0–20%), (iv) masking and unmasking (50–65%) and (v) stromal decorrelation signal (100%). Motion artefact in OCTA is characterized by horizontal dark lines or bands not apparent on OCTR map. Fringe washout creates signal void within choroidal vessels because of fast blood flow. Decorrelation projection from retinal vasculature and choroidal new vessels above the Bruch’s membrane are seen within the choroidal OCTA image. Masking and unmasking artefacts occur in regions of pigment epithelial detachment and atrophy. Decorrelation signals can also be
seen in the choroidal stroma.

CONCLUSIONS: Our classification system of artefact in choroidal OCTA establishes a common terminology for clinical interpretation. This is important in enhancing our understanding of the principles of OCTA acquisition, and it also serves as a benchmark for reading centres.

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Sympathetic Activation in Chronic Heart Failure: Potential Benefits of Interventional Therapies.


Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes.

UNLABELLED: A genome-wide exome association study has identified the transmembrane 6 superfamily member 2 (TM6SF2) rs58542926 variant encoding an E167K substitution as a genetic determinant of hepatic steatosis in nonalcoholic fatty liver disease (NAFLD). The roles of this variant across a spectrum of liver diseases and pathologies and on serum lipids comparing viral hepatitis to NAFLD and viral load in chronic viral hepatitis, as well as its intrahepatic molecular signature, have not been well characterized. We undertook detailed analyses in 3260 subjects with viral and nonviral liver diseases and in healthy controls. Serum inflammatory markers and hepatic expression of TM6SF2 and genes regulating lipid metabolism were assessed in a subset with chronic hepatitis C (CHC). The rs58542926 T allele was more prevalent in 502 NAFLD patients than controls (P = 0.02) but not different in cohorts with CHC (n = 2023) and chronic hepatitis B (n = 507). The T allele was associated with alterations in serum lipids and hepatic steatosis in all diseases and with reduced hepatic TM6SF2 and microsomal triglyceride transfer protein expression. Interestingly, the substitution was associated with reduced CHC viral load but increased hepatitis B virus DNA. The rs58542926 T allele had no effect on inflammation, impacted >F2 fibrosis in CHC and NAFLD assessed cross-sectionally (odds ratio = 1.39, 95% confidence interval 1.04-1.87, and odds ratio = 1.62, 95% confidence interval 1.03-2.52, respectively; P < 0.03 for both), but had no effect on fibrosis progression in 1174 patients with CHC and a known duration of infection.

CONCLUSION: The TM6SF2 E167K substitution promotes steatosis and lipid abnormalities in part by altering TM6SF2
and microsomal triglyceride transfer protein expression and differentially impacts CHC and chronic hepatitis B viral load, while effects on fibrosis are marginal. (Hepatology 2016;64:34-46).
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Survey of Australasian geriatricians' satisfaction with, and preferences for, continuing professional development.
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BACKGROUND: Continuing professional development (CPD) is an obligation for all Australasian geriatricians; however, there are no systematic data regarding Australian and New Zealand geriatricians’ satisfaction with, and preferences for, CPD.
AIMS: To inform understanding of Australasian geriatricians' satisfaction with, and preferences for, CPD.
METHODS: An electronic survey to collect data relating to demographics, current CPD activities, preferred CPD activities and perceived major barriers to CPD was distributed to 706 geriatricians in Australia and New Zealand.
RESULTS: Two hundred and thirteen (30%) responses were received. Respondents commonly reported CPD through participation in conferences (n=205 (96%)) and research/educational activity (n=146 (70%)). Most respondents agreed
that the annual scientific meeting (n=168 (79%)) and state-based meetings (n=135 (63%)) are valuable for their CPD. Respondents perceived their professional (n=155 (73%)) and non-professional (n=21 (57%)) commitments as the major barriers to quality CPD. Respondents supported additional electronic CPD resources being made available, improved integration of assessment in CPD activities and flexible methods of CPD participation to meet the diverse needs of geriatricians.

CONCLUSIONS: Respondents perceived the face-to-face CPD opportunities currently available to them as valuable for their CPD but seek additional, flexible products to enable CPD participation based on individual needs and preferences.

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**Determinants of image quality of rotational angiography for on-line assessment of frame geometry after transcatheter aortic valve implantation.**

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To study the determinants of image quality of rotational angiography using dedicated research prototype software for motion compensation without rapid ventricular pacing after the implantation of four commercially available catheter-based valves. Prospective observational study including 179 consecutive patients who underwent transcatheter aortic valve implantation (TAVI) with either the Medtronic CoreValve (MCS), Edward-SAPIEN Valve (ESV), Boston Sadra Lotus (BSL) or Saint-Jude Portico Valve (SJP) in whom rotational angiography (R-angio) with motion compensation 3D image reconstruction was performed. Image quality was evaluated from grade 1 (excellent image quality) to grade 5 (strongly degraded). Distinction was made between good (grades 1, 2) and poor image quality (grades 3-5). Clinical (gender, body mass index, Agatston score, heart rate and rhythm, artifacts), procedural (valve type) and technical variables (isocentricity) were related with the image quality assessment. Image quality was good in 128 (72%) and poor in 51 (28%) patients. By univariable analysis only valve type (BSL) and the presence of an artefact negatively affected image quality. By multivariate analysis (in which BMI was forced into the model) BSL valve (Odds 3.5, 95% CI [1.3-9.6], p=0.02), presence of an artifact (Odds 2.5, 95% CI [1.2-5.4], p=0.02) and BMI (Odds 1.1, 95% CI [1.0-1.2], p=0.04) were independent predictors of poor image quality. Rotational angiography with motion compensation 3D image reconstruction using a dedicated research prototype software offers good image quality for the evaluation of frame geometry after TAVI in the majority of patients. Valve type, presence of artifacts and higher BMI negatively affect image quality.

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The Potential Role of Catheter-Based Renal Sympathetic Denervation in Chronic and End-Stage Kidney Disease.
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Sympathetic activation is a hallmark of chronic and end-stage renal disease and adversely affects cardiovascular prognosis. Hypertension is present in the vast majority of these patients and plays a key role in the progressive deterioration of renal function and the high rate of cardiovascular events in this patient cohort. Augmentation of renin release, tubular sodium reabsorption, and renal vascular resistance are direct consequences of efferent renal sympathetic nerve stimulation and the major components of neural regulation of renal function. Renal afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in blood pressure control via hypothalamic integration. Renal denervation of the kidney has been shown to reduce blood pressure in many experimental models of hypertension. Targeting the renal nerves directly may therefore be specifically useful in patients with chronic and end-stage renal disease. In this review, we will discuss the potential role of catheter-based renal denervation in patients with impaired kidney function and also reflect on the potential impact on other cardiovascular conditions commonly associated with chronic kidney disease such as heart failure and arrhythmias.

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Malignant cerebral swelling following cranioplasty.
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Over the past few years there have been a number of case reports and small cohort studies that have described so called "malignant" cerebral swelling following an uneventful cranioplasty procedure. The pathophysiology remains to be established however it has been suggested that it may be related to a combination of failure of autoregulation and the use of closed vacuum suction drainage. The current study presents three further patients who had had a decompressive hemicraniectomy for ischaemic stroke. If decompressive craniectomy is utilised in the management of neurological emergencies, close attention and wider reporting of this type of complication is required not only to focus attention on possible management strategies, but also to determine which patients are at most risk of this devastating complication.

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The biology and clinical evidence of microfracture in hip preservation surgery.
The use of microfracture in hip arthroscopy is increasing dramatically. However, recent reports raise concerns not only about the lack of evidence to support the clinical use of microfracture, but also about the potential harm caused by violation of the subchondral bone plate. The biology and pathology of the microfracture technique were described based on observations in translational models and the clinical evidence for hip microfracture was reviewed systematically. The clinical outcomes in patients undergoing microfracture were the same as those not undergoing microfracture. However, the overall clinical evidence quality is poor in hips. This review identified only one study with Level III evidence, while most studies were Level IV. There were no randomized trials available for review. Repair tissue is primarily of fibrocartilaginous nature. Reconstitution of the subchondral bone is often incomplete and associated with poor quality repair tissue and faster degeneration. Subchondral bone cyst formation is associated with microfracture, likely secondary to subchondral bone plate disruption and a combination of pressurized synovial fluid and inflammatory mediators moving from the joint into the bone. There is a lack of clinical efficacy evidence for patients undergoing microfracture. There is evidence of bone cyst formation following microfracture in animal studies, which may accelerate joint degeneration. Bone cyst formation following microfracture has not been studied adequately in humans.

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Charlson Comorbidities Index.
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Durability of the balloon-expandable covered versus bare-metal stents in the Covered versus Balloon Expandable Stent Trial (COBEST) for the treatment of aortoiliac occlusive disease.
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OBJECTIVE: The Covered vs Balloon Expandable Stent Trial (COBEST) is the first multicenter trial to investigate the patency of covered stents (CSs) and bare-metal stents (BMSs) in the treatment of aortoiliac arterial disease. The short-term results demonstrated that CSs were superior to BMSs in maintaining patency for TransAtlantic Inter-Society Consensus (TASC) C and D lesions at 18 months and were equivalent to BMSs for TASC B lesions. The current study was conducted to determine if the initial patency advantage of CSs over BMSs was sustained at the 5-year follow-up.

METHODS: A retrospective post hoc analysis of COBEST was performed. Originally, 125 patients with 168 iliac arteries were prospectively enrolled and randomly assigned to receive a CS or BMS. In this study, 77 of the 125 patients (61.6%; 119 limbs) were assessed at 60 months for the primary and secondary end points, with particular attention paid to the outcomes stratified according to TASC lesion severity. The primary end point was the rate of binary stenosis or freedom from stent occlusion of the treated area, as determined by ultrasound imaging or quantitative visual angiography.

RESULTS: The 5-year results of the COBEST showed that the CS had a significantly higher patency rate than the BMS at 18, 24, 48, and 60 months (95.1%, 82.1%, 79.9%, 74.7% for CS vs 73.9%, 70.9%, 63% and 62.5% for BMS; log-rank test, \( P = .01 \)). On multivariate analysis, the type of stent used (hazard ratio [HR], 2.797; 95% confidence interval [CI], 1.471-5.318; \( P = .002 \)) and the Rutherford classification (HR, 2.019; 95% CI, 1.278-3.191; \( P = .026 \)) significantly affected the adjusted primary patency. On subgroup analysis, the CS showed significantly higher patency and a survival benefit compared with the BMS in TASC C and D lesions (HR, 6.839; 95% CI, 5.253-75.753; \( P = .003 \)). Moreover, fewer patients received target limb revascularization in the CS group than in the BMS group (odds ratio, 2.32; 95% CI, 1.47-3.36; \( P = .02 \)); however, there was no statistically significant difference in the rate of amputations between the groups.

CONCLUSIONS: The 5-year results of the COBEST demonstrated that the CS has an enduring patency advantage over the BMS in both the short and long terms. Furthermore, the CS showed acceptable patency rates for the treatment of more severe TASC C and D lesions, and patients who received a CS required fewer revascularization procedures. However, the choice of stent did not affect the rate of major limb amputations.

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Serum homocysteine is associated with the severity of primary chronic venous disease.

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OBJECTIVE: This study was conducted to assess whether serum homocysteine concentration was associated with the
severity of primary chronic venous disease.

**DESIGN:** Cross-sectional study.

**METHODS:** A total of 282 primary chronic venous disease patients were enrolled from outpatient vascular services. The severity of venous disease was graded using the Clinical Etiology Anatomy Pathophysiology classification system. The association of serum homocysteine concentration with advanced primary chronic venous disease (C4-6) was assessed using the Mann Whitney U test and logistic regression analysis.

**RESULTS:** Median (interquartile range) serum homocysteine concentrations were 9.10 μM (7.55-10.75) and 10.40 μM (8.85-13.10) in patients with primary chronic venous disease classified by C1-3 (n=209) and C4-6 (n=73) grades, respectively, p<0.001. Serum homocysteine concentration was positively associated with clinical grade 4-6 after adjusting for other risk factors including age, diabetes, male sex, hypertension, recurrent varicose veins and stroke. Patients with serum homocysteine in the third (odds ratio, 2.76, 95% confidence interval, 1.01-7.54) and fourth (odds ratio 3.29, 95% confidence interval 1.15-9.43) quartiles were more likely to have grade C4-6 chronic venous disease than subjects with serum homocysteine in the first quartile.

**CONCLUSIONS:** Serum homocysteine is positively associated with the severity of primary chronic venous disease and therefore could play a role in promoting chronic venous disease complications.

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Locomotor Performance During Rehabilitation of People With Lower Limb Amputation and Prosthetic Nonuse 12 Months After Discharge.

Roffman CE, Buchanan J, et al.

**BACKGROUND:** It is recognized that multifactorial assessments are needed to evaluate balance and locomotor function in people with lower limb amputation. There is no consensus on whether a single screening tool could be used to identify future issues with locomotion or prosthetic use.

**OBJECTIVE:** The purpose of this study was to determine whether different tests of locomotor performance during rehabilitation were associated with significantly greater risk of prosthetic abandonment at 12 months postdischarge.

**DESIGN:** This was a retrospective cohort study.

**METHOD:** Data for descriptive variables and locomotor tests (ie, 10-Meter Walk Test [10MWT], Timed “Up & Go” Test [TUGT], Six-Minute Walk Test [6MWT], and Four Square Step Test [FSST]) were abstracted from the medical records of 201 consecutive participants with lower limb amputation. Participants were interviewed and classified as prosthetic users or nonusers at 12 months postdischarge. The Mann-Whitney U test was used to analyze whether there were differences in locomotor performance. Receiver operating characteristic curves were generated to determine performance thresholds, and relative risk (RR) was calculated for nonuse.

**RESULTS:** At 12 months postdischarge, 18% (n=36) of the participants had become prosthetic nonusers. Performance thresholds, area under the curve (AUC), and RR of nonuse (95% confidence intervals [CI]) were: for the 10MWT, if walking speed was <0.44 m/s (AUC=0.743), RR of nonuse=2.76 (95% CI=1.83, 3.79; P<.0001); for the TUGT, if time was >21.4 seconds (AUC=0.796), RR of nonuse=3.17 (95% CI=2.17, 4.14; P<.0001); for the 6MWT, if distance was <191 m (AUC=0.788), RR of nonuse=2.84 (95% CI=2.05, 3.48; P<.0001); and for the FSST, if time was >36.6 seconds (AUC=0.762), RR of nonuse=2.76 (95% CI=1.99, 3.39; P<.0001).

**LIMITATIONS:** Missing data, potential recall bias, and assessment times that varied were limitations of the study.

**CONCLUSIONS:** Locomotor performance during rehabilitation may predict future risk of prosthetic nonuse. It may be implied that the 10MWT has the greatest clinical utility as a single screening tool for prosthetic nonuse, given the highest proportion of participants were able to perform this test early in rehabilitation. However, as locomotor skills
improve, other tests (in particular, the 6MWT) have specific clinical utility. To fully enable implementation of these locomotor criteria for prosthetic nonuse into clinical practice, validation is warranted.

Prostaglandins & Other Lipid Mediators. 2016; 124: 34-8. Controlled moderate hypovolaemia in healthy volunteers is not associated with the development of oxidative stress assessed by plasma F2-isoprostanes and isofurans.

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Hypovolaemia can be associated with substantial morbidity, particularly when it occurs in the setting of trauma and in patients with comorbid diseases. Hypovolaemia and inflammation such as occur in the setting of trauma and surgery, are associated with systemic oxidative stress and free-radical injury. Free-radical injury that results from hypovolaemia-induced organ reperfusion may further augment inflammatory processes. It is unknown exactly what proportion of free-radical injury is associated with isolated hypovolaemia as opposed to the contribution from inflammation from surgery or trauma. In the first human study of its kind, we exposed 8 adult male volunteers to venesection-induced hypovolaemia in progressive aliquots of 5% of total blood volume until 20% had been removed. This blood was subsequently reinfused. Plasma F2-isoprostanes and isofurans, markers of in vivo lipid oxidation, were measured by gas chromatography-mass spectrometry at each 5% aliquot venesected and at each 5% reinfused. Between baseline and maximal blood loss there was a minor fall in haemoglobin concentration from 143.9g/l to 138.8g/l (p=0.004, 95% CI 2.2, 8.0g/L). No significant change from baseline occurred in the concentrations of either plasma F2-isoprostanes or isofurans during venesection (p=0.116 and p=0.152, respectively) or blood reinfusion (p=0.553 and p=0.736, respectively). We can conclude that in healthy adult volunteers, isolated hypovolaemia to 20% total blood volume loss is not associated with detectable systemic oxidative stress. The free-radical injury identified in surgical and trauma patients may represent the effects of tissue damage and inflammation, with an uncertain contribution from tissue ischemia as may occur with hypovolaemia.

Human mesenchymal stem cells attenuate early damage in a ventilated pig model of acute lung injury.


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Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a major cause of global morbidity and mortality. Mesenchymal stem cells (MSC) have shown promise in treating inflammatory lung conditions. We hypothesised that human MSC (hMSC) can improve ALI/ARDS through their anti-inflammatory actions. We subjected pigs (n=6) to intravenous oleic acid (OA) injury, ventilation and hMSC infusion, while the controls (n=5) had intravenous OA, ventilation and an infusion vehicle control. hMSC were infused 1h after the administration of OA. The animals were monitored for additional 4h. Nuclear translocation of nuclear factor-light chain enhancer of activated B cells (NF-κB), a transcription factor that mediates several inflammatory pathways was reduced in hMSC treated pigs compared to controls (p=0.04). There was no significant difference in lung injury, assessed by histological scoring in hMSC treated pigs versus controls (p=0.063). There was no difference in neutrophil counts between hMSC-treated pigs and controls. Within 4h, there was no difference in the levels of IL-10 and IL-8 pre- and post-treatment with hMSC. In addition, there was no difference in hemodynamics, lung mechanics or arterial blood gases between hMSC treated animals and controls. Subsequent studies are required to determine if the observed decrease in inflammatory transcription factors will translate into improvement in inflammation and in physiological parameters over the long term.

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INTRODUCTION: Malignant pleural effusions (MPEs) can complicate most cancers, causing dyspnoea and impairing quality of life (QoL). Indwelling pleural catheters (IPCs) are a novel management approach allowing ambulatory fluid drainage and are increasingly used as an alternative to pleurodesis. IPC drainage approaches vary greatly between centres. Some advocate aggressive (usually daily) removal of fluid to provide best symptom control and chance of spontaneous pleurodesis. Daily drainages however demand considerably more resources and may increase risks of complications. Others believe that MPE care is palliative and drainage should be performed only when patients become symptomatic (often weekly to monthly). Identifying the best drainage approach will optimise patient care and healthcare resource utilisation.

METHODS AND ANALYSIS: A multicentre, open-label randomised trial. Patients with MPE will be randomised 1:1 to daily or symptom-guided drainage regimes after IPC insertion. Patient allocation to groups will be stratified for the cancer type (mesothelioma vs others), performance status (Eastern Cooperative Oncology Group status 0-1 vs >2), presence of trapped lung (vs not) and prior pleurodesis (vs not). The primary outcome is the mean daily dyspnoea score, measured by a 100 mm visual analogue scale (VAS) over the first 60 days. Secondary outcomes include benefits on physical activity levels, rate of spontaneous pleurodesis, complications, hospital admission days, healthcare costs and QoL measures. Enrolment of 86 participants will detect a mean difference of VAS score of 14 mm between the treatment arms (5% significance, 90% power) assuming a common between-group SD of 18.9 mm and a 10% lost to follow-up rate.

ETHICS AND DISSEMINATION: The Sir Charles Gairdner Group Human Research Ethics Committee has approved the study (number 2015-043). Results will be published in peer-reviewed journals and presented at scientific meetings.

TRIAL REGISTRATION NUMBER: ACTRN1261500963527; Pre-results.

Analysis of copy number variation at DMBT1 and age-related macular degeneration.

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BACKGROUND: DMBT1 is a gene that shows extensive copy number variation (CNV) that alters the number of bacteria-binding domains in the protein and has been shown to activate the complement pathway. It lies next to the ARMS2/HTRA1 genes in a region of chromosome 10q26, where single nucleotide variants have been shown to be strongly associated with age-related macular degeneration (AMD), the commonest cause of blindness in Western populations. Complement activation is thought to be a key factor in the pathogenesis of this condition. We sought to investigate whether DMBT1 CNV plays any role in the susceptibility to AMD.

METHODS: We analysed long-range linkage disequilibrium of DMBT1 CNV1 and CNV2 with flanking single nucleotide polymorphisms (SNPs) using our previously published CNV and HapMap Phase 3 SNP data in the CEPH Europeans from Utah (CEU). We then typed a large cohort of 860 AMD patients and 419 examined age-matched controls for copy number at DMBT1 CNV1 and CNV2 and combined these data with copy numbers from a further 480 unexamined controls.

RESULTS: We found weak linkage disequilibrium between DMBT1 CNV1 and CNV2 with the SNPs rs1474526 and rs714816 in the HTRA1/ARMS2 region. By directly analysing copy number variation, we found no evidence of association of CNV1 or CNV2 with AMD.

CONCLUSIONS: We have shown that copy number variation at DMBT1 does not affect risk of developing age-related macular degeneration and can therefore be ruled out from future studies investigating the association of structural variation at 10q26 with AMD.

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Melissa officinalis L. - A review of its traditional uses, phytochemistry and pharmacology.


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ETHNOPHARMACOLOGICAL RELEVANCE: Melissa officinalis L. is a medicinal plant that has long been used in different ethno-medical systems especially in the European Traditional Medicine and the Iranian Traditional Medicine for the treatment of several diseases. It is also widely used as a vegetable and to add flavor to dishes

AIM OF THE REVIEW: This review aimed to provide a summary on the botanical characterization, traditional uses, phytochemistry, pharmacological activities, pharmacokinetics and toxicity of M. officinalis, and discusses research gaps and future opportunities for investigations on this plant.

MATERIALS AND METHODS: We extensively reviewed major unpublished old texts, and published and electronic literature on traditional medicines of different regions of the world to find traditional uses of M. officinalis. Electronic databases including Web of Science, PubMed, ScienceDirect, Google Scholar and Scopus were searched to find
articles (published between 1956 and 2015) on pharmacology and phytochemistry of M. officinalis.

RESULTS: Traditional uses of M. officinalis have been recorded mostly in European countries, Mediterranean region and Middle East countries. Phytochemical investigations revealed that this plant contains volatile compounds, triterpenoids, phenolic acids and flavonoids. Crude extracts and pure compounds isolated from M. officinalis exhibited numerous pharmacological effects, from which only anxiolytic, antiviral and antispasmodic activities of this plant as well as its effects on mood, cognition and memory have been shown in clinical trials. AChE inhibitory activity, stimulation of the acetylcholine and GABAA receptors, as well as inhibition of matrix metalloproteinase-2 are the main mechanisms proposed for the widely discussed neurological effects of this plant.

CONCLUSIONS: Modern pharmacological studies have now validated many traditional uses of M. officinalis. The data reviewed here revealed that M. officinalis is a potential source for the treatment of a wide range of diseases especially anxiety and some other CNS disorders, though confirmatory trials are warranted to substantiate these effects in the clinical setting. Data regarding many aspects of this plant such as mechanisms of actions, pharmacokinetics, adverse effects of the extracts, potential interactions with standard-of-care medications and active compounds is still limited which call for additional studies particularly in humans.

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Optimal use of plasma and urine BK viral loads for screening and predicting BK nephropathy.
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BACKGROUND: BK virus is a polyoma virus causing renal allograft nephropathy. Reduction of immunosuppression with the early recognition of significant BK viral loads in urine and plasma can effectively prevent BKV associated nephropathy (BKVN), however the optimal compartment and frequency of BK viral load measurement post renal transplantation are undetermined. Our purpose was to examine time to detection and viral loads in urine compared to plasma, and establish viral load cut-offs associated with histological BKVN.

METHODS: We performed a retrospective analysis of the BKV screening frequency and compartment(s) of 277 adult renal transplant recipients (RTR).

RESULTS: BKVN was histologically diagnosed in 17 (6.1 %) RTR. In cases where both urine and plasma were tested fortnightly for 6 months (n=53), BKV was detected in the urine 29 days earlier than plasma. Fortnightly (n=72) versus 3-monthly (n=78) testing demonstrated that BKV was detected in the urine significantly earlier (median 63 versus 97 days, p=0.001) and at a lower level (median 3.27 versus 6.71 log10 c/mL, p<0.001) with more frequent testing, but this difference was not evident in plasma first detection (80 versus 95 days, p=0.536) or first positive viral load (3.18 versus 3.30 log10 c/mL, p=0.603). The optimum cut-off BK viral load for histological diagnosis of BKVN was 4.10 log10 c/mL for the first positive urine, 3.79 log10 c/mL for the first positive plasma, 9.24 log10 c/mL for the peak urine, and 4.53...
log10 c/mL for the peak plasma.

CONCLUSIONS: Frequent urinary BK viral load screening for the prevention of BKVN is suggested due to its high sensitivity and earlier detection.

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Efficacy of Statin Therapy in Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis.

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Since the evidence regarding statin therapy in PAH has not been conclusive, we assessed the impact of statin therapy in PAH through a systematic review and meta-analysis of available studies. We searched selected databases up to August 1, 2015 to identify the studies investigating the effect of statin administration on PAH. Meta-analysis was performed using either a fixed-effects or random-effect model according to I(2) statistic. Meta-analysis of 8 studies with 665 patients did not suggest any significant improvement in 6-min walking distance (6MWD) by statin therapy (weighed mean difference [WMD]: -6.08m, 95% confidence interval [CI]: -25.66, 13.50, p=0.543; Q=8.41, I(2)=28.64%).

Likewise, none of the other indices including pulmonary arterial pressure (WMD: -0.97mmHg, 95%CI: -4.39, 2.44, p=0.577; Q=14.64, I(2)=79.51%), right atrial pressure (WMD: 1.01mmHg, 95%CI: -0.93, 2.96, p=0.307; Q=44.88, I(2)=95.54%), cardiac index (WMD: 0.05L/min/m(2), 95%CI: -0.02, 0.15, p=0.323; Q=3.82, I(2)=21.42%), and pulmonary vascular resistance (WMD: -1.42dyn*s/cm(5), 95%CI: -72.11, 69.27, p=0.969; Q=0.69, I(2)=0%) was significantly altered by statin therapy. In conclusion, the results of the meta-analysis did not show a statistically significant effect of statin therapy in the improvement of 6MWD, pulmonary arterial pressure, right atrial pressure, cardiac index and pulmonary vascular resistance.
Unique and shared signaling pathways cooperate to regulate the differentiation of human CD4+ T cells into distinct effector subsets.

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Naive CD4(+) T cells differentiate into specific effector subsets—Th1, Th2, Th17, and T follicular helper (Tfh)—that provide immunity against pathogen infection. The signaling pathways involved in generating these effector cells are partially known. However, the effects of mutations underlying human primary immunodeficiencies on these processes, and how they compromise specific immune responses, remain unresolved. By studying individuals with mutations in key signaling pathways, we identified nonredundant pathways regulating human CD4(+) T cell differentiation in vitro. IL12Rbeta1/TYK2 and IFN-gammaR/STAT1 function in a feed-forward loop to induce Th1 cells, whereas IL-21/IL-21R/STAT3 signaling is required for Th17, Tfh, and IL-10-secreting cells. IL12Rbeta1/TYK2 and NEMO are also required for Th17 induction. Strikingly, gain-of-function STAT1 mutations recapitulated the impact of dominant-negative STAT3 mutations on Tfh and Th17 cells, revealing a putative inhibitory effect of hypermorphic
STAT1 over STAT3. These findings provide mechanistic insight into the requirements for human T cell effector function, and explain clinical manifestations of these immunodeficient conditions. Furthermore, they identify molecules that could be targeted to modulate CD4(+) T cell effector function in the settings of infection, vaccination, or immune dysregulation.

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'My independent streak may get in the way': how older adults respond to falls prevention education in hospital.
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OBJECTIVES: The aim of the study was to determine how providing individualised falls prevention education facilitated behaviour change from the perspective of older hospital patients on rehabilitation wards and what barriers they identified to engaging in preventive strategies.
DESIGN: A prospective qualitative survey.
METHODS: Older patients (n=757) who were eligible (mini-mental state examination score>23/30) received falls prevention education while admitted to eight rehabilitation hospital wards in Western Australia. Subsequently, 610 participants were surveyed using a semistructured questionnaire to gain their response to the in-hospital education and their identified barriers to engaging in falls prevention strategies. Deductive content analysis was used to map responses against conceptual frameworks of health behaviour change and risk taking.
RESULTS: Participants who responded (n=473) stated that the education raised their awareness, knowledge and confidence to actively engage in falls prevention strategies, such as asking for assistance prior to mobilising. Participants’ thoughts and feelings about their recovery were the main barriers they identified to engaging in safe strategies, including feeling overconfident or desiring to be independent and thinking that staff would be delayed in providing assistance. The most common task identified as potentially leading to risk-taking behaviour was needing to use the toilet.
CONCLUSIONS: Individualised education assists older hospital rehabilitation patients with good levels of cognition to engage in suitable falls prevention strategies while on the ward. Staff should engage with patients to understand their perceptions about their recovery and support patients to take an active role in planning their rehabilitation.
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In Memoriam: A cardiologist’s unique cholesterol journey in Malaysia: Dato’ Dr Kah-Lin Khoo, MD, FRCP, FACC, FESC, FCCP (December 18, 1938-November 7, 2014).

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Gunaratne GD, Khan RJ, et al.
INTRODUCTION: Psoas abscess is a recognized but under-diagnosed complication of prosthetic hip joint infections. CASE REPORT: We report a case of a 68-year-old man with right and left hip arthroplasties performed 22 and 14 years ago, respectively, who presented with non-specific symptoms and was subsequently diagnosed with left psoas abscess on CT scan. Drainage of the psoas abscess was complicated by the formation of a discharging sinus connected to the left hip. He then developed an infected right thigh haematoma, which also formed a discharging sinus connecting to the right hip post-drainage. He was treated with bilateral two-stage revision total hip arthroplasties and multiple courses of prolonged antibacterial therapy. Both abscesses and hip joints cultured the same species of multi-sensitive Staphylococcus aureus. The causal link between the psoas abscess and the prosthetic hip infections is discussed, as well as the investigation and management. CONCLUSION: We recommend routine exploration of the iliopsoas bursa when revision of an infected total hip arthroplasty is performed to rule out intrapelvic spread of the infection [3]. There should be high index of suspicion of prosthetic hip infection in patients presenting with Psoas abscess and vice versa. A CT scan might be warranted to rule out concomitant infection in both these patients.

Predictors of dementia and mortality in indigenous Australians.
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Background:We have previously demonstrated that Indigenous Australians have a very high prevalence rate of dementia, 5 times that of non-Indigenous Australians. We followed our original cohort to determine predictors of mortality in this population. Methods: Between 2004 and 2006, 363 Aboriginal people over the age of 45 years, living in remote Western Australia (WA) completed a comprehensive questionnaire and culturally appropriate diagnostic
assessment for dementia. All participants were invited for reassessment between 2011 to 2013. We obtained mortality records for the cohort from the WA Data Linkage System and compared them to data for the general population. We used Cox proportional hazards regression to identify predictors of mortality over a 9-year follow-up period. Results: The leading causes of mortality were diabetes, renal failure, and ischaemic heart disease. Of 40 participants with dementia at baseline, 31 (77%) had died. For the cohort as a whole diabetes and renal failure accounted for 28% of all deaths. This differed from both the Australian population as a whole, and the general Indigenous Australian population. The presence of chronic disease did not predict mortality, nor did behaviours such as smoking. Multivariate predictors of mortality included age (Hazard ratio (95% CI), 1.03 (1.01, 1.05), male sex, 2.17 (1.39, 3.39), poor mobility, 2.11 (1.34, 3.30) and cognitive impairment 2.19 (1.31, 3.65). Conclusions: Cognitive impairment and dementia are major predictors of mortality in remote Indigenous Australians.

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**Does frame geometry play a role in aortic regurgitation after Medtronic CoreValve implantation?**

Rodriguez-Olivares R, El Faquir N, et al. (Rodriguez-Olivares, El Faquir, Rahhab, Geeve, Maugenest, Van Weenen, Ren, Galema, Geleijnse, Van Mieghem, Van Domburg, Bruining, De Jaegere) Department of Cardiology, Erasmus Medical Center, Gravendijkwal 230, Rotterdam 3015 CE, Netherlands (Schultz) Department of Cardiology, Royal Perth Hospital Campus, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia (Lauritsch) Siemens Healthcare GmbH, Forchheim, Germany

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Aims: Aortic regurgitation (AR) after Medtronic CoreValve System (MCS) implantation may be explained by patient-, operator-and procedure-related factors. We sought to explore if frame geometry, as a result of a specific device-host interaction, contributes to AR. Methods and results: Using rotational angiography with dedicated motion compensation, we assessed valve frame geometry in 84 patients who underwent TAVI with the MCS. Aortic regurgitation was assessed by angiography (n=84, Sellers) and echocardiography at discharge (n=72, VARC-2). Twenty-two patients (26%) had AR grade ≥2 using contrast angiography, and 17 (24%) by echocardiography. Balloon predilatation and sizing and depth of implantation did not differ between the two groups. Despite more frequent balloon post-dilatation in patients with AR (40.9 vs. 9.7%, p=0.001), the frame was more elliptical at its nadir relative to the patient’s annulus (6+/−13 vs.−1+/−11%, p=0.046) and occurred in a larger proportion of patients (61.9 vs. 26.8%, p=0.004). Although the Agatston score and the eccentricity of the MCS frame relative to the annulus were independent determinants of AR (odds ratio: 1.635 [1.151-2.324], p=0.006, and 4.204 [1.237-14.290], p=0.021), there was a weak association between the Agatston score and the adjusted eccentricity (Spearman’s rank correlation coefficient =−0.24, p=0.046). Conclusions: These findings indicate that AR can be explained by a specific device-host interaction which can only partially be explained by the calcium load of the aortic root. Copyright © Europa Digital & Publishing 2016. All rights reserved.

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**Short Communication: Do Cytomegalovirus Antibody Levels Associate with Age-Related Syndromes in HIV Patients Stable on Antiretroviral Therapy?**

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HIV(+) persons stable on antiretroviral therapy (ART) face early onset of age-related diseases. This may arise from a high burden of cytomegalovirus (CMV). To address the role of CMV, we investigated univariate and multivariate associations between markers of systemic and endothelial inflammation, vascular damage, insulin resistance (IR), neurocognitive decline, and antibodies reactive with CMV. In this study, HIV(+) participants (n=91) aged >45 years with <50 copies HIV RNA/ml plasma after >2 years on ART were assessed for cardiovascular risk (the D:A:D algorithm), type II diabetes (the HOMA-IR index), and neurocognitive performance. Blood samples were assayed for lipids, T cells, insulin, glucose, C-reactive protein, CX3CL1, sTNF-R1, total immunoglobulin G (IgG), and antibodies reactive with CMV lysate, glycoprotein B, or immediate-early-1. Levels of antibodies detected with the three antigens were tightly correlated. Levels of CMV lysate antibody were higher in patients than in age-matched healthy controls and reflected their nadir CD4 T-cell count (p=0.001), total IgG (p=0.02), and age (p=0.08). Levels of CMV lysate antibody correlated with D:A:D score (p=0.04), neurocognitive performance (p=0.045), and fasting insulin (p=0.02). In multivariable analyses, some associations reflected the effect of age, but CMV lysate antibody and CD8 T-cell counts were significant predictors of the HOMA-IR index (R²=0.09, p=0.01) independent of age. We conclude that associations between levels of CMV antibodies, cardiovascular risk, and neurocognitive health in HIV(+) patients stable on ART are moderated by age-associated increases in response to CMV, while CMV antibodies may be independently linked with IR.

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The ICU Mobility Scale Has Construct and Predictive Validity and Is Responsive. A Multicenter Observational Study.

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RATIONALE: The ICU Mobility Scale (IMS) is a measure of mobility milestones in critically ill patients.
OBJECTIVES: This study aimed to determine the validity and responsiveness of the IMS from a prospective cohort study of adults admitted to the intensive care unit (ICU).
METHODS: Construct and predictive validity were assessed by comparing IMS values at ICU discharge in 192 patients to other variables using Spearman rank correlation coefficient, Mann-Whitney U tests, and logistic regression. Responsiveness was assessed using change over time, effect size, floor and ceiling effects, and percentage of patients showing change.
MEASUREMENTS AND MAIN RESULTS: The IMS at ICU discharge demonstrated a moderate correlation with muscle strength (r=0.64, P<0.001). There was a significant difference between the IMS at ICU discharge in patients with ICU-acquired weakness (median, 4.0; interquartile range, 3.0-5.0) compared with patients without (median, 8.0; interquartile range, 5.0-8.0; P<0.001). Increasing IMS values at ICU discharge were associated with survival to 90 days (odds ratio [OR], 1.38; 95% confidence interval [CI], 1.14-1.66) and discharge home (OR, 1.16; 95% CI, 1.02-1.32) but not with return to work at 6 months (OR, 1.09; 95% CI, 0.92-1.28). The IMS was responsive with a significant change from study enrollment to ICU discharge (d=0.8, P<0.001), with IMS values increasing in 86% of survivors during ICU admission. No substantial floor (14% scored 0) or ceiling (4% scored 10) effects were present at ICU discharge.
CONCLUSIONS: Our findings support the validity and responsiveness of the IMS as a measure of mobility in the ICU.
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**Dramatic presentation of a giant fibrovascular polyp of Laimer’s triangle.**

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**Anticoagulant therapy and its impact on dental patients: a review.**

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Several new oral anticoagulants have been studied in the past decade, and have now started to enter the market. These drugs are reported to be as effective as, or more effective than, warfarin. In Australia, the Therapeutic Goods Administration has approved dabigatran, rivaroxaban and apixaban. The use of these newer anticoagulants is likely to increase in time, and it is important for dentists to have a sound understanding of the mechanisms of action, reversal strategies, and management guidelines for patients taking oral anticoagulants. This article discusses the process of coagulation, available anticoagulants and their monitoring and reversal, and provides clinical advice on the management of patients on anticoagulants who require dental treatment.

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Effect of monoclonal antibodies to PCSK9 on high-sensitivity C-reactive protein levels: a meta-analysis of 16 randomized controlled treatment arms.

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AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an emerging class of low-density lipoprotein cholesterol (LDL-C)-lowering agents. In spite of their known effects on lipids, the impact of these drugs on systemic inflammation is less known. We aimed to investigate the effect of PCSK9 inhibitors on high-sensitivity C-reactive protein (hs-CRP) levels through a meta-analysis of randomized controlled trials (RCTs).

METHODS: A systematic literature search of Medline, SCOPUS and Google Scholar was conducted up to December 2015 to identify RCTs assessing changes in hs-CRP concentrations during treatment with PCSK9 inhibitors. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics.

RESULTS: Sixteen treatment arms, with a total of 2546 participants, were included. Random-effects meta-analysis did not show any significant effect of PCSK9 inhibitors on hs-CRP levels (WMD: 0.002 mg l(-1) , CI: -0.017, 0.021; P = 0.807; I(2) = 37.26%). This effect size was robust, not sensitive to any single study, and not affected by the type of PCSK9 inhibitor (evolocumab: WMD: 0.002 mg l(-1) , CI: -0.02, 0.02; P = 0.855; alirocumb WMD: 0.15 mg l(-1) , CI: -0.11, 0.40; P = 0.259; I(2) = 0%), or dosing frequency (biweekly: WMD: 0.13 mg l(-1) , CI: -0.20, 0.46; P = 0.433; I(2) = 55.19%; monthly: WMD: 0.003 mg l(-1) , CI: -0.01, 0.01; P = 0.59; I(2) = 0%). Random-effects meta-regression did not suggest any association of changes in hs-CRP levels with changes in plasma LDL-C concentrations (P = 0.697) or cumulative dosage of the drug (P = 0.980).

CONCLUSIONS: This meta-analysis of RCTs did not suggest an effect of PCSK9 inhibitors on hs-CRP concentrations.

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Mental health and itch in burns patients: Potential associations.


Mental health is significantly associated with itch after adjusting for variation in itch over time (p=0.001). The regression coefficient indicates that as mental health increases by one unit, itch decreases by 0.03. Of importance, the relationship remained significant after adjusting for total burn surface area (p<0.001).

CONCLUSION: These findings suggest there is a relationship between mental health and itch. Given the powerful impact itch can have on an individual's wellbeing health professionals can begin to further investigate itch from a bio-psychosocial perspective. Further research to investigate causal relationships between mental health and itch is important.

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Lipoprotein metabolism in an apoB-80 familial hypobetalipoproteinemia heterozygote.


Conclusions: The observation that the apoB-80 protein was metabolized similarly to apoB-100 is important, as it suggests that apoB-80 in this particular patient is not transported to the liver, and therefore, it is not a factor in this patient.

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OBJECTIVE: Familial hypobetalipoproteinemia (FHBL) is characterized by mutations in APOB, the majority of these
causing protein truncations, and low plasma levels of apolipoprotein (apo) B. The hypobetalipoproteinemia may be
due to enhanced clearance and possibly reduced production of apoB-containing lipoproteins; the mechanism may
depend on the length of the apoB truncation. We studied fasting lipoprotein metabolism in an FHBL subject
heterozygous for a mutation causing a truncated apoB, apoB-80.

DESIGN AND METHODS: Very low density lipoprotein (VLDL)-, intermediate density lipoprotein (IDL)-, and low density
lipoprotein (LDL)-apoB kinetics were determined in the fasting state using stable isotope methods and
compartmental modeling.

RESULTS: Compared with lean normolipidemic controls the apoB-80 FHBL subject had an elevated VLDL-apoB
fractional catabolic rate and lower LDL production. ApoB production rates and IDL- and LDL-apoB fractional catabolic
rates were not different.

CONCLUSION: FHBL subjects heterozygous for a mutation truncating apoB to 80% of full-length are able to produce
VLDL-apoB normally, but have rapid clearance of these particles, resulting in low levels of circulating apoB.


Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled
clinical trial.

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BACKGROUND & AIMS: Many experimental and clinical trials suggested that flaxseed might be a potent
antihypertensive, but the evidences concerning the effects of flaxseed supplements on blood pressure (BP) has not
been fully conclusive. We aimed to assess the impact of the effects of flaxseed supplements on blood pressure
through systematic review of literature and meta-analysis of available randomized controlled trials (RCTs).

METHODS: The literature search included PUBMED, Cochrane Library, Scopus, and EMBASE up to February 2015 to
identify RCTs investigating the effect of flaxseed supplements on plasma blood pressure. Effect size was expressed as
weighed mean difference (WMD) and 95% confidence interval (CI).

RESULTS: 15 trials (comprising 19 treatment arms) with 1302 participants were included in this meta-analysis.
Random-effects meta-analysis suggested significant reductions in both systolic BP (SBP) (WMD: -2.85 mmHg, 95%CI:
-5.37 to -0.33, p = 0.027) and diastolic BP (DBP) (WMD: -2.39 mmHg, 95%CI: -3.78 to -0.99, p = 0.001) following
supplementation with flaxseed products. When the studies were stratified according to their duration, there was a
greater effect on both SBP and DBP in the subset of trials with >12 weeks of duration (WMD: -3.10 mmHg, 95%CI:
-6.46 to 0.27, p = 0.072 and -2.62 mmHg, 95%CI: -4.39 to -0.86, p = 0.003, respectively) vs the subset lasting <12
weeks (WMD: -1.60 mmHg, 95%CI: -5.44 to 2.24, p = 0.413, and -1.74 mmHg, 95%CI: -4.41 to 0.93, p = 0.202,
respectively). Another subgroup analysis was performed to assess the impact of flaxseed supplement type on BP.
Reduction of SBP was significant with flaxseed powder (WMD: -1.81 mmHg, 95% CI: -2.03 to -1.59, p < 0.001) but not
oil (WMD: -4.62 mmHg, 95%CI: -11.86 to 2.62, p = 0.211) and lignan extract (WMD: 0.28 mmHg, 95% CI: -3.49 to 4.04,
p = 0.885). However, DBP was significantly reduced with powder and oil preparations (WMD: -1.28 mmHg, 95% CI:
-2.44 to -0.11, p = 0.031, and -4.10 mmHg, 95%CI: -6.81 to -1.39, p = 0.003, respectively), but not with lignan extract.
CONCLUSIONS: This meta-analysis of RCTs showed significant reductions in both SBP and DBP following supplementation with various flaxseed products.

**Repair of a Large Nasal Sidewall Defect.**
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**Metabolic memory and all-cause death in community-based patients with type 2 diabetes: the Fremantle Diabetes Study.**
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AIMS: To validate the findings, in a usual care setting, of glycaemic intervention trials, which have shown that tight control in patients with recently diagnosed type 2 diabetes protects against death during post-study monitoring, but that it may be deleterious in long-duration diabetes with vascular complications.
METHODS: A subset of 531 patients with type 2 diabetes from the community-based observational Fremantle Diabetes Study Phase 1, who attended >5 annual reviews (mean follow-up 15.9 years), were categorized by baseline diabetes duration (<1 year (Group 1); 1 to <5 years (Group 2); and >5 years (Group 3)). Glycated haemoglobin (HbA1c) trajectories over the first 5 years were determined [low, medium and high; equivalent to mean HbA1c <6.6% (<49 mmol/mol), 6.7-8.0% (50-64 mmol/mol) and >8.0% (>64 mmol/mol), respectively]. Kaplan-Meier analysis was used to assess survival by duration and HbA1c trajectory. Cox proportional hazards modelling identified predictors of all-cause death.
RESULTS: There was greater mortality in patients with a medium versus those with a low trajectory in Group 1: hazard ratio (HR) 1.99 [95% confidence interval (CI) 1.003-3.94; p = 0.049], and in patients with a high versus a low trajectory in Group 2: HR 2.02 (95% CI 1.11-3.71; p = 0.022). In Group 3, both medium [HR 0.57 (95% CI 0.35-0.92; p = 0.022)] and high [HR 0.56 (95% CI 0.32-0.96); p = 0.035] trajectories were independently and inversely associated with death.
CONCLUSIONS: In community-based patients with newly or recently diagnosed type 2 diabetes, poor glycaemic control was an adverse prognostic indicator. Tight control was independently associated with death in patients with diabetes duration >5 years. These data parallel intervention trial findings and support individualization of HbA1c targets.
Residual Sympathetic Responsiveness After Catheter-Based Renal Denervation: Lessons From Renal Nerve Stimulation.
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Predicting Self-Management Behaviors in Familial Hypercholesterolemia Using an Integrated Theoretical Model: the Impact of Beliefs About Illnesses and Beliefs About Behaviors.
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PURPOSE: Patients with familial hypercholesterolemia (FH) are at markedly increased risk of coronary artery disease. Regular participation in three self-management behaviors, physical activity, healthy eating, and adherence to medication, can significantly reduce this risk in FH patients. We aimed to predict intentions to engage in these self-management behaviors in FH patients using a multi-theory, integrated model that makes the distinction between beliefs about illness and beliefs about self-management behaviors.
METHODS: Using a cross-sectional, correlational design, patients (N=110) diagnosed with FH from a clinic in Perth, Western Australia, self-completed a questionnaire that measured constructs from three health behavior theories: the common sense model of illness representations (serious consequences, timeline, personal control, treatment control, illness coherence, emotional representations); theory of planned behavior (attitudes, subjective norms, perceived behavioral control); and social cognitive theory (self-efficacy).
RESULTS: Structural equation models for each self-management behavior revealed consistent and statistically significant effects of attitudes on intentions across the three behaviors. Subjective norms predicted intentions for health eating only and self-efficacy predicted intentions for physical activity only. There were no effects for the perceived behavioral control and common sense model constructs in any model.

CONCLUSIONS: Attitudes feature prominently in determining intentions to engage in self-management behaviors in FH patients. The prominence of these attitudinal beliefs about self-management behaviors, as opposed to illness beliefs, suggest that addressing these beliefs may be a priority in the management of FH.

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The aim of this study is to examine the acceptability and effectiveness of a nurse-led hepatocellular carcinoma (HCC) surveillance clinic in high-risk patients with cirrhosis/advanced fibrosis. Early detection of HCC is associated with better treatment outcomes and improved survival. International guidelines recommend 6-monthly surveillance of patients at risk of developing HCC. A nurse-led HCC surveillance protocol was established to support patients in adherence to surveillance protocols. The design used was retrospective document analysis. Retrospective analysis of healthcare records of patients referred to the clinic between August 2009 and December 2015. Extracted data included attendance of clinic visits, blood testing, ultrasound or other imaging, and outcomes. Ultrasound was attended within 6months in 30.3% of cases and within 7months in 71.2% of cases. The median time between Nurse-Led Clinic appointments, ultrasound scans and blood testing did not exceed 9months. First year FibroScans were attended by 82.9% (63/76) patients; endoscopy was indicated for 42 and attended by 35 (83.3%) patients. Lesions were identified in 16 patients (21.5%) and HCC diagnosed in two patients. One patient died because of HCC and one to sub-dural haematoma. Nurse-led HCC surveillance was an effective method of monitoring patients with cirrhosis at high risk of developing HCC. Well-defined protocols enable timely identification of patients with HCC or hepatic decompensation so that management strategies can be implemented without delay. The potential benefits identified by this study warrant further, rigorous evaluation.

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PMID: 27476494
Optical coherence tomography for longitudinal monitoring of vasculature in scars treated with laser fractionation.

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This study presents the first in vivo longitudinal assessment of scar vasculature in ablative fractional laser treatment using optical coherence tomography (OCT). A method based on OCT speckle decorrelation was developed to visualize and quantify the scar vasculature over the treatment period. Through reliable co-location of the imaging field of view across multiple imaging sessions, and compensation for motion artifact, the study was able to track the same scar tissue over a period of several months, and quantify changes in the vasculature area density. The results show incidences of occlusion of individual vessels 3 days after the first treatment. The subsequent responses ~20 weeks after the initial treatment show differences between immature and mature scars. Image analysis showed a distinct decrease (25 +/- 13%, mean +/- standard deviation) and increase (19 +/- 5%) of vasculature area density for the immature and mature scars, respectively. This study establishes the feasibility of OCT imaging for quantitative longitudinal monitoring of vasculature in scar treatment. En face optical coherence tomography vasculature images pre-treatment (top) and ~20 weeks after the first laser treatment (bottom) of a mature burn scar. Arrows mark the same vessel pattern.

Covered stents in iliac artery occlusive disease: what is the evidence?

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The last two decades have seen a revolution in the treatment of aortoiliac occlusive disease (AIOD). Acceptable safety
and durability outcomes have now been realized with endovascular treatments, which is increasingly finding a place in the treatment of AIOD. Evolution of stent technologies and endovascular techniques is seeing an expansion of AIOD lesions indicated for primary endovascular treatment. The literature evidence basis is continuously evolving, and questions remain as to the optimal form of vessel treatment. Covered stents have been increasingly promoted for their long-term durability, particularly in extensive, challenging AIOD lesions. Here, we explore the seminal evidence basis for covered stents in the treatment of AIOD, and aim to provide a sound evidence based argument for their use.

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Reconsidering the role of hypothermia in management of severe traumatic brain injury.

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Over the past two decades there has been considerable interest in the use of hypothermia in the management of severe traumatic brain injury. However despite promising experimental evidence, results from clinical studies have failed to demonstrate benefit. Indeed recent studies have shown a tendency to worse outcomes in those patients randomised to therapeutic hypothermia. In this narrative review the pathophysiological rationale behind hypothermia and the clinical evidence for efficacy are examined. There would still appear to be a role for hypothermia in the management of intractable intracranial hypertension. However optimising therapeutic time frames and better management of strategies for complications will be required if experimental evidence for neuroprotection is to be translated into clinical benefit.
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Procalcitonin concentrations as a predictor of unexpected readmission and mortality after intensive care unit discharge: A retrospective cohort study.

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Procalcitonin (PCT) has been used to guide treatment in critically ill patients with sepsis, but whether PCT at intensive care unit (ICU) discharge can stratify risks of post-ICU readmission or mortality is unknown. This cohort study compared the ability of PCT with C-reactive protein (CRP) in predicting unexpected adverse post-ICU events. Of the 1877 patients admitted to the multidisciplinary ICU between 1 April 2012 and 31 March 2014, 1653 (88.1%) were discharged without treatment limitations. A total of 71 (4.3%) were readmitted and 18 patients (1%) died unexpectedly after ICU discharge during the same hospitalization. Both PCT (0.6 vs 0.4 mug/L, P = .002) and a high CRP concentration >100 mg/L (58% vs 41%, P = .004) at ICU discharge were associated with an increased risk of adverse post-ICU events in the univariate analyses; however, the ability of PCT to discriminate between patients with and without adverse post-ICU outcomes was limited (area under the receiver operating characteristic curve = 0.61; 95% confidence interval, 0.55-0.66). In the multivariable analysis, only a high CRP concentration (odds ratio, 1.92; 95% confidence interval, 1.12-3.11; P = .008) was associated with an increased adverse post-ICU events. Elevated PCT concentration at ICU discharge was inadequate in its predictive ability to guide ICU discharge.
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Magnetic resonance imaging of perianal Crohn’s disease.

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Depressive symptoms in midlife: the role of reproductive stage.

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OBJECTIVE: The aim of the study was to determine the prevalence of depression among community-dwelling women in the premenopause, menopausal transition (MT), and postmenopause stage. We also sought to clarify the direct and indirect contribution of menopausal status on the risk of depression.

METHODS: Cross-sectional survey of 1,612 women aged 45 to 55 years living in the Perth metropolitan region, who were recruited using a random sample of the electoral roll (voting is compulsory in Australia), was conducted. Women with clinically significant symptoms of depression had Patient Health Questionnaire (PHQ-9) scores of at least 10, and those with major depression, reported symptoms consistent with Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5), criteria. We used past and current gynecological and reproductive data to classify women as premenopausal, undergoing the MT, and postmenopausal. Other study measures included age, place of birth, education, marital status, drinking habit, number of children, medical illnesses, and history of premenstrual syndrome, postnatal depression, and past depression or anxiety. We investigated the direct and indirect effect of reproductive status with mediation/modulation analysis.

RESULTS: Among the women included in the survey, 8.2%, 11.5%, and 13.0% of women in premenopause, MT, and postmenopause had PHQ-9 at least 10, whereas major depression was present in 2.2%, 3.4%, and 3.6% of them. Reproductive status did not affect the prevalence of major depression, but more postmenopausal than premenopausal women had PHQ-9 score equal to or greater than 10 (P = 0.013). Compared with premenopausal women, MT was associated with a direct odds ratio (OR) 1.35 (95% confidence interval [CI] = 0.90, 2.01) and indirect OR 1.08 (95% CI = 0.92, 1.26) for PHQ-9 at least 10. Similarly, the direct and indirect effect of the postmenopause on the odds of PHQ-9 at least 10 was OR 1.31 (95% CI = 0.87, 1.98) and OR 1.29 (95% CI = 1.10, 1.52).

CONCLUSIONS: The slight, but not significant, excess of depressive symptoms during MT and early postmenopause cannot be attributed to a direct effect of reproductive status.

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Impact of pre-adapted HIV transmission.

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Human leukocyte antigen class I (HLA)-restricted CD8(+) T lymphocyte (CTL) responses are crucial to HIV-1 control. Although HIV can evade these responses, the longer-term impact of viral escape mutants remains unclear, as these variants can also reduce intrinsic viral fitness. To address this, we here developed a metric to determine the degree of HIV adaptation to an HLA profile. We demonstrate that transmission of viruses that are pre-adapted to the HLA molecules expressed in the recipient is associated with impaired immunogenicity, elevated viral load and accelerated CD4(+) T cell decline. Furthermore, the extent of pre-adaptation among circulating viruses explains much of the variation in outcomes attributed to the expression of certain HLA alleles. Thus, viral pre-adaptation exploits 'holes' in the immune response. Accounting for these holes may be key for vaccine strategies seeking to elicit functional responses from viral variants, and to HIV cure strategies that require broad CTL responses to achieve successful eradication of HIV reservoirs.

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Analgesic Efficacy and Safety of Curcuminoids in Clinical Practice: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.
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BACKGROUND: Curcuminoids are natural products with potent anti-inflammatory and antioxidant properties. There have been a number of reports on the analgesic effects of curcuminoids in clinical trials, yet data have not been fully conclusive.
OBJECTIVES: To provide the highest level of evidence on the efficacy of curcuminoids in patients with painful conditions through meta-analysis of data from randomized controlled trials (RCTs).
METHODS: A systematic review and meta-analysis was conducted using data reported by RCTs. The primary efficacy measure was pain intensity or algofunctional status. Treatment effect was summarized with standardized mean difference (SMD) calculated from differences in means of pain measures between treatment and control groups using a random-effects model.
RESULTS: A total of eight RCTs met our inclusion criteria that included 606 randomized patients. Curcuminoids were found to significantly reduce pain (SMD:-0.57, 95% CI:-1.11 to-0.03, P=0.04). This pain-relieving effect was found to be independent of administered dose and duration of treatment with curcuminoids, and was free from publication bias. Curcuminoids were safe and well tolerated in all evaluated RCTs.
CONCLUSION: Curcuminoids supplements may be a safe and effective strategy to improve pain severity, by warranting further rigorously conducted studies to define the long-term efficacy and safety.
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**Paramedic Checklists do not Accurately Identify Post-ictal or Hypoglycaemic Patients Suitable for Discharge at the Scene.**

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**OBJECTIVES:** The objective of this study was to assess the accuracy and safety of two pre-defined checklists to identify prehospital post-ictal or hypoglycemic patients who could be discharged at the scene.

**METHODS:** A retrospective cohort study of lower acuity, adult patients attended by paramedics in 2013, and who were either post-ictal or hypoglycemic, was conducted. Two self-care pathway assessment checklists (one each for post-ictal and hypoglycemia) designed as clinical decision tools for paramedics to identify patients suitable for discharge at the scene were used. The intention of the checklists was to provide paramedics with justification to not transport a patient if all checklist criteria were met. Actual patient destination (emergency department [ED] or discharge at the scene) and subsequent events (e.g., ambulance requests) were compared between patients who did and did not fulfill the checklists. The performance of the checklists against the destination determined by paramedics was also assessed.

**RESULTS:** Totals of 629 post-ictal and 609 hypoglycemic patients were identified. Of these, 91 (14.5%) and 37 (6.1%) patients fulfilled the respective checklist. Among those who fulfilled the checklist, 25 (27.5%) post-ictal and 18 (48.6%) hypoglycemic patients were discharged at the scene, and 21 (23.1%) and seven (18.9%) were admitted to hospital after ED assessment. Amongst post-ictal patients, those fulfilling the checklist had more subsequent ambulance requests (P=.01) and ED attendances with seizure-related conditions (P=.04) within three days than those who did not. Amongst hypoglycemic patients, there were no significant differences in subsequent events between those who did and did not meet the criteria. Paramedics discharged five times more hypoglycemic patients at the scene than the checklist predicted with no significant differences in the rate of subsequent events. Four deaths (0.66%) occurred within seven days in the hypoglycemic cohort, and none of them were attributed directly to hypoglycemia.

**CONCLUSIONS:** The checklists did not accurately identify patients suitable for discharge at the scene within the Emergency Medical Service. Patients who fulfilled the post-ictal checklist made more subsequent health care service requests within three days than those who did not. Both checklists showed similar occurrence of subsequent events to paramedics’ decision, but the hypoglycemia checklist identified fewer patients who could be discharged at the scene than paramedics actually discharged. Reliance on these checklists may increase transportations to ED and delay...

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BACKGROUND: Rates of the metabolic syndrome in people with psychotic illness are high. Emerging evidence suggests that cannabis use may have a positive impact on cardiometabolic risk factors in the general population, but little is known about its impact for people with psychotic illness. Our aim was to investigate whether the rate of the metabolic syndrome in people with psychotic illness was associated with frequency of cannabis use.

METHOD: The 2010 Australian psychosis survey used a two-phase design to randomly select a nationally representative sample of 1825 adults with psychotic illness for interview and physical assessment. This study is based on 1813 participants who provided data on cannabis use. Multiple logistic regression was used to model the influence of frequency of cannabis use on the metabolic syndrome, adjusting for potential covariates including antipsychotic medication use, smoking, alcohol use and cognitive function.

RESULTS: One-third (33.0%) of participants had used cannabis in the past year. The proportion of non-users, occasional users and frequent users with the metabolic syndrome was 63.0, 51.7 and 43.5%, respectively (p < 0.001). In unadjusted analyses, both occasional use and frequent cannabis use were associated with significantly lower odds of the metabolic syndrome. In the adjusted analyses, the association between the metabolic syndrome and frequent cannabis use remained significant [odds ratio = 0.56, 95% confidence interval (CI) 0.39-0.80], but not the association with occasional use (odds ratio = 0.75, 95% CI 0.49-1.13).

CONCLUSIONS: While cannabis use may be detrimental for mental health, these data suggest that it may also have a cardiometabolic protective effect. Further investigation is required to understand the mechanism underlying this paradoxical finding.
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There is a considerable amount of evidence that supports the possibility of an increased risk of pneumonia associated with prolonged use of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD).
However, as yet, no statistically significant increase in pneumonia-related 30-day mortality in patients on ICS has been demonstrated. The lack of objective pneumonia definitions and radiological confirmations have been a major source of bias, because of the similarities in clinical presentation between pneumonia and acute exacerbations of COPD. One of the newer fluticasone furoate studies overcomes these limitations and also provides an assessment of a range of doses, suggesting that the therapeutic window is quite narrow and that conventional dosing has probably been too high, although the absolute risk may be different compared to other drugs. Newer studies were not able to rule out budesonide as responsible for pneumonia, as previous evidence suggested, and there is still need for evidence from head-to-head comparisons in order to better assess possible intra-class differences. Although the exact mechanisms by which ICS increase the risk of pneumonia are not fully understood, the immunosuppressive effects of ICS on the respiratory epithelium and the disruption of the lung microbiome are most likely to be implicated. Given that COPD represents such a complex and heterogeneous disease, attempts are being made to identify clinical phenotypes with clear therapeutic implications, in order to optimize the pharmacological treatment of COPD and avoid the indiscriminate use of ICS. If deemed necessary, gradual withdrawal of ICS appears to be well tolerated. Vaccination against pneumococcus and influenza should be emphasized in patients with COPD receiving ICS. Physicians should keep in mind that signs and symptoms of pneumonia in COPD patients may be initially indistinguishable from those of an exacerbation, and that patients with COPD appear to be at increased risk of developing pneumonia as a complication of ICS therapy.

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**A new electronic screening tool for identifying risk of familial hypercholesterolaemia in general practice.**

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**OBJECTIVE:** To evaluate the performance of a new electronic screening tool (TARB-Ex) in detecting general practice patients at potential risk of familial hypercholesterolaemia (FH).

**METHODS:** Medical records for all active patients seen between 2012 and 2014 (n=3708) at a large general practice in Perth, Western Australia were retrospectively screened for potential FH risk using TARB-Ex. Electronic extracts of medical records for patients identified with potential FH risk (defined as Dutch Lipid Clinic Network Criteria (DLCNC) score >5) through TARB-Ex were reviewed by a general practitioner (GP) and lipid specialist. High-risk patients were recalled for clinical assessment to determine phenotypic FH diagnosis. Performance was evaluated against a manual record review by a GP in the subset of 360 patients with high blood cholesterol (cholesterol >7 mmol/L or low-density lipoprotein cholesterol >4.0 mmol/L).
RESULTS: Thirty-two patients with DLCNC score >5 were identified through electronic screening compared with 22 through GP manual review. Sensitivity was 95.5% (95% CI 77.2% to 99.9%), specificity was 96.7% (95% CI 94.3% to 98.3%), negative predictive accuracy was 99.7% (95% CI 98.3% to 100%) and positive predictive accuracy was 65.6% (95% CI 46.9% to 8%). Electronic screening was completed in 10 min compared with 60 h for GP manual review. 10 of 32 patients (31%) were considered high risk and recalled for clinical assessment. Six of seven patients (86%) who attended clinical assessment were diagnosed with phenotypic FH on examination.

CONCLUSIONS: TARB-Ex screening is a time-effective and cost-effective method of systematically identifying potential FH risk patients from general practice records for clinical follow-up. Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://www.bmj.com/company/products-services/rights-and-licensing/

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Effects of statin therapy on augmentation index as a measure of arterial stiffness: A systematic review and meta-analysis.
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OBJECTIVE: To evaluate the effects of statin therapy on augmentation index (AIx) as a measure of arterial stiffness using a meta-analysis of clinical trials.

METHODS: The search included PubMed-Medline, Embase, SCOPUS, Web of Science and Google Scholar databases to identify randomized controlled trials investigating the effects of statin therapy on arterial stiffness measured as AIx. A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of potential confounders.

RESULTS: 18 trials examining the effects of statin therapy on arterial stiffness were included. A significant reduction in aortic AIx following statin therapy was proven (WMD: -2.40%, 95% CI: -4.59, -0.21, p=0.032; I(2): 51.20%). HR-adjusted AIx 75% values also revealed a significant improvement by statin therapy (WMD: -5.04%, 95% CI: -7.81, -2.27, p<0.001; I(2): 0%), but not when analysis was restricted to unadjusted AIx values (WMD: -2.30%, 95% CI: -4.83, 0.23, p=0.075; I(2): 53.83%). There was no significant change in carotid (WMD: -2.75%, 95% CI: -8.06, 2.56, p=0.309; I(2): 26.86%) and peripheral (WMD: 0.25%, 95% CI: -3.31, 3.82, p=0.889; I(2): 72.19%) AIx due to statin treatment. There was also no difference in the effect size calculated for different statins subgroups. The impact of statins on AIx was independent of LDL-cholesterol level (slope: 0.05; 95% CI: -0.02, 0.13; p=0.181).

CONCLUSION: Statin therapy causes a significant reduction in aortic AIx which is independent of LDL-cholesterol changes.

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Delayed iliaca compartment syndrome following femoral artery puncture: case report and literature review.

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Iliaca compartment syndrome is a rare retroperitoneal compartment neuropathy caused by bleeding within the iliaca muscle leading to hematoma formation and compression upon the femoral nerve, causing both sensory and motor deficits. A 75-year-old Caucasian man presented with severe right hip pain associated with motor and sensory deficit in the right lower extremity, 2 weeks post elective balloon aortic valvuloplasty for critical aortic stenosis. A non-contrast computed tomography scan revealed low-attenuation areas in keeping with an iliaca hematoma. An iliaca fasciotomy and hematoma evacuation was performed with retroperitoneal approach. The patient reported marked reduction in his groin pain with clinical improvement of the right hip flexion though the sensory deficit was unchanged. On Day 3, postoperatively the patient died from respiratory and multi-organ failure. Iliaca hematomas are rare and can be caused by traumatic and non-traumatic injury, and can be exacerbated by complications of anticoagulant therapy. Delaying surgical evacuation of the hematoma can lead to prolonged or permanent disability. However, there are other reports describing good recovery with non-operative management. Non-surgical intervention is recommended if radiological studies do not explicitly confirm the presence of a discreet hematoma compressing the femoral nerve, unless progression of symptoms increases.

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Early Decompression following Cervical Spinal Cord Injury: Examining the Process of Care from Accident Scene to Surgery.


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Early decompression may improve neurological outcome after spinal cord injury (SCI), but is often difficult to achieve because of logistical issues. The aims of this study were to 1) determine the time to decompression in cases of isolated cervical SCI in Australia and New Zealand and 2) determine where substantial delays occur as patients move from the accident scene to surgery. Data were extracted from medical records of patients aged 15-70 years with C3-T1 traumatic SCI between 2010 and 2013. A total of 192 patients were included. The median time from accident scene to decompression was 21h, with the fastest times associated with closed reduction (6h). A significant decrease in the time to decompression occurred from 2010 (31h) to 2013 (19h, p=0.008). Patients undergoing direct surgical hospital admission had a significantly lower time to decompression, compared with patients undergoing pre-surgical hospital admission (12h vs. 26h, p<0.0001). Medical stabilization and radiological investigation appeared not to influence the timing of surgery. The time taken to organize the operating theater following surgical hospital admission was a further factor delaying decompression (12.5h). There was a relationship between the timing of decompression and the proportion of patients demonstrating substantial recovery (2-3 American Spinal Injury Association Impairment Scale grades). In conclusion, the time of cervical spine decompression markedly improved over the study period. Neurological recovery appeared to be promoted by rapid decompression. Direct surgical hospital admission, rapid organization of theater, and where possible, use of closed reduction, are likely to be effective strategies to reduce the time to decompression.

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Postcards.
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Difficult diagnosis: strangulated obturator hernia in an 88-year-old woman.

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The obturator hernia is a rare type of hernia that can present a diagnostic challenge for the clinician. We report a case of an 88-year-old woman who presented with a history of right iliac fossa pain, bilious vomiting and diarrhoea. Non-specific findings on examination and blood tests made the diagnosis difficult, however, a CT scan of her
abdomen revealed the site of the obstruction and the patient was taken to theatre for emergency surgery. We review the literature with focus on the diagnosis of obturator hernias and the different surgical approaches used. The authors believe that this case is of educational value to healthcare professionals, particularly those working in general practice, emergency departments and on surgical teams. It highlights to doctors that patients with incarcerated obturator hernias can present with or without overt signs of intestinal obstruction and emphasises the fact that an obturator hernia can be an important cause of intestinal obstruction in a thin, elderly woman.

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**Urinary albumin-to-creatinine ratio is associated with endothelial dysfunction in HIV-infected patients receiving antiretroviral therapy.**


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Mannarino, Elmo. Unit of Internal Medicine, Department of Medicine, University of Perugia, Perugia, Italy. Baldelli, Franco. Unit of Infectious Diseases, Department of Medicine, University of Perugia, Perugia, Italy. Endothelial dysfunction, a marker of cardiovascular (CV) risk, is common in human immunodeficiency virus (HIV)-infected patients. Microalbuminuria is frequent in HIV-infected patients, and is a predictor of renal impairment and CV risk. We investigated the association between microalbuminuria and endothelial dysfunction among HIV-infected patients receiving highly-active antiretroviral therapy (HAART). Endothelial function, measured by brachial artery flow-mediated dilatation (bFMD), and urine albumin-to-creatinine ratio (UACR), were measured in 170 HAART-treated HIV-infected adults. The relationship between UACR and bFMD was evaluated. The prevalence of increased UACR, defined by two cut-off levels (20mg/g and 30mg/g), was 29% and 17%. UACR was significantly higher while bFMD was lower among patients with metabolic syndrome (MS). UACR was associated with bFMD (r =-0.31; p=0.001). This association was stronger in MS-patients (r=-0.44; p=0.003). UACR above 20mg/g was associated with an increased risk (OR 2.37, 95% CI 1.15-4.89, p=0.020) of severely impaired bFMD (bFMD<2.1%). Patients with MS and increased UACR had the lowest bFMD compared with those with none or one of the two conditions. Microalbuminuria and endothelial dysfunction are positively associated in HIV-infected patients regardless of known confounders. The coexistence of microalbuminuria and MS amplifies their deleterious influence on endothelial function.

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**Long-term efficacy and tolerability of mycophenolate mofetil therapy in diffuse scleroderma skin disease.**

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Background: Skin involvement in diffuse systemic sclerosis (dSSc) is progressive and can be extremely debilitating, however, treatment options remain limited. Although many disease modifying agents have been examined in dSSc, only cyclophosphamide has randomised controlled data suggesting efficacy in the treatment of skin thickening.1 Several observational studies suggest benefit in skin disease with mycophenolate mofetil (MMF) therapy,2 which, given its more favourable side effect profile, would be a preferable alternative to cyclophosphamide. Objectives: To assess the long-term efficacy and tolerability of MMF in patients with dSSc in the Australian Scleroderma Cohort Study. Methods: The Australian Scleroderma Cohort Study is a longitudinal study of disease outcomes in patients with SSC. Patients with dSSc and baseline modified Rodnan skin score (mRSS) >12 who were treated for a minimum twelve months with MMF for the primary indication of skin disease were included, and their prospectively collected data were retrieved. The proportion with clinically significant improvement in skin scores (defined as reduction in mRSS>4 from baseline) and stable disease (change in mRSS <4) were compared to those with clinical deterioration (increase in mRSS>4) as well as adverse effects resultant of therapy. Results: 74 participants were identified and of these, 44 met inclusion criteria. The mean age of participants was 53 +/- 12 years and 36 (82%) were female. The mean duration of disease at MMF commencement was 4.9 +/- 4.3 years, with 23 participants (52%) commencing MMF within 2.5 years. The mean duration of therapy was 2.7 +/- 1.7 years. The mean mRSS at baseline was 25.3 with a reduction of 3.7 (p-value <0.01) after one year of therapy and a mean total reduction in mRSS of 8.0 (p-value <0.01). Response to treatment was not affected by disease duration at onset of MMF therapy as expected. Over the first year of therapy, 24 participants (48%) demonstrated clinically significant improvement in skin scores, increasing to 92% clinically improved after four years of therapy. MMF was well tolerated, with two participants (5%) ceasing the drug due to adverse effects. Conclusions: MMF was associated with improved skin scores and was well tolerated in the treatment of dSSc. Given the natural history of dSSc where skin involvement can spontaneously improve, placebo-controlled studies are required to confirm whether improvement can be attributed to MMF therapy.

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Results of a first-in-man study of mesenchymal stem cell therapy for bronchiolitis obliterans syndrome.
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Introduction: Bone marrow derived mesenchymal stem cells (MSC) represent an attractive cellular therapeutic target given their immunosuppressive and tolerogenic properties and relative immune privilege. Preclinical studies and human trials in graft versus host disease suggest potential efficacy in bronchiolitis obliterans syndrome (BOS). The purpose of this dual centre, phase 1 study (www.clinicaltrials.gov NCT01175655) was to explore the feasibility and safety of delivery of allogeneic MSC in patients with BOS complicating lung transplantation. Methods: MSC from unrelated donors were isolated, expanded and cryopreserved in DMSO according to GMP principles in an accredited manufacturing facility. Patients had BOS grade > 2 or 1 with risk factors for rapid progression. Patients with > 3 infective exacerbations in the preceding year or a history of CMV pneumonitis were excluded. MSC (2 x10^6 cells/kg patient weight) were infused via a peripheral vein twice weekly for two weeks, with 52 weeks follow-up. Results: 10 Patients (5 male, 4 CF, 2 COPD, 3 IPF, 8 BSSLTx, median (IQR) age 40 (30-59) years, 3 BOS2, 7 BOS3) participated. MSC treatment was well tolerated with all patients receiving the full dosing schedule without any procedure-related serious adverse events. Most patients experienced stabilisation of lung function (Figure). Two patients died at 152 and 270 days post-MSC treatment, both from progressive BOS. Conclusion: Infusion of allogeneic bone marrow-derived MSC is feasible and appears safe in patients with BOS. As a result of this study, the Australian Lung Transplant Collaborative will be commencing a phase 2 randomised controlled trial to assess the efficacy of MSC therapy in patients with new-onset BOS (total n = 82) in 2016. (Figure presented).

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Comparison of clinical outcomes between bioresorbable vascular stents versus conventional drug-eluting and metallic stents: A systematic review and meta-analysis.
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Aims: Several studies have suggested good procedural and similar clinical outcomes between everolimus-eluting Absorb bioresorbable stents (BRS) versus conventional drug-eluting stents (DES), but the evidence is not definitive. Our aim was to perform a systematic review and meta-analysis to investigate the effects of BRS versus conventional drug-eluting and bare metallic stents on the cardiovascular endpoints and all-cause mortality. Methods and results: The follow-up in the included studies was up to 13 months. The following endpoints were evaluated: all-cause mortality, cardiac death, patient-oriented major adverse cardiac events (POCE), device-oriented major adverse cardiac events (DOCE), any-cause myocardial infarction (MI), target vessel MI (TVMI), target vessel revascularisation (TVR) and target lesion revascularisation (TLR). The results of 10 studies with 5,773 subjects showed a statistically significant increase in the risk of TVMI between BRS and conventional stents (odds ratio [OR]: 1.45, 95% confidence interval [CI]: 1.03-2.05, p=0.032). None of the other differences reached statistical significance: all-cause mortality (OR: 0.67, 95% CI: 0.30-1.49, p=0.333), cardiac death (OR: 1.00, 95% CI: 0.47-2.12, p=0.996), POCE (OR: 0.91, 95% CI: 0.68-1.22, p=0.546), DOCE (OR: 1.12, 95% CI: 0.86-1.46, p=0.387), any-cause MI (OR: 1.34, 95% CI: 0.98-1.82, p=0.064), TVR (OR: 0.99, 95% CI: 0.73-1.33, p=0.934) and TLR (OR: 0.92, 95% CI: 0.66-1.29, p=0.641). Similar results were observed after restricting the meta-analysis to the comparison of BRS vs. EES. Conclusions: Our meta-analysis suggests a significantly higher risk of TVMI with BRS compared with conventional stents and no significant differences in the rates of occurrence of the other outcomes during one-year follow-up. Further studies with larger samples sizes, longer follow-up, different clinical scenarios and more complex lesions are required to confirm or refute our findings.
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Over the past 2 decades there has been a resurgence of interest in the use of decompressive craniectomy in the management of neurological emergencies. While technically straightforward, the procedure is associated with a number of complications relating to the initial decompression and subsequent cranioplasty. One complication that has received relatively little attention relates to the management of the temporal muscle. Here, through an illustrative case, the author describes a novel method of minimizing dissection of the temporal muscle during a cranioplasty procedure. Rather than placing a synthetic material over the dura mater to prevent adhesions or dissecting the muscle off the dura, the dura was opened and reflected laterally, pedicled to the temporal muscle. The dural defect was closed with a dural substitute, and the bone flap was secured in a routine fashion. The temporal muscle was then secured in its anatomical position. At the 6-month follow-up, radiological and clinical examination confirmed the restoration of muscle volume with excellent cosmetic and functional results. Opening the dura on a temporal muscle pedicle does not represent a routine form of surgical reconstruction; however, the use of this technique may have some advantages especially in young patients who have made a good recovery and for whom facial aesthetics may be particularly important.


**Longitudinal Trends in Western Australian HIV-1 Sequence Diversity and Viral Transmission Networks and Their Influence on Clinical Parameters: 2000-2014.**

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We examined baseline HIV-1 protease and reverse transcriptase sequences and HIV clinical parameters from 1,021 consecutive patients (814 male, 207 female) through the Royal Perth Hospital HIV service to investigate HIV-1 subtype diversity and local phylogenetic networks from 2000 to 2014. HIV-1 subtype B virus sequences were demonstrated in 619 (61%) of cases, with increasing non-B HIV-1 subtypes from 23.2% (2000-2003) to 48% (2008-2011) and 43% (2012-2014) (p < 0.001), including the CRF01_AE subtype [6.6% (2000-2003) to 21.5% (2008-2011)] and HIV-1 C subtype [9.5% (2000-2003) to 20.2% (2008-2011)]. More HIV-1 B subtypes were assigned to phylogenetic clusters compared to non-B subtypes (34% vs. 18%; p < 0.001), with larger clusters identified (cluster size >2: 135/211; 64% vs. 13/69; 19%; p = 0.001), including one cluster of 53 HIV-1 B subtype sequences that evolved from 2008 to 2014. Non-B subtype HIV-1 was associated with lower baseline CD4 T cell count (p = 0.005) but not plasma HIV-1 RNA levels (p = 0.31), suggesting relatively delayed diagnosis. Baseline viral load was strongly associated with calendar time [mean 18,620 copies/ml in 2000-2003; 75,858 copies/ml in 2012-2014 (p < 0.001)], and was also associated with larger phylogenetic clusters (size >2) in adjusted analyses (p = 0.03). This study identifies a number of temporal trends over the past 15 years, including an increasing prevalence of non-B subtype HIV-1 that highlights the growing influence of migration and travel on the Australian HIV-1 epidemic and the associated increased role of heterosexual HIV-1 transmission in this context. At the same time, these data indicate that local transmission within predominantly male
networks remains a challenging issue for HIV-1 prevention.


Incidence and predictors of cognitive impairment and dementia in Aboriginal Australians: A follow-up study of 5 years.

INTRODUCTION: Aboriginal Australians are reported to develop dementia earlier than the general population. The causes remain unknown.

METHODS: This was a longitudinal study of 363 participants aged >45 years. Consensus diagnoses were established for cognitive impairment or dementia.

RESULTS: At follow-up, 189 people (mean +/- standard deviation age, 65.4 +/- 10.3 years) participated, as 109 (30%) had died and 65 (18%) were unavailable. The incidence of cognitive impairment or dementia was 52.6 (95% confidence interval 33.9, 81.5) per 1000 person-years (380.3 total person-years) and for dementia was 21.0 (10.5, 42.1) per 1000 person-years (380.3 person-years total) over the age 60 years. Longitudinal risk factors associated with a decline from normal cognition to impairment were age and head injury. Other associations with cognitive decline were stroke, head injury, nonaspirin analgesics, lower BMI, and higher systolic BP.

DISCUSSION: Dementia incidence in Aboriginal Australians is among the highest in the world, and is associated with age and head injury.

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Vascular trauma in Western Australia: a comparison of two study periods over 15 years.

BACKGROUND: Royal Perth Hospital (RPH) has become Western Australia's only designated adult major trauma facility since a previous study of vascular trauma was conducted in 2001 at the same facility. The aim of this study is to identify changes in vascular trauma patterns over the two study periods and compare these changes with international literature.
METHODS: All individuals presenting to RPH between January 2000 and December 2010 with vascular injury were identified from a prospective trauma database for this descriptive study. Injuries were classified using the Abbreviated Injury Score (AIS).

RESULTS: The incidence of vascular trauma as a percentage of total trauma increased over the two study periods. The current 10-year study included 45164 patients on the trauma database, of which 1205 patients (2.6%) sustained 1335 vascular injuries, an increase from 1% in the previous 5-year study at the same facility. Males aged 20-29 years were more frequently injured. Blunt trauma occurred more frequently than penetrating. The extremities, particularly the upper limbs were most commonly injured. The most common causes of injury for each region were as follows; motorbike crash (MBC), motor vehicle crash (MVC) and stabbing (neck, thorax and abdomen), MBC and MVC (lower limb) and piercing injuries (upper limb). Injury Severity Score (ISS) and mortality 43% (32 of 75) were highest for thoracic injuries, particularly thoracic aorta injury. Mortality rate has decreased.

CONCLUSION: Vascular injuries in Western Australia are increasing. MVC are the most common cause of life threatening injury. Road safety interventions targeting young males are likely to reduce trauma.

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Dubious findings concerning the prevalence of late-life depression.
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A surprising presentation of blistering mouth ulcers.
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Understanding the long-term impacts of burn on the cardiovascular system.
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BACKGROUND: Whilst the most obvious impact of burn is on the skin, systemic responses also occur after burn that lead to wide-spread changes to the body, including the heart. The aim of this study was to assess if burn in mid-aged and older adults is associated with increased long-term admissions and death due to diseases of the circulatory system.

METHODS: A population-based longitudinal study using linked hospital morbidity and death data from Western Australia was undertaken of adults aged at least 45 years when hospitalized for a first burn (n=6004) in 1980-2012 and a frequency matched non-injury comparison cohort, randomly selected from Western Australia’s electoral roll (n=22,673). Crude admission rates and cumulative length of stay for circulatory diseases were calculated. Negative binomial and Cox proportional hazards regression modelling were used to generate incidence rate ratios (IRR) and hazard ratios (HR), respectively. HR was used as a measure of the mortality rate ratio (MRR).

RESULTS: After adjustment for demographic factors and pre-existing health status, the burn cohort had 1.46 times (95% confidence interval (CI): 1.36-1.56) as many admissions and almost three times the number of days in hospital with a circulatory system diagnosis (IRR, 95%CI: 2.90, 2.60-3.25) than the uninjured cohort for circulatory diseases. The burn cohort had higher admission rates for ischaemic heart disease (IRR, 95%CI: 1.21, 1.07-1.36), heart failure (IRR, 95%CI: 2.29, 1.85-2.82) and cerebrovascular disease (IRR, 95%CI: 1.57, 1.33-1.84). The burn cohort was found to have increased long-term mortality caused by circulatory system diseases (MRR, 95%CI: 1.11, 1.02-1.20).

CONCLUSIONS: Findings of increased hospital admission rates, prolonged length of hospital stay and increased long-term mortality related to circulatory system diseases in the burn cohort provide evidence to support that burn has long-lasting systemic impacts on the heart and circulation.

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Analysing breast tissue composition with MRI using currently available short, simple sequences.

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AIM: To determine the most robust commonly available magnetic resonance imaging (MRI) sequence to quantify breast tissue composition at 1.5 T.

MATERIALS AND METHODS: Two-dimensional (2D) T1-weighted, Dixon fat, Dixon water and SPAIR images were obtained from five participants and a breast phantom using a 1.5 T Siemens Aera MRI system. Manual segmentation of the breasts was performed, and an in-house computer program was used to generate signal intensity histograms. Relative trough depth and relative peak separation were used to determine the robustness of the images for quantifying the two breast tissues. Total breast volumes and percentage breast densities calculated using the four sequences were compared.

RESULTS: Dixon fat histograms had consistently low relative trough depth and relative peak separation compared to those obtained using other sequences. There was no significant difference in total breast volumes and percentage breast densities of the participants or breast phantom using Dixon fat and 2D T1-weighted histograms. Dixon water and SPAIR histograms were not suitable for quantifying breast tissue composition.

CONCLUSION: Dixon fat images are the most robust for the quantification of breast tissue composition using a signal intensity histogram.

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Cardiac Troponin and its Relationship to Cardiovascular Outcomes in Community Populations - A Systematic Review and Meta-analysis.

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BACKGROUND: The clinical relevance of minor elevations of cardiac troponin (cTn) in the general population remains uncertain. The objective of this systematic review was to examine the literature and evaluate the prevalence of raised cTn in asymptomatic, community populations and explore the strength of the relationship between cTn and cardiovascular mortality amongst those studied.

METHODS: Studies were identified by searching Medline, Embase, CINAHL, EBM Reviews, Cochrane Library and using the “related citation” search tool in PubMed from inception through August 2014. Prospective cohort studies of asymptomatic individuals recruited from the community (age > 18 years) that assessed the relationship between cTn levels and mortality or cardiovascular events were included.

RESULTS: Twenty-one prospective studies involving 64,855 participants were identified. An elevated cTn measurement (>99th percentile) occurred in 5% of individuals and was associated with a tripling of risk of mortality (adjusted RR 3.07, 95% confidence interval [CI] 2.32-4.06) and cardiovascular mortality (adjusted RR 3.30, 95% CI 1.77-6.12). In studies including high sensitivity assays, cTn was detectable in 58% of individuals. A detectable cardiac troponin T (cTnT) was also associated with an increased risk of cardiovascular mortality (adjusted RR 1.32, 95% CI 1.10 - 1.59). The risk increased with increasing cTnT level.

CONCLUSIONS: Elevated troponin in asymptomatic individuals in the community is associated with a tripling of risk of all-cause and cardiovascular mortality. Cardiac troponin T (cTnT) is generally not measured in this group of patients, but may potentially have utility in predicting risk in this population. Further research is required to assess if this risk is modifiable with usual primary prevention treatments.

Organ donation in adults: a critical care perspective.

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Purpose: The shortage of organs for transplantation is an important medical and societal problem because transplantation is often the best therapeutic option for end-stage organ failure.

Methods: We review the potential deceased organ donation pathways in adult ICU practice, i.e. donation after brain death (DBD) and controlled donation after circulatory death (cDCD), which follows the planned withdrawal of life-sustaining treatments (WLST) and subsequent confirmation of death using cardiorespiratory criteria.

Results: Strategies in the ICU to increase the number of organs available for transplantation are discussed. These include timely identification of the potential organ donor, optimization of the brain-dead donor by aggressive management of the physiological consequence of brain death, implementation of cDCD protocols, and the potential for ex vivo perfusion techniques.

Conclusions: Organ donation should be offered as a routine component of the end-of-life care plan of every patient dying in the ICU where appropriate, and intensivists are the key professional in this process.

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Estimation of clinical and economic effects of prophylaxis against venous thromboembolism in medical patients, including the effect of targeting patients at high-risk.

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Background: The clinical and economic effects of medical thromboprophylaxis (MT) using low molecular weight heparin in Australia are unknown.

AIM: To estimate the effects of MT in Australia.

Methods: A decision tree model of MT was populated with national data for medical admissions. The Prevention of Recurrent Venous Thromboembolism (PREVENT) trial was chosen as the primary data source because its design uniquely avoided bias caused by treatment of sub-clinical events. Clinical efficacy and costs were estimated compared with no prophylaxis, assuming full compliance and according to three definitions of eligibility. Effectiveness was estimated as thrombotic events saved, mortality from bleeding or pulmonary embolus (PE), cost and $/year of life saved. Model outputs were subjected to sensitivity analysis.

Results: MT decreased thrombotic events, and the numbers avoided increased as eligibility broadened (deep vein thrombosis (DVT): 2597, 2771 and 3232 at restricted, intermediate and broad eligibility; PE: 454, 484 and 565 respectively). The annual cost of no prophylaxis was $88.7m. Costs were reduced at most restricted eligibility (-$7.9m), but increased by $3.0 and $32.1m at broader eligibility. PE deaths declined, but this was offset by deaths from haemorrhage, causing a net increase (158, 299 and 672 respectively). Estimates were sensitive to the incidence of venous thromboembolic event (VTE), case-fatality rates for PE and bleeds and the relative risk reduction for PE with prophylaxis.

Conclusions: Under PREVENT trial conditions, MT avoids up to 3200 DVT and 565 PE events annually, but may increase mortality.

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Lipidomics Reveals Associations of Phospholipids With Obesity and Insulin Resistance in Young Adults.

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CONTEXT: Obesity and related diseases have become a global public health burden. Identifying biomarkers will lead to a better understanding of the underlying mechanisms associated with obesity and the pathways leading to insulin resistance (IR) and diabetes.
OBJECTIVE: This study aimed to identify the lipidomic biomarkers associated with obesity and IR using plasma samples from a population-based cohort of young adults.

DESIGN AND SETTING: The Western Australian Pregnancy Cohort (Raine) study enrolled 2900 pregnant women from 1989 to 1991. The 20-year follow-up was conducted between March 2010 and April 2012. Participants and Samples: Plasma samples from 1176 subjects aged 20 years were analyzed using mass spectrometry-based metabolomics.

MAIN OUTCOME MEASURES: Associations of analytes with markers of obesity and IR including body mass index, waist circumference, homeostasis model assessment (HOMA-IR), and insulin were examined. Analyses were stratified by body mass index and adjusted for lifestyle and other factors.

RESULTS: Waist circumference was positively associated with seven sphingomyelins and five diacylphosphatidylcholines and negatively associated with two lysophosphatidylcholines. HOMA-IR was negatively associated with two diacylphosphatidylcholines and positively with one lysophosphatidylcholine and one diacylphosphatidylcholine. No significant association was found in the obese/overweight group of the HOMA-IR model. In the normal-weight group, one lysophosphatidylcholine was increased.

CONCLUSION: A possible discriminative effect of sphingomyelins, particularly those with two double bonds, and lysophosphatidylcholines was identified between subjects with normal weight and obesity independent of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol concentrations. Our results suggest weight-status-dependent mechanisms for the development of IR with lysophosphatidylcholine C14:0 as a key metabolite in nonobese IR.

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The effects of alcohol on ambulatory blood pressure and other cardiovascular risk factors in type 2 diabetes: a randomized intervention.

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OBJECTIVE: Although prospective studies suggest light-to-moderate chronic alcohol intake protects against coronary artery disease in type 2 diabetic patients, the balance of effects on individual cardiovascular risk factors needs further assessment. We examined the effects of alcohol consumption on 24-h ambulatory blood pressure (BP) and heart rate (HR), high-density lipoprotein cholesterol, fibrinogen, C-reactive protein, homocysteine, and glycemic control in well controlled type 2 diabetes.

METHODS: Twenty-four participants aged 49-66 year were randomized to a three-period crossover study with women drinking red wine 230 ml/day (~24 g alcohol/day) and men drinking red wine 300 ml/day (~31 g alcohol/day), or equivalent volumes of dealcoholized red wine (DRW) or water, each for 4 weeks. Ambulatory BP and HR were monitored every 30 min for 24 h at the end of each period. Home blood glucose monitoring was carried out twice weekly throughout.

RESULTS: Red wine increased awake SBP and DBP relative to water by 2.5 +/- 1.2 /1.9 +/- 0.7 mmHg (P = 0.033, P = 0.008, respectively), with a similar nonsignificant trend relative to DRW. Asleep DBP fell with red wine relative to DRW (2.0 +/- 0.8 mmHg, P = 0.016) with a similar nonsignificant trend relative to water. Red wine increased 24-h, awake and asleep HR relative to water and DRW. Relative to DRW, red wine did not affect glycemic control or any other cardiovascular risk factor.

CONCLUSION: In well controlled type 2 diabetic individuals 24-31 g alcohol/day (~2-3 standard drinks) raises awake BP and 24-h HR and lowers asleep BP but does not otherwise favourably or adversely modify cardiovascular risk factors.

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Sudden Death Following Cranioplasty.

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DOI:https://dx.doi.org/10.3340/jkns.2016.59.2.182

En Bloc Resection of Desmoplastic Neurotropic Melanoma with Perineural Invasion of the Intracranial Trigeminal and Intraparotid Facial Nerve: Case Report and Review of the Literature.

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Background Desmoplastic neurotropic melanoma (DNM) is a rare, highly malignant, and locally invasive form of cutaneous melanoma with a tendency for perineural invasion (PNI). Methods We report a case of a 61-year-old man presenting with right-sided trigeminal neuralgia and progressive facial paresis due to the PNI of the intracranial trigeminal nerve and the intraparotid facial nerve from DNM. We also present a review of the literature with six cases of DNM with PNI of the intracranial trigeminal nerve identified. Results The combined transtemporal-infratemporal fossa approach was performed to achieve total en bloc resection of the tumor mass followed by postoperative radiotherapy (PORT). After 24 months of follow-up, the patient remains disease free with no signs of recurrence on magnetic resonance imaging. Conclusion We recommend the en bloc resection of the tumor mass followed by PORT for the management of DNM with PNI. A high index of suspicion for PNI as a cause of cranial neuropathies is essential for the early detection and treatment of patients with known melanoma.
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DOI:https://dx.doi.org/10.1055/s-0035-1566254

Prevalence of Familial Hypercholesterolemia in Adolescents: Potential Value of Universal Screening?

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Sudden death following cranioplasty: autoregulatory failure?

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DOI:https://dx.doi.org/10.3171/2015.7.JNS151538

Prevalence of Familial Hypercholesterolemia in Adolescents: Potential Value of Universal Screening?
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Familial hypercholesterolemia (FH) significantly increases the risk of coronary heart disease. Most individuals are unaware they have the condition. In the Western Australian Pregnancy Cohort (Raine) Study, 1 in 267 adolescents were found to have FH. Universal cholesterol screening in childhood may offer the best strategy for diagnosing FH. Copyright © 2016 Elsevier Inc. All rights reserved. PMID:26690851 DOI:https://dx.doi.org/10.1016/j.jpeds.2015.11.019


Muscle histopathology in children with spastic cerebral palsy receiving botulinum toxin type A.
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INTRODUCTION: Botulinum toxin A (BoNTA) is routine treatment for hypertonicity in children with cerebral palsy (CP).
METHODS: This single-blind, prospective, cross-sectional study of 10 participants (mean age 11 years 7 months) was done to determine the relationship between muscle histopathology and BoNTA in treated medial gastrocnemius muscle of children with CP. Open muscle biopsies were taken from medial gastrocnemius muscle and vastus lateralis (control) during orthopedic surgery.
RESULTS: Neurogenic atrophy in the medial gastrocnemius was seen in 6 participants between 4 months and 3 years post-BoNTA. Type 1 fiber loss with type 2 fiber predominance was significantly related to the number of BoNTA injections (r = 0.89, P < 0.001).
CONCLUSIONS: The impact of these changes in muscle morphology on muscle function in CP is not clear. It is important to consider rotating muscle selection or injection sites within the muscle or allowing longer time between injections.
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Supplementation with coenzyme Q10 reduces plasma lipoprotein(a) concentrations but not other lipid indices: A systematic review and meta-analysis.
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 Plasma lipoprotein(a) \([\text{Lp}(a)]\) elevations are associated with increased cardiovascular risk. Coenzyme Q10 (CoQ10) is a member of the mitochondrial respiratory chain with a prominent role as a potent gene regulator. The \(\text{Lp}(a)\)-lowering efficacy of CoQ10 has been investigated in different clinical settings with contrasting results. A systematic literature search in Medline, SCOPUS, Web of Science and Google Scholar databases was conducted to identify controlled trials investigating the efficacy of CoQ10 supplementation on plasma \(\text{Lp}(a)\) levels. Inverse variance-weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in \(\text{Lp}(a)\) levels using a random-effects model. Random-effects meta-regression was performed to assess the effect of putative confounders on plasma \(\text{Lp}(a)\) levels. Seven randomized controlled trials with a total of 409 subjects (206 in the CoQ10 arm and 203 in the control arm) met the eligibility criteria. Overall, CoQ10 supplementation was paralleled by a slight but significant reduction of plasma \(\text{Lp}(a)\) levels (WMD: \(-3.54\) mg/dL, 95% CI: \(-5.50\), \(-1.58\); \(p<0.001\)), this effect being more robust in those trials with higher baseline \(\text{Lp}(a)\) levels (slope: \(-0.44\); 95% CI: \(-0.80\), \(-0.08\); \(p=0.018\)). Reduction of plasma \(\text{Lp}(a)\) levels was consistent across different CoQ10 doses, with an inverse association between administered CoQ10 dose and \(\text{Lp}(a)\) lowering (slope: \(0.04\); 95% CI: \(0.01\), \(0.07\); \(p=0.004\)). Neither total cholesterol and cholesterol subfractions, nor triglyceride levels were affected by CoQ10 supplementation. In conclusion, CoQ10 supplementation, in the tested range of doses, reduces plasma \(\text{Lp}(a)\) concentrations, particularly in patients with \(\text{Lp}(a)>30\) mg/dL. Other lipid indices were not altered by CoQ10 supplementation.

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**Bilateral Distraction Osteogenesis of Vascularized Iliac Crest Free Flaps Used in Mandibular Reconstruction.**

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DOI:https://dx.doi.org/10.1097/GOX.0000000000000623
Letter to the Editor: “Risk factors for postoperative pneumonia after lung cancer surgery and impact of pneumonia on survival”.
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Investigation of the efficacy of generic and brand-name tiotropium bromide in the management of chronic obstructive pulmonary disease: A randomized comparative trial.
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INTRODUCTION: The beneficial effects of tiotropium bromide, a long acting anticholinergic bronchodilator, in the management of chronic obstructive pulmonary disease have been shown in previous studies. The present study aimed to compare the efficacy and safety of generic (Tiova) and brand-name (Spiriva) tiotropium preparations in patients with COPD.
METHODS AND MATERIALS: In this randomized double-blind parallel-group trial, 79 patients with documented COPD were assigned to Tiova or Spiriva for a period of 4 weeks. Assessment of pulmonary function (using spirometry), quality-of-life (using St. George respiratory Questionnaire [SGRQ]) and severity of respiratory symptoms (using breathlessness, cough and sputum scale [BCSS]) was performed at baseline and at the end of treatment period. RESULTS: There were significant increases in FEV1 and reductions in FVC by the end of study in both Tiova and Spiriva groups. FEV1/FVC ratio did not change significantly neither in the Tiova nor in Spiriva group. Overall SGRQ score as well as subscale scores of symptoms, activity and impacts were improved by both drugs. In the BCSS scale, the frequency and severity of three main symptoms (dyspnea, cough and sputum) was decreased by both drugs. Baseline as well as post-treatment values of spirometric parameters, SGRQ and BCSS scores was comparable between the groups, apart from a lower post-treatment frequency of cough and sputum in the Spiriva versus Tiova group. There was no report of adverse events in either of the study groups.
CONCLUSION: The findings of this comparative trial showed equivalent efficacy and safety of Spiriva and Tiova in lessening the symptoms as well as improving the quality of life in patients with COPD. This finding has an important translational value given the significantly lower costs of generic versus brand-name products.
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Cause of Death and Predictors of All-Cause Mortality in Anticoagulated Patients With Nonvalvular Atrial
Fibrillation: Data From ROCKET AF.
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BACKGROUND: Atrial fibrillation is associated with higher mortality. Identification of causes of death and contemporary risk factors for all-cause mortality may guide interventions.
METHODS AND RESULTS: In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study, patients with nonvalvular atrial fibrillation were randomized to rivaroxaban or dose-adjusted warfarin. Cox proportional hazards regression with backward elimination identified factors at randomization that were independently associated with all-cause mortality in the 14 171 participants in the intention-to-treat population. The median age was 73 years, and the mean CHADS2 score was 3.5. Over 1.9 years of median follow-up, 1214 (8.6%) patients died. Kaplan-Meier mortality rates were 4.2% at 1 year and 8.9% at 2 years. The majority of classified deaths (1081) were cardiovascular (72%), whereas only 6% were nonhemorrhagic stroke or systemic embolism. No significant difference in all-cause mortality was observed between the rivaroxaban and warfarin arms (P=0.15). Heart failure (hazard ratio 1.51, 95% CI 1.33–1.70, P<0.0001) and age >75 years (hazard ratio 1.69, 95% CI 1.51–1.90, P<0.0001) were associated with higher all-cause mortality. Multiple additional characteristics were independently associated with higher mortality, with decreasing creatinine clearance, chronic obstructive pulmonary disease, male sex, peripheral vascular disease, and diabetes being among the most strongly associated (model C-index 0.677).
CONCLUSIONS: In a large population of patients anticoagulated for nonvalvular atrial fibrillation, =7 in 10 deaths were cardiovascular, whereas <1 in 10 deaths were caused by nonhemorrhagic stroke or systemic embolism. Optimal prevention and treatment of heart failure, renal impairment, chronic obstructive pulmonary disease, and diabetes may improve survival.
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Fruit Intake and Abdominal Aortic Calcification in Elderly Women: A Prospective Cohort Study.
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Cardiovascular disease (CVD) is the leading cause of death worldwide. There is a consistent inverse relationship between fruit intake with CVD events and mortality in cross-sectional and prospective observational studies, but the relationship of fruit intake with measurements of atherosclerosis in humans is less clear. Nutritional effects on abdominal aortic calcification (AAC), a marker for subclinical intimal and medial atherosclerotic vascular disease, have not been studied previously. The aim of this study was to examine the cross-sectional relationship of total and individual fruit (apple, pear, orange and other citrus, and banana) intake with AAC, scored between 0 and 24. The current study assessed baseline data for a cohort of 1052 women over 70 years of age who completed both a food frequency questionnaire assessing fruit intake, and underwent AAC measurement using dual energy X-ray absorptiometry. AAC scores were significantly negatively correlated with total fruit and apple intakes (p < 0.05), but not with pear, orange or banana intakes (p > 0.25). In multivariable-adjusted logistic regression, each standard deviation (SD; 50 g/day) increase in apple intake was associated with a 24% lower odds of having severe AAC (AAC score >5) (odd ratio OR): 0.76 (0.62, 0.93), p = 0.009). Total and other individual fruit intake were not associated with increased odds of having severe AAC. Apple but not total or other fruit intake is independently negatively associated with AAC in older women.
Apple intake is inversely associated with all-cause and disease-specific mortality in elderly women.
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Higher fruit intake is associated with lower risk of all-cause and disease-specific mortality. However, data on individual fruits are limited, and the generalisability of these findings to the elderly remains uncertain. The objective of this study was to examine the association of apple intake with all-cause and disease-specific mortality over 15 years in a cohort of women aged over 70 years. Secondary analyses explored relationships of other fruits with mortality outcomes.
Usual fruit intake was assessed in 1456 women using a FFQ. Incidence of all-cause and disease-specific mortality over 15 years was determined through the Western Australian Hospital Morbidity Data system. Cox regression was used to determine the hazard ratios (HR) for mortality. During 15 years of follow-up, 607 (41.7%) women died from any cause. In the multivariable-adjusted analysis, the HR for all-cause mortality was 0.89 (95% CI 0.81, 0.97) per sd (53 g/d) increase in apple intake, HR 0.80 (95% CI 0.65, 0.98) for consumption of 5-100 g/d and HR 0.65 (95% CI 0.48, 0.89) for consumption of >100 g/d (an apple a day), compared with apple intake of <5 g/d (P for trend 0.03). Our analysis also found that higher apple intake was associated with lower risk for cancer mortality, and that higher total fruit and banana intakes were associated lower risk of CVD mortality (P<0.05). Our results support the view that regular apple consumption may contribute to lower risk of mortality.
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n-3 Fatty Acid Supplementation and Leukocyte Telomere Length in Patients with Chronic Kidney Disease.
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DNA telomere shortening associates with the age-related increase cardiovascular disease (CVD) risk. Reducing oxidative stress, could modify telomere erosion during cell replication, and CVD risk in patients with chronic kidney disease (CKD). The effect of n-3 fatty acids and coenzyme Q10 (CoQ) on telomere length was studied in a double-blind placebo-controlled trial in CKD. Eighty-five CKD patients were randomized to: n-3 fatty acids (4 g); CoQ (200 mg); both supplements; or control (4 g olive oil), daily for 8 weeks. Telomere length was measured in neutrophils and peripheral blood mononuclear cells (PBMC) at baseline and 8 weeks, with and without correction for cell counts. Main and interactive effects of n-3 fatty acids and CoQ on telomere length were assessed adjusting for baseline values. F2-isoprostanes were measured as markers of oxidative stress. There was no effect of n-3 fatty acids or CoQ on neutrophil or PBMC telomere length. However, telomere length corrected for neutrophil count was increased after n-3 fatty acids (p = 0.015). Post-intervention plasma F2-isoprostanes were negative predictors of post-intervention telomere length corrected for neutrophil count (p = 0.025). The effect of n-3 fatty acids to increased telomere length corrected for neutrophil count may relate to reduced oxidative stress and increased clearance of neutrophils with shorter telomeres from the circulation. This may be a novel mechanism of modifying CVD risk in CKD patients.

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The Burns Registry of Australia and New Zealand: progressing the evidence base for burn care.
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OBJECTIVE: Analysis of data from the Burns Registry of Australia and New Zealand (BRANZ) to determine the extent of variation between participating units in treatment and in specific outcomes during the first 4 years of its operation.

DESIGN: BRANZ, an initiative of the Australian and New Zealand Burn Association, is a clinical quality registry developed in accordance with the Australian Commission on Safety and Quality in Healthcare national operating principles.

SETTING: Patients with burn injury who fulfil pre-defined criteria are transferred to and managed in designated burn units. There are 17 adult and paediatric units in Australia and New Zealand that manage almost all patients with significant burn injury. Twelve of these units treat adult patients.

PARTICIPANTS: Data on 7184 adult cases were contributed by ten acute adult burn units to the registry between July 2010 and June 2014. Major outcomes: In-hospital mortality, hospital length of stay, skin grafting rates, and rates of admission to intensive care units.
RESULTS: Considerable variations in unit profiles (including numbers of patients treated), in treatment and in outcomes were identified.

CONCLUSIONS: Despite the highly centralised delivery of care to patients with severe or complex burn injury, and the relatively small number of specialist burn units, we found significant variation between units in clinical management and in outcomes. BRANZ data from its first 4 years of operation support its feasibility and the value of further development of the registry. Based on these results, the focus of ongoing research is to improve understanding of the reasons for variations in practice and of their effect on outcomes for patients, and to develop evidence-informed clinical guidelines for burn management in Australia and New Zealand.

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Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up.

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BACKGROUND: Familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD). There are sparse data on attainment of treatment targets; large registries that reflect real-life clinical practice can uniquely provide this information.

OBJECTIVES: We sought to evaluate the achievement of low-density lipoprotein cholesterol (LDL-C) treatment goals in FH patients enrolled in a large national registry.

METHODS: The SAFEHEART study (Spanish Familial Hypercholesterolemia Cohort Study) is a large, ongoing registry of molecularly defined patients with heterozygous FH treated in Spain. The attainment of guideline-recommended plasma LDL-C goals at entry and follow-up was investigated in relation to use of lipid-lowering therapy (LLT).

RESULTS: The study recruited 4,132 individuals (3,745 of whom were >18 years of age); 2,752 of those enrolled were molecularly diagnosed FH cases. Mean follow-up was 5.1 +/- 3.1 years; 71.8% of FH cases were on maximal LLT, and an LDL-C treatment target <100 mg/dl was reached by only 11.2% of patients. At follow-up, there was a significant increase in the use of ezetimibe, drug combinations with statins, and maximal LLT. The presence of type 2 diabetes mellitus, a defective allele mutation, ezetimibe use, and the absence of previous ASCVD were predictors of the attainment of LDL-C goals.

CONCLUSIONS: Despite the use of intensified LLT, many FH patients continue to experience high plasma LDL-C levels.
and, consequently, do not achieve recommended treatment targets. Type of LDL-receptor mutation, use of ezetimibe, coexistent diabetes, and ASCVD status can bear significantly on the likelihood of attaining LDL-C treatment goals.


**Human factors and the death of a child in hospital: a case review.**

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Learning from adverse events and errors is important if systems and processes are to be improved and to minimise the likelihood of similar events in the future. This article uses the report from a coroner’s inquest into the death of a seven-year-old child in hospital to examine errors that contributed to the child’s death. These errors are reviewed from a human factors perspective. The article provides an overview of error causation concepts and offers strategies that healthcare organisations can implement to reduce the incidence of such errors.


**CAMERA2 - combination antibiotic therapy for methicillin-resistant Staphylococcus aureus infection: study protocol for a randomised controlled trial.**

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BACKGROUND: Methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia is a serious infection resulting in 20-50% 90-day mortality. The limitations of vancomycin, the current standard therapy for MRSA, make treatment difficult. The only other approved drug for treatment of MRSA bacteraemia, daptomycin, has not been shown to be superior to vancomycin. Surprisingly, there has been consistent in-vitro and in-vivo laboratory data demonstrating synergy between vancomycin or daptomycin and an anti-staphylococcal beta-lactam antibiotic. There is also growing clinical data to support such combinations, including a recent pilot randomised controlled trial (RCT) that demonstrated a trend towards a reduction in the duration of bacteraemia in patients treated with vancomycin plus flucloxacillin compared to vancomycin alone. Our aim is to determine whether the addition of an anti-staphylococcal penicillin to standard therapy results in improved clinical outcomes in MRSA bacteraemia.

METHODS/DESIGN: We will perform an open-label, parallel-group, randomised (1:1) controlled trial at 29 sites in Australia, New Zealand, Singapore, and Israel. Adults (aged 18 years or older) with MRSA grown from at least one blood culture and able to be randomised within 72 hours of the index blood culture collection will be eligible for inclusion. Participants will be randomised to vancomycin or daptomycin (standard therapy) given intravenously or to standard therapy plus 7 days of an anti-staphylococcal beta-lactam (flucloxacillin, cloxacillin, or cefazolin). The primary endpoint will be a composite outcome at 90 days of (1) all-cause mortality, (2) persistent bacteraemia at day 5 or beyond, (3) microbiological relapse, or (4) microbiological treatment failure. The recruitment target of 440 patients is based on an expected failure rate for the primary outcome of 30% in the control arm and the ability to detect a clinically meaningful absolute decrease of 12.5%, with a two-sided alpha of 0.05, a power of 80%, and assuming 10% of patients will not be evaluable for the primary endpoint.

DISCUSSION: Key potential advantages of adding anti-staphylococcal beta-lactams to standard therapy for MRSA bacteraemia include their safety profile, low cost, and wide availability.


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Pulmonary Rehabilitation Exercise Prescription in Chronic Obstructive Pulmonary Disease: Review of Selected Guidelines: AN OFFICIAL STATEMENT FROM THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION.

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Chronic obstructive pulmonary disease (COPD) is associated with disabling dyspnea, skeletal muscle dysfunction, and significant morbidity and mortality. Current guidelines recommend pulmonary rehabilitation (PR) to improve dyspnea, functional capacity, and quality of life. Translating exercise science into safe and effective exercise training requires interpretation and use of multiple guidelines and recommendations. The purpose of this statement is to summarize for clinicians 3 current chronic obstructive pulmonary disease guidelines for exercise that may be used to develop exercise prescriptions in the PR setting. The 3 guidelines have been published by the American College of Sports Medicine, the American Thoracic Society/European Respiratory Society, and the American Association of
Cardiovascular and Pulmonary Rehabilitation. In addition to summarizing these 3 guidelines, this statement describes clinical applications, explores areas of uncertainty, and suggests strategies for providing effective exercise training, given the diversity of guidelines and patient complexity.

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Ten years’ experience of decompressive craniectomy for severe traumatic brain injury.

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Introduction: There is considerable in the long term outcome in patients who have had a decompressive craniectomy following severe traumatic brain injury. Study Objectives: The aim of this study was to assess the impact that injury severity has on long term outcome and surgical complications in patients who have had a decompressive craniectomy for severe traumatic brain injury (TBI) over a period of 10 years in the two neurotrauma hospitals in Western Australia.

Methods: This is a prospective observational cohort study. The CRASH (corticosteroid randomization after significant head injury) collaborators outcome prediction model was used to stratify patients according to injury severity. Clinical and radiological data on initial presentation were entered into the web-based model and the prediction of an unfavourable outcome was compared with the observed outcome at eighteen month follow up. Results: Amongst a cohort of three hundred and twenty patients, comparing the predicted outcome with the observed long term outcome provided an objective assessment of the most likely outcome following surgical intervention. The ability of the model to differentiate between unfavourable and favourable outcomes at 18 months was good, however, the model’s calibration was not perfect. The predicted risk of unfavourable outcome was also strongly associated with post-operative complications. Conclusions: The CRASH collaborators prediction model appears to be a valuable tool which can be used as a surrogate index of injury severity to stratify patients according to injury severity. Used wisely, the CRASH model may add to a clinician’s ability have better informed conversations with colleagues and patients’ relatives about realistic long term outcome expectations following surgical intervention in the context of severe traumatic brain injury.

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Anesthesia Outcome and Chance.

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Severe Nausea and Vomiting in the Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II Trial.

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BACKGROUND: The Evaluation of Nitrous oxide in the Gas Mixture for Anesthesia II trial randomly assigned 7,112 noncardiac surgery patients to a nitrous oxide or nitrous oxide-free anesthetic; severe postoperative nausea and vomiting (PONV) was a prespecified secondary end point. Thus, the authors evaluated the association between nitrous oxide, severe PONV, and effectiveness of PONV prophylaxis in this setting.

METHODS: Univariate and multivariate analyses of patient, surgical, and other perioperative characteristics were used to identify the risk factors for severe PONV and to measure the impact of severe PONV on patient outcomes.

RESULTS: Avoiding nitrous oxide reduced the risk of severe PONV (11 vs. 15%; risk ratio [RR], 0.74 [95% CI, 0.63 to 0.84]; P < 0.001), with a stronger effect in Asian patients (RR, 0.55 [95% CI, 0.43 to 0.69]; interaction P = 0.004) but lower effect in those who received PONV prophylaxis (RR, 0.89 [95% CI, 0.76 to 1.05]; P = 0.18). Gastrointestinal surgery was associated with an increased risk of severe PONV when compared with most other types of surgery (P < 0.001). Patients with severe PONV had lower quality of recovery scores (10.4 [95% CI, 10.2 to 10.7] vs. 13.1 [95% CI, 13.0 to 13.2], P < 0.0005); severe PONV was associated with postoperative fever (15 vs. 20%, P = 0.001). Patients with severe PONV had a longer hospital stay (adjusted hazard ratio, 1.14 [95% CI, 1.05 to 1.23], P = 0.002).

CONCLUSIONS: The increased risk of PONV with nitrous oxide is near eliminated by antiemetic prophylaxis. Severe PONV, which is seen in more than 10% of patients, is associated with postoperative fever, poor quality of recovery, and prolonged hospitalization.

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Surgical resection of a giant cardiac fibroma.
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A 42-year-old woman presented to a regional hospital emergency room with palpitations and was found to be in ventricular tachycardia. Chest radiography demonstrated a massively enlarged cardiac silhouette. Echocardiography and cardiac magnetic resonance imaging demonstrated a mass within the left ventricular free wall, consistent with a cardiac fibroma. The patient proceeded to have surgical resection of the mass. Left ventricular function was preserved postoperatively.
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A review of the current sunscreen products in Australia.
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Melanoma (MM) and Non Melanoma Skin cancer (NMSC) are leading causes of morbidity and mortality in Australia, and of significant cost to the community. Public health campaigns to reduce skin cancer include advice on the use of adequate sun screen preparations. The Australian market has about 911 sunscreen products, each with different formulation and ingredients, making it difficult for consumers and health care professionals to determine which products to use. We list and discuss the specific ingredients found in sunscreen formulations available in Australia, the mode and range of protection, photostability, solubility, side effects such as irritant and allergic contact dermatitis, vitamin D deficiency and the safety of nanoparticles. Vehicle effects on compliance and efficacy are also discussed.

A review of dermatology mobile apps.
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Medical apps for mobile devices have been an intense area of development over the past several years. They provide fast and convenient access to information. We investigate and review mobile apps that have a focus in the area of dermatology. These may be useful resources for dermatologists and trainees in their clinical practice.

Chemotherapy induced vesico-bullous disseminated superficial actinic porokeratosis.
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Disseminated Superficial Actinic Porokeratosis (DSAP) is the commonest variant of Porokeratoses, commonly seen in fair skin exposed excessive sun exposure. The classic morphology of well demarcated slightly scaly annular plaques with thread-like keratotic rim as well as the histological hallmark "cornoid lamella" are characteristic of this condition. Exacerbations of DSAP are sometimes linked to various factors including malignancy, immunosuppression, drugs and chemotherapy. Herein we report a case of exacerbation of the pre-existing DSAP lesions with erythema and vesicle/bulla formation following administration of carboplatin and paclitaxel for uterine sarcoma secondaries complicated by bilateral lower limb lymphedema. Neither uterine sarcoma nor carboplatin/paclitaxel combination has been reported to trigger/exacerbate DSAP in literature and the bullous form is extremely rare with only one case reported so far. We propose that an immune mediated intense inflammatory reaction precipitated by chemotherapy and the probable epidermal barrier defect due to defective keratinization of DSAP lesions along with the background of lymphedema as possible mechanisms for bullae formation limited to DSAP lesions in lymphedematous areas.

Topical crushed prednisolone use in recalcitrant peristomal pyoderma gangrenosum.
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We present a 63-year-old lady with recalcitrant peristomal pyoderma gangrenosum (PPG) developing next to her urostomy site. Local therapies in the form of betamethasone dipropionate 0.05%, tacrolimus 0.1%, dapsone (25 mg daily) and intralesional triamcinolone injections (10 mg/mL) provided no benefit. Systemic therapies including oral prednisolone (35 mg daily), infliximab (5 mg/kg 8weekly) and mycophenolate mofetil (1 g twice daily) also failed to induce a response. A trial of 1 mg crushed prednisolone applied topically to her PPG three times per week resulted in a significant reduction in ulcer size and successful cessation of all systemic therapies. Encouraging results from our case and a previous case series suggests that further research is warranted for the use of topical crushed prednisolone in the treatment of PPG.

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Cutaneous pyogenic granuloma treated with intralesional triamcinolone injection: A case and review.
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Pyogenic granuloma is a rapidly developing, non-neoplastic vascular proliferation. It characteristically presents as a friable, verrucous polypoid tumour, with a tendency to bleed, and association with hormonal factors and minor trauma. Conventional treatment of pyogenic granuloma is with surgical techniques such curettage and cautery or imiquimod therapy. We present this case of a 58-year-old man on haemodialysis with a pyogenic granuloma over the anterior chest wall. The location of the lesion, adjacent to a Hickman line, and a palpable deeper component, proved problematic for routine surgical excision. An alternative approach was taken, and the lesion treated with intralesional steroid injection, a method infrequently described for cutaneous pyogenic granuloma. We aim to review the treatment options of pyogenic granulomas, discuss implications for surgically challenging PG lesions and present our results with intralesional triamcinolone.
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Common familial risk factors for schizophrenia and diabetes mellitus.
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OBJECTIVE: The co-occurrence of type 2 diabetes and psychosis is an important form of medical comorbidity within individuals, but no large-scale study has evaluated comorbidity within families. The aim of this study was to determine whether there is evidence for familial comorbidity between type 2 diabetes and psychosis.
METHOD: Data were analysed from an observational study of a nationally representative sample of 1642 people with
psychosis who were in contact with psychiatric services at the time of survey (The 2010 Australian National Survey of Psychosis). Participants were aged 18-64 years and met World Health Organization's International Classification of Diseases, 10th Revision diagnostic criteria for a psychotic disorder (857 with schizophrenia, 319 with bipolar disorder with psychotic features, 293 with schizoaffective disorder, 81 with depressive psychosis and 92 with delusional disorder or other non-organic psychoses). Logistic regression was used to estimate the association between a family history of diabetes and a family history of schizophrenia.

RESULTS: A positive family history of diabetes was associated with a positive family history of schizophrenia in those with a psychotic disorder (odds ratio = 1.35, p = 0.01, adjusted for age and gender). The association was different in those with an affective versus non-affective psychosis (odds ratio = 0.613, p = 0.019, adjusted for age and gender) and was significant only in those with a non-affective psychosis, specifically schizophrenia (odds ratio = 1.58, p = 0.005, adjusted for age and sex). Adjustment for demographic factors in those with schizophrenia slightly strengthened the association (odds ratio = 1.74, p = 0.001, adjusted for age, gender, diagnosis, ethnicity, education, employment, income and marital status).

CONCLUSION: Elevated risk for type 2 diabetes in people with schizophrenia is not simply a consequence of antipsychotic medication; type 2 diabetes and schizophrenia share familial risk factors.

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Improvement of plasma adiponectin, leptin and C-reactive protein concentrations by orlistat: a systematic review and meta-analysis.
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AIMS: To conduct a systematic review and meta-analysis of relevant randomized clinical trials (RCTs) to ascertain the effect size of orlistat in modulating plasma levels of adipokines, ghrelin and C-reactive protein (CRP).

METHODS: Medline, SCOPUS, Web of Science and Google Scholar databases were searched. A random-effects model and the generic inverse variance method were used for quantitative data synthesis. Heterogeneity was quantitatively assessed using I(2) index. Sensitivity analyses were conducted using the one-study remove approach. Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of duration of treatment, percentage change in body mass index (BMI) and baseline BMI values as potential confounders of the estimated effect size.

RESULTS: Meta-analysis suggested a significant increase in plasma levels of adiponectin [weighted mean difference (WMD): 19.18%, 95% confidence interval (CI): 5.80, 32.57, p = 0.005] and significant reductions in plasma levels of leptin (WMD: -13.24%, 95% CI: -20.69, -5.78, p = 0.001) and CRP (WMD: -11.52%, 95% CI: -16.55, -6.49, p < 0.001) following treatment with orlistat. In meta-regression, changes in plasma concentrations of adiponectin, leptin and CRP were associated with duration of treatment, but not with either change in BMI or baseline BMI values.

CONCLUSION: Orlistat is effective in increasing plasma concentrations of adiponectin and decreasing those of leptin and CRP.

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**Statin therapy and plasma free fatty acids: a systematic review and meta-analysis of controlled clinical trials.**
Sahebkar A, Simental-Mendia LE, et al.


AIM: The aim of this meta-analysis was to evaluate the effect of statin therapy on plasma FFA concentrations in a systematic review and meta-analysis of controlled clinical trials.

METHODS: PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched (from inception to February 16 2015) to identify controlled trials evaluating the impact of statins on plasma FFA concentrations. A systematic assessment of bias in the included studies was performed using the Cochrane criteria. A random effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Random effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of potential moderators.

RESULTS: Meta-analysis of data from 14 treatment arms indicated a significant reduction in plasma FFA concentrations following treatment with statins (weighted mean difference (WMD) -19.42%, 95% CI -23.19, -15.64, P < 0.001). Subgroup analysis confirmed the significance of the effect with both atorvastatin (WMD -20.56%, 95% CI -24.51, -16.61, P < 0.01) and simvastatin (WMD -18.05%, 95% CI -28.12, -7.99, P < 0.001). Changes in plasma FFA concentrations were independent of treatment duration (slope -0.10, 95% CI -0.30, 0.11, P = 0.354) and magnitude of reduction in plasma low density lipoprotein cholesterol concentrations (slope 0.55, 95% CI -0.17, 1.27, P = 0.133) by statins.

CONCLUSIONS: The results of the present study suggest that statin therapy may lower plasma FFA concentrations. The cardiovascular and metabolic significance of this finding requires further investigation.

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**Comparison of the six-minute walk test with a cycle-based cardiopulmonary exercise test in people following curative intent treatment for non-small cell lung cancer.**
Cavalheri V, Jenkins S, et al.


Comparison of the six-minute walk test with a cycle-based cardiopulmonary exercise test in people following curative intent treatment for non-small cell lung cancer.
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This study is aimed to (i) compare both the magnitude of impairment in exercise capacity and exercise responses measured during the six-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET) and (ii) investigate the effect of test repetition on six-minute walk distance (6MWD) in people following curative intent treatment for non-small cell lung cancer (NSCLC). Twenty participants (67 +/- 10 years; 14 females), 6-10 weeks following lobectomy, underwent a CPET and two 6MWTs. Peak exercise responses, dyspnoea and leg fatigue, as well as heart rate (HR) and oxygen saturation (SpO2) during the 6MWT, were compared to those during the CPET. Compared with exercise capacity when expressed as peak rate of oxygen consumption (%pred) measured during the CPET, exercise capacity when expressed as 6MWD (%pred) was less impaired (81 +/- 10 vs. 63 +/- 15 %pred; p < 0.001). Compared with the CPET, the 6MWT elicited lower peak HR (119 +/- 15 vs. 128 +/- 18 beats minute(-1); p = 0.02), lower SpO2 (93 +/- 2 vs. 95 +/- 3%; p < 0.05), less dyspnoea (3.1 +/- 1.6 vs. 6.9 +/- 2.6; p < 0.01) and less leg fatigue (2.0 +/- 1.9 vs. 6.8 +/- 2.4; p < 0.01). The 6MWD increased 19 +/- 19 metre (4 +/- 4%) with test repetition (p < 0.001). In people following curative intent treatment for NSCLC, the 6MWT appears to elicit sub-maximal exercise responses when compared with the CPET. There is a significant effect of test repetition on 6MWD.


Should 30 letters be added to the 4m visual acuity score on the Early Treatment Diabetic Retinopathy Study Chart?
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DOI:http://dx.doi.org/10.1111/ceo.12714


Comparison of clinical cut-points and treatment targets for urine NTX and plasma betaCTX-I in osteoporosis.
Chubb SA, Mandelt C, et al.
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OBJECTIVE: We undertook to identify levels for plasma beta isomerised carboxy-terminal telopeptides of type I collagen (p-betaCTX-I) that are comparable to currently used urine amino-terminal telopeptides of type I collagen (u-NTX) cut-points and treatment targets in osteoporosis.

DESIGN AND METHODS: Fasting morning samples were collected from patients attending tertiary hospitals and clinics for investigation of metabolic bone disease. Patients with Paget’s disease or <20 years of age were excluded. Second void spot urine for NTX and plasma (EDTA) samples were utilised. Urine was analysed routinely and plasma stored at -20°C until analysis by enzyme-linked immunosorbent assay (ELISA) (Immunodiagnostic Systems plc), E170 (Roche Diagnostics) and IDS-iSYS (Immunodiagnostic Systems plc) methods. The relationship of u-NTX with each p-betaCTX-I method’s results was assessed by Passing and Bablok regression, and p-betaCTX-I levels equivalent to u-NTX cut-points and targets were interpolated.

RESULTS: One hundred and forty six patients were included. Spearman correlation coefficients ranged from 0.71 to 0.75 for the three betaCTX-I assays. The equivalent betaCTX-I concentrations for NTX/Cr values of 21 (fracture risk reduction target following risedronate therapy), 27 (healthy pre-menopausal women’s mean value), and 38 (threshold for reduction of BMD on calcium alone) nmol BCE/mmol were 230, 312 and 462 ng/L for the automated Roche assay and 271, 395 and 624 ng/L for the automated IDS i-SYS assay respectively.

CONCLUSIONS: The p-betaCTX-I equivalent to the only available fracture outcome based absolute treatment threshold of 21 nmol BCE/mmol established for u-NTX, is close to 250 ng/L but will vary between p-betaCTX-I assays.

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The Efficacy of Earplugs as a Sleep Hygiene Strategy for Reducing Delirium in the ICU: A Systematic Review and Meta-Analysis.

Litton E, Carnegie V, et al.

OBJECTIVE: A systematic review and meta-analysis to assess the efficacy of earplugs as an ICU strategy for reducing delirium.

DATA SOURCES: MEDLINE, EMBASE, and the Cochrane Central Register of controlled trials were searched using the terms “intensive care,” “critical care,” “earplugs,” “sleep,” “sleep disorders,” and “delirium.”

STUDY SELECTION: Intervention studies (randomized or nonrandomized) assessing the efficacy of earplugs as a sleep hygiene strategy in patients admitted to a critical care environment were included. Studies were excluded if they included only healthy volunteers, did not report any outcomes of interest, did not contain an intervention group of interest, were crossover studies, or were only published in abstract form.

DATA EXTRACTION: Nine studies published between 2009 and 2015, including 1,455 participants, fulfilled the eligibility criteria and were included in the systematic review. Studies included earplugs as an isolated intervention (n = 3), or as part of a bundle with eye shades (n = 2), or earplugs, eye shades, and additional sleep noise abatement strategies (n = 4). The risk of bias was high for all studies.

DATA SYNTHESIS: Five studies comprising 832 participants reported incident delirium. Earplug placement was
associated with a relative risk of delirium of 0.59 (95% CI, 0.44-0.78) and no significant heterogeneity between the studies (I², 39%; p = 0.16). Hospital mortality was reported in four studies (n = 481) and was associated with a relative risk of 0.77 (95% CI, 0.54-1.11; I², 0%; p < 0.001). Compliance with the placement of earplugs was reported in six studies (n = 681). The mean per-patient noncompliance was 13.1% (95% CI, 7.8-25.4) of those assigned to receive earplugs.

CONCLUSIONS: Placement of earplugs in patients admitted to the ICU, either in isolation or as part of a bundle of sleep hygiene improvement, is associated with a significant reduction in risk of delirium. The potential effect of cointerventions and the optimal strategy for improving sleep hygiene and associated effect on patient-centered outcomes remains uncertain.

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Long-term (three-year) safety and effectiveness from the global SYMPLICITY registry of renal denervation in a real-world patient population with uncontrolled hypertension.

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Aims: The Global SYMPLICITY Registry is a prospective, international, open-label, multicentre registry designed to assess the safety and effectiveness of the SymplicityTM catheter-based renal denervation system in patients with uncontrolled hypertension. Methods and results: The Global SYMPLICITY Registry is enrolling up to 3,000 subjects from 245 centers in 37 countries. In the first 2,037 patients enrolled, mean age was 61+/−12 years, 59% were men and mean body mass index was 31+/−6 kg/m². Over a third of subjects had at least 1 comorbidity, including type 2 diabetes mellitus (38%), chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m², 22%), and history of cardiac disease (48%). Baseline office and 24-hour blood pressures were 165/89+/−25/16 mm Hg and 154/86+/−24.8/14 mm Hg, respectively. After 1 and 2 years, the change in office systolic blood pressure was -13.5+/−24.8 and -14.8+/−25.4 mm Hg (n=447, p<0.001 for both), and -8.1+/−18.2 (n=195) and -8.0+/−17.8 mm Hg (n=171, p<0.001 for both), for 24-hour systolic blood pressure. At 2 years, the incidence of cardiovascular death was 1.2%, hospitalisation for hypertensive crisis 3.8%, new renal artery stenosis (>70% stenosis) 0%, and new onset end stage renal disease 1.4%. Mean eGFR decreased from 76.3+/−24.0 ml/min/1.73m² at baseline to 70.7+/−25.4 ml/min/1.73m² at 2 years, n=244, p<0.01. However, eGFR did not change significantly in the subgroup with chronic kidney disease (45.1+/−13.8 at baseline to 43.0+/−17.7 ml/min/1.73m² n=60, p=0.15). At the time of PCR 2016, 2-year outcomes will be available for presentation in over 2,000 subjects and 3-year outcomes in over 400 subjects.

Conclusions: The Global SYMPLICITY Registry is the first large trial of renal denervation in a real-world population. After 2 years of follow-up in over 400 patients, renal denervation resulted in significant blood pressure reduction. The decline in eGFR remained within the expected range, and declined to a lesser extent than expected in patients with chronic kidney disease. There were no long-term safety concerns following the denervation procedure. Three-year follow-up will be available for presentation at PCR.

PMID:611934987

The CRUSADE score is useful in stratifying risk of major bleeding and death following STEMI PCI.

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The CRUSADE score is useful in stratifying risk of major bleeding and death following STEMI PCI.
Aims: To determine if the CRUSADE bleeding risk score, developed for NSTEMI, is discriminating for bleeding and mortality risk in patients with STEMI undergoing PCI. Methods and results: All patients with PCI-treated STEMI admitted to Western Australian public hospitals between 2000 and 2005 were identified from the hospital admissions database of the Western Australian Data Linkage System. STEMI was identified from the International Classification of Diseases 10th edition (ICD-10) code in the principal diagnosis field. The sample represented 98.6% of STEMI PCI cases in Western Australia. Hospital admissions and mortality data (from the Western Australian Data Linkage System) were linked with procedural and transfusion databases obtained electronically from the hospitals. Major bleeding was defined as admissions for GI bleeds, intracranial haemorrhage, or other major bleeds not elsewhere classified, within 30 days and 1 year from PCI, or a haemoglobin drop >2 AND transfusion of >1 unit of packed red cells within 7 days of PCI. The calculated CRUSADE score has a range of 1 to 100 and was stratified into its 5 risk categories (<20, 21-30, 31-40, 41-50, >50). Associations with major bleeding and mortality at 30 days and 1 year were assessed using the Cochran-Armitage trend test and logistic regression (unadjusted and age-adjusted models). The c-statistic from the logistic regression models was used to assess the model discrimination (values >0.7 indicate reasonable discrimination; >0.8 indicate strong model discrimination). We identified 2,308 patients with mean age 60 years (range 24-91) and 76.4% were male. Mortality at 30 days and 1 year was 3.6% (n=83) and 5.9% (n=136), respectively. The major bleeding rates at 30 days and 1 year were 4.3% (n=99) and 5.4% (n=124), respectively. There was a significant increasing trend across CRUSADE risk strata for all outcomes (p<0.0001) which persisted after adjusting for age. The age-adjusted odds ratio for 30-day death increased rapidly with CRUSADE risk stratum, from 1.0 (very low risk stratum: score <20) to 6 (95% CI: 2-22) for low risk stratum, 17 (95% CI: 5-59) for moderate risk stratum, 51 (95% CI: 14-177) for high risk stratum, and 118 (95% CI: 33-420) for the very high risk stratum. For 1-year death, the odds ratio increased to 40 (95% CI: 18-90) for the very high risk stratum. Corresponding odds ratios for 30-day major bleeding were 1.0 (very low risk), 3 (95% CI: 1-6) for the low risk stratum, 5 (95% CI: 2-11) for moderate risk, 8 (95% CI: 4-19) for high risk, and 9 (95% CI: 4-24) for the very high risk stratum. For 1-year major bleeding, the odds ratio increased to 7 (95% CI: 3-15) for the very high risk stratum. The c-statistic was 0.84 for the age-adjusted logistic regression model for outcome of 30-day death and 0.75 for 30-day major bleeding (the CRUSADE study had a c-statistic of 0.7 for major bleeding). Conclusions: The CRUSADE score has strong associations with 30-day and 1-year death and bleeding in STEMI PCI, and can be used for stratifying both bleeding and mortality risks in these patients.

PMID:611934769


A step-by-step technique to determine an overlap-free projection for quality improvement and standardisation of contrast aortography.

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Aims: We developed a method to determine an overlap-free projection which enables standardisation of contrast aortography and improves quantification of aortic regurgitation, particularly paravalvular regurgitation in TAVI.

Methods and results: In patients referred for consideration for TAVI, a total of 75 computed tomography angiogram (CTA) scans and 19 prospectively collected aortograms were analysed. Using volume-rendered three-dimensional (3D) reconstruction, the overlap-free projection (OFP), defined as the C-arm angulation with no overlap of the descending aorta on the aortic root or left ventricle, was determined in both right anterior oblique (RAO) and left anterior oblique (LAO) orientation and a rule developed to predict the lowest angulation. In the prospectively collected aortograms there were no cases of overlap when the OFP rule was correctly applied. Conclusions: The OFP rule is an easy to use method for reliable determination of a patient-specific projection for standardised contrast...

**Medium-term outcomes in patients post VA-ECMO.**
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**Purpose:** Venous-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) has been shown to improve short-term outcomes in patients with refractory cardiogenic shock (RCS). However the medium-term outcomes are unclear. We aim to examine the course of those patients surviving their initial admission requiring VA-ECMO.  

**Methods:** This study was a retrospective, single-centre review of patients who received VA-ECMO for RCS. Baseline patient characteristics, aetiology of RCS, survival as well as cardiovascular and neurological outcomes both at hospital discharge and at 1 year were collected by review of medical records.  

**Results:** From 2008 to 2014, 34 patients received VA-ECMO for RCS. Mean age was 43 years (+ 19), 65% were male and total time on VA-ECMO was 6 days (+ 4.3). The aetiology of RCS was acute myocarditis in 9 (25%), post-cardiac surgery in 6 (18%), post heart/lung transplant in 5 (15%), acute myocardial infarction in 4 (12%), decompensated cardiomyopathy in 4 (12%), right heart failure in 3 (9%) and other in 3 (9%). 18 (53%) patients survived to hospital discharge, of whom 14 (41%) made a full neurological recovery. 8 (24%) patients were medically managed without advanced therapy, 6 (18%) required heart transplantation, 3 (9%) required left ventricular assist devices (LVAD) and 1 patient (3%) was listed for heart transplantation. At 1 year, 14 patients (44%) were still alive. 5 (16%) patients were medically managed. 6 (19%) patients had required heart transplantation. 2 (6%) patients required LVAD support and 1 (3%) was listed for transplant. During this time, 1 patient was newly listed for transplant, 1 patient had progressed from medical therapy to LVAD and 1 patient progressed from LVAD to transplant.  

**Conclusion:** Patients receiving VA-ECMO for RCS who survive to discharge have a favourable medium-term prognosis however a significant proportion will require LVAD support or transplantation. A minority of patients survive to 1 year without advanced therapy highlighting the need for all ECMO survivors to have close follow-up by a heart failure/transplant unit. (Figure Presented).

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DOI:http://dx.doi.org/10.1002/ejhf.539  


**Does restarting novel oral anticoagulants increase the clinical risk of delayed bleeding after endoscopic resection of colorectal polyps?**
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**Background and Aim:** Consumption of novel oral anticoagulants (NOACs) such as dabigatran and rivaroxaban is rising worldwide as an alternative to the vitamin K antagonist warfarin for thromboembolic prevention in patients with non-valvular atrial fibrillation. However, current medical society guidelines on management of antithrombotic agents for endoscopic procedure do not determine when to restart NOACs after endoscopic resection of colorectal polyps and little to no data on delayed bleeding risk of NOACs has been publicly available. The aim of this study was to evaluate the clinical risk of post-endoscopic resection bleeding from NOACs.  

**Method:** Delayed bleeding occurred in 67 cases (2.7%) of 2,485 cases with polyps larger than 5 mm removed by hot biopsy, polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection between 2011 and 2015. 201 ageand gender-matched controls were selected from non-bleeding cases in this casecontrol study. Risk factors for bleeding were assessed among patient factors (NOACs, which include dabigatran, rivaroxaban, apixaban and edoxaban, heparin,
thienopyridines, aspirin, hypertension, diabetes mellitus) and polyp factors (size, morphology, location, resection technique) by multivariate logistic regression analysis. Cessation period of antithrombotic agents before and after endoscopic resection was within 3 days. We also studied the length of hospital stay during endoscopic resection in cases using NOACs and heparin bridging therapy. Results: Of the 67 bleeding cases, 76% were males and the mean age was 65.0 +/- 10.6 y (mean +/- SD). Multivariate analysis indicated that restarting NOACs (OR 1.5; 95% CI 0.4-5.2; p=0.56) was not found to be a significant risk factor for delayed bleeding compared with the control group. In contrast, heparin was restarted within 3 days following endoscopic resection in 21% of bleeding cases compared with 6% of the control group (OR 4.4; 95% CI 1.9-10.5; p=0.0007). Thienopyridines (OR 2.1; 95% CI 0.6-8.1; p=0.26), aspirin (OR 2.5; 95% CI 0.9-7.0; p=0.08), aspirin with thienopyridines (OR 0.7; 95% CI 0.03-19.7; p=0.84), polyp morphology (OR 1.6; 95% CI 0.8-3.0; p=0.15) and polyp size (OR 1.3; 95% CI 0.6-2.5; p=0.50) also did not increase the risk of delayed bleeding. There were no thromboembolic events in either the case or control group. In addition, the length of hospital stay was significantly shorter in cases using NOACs (median 3 days, range 2-3 days) than in those using heparin bridging therapy (11 days, 4-20 days; p=0.0001 by Mann-Whitney U test). Conclusions: Restarting NOACs after endoscopic resection did not increase the risk of delayed bleeding. NOACs present a low risk for delayed bleeding and reduce the length of hospital stay compared with heparin bridging therapy; hence NOACs may be safe and useful for perendoscopic management of patients requiring anticoagulants.

PMID:72292716


Biomonitor 2 pilot study: First-in-human experience with the implantation of the biotronik biomonitor 2 implantable cardiac monitor.

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B. Ng

Introduction: The BioMonitor 2 Pilot Study was a first-in-human study assessing the efficacy and safety of the insertion procedure, and the sensing amplitude and quality of the second generation implantable cardiac monitor, the BioMonitor 2 (Biotronik, Berlin, Germany). Methods: This was a prospective, multi-center, single-arm, non-randomized study involving 5 operators in 5 sites across Australia. Data was collected at insertion and during clinic visits at 1 week and 1 month post-insertion. We evaluated R-wave amplitudes, noise burden and operators’ assessments of the insertion tool set handling. Noise burden was defined as the percentage of time in which detection of high rates render the device effectively unable to monitor the patient’s rhythm. Results: Thirty-one patients with indications for long-term cardiac monitoring were enrolled from December 18, 2014 to July 6, 2015. One enrolled patient dropped out before insertion due to a pacemaker indication and was excluded from the analysis. Patients had a mean age of 63 +/- 14 years and 73% were male. The indication for the device included syncope in 13 (42%), atrial arrhythmia in 13 (42%), palpitations in 3 (10%) and cryptogenic stroke in 1 (3%). All BioMonitor 2 insertions were successfully performed without intraoperative complications. The median time from skin cut to final positioning was 2.5 minutes (interquartile range [IQR] 1 - 4), and from skin cut to last suture was 9 minutes (IQR 5-14). The tunneling tool was assessed as “acceptable” or “good” by the operator in 97% of the cases, and in 100% of the cases for the insertion tool. The median incision needed to insert the device was 15 mm long (IQR 15 -16). The median R-wave amplitude at insertion was 0.7 mV (IQR 0.6 -1.1). R-wave amplitudes were unchanged at one week (0.6 mV; IQR 0.5 -1.0) and at one month (0.7 mV; IQR 0.5 -1.0). The mean noise burden was 1.3 +/- 2.3 % (median 0.0, IQR 0.0 - 2.0 %) at one week and 2.3 +/- 3.1 % (median 1.0, IQR 0.0 - 3.0 %) at one month. Conclusions: The results of the BioMonitor 2 Pilot Study confirm the utility of the insertion tools and technique and the excellent sensing amplitudes afforded by this new device.

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Impact of acute atrial fibrillation termination and prolongation of AF cycle length on the outcome of ablation
of persistent AF: A sub-study of the star AF II trial.


S. Kochhauser

Introduction: There is controversy about the impact of acute atrial fibrillation (AF) termination and prolongation of AF cycle length (AFCL) acutely during ablation on the long-term procedural outcome. We analyzed the influence of AF termination and AFCL-prolongation on freedom from AF in patients from the STAR-AF II trial. Methods: STAR-AF II was a large, multicenter trial randomizing 589 patients with persistent AF to different ablation strategies. Acute changes in AFCL and AF termination were collected during the index procedure and both were compared to recurrence of AF at 18 months. Recurrence was defined as AF > 30 seconds based on ECG, Holters (3,6,9,12,18 months), and weekly transtelephonic monitor ECGs for 18 months. The impact of AF termination was also compared to other predictors of procedural outcome by Cox regression analysis. Results: AF terminated in 8% of the pulmonary vein isolation (PVI) arm, 45% in the PVI+complex electrogram arm, and 22% of the PVI+linear ablation arm (p<0.001) but the 18 month freedom from AF did not differ between the 3 groups (p=0.15). Freedom from AF at 18 months was significantly higher in patients who presented to the lab in sinus rhythm compared to those who presented in AF but did not terminate during ablation (63% vs. 44%; p=0.007). Those who presented in AF but terminated during ablation had an intermediate outcome (53% AF freedom at 18 months) but this was not significantly different from either those in sinus (p=0.84) or those who did not terminate (p=0.08). AF termination was a univariate predictor of success at 18 months (p=0.007) but by multivariable analysis, performing PVI predominantly during sinus rhythm was the strongest predictor (HR 1.80, p<0.001). Prolongation of the AFCL was not predictive of 18 month freedom from AF. Conclusions: Acute AF termination and prolongation in AFCL did not predict 18 month freedom from AF. Performing PVI predominantly during sinus rhythm was the strongest predictor and could explain better outcome in patients with early AF termination during ablation.


Knowledge and Awareness of Familial Hypercholesterolaemia among Registered Medical Practitioners in Tamil Nadu: Are They Suboptimal?
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INTRODUCTION: Familial Hypercholesterolaemia (FH) is the most common monogenic disorder causing premature Coronary Artery Disease (CAD). However, the majority of people with FH are undiagnosed and under treated.
AIM: To determine awareness, knowledge and practices of registered medical practitioners regarding FH in India.
MATERIALS AND METHODS: Physicians from a southern state of India (Tamil Nadu) who see the general cases were requested to complete a structured online survey questionnaire based on the outcomes on screening, diagnostic and service aspects of FH.
RESULTS: A total of 133 physicians were surveyed, 27.9% perceived themselves to have above average familiarity with FH and 71.4% correctly described FH. 41.4% of physicians were unaware and unsure whether they had FH patients under their care. The awareness of specific aspects of FH were as follows: heritability 35.3%, prevalence 31.6%, typical lipid profile 34.6%, CVD relating to FH13.5%, genetic testing 33.1%, cascade screening 41.4%, preventive,
management and referral services for FH 12.8%, 49.6% of them thought that the age for screening young people for FH should be 13 to 18 years. 84.2% selected GP’s as the most effective health care provider for the early detection and care of FH as being useful. 69.2% selected interpretive commenting on lipid profile to highlight patients at risk of FH. 91.7% and 19.5% of physicians identified statins as monotherapy and statin with ezetimibe as combination therapy for FH, respectively.

CONCLUSION: The study identified substantial deficit in the awareness and knowledge of FH among primary care physicians in Tamil Nadu. Extensive and continuous medical education programs are required to close the gap in coronary prevention.

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Extended Posterior Auricular Artery Flap for Temporo-Parietal Scalp Defect in Previously Irradiated Scalp.
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BACKGROUND: Temperoparietal scalp defects are fairly common resulting from varied array of etiology. Various reconstructive options exist, but the aim was to achieve a reliable and simple solution keeping in mind the principle of replacing “like with like.”

METHODS: The authors present a 83-year-old lady who had a fall at her home and was lying unconscious for quite some time on her right side of her temple, leading to full thickness necrosis of overlying scalp. She had received surgery and prior radiotherapy for her basal cell carcinoma of the scalp at the same site of her present injury. She was treated with single stage debridement and reconstruction using extended posterior auricular artery flap. She had no issues with wound healing.

DISCUSSION: Extended posterior auricular artery flap for temporo-parietal scalp defects is a reliable local option as it has the several advantages over the traditional scalp flaps. It preserves the direction of hair follicles, no long scalping incisions, no unsightly dog ears, no need for donor area grafts. In this scenario, the robustness of this flap was truly tested as it was raised from a previously irradiated site and did not have any issues of necrosis. To the best of our knowledge, this is the first report confirming the safety of this reliable local option postirradiation.

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Gastrointestinal: Severe de novo stricture formation following biodegradable esophageal stent.
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Prevalence and incidence of frailty in Aboriginal Australians, and associations with mortality and disability.
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OBJECTIVES: Frailty represents a loss of homeostasis, markedly increasing the risk of death and disability. Frailty has been measured in several ethnic groups, but not, to our knowledge, in Aboriginal Australians. We aimed to determine the prevalence and incidence of frailty, and associations with mortality and disability, in remote-living Aboriginal people.

STUDY DESIGN: Between 2004 and 2006, we recruited 363 Aboriginal people aged > 45 years from 6 remote communities and one town in the Kimberley region of Western Australia (wave 1). Between 2011 and 2013, 182 surviving participants were followed-up (wave 2). We assessed frailty with an index, comprising 20 health-related items. Participants with > 4 deficits (frailty index > 0.2) were considered frail. Disability was assessed by family/carer report. Those unable to do > 2 of 6 key or instrumental activities of daily living were considered disabled. We investigated associations between frailty, and disability and mortality, with logistic regression and Cox proportional hazards models.

RESULTS: At wave 1 (W1), 188 participants (65.3%) were frail, and of robust people at W1 who participated in wave 2, 38 (51.4%) had become frail. Frailty emerged at a younger age than expected. A total of 109 people died (30.0%), of whom 80 (73.4%) were frail at W1. Frailty at W1 was not associated with becoming disabled, but was associated with mortality (HR = 1.9; 95% CI 1.2, 3.0).

CONCLUSIONS: Frailty in remote-living Aboriginal Australians is highly prevalent; substantially higher than in other populations. Research to understand the underlying causes of frailty in this population, and if possible, reverse frailty, is urgently needed.

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**Palliative care: Physical and spiritual wellbeing at the end of life.**

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Palliative care can improve quality of life and potentially prolong survival through early management of physical symptoms and psychospiritual distress. It should be considered for any patient with a life-limiting illness, well before they require terminal care, and can be offered alongside active treatment. Every healthcare provider should have the skills to offer general palliative care, with referral to specialist palliative care services in more challenging situations.

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The ability of early warning scores (EWS) to detect critical illness in the prehospital setting: A systematic review.

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AIM: To examine whether early warning scores (EWS) can accurately predict critical illness in the prehospital setting and affect patient outcomes.

METHODS: We searched bibliographic databases for comparative studies that examined prehospital EWS for patients transported by ambulance in the prehospital setting. The ability of the different EWS, including pre-alert protocols and physiological-based EWS, to predict critical illness (sensitivity, odds ratio [OR], area under receiver operating characteristic [AUROC] curves) and hospital mortality was summarised. Study quality was assessed using the Newcastle-Ottawa Scale.

RESULTS: Eight studies were identified. Two studies compared the use of EWS to standard practice using clinical judgement alone to identify critical illness: the pooled diagnostic OR and summary AUROC for EWS were 10.9 (95%CI 4.2-27.9) and 0.78 (95%CI 0.74-0.82), respectively. A study of 144,913 patients reported age and physiological variables predictive of critical illness: AUROC in the independent validation sample was 0.77, 95% CI 0.76-0.78. The high-risk patients stratified by the national early warning score (NEWS) were significantly associated with a higher risk of both mortality and intensive care admission. Data on comparing between different EWS were limited; the Prehospital Early Sepsis Detection (PRESEP) score predicted occurrence of sepsis better than the Modified EWS (AUROC 0.93 versus 0.77, respectively).

CONCLUSION: EWS in the prehospital setting appeared useful in predicting clinically important outcomes, but the significant heterogeneity between different EWS suggests that these positive promising findings may not be generalisable. Adequately powered prospective studies are needed to identify the EWS best suited to the prehospital setting.

Mutations causative of familial hypercholesterolaemia: screening of 98,098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217.

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AIMS: Ideally, familial hypercholesterolaemia (FH) is diagnosed by testing for mutations that decrease the catabolism of low-density lipoprotein (LDL) cholesterol; however, genetic testing is not universally available. The aim of the present study was to assess the frequency and predictors of FH causing mutations in 98 098 participants from the general population, the Copenhagen General Population Study.

METHODS AND RESULTS: We genotyped for LDLR[W23X;W66G;W556S] and APOB[R3500Q] accounting for 38.7% of pathogenic FH mutations in Copenhagen. Clinical FH assessment excluded mutation information. The prevalence of the four FH mutations was 0.18% (1:565), suggesting a total prevalence of FH mutations of 0.46% (1:217). Using the Dutch Lipid Clinic Network (DLCN) criteria, odds ratios for an FH mutation were 439 (95% CI: 170-1 138) for definite FH, 90 (53-152) for probable FH, and 18 (13-25) for possible FH vs. unlikely FH. Using the Simon Broome criteria, the odds ratio was 27 (20-36) for possible vs. unlikely FH, and using the Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, 40 (28-58) for probable vs. unlikely FH. Odds ratios for an FH mutation were 17 (9-31) for LDL-cholesterol of 4-4.9 mmol/L, 69 (37-126) for LDL-cholesterol of 5-5.9 mmol/L, 132 (66-263) for LDL-cholesterol of 6-6.9 mmol/L, 264 (109-637) for LDL-cholesterol of 7-7.9 mmol/L, and 320 (129-798) for LDL-cholesterol above 7.9 mmol/L vs. LDL-cholesterol below 4 mmol/L. The most optimal threshold for LDL-cholesterol concentration to discriminate between mutation carriers and non-carriers was 4.4 mmol/L.

CONCLUSION: Familial hypercholesterolaemia-causing mutations are estimated to occur in 1:217 in the general population and are best identified by a definite or probable phenotypic diagnosis of FH based on the DLCN criteria or an LDL-cholesterol above 4.4 mmol/L.
BACKGROUND: Depression has been associated with impaired nitric oxide (NO)-mediated vasodilation and vascular dysregulation (VD). Whether depression and NO levels will disturb retinal haemodynamics is not clear.

OBJECTIVES AND METHODS: Associations between the retinal vasculature, diastolic ocular perfusion pressure (DOPP) as measure of hypoperfusion, NO metabolites (NOx) and depression symptoms were assessed. Chronic VD risk markers [depression symptoms (Patient Health Questionnaire/PHQ-9 > 10) and 24 h pulse pressure] were determined in a bi-ethnic cohort (n = 313; 48.6 +/- 9 years; 53.9% men). At 3 year follow-up, retinal vessel calibre and retinopathy signs were quantified from digital images. Salivary NOx was obtained pre- and post-flicker light-induced provocation (FLIP). DOPP was defined as diastolic blood pressure minus intraocular pressure.

RESULTS: Chronic VD risk was evident in Blacks opposed to acute risk in Whites (P < 0.05). At follow-up, retinopathy (Blacks 60.4%/Whites 39.6%), lower pre-FLIP (μM) and higher post-FLIP NOx (changes from baseline, %), arteriolar narrowing and wider venular calibre values were evident in Blacks compared to Whites, independent of confounders. A wider venular calibre, an index of stroke risk, was associated with chronic depression symptoms [cut point 248 MU: Area under the curve 0.61 (95% CI: 0.51, 0.72); 71% sensitivity; 55% specificity] as well as with hypoperfusion in the Blacks. In this group, arteriolar narrowing was associated with hypoperfusion; and attenuated arteriolar dilation with increased post-FLIP NOx responses.

CONCLUSIONS: Chronic depression symptoms may alter NO regulation and facilitate VD. NO-mediated vasoconstriction presumably impeded perfusion, retinal haemodynamics and -remodelling; potentiating stroke risk in Blacks.

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Kitesurfing - playing with water or with fire?
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Spontaneous cutaneous extrusion of a parotid gland sialolith.
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Parotid gland sialolithiasis is an uncommon condition that can cause pain and recurrent infection in affected patients. Migration of a stone through a fistula is a rare but possible complication of untreated sialolithiasis. We present a case of parotid gland sialolithiasis in a 63-year-old woman with recurrent episodes of parotitis and facial pain, which resolved through spontaneous extrusion of the stone (11 mm) through a cutaneous fistula while awaiting surgery. Management is typically conservative or surgical, depending on the location and size of the stone, and the clinical presentation.

Aberrant Inflammasome Activation Characterizes Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome.

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Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) complicates combination antiretroviral therapy (cART) in up to 25% of patients with HIV/TB coinfection. Monocytes and IL-18, a signature cytokine of inflammasome activation, are implicated in TB-IRIS pathogenesis. In this study, we investigated inflammasome activation both pre- and post-cART in TB-IRIS patients. HIV/TB patients exhibited higher proportions of monocytes expressing activated caspase-1 (casp1) pre-cART, compared with HIV patients without TB, and patients who developed TB-IRIS exhibited the greatest increase in casp1 expression. CD64(+) monocytes were a marker of increased casp1 expression. Furthermore, IL-1beta, another marker of inflammasome activation, was also elevated during TB-IRIS. TB-IRIS patients also exhibited greater upregulation of NLRP3 and AIM2 inflammasome mRNA, compared with controls. Analysis of plasma mitochondrial DNA levels showed that TB-IRIS patients experienced greater cell death, especially pre-cART. Plasma NO levels were lower both pre- and post-cART in TB-IRIS patients,
providing evidence of inadequate inflammasome regulation. Plasma IL-18 levels pre-cART correlated inversely with NO levels but positively with monocyte casp1 expression and mitochondrial DNA levels, and expression of IL-18Ralpha on CD4(+) T cells and NK cells was higher in TB-IRIS patients, providing evidence that IL-18 is a marker of inflammasome activation. We propose that inflammasome activation in monocytes/macrophages of HIV/TB patients increases with ineffective T cell-dependent activation of monocytes/macrophages, priming them for an excessive inflammatory response after cART is commenced, which is greatest in patients with TB-IRIS.

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SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer.

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PURPOSE: SIRFLOX was a randomized, multicenter trial designed to assess the efficacy and safety of adding selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy in patients with previously untreated metastatic colorectal cancer.

PATIENTS AND METHODS: Chemotherapy-naive patients with liver metastases plus or minus limited extrahepatic metastases were randomly assigned to receive either modified FOLFOX (mFOLFOX6; control) or mFOLFOX6 plus SIRT (SIRT) plus or minus bevacizumab. The primary end point was progression-free survival (PFS) at any site as assessed by independent centralized radiology review blinded to study arm.

RESULTS: Between October 2006 and April 2013, 530 patients were randomly assigned to treatment (control, 263; SIRT, 267). Median PFS at any site was 10.2 v 10.7 months in control versus SIRT (hazard ratio, 0.93; 95% CI, 0.77 to 1.12; P = .43). Median PFS in the liver by competing risk analysis was 12.6 v 20.5 months in control versus SIRT (hazard ratio, 0.69; 95% CI, 0.55 to 0.90; P = .002). Objective response rates (ORRs) at any site were similar (68.1% v 76.4% in control v SIRT; P = .113). ORR in the liver was improved with the addition of SIRT (68.8% v 78.7% in control v SIRT; P = .042). Grade > 3 adverse events, including recognized SIRT-related effects, were reported in 73.4% and 85.4% of patients in control versus SIRT.

CONCLUSION: The addition of SIRT to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver-only metastatic colorectal cancer did not improve PFS at any site but significantly delayed disease progression in the liver. The safety profile was as expected and was consistent with previous studies.

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Chronic Cystoisospora belli infection in an immunocompetent Myanmar refugee - microscopy is not sensitive enough.


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BACKGROUND: Cystoisosporiasis is an opportunistic infection seen more commonly in patients with acquired immunodeficiency syndrome. Although uncommon, Cystoisospora infection can occur in immunocompetent individuals but tend to be benign and self-limiting. Chronic infection however, has been described but diagnosis can often be challenging and requires a high clinical index of suspicion.

CASE PRESENTATION: We present a case of delayed diagnosis of Cystoisospora belli (C. belli) in an immunocompetent 28-year-old refugee from Myanmar. She had a history of chronic diarrhea where exhaustive investigations over many years failed to reveal a diagnosis. Cystoisospora belli cysts were finally detected in stool 4 years after investigation commenced, and PCR testing on stored colon biopsies amplified a molecular product with 99% sequence homology to C. belli. The patient improved promptly with trimethoprim-sulfamethoxazole treatment.

CONCLUSION: In the appropriate clinical context we suggest molecular testing for C. belli or an empirical therapeutic trial.

Transcriptome analysis of human ageing in male skin shows mid-life period of variability and central role of NF-kappaB.

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Age is well-known to be a significant factor in both disease pathology and response to treatment, yet the molecular changes that occur with age in humans remain ill-defined. Here, using transcriptome profiling of healthy human male skin, we demonstrate that there is a period of significantly elevated, transcriptome-wide expression changes occurring predominantly in middle age. Both pre and post this period, the transcriptome appears to undergo much smaller, linear changes with increasing age. Functional analysis of the transient changes in middle age suggest a period of heightened metabolic activity and cellular damage associated with NF-kappa-B and TNF signaling pathways. Through meta-analysis we also show the presence of global, tissue independent linear transcriptome changes with age which appear to be regulated by NF-kappa-B. These results suggest that aging in human skin is associated with a critical mid-life period with widespread transcriptome changes, both preceded and proceeded by a relatively steady rate of linear change in the transcriptome. The data provides insight into molecular changes associated with normal aging and will help to better understand the increasingly important pathological changes associated with aging.

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**Novel APOB missense variants, A224T and V925L, in a black South African woman with marked hypcholesterolemia.**


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BACKGROUND: One genetic cause of markedly low plasma concentrations of apolipoprotein (apo) B and low density lipoprotein (LDL)-cholesterol is familial hypobetalipoproteinemia.

OBJECTIVE: We aimed to determine the molecular basis for the marked hypocholesterolemia consistent with heterozygous familial hypobetalipoproteinemia in a black female subject of Xhosa lineage.

METHODS: Coding regions of APOB, MTTP, PCSK9, ANGPTL3, SAR1B and APOC3 were sequenced, and APOE was genotyped. COS-7 cells were transfected with plasmids containing apoB variants. Western blotting was used to detect cellular and secreted apoB, and co-immunoprecipitation performed to assess binding with the microsomal triglyceride transfer protein (MTP).

RESULTS: Sequence analysis of the APOB gene revealed her to be heterozygous for two novel variants, c.751G>A (A224T) and c.2854G>C (V925L). She was also homozygous for the APOEepsilon2 allele, and did not carry a PCSK9 loss-of-function mutation. Although Ala(224) is within the postulated MTP binding region in apoB, it is not conserved among mammalian species. Subsequent genotyping showed that Ala224Thr is found in a southern African population (n=654) with an allele frequency of 1.15% and is not associated with plasma lipid levels. Val(925), like Ala(224), is within the N-terminal 1000 amino acids required for lipoprotein assembly, but was not found in the population screen. However, in vitro studies showed that apoB V925L did not affect apoB48 production or secretion nor have a deleterious effect on MTP interaction with apoB.

CONCLUSION: Taken together, this suggests that the hypocholesterolemia in our case may be a result of being homozygous for APOEepsilon2 with a low baseline cholesterol.

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Deprescribing in frail older people--Do doctors and pharmacists agree?


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BACKGROUND: Deprescribing may reduce harmful polypharmacy in older people and is an accepted clinical practice; however, data to guide deprescribing decisions are scarce.

OBJECTIVES: This study aimed to determine if physicians and pharmacists agree on medicines to deprescribe.

METHODS: Two physicians and two pharmacists independently applied a deprescribing decision-making aid to clinical and medicines data collected during a deprescribing trial of frail older people in four residential aged care facilities. The consensus list of medicines selected for deprescribing by the physicians was compared with the consensus list selected by the pharmacists. Lin's concordance correlation coefficient (CCC) was used to assess agreement in the number of medicines, and agreement on each specific medicine was assessed using the level 2 intra-cluster correlation (ICC) for medicine within patient.

RESULTS: Physicians and pharmacists had substantial agreement on the number of medicines to deprescribe (CCC = 0.70; 95% CI: 0.58, 0.82), with a difference of 1.8 +/- 2.0 total targeted medicines. For specific medicines, the agreement was moderate (ICC = 0.45, 95% CI: 0.32, 0.58). When considering only orally administered medicines,
physicians and pharmacists had substantial agreement (CCC = 0.73; 95% CI: 0.61, 0.84) in the number of medicines, but only moderate agreement for the specific medicines (ICC = 0.44, 95% CI: 0.30, 0.59).

CONCLUSIONS: Physicians and pharmacists had substantial agreement in the number of medicines they targeted to deprescribe and to continue, but physicians targeted a greater number of medicines for deprescribing than pharmacists. However, they had only moderate agreement in the specific medicines to deprescribe. This suggests that the deprescribing decision-making aid is a useful tool for health professionals to use when considering medicines to deprescribe.

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High-flow humidified nasal oxygenation vs. standard face mask oxygenation.
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Ten healthy volunteers received oxygen for 1 min, 2 min and 3 min at 10 l.min$^{-1}$ via a face mask, or humidified oxygen at 60 l.min$^{-1}$ via nasal prongs (Optiflow$^\text{TM}$T) with the mouth closed and with the mouth open. The mean (SD) end-tidal oxygen partial pressure after 3 min face mask and Optiflow oxygenation, with mouth closed and open, were: 88.5 (6.2) kPa; 85.6 (6.4) kPa and 48.7 (26.4) kPa, respectively, p = 0.001. The equivalent mean (SD) transcutaneous oxygen partial pressures were: 34.6 (5.4) kPa; 36.4 (6.5) kPa and 25.5 (15.7) kPa, respectively, p = 0.03. High-flow humidified nasal oxygenation for 3 min with the mouth closed was as effective as 3 min face mask oxygenation.

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The influence of introducing unrestricted access to sugammadex and quantitative neuromuscular monitors on the incidence of residual neuromuscular block at a tertiary teaching hospital. An audit of ‘real-life’.
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Balancing the risks and benefits of using emergency diagnostic radiocontrast studies to diagnose life-threatening illness in critically ill patients: a decision analysis.
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Diagnosis of many life-threatening illnesses, including acute pulmonary embolism, aortic dissection, and ischaemic bowel disease, requires confirmatory radiological imaging with radiocontrast. It is well established that radiocontrast can induce acute kidney injury, especially in patients with pre-existing renal impairment. The decision to proceed with a radiological study with radiocontrast to confirm or exclude a life-threatening, but potentially reversible, illness in patients with renal impairment is difficult. Theoretically, a radiocontrast study will be justifiable provided its benefits outweigh its harms. Using published prognostic data of contrast-induced nephropathy (CIN), this decision analysis aimed to assess whether a certain threshold of pre-test probability of a life-threatening illness is needed before a radiocontrast study can be justified for patients with different levels of renal impairment. In critically ill patients presenting with a life-threatening illness with hypotension requiring vasopressors or inotropes, the risk of CIN (defined by an increment in plasma creatinine of 40 micro mol/l) and the associated attributable mortality after using 50 to 100 ml of radiocontrast was about 30% and 4%, respectively, for patients with baseline plasma creatinine concentrations <400 micro mol/l. The risk of CIN and its associated attributable mortality increased substantially and exceeded 80% and 10%, respectively, if patients also had diabetes mellitus and their baseline plasma creatinine concentrations were >400 micro mol/l. In the latter high-risk patients, using a radiocontrast study to diagnose or exclude a life-threatening illness could only be justified if the life-threatening illness was readily treatable and the pre-test probability of having such disease was greater than 15%-20%.

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Association between functional iron deficiency and reactive thrombocytosis in hospitalised patients: a case-control study.
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The association of deficiency in total body iron with an increased risk of reactive thrombocytosis is well known, but whether ‘functional iron deficiency’ is also associated with reactive thrombocytosis is unknown. This retrospective case-control study assessed the relationships between functional iron deficiency, reactive thrombocytosis and risk of thromboembolism. A total of 150 patients with reactive thrombocytosis (platelet count >400 x 10<sup>9</sup>/l) and 343 controls (platelet count <400 x 10<sup>9</sup>/l) were selected from the hospital laboratory database system. Patients with haematological disease or recent chemotherapy were excluded. Reactive thrombocytosis, infection, and an elevated C-reactive protein (CRP) concentration were all significantly more common in patients with functional iron deficiency than in those without functional iron deficiency (all P <0.01). After adjusting for infection and CRP concentration, functional iron deficiency was the only marker of iron status significantly associated with reactive thrombocytosis (odds ratio 1.66, 95% confidence interval 1.10-2.75; P=0.048). Thromboembolic events occurred in 32 patients (6.6%). This was not significantly associated with functional iron deficiency. Our results suggest that in patients without haematological malignancy or recent chemotherapy there might be a link between functional iron deficiency and reactive thrombocytosis. Whether treating patients with functional iron deficiency with intravenous iron corrects reactive thrombocytosis without inducing infection remains uncertain, but merits further investigation.
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The effect of the native kinematics of the knee on the outcome following total knee arthroplasty.
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Aims: The aim of this study was to investigate differences in pain, range of movement function and satisfaction at three months and one year after total knee arthroplasty (TKA) in patients with an oblique pattern of kinematic graph of the knee and those with a varus pattern.

Patients and Methods: A total of 91 patients who underwent TKA were included in this retrospective study. Patients (59 women and 32 men with mean age of 68.7 years; 38.6 to 88.4) were grouped according to kinematic graphs which were generated during navigated TKA and the outcomes between the groups were compared.

Results: The graphs were varus in 50 patients (55%), oblique in 19 (21%), neutral in 17 (18.5%) and valgus in five (5.5%). After adjustment for pre-operative scores and gender, compared with patients with varus knee kinematics, patients with an oblique kinematic graph had a poorer outcome with lower Knee Society scores at three months (9.2 points, p = 0.038).

Conclusion: We found four distinct kinematic graphs in knees and that patients with an oblique graph have a poorer outcome in the short-term after TKA.


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The log TSH-free T4 relationship in a community-based cohort is nonlinear and is influenced by age, smoking and thyroid peroxidase antibody status.

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Background: The TSH-T4 relationship was thought to be inverse log-linear, but recent cross-sectional studies of selected populations report a complex, nonlinear relationship. The TSH-T4 relationship has not been evaluated in an unselected, community-based cohort, and there are limited data regarding clinical factors which affect it.

Objective: To analyse the TSH-free T4 relationship in a community-based cohort.

Design, Participants and Methods: In a cross-sectional, retrospective study, we analysed serum TSH and free T4 concentrations from 4427 participants (55% female) in the 1994 Busselton Health Study who were not taking thyroxine. Simple linear, segmented-linear and nonlinear regression models of log TSH on free T4 were compared for goodness of fit.

Results: All 5 log TSH-free T4 models tested (separate lines, segmented conterminal line, quartic, error function, double-sigmoid curve) fitted significantly better than a simple linear model (each P < 0.01 by Vuong test). Ranking by Akaike information criterion indicated that the segmented conterminal line and double-sigmoid models provided best fit, followed by the error function, quartic and separate lines models. From multiple regression analysis, age tertile, current smoking and TPOAb status each significantly influenced the TSH-free T4 relationship, whereas BMI category and diabetes did not. A sex difference in the TSH-free T4 relationship was apparent only in the lower part of the free T4 reference range.
CONCLUSION: In a community-based setting, the relationship between log TSH and free T4 is complex, nonlinear and influenced by age, smoking and TPOAb status.


Davis TM, Badshah I, et al.


Evaluation of the HeartWare ventricular assist device Lavare cycle in a particle image velocimetry model and in clinical practice.

OBJECTIVES: Ventricular blood stasis is a concern for continuous flow mechanical support devices and might contribute to the formation of thromboembolic events. The HeartWare Ventricular Assist System (HVAD) is equipped with the LavareTM cycle that is a periodic speed modulation feature designed to alter flow patterns within the left ventricle and reduce areas of potential blood stasis. Here, we report in vitro and clinical findings on the effects of the Lavare cycle.

METHODS: The effect of pump speed changes on the intraventricular flow field was examined with an in vitro particle image velocimetry model. The clinical impact of the Lavare cycle was evaluated through a retrospective review of the ReVOLVE study which includes 248 patients implanted with the HVAD following Conformite Europeenne Mark in nine centres in Europe and Australia. Baseline characteristics, adverse event profiles and Kaplan-Meier survival estimates were stratified by patients using/not using the Lavare cycle.

RESULTS: Particle image velocimetry showed increased ventricular washout with an active Lavare cycle as measured by the fluid velocities and angular dispersion parameters. With the Lavare cycle on, there was also a 22% decrease in the stagnation index compared with when the Lavare cycle was off. In the ReVOLVE registry, patients with the Lavare cycle turned on (n = 215) were supported for 497 patient-years, whereas patients who did not use the speed modulation (n = 33) were supported for 39.3 patient-years. The Lavare cycle did not significantly affect patient survival as both groups had approximately an 80% survival after 1 year. Patients using the Lavare cycle had significantly fewer rates of stroke [0.06 vs 0.20 events per patient-year (EPPY), P = 0.0008], sepsis (0.03 vs 0.15 EPPY, P = 0.0003) and right heart failure (0.03 vs 0.18 EPPY, P < 0.0001) with no difference in the transplant or recovery rates among the two cohorts.

CONCLUSIONS: The Lavare cycle effectively generates ventricular washout and the adverse event profiles of ReVOLVE patients with the Lavare cycle on were better than those with the Lavare cycle off. Larger studies are warranted to verify the positive effect of the Lavare cycle and to optimize speed modulation settings, so additional clinically relevant improvements can be realized.

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Long-term support of patients receiving a left ventricular assist device for advanced heart failure: a follow-up analysis of the Registry to Evaluate the HeartWare Left Ventricular Assist System.

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OBJECTIVES: The Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE) is an investigator-initiated multicentre, prospective, single-arm database established to collect post-Conformite Europeenne Mark clinical information on patients receiving the HeartWare Ventricular Assist System (HVAD). The number of patients requiring longer periods of mechanical circulatory support is ever increasing and so further investigation into long-term outcomes in bridge-to-transplant populations is necessary.
METHODS: Data were collected on 254 commercial implants performed between February 2009 and March 2012 from nine centres in Europe (7 centres) and Australia (2 centres). Patients were followed to device explant, heart transplant or death, and the outcomes of patients who remained on support longer than 2 years were analysed. Summary statistics were used to describe patient demographics, adverse events, length of support and outcomes for this long-term cohort.

RESULTS: A total of 124 patients (49% of the original ReVOLVE population) were on support for more than 2 years (range: 731–2108 days), 76 of whom are still alive on support. Overall survival through 5 years was 59%.

CONCLUSIONS: Owing to the low rate of heart transplants, a significant number of patients receiving a left ventricular assist device as a bridge to transplant remain on support for prolonged periods, often exceeding 2, 3 and even 4 years. Real-world use of the HVAD system continues to show excellent outcomes for patients on the device, including those on support beyond 2 years.

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Asymptomatic CMV infections in long-term renal transplant recipients are associated with the loss of FcRgamma from LIR-1<sup>+</sup> NK cells.
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While it is established that cytomegalovirus (CMV) disease affects NK-cell profiles, the functional consequences of asymptomatic CMV replication are unclear. Here, we characterize NK cells in clinically stable renal transplant recipients (RTRs; n = 48) >2 years after transplantation. RTRs and age-matched controls (n = 32) were stratified by their CMV serostatus and the presence of measurable CMV DNA. CMV antibody or CMV DNA influenced expression of NKG2C, LIR-1, Nkp30, Nkp46, and FcRgamma, a signaling adaptor molecule, on CD56<sup>dim</sup> NK cells. Phenotypic changes ascribed to CMV were clearer in RTRs than in control subjects and affected NK-cell function as assessed by TNF-alpha and CD107a expression. The most active NK cells were FcRgamma<sup>-</sup> LIR-1<sup>+</sup> NKG2C<sup>-</sup> and displayed high antibody-dependent cell cytotoxicity responses in the presence of immobilized CMV glycoprotein B reactive antibody. However, perforin levels in supernatants from RTRs with active CMV replication were low. Overall we demonstrate that CMV can be reactivated in symptom-free renal transplant recipients, affecting the phenotypic, and functional profiles of NK cells. Continuous exposure to CMV may maintain and expand NK cells that lack FcRgamma but express LIR-1.

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**Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial: A randomized trial of IV iron in critical illness.**

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**PURPOSE:** Both anaemia and allogenic red blood cell transfusion are common and potentially harmful in patients admitted to the intensive care unit. Whilst intravenous iron may decrease anaemia and RBC transfusion requirement, the safety and efficacy of administering iron intravenously to critically ill patients is uncertain.

**METHODS:** The multicentre, randomized, placebo-controlled, blinded Intravenous Iron or Placebo for Anaemia in Intensive Care (IRONMAN) study was designed to test the hypothesis that, in anaemic critically ill patients admitted to the intensive care unit, early administration of intravenous iron, compared with placebo, reduces allogeneic red blood cell transfusion during hospital stay and increases the haemoglobin level at the time of hospital discharge.

**RESULTS:** Of 140 patients enrolled, 70 were assigned to intravenous iron and 70 to placebo. The iron group received 97 red blood cell units versus 136 red blood cell units in the placebo group, yielding an incidence rate ratio of 0.71 [95 % confidence interval (0.43-1.18), P = 0.19]. Overall, median haemoglobin at hospital discharge was significantly higher in the intravenous iron group than in the placebo group [107 (interquartile ratio IQR 97-115) vs. 100 g/L (IQR 89-111), P = 0.02]. There was no significant difference between the groups in any safety outcome.

**CONCLUSIONS:** In patients admitted to the intensive care unit who were anaemic, intravenous iron, compared with placebo, did not result in a significant lowering of red blood cell transfusion requirement during hospital stay. Patients who received intravenous iron had a significantly higher haemoglobin concentration at hospital discharge. The trial was registered at http://www.anzctr.org.au as # ACTRN12612001249842.

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**The revolving door: antibiotic allergy labelling in a tertiary care centre.**
BACKGROUND: Patients frequently report antibiotic allergies; however, only 10% of labelled patients have a true allergy.

AIM: We investigated the documentation of antibiotic 'allergy' labels (AAL) and the effect of labelling on clinical outcomes, in a West Australian adult tertiary hospital.

METHODS: Retrospective cross-sectional analysis of patients captured in the 2013 and 2014 National Antimicrobial Prescribing Surveys was carried out. Data were collected on documented antibiotic adverse drug reactions, antibiotic cost, prescribing appropriateness, prevalence of multi-drug resistant organisms, length of stay, intensive care admission and readmissions.

RESULTS: Of the 687 patients surveyed, 278 (40%) were aged 70 or above, 365 (53%) were male and 279 (41%) were prescribed antibiotics. AAL were recorded in 122 (18%) patients and the majority were penicillin labels (n=87; 71%). Details of AAL were documented for 80 of 141 (57%) individual allergy labels, with 61 describing allergic symptoms. Patients with beta-lactam allergy labels received fewer penicillins (P=0.0002) and more aminoglycosides (P=0.043) and metronidazole (P=0.021) than patients without beta-lactam labels. Five patients received an antibiotic that was contraindicated according to their allergy status. Patients with AAL had significantly more hospital readmissions within 4 weeks (P=0.001) and 6 months (P=0.025) of discharge, compared with unlabelled patients. The majority (81%) of readmitted labelled patients had major infections.

CONCLUSIONS: AAL are common, but poorly documented in hospital records. Patients with AAL are significantly more likely to require alternative antibiotics and hospital readmissions. There may be a role for antibiotic allergy delabelling to mitigate the clinical and economic burdens for patients with invalid allergy labels.

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A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with Nigella sativa (black seed) on blood pressure.
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Several reports suggest a beneficial effect of Nigella sativa on cardiometabolic risk factors, including blood pressure (BP). However, the magnitude of the BP-lowering effect of N. sativa remains controversial. We aimed to calculate this effect size of N. sativa through a systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Cochrane Collaboration Library, and SCOPUS were used as data sources of RCTs published before 30 August 2015 (in English only) comparing N. sativa treatment with placebo or standard treatment. We used random effect models to estimate the difference in BP reductions, I index and chi statistics to measure and test the interstudy heterogeneity. Random effect metaregression models were applied to explore the associations between BP reduction and duration of treatment, dosage of N. sativa, and type of black seed as potential confounders. Publication bias was evaluated using funnel plot and Egger's regression asymmetry test. Total 11 RCTs, including 860 hypertensive or normotensive individuals were eligible, of which 10 compared N. sativa versus placebo and one versus standard treatment. SBP and DBP means decreased from 132.85 to 125.19 mmHg and from 82.63 to 77.74 mmHg after mean treatment duration of 8.3 weeks in N. sativa groups, respectively. The difference in reductions as compared with control/standard groups were -3.26 (-5.10, -1.42; I = 59%) mmHg in SBP and -2.80 (-4.28, -1.32; I = 60%) mmHg in DBP. Pharmaceutical preparations of N. sativa in powder and oil demonstrated a different lowering effect (in favour of the former) on both SBP and DBP. No association was observed between SBP lowering and time on treatment, N. sativa dosage or type of N. sativa. The results of Egger's test did not indicate any publication bias. Our meta-analysis suggests that short-term treatment with N. sativa powder can significantly reduce SBP and DBP levels. More evidence is needed, however, to strengthen the available evidence and to further explore the long-term BP-lowering effect of N. sativa.

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**Urethral Recanalization Using a Radiofrequency Guide Wire and a Rendezvous Approach for Traversal of a Pelvic Fracture Urethral Distraction Defect.**


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DOI:https://dx.doi.org/10.1016/j.jvir.2016.03.026


**Effect of extended-release niacin on plasma lipoprotein(a) levels: A systematic review and meta-analysis of randomized placebo-controlled trials.**


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Lipoprotein(a) (Lp(a)) is a proatherogenic and prothrombotic lipoprotein. Our aim was to quantify the extended-release nicotinic acid Lp(a) reducing effect with a meta-analysis of the available randomized clinical trials.

RESULTS: The impact of ER niacin on plasma Lp(a) concentrations was reported in 17 treatment arms. Meta-analysis suggested a significant reduction of Lp(a) levels following ER niacin treatment (weighted mean difference - WMD: -22.90%, 95% CI: -27.32, -18.48, p<0.001). Results also remained similar when the meta-analysis was repeated with standardized mean difference as summary statistic (WMD: -0.66, 95% CI: -0.82, -0.50, p<0.001). When the studies were categorized according to the administered dose, there was a comparable effect between the subsets of studies with administered doses of <2000mg/day (WMD: -21.85%, 95% CI: -30.61, -13.10, p<0.001) and >2000mg/day (WMD: -23.21%, 95% CI: -28.41, -18.01, p<0.001). The results of the random-effects meta-regression did not suggest any significant association between the changes in plasma concentrations of Lp(a) with dose (slope: -0.0001; 95% CI: -0.01, 0.01; p=0.983), treatment duration (slope: -0.40; 95% CI: -0.97, 0.17; p=0.166), and percentage change in plasma HDL-C concentrations (slope: 0.44; 95% CI: -0.48, 1.36; p=0.350).

CONCLUSION: In this meta-analysis of randomized placebo-controlled clinical trials, treatment with nicotinic acid was associated with a significant reduction in Lp(a) levels.

Necrotising Autoimmune Myopathy (NAM) presents as a subacute proximal myopathy with high creatine kinase levels. It is associated with statin exposure, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibody, connective tissue diseases, signal recognition particle (SRP) antibody and malignancy. This case series presents our Western Australian NAM patient cohort: comparing the subgroup presentations, biopsy appearance and treatment outcomes.

We retrospectively collected data on patients diagnosed with NAM at the Western Australian Neuroscience Research Institute between the years 2000 and 2015. We identified 20 patients with Necrotising Autoimmune Myopathy: 14 with anti-HMGCR antibodies; two with anti-SRP antibodies; three with connective tissue disease; two as yet unspecified. Median creatine kinase level was 6047 units/L (range 1000-17000). The statin naive patients with HMGCR antibodies and patients with SRP antibodies were the most severely affected subgroups, with higher creatine kinase levels, and were more resistant to immunotherapy. Two or more immunotherapy agents were required in 90%; eight patients required IVIG and rituximab. Steroid weaning commonly precipitated relapses. Four patients had complete remission, and the remaining patients still require immunotherapy. Necrotising Autoimmune Myopathy is a potentially treatable myopathy, which can be precipitated by statin therapy and requires early, aggressive immunotherapy, usually requiring multiple steroid sparing agents for successful steroid weaning.

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**Expert panel consensus recommendations for postoperative pain management in the Gulf region.**

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Postoperative pain is a considerable issue in the Gulf region; however, at present there is a lack of comprehensive guidelines addressing postoperative pain management in the region. Therefore, an expert panel of pain specialists convened to address this issue and a set of key recommendations has been developed pertinent to the practice of postoperative pain management in the Gulf region (Bahrain, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen). These recommendations take into consideration the unique variation in cultural, religious and societal beliefs found in the region, as well as varying accessibility to pain medications, thereby aiming to serve as evidence-based guidance on the best practice management of postoperative pain in the Gulf region.

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**Ultra low dose CT screen-detected non-malignant incidental findings in the Western Australian Asbestos Review Programme.**

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**BACKGROUND AND OBJECTIVE:** Computed tomography (CT)-based studies of asbestos-exposed individuals report a high prevalence of lung cancer, but the utility of low dose CT (LDCT) to screen asbestos-exposed populations is not established. We aimed to describe the prevalence of indeterminate pulmonary nodules and incidental findings on chest LDCT of asbestos-exposed subjects in Western Australia.
METHODS: A total of 906 subjects from the Western Australian Asbestos Review Programme underwent LDCT of the chest as part of regular annual review. An indeterminate (solid) nodule was defined as >50mm$^3$ and part-solid/non-solid nodules >5mm. The presence of asbestos-related diseases was recorded with a standardized report.

RESULTS: Subjects were mostly (81%) men with a median age of 70 years. Fifty-eight (6.5%) participants were current smokers, 511 (56.4%) ex-smokers and 325 (36.4%) never-smokers. One hundred and four indeterminate nodules were detected in 77 subjects (8.5%); of these, eight cases had confirmed lung cancer (0.88%). Eighty-seven subjects (9.6%) had incidental findings that required further investigation, 42 (4.6%) from lower airways inflammation. The majority of nodules were solid, 4-6mm and more common with age. Five hundred and eighty (64%) subjects had pleural plaques, and 364 (40.2%) had evidence of interstitial lung disease.

CONCLUSION: The prevalence of LDCT-detected indeterminate lung nodules in 906 individuals with significant asbestos exposure was 8.5%, lower than many other CT studies. Clinically important incidental findings were found in 9.4%, predominantly related to lower respiratory tract inflammation. LDCT appears to effectively describe asbestos-related diseases and is likely to be an acceptable modality to monitor asbestos-exposed individuals.

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Bone marrow transplantation (BMT) has been performed as a successful life-saving treatment for hematological and neoplastic diseases. Despite the predictable long-term survival rates in BMT, pulmonary complications reduce the survival rates significantly mainly because of chronic graft-versus-host disease (GVHD). This report briefly discusses a successful lung transplantation case for severe lung GVHD after allograft for acute lymphoblastic leukemia. This case report supports the scarce evidence in the literature for the importance of lung transplantation as a therapeutic option for patients who develop respiratory failure secondary to BMT.
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Current practices of Asia-Pacific cardiologists in the utilization of bioresorbable scaffolds.
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BACKGROUND & AIMS: Although Absorb Bioresorbable Vascular Scaffolds (A-BVS) are routinely used in the Asia-Pacific, there is little information on patient selection or deployment technique here. This document investigates the experiences of leading interventional cardiologists from the Asia-Pacific region with a focus on patient characteristics, deployment techniques and management.

METHODS AND RESULTS: A detailed questionnaire was distributed to 28 highly-experienced interventional cardiologists ('Authors') from 13 Asia-Pacific countries. The results were discussed at a meeting on patient selection, technical consideration, deployment practices and patient management. Potential patient benefits of Absorb compared to metallic DES, the learning curve for patient selection and preparation, device deployment, and subsequent patient management approaches are presented.

CONCLUSIONS: Current practices are derived from guidelines optimized for European patients. Differences in approach exist in the Asia-Pacific context, including limited access to imaging and frequency of occurrence of complex lesions. Nevertheless, the use of the Absorb BVS ('Absorb') in certain Asia-Pacific countries has flourished and practices here are continuing to mature.

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TCT-681 SOLACE AU Study: Interim results at one year of the Edwards SAPIEN XT TM Transcatheter Heart Valve in intermediate risk patients with severe aortic stenosis in Australia.
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Hypertension and cognitive dysfunction in elderly: blood pressure management for this global burden.
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Arterial hypertension and stroke are strong independent risk factors for the development of cognitive impairment and dementia. Persistently elevated blood pressure (BP) is known to impair cognitive function, however onset of new cognitive decline is common following a large and multiple mini strokes. Among various forms of dementia the most prevalent include Alzheimer’s disease (AD) and vascular dementia (VaD) which often present with similar clinical symptoms and challenging diagnosis. While hypertension is the most important modifiable vascular risk factor with antihypertensive therapy reducing the risk of stroke and potentially slowing cognitive decline, optimal BP levels for maintaining an ideal age-related mental performance are yet to be established. Cognition has improved following the use of at least one representative agent of the major drug classes with further neuroprotection with renin angiotensin inhibitors and calcium channel blockers in the hypertensive elderly. However, a reduction in BP may worsen cerebral perfusion causing an increased risk of CV complications due to the J-curve phenomenon. Given the uncertainties and conflicting results from randomized trials regarding the hypertension management in the elderly, particularly octogenarians, antihypertensive approaches are primarily based on expert opinion. Herein, we summarize available data linking arterial hypertension to cognitive decline and antihypertensive approach with potential benefits in improving cognitive function in elderly hypertensive patients.

Structured white light scanning of rabbit Achilles tendon.
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BACKGROUND: The cross-sectional area (CSA) of a material is used to calculate stress under load. The mechanical behaviour of soft tissue is of clinical interest in the management of injury; however, measuring CSA of soft tissue is challenging as samples are geometrically irregular and may deform during measurement. This study presents a simple method, using structured light scanning (SLS), to acquire a 3D model of rabbit Achilles tendon in vitro for measuring CSA of a tendon.
METHOD: The Artec SpiderTM 3D scanner uses structured light and stereophotogrammetry technologies to acquire shape data and reconstruct a 3D model of an object. In this study, the 3D scanner was integrated with a custom
mechanical rig, permitting 360-degree acquisition of the morphology of six New Zealand White rabbit Achilles tendons. The reconstructed 3D model was then used to measure CSA of the tendon. SLS, together with callipers and micro-CT, was used to measure CSA of objects with a regular or complex shape, such as a drill flute and human cervical vertebra, for validating the accuracy and repeatability of the technique.

RESULTS: CSA of six tendons was measured with a coefficient of variation of less than 2%. The mean CSA was 9.9 +/- 1.0 mm<sup>2</sup>, comparable with those reported by other researchers. Scanning of phantoms demonstrated similar results to muCT.

CONCLUSION: The technique developed in this study offers a simple and accurate method for effectively measuring CSA of soft tissue such as tendons. This allows for localised calculation of stress along the length, assisting in the understanding of the function, injury mechanisms and rehabilitation of tissue.


Investigation of optical coherence micro-elastography as a method to visualize micro-architecture in human axillary lymph nodes.

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BACKGROUND: Evaluation of lymph node involvement is an important factor in detecting metastasis and deciding whether to perform axillary lymph node dissection (ALND) in breast cancer surgery. As ALND is associated with potentially severe long term morbidity, the accuracy of lymph node assessment is imperative in avoiding unnecessary ALND. The mechanical properties of malignant lymph nodes are often distinct from those of normal nodes. A method to image the micro-scale mechanical properties of lymph nodes could, thus, provide diagnostic information to aid in the assessment of lymph node involvement in metastatic cancer. In this study, we scan axillary lymph nodes, freshly excised from breast cancer patients, with optical coherence micro-elastography (OCME), a method of imaging micro-scale mechanical strain, to assess its potential for the intraoperative assessment of lymph node involvement.
METHODS: Twenty-six fresh, unstained lymph nodes were imaged from 15 patients undergoing mastectomy or breast-conserving surgery with axillary clearance. Lymph node specimens were bisected to allow imaging of the internal face of each node. Co-located OCME and optical coherence tomography (OCT) scans were taken of each sample, and the results compared to standard post-operative hematoxylin-and-eosin-stained histology.

RESULTS: The optical backscattering signal provided by OCT alone may not provide reliable differentiation by inspection between benign and malignant lymphoid tissue. Alternatively, OCME highlights local changes in tissue strain that correspond to malignancy and are distinct from strain patterns in benign lymphoid tissue. The mechanical contrast provided by OCME complements the optical contrast provided by OCT and aids in the differentiation of malignant tumor from uninvolved lymphoid tissue.

CONCLUSION: The combination of OCME and OCT images represents a promising method for the identification of malignant lymphoid tissue. This method shows potential to provide intraoperative assessment of lymph node involvement, thus, preventing unnecessary removal of uninvolved tissues and improving patient outcomes.

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An online questionnaire survey of UK general practitioners’ knowledge and management of familial hypercholesterolaemia.

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OBJECTIVE: Early diagnosis and treatment of heterozygous familial hypercholesterolaemia (HeFH) is known to be associated with reduced mortality from premature coronary artery disease, but HeFH remains underdiagnosed. This survey aims to determine knowledge and current management of HeFH in general practice.

SETTING: An online questionnaire was administered to general practitioners’ (GPs’) in the North West of England to assess their knowledge and management of HeFH.

PARTICIPANTS: Practising GPs in the North West of England were contacted by email and invited to complete an online questionnaire. Recruitment discontinued when the target of 100 was reached.

PRIMARY OUTCOME: An assessment of the knowledge and current management of HeFH in GPs.

RESULTS: 100 GP responses were analysed. Although only 39% considered themselves to have reasonable knowledge of HeFH, 89% knew that HeFH was a genetic disorder and 74% selected the correct lipid profile for diagnosing the condition. More than half (61%) were aware of current guidelines on HeFH. Gaps in knowledge were evident when only 30% correctly identified the prevalence of HeFH and half were not aware of the pattern of inheritance. Increased cardiovascular risk was underestimated by majority. 33% thought that they had HeFH patients in their practice confirming underdiagnosis of the condition. Statin therapy was recognised by 94% to be the right medication for treating HeFH. The majority (82%) regarded GPs to be the most effective healthcare professional for early recognition of HeFH.

CONCLUSIONS: GPs have an above-average knowledge of familial hypercholesterolaemia (FH) and almost universally consider that they have a key role in the early recognition of undiagnosed HeFH patients in the community. However, there are gaps in awareness that need to be addressed to further enhance the care of FH in the community.

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Do photographs, older adults' narratives and collaborative dialogue foster anticipatory reflection ("preflection") in medical students?

BACKGROUND: In changing higher education environments, medical educators are increasingly challenged to prepare new doctors to care for ageing populations. The Depth of Field: Exploring Ageing resource (DOF) uses photographs, reflective questioning prompts, older adults' narratives and collaborative dialogue to foster anticipatory reflection or 'preflection' in medical students prior to their first geriatric medicine clinical placement. The aim of this research is to explore whether photographs, narratives and small group collaborative dialogue fosters reflective learning, enhances reflective capacity and has the potential to shift medical students' attitudes towards caring for older adults.

METHODS: This study used a mixed method evaluation design, measuring attitudes using pre and post questionnaire responses and individual written reflections drawn from 128 second year medical students, exploring their perceptions toward older adults.

RESULTS: Quantitative and qualitative data indicated that the DOF session generated reflective learning that resulted in positive shifts in medical students' perceptions towards older adults. The qualitative reflections were captured in four main themes: the opportunity provided to Envision working with older adults; the Tension created to challenge learners' misinformed assumptions, and the work of Dismantling those assumptions, leading to Seeing older people as individuals.

CONCLUSIONS: These findings highlight how visual and narrative methodologies can be used as an effective reflective learning tool to challenge medical students’ assumptions around ageing and how these may influence their care of older adults.

PMID:27835991


Aerobic exercise: A possible therapy for vascular cognitive impairment.
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Mycobacterium chimaera colonisation of heater-cooler units (HCU) in Western Australia, 2015: investigation of possible iatrogenic infection using whole genome sequencing.
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Following the reported link between heater-cooler unit (HCU) colonisation with Mycobacterium chimaera and endocarditis, mycobacterial sampling of all HCUs in use in Western Australia was initiated from August 2015, revealing M. chimaera colonisation in 10 of 15 HCUs. After M. chimaera was isolated from a pleural biopsy from a cardiothoracic patient who may have been exposed to a colonised HCU, a whole genome sequencing investigation was performed involving 65 specimens from 15 HCUs across five hospitals to assess if this infection was related to the HCU. Genetic relatedness was found between the 10 HCU M. chimaera isolates from four hospitals. However the M. chimaera isolate from the cardiothoracic patient was not genetically related to the HCU M. chimaera isolates from that hospital, nor to the other HCU isolates, indicating that the HCUs were not the source of the infection in this patient.
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Plasma Lipidomic Profiles Improve on Traditional Risk Factors for the Prediction of Cardiovascular Events in Type 2 Diabetes Mellitus.
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BACKGROUND: Clinical lipid measurements do not show the full complexity of the altered lipid metabolism associated with diabetes mellitus or cardiovascular disease. Lipidomics enables the assessment of hundreds of lipid species as potential markers for disease risk.

METHODS: Plasma lipid species (310) were measured by a targeted lipidomic analysis with liquid chromatography electrospray ionization-tandem mass spectrometry on a case-cohort (n=3779) subset from the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation). The case-cohort was 61% male with a mean age of 67 years. All participants had type 2 diabetes mellitus with >1 additional cardiovascular risk factors, and 35% had a history of macrovascular disease. Weighted Cox regression was used to identify lipid species associated with future cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) and cardiovascular death during a 5-year follow-up period. Multivariable models combining traditional risk factors with lipid species were optimized with the Akaike information criteria. C statistics and NRIs were calculated within a 5-fold cross-validation framework.

RESULTS: Sphingolipids, phospholipids (including lyso- and ether- species), cholesteryl esters, and glycerolipids were associated with future cardiovascular events and cardiovascular death. The addition of 7 lipid species to a base model (14 traditional risk factors and medications) to predict cardiovascular events increased the C statistic from 0.680 (95% confidence interval [CI], 0.678-0.682) to 0.700 (95% CI, 0.698-0.702; P<0.0001) with a corresponding continuous NRI of 0.227 (95% CI, 0.219-0.235). The prediction of cardiovascular death was improved with the incorporation of 4 lipid species into the base model, showing an increase in the C statistic from 0.740 (95% CI, 0.738-0.742) to 0.760 (95% CI, 0.757-0.762; P<0.0001) and a continuous net reclassification index of 0.328 (95% CI, 0.317-0.339). The results were validated in a subcohort with type 2 diabetes mellitus (n=511) from the LIPID trial (Long-Term Intervention With Pravastatin in Ischemic Disease).

CONCLUSIONS: The improvement in the prediction of cardiovascular events, above traditional risk factors, demonstrates the potential of plasma lipid species as biomarkers for cardiovascular risk stratification in diabetes mellitus.


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Control of early HIV-1 infection associates with plasmacytoid dendritic cell-reactive opsonophagocytic IgG antibodies to HIV-1 p24.

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OBJECTIVES: We have previously demonstrated that HIV-1 p24-specific plasmacytoid dendritic cell-reactive opsonophagocytic antibody (PROAb) responses associate with control of chronic HIV infection. Here, we examined whether HIV-1 p24-specific PROAbs associate with control of early HIV infection and their relationship with HIV-1 p24-specific IgG subclasses.

METHODS: Plasma collected at 8 and 52 weeks following primary HIV-1 infection was obtained from antiretroviral therapy-naive patients who were classified as ‘good’ (plasma HIV-1 RNA < 5000 copies/ml; n = 17) or ‘poor’ (HIV-1 RNA > 50 000 copies/ml; n = 15) controllers at week 52. HIV-1 p24-specific PROAb responses were assayed using a plasmacytoid dendritic cell line (Gen2.2), and HIV-1 p24-specific IgG3, IgG1 and IgG2 levels were assayed by ELISA.

RESULTS: HIV-1 p24-specific PROAb responses increased in ‘good controllers’ (P = 0.01) but remained unchanged in ‘poor controllers’ between weeks 8 and 52. Of the HIV-1 p24-specific IgG subclasses measured, only IgG1 increased over this time period in ‘good controllers’ alone (P = 0.003), which correlated with the increase in HIV-1 p24-specific PROAb responses (r = 0.83, P < 0.0001). Depletion of IgG1 from IgG preparations of ‘good controllers’ resulted in the inhibition of HIV-1 p24-specific PROAb responses. In the total patient cohort, plasma HIV-1 RNA levels at week 52 correlated inversely with changes in HIV-1 p24-specific PROAb responses (r = -0.37, P = 0.04) and IgG1 (r = -0.51, P = 0.003) levels between weeks 8 and 52.

CONCLUSION: Control of early HIV-1 infection was associated with an increase in HIV-1 p24-specific PROAb responses, which was mediated by HIV-1 p24-specific IgG1 antibodies. These findings provide further evidence that antibodies to HIV core proteins may contribute to control of HIV-1 infection.

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Familial combined hyperlipidemia and hyperlipoprotein(a) as phenotypic mimics of familial hypercholesterolemia: Frequencies, associations and predictions.

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BACKGROUND: A significant proportion of index cases presenting with phenotypic familial hypercholesterolemia (FH) are not found to have a pathogenic mutation and may have other inherited conditions.

OBJECTIVES: Familial combined hyperlipidemia (FCHL) and elevated lipoprotein(a) [Lp(a)] may mimic FH, but the
frequency and correlates of these disorders among mutation-negative FH patients have yet to be established.

METHODS: The frequency of FCHL and elevated Lp(a) was investigated in 206 FH mutation-negative index cases attending a specialist lipid clinic. An FCHL diagnostic nomogram was applied to each index case; a positive diagnosis was made in patients with a probability score exceeding 90%. Plasma Lp(a) concentration was measured by immunoassay, with an elevated level defined as >0.5 g/L. Clinical characteristics, including coronary artery disease (CAD) events, were compared between those with and without FCHL and hyper-Lp(a).

RESULTS: Of mutation-negative FH patients, 51.9% had probable FCHL. These patients were older (P = .002), had a higher BMI (P = .019) and systolic (P = .001) and diastolic blood pressures (P = .001) compared with those without FCHL. Elevated Lp(a) was observed in 44.7% of cases, and there were no significant differences in clinical characteristics with Lp(a) status. The presence of elevated Lp(a) (P = .002), but not FCHL, predicted CAD events. This association was independent of established CAD risk factors (P = .032).

CONCLUSION: FCHL and elevated Lp(a) are common disorders in patients with mutation-negative FH. Among such patients, FCHL co-expresses with components of the metabolic syndrome, and elevated Lp(a) is the major contributor to increased CAD risk.

Grip and Muscle Strength Dynamometry Are Reliable and Valid in Patients With Unhealed Minor Burn Wounds.


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Small burns are common and can cause disproportionate levels of disability. The ability to measure muscle impairment and consequent functional disability is a necessity during rehabilitation of patients. This study aimed to determine the reliability and validity of grip and muscle strength dynamometry in patients with unhealed, minor burn wounds. Grip and muscle strength were assessed three times on each side. Assessment occurred at presentation for the initial injury and again every other day (or every 5 days beyond 10 days post injury) until discharge from the service. Reliability was assessed using intraclass correlation. Minimum detectable differences were calculated for each muscle group. Validity was assessed using regression analysis, incorporating appropriate burn severity measures and patient demographics. Thirty patients with TBSA <15% were assessed. Both grip and muscle strength demonstrated very good reliability (intraclass correlation coefficient: 0.85-0.96). Minimum detectable differences ranged from 3.8 to 8.0kg. Validity of both forms of dynamometry was confirmed through associations with gender for all muscle groups (P < .001). In addition, grip strength was associated with the dominant hand (P = .002) and time to assessment (P < .001). Strength was seen to improve over time in all muscle groups. Grip and muscle strength dynamometry are reliable and valid assessments of strength and are applicable for clinical use in patients who have unhealed, minor burn wounds.

Whole Arm Water Displacement Volumetry Is a Reliable and Sensitive Measure: A Pilot to Assess Acute Postburn Volume Change.

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Water displacement volumetry (WDV) is a reliable method for measurement of wrist and hand volume in lymphedema patients. However, within session WDV reliability for the whole upper limb (UL) lacks comprehensive investigation, particularly in acute edema populations. This study aimed to confirm the reliability and investigate the impact of time between repeated trials on the sensitivity of WDV as a measure of whole UL volume change in an uninjured cohort and a burn injured pilot group. Within session, duplicate measures of whole UL WDV were recorded in two groups of noninjured volunteers and a group of burn patients. Each noninjured group differed only in the time between WDV repeats. The reliability trials were performed <10 minutes apart (T10) and 20 to 30 minutes apart (T20). The time between repetitions for burn patients was 20 to 30 minutes, based on the results of the noninjured participant trials. All trial groups demonstrated excellent correlation between trials (ICCT10 = 0.999, ICCT20 = 0.997). The minimum detectable difference calculated for WDV when measuring whole UL volume change of >50ml for noninjured and >100ml for burn patients. Despite this, a systematic bias was demonstrated between the T10 group means. The T20 group trials did not indicate such error on statistical testing (P = .297). The study confirms that WDV measurement of whole ULs is reliable and sensitive, if used at least 20 minutes apart. However, a significant and clinically relevant subject-by-method interaction was demonstrated. Researchers and clinicians are reminded to be aware of the performance of the technique when designing investigations in patient populations.

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A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: The Lancet commission on hypertension.

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The current article introduces to the Lancet Commission on hypertension. The aim is to identify key actions to improve the management of blood pressure both at the population and the individual level, and to generate a campaign to adopt the suggested actions at national levels to reduce the impact of elevated blood pressure globally. The first task of the Commission is this report, which briefly reviews the available evidence for prevention, identification, and treatment of elevated blood pressure, hypertension, and its cardiovascular complications. The report focuses on how as-yet unsolved issues might be tackled using approaches with population-wide impact and new methods for patient evaluation and education in the broadest sense (some of which are not always strictly evidence based) to manage blood pressure worldwide. (PsycINFO Database Record (c) 2017 APA, all rights reserved) PMID:2016-60572-036
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Lipid-modifying effects of nutraceuticals: An evidence-based approach.
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The present review provides an up-to-date summary of the findings on the lipid-lowering effects of the most important nutraceuticals and functional foods. Based on current knowledge, nutraceuticals might exert significant lipid-lowering, and their use has several advantages: A number of important questions remain to be addressed, including whether longer durations of therapy would result in a better response and the exact safety profile of nutraceuticals, especially at doses higher than those consumed in an average diet. Additionally, data regarding the effects of nutraceutical supplementation on the incidence of cardiovascular outcomes are lacking, and it is not clear whether additional lipid lowering by nutraceuticals can modify the residual cardiovascular risk that remains after statin therapy.
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Guideline-adherent treatment for women with breast cancer: Do they receive what the multidisciplinary Team recommend and does this affect survival.
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Introduction: Treatment recommendations for cancer patients are more likely to be consistent with clinical practice guidelines (CPGs) when discussed at multidisciplinary cancer team meetings (MDMs). Adherence to CPG and patient compliance with recommended treatment(s) (i.e. completion of treatment that was started) may affect patient survival.

Aim: (i) To examine adherence of (a) MDM treatment recommendations to CPG and (b) treatment to CPG and MDM recommendations for women with breast cancer. (ii) To assess the effect of guideline adherent treatment and patient compliance on survival.

Methods: This retrospective, single-center study included women diagnosed with primary breast cancer between January 2006 and December 2009. MDM treatment recommendations and the treatment(s) received (surgery) or started (adjuvant therapies) were compared with hospital CPG to assess guideline adherence. Overall and recurrence-free survival was investigated using Kaplan-Meier analysis and multivariable Cox regression models.

Outcomes: The study included 1028 patients (mean age 58 years). Most MDM recommendations were guideline-adherent (n = 1014, 98.6%). MDM recommendations were implemented for 922 (89.7%) patients and 929 (90.4%) patients received guideline-adherent treatment. Reasons for deviation from CPG included: patient preferences (n = 81, 81.7%), physician decision (n = 8, 8.0%), comorbidities (n = 7, 7.1%) and were not established for three patients. Treatment adherence with CPGs was associated with a 30% lower risk of death (95% CI: 0.46-1.06) and a 52% lower risk of recurrence (95% CI: 0.28-0.81) in initial unadjusted analysis. Patient compliance was associated with a 49% lower risk of death (95% CI: 0.35-0.74) and 73% lower risk of recurrence (95% CI: 0.17-0.44). However, further investigations revealed that patients who complied with treatment were more likely to have favorable tumor characteristics. Conclusions: The majority of MDM recommendations were adherent to CPG and were implemented. Treatment adherence with CPG and patient compliance both favorably predicted overall and recurrence-free survival.

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Mammographic breast-density change as a predictor of outcome in hormone receptor positive breast cancer.
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Aim: To investigate the association between mammographic breast-density (MBD) change and disease-free survival in hormone receptor positive breast cancer during antiestrogen therapy. Methods: This was a single center study performed at Royal Perth Hospital. Patients were identified from the hospital breast unit database with hormone receptor positive breast cancer planned for curative treatment between 1994 and 2011. Demographic, pathology, treatment and outcome data were obtained from the unit database, case notes, clinic letters, electronic radiology and pathology systems and the Western Australian Cancer Registry. Mammograms were obtained from the hospital radiology archives and Breastscreen Western Australia. Film mammograms were scanned to obtain digital images. MBD was read by single reader using Cumulus software. Percentage change in MBD was compared between groups. The mammogram taken at diagnosis and the first mammogram taken in the 9-18-month period post-diagnosis were compared. Results: A total of 1921 patients were identified. At diagnosis, 22% were premenopausal, 8% perimenopausal and 69% postmenopausal. 62% received tamoxifen as initial endocrine therapy, 13% letrozole, 18% anastrazole and 5% ovariain suppression plus and aromatase inhibitor or tamoxifen. Interim univariate analysis of 921 patients gave a disease-free survival hazard ratio of 0.45 (95% CI 0.25-0.8; P = 0.006) for those with MBD reduction of >20% relative to those with MBD reduction of <0%. MBD measurement has now been completed on the remaining mammograms and analysis of the full cohort will be presented. Conclusion: Interim analysis shows that a greater reduction in MBD during antiestrogen therapy is associated with improved breast cancer outcome. Measurement of MBD change has the potential to allow tailoring of adjuvant endocrine therapy.

PMID:613440255

Klebsiella endogenous endophthalmitis—the Perth experience.

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Purpose: Endogenous endophthalmitis is a rare ophthalmic emergency that is potentially both life and sight threatening. Although multiple pathogens have been identified, Klebsiella pneumoniae is reported as a leading cause of endogenous endophthalmitis, particularly in Southeast Asian populations. The purpose of this study is to report our experience in Perth with Klebsiella endogenous endophthalmitis. Method: A retrospective case review of consecutive endogenous Klebsiella pneumoniae endophthalmitis managed at three major hospitals in Perth between 2002 and 2016. Clinical and electronic records were analysed. Results: A total of 9 patients with Klebsiella pneumoniae endogenous endophthalmitis were identified for analysis. Patient age ranged from 36 to 81 years, and four patients (44%) were of Southeast Asian descent. One patient was treated for bilateral endophthalmitis. All patients were previously medically well. All patients presented with a visual acuity of hand movements or worse, and clinical signs of septicemia. The most common source of infection was liver abscess (n = 6). All patients received intravenous and intravitreal antibiotics. Final visual acuity outcomes were poor: One patient achieved 6/9 and another patient HM acuity. The remainder were blinded (NPL), with three patients requiring evisceration. All patients survived. Conclusion: Klebsiella pneumoniae endogenous endophthalmitis is uncommon in Perth. However, it should be considered in patients presenting with septicaemia and endophthalmitis, particularly in previously healthy people of Southeast Asian descent. Liver abscess is the most common source for haematogenous infection. Despite appropriate management visual outcomes are poor, although chances of survival are high.

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Klebs and clots-an unusual case of klebsiella endogenous endophthalmitis complicated by superior ophthalmic vein occlusion.
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Purpose: To report an unusual case of hypermucoviscous Klebsiella pneumoniae endogenous endophthalmitis complicated by superior ophthalmic vein occlusion. Methods: Retrospective case and literature review, reporting the presentation, management and pathogenesis. The patient underwent B-scan ultrasonography, computed tomography, magnetic resonance imaging and systemic microbiological workup. Results: A previously healthy Filipino man presented with unilateral painful red eye and reduced vision on the background of fever, lung and liver abscesses. Examination revealed hypopyon with dense vitritis consistent with endophthalmitis. Extreme conjunctival chemosis and restricted ocular motility led to the suspicion of additional orbital pathology. B-scan ultrasound showed vitreous opacity, severe diffuse choroidal thickening and likely posterior scleritis. MRI confirmed superior ophthalmic vein thrombosis. Despite intensive antibiotic therapy, the patient's eye and vision deteriorated. The eye was eviscerated and the patient made a full systemic recovery. A strain of hypermucoviscous Klebsiella pneumoniae was identified on blood culture and pathological specimens from the eviscerated eye. Conclusion: Hypermucoviscous Klebsiella pneumoniae is an emerging cause of virulent endogenous endophthalmitis, particularly in Southeast Asian populations. It is often associated with pneumonia, liver abscess and meningitis in otherwise healthy adults. Although superior ophthalmic vein occlusion secondary to orbital cellulitis is a recognized complication, we are unaware of this being reported in the setting of endogenous endophthalmitis. This case highlights the unusual presentation of two serious eye conditions not often seen in combination. Marked conjunctival congestion/ chemosis and reduced ocular motility in combination with any intraocular infection should lead to suspicion of superior ophthalmic vein occlusion.

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Glistenings are microvacuoles within the material of implanted intraocular lenses and vary in size, density and content. Amongst the plethora of intraocular lenses [IOLs] available, some clearly develop worse glistenings than others. Their clinical significance is debated, but in some cases, glistenings appear to worsen progressively and impact increasingly over time on quality of post-operative visual function. Some companies claim their IOLs are free of glistenings, but little is published about this reality in clinical practice. Risk factors for development of glistenings such as glaucoma, uveitis and diabetes are not widely considered by clinicians in the IOL selection process. This audit was conceived to reduce the incidence of clinically significant glistenings by providing data for reflection, to provide individual clinicians and the collective RANZCO membership a collection of observations that are not readily available in the literature and that are unlikely to be forthcoming from the industry. This will improve the ability to select lenses based on both lens and patient risk factors. RANZCO fellows entered five patient case reviews with glistenings from July 2015 onwards. Results of this audit will be finalized and presented at the RANZCO Congress in November 2016.

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9. Collective audit in Western Australia.
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Background: Audit is a valuable tool for assessing and improving clinical practice. It is now a requirement of many medical colleges. Individuals in non surgical special interest groups and rural locations often struggle to find audit topics that will result in meaningful findings and provide useful learning experiences. The WA branch has embarked on an evolving program of co-operative clinical audit. Benchmarking/standard: Thus far, five clinical cooperative audits have been run in WA. Topics covered have included intraocular steroid injection, plaquenil screening, glistenings in intraocular lenses, neuro-imaging practices and colour vision testing audits. The process has evolved from a single-page tick box questionnaire discussed at a meeting, to a five-stage clinical audit cycle cycle. This involves a pre-test online survey, a didactic educational session (available at a meeting and online), submission of clinical cases online, a collegial discussion of analysed pooled results and a final post-test survey, testing improvement in knowledge and clinical practice. Results: Co-operative audits have been enthusiastically supported by over half of our branch members. Positive feedback has been received indicating that ophthalmologists appreciate facilitation of the process and value the learning opportunity. Lively collegial discussions and locally initiated research opportunities for our community have ensued. Improved knowledge and changes to clinical practice have been demonstrated. Recommendations: A co-operative audit library using the above online resources should be maintained as a RANZCO college CPD tool.
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12. Is inherited retinal disease truly symmetrical? a case-control study using spectral domain optical coherence tomography.
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Purpose: Symmetry is used to justify trial design that compares treatment outcome in study eye to untreated fellow eye in inherited retinal disease (IRD). We investigate whether the inter-ocular symmetry of macular thickness and volume in IRD patients is comparable to controls using spectral domain optical coherence tomography (SD-OCT).

Method: This was a case-control study of 108 IRD patients 25 controls who underwent bilateral macular SD-OCT. Central subfield thickness (CST) and total macular volume (TMV) were measured after manual correction of segmentation error. Inter-ocular asymmetry was defined as absolute difference in CST and TMV. Mean and standard deviation (SD) were reported. Proportion of IRD with inter-ocular differences exceeding 2*SD of the difference in controls was calculated. Results: Among 108 participants, pathogenic variants were confirmed in 51. The 3 most common genes were ABCA4 (13.9%), CRB1 (3.7%) and PRPF31 (2.8%). The mean (SD) CST and TMV were 219 (76) vs 269 (25) mum, and 7.06 (1.32) vs 8.49 (0.48) mm3 in cases and controls, respectively. The median (range) absolute difference between two eyes was 8 (0-152) and 5 (1-39) mum for CST and 0.21 (0.02-1.29) and 0.07 (0-0.25) mm3 for TMV in cases and controls, respectively. The inter-ocular difference in CST and TMV exceeded 2SD of the expected difference in controls were 27% and 64% in IRD cases. Conclusion: A significant proportion of IRD patients have asymmetrical CST and TMV beyond the range observed in normal subjects. This suggests caution in the use of fellow eyes as controls in IRD treatment trials.

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Proptosis in erdheim-chester disease: A rare cause from a rare disease.
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Purpose: To describe a case report of a rare cause of proptosis. Erdheim-Chester Disease (ECD) is a rare non-Langerhans histiocytosis with fewer than 400 cases described in world literature and of these described cases, less than 30 described cases with orbital involvement. Method: We describe a case of a man with bilateral proptosis and a history of systemic manifestations of Erdheim-Chester Disease, which provides a framework for describing this condition. Results: This case exhibits clinicoradiographic evidence of orbital, as well as cardiac, endocrine, renal and cutaneous involvement of the disease. He has also been typed with a BRAF V600E gene mutation, which so far has been identified in 50% of known cases. Conclusion: Erdheim-Chester Disease is a rare condition with few described cases with ophthalmic involvement. This may be part of multi-system involvement of disease. Despite significant morbidity and mortality involved, treatment options for this disease remain limited with no definitive consensus regarding management.

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Clinical features and management of peripheral hypertrophic subepithelial corneal degeneration (PHSCD).
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Purpose: The aim of this paper is to characterize and discuss the history, clinical presentation, histopathological features and therapeutic options available for patients with PHSCD. Methods: This paper is a case review series of 30 patients who presented to a tertiary referral centre in Western Australia with clinical findings consistent with a diagnosis of PHSCD. History, clinical presentation, histopathological features and treatments were all reviewed. Where superficial keratectomy or pseudopterygium excision was performed, excised tissues were studied for histopathological features. Results: Thirty patients presented over a 10-year period with clinical features of PHSCD.
Nineteen patients had a superficial keratectomy or pseudopterygium excision for symptoms related to discomfort or irregular astigmatism. There were no specific findings on histopathologic examination. Recurrence of subepithelial fibrotic degeneration occurred in three cases despite intraoperative use of mitomycin. Conclusion: Peripheral hypertrophic subepithelial corneal degeneration is an uncommon, usually bilateral, idiopathic disorder. The pathophysiology to date is poorly understood. Astigmatism secondary to PHSCD can be effectively treated with keratectomy, but the degenerative change may recur despite use of mitomycin.


Past, present and future concepts of the choroidal scleral interface morphology on optical coherence tomography.

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Purpose: The definition of the choroidal scleral interface (CSI) is inconsistent in the literature contributing to inter-study variation in choroidal thickness measurements. The purpose of this review is to provide an overview of the literature on the definition of choroidal layers and choroidal scleral boundary, review the discrepancies and harmonize the terminology so that a consensus nomenclature can be proposed. Methods: A literature search was performed using the following keywords, synonyms and their combinations: ‘optical coherence tomography’, ‘choroidal thickness’, ‘suprachoroid’, ‘choroidal scleral interface’, ‘suprachoroidal space’, ‘swept source’ and ‘spectral domain’. Articles were included if they provided a detailed definition and description of the choroidal scleral interface. Results: Five studies were included in this review. The anterior border of the choroid was identified by all studies as RPE/Bruch’s membrane. The vessel layer was either termed the choroidal vessels in two studies subdivided further into the three vessel layers in the other three studies. All studies acknowledged the presence of the hyper and hypo reflective bands below the vascular layer. Conclusion: The nomenclature for histologic correlates of OCT layers were harmonized. The anterior boundary of the choroid was termed the RPE/Bruch’s membrane complex. The vascular layer was termed the choroidal vessels with the 3 layers of vessels lying within. The next layer was termed the Suprachoroidal layer within which the hype reflective suprachoroidal stroma and hypo reflective suprachoroidal space was noted.

Visual enhancement of cervical ring reduces ureteric injury and complications in TLH.

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Study Objective: To investigate the reduced complications associated with a measuring margin and ureteric landmark during TLH and other advanced laparoscopic surgery. Design: Surgery was performed using a colpotomizer with two raised margins 20mm apart, indicating (respectively) the position of the vaginal fiorces and the position of the ureteric tunnels. Setting: Laparoscopic procedures performed in private hospitals in Australia, Europe and Southeast Asia. Patients: Over 500 patients undergoing total laparoscopic hysterectomy and laparoscopic radical hysterectomy. Intervention: Total laparoscopic hysterectomy was performed by experienced gynaecologists and by gynaecological fellows under the supervision of experienced gynaecologists. Measurements and Main Results: Real-time X-Ray video footage confirmed displacement of the ureters away from the colpotomizer's first raised margin at the vaginal
fornices. This was interpreted as a “green light” safety signal showing the safe position to perform dissection and colpotomy incisions in line with the uterine arteries’ ascending branches. The raised margin lifted tissue and the increased traction resulted in less than typical bleeding from incisions. The proximity of the ureteric tunnels to the colpotomizer’s second raised margin was interpreted as a “red light” warning signal showing the dangers of dissecting close to the ureters where their position is fixed lateral to the uterine arteries’ descending branches. No ureteric injuries or complications requiring intervention were encountered in this study. The second raised margin also indicated the 20mm oncology clearance margin for radical hysterectomy after the ureters were freed from their tunnels. Conclusion: Gynaecologists and fellows enjoyed confidence and certainty during surgery, with predictable positions of the uterine arteries and ureters pinpointing the appropriate site of uterine artery coagulation and avoiding progressive coagulation approaching the ureters that can cause thermal spread injuries. Precise physical reference landmarks during straight stick laparoscopy reduces ureteric injuries during TLH and mesh placement and would seem to be of equal benefit in robotic surgery.

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Quick and easy acquisition of laparoscopic suturing skills.
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Study Objective: To investigate the learning curve for surgeons acquiring laparoscopic suturing skills. Design: Surgery and training was performed using a needle holder with an integrated needle that articulates through 90oo. Setting: Laparoscopic procedures performed in private hospitals in Australia and Indonesia, and laparoscopic training exercises performed in training centres. Patients: 40 patients undergoing advanced laparoscopic surgery, and training models resembling vaginal and bowel tissue. Intervention: Gynaecologists performed laparoscopic surgery. Gynaecologists and fellows participated in suturing skills exercises in training centres. Measurements and Main Results: Quick uptake of laparoscopic suturing skills during training was confidently translated to laparoscopic surgery. Laparoscopic surgery exhibited less than typical bleeding and short vaginal cuff closure times. While present for surgeons familiar with conventional laparoscopic suturing techniques, this trend was particularly apparent in the inexperienced. LAVH surgeons found the transition to TLH requiring pedicle ligation and laparoscopic vaginal cuff closure easier than when attempting conventional laparoscopic suturing. Removing complicated needle-handling manoeuvres, through the use of a needle holder with an integrated needle capable of articulation, assisted in shortening the learning curve and building basic skills and dexterity for laparoscopic suturing. Extracorporeal knot-tying was the preferred method for initial tissue-securing, with an intracorporeal tie to follow. Additional timesaving was achieved by using an integrated laparoscopic grasper-and-scissors that avoided repetitive instrument changes. Conclusion: This study demonstrated quick acquisition of the skills necessary for confident and efficient laparoscopic pedicle ligation and cuff closure. Specialised suturing equipment fast-tracks surgeons to an advanced level otherwise requiring years of practice and attendance at suturing workshops. With the elimination of complicated needle-handling, only extracorporeal knot-tying abilities is required for the immediate acquisition of suturing skills. The reduced learning curve is especially valuable for fellows and entry level GYNs or surgeons transitioning from LAVH to TLH.
PMID:613267663


Aussie solutions to uterine and camera assistants.
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Study Objective: Investigate the ability to replace human pelvic and camera assistants with an affordable and
easy-to-use mechanical alternative. Design: Over 1000 cases of laparoscopic surgery performed using a mechanical uterine positioner and camera holder that did not require electrical or hydraulic power. Setting: Laparoscopic procedures performed in private hospitals in Australia. Patients: Over 1000 patients undergoing laparoscopic procedures in city and country hospitals. Intervention: Laparoscopic procedures including TLH, chromotubation, endometriosis, pelvic repair. Measurements and Main Results: This study used a mechanical system modelled on a human arm and operating on precision tensioning without external power or hydraulics. The positioning systems were used to hold uterine manipulators, probes and laparoscopic cameras. Surgeons and surgical assistants moved the system to the required positions, and the system held the devices in place. Precise and immediate movements were able to be initiated without needing to unlock and lock the system. Procedures were able to proceed smoothly without fatigue or communication issues between surgeons and assistants. Conclusion: From a surgical perspective, the stability of the pelvic platform and laparoscopic image compared favourably with that provided by human assistants. This study, while not undertaken from a hospital and legal perspective, suggests a means of reducing the risk of workplace injury, fatigue and boredom for human assistants without incurring higher costs for institutions. Observations were that reusable models of the positioners (supplied non-sterile for reprocessing) would be most appropriate for larger institutions that perform a lot of laparoscopic surgery, while smaller facilities that only perform laparoscopic surgery infrequently would work best with robust but cheaper single use models (supplied sterile for disposal/recycling). Across the world, concerns are being raised about having non-physicians holding and moving surgical instruments. Mechanical assistants are suggested as an easier and more economical solution than having extra physicians present at surgery to act as assistants.

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**Breast localization techniques and margin definitions used by Australian and New Zealand surgeons.**
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The **Generic Surgical Sciences Examination training programme improves participant’s knowledge and pass rates.**
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BACKGROUND AND AIMS: Our aim was to gain insight into the role that lipoprotein lipase (LPL) and hepatic lipase (HL) plays in HDL metabolism and to better understand LPL- and HL-deficiency states.

METHODS: We examined the apolipoprotein (apo) A-I-, A-II-, A-IV-, C-I-, C-III-, and E-containing HDL subpopulation profiles, assessed by native 2-dimensional gel-electrophoresis and immunoblotting, in 6 homozygous and 11 heterozygous LPL-deficient, 6 homozygous and 4 heterozygous HL-deficient, and 50 control subjects.

RESULTS: LPL-deficient homozygotes had marked hypertriglyceridemia and significant decreases in LDL-C, HDL-C, and apoA-I. Their apoA-I-containing HDL subpopulation profile was shifted toward small HDL particles compared to controls. HL-deficient homozygotes had moderate hypertriglyceridemia, modest increases in LDL-C and HDL-C level, but normal apoA-I concentration. HL-deficient homozygotes had a unique distribution of apoA-I-containing HDL particles. The normally apoA-I:A-II, intermediate-size (alpha-2 and alpha-3) particles were significantly decreased, while the normally apoA-I only (very large alpha-1, small alpha-4, and very small prebeta-1) particles were significantly elevated. In contrast to control subjects, the very large alpha-1 particles of HL-deficient homozygotes were enriched in apoA-II. Homozygous LPL- and HL-deficient subjects also had abnormal distributions of apo C-I, C-III, and E in HDL particles. Values for all measured parameters in LPL- and HL-deficient heterozygotes were closer to values measured in controls than in homozygotes.

CONCLUSIONS: Our data are consistent with the concept that LPL is important for the maturation of small discoidal HDL particles into large spherical HDL particles, while HL is important for HDL remodeling of very large HDL particles into intermediate-size HDL particles.

Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms.


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BACKGROUND AND AIMS: The effect of statin therapy on plasma adiponectin levels has not been conclusively studied. Therefore, we aimed to evaluate this effect through a systematic review and meta-analysis of available randomized controlled trials (RCTs).

METHODS: Quantitative data synthesis was performed using a random-effects model with weighted mean difference (WMD) and 95% confidence interval (CI) as summary statistics.

RESULTS: In 30 studies (43 study arms) with 2953 participants, a significant increase in plasma adiponectin levels was observed after statin therapy (WMD: 0.57 μg/mL, 95% CI: 0.18, 0.95, p = 0.004). In subgroup analysis, atorvastatin, simvastatin, rosuvastatin, pravastatin and pitavastatin were found to change plasma adiponectin concentrations by 0.70 μg/mL (95% CI: -0.26, 1.65), 0.50 μg/mL (95% CI: -0.44, 1.45), -0.70 μg/mL (95% CI: -1.08, -0.33), 0.62 μg/mL (95% CI: -0.12, 1.35), and 0.51 μg/mL (95% CI: 0.30, 0.72), respectively. With respect to duration of treatment, there was a significant increase in the subset of trials lasting >12 weeks (WMD: 0.88 μg/mL, 95% CI: 0.19, 1.57, p = 0.012) but not in the subset of <12 weeks of duration (WMD: 0.18 μg/mL, 95% CI: -0.23, 0.58, p = 0.390).

Random-effects meta-regression suggested a significant association between statin-induced elevation of plasma adiponectin and changes in plasma low density lipoprotein cholesterol levels (slope: 0.04; 95% CI: 0.01, 0.06; p = 0.002).

CONCLUSIONS: The meta-analysis showed a significant increase in plasma adiponectin levels following statin therapy. Although statins are known to increase the risk for new onset diabetes mellitus, our data might suggest that the mechanism for this is unlikely to be due to a reduction in adiponectin expression.


PCS9 inhibitors - mechanisms of action.

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The Australian laparoscopic non robotic radical prostatectomy experience - analysis of 2943 cases (USANZ supplement).

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OBJECTIVES: To analyse the Australian experience of high-volume Fellowship-trained Laparoscopic Radical Prostatectomy (LRP) surgeons.

MATERIALS AND METHODS: 2943 LRP cases were performed by nine Australian surgeons. The inclusion criteria were a prospectively collected database with a minimum of 100 consecutive LRP cases. The surgeons' LRP experience commenced at various times from July 2003 to September 2009. Data were analysed for demographic, peri-operative, oncological and functional outcomes.

RESULTS: The mean age of patients were 61.5 years and mean preoperative PSA 7.4 ng/ml. Mean operating time was 168 minutes with conversion to open surgery in 0.5% and a blood transfusion rate of 1.1%. Overall mean length of stay was 2.5 days. 73.6% of pathological specimens were pT2 and 86.3% had Gleason Score >7. Overall positive surgical margins (PSM) occurred in 15.9% with pT2 PSM 9.8%, pT3a PSM 30.8% and pT3b PSM 39.2%. Mean urinary continence at 12 months was 91.4% (data available from five surgeons). Mean 12 months potency after bilateral nerve sparing was 47.2% (data available from four surgeons). Biochemical recurrence occurred in 10.6% (mean follow up 17 months).

CONCLUSION: The Australian experience of Fellowship trained surgeons performing LRP demonstrates favourable peri-operative, oncological and functional outcomes in comparison to published data for open, laparoscopic and robotic assisted radical prostatectomy. In our Australian centres, LRP remains an acceptable minimally invasive surgical treatment for prostate cancer despite the increasing use of robotic assisted surgery.

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Active surveillance is suitable for intermediate term follow-up of renal oncocytoma diagnosed by percutaneous core biopsy.

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OBJECTIVES: To evaluate the intermediate outcome of conservative management in patients with biopsy-proven oncocytoma.

PATIENTS AND METHODS: Patients with oncocytoma diagnosed on percutaneous core biopsy between January 2000 to December 2014 were identified from the renal biopsy database of a large specialist urologic pathology laboratory. After review of patient clinical records, the study cohort comprised only of patients enrolled in active surveillance. Clinicopathological and follow-up details were reviewed for each case, in particular: type and interval of surveillance imaging, tumour growth, definitive intervention and reason for intervention. Where possible, correlation was made between the final surgical and the initial biopsy specimens.

RESULTS: Fifty three patients diagnosed with oncocytoma on core biopsy were initially placed on active surveillance with median follow-up of 34 months (range 6-109). The median age at diagnosis was 65 years (range 20-85) and median tumour size was 30 mm (range 13-87). Mean average tumour growth was 1.4 mm per annum (median 0 mm/year) with the majority (36 of 53, 68%) exhibiting minimal growth (less than 2 mm per annum) or partial regression. Forty seven of the 53 patients remained on active surveillance with no significant progression. Six patients elected to undergo definitive intervention (five surgical excision, one ablation). Renal oncocytoma was confirmed in all five patients who underwent surgical excision of their lesions.

CONCLUSIONS: The majority of oncocytomas in this study showed minimal growth rate or regression. Patients with biopsy proven oncocytoma can be conservatively managed with active surveillance.

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Cranioplasty: morbidity and failure.

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OBJECTIVE: Cranioplasty is a technically straightforward procedure; however, it is becoming increasingly apparent that it is associated with relatively high morbidity and a significant failure rate due to either infection or autologous bone flap resorption. The aim of this study was to determine which factors influenced the incidence of cranioplasty complications and failure.

METHODS: A retrospective analysis was undertaken of all patients who had a cranioplasty at the two major trauma hospitals in Western Australia between the start of 2004 and the middle of 2015.

RESULTS: Five hundred and twelve had a cranioplasty after craniectomy for a variety of different indications. Sixty-three patients developed a postoperative intracranial collection following cranioplasty (12.3%, 95% confidence interval [CI] 9.7-15.4), however only 19 required surgical evacuation. One hundred and twenty-one patients had seizures following cranioplasty (23.6%, 95% CI 20.2-27.5) Nine patients died within six months following cranioplasty. Forty-two patients (8.2%, 95% CI 6.1-10.9) developed cranioplasty infection that necessitated removal of the implant. However a change in clinical management of these patients had led to no infections for the past three years. Amongst 330 patients who had autologous cranioplasty, clinically significant bone resorption occurred in 69 patients (20.9%, 95% CI 16.9-25.6).

CONCLUSION: One key finding in this study is the reduction in infection rate that can occur when a single senior
clinician performs the procedure and there is strict adherence to aseptic technique. This may result in a significant reduction in morbidity.

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**Coronary Artery Disease in French Canadians-Investigation of a Suggested Vulnerable Population.**

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BACKGROUND: There is a perception among Canadian physicians that coronary artery disease (CAD) and adverse cardiac events are more common in those of French Canadian heritage. We sought to compare the prevalence of CAD using coronary computed tomographic angiography (CCTA) in French Canadians and non-French white Canadians.

METHODS: Consecutive patients were prospectively enrolled in our institutional CCTA registry. Of 10,868 CCTA examinations, we analyzed white patients who identified themselves as French Canadian or non-French Canadian. These 2 groups were compared for baseline characteristics, cardiovascular risk factors, and routine markers for CAD on CTCA. Propensity score adjustments were also made to account for differences in demographics.

RESULTS: We identified 1683 French Canadians (mean age, 58.5 +/- 10.7 years; 54.2% men) and 5077 non-French white Canadians (mean age, 59.4 +/- 11.4 years; 57.3% men). French Canadians were more likely to have a smoking history (64.1% vs 56.1%), diabetes (15.6% vs 13.6%), and a family history of premature CAD (53.3% vs 44.6%) (P < 0.05 for all). There was no significant difference in measures of CAD between French Canadians and non-French white Canadians in obstructive CAD (32.5% vs 32.2%; P = 0.997), total plaque score (4.6 +/- 4.3 vs 4.5 +/- 4.4; P = 0.616) and Agatston score (168.1 +/- 319.8 vs 183.6 +/- 433.7; P = 0.371). After propensity score adjustment, there was still no significant difference between the groups.

CONCLUSIONS: Our study suggests that French Canadians in the Champlain region have a greater prevalence of cardiovascular risk factors compared with non-French Canadians; however, they do not appear to have a greater prevalence or severity of coronary atherosclerosis as assessed by CCTA.

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**Device Therapies for Resistant Hypertension.**
PURPOSE: Resistant hypertension (RH) is a major and growing public health problem. While noncompliance to antihypertensive medication is a major concern in RH patients, it is estimated that even with adequate multi-drug regimens, approximately 10% of patients diagnosed with hypertension fulfill the criteria of true RH. Patients with sustained blood pressure (BP) elevation display high risk for development of target organ damage and associated cardiovascular morbidity and mortality. While optimized pharmacologic therapy, including the use of mineralocorticoid receptor antagonists to guideline-based antihypertensive drug therapy, is effective for improving BP control in this patient cohort, a sizable proportion of RH patients' BP remains uncontrolled, and alternative therapeutic strategies are warranted.

METHODS: In the past few years, device-based approaches have been studied extensively. Among these, robust clinical experience in patients with RH exists for renal denervation, baroreflex activation therapy, central arteriovenous anastomosis, and, to a lesser extent, deep brain stimulation. Carotid body modulation is the most recent approach under clinical investigation. The common aim of these approaches is direct targeting of relevant pathophysiologic mechanisms involved in BP control, most commonly activation of the sympathetic nervous system.

FINDINGS: This review article briefly summarizes relevant clinical and experimental evidence and highlights the potential utility, as well as limitations, of each approach.

IMPLICATIONS: Several device-based approaches show promise in the treatment of RH and have been associated with improved BP control, while generally finding an acceptable side effect profile. Ongoing research is addressing relevant issues relating to patient selection and technical and procedural aspects, and will help to define the future role of device-based approaches for RH in the next few years.

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Developing an evidence-based transition program for graduate nurses.
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BACKGROUND: The catalyst to revise the graduate nurse program at an inner city hospital was a major service reconfiguration, which reduced services, staffing and graduate nurse positions. Parameters for the new program were that it was evidence-based and could function within the reduced resources.

OBJECTIVE: Review current literature and design an evidence-based transition program.

METHODS: Eight databases were searched for primary and secondary research and unpublished theses (2004-2014), which were then hand searched. Eighty-three articles were reviewed and 50 retained as they informed development of a program designed to actively promote the graduates’ transition from undergraduate to independent health professional.

RESULTS: Three key concepts emerged from the literature: the graduates’ need for support, socialisation and facilitated learning opportunities. This article reviews the literature and outlines a program designed to maximise these concepts in an evidence-based transition program. Proposed evaluation tools are identified for use throughout the program.

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The authors reply.
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Determinants of Urinary Output Response to IV Furosemide in Acute Kidney Injury: A Pharmacokinetic/Pharmacodynamic Study.
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OBJECTIVES: This study assessed the determinants of urinary output response to furosemide in acute kidney injury; specifically, whether the response is related to altered pharmacokinetics or pharmacodynamics.
DESIGN: Prospective cohort.
SETTING: Tertiary ICU.
PATIENTS: Thirty critically ill patients with acute kidney injury without preexisting renal impairment or recent diuretic exposure.
INTERVENTION: A single dose of IV furosemide.
MEASUREMENTS AND MAIN RESULTS: Baseline markers of intravascular volume status were obtained prior to administering furosemide. Six-hour creatinine clearance, hourly plasma/urinary furosemide concentrations, and hourly urinary output were used to assess furosemide pharmacokinetics/pharmacodynamics parameters. Of 30 patients enrolled, 11 had stage-1 (37%), nine had stage-2 (30%), and 10 had stage-3 (33%) Acute Kidney Injury Network acute kidney injury. Seventy-three percent were septic, 47% required norepinephrine, and 53% were mechanically ventilated. Urinary output doubled in 20 patients (67%) following IV furosemide. Measured creatinine clearance was strongly associated with the amount of urinary furosemide excreted and was the only reliable predictor of the urinary output after furosemide (area under the receiver-operating-characteristic curve, 0.75; 95% CI, 0.57-0.93). In addition to an altered pharmacokinetics (p < 0.01), a reduced pharmacodynamics response to furosemide also became important when creatinine clearance was reduced to less than 40mL/min/1.73 m (p = 0.01). Acute kidney injury staging and markers of intravascular volume, including central venous pressure, brain-natriuretic-peptide concentration, and fractional urinary sodium excretion were not predictive of urinary output response to furosemide.
CONCLUSIONS: The severity of acute kidney injury, as reflected by the measured creatinine clearance, alters both pharmacokinetics and pharmacodynamics of furosemide in acute kidney injury, and was the only reliable predictor of the urinary output response to furosemide in acute kidney injury.
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Truth, thinking and thrombolysis.
Impact of population ageing on growing demand for emergency transportation to emergency departments in Western Australia, 2005–2020.

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OBJECTIVE: The aim of the present paper is to quantify the impact of population ageing on demand for emergency transportation (ET) to EDs in Western Australia (WA).

METHODS: A population-based longitudinal study using the statewide ED presentation data from 2005-2014 was used to predict ET demand in 2020, stratified by age group and sex.

RESULTS: From 2005 to 2014, 14.9% of all ED presentations arrived by ET. The number rose from 94369 (13.9%) in 2005 to 153374 (15.5%) in 2014, a compound annual growth of 5.5%. Of those presentations, 55.2% resulted in hospital admission. The proportion was higher in older age groups (64.5% in 65-74 years, 67.1% in 75-84 years and 68.4% in >85 years). Of ED presentations arriving by ET in age group >65 years, 70.9% were Australasian Triage Scale category 1, 2 or 3. The rate of ET per 1000 population increased in all age groups and sex. The highest growth was in the older age groups: from 86.6, 187.0 and 512.1 in ages 65-74 years, 75-84 years and >85 years, respectively, in 2005 to 102.5, 226.7 and 613.6 in 2014, and are expected to increase to 115.1, 264.3 and 707.7 by 2020. The ET demands in these age groups were projected to increase annually by 5.0%, 3.6% and 4.9%, respectively, in the next 6 years, comparing to less than 4.5% in the younger age groups.

CONCLUSION: There has been a continuous rise in ET demand in WA, particularly in older people who have a higher urgency and requirement for admission.

The TARGET pain study: Lessons from a painful marathon.
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This perspective article summarises the experience of conducting a multicentre research project. We describe expected and unexpected hurdles we experienced as well as suggesting possible solutions for researchers embarking on multicentre studies.


Are there too few women presenting at emergency medicine conferences?


INTRODUCTION: There is a perception that women are under-represented as speakers at emergency medicine (EM) conferences. We aimed to evaluate the ratio of male to female speakers and the proportion of presenting time by gender at major international EM conferences.

METHODS: Conference programmes of the major English-speaking EM conferences occurring from 2014 to 2015 were obtained. The number of presentations, the gender of the speaker and the duration of each presentation were recorded.

RESULTS: We analysed eight major EM conferences. These included 2382 presentations, of which 29.9% (range 22.5%-40.9%) were given by women. In total, 56 104 min of presentations were analysed, of which 27.6% (range 21%-36.7%) were delivered by women. On average, presentations by women were 95 s shorter than presentations by men (23 vs 21 min 25 s).

CONCLUSIONS: Male speakers exceed female speakers at major EM conferences. The reasons for this imbalance are likely complex and multifactorial and may reflect the gender imbalance within the specialty.

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Impact of nurse-mediated management on achieving blood pressure goal levels in primary care: Insights from the Valsartan Intensified Primary care Reduction of Blood Pressure Study.

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BACKGROUND: Blood pressure targets in individuals treated for hypertension in primary care remain difficult to attain.

AIMS: To assess the role of practice nurses in facilitating intensive and structured management to achieve ideal BP levels.

METHODS: We analysed outcome data from the Valsartan Intensified Primary care Reduction of Blood Pressure Study. Patients were randomly allocated (2:1) to the study intervention or usual care. Within both groups, a practice nurse mediated the management of blood pressure for 439 patients with endpoint blood pressure data (n=1492). Patient management was categorised as: standard usual care (n=348, 23.3%); practice nurse-mediated usual care (n=156, 10.5%); standard intervention (n=705, 47.3%) and practice nurse-mediated intervention (n=283, 19.0%). Blood pressure goal attainment at 26-week follow-up was then compared.

RESULTS: Mean age was 59.3 +/- 12.0 years and 62% were men. Baseline blood pressure was similar in practice nurse-mediated (usual care or intervention) and standard care management patients (150 +/- 16/88 +/- 11 vs. 150 +/- 17/89 +/- 11 mmHg, respectively). Practice nurse-mediated patients had a stricter blood pressure goal of 125/75 mmHg (33.7% vs. 27.3%, p=0.026). Practice nurse-mediated intervention patients achieved the greatest blood pressure falls and the highest level of blood pressure goal attainment (39.2%) compared with standard intervention (35.0%), practice nurse-mediated usual care (32.1%) and standard usual care (25.3%; p<0.001). Practice nurse-mediated intervention patients were almost two-fold more likely to achieve their blood pressure goal compared with standard usual care patients (adjusted odds ratio 1.92, 95% confidence interval 1.32 to 2.78; p=0.001).

CONCLUSION: There is greater potential to achieve blood pressure targets in primary care with practice nurse-mediated hypertension management.


Tigecycline use in the outpatient parenteral antibiotic therapy setting.

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In the context of globally increasing antimicrobial resistance, tigecycline appears to be a useful therapeutic option. The need for prolonged courses for complex infections has prompted consideration of its use via outpatient parenteral antibiotic therapy (OPAT) programmes, although clinical outcomes when used in this setting remain unknown. We retrospectively reviewed the patient characteristics and outcomes of 11 patients who received tigecycline, most commonly delivered as 100 mg once daily, via OPAT at three tertiary Australian hospitals. Rates of co-morbidity and prior antibiotic use were high. Patients had a wide range of infections including bone and/or joint (n=5), intra-abdominal (n=3), lower respiratory tract (n=2) and parapharyngeal abscess (n=1). Mycobacterial species (n=5) were the most frequent pathogen, and multi-resistant organisms were common (n=4). The median OPAT duration was 14 days (IQR 6-30). Nausea was encountered in 45 % of cases. At completion of OPAT, 1 patient (9 %) was cured, 2 (18 %) had improved and 8 (73 %) failed therapy. Failure occurred due to either progression or non-response of infection (n=4), re-admission (n=3), premature cessation of tigecycline due to nausea (n=3) or death (n=1). Whilst OPAT delivery of tigecycline is a therapeutic option, when used as second-line therapy for complex, often multi-resistant infections in patients with multiple comorbidities, high rates of clinical failure, readmissions and adverse effects, especially nausea, should be anticipated.
Adequate exposure is fundamental to safely and correctly perform open procedures around the knee. Tibial tubercle osteotomy (TTO) has previously been described as a method to improve exposure, particularly in complex primary elective knee arthroplasty or revision surgery. We describe a tibial tubercle osteotomy technique to improve exposure in complex knee fractures and a cadaveric study and trauma case series.

METHODS: A cadaveric study using 8 knee specimens was conducted using a lateral subvastus approach to the knee. Standardised pictures were taken of the exposure, the tibial tubercle osteotomy was performed and pictures were taken of the new exposed area. These images were compared using a computer program that calculated the area of exposure before and after tibial tubercle osteotomy and the results analysed. The technique was then used in a case series of 6 different complex knee fractures including three distal femoral, one periprosthetic distal femur and two tibial plateau fractures. The outcomes of these patients were followed clinically and radiologically.

RESULTS: All specimens in the cadaveric study demonstrated an increase in area of exposure after the TTO with a mean increase of 148%. All tibial tubercle osteotomies performed in the trauma case series were united by 6 months without complication.

CONCLUSIONS: Tibial tubercle osteotomy is a recognised technique for improving exposure to the knee. This has been demonstrated in a cadaveric study and in a case series of six complex fractures around the knee. If performed properly, this technique can be extended to appropriate trauma cases with good results.
Antifungal susceptibilities of non-Aspergillus filamentous fungal pathogens cannot always be inferred from their identification. Here we determined, using the Sensititre(YeastOne) YO10 panel, the in vitro activities of nine antifungal agents against 52 clinical isolates of emergent non-Aspergillus moulds representing 17 fungal groups in Australia. Isolates comprised Mucorales (n=14), Scedosporium/Lomentospora spp. (n=18) and a range of hyaline hyphomycetes (n=9) and other dematiaceous fungi (n=11). Excluding Verruconis gallopava, echinocandins demonstrated poor activity (MICs generally >8mg/L) against these moulds. Lomentospora prolificans (n=4) and Fusarium spp. (n=6) demonstrated raised MICs to all antifungal drugs tested, with the lowest being to voriconazole and amphotericin B (AmB), respectively (geometric mean MICs of 3.4mg/L and 2.2mg/L, respectively). All Scedosporium apiospermum complex isolates (n=14) were inhibited by voriconazole concentrations of <0.25mg/L, followed by posaconazole and itraconazole at <1mg/L. Posaconazole and AmB were the most active agents against the Mucorales, with MIC90 values of 1mg/L and 2mg/L, respectively, for Rhizopus spp. For dematiaceous fungi, all isolates were inhibited by itraconazole and posaconazole concentrations of <0.5mg/L (MIC90, 0.12mg/L and 0.25mg/L, respectively), but voriconazole and AmB also had in vitro activity (MIC90, 0.5mg/L and 1mg/L, respectively). Differences in antifungal susceptibility within species and between species within genera support the need for testing individual patient isolates to guide therapy. The Sensititre(YeastOne) offers a practical alternative to the reference methodology for susceptibility testing of moulds.
Elevated expression of the efflux transporter, ATP-binding cassette subfamily G isoform 2 (ABCG2) on the plasma membrane of cancer cells contributes to the development of drug resistance and is a key characteristic of cancer stem cells. In this study, gene expression analysis identified that treatment of the MCF-7 and T-47D breast cancer cell lines with the androgen, 5alpha-dihydrotestosterone (DHT), and the Hedgehog signaling inhibitor, cyclopamine, downregulated ABCG2 mRNA levels. In MCF-7 cells, and in Hoechst 33342(lo) /CD44(hi) /CD24(lo) breast cancer stem-like cells isolated from MCF-7 cultures, ABCG2 was accumulated in cell-to-cell junction complexes and in large cytoplasmic aggresome-like vesicles. DHT treatments, which decreased cellular ABCG2 protein levels, led to diminished ABCG2 localization in both cell-to-cell junction complexes and in cytoplasmic vesicles. In contrast, cyclopamine, which did not alter ABCG2 protein levels, induced accumulation of ABCG2 in cytoplasmic vesicles, reducing its localization in cell-to-cell junction complexes. The reduced localization of ABCG2 at the plasma membrane of MCF-7 cells was associated with decreased efflux of the ABCG2 substrate, mitoxantrone, and increased sensitivity of cyclopamine-treated cultures to the cytotoxic effects of mitoxantrone. Together, these findings indicate that DHT and cyclopamine reduce ABCG2 activity in breast cancer cells by distinct mechanisms, providing evidence to advocate the adjunct use of analogous pharmaceutics to increase or prolong the efficacy of breast cancer treatments.


**omega-3 Fatty Acid Ethyl Esters Diminish Postprandial Lipemia in Familial Hypercholesterolemia.**

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CONTEXT: Impaired postprandial chylomicron metabolism induces hypertriglyceridemia and may increase the risk of atherosclerotic cardiovascular disease. Omega-3 fatty acid ethyl ester (omega-3 FAEE) supplementation decreases plasma triglycerides. However, its effect on postprandial chylomicron metabolism in familial hypercholesterolemia (FH) has not yet been investigated.

OBJECTIVE: We aimed to examine the effect of omega-3 FAEE supplementation on postprandial responses in plasma triglycerides, very-low-density lipoprotein (VLDL) apolipoprotein B (apoB)-100, and apoB-48 in FH patients receiving standard cholesterol-lowering treatment.

DESIGN, SETTING, AND PATIENTS: We carried out an 8-week open-label, randomized, crossover intervention trial to test the effect of oral supplementation with 4 g/d omega-3 FAEE (46% eicosapentaenoic acid and 38% docosahexaenoic acid) on postprandial triglyceride, VLDL-apoB-100, and apoB-48 responses in FH patients after ingestion of an oral fat load.

OUTCOMES MEASURES: Plasma total and incremental triglyceride, VLDL-apoB-100, and apoB-48 0- to 10-hour area under the curve (AUC).

RESULTS: omega-3 FAEE supplementation significantly (P < .05 in all) reduced concentrations of fasting plasma triglyceride (-20%), apoB (-8%), VLDL-apoB-100 (-26%), and apoB-48 (-36%); as well as systolic blood pressure (-6%) and diastolic blood pressure (-6%). Postprandial triglyceride and VLDL-apoB-100 total AUCs (-19% and -26%, respectively; P < .01) and incremental AUCs (-18% and -35%, respectively; P < .05), as well as postprandial apoB-48 total AUC (-30%; P < .02) were significantly reduced by omega-3 FAEE supplementation.

CONCLUSION: Supplementation with omega-3 FAEEs improves postprandial lipemia in FH patients receiving standard care; this may have implications for further reducing atherosclerotic cardiovascular disease in this high-risk patient group.

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Improvement of hypertension, endothelial function and systemic inflammation following short-term supplementation with red beet (Beta vulgaris L.) juice: a randomized crossover pilot study.
Hypertension is a major risk factor for cardiovascular disease and has a prevalence of about one billion people worldwide. It has been shown that adherence to a diet rich in fruits and vegetables helps in decreasing blood pressure (BP). This study aimed to investigate the effect of raw beet juice (RBJ) and cooked beet (CB) on BP of hypertensive subjects. In this randomized crossover study, 24 hypertensive subjects aged 25-68 years old were divided into two groups. One group took RBJ for 2 weeks and the other group took CB. After 2 weeks of treatment, both groups had a washout for 2 weeks then switched to the alternate treatment. Each participant consumed 250 ml/day (−1) of RBJ or 250 g/day (−1) of CB each for a period of 2 weeks. Body weight, BP, flow-mediated dilation (FMD), lipid profile and inflammatory parameters were measured at baseline and after each period. According to the results, high-sensitivity C-reactive protein (hs-CRP) and tumour necrosis factor alpha (TNF-alpha) were significantly lower and FMD was significantly increased, but systolic and diastolic BP, intracellular adhesion molecule-1 (ICAM-1), vascular endothelial adhesion molecule-1 (VCAM-1), hs-CRP, interleukin-6, E-selectin and TNF-alpha were significantly decreased with RBJ or CB. Total antioxidant capacity was increased and non-high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol (TC) were decreased with RBJ but not with CB. Although both forms of beetroot were effective in improving BP, endothelial function and systemic inflammation, the raw beetroot juice had greater antihypertensive effects. Also more improvement was observed in endothelial function and systemic inflammation with RBJ compared with CB.


Pulmonary sclerosing pneumocytoma (sclerosing haemangioma): Radical radiation therapy.
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We present a case of pulmonary sclerosing pneumocytoma (PSP) - (Formerly known as pulmonary sclerosing haemangioma) which was successfully treated with definitive radical external beam radiation therapy (EBRT). To our knowledge, such a treatment response has not been described in the literature.

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Hemobilia due to a portal vein to common bile duct fistula from a seatbelt injury.
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Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel.
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Familial hypercholesterolaemia is common in individuals who had a myocardial infarction at a young age. As many as one in 200 people could have heterozygous familial hypercholesterolaemia, and up to one in 300 000 individuals could be homozygous. The phenotypes of heterozygous and homozygous familial hypercholesterolaemia overlap
considerably; the response to treatment is also heterogeneous. In this Review, we aim to define a phenotype for severe familial hypercholesterolaemia and identify people at highest risk for cardiovascular disease, based on the concentration of LDL cholesterol in blood and individuals' responsiveness to conventional lipid-lowering treatment. We assess the importance of molecular characterisation and define the role of other cardiovascular risk factors and advanced subclinical coronary atherosclerosis in risk stratification. Individuals with severe familial hypercholesterolaemia might benefit in particular from early and more aggressive cholesterol-lowering treatment (eg, with PCSK9 inhibitors). In addition to better tailored therapy, more precise characterisation of individuals with severe familial hypercholesterolaemia could improve resource use.

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Reducing depression during the menopausal transition with health coaching: Results from the healthy menopausal transition randomised controlled trial.

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OBJECTIVE: To determine if health coaching (HC) decreases the incidence of depression, reduces the severity of symptoms, and increases quality of life during the menopausal transition (MT).

RESEARCH DESIGN AND METHODS: Parallel, single-blinded, randomised controlled trial of 6 sessions of phone-delivered HC compared with usual care. Participants were 351 community-dwelling women free of major depression going through the MT, of whom 180 were assigned the intervention and 171 usual care. The primary outcome of interest was the incidence of clinically significant depressive symptoms over 52 weeks. Other study measures included the Hospital Anxiety and Depression Scale, quality of life (SF-12), the Menopause Rating Scale (MRS), diet, body mass index, alcohol use, smoking and physical activity. We considered that women with Patient Health Questionnaire (PHQ-9) scores between 5 and 14 (inclusive) had sub-threshold depressive symptoms.

RESULTS: Nine women developed clinically significant symptoms of depression during the study-2 had been assigned HC (odds ratio, OR=0.26, 95%CI=0.05, 1.29, p=0.099). Intention-to-treat showed that, compared with usual care, the intervention led to a greater decline in depressive scores, most markedly for participants with sub-threshold depressive symptoms. Similar, but less pronounced, benefits were noticed for anxiety scores and the mental component summary of the SF-12. The intervention led to a decline in MRS scores by week 26 and subtle improvements in body mass, consumption of vegetables and smoking.
CONCLUSIONS: HC addressing relevant risk factors for depression during the MT improves mental health measures. Our findings indicate that women with sub-threshold depressive symptoms may benefit the most from such interventions, and suggest that HC could play a useful role in minimizing mental health disturbance for women going through the MT.

Overexpression and knock-down studies highlight that a disintegrin and metalloproteinase 28 controls proliferation and migration in human prostate cancer.

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Prostate cancer is one of the most prevalent cancers in men. It is critical to identify and characterize oncogenes that drive the pathogenesis of human prostate cancer. The current study builds upon previous research showing that a disintegrin and metallproteinase (ADAM)28 is involved in the pathogenesis of numerous cancers. Our novel study used overexpression, pharmacological, and molecular approaches to investigate the biological function of ADAM28 in human prostate cancer cells, with a focus on cell proliferation and migration. The results of this study provide important insights into the role of metalloproteinases in human prostate cancer. The expression of ADAM28 protein levels was assessed within human prostate tumors and normal adjacent tissue by immunohistochemistry. Immunocytochemistry and western blotting were used to assess ADAM28 protein expression in human prostate cancer cell lines. Functional assays were conducted to assess proliferation and migration in human prostate cancer cells in which ADAM28 protein expression or activity had been altered by overexpression, pharmacological inhibition, or by siRNA gene knockdown. The membrane bound ADAM28 was increased in human tumor biopsies and prostate cancer cell lines. Pharmacological inhibition of ADAM28 activity and/or knockdown of ADAM28 significantly reduced proliferation and migration of human prostate cancer cells, while overexpression of ADAM28 significantly increased proliferation and migration. ADAM28 is overexpressed in primary human prostate tumor biopsies, and it promotes human prostate cancer cell proliferation and migration. This study supports the notion that inhibition of ADAM28 may be a potential novel therapeutic strategy for human prostate cancer.

Effects of supplementation with curcumin on serum adipokine concentrations: A randomized controlled trial.
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OBJECTIVE: Previous experimental studies have suggested curcumin as a safe phytochemical that can improve insulin
resistance through effects on adiponectin and leptin. This study aimed to investigate the effect of curcumin on circulating adiponectin and leptin concentrations in patients with metabolic syndrome.

**METHODS:** In this pilot, randomized, double-blind, placebo-controlled trial, subjects who met the criteria of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria were randomly assigned to curcumin (n = 59; 1000 mg/d) or a placebo (n = 58) for 8 wk. Serum adiponectin and leptin concentrations were determined before and after intervention. The pooled effect size for the impact of curcumin supplementation on serum adiponectin and leptin levels was also estimated using random-effects metaanalysis.

**RESULTS:** Eight-week supplementation with curcumin was associated with a significant increase in serum adiponectin levels (P < 0.001) and a reduction in serum leptin concentrations (P < 0.001). Serum leptin:adiponectin ratio was also improved by curcumin (P < 0.001). These beneficial effects of curcumin remained significant after adjustment for changes in serum lipids and glucose concentrations and baseline differences in body mass index and serum levels of glucose and glycated hemoglobin as potential confounders of treatment response. Metaanalysis suggested that curcumin supplementation can increase adiponectin levels by 76.78% (95% CI: 6.14-147.42; P = 0.0330), and reduce leptin by 26.49% (95% CI: -70.44 to 17.46), however this latter effect size did not reach statistical significance (P = 0.238).

**CONCLUSIONS:** Curcumin can improve serum levels of adiponectin and leptin in patients with metabolic syndrome. This trial was registered at the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) under Trial No. UMIN000018339.

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**Impact of commonly prescribed exercise interventions on platelet activation in physically inactive and overweight men.**

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The exercise paradox infers that, despite the well-established cardioprotective effects of repeated episodic exercise (training), the risk of acute atherothrombotic events may be transiently increased during and soon after an exercise bout. However, the acute impact of different exercise modalities on platelet function has not previously been addressed. We hypothesized that distinct modalities of exercise would have differing effects on in vivo platelet activation and reactivity to agonists which induce monocyte-platelet aggregate (MPA) formation. Eight middle-aged (53.5 +/- 1.6 years) male participants took part in four 30 min experimental interventions (aerobic AE, resistance RE, combined aerobic/resistance exercise CARE, or no-exercise NE), in random order. Blood samples were collected before, immediately after, and 1 h after each intervention, and incubated with one of three agonists of physiologically/clinically relevant pathways of platelet activation (thrombin receptor activating peptide-6 TRAP,
arachidonic acid AA, and cross-linked collagen-related peptide xCRP). In the presence of AA, TRAP, and xCRP, both RE and CARE evoked increases in MPAs immediately post-exercise (P < 0.01), whereas only AA significantly increased MPAs immediately after AE (P < 0.01). These increases in platelet activation post-exercise were transient, as responses approached pre-exercise levels by 1 h. These are the first data to suggest that exercise involving a resistance component in humans may transiently increase platelet-mediated thrombotic risk more than aerobic modalities.

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Wide-field optical coherence micro-elastography for intraoperative assessment of human breast cancer margins.
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Incomplete excision of malignant tissue is a major issue in breast-conserving surgery, with typically 20 - 30% of cases requiring a second surgical procedure arising from postoperative detection of an involved margin. We report advances in the development of a new intraoperative tool, optical coherence micro-elastography, for the assessment of tumor margins on the micro-scale. We demonstrate an important step by conducting whole specimen imaging in intraoperative time frames with a wide-field scanning system acquiring mosaicked elastograms with overall dimensions of ~50 x 50 mm, large enough to image an entire face of most lumpectomy specimens. This capability is enabled by a wide-aperture annular actuator with an internal diameter of 65 mm. We demonstrate feasibility by presenting elastograms recorded from freshly excised human breast tissue, including from a mastectomy, lumpectomies and a cavity shaving.

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Gluten content of imported gluten-free foods: national and international implications.
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Development of a video-based education and process change intervention to improve advance cardiopulmonary resuscitation decision-making.
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BACKGROUND: Advance cardiopulmonary resuscitation (CPR) decision-making and escalation of care discussions are variable in routine clinical practice. We aimed to explore physician barriers to advance CPR decision-making in an inpatient hospital setting and develop a pragmatic intervention to support clinicians to undertake and document routine advance care planning discussions.

METHODS: Two focus groups, which involved eight consultants and ten junior doctors, were conducted following a review of the current literature. A subsequent iterative consensus process developed two intervention elements: (i) an updated ‘Goals of Patient Care’ (GOPC) form and process; (ii) an education video and resources for teaching advance CPR decision-making and communication. A multidisciplinary group of health professionals and policy-makers with experience in systems development, education and research provided critical feedback.

RESULTS: Three key themes emerged from the focus groups and the literature, which identified a structure for the intervention: (i) knowing what to say; (ii) knowing how to say it; (iii) wanting to say it. The themes informed the development of a video to provide education about advance CPR decision-making framework, improving communication and contextualising relevant clinical issues. Critical feedback assisted in refining the video and further guided development and evolution of a medical GOPC approach to discussing and recording medical treatment and advance care plans.

CONCLUSION: Through an iterative process of consultation and review, video-based education and an expanded GOPC form and approach were developed to address physician and systemic barriers to advance CPR decision-making and documentation. Implementation and evaluation across hospital settings is required to examine utility and determine effect on quality of care.
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Cerebral metastases from Merkel cell carcinoma: long-term survival.

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Merkel cell carcinoma is a rare primary cutaneous neuroendocrine tumour that is locally aggressive. In most cases the primary treatment is local surgical excision; however, there is a high incidence recurrence both local and distant. Cerebral metastases from Merkel cell carcinoma are extremely uncommon with only 12 cases published in the literature. This case is particularly unusual in that, not only was no established primary lesion identified, but also the patient has survived for 10 years following initial diagnosis and for 9 years following excision of a single brain metastasis.


Genome-wide associations for birth weight and correlations with adult disease.

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Birth weight (BW) has been shown to be influenced by both fetal and maternal factors and in observational studies is reproducibly associated with future risk of adult metabolic diseases including type 2 diabetes (T2D) and cardiovascular disease. These life-course associations have often been attributed to the impact of an adverse early life environment. Here, we performed a multi-ancestry genome-wide association study (GWAS) meta-analysis of BW in 153,781 individuals, identifying 60 loci where fetal genotype was associated with BW ($P < 5 \times 10^{-8}$).

Overall, approximately 15% of variance in BW was captured by assays of fetal genetic variation. Using genetic association alone, we found strong inverse genetic correlations between BW and systolic blood pressure ($R_g = -0.22, P = 5.5 \times 10^{-13}$), T2D ($R_g = -0.27, P = 1.1 \times 10^{-6}$) and coronary artery disease ($R_g = -0.30, P = 6.5 \times 10^{-9}$). In addition, using large-cohort datasets, we demonstrated that genetic factors were the major contributor to the negative covariance between BW and future cardiometabolic risk. Pathway analyses indicated that the protein products of genes within BW-associated regions were enriched for diverse processes including insulin signalling, glucose homeostasis, glycogen biosynthesis and chromatin remodelling. There was also enrichment of associations with BW in known imprinted regions ($P = 1.9 \times 10^{-4}$). We demonstrate that life-course associations between early growth phenotypes and adult cardiometabolic disease are in part the result of shared genetic effects and identify some of the pathways through which these causal genetic effects are mediated.

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Effects of supplementation with pomegranate juice on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials.

Sahebkar A, Gurban C, et al.
BACKGROUND: Pomegranate juice (PJ) has a high content of antioxidants and bioactive polyphenols, being widely used for its antioxidant, anti-inflammatory and chemopreventive effects.

PURPOSE: The objective of this meta-analysis consisted in investigating the impact of PJ on plasma C-reactive protein (CRP) concentrations.

METHODS: The search included SCOPUS, Medline and two Iranian bibliographic databases namely MagIran and Scientific Information Database (from inception to December 09, 2014) to identify prospective trials for investigating the impact of pomegranate preparations on serum concentrations of CRP. Two independent reviewers extracted data on study characteristics, methods and outcomes.

RESULTS: Among 427 participants in the selected studies, 216 were allocated to PJ groups, and 211 to control group. Meta-analysis of data from 5 eligible randomized controlled trials (RCTs) arms did not provide compelling evidence as to a significant CRP-lowering effect of supplementation with pomegranate juice (WMD: -0.22 mg/l, 95% CI: -0.45, 0.01, p = 0.061). The impact of pomegranate juice on plasma CRP levels was found to be independent of duration of supplementation (slope: 0.003; 95% CI: -0.005, 0.011; p = 0.444).

CONCLUSION: In conclusion, this meta-analysis of data from 5 prospective trials did not indicate a significant effect of PJ on plasma CRP levels, and this effect was independent of duration of supplementation.

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Lipid profile changes after pomegranate consumption: A systematic review and meta-analysis of randomized controlled trials.
Sahebkar A, Simental-Mendia LE, et al.

BACKGROUND: Transport of oxidized low-density lipoprotein across the endothelium into the artery wall is considered a fundamental priming step for the atherosclerotic process. Recent studies reported potential therapeutic effects of micronutrients found in natural products, indicating positive applications for controlling the pathogenesis of chronic cardiovascular disease driven by cardiovascular risk factors and oxidative stress. A particular attention has been recently addressed to pomegranate; however findings of clinical studies have been contrasting.

PURPOSE: To evaluate the effects of pomegranate consumption on plasma lipid concentrations through a systematic review and meta-analysis of randomized controlled trials (RCTs).

METHODS: The study was designed according to the preferred reporting items for systematic reviews and
meta-analysis (PRISMA) statement. Scopus and Medline databases were searched to identify randomized placebo-controlled trials investigating the impact of pomegranate on plasma lipid concentrations. A fixed-effects model and the generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the one-study remove approach. Random-effects meta-regression was performed to assess the impact of potential confounders on the estimated effect sizes.

RESULTS: A total of 545 individuals were recruited from the 12 RCTs. Fixed-effect meta-analysis of data from 12 RCTs (13 treatment arms) did not show any significant effect of pomegranate consumption on plasma lipid concentrations. The results of meta-regression did not suggest any significant association between duration of supplementation and impact of pomegranate on total cholesterol and HDL-C, while an inverse association was found with changes in triglycerides levels (slope: -1.07; 95% CI: -2.03 to -0.11; \( p = 0.029 \)). There was no association between the amount of pomegranate juice consumed per day and respective changes in plasma total cholesterol, LDL-C, HDL-C and triglycerides.

CONCLUSION: The present meta-analysis of RCTs did not suggest any effect of pomegranate consumption on lipid profile in human.

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Traumatic gallbladder rupture: a patient with multiple risk factors.
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Isolated gallbladder rupture following blunt thoracoabdominal trauma is rare; gall bladder rupture is seen in <1% of blunt abdominal trauma. This case report describes a significant mechanism of blunt force injury resulting in an isolated gallbladder rupture. Risk factors for traumatic gallbladder rupture are reviewed and the authors propose that a stiff, cirrhotic liver may exacerbate shear forces in the gallbladder fossa and represents an important risk factor for blunt gallbladder injury. Cholecystectomy remains the definitive management for gallbladder trauma. Almost all gallbladder injuries following blunt trauma are associated with other significant intra-abdominal injuries and in the setting of acute trauma, the authors recommend an open procedure to facilitate a detailed exploration of the peritoneal cavity to exclude associated injuries.

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Leiomyosarcoma of great saphenous vein localised to the calf.
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We present the case of a 76-year-old man with a 2-month history of mildly tender swelling in the right calf for which he had an initial excision and then a wide local excision followed by a split skin graft because the initial histopathology confirmed that there was a Grade I leiomyosarcoma of great saphenous vein. A simple lump in the lower limb could be a malignant vascular tumour and should always be considered in the list of differential diagnosis of a lump in the lower limb.


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BACKGROUND: In some rheumatic diseases such as systemic lupus erythematosus (SLE), low serum complement ('hypocomplementaemia') is a feature of active disease. However, the role of hypocomplementaemia in systemic sclerosis (SSc) is unknown. We sought to determine the frequency, clinical associations and relationship to disease activity of hypocomplementaemia in SSc.

METHODS: The study included 1140 patients fulfilling the 2013 American College of Rheumatology criteria for SSc. Demographic, serological and clinical data, obtained prospectively through annual review, were analysed using univariable methods. Linear and logistic regression, together with generalised estimating equations, were used to determine the independent correlates of hypocomplementaemia ever, and at each visit, respectively.

RESULTS: At least one episode of hypocomplementaemia (low C3 and/or low C4) occurred in 24.1 % of patients over 1893 visits; these patients were more likely to be seropositive for anti-ribonucleoprotein (OR=3.8, p=0.002), anti-Ro (OR=2.2, p=0.002), anti-Smith (OR=6.3, p=0.035) and anti-phospholipid antibodies (OR=1.4, p=0.021) and were more likely to display features of overlap connective tissue disease, in particular polymyositis (OR=16.0, p=0.012). However, no association was found between hypocomplementaemia and either the European Scleroderma Study Group disease activity score or any of its component variables (including erythrocyte sedimentation rate) in univariate analysis. Among patients with SSc overlap disease features, those who were hypocomplementaemic were more likely to have digital ulcers (OR=1.6, p=0.034), tendon friction rubs (OR=2.4, p=0.037), forced vital capacity <80 % predicted (OR=2.9, p=0.008) and lower body mass index (BMI) (OR for BMI=0.9, p<0.0005) at that visit, all of which are features associated with SSc disease activity and/or severity.

CONCLUSIONS: While hypocomplementaemia is not associated with disease activity in patients with non-overlap SSc,
it is associated with some features of increased SSc disease activity in patients with overlap disease features.

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**Maintaining sufficient serum vitamin d levels over 2 years is associated with reduced knee structural and symptomatic changes in patients with knee osteoarthritis.**

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Background/Purpose: To examine whether those maintaining sufficient serum vitamin D levels have reduced knee structural changes and symptomatic improvement compared with those not maintaining sufficient serum vitamin D levels over 2 years in patients with knee osteoarthritis (OA). Methods: Participants (n= 413, age 63.2; 50% females) with symptomatic knee OA and vitamin D insufficiency were enrolled in a multicentre, parallel randomized, placebo-controlled and double-blind clinical trial. 340 participants (82.3%) completed the study as well as 25-hydroxyvitamin D [25(OH)D] measurements at month 3 and month 24. In the post-hoc analyses, participants were classified as maintaining insufficient vitamin D group (Group 1, serum 25(OH)D<50nmol/l at month 3 and month 24, n=45), fluctuating vitamin D group (Group 2, 25(OH)D>50nmol/l only at one point, n=68) and maintaining sufficient vitamin D group (Group 3, 25(OH)D>50nmol/l at month 3 and month 24, n=226). Serum 25(OH)D were measured at baseline, month 3 and month 24 using direct competitive chemiluminescent immunoassays. Knee structural changes including cartilage volume, cartilage defects, bone marrow lesions (BML) and effusion-synovitis volume were assessed using magnetic resonance imaging (MRI) at baseline and month 24. Knee pain was assessed at baseline, month 3, 6 12 and 24 using Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analogue scale. Results: Patients in Group 3 had significantly less tibial cartilage volume loss per year (beta: 2.2, 95% CI: 0.4, 4.0) and change in effusionsynovitis volume per year (beta: -61.8, 95% CI: -133.4, -1.7) than participants in Group 1 (Figure 1 and Figure 2). The differences remained significantly after further adjustment for age, sex, BMI and season of blood sampling (beta: 2.1, 95 CI%: 0.3, 3.9 and beta: -61.8, 95 CI%: -121.9, -1.7, respectively). There were no significant differences in changes of tibiofemoral cartilage defects and BML between Group 3 and other two groups. Patients in Group 3 had significantly less loss of WOMAC physical function (beta: -94.8, 95% CI: -183.1, -6.6) than others two groups in the mixed-effect models. Conclusion: Patients maintaining sufficient serum vitamin D at month 3 and 24 had less cartilage volume loss, less increase in effusionsynovitis volume and more improvement in physical function compared with those not maintaining sufficient serum vitamin D over 2 years in symptomatic knee OA patients with vitamin D insufficiency. These findings suggesting that maintaining sufficient 25(OH)D is beneficial for structural change and functional improvement in knee osteoarthritis. (Figure presented).

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**Can the use of customised growth charts at a low/medium risk maternity service improve the the detection of intrauterine growth restriction?**
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Introduction: A Small-for-Gestational-Age (SGA) fetus is one weighing less than the tenth centile for its gestation. It is important to differentiate SGA babies who are constitutionally small, but physiologically normal, from those pathologically growth restricted. Correctly identifying intrauterine growth restriction (IUGR) allows better antenatal,
intrapartum and postnatal care. Customised growth charts (CGC) have been proposed as a means of adjusting growth charts for tailor-made fetal growth assessment based on maternal parameters (age, parity, weight, height, ethnicity). This can be valuable with changing obstetric trends, e.g. increasing obesity, immigration, childbearing age. However, introducing CGC implies a change in clinical practice, resource management, cost and potential clinical errors. A 2014 Cochrane review shows little research on CGC in low-risk women. We investigate if CGC can improve IUGR detection in a low/medium-risk population. Method: All singletons over 34 weeks, born over a one-year period at a low/medium-risk hospital and weighing less than the standard 10th centile for their gestation were re-plotted on CGC. Cases with differing results were examined. Results: Of 2137 births, 139 (6.5%) were SGA. 18 were excluded (insufficient data, multiple births). Of the remaining 121 (5.7%), 104 (86%) remained SGA on CGC. The physiological parameters of the other 14% were appreciably different (e.g. 72% v/s 31% non-Caucasians). The likelihood ratio of using CGC was 1.008, implying minimal difference between the charts. Number needed to treat is 125 to avoid one misdiagnosis. Conclusion: Routine use of CGC is unlikely to benefit our institution, but care providers should consider them when significant maternal physiological deviations exist.

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**Systematic review of randomised controlled trials of vaginal hysterectomy (VH), laparoscopically assisted vaginal hysterectomy (LAVH), and total laparoscopic hysterectomy (TLH) in women with benign gynaecological disease.**

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Introduction: The recent Cochrane review on benign hysterectomy suggests that laparoscopic hysterectomies were slower and associated with more bleeding than VH. The role of Total Laparoscopic Hysterectomy (TLH) or Laparoscopically Assisted Vaginal Hysterectomy (LAVH) in women suitable for VH remains uncertain. Hence we aim to present a systematic review of randomised controlled trials (RCTs) comparing TLH, LAVH and VH for the benign gynaecological disease. Methods: Six electronic databases and the world-wide-web without language restrictions were searched from 1989 until date. The manual search included journals and abstracts of international conferences. The keywords used were: laparoscopic, hysterectomy, laparoscopically assisted, vaginal, outcome, randomiz(s)ed and benign. Results: Out of the 757 articles identified in the primary search, three RCTs fulfilled the criteria for this systematic review. Of 323 women in three RCTs 107 were allocated to the TLH group, 110 to the LAVH group, 106 to the VH group. Outcomes evaluated were operative time, complications, blood loss, hospital stay, conversion rate and paralytic ileus duration time. Pooled results indicate that VH (65.3 19 min) required the shortest operating time in contrast to LAVH (99.8 47 min) or TLH (120 36 min); VH had the lowest blood loss (163.6 53 ml) compared to LAVH (321.33 67 ml) or TLH (212.66 68 ml); Women who underwent VH had the shortest hospital stay (49.35 24 hours) versus LAVH (74.35 35 hours) or TLH (62.65 28 hours). Complications, conversion rate and paralytic ileus duration were similar in all three groups. Discussion: Vaginal hysterectomy had the shortest operating time, the shortest hospital stay and least drop in Hb, making it a preferred technique for benign gynaecological disease if technically feasible.

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**Laparoscopic suturing in 2 easy steps.**

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Introduction: In open and vaginal surgery, haemostasis is usually secured using sutures. In laparoscopic surgery, we rely on energy because laparoscopic suturing is challenging. Thermal spread from repeated energy application near the uterine or IP ligament can cause immediate or delayed damage to the ureters, but laparoscopic suturing has too
long a learning curve despite the many suturing workshops that are run. Methods: Laparoscopic surgery was performed in hospitals following laparoscopic skills exercises in training centres. Surgery and training compared the uptake of laparoscopic suturing skills when using (a) conventional needle-handling techniques and technology and (b) an innovative needleholder with an integrated needle that articulates through 90 degrees. Results: During training, surgeons and fellows in cohort (b) experienced quick uptake of laparoscopic suturing skills which were then confidently translated to laparoscopic surgery. Laparoscopic surgery in this study exhibited less bleeding and quicker suturing completion than is typical with conventional suturing techniques and technology. These trends were particularly apparent for surgeons previously less comfortable with laparoscopic suturing. For VH/LAVH surgeons, the transition to TLH requiring pedicle ligation and laparoscopic vaginal cuff closure was easier than previously experienced when attempting conventional laparoscopic suturing techniques. Discussion: Incorporating the needle-holder and needle in a single device frees the user from complicated needle-handling manoeuvres. Even inexperienced users performed Laparoscopic Suturing in 2 Steps by learning an extracorporeal knot and using the device to place the suture, starting with simple exercises, after only minutes of basic training. Pedicle ligation, cuff closure and organ repairs are possible for gynaecologists at any level.

PMID:613101679

Laser therapy as a treatment modality for genitourinary syndrome of menopause: A critical appraisal of evidence.
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Introduction: Genitourinary syndrome of menopause (GSM) is characterised by symptoms such as vaginal dryness, dyspareunia, pain, urinary incontinence, and urinary tract infections. Several therapeutic options are available to alleviate these symptoms including hormonal and non-hormonal products. Laser therapy has gained interest as a nonhormonal therapeutic option for GSM. We aimed to do a systematic review on laser therapy for symptoms of GSM. Methods: Six electronic databases and the world-wide-web without language restrictions were searched from inception until date. The manual search included journals and abstracts of international conferences, including oral podium and poster presentations. The keywords used when searching for the relevant articles were: Genitourinary syndrome, vulvovaginal atrophy, postmenopausal symptoms, laser therapy and fractional laser treatment. Results: Out of the 165 articles identified in the search, no randomised controlled trials were found. As a result, we included five well-designed multi-centric case-control/cohort studies that met our inclusion criteria. The total number of women included in the 4 studies was 224. Due to lack of Level-1 evidence (RCTs), it was impossible to compare the studies. Median follow-up was 12 weeks. Discussion: The collated evidence data suggest that the laser therapy appears to be effective in the treatment of GSM. The lack of RCTs made it difficult to meta-analyse the studies based on the PRISMA statement. All studies report observed results up to a maximum of 6 months with no further followup. Higher quality of evidence in the form of randomised controlled trials involving laser treatment is required to investigate the efficacy in the treatment of GSM.
PMID:613101659

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Excellent SVR12 rates with Viekira Pak in a real-world cohort of HCV Genotype 1 patients predominantly with cirrhosis—the Australian REVITAL Study.
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Background In phase III registration trials, ritonavir boosted paritaprevir, with ombitasvir and dasabuvir (PrOD) +/- ribavirin was safe, well tolerated and had excellent efficacy with SVR12 rates >95%. However, real-world data on the safety and efficacy of PrOD therapy in cirrhotic patients is limited. Methods Between October 2014 and July 2015, a compassionate access program supported by AbbVie Pty Ltd was conducted in Australia across 47 treatment centers. Patients were included if they received at least one dose of PrOD. Primary end-points were SVR12 (HCV viral load < LLOQ at least 12 weeks post treatment) and drug discontinuation rates due to adverse events. The frequency and nature of serious adverse events with particular focus on death, hepatic decompensation and grade 4 biochemical abnormalities were collected. Results In this current analysis of 461 patients (74% cirrhosis, 9.8% CPB) complete treatment outcome data was available in 86% (n=395), with an overall SVR of 95.5%. SVR12 rates were similar for cirrhotic and non-cirrhotic patients (95.5% and 97.8%, respectively). Most patients were infected with Genotype 1a (64%) and most received ribavirin (90%). Baseline features of the fully characterized patients are shown in Table 1. Similar to previous reports, baseline viral load, MELD score and liver stiffness did not influence SVR. Early cessation of therapy occurred in 6.1% of patients and in these patients SVR12 was lower at 53%. Hyperbilirubinaemia on therapy was common with 4.3% of patients developing hyperbilirubinaemia > 100mumol/L. To date no deaths have been reported, 34 patients (7.4%) required hospital admission, 9 patients (2.0%) developed hepatic decompensation, Grade 4 laboratory abnormalities occurred in 10 patients (2.2%). Conclusion In a real-world setting, treatment with PrOD in Genotype 1 HCV infection achieves excellent SVR12 rates including in those with cirrhosis. Hepatic decompensation occurred infrequently. (Table Presented).

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Background: The objective of this analysis was to evaluate factors associated with rapid biochemical and virologic responses to treatment with tenofovir alafenamide (TAF) or tenofovir dipiroxil (TDF), and predictors of discordance between ALT normalization and viral suppression. Methods: The study included HBV-infected adults enrolled in two Phase 3 studies of TAF 25 mg QD vs. TDF 300 mg QD (Study GS-US-321-0108 in HBeAg- and GS-US-321-110 in HBeAg+ subjects). At Week 12, virologic suppression was defined as HBV DNA <29 IU/mL (Roche COBAS Taqman) and ALT normalization was defined according to reference ranges recommended by AASLD (<19 U/L for women, <30 U/L for men). The associations between host, viral, and treatment-related predictors with combined virologic suppression and ALT normalization at Week 12 were determined using logistic regression analyses. Among patients
with HBV DNA suppression at Week 12, the characteristics of patients with normal vs. elevated ALT were also compared. Results: Based on AASLD criteria, 1,276 of 1,301 randomized subjects (98%) had abnormal baseline (BL) ALT. The median BL ALT and HBV DNA were 82 U/L (IQR 56-126) and 7.4 log<sub>10</sub> IU/mL (IQR 5.8-8.3), respectively. In total, 194 patients (16%) normalized ALT by Week 12; 96 of these patients (49%; 8% of the total) also achieved virologic suppression. The proportion of subjects achieving ALT normalization and virologic suppression at Week 12 was higher among TAF- vs. TDF-treated subjects (9.0% vs. 5.0%; P=0.013). Among patients with suppressed HBV DNA at Week 12, 39% (75/190) in the TAF group and 24% (21/89) in the TDF group normalized serum ALT (P=0.010). Patients with persistently elevated ALT despite virologic suppression at Week 12 had a higher prevalence of diabetes (8.7% vs. 5.2%; P=0.346), hypertension (16.9% vs. 6.3%; P=0.015), dyslipidemia (9.3% vs. 4.2%; P=0.154), and overweight (BMI>=25, 37.7% vs. 27.1%; P=0.085) compared with those with normal ALT. In a multivariate analysis, treatment with TAF (odds ratio [OR] 2.78; 95% CI 1.44-5.37; P=0.002), HBeAg-negativity (OR 3.12; 95% CI 1.63-5.98; P=0.001), lower BL HBV DNA (OR per log<sub>10</sub> IU/mL: 0.53; 95% CI 0.43-0.64; P<0.001), male sex (OR 2.48; 95% CI 1.38-4.45; P=0.002), and the absence of cirrhosis (OR 7.35; 95% CI 1.70-31.87; P=0.008), were independent predictors of achieving biochemical normalization and virologic suppression at Week 12. Conclusions: A minority of patients with CHB achieve ALT normalization and virologic suppression after 12 weeks of oral antiviral therapy. Treatment with TAF compared with TDF is independently associated with achieving this endpoint.

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Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard therapy: The Australian tapestry study.

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Background Conventional therapy of autoimmune hepatitis (AIH) is with corticosteroids with or without azathioprine. However 20% of patients do not respond or are intolerant to standard therapy. Thus, we evaluated the efficacy and safety of mycophenolate mofetil (MMF) in AIH patients who had failed or were intolerant to corticosteroids with or without azathioprine. Methods A retrospective study was performed of AIH patients who received MMF alone or in combination with prednisolone after failure or intolerance of standard therapy. Patients were recruited from 16 liver clinics across Australia via the ALA Clinical Research Network. Records were reviewed for baseline demographics and liver disease characteristics, initial therapy, indications for MMF initiation, treatment outcome and complications. Results A total of 96 patients (mean age 45.3 yrs, females 86.5%, Caucasian 53%, cirrhosis 19.8%) received treatment with MMF for AIH across the 16 centres including 95 in combination with corticosteroids. The majority (73%) had received prior combination therapy with corticosteroids plus azathioprine/6-mercaptopurine. The indication for MMF was non-response in 43% and intolerance to standard therapy in 53%. The median starting and maximal doses of MMF received was 1g/m/d and 2g/m/d respectively; the median treatment duration was 31.9 months. Overall, 44 (45.9%) patients achieved biochemical remission on MMF after a median treatment duration of 11 weeks, 8 (18%) of whom relapsed during follow up. Of the 40 patients treated for non-response, 17 (42.5%) achieved biochemical remission after a median of 12 weeks, while 8 (20%) had an incomplete response and 3 (7.5%) had treatment failure. Of the 49 patients receiving MMF for intolerance/toxicity, 27 (55%) achieved remission, with 4 (8%) having an
incomplete response and 1 (2%) treatment failure. 8 patients required dose-reduction and 16 discontinued MMF mainly due to lack of efficacy (n=6) or intolerance (n=6). Serious adverse events occurred in 3 patients (1 death, 2 hospitalisations), while there were 23 significant complications including GI toxicity (n=8), infection (n=5), cytopenias (n=3), neuropsychiatric (n=3), skin cancer (n=2), and lymphoproliferative disorder (n=1). Conclusions Treatment with MMF combined with corticosteroids in AIH patients who fail to respond or are intolerant to standard therapy is moderately effective achieving an overall remission rate of around 50% including 43% in non-responders to standard therapy. MMF appears relatively safe and well tolerated with the main side-effects being GI toxicity, infection, and cytopenias.

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Background and Aims In October 2015 the FDA released a warning on the use of ritonavir-boosted paritaprevir, with ombitasvir and dasabuvir (PrOD) +/- ribavirin in patients with cirrhosis. Consequently PrOD is now contraindicated in patients with Child-Turcotte Pugh class B/C hepatic impairment. Both hyperbilirubinemia and elevated ALT concentrations have been observed during therapy but the severity and clinical significance of these abnormalities in a real-world setting have not been reported. The aims of this study were to characterize the bilirubin and ALT changes observed during PrOD therapy in a large real-world population and to determine the impact of these changes on outcome (SVR12 and early discontinuation of therapy). Methods Patients who participated in an Australian compassionate access program to treat hepatitis C between October 2014 and July 2015 were included in the analysis if they received at least one dose of PrOD. Elevations in bilirubin were characterized in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Results There were 461 patients included in this analysis. The majority had cirrhosis (74%). In the 88% of cirrhotic patients with complete response data, the SVR12 was 95.5%. Hyperbilirubinemia on PrOD was very common with elevated values > 2mg/dL (34mumol/L) occurring in 45.1 % of subjects (Table 1). A small proportion of patients had mild elevation (>2mg/dL in 6.5%) prior to comemncing. In the 9 patients that experienced elevations in bilirubin >10 mg/dL, all were cirrhotic, 89% developed hyperbilirubinemia within the first 4 weeks of therapy and 78% ceased therapy early (mean 4.79 weeks +/- 1.5). In most instances the ALT diminished on PrOD (88%, mean 58 IU/L +/-4.4), however in 11 patients (2.4%) there was an increase in ALT of at least 100 IU/L from baseline. This was not associated with hyperbilirubinemia and 73% were cirrhotic with SVR12 of 80%. Conclusions In this real-world study of HCV genotype 1 patients mostly with cirrhosis, SVR12 rates were excellent. Hyperbilirubinemia occurred commonly but in most instances the abnormality was only mild-moderate and did not lead to discontinuation or significantly impact upon SVR 12. In a small proportion of patients the bilirubin exceeded 10mg/dL and this frequently resulted in early discontinuation. (Table Presented).
**High efficacy in patients with chronic hepatitis C virus (HCV) Genotype (GT)1b infection treatment with elbasvir/grazoprevir for 12 weeks: An integrated analysis.**

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GT1b is the most common HCV genotype globally, accounting for the largest proportion of infections in Europe, Latin America, Russia, Turkey, and East Asia. We report the efficacy of 12 weeks of once-daily elbasvir/grazoprevir (50 mg/100 mg) (NS5A inhibitor/NS3/4 protease inhibitor) in HCV GT1b-infected patients enrolled in the clinical development program. This analysis of treatment-naive and treatment-experienced GT1b-infected patients used data pooled from 11 trials involving 30 countries and included 1070 patients with/without cirrhosis, chronic kidney disease (CKD), and HIV co-infection. Cirrhosis (F4, compensated) was confirmed by either liver biopsy or noninvasive tests. Patients with Stage 4 or Stage 5 CKD on hemodialysis were included. HIV/HCV co-infected patients were required to be on a stable antiretroviral regimen (ARV) (tenofovir or abacavir, emtricitabine or lamivudine, and either raltegravir, dolutegravir, or rilpivirine) with CD4 >200/mL and HIV viral load undetectable, or if not on ARVs, have CD4 >500/mL and viral load <50,000 IU/mL. The primary endpoint was the proportion of patients with HCV RNA below the lower limit of quantitation 12 weeks after treatment (SVR12). Efficacy data are presented for the full analysis set (FAS), which includes all patients who received at least one dose of study medication, and for the per-protocol (PP) population, which excludes nonvirologic failures. A total of 1,070 patients were included in the analysis. Mean patient age was 53.7 years (range, 19-80); 50% were male; 47% were white, 43% were Asian, and 9% were black or African American; 20% were treatment-experienced; 39% had a baseline viral load >2,000,000 IU/mL; and 18% had evidence of cirrhosis. SVR12 was 97% (1040/1070) in the FAS; 15 patients (1.4%) were categorized as virologic failures and 15 (1.4%) were categorized as nonvirologic failures (lost-to-follow-up or withdrawal). Excluding the nonvirologic failures, SVR12 was 99% (1040/1055) in the PP analysis. There were no notable differences in subgroup analyses: SVR12 was 97% in both treatment-naive and treatment-experienced patients; 99% in cirrhotics and 97% in noncirrhotics; 98% in patients with a baseline viral load <2,000,000 IU/mL and 97% in patients with a baseline viral load >2,000,000 IU/mL; 94% in HIV/HCV co-infected patients; and 100% and 95% in patients with Stage 4 or 5 CKD, respectively. High efficacy was achieved in the GT1b-infected population treated with elbasvir/grazoprevir for 12 weeks, with comparable efficacy across subgroups, including those with cirrhosis, high baseline viral load, and prior treatment failures.

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**-3 fatty acid ethyl esters diminish postprandial lipemia in familial hypercholesterolemia.**

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Context: Impaired postprandial chylomicron metabolism induces hypertriglyceridemia and may increase the risk of atherosclerotic cardiovascular disease. Omega-3 fatty acid ethyl ester (-3 FAEE) supplementation decreases plasma triglycerides. However, its effect on postprandial chylomicron metabolism in familial hypercholesterolemia (FH) has not yet been investigated. Objective: We aimed to examine the effect of -3 FAEE supplementation on postprandial responses in plasma triglycerides, very-low-density lipoprotein (VLDL) apolipoprotein B (apoB)-100, and apoB-48 in FH patients receiving standard cholesterol-lowering treatment. Design, Setting, and Patients: We carried out an 8-week open-label, randomized, crossover intervention trial to test the effect of oral supplementation with 4 g/d -3 FAEE (46% eicosapentaenoic acid and 38% docosahexaenoic acid) on postprandial triglyceride, VLDL-apoB-100, and apoB-48 responses in FH patients after ingestion of an oral fat load. Outcomes Measures: Plasma total and incremental triglyceride, VLDL-apoB-100, and apoB-48 0-to 10-hour area under the curve (AUC). Results: -3 FAEE supplementation significantly (P <.05 in all) reduced concentrations of fasting plasma triglyceride (-20%), apoB (-8%), VLDL-apoB-100 (-26%), and apoB-48 (-36%); as well as systolic blood pressure (-6%) and diastolic blood pressure (-6%). Postprandial triglyceride and VLDL-apoB-100 total AUCs (-19% and -26%, respectively; P <.01) and incremental AUCs (-18% and -35%, respectively; P <.05), as well as postprandial apoB-48 total AUC (-30%; P <.02) were significantly reduced by -3 FAEE supplementation. Conclusion: Supplementation with -3 FAEs improves postprandial lipemia in FH patients receiving standard care; this may have implications for further reducing atherosclerotic cardiovascular disease in this high-risk patient group. Copyright © 2016 by the Endocrine Society.


Results of vedolizumab use in the ‘real world’.
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Background and Aims: Vedolizumab was approved for the treatment of moderate to severe Crohn’s disease (CD) and ulcerative colitis (UC) on the PBS on 1 August 2015. The published data from the registration studies of this medication have been impressive for UC and to a lesser extent, for CD. The aim of this study was to evaluate the efficacy and safety of vedolizumab in the treatment of moderate to severe CD and UC in the ‘real world’ setting. Methods: This was a retrospective chart analysis of 21 patients that completed at least 3 induction doses of vedolizumab (300 mg) at two tertiary hospitals. Patients were at least 18 years of age and satisfied the PBS criteria for the treatment of moderate to severe CD and UC with vedolizumab. Only patients with complete data were included. Efficacy was defined by a response (CDAI drop of 100 points for CD and a 30% or a 3 point drop in partial mayo score for UC), or remission (CDAI<150 for CD or partial Mayo score <2 with no individual score >1 for UC). Results: Twenty-one patients met the inclusion criteria. Ten (48%) were males. The mean age in years was 41. Nine patients (43%) had CD, and the rest had UC. The mean duration of disease was 8 years. The mean duration of treatment with vedolizumab for both conditions overall was 26 weeks. Ten patients had failed 1 anti-TNFa agent, while another 7 had failed 2 agents. Twelve of 21 (57%) patients were not on an immunomodulator at the time of vedolizumab commencement due to intolerance or previous inefficacy. Overall, at the time of follow up, as of 5 May 2016, 18 patients (85%) had achieved a response (89% for CD, 83% for UC), and 15 (71%) had achieved remission (78% for CD, 67% for UC). Neurological symptoms were the most commonly reported adverse event, including headaches (n = 2), memory loss and mild confusion in 1 patient. The latter patient also had severe prolonged nasopharyngitis. No hospitalisations or deaths occurred during the follow up period. No patients had required surgery at the time of follow up. Conclusions: The efficacy of vedolizumab in ‘real world’ practice appears to be superior to published data, and no major safety concerns have been observed.

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Frequency and severity of hyperbilirubinaemia with Viekira Pak in a real-world cohort of HCV genotype 1 patients-Predictors and clinical significance.

Background and Aims: Ritonavir-boosted paritaprevir, with ombitasvir and dasabuvir (PrOD or Viekira Pak) +/- ribavirin was listed on the PBS in May 2016 and is indicated for patients with compensated hepatitis C virus (HCV) genotype 1. In phase 3 clinical trials, PrOD has been shown to be safe, well tolerated and have excellent efficacy with SVR12 rates >95%. Hyperbilirubinaemia has been observed during therapy, but the severity and clinical significance of these abnormalities in a real-world setting have not been widely reported. The aims of this study were to characterize the bilirubin changes observed during PrOD therapy and to determine the impact of these changes on outcome (SVR12; defined as HCV viral load < LLOQ at least 12 weeks post treatment) and early discontinuation of therapy.

Methods: Biochemical data were obtained from patients who received PrOD therapy as part of an Australian compassionate access program to treat hepatitis C (supported by AbbVie Pty Ltd) between October 2014 and July 2015. Patients were included in the analysis if they received at least one dose of PrOD. Elevations in bilirubin were characterized in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Results: There were 404 patients included. The majority of patients had cirrhosis (74%) with genotype 1a (65%) infection. Key baseline features of the patients are shown in Table 1. The overall SVR12 was 96% (data complete in 85%). Hyperbilirubinaemia on therapy was very common, with elevated values >17 mumol/L occurring in 82.6% (Table 2). Nearly 5% of patients on PrOD therapy developed bilirubin values >100 mumol/L. However, hyperbilirubinaemia was noted at baseline in 39% of patients prior to commencing PrOD although most of these patients had only mild elevation (17> and < 34, 83%). During therapy, 19 patients experienced Grade 3 or 4 (14 Grade 3, 5 Grade 4) elevations in bilirubin (range 101-578 mumol/L), and these occurred exclusively in cirrhotic patients (4.6% of CPA, 19.4% of CPB, P = 0.0076). Nearly all Grade 3/4 elevations in bilirubin occurred in the first 4 weeks of therapy (84%). Only 14% of patients with elevations between 100 and 200 mumol/L (Grade 3) received a shortened duration of therapy and the SVR12 rate was 91.7% (data available in 85.7%), whereas all those with bilirubin >200 mumol/L (Grade 4) ceased therapy early (mean 3.26 weeks +/- 2.2) with a significantly reduced SVR12 of 25% (data available in 80%). Changes in mean bilirubin concentration in cirrhotic and non-cirrhotic patients during therapy are shown in Fig. 1. Conclusions: In this real-world study of HCV genotype 1 patients mostly with cirrhosis, SVR12 rates were excellent. Hyperbilirubinaemia occurred commonly, but in most instances, the abnormality was only mild-moderate and did not lead to discontinuation or significantly impact upon SVR12. In a small proportion of patients, the bilirubin exceeded 200 mumol/L, and this frequently resulted in early discontinuation. As a result of discontinuation, the SVR12 was significantly reduced in these patients, all of whom were cirrhotic and more commonly with Child-Pugh Class B. (Figure Presented).

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Excellent SVR12 rates with Viekira Pak in a realworld cohort of HCV genotype 1 patients predominantly with cirrhosis-the Australian REV1TAL study.
Background and Aims: In phase III registration trials, ritonavir boosted paritaprevir, with ombitasvir and dasabuvir (PrOD or Viekira Pak) +/- ribavirin was safe, well tolerated and had excellent efficacy with SVR12 rates >95%. However, real-world data on the safety and efficacy of PrOD therapy in cirrhotic patients are limited. Recently, the FDA requested additional information to the drug label, warning of the possibility of liver injury in those with advanced liver disease. The REV1TAL study is the largest real-world study evaluating the safety and efficacy of PrOD therapy in cirrhotic patients with genotype 1 chronic hepatitis C infection. Methods: Between October 2014 and July 2015, a compassionate access program supported by AbbVie Pty Ltd was conducted in Australia across 47 viral hepatitis treatment centers most of which were affiliated with the Australian Liver Association Clinical Research Network (ALA CRN). Patients were included if they received at least one dose of PrOD. The primary end-points were SVR12 (HCV viral load<LLOQ at least 12 weeks post treatment) and drug discontinuation rates due to adverse events. Local physicians reported the frequency and nature of serious adverse events with particular focus on death, hepatic decompensation and grade 4 biochemical abnormalities observed within 3 months of completing therapy. Results: The program provided PrOD therapy to 582 adult patients with HCV genotype 1. The top 20 ALA CRN treating sites recruited approximately 500 patients, and complete data are available on 404 patients. The majority of patients had cirrhosis (74%) with genotype 1a (65%) infection. Baseline features of the fully characterized patients are shown in Table 1. In this interim analysis of 404 patients (74% cirrhosis, 9.3% CPB), the overall SVR12 was 96% (data complete in 85%). SVR12 rates were similar for cirrhotic and non-cirrhotic patients (96.0% and 97.4%, respectively). Similar to previous reports, baseline viral load, MELD score and liver stiffness did not influence SVR. Early cessation of therapy occurred in 5.5% of patients and in these patients SVR12 was lower at 56%. Hyperbilirubinaemia on therapy was common, with nearly 5% of patients developing hyperbilirubinaemia > 100 mumol/L. Serious adverse effects are shown in Table 2. Conclusions: In a real-world setting, treatment with PrOD in genotype 1 HCV infection achieves excellent SVR12 rates including those with cirrhosis. Hyperbilirubinaemia is a frequent on-treatment finding, but hepatic decompensation resulting in early cessation of therapy is rare. (Table Presented).
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Background: Conventional therapy of autoimmune hepatitis (AIH) is with corticosteroids with or without azathioprine. However, 20% of patients do not respond or are intolerant to standard therapy. Thus, we evaluated the efficacy and safety of mycophenolate mofetil (MMF) in AIH patients who had failed or were intolerant to corticosteroids with or without azathioprine. Methods: A retrospective study was performed of AIH patients who received MMF alone or in combination with prednisolone after failure or intolerance of standard therapy. Patients were recruited from 16 liver clinics across Australia via the ALA Clinical Research Network. Records were reviewed for baseline demographics and liver disease characteristics, initial therapy, indications for MMF initiation, treatment outcome and complications.

Results: A total of 96 patients (mean age 45.3 yrs, females 86.5%, Caucasian 53% and cirrhosis 19.8%) received treatment with MMF for AIH across the 16 centres including 95 in combination with corticosteroids. The majority (73%) had received prior combination therapy with corticosteroids plus azathioprine/6-mercaptopurine. The indication for MMF was non-response in 43% and intolerance to standard therapy in 53%. The median starting and maximal doses of MMF received was 1 g/d and 2 g/d, respectively; the median treatment duration was 31.9 months. Overall, 44 (45.9%) patients achieved biochemical remission on MMF after a median treatment duration of 11 weeks, 8 (18%) of whom relapsed during follow up. Of the 40 patients treated for non-response, 17 (42.5%) achieved biochemical remission after a median of 12 weeks, while 8 (20%) had an incomplete response and 3 (7.5%) had treatment failure. Of the 49 patients receiving MMF for intolerance/toxicity, 27 (55%) achieved remission, with 4 (8%) having an incomplete response and 1 (2%) treatment failure. Eight patients required dose-reduction, and 16 discontinued MMF mainly due to lack of efficacy (n = 6) or intolerance (n = 6). Serious adverse events occurred in 3 patients (1 death and 2 hospitalisations), while there were 23 significant complications including GI toxicity (n = 8), infection (n = 5), cytopenias (n = 3), neuropsychiatric (n = 3), skin cancer (n = 2), and lymphoproliferative disorder (n = 1).

Conclusions: Treatment with MMF combined with corticosteroids in AIH patients who fail to respond or are intolerant to standard therapy is moderately effective achieving an overall remission rate of around 50% including 43% in non-responders to standard therapy. MMF appears relatively safe and well tolerated with the main side-effects being GI toxicity, infection, and cytopenias.

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Screening blood tests in the management of hepatitis C.
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Introduction: Screening blood tests to exclude other causes of liver disease were a routine part of the pre-treatment protocol of hepatitis C (HCV) management in the era of interferon based therapy. Additional screening tests cost approximately $179 (per patient) to the health system. Methods: Retrospective analysis of 333 patients who underwent HCV treatment. We analyzed the number of abnormal results from commonly performed screening tests. We determined the use of metabolic tests in identifying patients who should be followed up following HCV eradication. Results: Patients ranged from age 17 to 76 years (mean age of 46). 71.2% of patients were male and were predominantly of Caucasian descent (74.8%). On screening, none of the patients had a low (<0.17 g/L) caeruloplasmin, 1.3% had a low (<0.9 g/L) alpha-1 antitrypsin level (A1AT), 9.6% had a positive smooth muscle antibody (SMA), with majority of patients having a low titre, and 9.4% had a positive antinuclear antibody (ANA) (5/15 patients had cryoglobulinaemia). Two hundred fifteen patients (64.6%) had BMI >25, with 82 (24.6%) of those having a BMI >30. Consistent with general population data, mean values for metabolic risk factors (apart from LDL) were significantly higher in overweight/obese patients who had HCV. In the group of patients who have achieved a SVR, 36/217 had a persistently elevated ALT (ALT > 19U/L for women, >30U/L for men). In this group, 13 of 36 were cirrhotic. There was a positive correlation between BMI, insulin, triglyceride, and TC:HDL with ALT (Table 1). There was also an inverse relationship between HDL and ALT. The number of metabolic risk factors was also significantly higher in the group with persistently high ALT (2.4 vs 1.9, p = 0.0286). Both groups were well matched for Hepscore and alcohol intake. There was a significant difference in mean values of BMI, insulin, and insulin resistance index.
(HOMA-IR) between the 2 groups (Table 2). Conclusion: Screening tests (caeruloplasmin, A1AT, SMA, ANA) in patients with HCV should not be routinely performed due to low yield. This would allow for significant cost savings to the health system. Patients with elevated ALT post SVR should be investigated for multiple metabolic risk factors which could increase the risk of hepatic inflammation and progressive liver disease. (Table Presented).

Conclusion: Screening tests (caeruloplasmin, A1AT, SMA, ANA) in patients with HCV should not be routinely performed due to low yield. This would allow for significant cost savings to the health system. Patients with elevated ALT post SVR should be investigated for multiple metabolic risk factors which could increase the risk of hepatic inflammation and progressive liver disease. (Table Presented).
TAF, a novel prodrug of tenofovir (TFV), is more stable in plasma and enhances delivery of TFV into hepatocytes while lowering circulating levels of TFV by approximately 90% compared to TDF. In this Phase 3 study, patients with HBeAg-negative CHB were randomized 2:1 to TAF 25mg QD or TDF 300mg QD, each with matching placebo, for 96weeks. After Week 96, patients receive open label TAF for 48weeks. The primary efficacy analysis was the percent of patients with HBV DNA <29 IU/mL at Week 48; the study was powered to demonstrate non-inferiority in efficacy of TAF compared to TDF, with a 10% margin. Key prespecified secondary safety endpoints were assessed sequentially: changes in hip and spine bone mineral density (BMD), changes in serum creatinine (sCr), and dipstick proteinuria. Markers of bone formation and resorption, and renal tubular function were also assessed. Viral resistance was evaluated by population sequencing those patients with virologic breakthrough, or viremia at time of discontinuation. A total of 425 patients were randomized and treated at 105 sites in 17 countries. Baseline characteristics included mean age 46 years, 61% males, 72% Asians, genotypes A through D (5%, 24%, 38%, and 31%); 19% had HBV DNA> 7 log10 IU/mL, and 21% were previously treated with nucleos(t)ides. Key efficacy/safety end points are summarized in the Table. At Week 48, TAF was non-inferior in efficacy to TDF with virologic response rates of 94.0% with TAF and 92.9% with TDF (difference in proportions: +1.8%, 95% CI, -3.6% to +7.2%). A greater percentage of patients treated with TAF also achieved normalization of serum ALT values. Patients on TAF experienced significantly less declines in hip and spine BMD than TDF. No differences were seen in sCr change and proteinuria; however, smaller declines in eGFR and smaller changes in renal tubular markers were observed in the TAF arm. The rates of treatment discontinuations and serious adverse events were low and similar in the two arms. No viral resistance was observed in the4 patients (2 per group) who qualified for testing. Compared to TDF 300mg, the efficacy of TAF 25mg in patients with HBeAg-negative CHB was noninferior. Safety was also improved, with less change in bone and renal parameters. (Table Presented).

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**The effect of omitting alfa-fetoprotein in surveillance of hepatocellular carcinoma.**


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Background: Surveillance for hepatocellular carcinoma (HCC) in patients with cirrhosis improves early detection and survival. Screening techniques have traditionally included 6 monthly serum alfa-feto protein (AFP) and liver ultrasound (US). Due to its low sensitivity and specificity, AFP has been recently removed from the EASL guidelines that now recommend US as the sole screening technique. However, it is also noted that certain HCC may express AFP and not be detected on initial US. This usually prompts further investigation with CT or MRI scan. Omitting AFP from screening may result in a delay in diagnosis or missed cancer. Aims: To determine the proportion of HCC patients from our database with raised AFP and a negative ultrasound at time of diagnosis. Methods: We retrospectively reviewed the AFP and US results of our HCC patients from 2008 to 2015. HCC was diagnosed predominantly on the basis of cross sectional imaging criteria (MRI or CT scan), with others having histological evidence. The two groups were compared using the Fisher’s exact test. Results: One-hundred twelve patients were diagnosed with HCC during this period. Fifty-four patients were diagnosed on surveillance US, and 58 diagnosed due to symptoms or abnormal blood tests. A greater proportion of patients undergoing surveillance were diagnosed at early BCLC stage (0-B) compared with those with symptoms (P = 0.0067) (Table 1). Seventeen of the 54 patients who were diagnosed on screening had died, with the mean time to death from diagnosis of 20.9 months. Twenty-one of 58 patients that were diagnosed due to symptoms/abnormal blood tests died, with a mean time to death of 13.8 months. Ninety-five patients had both an initial US and AFP done. Of these, 7 (7.4%) had a raised AFP (with a normal US) that prompted further investigation with CT or MRT, which subsequently led to a diagnosis of HCC. The patients with a raised AFP and normal initial US were diagnosed at the following Barcelona Clinic Liver Cancer (BCLC) stage - 4 stage A, 1 stage B and 2 stage C. Four
out of five of the patients with early stage (0-B) HCC were treated with a curative intent: 1 microwave ablation, 2 referred for liver transplantation assessment, and 1 patient received transarterial chemoembolization (TACE) and subsequently referred for liver transplant assessment. Conclusion: Surveillance in appropriate patient populations results in diagnosis of earlier stage HCCs. Concurrent use of AFP for screening contributed to the diagnosis of 7.4% of HCCs, which would have otherwise been missed or had delayed diagnosis. Furthermore, AFP allowed diagnosis of HCC at earlier stage which helped facilitate curative therapies. Despite its limitations, AFP remains an important component of HCC surveillance. (Table Presented).

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Ruptured hepatocellular carcinoma-experience in a tertiary centre.
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Introduction: Ruptured hepatocellular carcinoma (HCC), although uncommon, is associated with poor outcomes. It is often associated with cirrhosis and reported to occur in 3-15% of HCC. We present our experience in the management of ruptured HCC in a tertiary centre over a 15-year period. Design: Retrospective review of patients from 2000 to 2015 who had spontaneous HCC rupture, also including one case of intraoperative tumour rupture. Data was extracted from case notes as well as electronic laboratory management system, and imaging results from IMPAX 6.5.
Results: Four of 5 cases were identified from the HCC database (2008- 2016) of 150 patients with HCC, from Royal Perth Hospital. All but 1 patient was under the age of 50 years, and all but 1 patient was male. Four of 5 had hepatitis B (HBV) as the underlying aetiology. Four of 5 had a single lesion, with the remaining 1 patient presenting with multifocal HCC. They all had large lesions >6 cm. One patient had portal vein invasion, and 1 other patient had gallbladder/hepatic vein invasion on histology. Only 2 patients underwent resection. Two had transarterial chemoembolization (TACE), and one had only sorafenib. In one patient (Case 1), delayed treatment (due the patient’s initial reluctance) led to significant tumour growth, and ultimately rupture. Only 2/5 patients developed intra-abdominal metastatic disease. All patients eventually developed progression of their disease. Conclusion: 1 In our series of patients, the most common aetiology for HCC was hepatitis B (HBV). 2 Rupture of HCC occurred in 3/5 patients in the absence of cirrhosis. 3 All of the lesions were large, and most were solitary. 4 HCC rupture is generally associated with a poor prognosis, with early recurrence and death. Early treatment of tumours is vital to prevent growth and potential rupture. (Table Presented).
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Radio-guided occult lesion localisation using Iodine-125 seeds (ROLLIS) randomised controlled trial: Impact on patient satisfaction.
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Objective/Introduction: Radioguided occult lesion localisation using iodine-125 seed (ROLLIS) is an emerging alternative to standard hookwire localisation (HWL). (1-6) We present patient satisfaction survey results from an ongoing randomised controlled trial (RCT) comparing ROLLIS and HWL. Methods and materials: In the institutional
ethics board approved RCT, participants with biopsy proven breast cancer were randomised and underwent either ROLLIS insertion or HWL prior to excision at three major Western Australian tertiary health institutions. Patient satisfaction surveys were administered consisting of questions pertaining to additional stress and discomfort caused by the localisation procedure. Participants provided a score for the questions on a Likert scale from 1 to 7. In all cases, higher scores reflected greater stress and discomfort. Clinical parameters were also obtained. Statistical analysis of localisation technique against the scores of the questionnaire was performed. Results: Satisfaction responses from 217 participants were obtained, with 108 participants randomised to HWL and 109 randomised to ROLLIS. Participants who underwent ROLLIS were less likely to report greater stress (OR 0.53, p = 0.014) and discomfort (OR 0.54, p = 0.016) than if they underwent HWL. Conclusion: These findings indicate that pre-operative localisation with ROLLIS induces less stress and discomfort in breast cancer patients undergoing breast conserving surgery when compared to conventional HWL.

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**Acute gastrointestinal bleeding: An algorithmic approach.**
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Learning objectives: 1 To develop a diagnostic imaging algorithm based on the best available evidence. 2 Computed tomography angiogram (CTA) is a precursor to angiography and embolisation. Background: Acute gastrointestinal (GI) bleeding is a potentially life-threatening condition that requires rapid assessment, diagnosis and treatment.1 Distinction between upper and middle or lower GI bleeding may be made clinically or by passage of a nasogastric tube. Dependent on this, endoscopy and/or sigmoidoscopy (or colonoscopy where feasible) are recommended for initial diagnostic evaluation. If a source is not identified, or is identified but unable to be treated by endoscopic means at this time, then further radiological investigation is required. Imaging details: CTA is the recommended first line radiological modality to investigate acute gastrointestinal bleeding following nondiagnostic and/or non-therapeutic endoscopy. It is rapid, non-invasive and able to identify the source of bleeding at rates as low as 0.5 mL/min.1,2,3 Recent evidence has shown that CTA can be used for risk stratification - a positive result can guide angiography and embolization or surgery, while a negative result can suggest a 'watch and wait' approach.2,3 Angiographic embolization has comparable results to surgery for rebleeding rates and mortality.4,5 Red blood cell scintigraphy is useful in selected cases when bleeding is intermittent and the cause remains obscure. Unless there is haemodynamic instability, localising studies such as CTA and RBC scintigraphy should be undertaken prior to angiography to ensure that there is active bleeding.1,3,6 Follow-up studies, usually by endoscopic means, are required following successful non-surgical intervention to clarify or diagnose the exact aetiology of the bleed. Other follow-up modalities, such as capsule endoscopy, enteroscopy or radiological small bowel studies, are needed for obscure GI bleeds that cease spontaneously. Conclusion: A diagnostic imaging algorithm for acute gastrointestinal bleeding will aid appropriate use of investigations and reduce unnecessary exposure to ionizing radiation. CTA as a first line radiological investigation will aid with risk stratification and can be used to guide angiographic intervention or surgery.
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**Pictorial review of the ultrasound appearances of ductal carcinoma in situ.**
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Learning Objectives: To increase awareness of the range of sonographic appearances of ductal carcinoma in situ (DCIS). Background: DCIS is a tumour cell proliferation within the terminal ductal lobular unit, confined by an intact basement membrane. While extensive research is occurring into ways to distinguish biologically significant DCIS, early detection and core biopsy sampling remain vital. While often detected on mammography as a calcified lesion, awareness of the spectrum of sonographic appearances is important. Identification of a sonographic lesion in association with mammographically indeterminate microcalcifications can enable realtime sampling using ultrasound guidance, replace time-consuming radiographic biopsies and increase the likelihood of detecting the biologically significant invasive component.1, 3, 4 Imaging Findings: The sonographic appearances of DCIS may include: an isoechoic or hypoechoic mass, dilated ducts with or without irregular walls or internal nodularity and subtle areas of altered echotexture. Clustered microcysts may also be seen which can mimic benign breast change. Calcified lesions may contain echogenic foci. Mass lesions are round, oval or irregular shape with partially circumscribed margins which may show micro or macrolobulations. In some lesions vascularity is detected with Doppler ultrasound, a feature known to increase the positive predictive value.1 Conclusion: Sonographic manifestations of DCIS may be subtle and challenging, requiring the use of high resolution transducers and optimal technique.5 Awareness of the range of possible appearances is important to maximize detection.


12-month cumulative radiation dose exposure in premature infants born in Western Australia.
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Purpose: Ionizing radiation exposure in premature infants is an important public health concern as the long term effects of early radiation exposure at this age are still not known.1 Animal studies have suggested that premature newborns have increased radiosensitivity and yet monitoring of the amount of ionizing radiation exposure during an infant’s hospital stay is not routinely practiced.2,3 The purpose of this study was to quantify the number of imaging instances and the amount of ionizing radiation exposure in infants <37 weeks gestational age. Methods and materials: A retrospective audit was undertaken of the number and type of imaging instances in children born at a quaternary obstetrics hospital in W.A over a 12-month period. The population was derived from the statewide midwives database “Neobase” and linked with the radiological information system (RIS) database. Between October 2013 and September 2014, 865 premature infants (mean gestational age 32 weeks, range of gestational age 23- 36.9 weeks) had imaging instances. Imaging instances were classified as chest radiograph, abdominal radiograph, combined abdominal and chest radiograph ("babygram"), peripheral radiograph (e.g. skull or limb), pelvis radiograph, computed tomography, nuclear medicine, fluoroscopy and other. Results: A total of 5286 imaging instances occurred during the 12- month period. The median number of imaging instances per infant was three and there was a range of 1-87. In decreasing order of frequency, chest radiography had 3199 instances (60.5%), abdominal radiograph had 738 instances (14.0%) and combined abdominal and chest radiograph had 596 instances (11.3%). Computed tomography made up only 45 imaging instances (0.9%) and this statistic is similar to earlier publications.2 A significant Pearson correlation was found between gestational age and the number of imaging instances, with each additional week of gestational age leading to a 13% reduction in imaging instances undertaken to the infant. Conclusion: Auditing our imaging practice is essential to limiting radiation exposure to premature neonates as we are not certain of its long term effects to their health. Our results indicate that we have a comparable number of imaging instances to other international published cohorts.1,2,3,4,5.

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Could parenchymal enhancement on Contrast Enhanced Spectral Mammography (CESM) represent a new breast cancer risk factor?
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Purpose: Contrast Enhanced Spectral Mammography (CESM) has similar accuracy to Contrast Enhanced MRI (CEMRI)1-4 and may offer an economical alternative. Mammographic Breast Density (MBD)5, MRI Fibroglandular Tissue volume (FTV)6 and CEMRI Background Parenchymal Enhancement (BPE)7 are recognised breast cancer risk factors. Whether this is true for CESM BPE is currently unknown. Emerging evidence suggests CESM BPE correlates with MBD and CEMRI BPE.8,9 We evaluate possible relationships between CESM BPE, CEMRI BPE, MBD and FTV.

Methods and materials: Participants enrolled into an Ethics Committee- approved breast cancer staging study between June 2012- Oct 2015 underwent full field digital mammograms (FFDM), CEMRI and CESM. Modalities were rated by two independent readers. MBD was assessed on FFDM, and FTV on CEMRI using ACR BI-RADS 2003 criteria: 1 = predominantly fatty 0-24%; 2 = mixed fibroglandular densities 25-49%; 3 = heterogeneously dense 50-74%, 4 = extremely dense 75-100%. CESM BPE was assessed using ACR MRI BI-RADS criteria: minimal, mild, moderate, marked.11 Inter-reader reliability was estimated using a weighted kappa(k) coefficient. Correlations between CESM BPE, FTV, MBD and MRI BPE were calculated using Spearman correlation coefficient. Time between CESM and CEMRI, date of last menstrual period and menopausal status was recorded. Association with hormone status and BPE was determined using multilevel mixed model analysis. Results: 62 women (35-77 years) were included. Median time between CESM and CEMRI was 4 days (range: 0-15 days). MBD was measured as BI-RADS level 1 in 33%, 2 in 38%, 3 in 23%, 4 in 6%; with moderate inter-reader agreement (k = 0.52 95% CI: 0.355- 0.648). FTV was scored as BI-RADS level 1 in 25%, 2 in 30%, 3 in 35%, 4 in 10% with substantial inter-reader agreement (k = 0.77 95% CI: 0.626-0.857). CESM BPE was minimal in 42%, mild in 30%, moderate in 22%, marked in 6%; with substantial inter-reader agreement (k = 0.84 95% CI: 0.76-0.91). CEMRI BPE was minimal in 28%, mild in 29%, moderate in 35%, marked in 8% with fair interreader agreement (k = 0.25 95% CI: 0.04-0.47). CESM BPE showed significant correlation with FTV (q = 0.50, p < 0.0001), MBD (q = 0.356, p < 0.001); and MRI BPE (q = 0.46, p < 0.0001). BPE was significantly reduced in the post menopausal group for both MRI and CESM (p < 0.001). There is a similar association with menstrual phase and BPE on MRI and CESM. Conclusion: CESM BPE is significantly correlated with MBD, FTV and CEMRI BPE. Inter-reader reliability is better in CESM compared to CEMRI. Thus, CESM BPE may have an important role as a predictor of breast cancer risk.

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Does the radiographer influence a women's likelihood of attending subsequent rounds of breast cancer screening?
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Purpose: Breast cancer is the most common cancer affecting women in Australia and remains the second most common cause of cancer-related death among women.1 Screening programmes can be effective in lowering breast cancer mortality, with a 70% biennial screening rate associated with a 32% lower breast cancer mortality (compared to zero screening).2,3 It is vital to encourage and maintain attendance to screening programmes. Multiple factors have previously been investigated including physical barriers and patient factors. 2,4,5 Qualitative evidence has shown that care and communication at time of initial mammogram can affect a women’s decision to attend subsequent screening rounds.6,7,8 To our knowledge individual re-screen rate according to radiographer has not previously been investigated. Methods and materials: Eleven radiographers employed by WA Breastscreen continuously for the period 2007 - 2013 were identified. Women that were screened during this period were identified according to the radiographer performing the mammogram. The proportion of women who returned for subsequent screens was then calculated according to index radiographer. Chi square test was performed, using R version 3.2.2, to analyse this data. Complaints made by women against screening radiographers were reviewed. Results: 31613 women had an initial
screening mammogram between 2007-2013 performed by one of 11 radiographers. Rates of re-attendance to any subsequent screening rounds varied significantly according to the radiographer performing the initial screen, range 75.5% - 88.5%, p < 0.001. Rates of complaints against individual radiographers also varied. Conclusion: Radiographers have significantly differing re-attendance rates. There is also variation in the frequency of complaints made against individual radiographers, these factors may be related. Our findings provide quantitative evidence to support published literature, derived from focus groups and questionnaires, which demonstrated a women’s experience of care and communication with staff influenced her intention to attend subsequent screens.6,7,8 Maintaining high re-screen rates is essential to a successful screening program. Therefore it is essential that further research is performed to identify the reasons behind these differing rates and provide education and retraining as appropriate.

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Inter-observer variation of polyp measurement at CT colonography (CTC).
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Purpose: The concept of ‘advanced polyps’ is well accepted - polyps >10 mm and/or a villous component and/or areas of dysplasia. CTC can only document size. The management of CTC-discovered ‘advanced polyps’ is to recommend excision, whereas management of ‘intermediate’ (6-9 mm) polyps it is more controversial; interval surveillance is acceptable. Therefore, distinction between 6-9 mm and >10 mm is important. Since a variation in measurement of 1 mm may lead to a category difference and change in patient management,1-4 we investigated observer variation in polyp measurement within a range around 10 mm. Methods and Materials: Datasets were reviewed by four radiologists, independently, showing 26 polyps originally reported as between 8 and 12 mm in diameter. The polyps were ‘bookmarked’ to ensure that each observer examined the same polyps. Datasets were viewed on a Philips workstation (Extended Brilliance Workspace v.June 20th 2012; CT Colonography software v4.5.5.51035). Observers tabulated the largest measurement for each polyp on axial, coronal, sagittal and endoluminal views at lung-window settings. The largest measurement for each polyp for each observer was used to determine inter-observer variation. These measurements were also compared to those determined by the computer-aided detection (CAD) software. Results: The inter-observer reliability intra-class correlation coefficient (ICC) for sagittal projection was 0.80 ['excellent' category of Hosmer and Lemeshow (2004)], 0.71 for axial ('acceptable'), 0.69 for coronal and 0.41 for endoluminal ('unacceptable'). However, there was a large variance for each of these projections so that the largest of sagittal/axial/coronal gave the best reliability with the smallest variance (ICC = 0.80, 95% CI 0.67-0.89). For 8 of 26 polyps (31%), at least one radiologist measured the polyp in a different category compared to a colleague. For the majority of the polyps, the CAD significantly over-estimated the readings compared to the largest of the manual measurements with an average difference of 1.6 mm (p < 0.0001 for sagittal/axial/coronal). This resulted in 33% of polyps falling into a different category, 10% were lower and 23% were higher (p < 0.034). Conclusion: It is apparent that around the cut-off point of 10 mm between ‘advanced’ and ‘intermediate’ polyps, inter-observer performance is variable. The implications of this result for readers of CTC examinations will be discussed. Options for improvement include, taking the maximum measurement from sagittal, axial and coronal projections; double/multiple reporting of relevant polyps. In addition, nuanced reporting should be practised taking into account the patient’s age and co-morbidities.

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Inflammatory breast diseases: Mimics of breast carcinoma.
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Background: The radiologist plays a central role in the diagnosis and appropriate management of breast disease in both diagnostic and screening settings. Therefore, the breast radiologist needs to be aware of benign inflammatory conditions that resemble breast carcinoma. Non-puerperal sub-areolar abscess, Mammary duct ectasia, Granulomatous mastitis and Diabetic mastopathy are such conditions that are illustrated here with pathological correlation. Imaging Findings: Non-puerperal sub-areolar abscess is strongly associated with cigarette smoking and tend to recur. On mammography it will exhibit retro areolar skin thickening associated with ill-defined mass or asymmetry. On ultrasound they can be complex cystic lesions or masses with increased vascularity. It needs to be differentiated from an inflammatory breast carcinoma at initial presentation (1). Mammary duct ectasia is characterized by dilatation, periductal inflammation and fibrosis of central mammary ducts. On mammography it is visualized as needle-like calcifications, dilated ducts or a stellate mass. On ultrasound the dilated ducts in the sub-areolar region are seen filled with echogenic material together with surrounding inflammation (2). Granulomatous Mastitis (GM) of the breast is either idiopathic or secondary to infections or other systemic disease. On ultrasound GM is described as exhibiting multiple irregular hypoechoic masses or collections with finger like tubular interconnections. At initial stages it could be a heterogeneous hypoechoic mass. Mammographic features are non-specific with asymmetric opacities and parenchymal distortion (3). Biopsy diagnosis is essential to exclude a breast carcinoma. Diabetic mastopathy (DM) is uncommon and linked to longstanding diabetes. It frequently portrays appearance of a lobular carcinoma. On mammography, it may show asymmetry. On ultrasonography, it can be an irregular hypoechoic mass exhibiting significant acoustic shadowing(4). Presentation could be incidental or a breast lump. Identical histological appearance in the absence of diabetes is reported as Lymphocytic mastitis. Conclusion: It is important for radiologists to be aware of clinical, radiological and pathological appearances of inflammatory breast diseases for their optimal management.

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Painless visible haematuria: An algorithmic approach to diagnosis.
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Learning Objectives: Any single episode of visible haematuria (VH) is significant and may be a sign of serious underlying disease, including malignancy.1 Prompt diagnosis is essential and appropriate imaging strategies, based on risk stratification, are discussed. Background: The prevalence of all urologic malignancies among patients who present with VH is 22.0-24.2%.2-4 Symptoms overlap with benign disorders, therefore diagnosis is often delayed and can lead to a worsened prognosis. A literature search of MEDLINE through PubMed was conducted in September 2015 for evidence regarding imaging in VH. The following diagnostic imaging algorithm for painless VH (pVH) takes into consideration the pre-test probabilities for UCC and has been proposed by combining best evidence with expert consensus. Imaging Findings: Ultrasound (US) 1 Has a higher sensitivity (96% versus 25%) and negative predictive value (98% versus 91%) than IVU in detecting abnormalities of the upper urinary tract (UUT).5-7 2 Useful in radiation-sensitive populations (children, pregnancy and child-bearing age women). However, when compared with CT, US has an overall lower sensitivity in detecting urinary tract abnormalities.6 Computed tomographic urography (CTU): Has a sensitivity of 88- 100% and specificity of 93-100% for UCC detection 8 but is associated with a relatively
high dose of ionising radiation.5-9 Magnetic resonance urography (MRU): Is emerging as an alternative method for imaging the urinary tract and is useful especially in imaging obstructive uropathy. Its sensitivity in detecting urothelial lesions remains under investigation but is believed to be lower than CTU.5, 10 Static-fluid MRU is useful for patients with renal impairment. Demonstrates promising results for diagnosing bladder tumours (T2WI+DWI) and UUT cancers (T1 + T2WI+DWI), with good sensitivities and excellent inter-observer agreement.11, 12 Cystoscopy: Remains the reference standard for detection of lower urinary tract (bladder) urothelial tumours 9,13 and should be performed following initial non-invasive imaging on all patients with pVH and risk factors for malignancy, regardless of age.13. Conclusion: In low risk patients (<40 years of age) with pVH, the prevalence of UCC does not justify the risk of radiation exposure with CTU and US is recommended as the initial investigation. Any patient with pVH >40 years of age are classified as high risk and CTU is indicated due to the higher prevalence of UCC in this group.14, 15 Cystoscopy is still the method of choice for the evaluation of the urinary bladder and should not be replaced by any excretory imaging technique.8.

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The diagnostic imaging dilemmas of suspected pulmonary embolism in pregnancy: What is the current evidence?

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Solid pulmonary nodules (SPNs): An update on the approach to investigation.

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Learning Objectives: Investigation of SPNs should be guided by risk of malignancy. Background: The aim of investigation of SPNs is to determine which nodules are malignant early, whilst limiting unnecessary ionising radiation exposure and invasive procedures.1 Radiological and clinical criteria are used to stratify nodules according to malignancy risk. A PubMed literature search was conducted in February 2016 for evidence regarding imaging surveillance of SPNs. A diagnostic imaging algorithm for SPNs detected on CT is proposed by combining best evidence with expert consensus. Imaging Findings: Computed tomography (CT) Nodule size and characteristics provide information regarding malignancy risk and determine need for further investigations. Patients with nodules diameter <5 mm have a probability of malignancy that is not statistically different to patients without nodules and thus require no further investigation.2 Patients with nodules 5-8 mm are at intermediate risk and nodules >8 mm are high risk. These warrant CT surveillance or further investigation such as biopsy.2 Diagnostic yield of CT-guided biopsy decreases with decreasing nodule size and is higher with core biopsy than with aspiration.3 SPNs are classified as solid or sub-solid (part-solid or pure ground glass) according to attenuation. Being different pathologically and prognostically 4, 5 they require different management Benignity predictors include diffuse, central, laminated or popcorn calcification and perifissural location.5-7 Malignancy predictors include increasing diameter, spiculation, pleural indentation and upper lobe location.4 Risk prediction models (e.g the Brock model) combine radiological and clinical predictors to assess malignancy risk, and have been shown to be more accurate than individual clinical judgement.8 Intermediate and low risk nodules following <sup>18</sup>FDG-PET are suitable for CT surveillance. Repeat CT at 3 months for larger nodules will reliably detect growth but will have greater accuracy for detecting malignancy at 1 year. 9 3D volumetric analysis is more accurate than diameter measurements and, where available, should be used to calculate Volume Doubling Time (VDT).4,10 VDT<400 days indicates significantly higher cancer risk.2 The point of termination for surveillance has been proposed by comparing the risk of malignancy compared to baseline risk.218 FDG-PET FDG-PET remains the preferred investigation for further SPN evaluation as it has high sensitivity and moderate specificity for large solid nodules.4,11 Risk prediction models (Herder model) are improved by the addition of FDG-PET scan results.12 Conclusion: Early detection of SPNs with malignant potential may have a significant impact on outcomes. CT characteristics and risk prediction models help determine risk of malignancy and guide further investigation.

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Cytomegalovirus reactivation in the critically ill septic intensive care patient: pathogen or passenger?

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Cytomegalovirus reactivation in the critically ill septic intensive care patient: pathogen or passenger?

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**25-Hydroxyvitamin D C3-epimer is universally present in neonatal Western Australian samples but is unlikely to contribute to diagnostic misclassification.**

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BACKGROUND: The presence of C3-epimer (C-3-epi-25-hydroxyvitamin D) in infant serum may complicate 25-hydroxyvitamin D (25(OH)D) measurement when using liquid chromatography tandem mass spectrometry assays that do not separately measure the epimer. We measured the concentration of C3-epi-25(OH)D in neonatal samples in Western Australian using umbilical cord blood samples and a liquid chromatography tandem mass spectrometry assay that separately quantifies 25(OH)D and C3-epi-25(OH)D.

METHODS: A total of 120 anonymized cord blood samples were analysed using a liquid chromatography tandem mass spectrometry assay that utilizes two CSH fluoro-phenyl columns in series. Chromatography was performed on a Waters Acquity Ultra Performance Liquid system, and quantification was using a Waters Quattro Premier XE mass spectrometer.

RESULTS: C3-epi-25(OH)D3 was detected in all umbilical cord blood samples (median 5.2nmol/L, IQR 3.7-6.6nmol/L) and contributed 6.6% (SD 2.6, 95% CI [6.1, 7.1]) of the total 25(OH)D concentration. Mean 25(OH)D3 measured in cord blood was 79.1nmol/L (SD 22.7nmol/L). A positive relationship (R(2)=0.35, P<0.0005) between 25(OH)D3 levels and C3-epi-25(OH)D3 was noted in this cohort. No samples contained 25(OH)D2 or C3-epi-25(OH)D2.

CONCLUSION: C3-epi-25(OH)D3 is present in all neonatal samples but contributes <10% of the total 25(OH)D concentration which is unlikely to be clinically significant. Liquid chromatography tandem mass spectrometry assays that do not separately quantify C3-epi-25(OH)D3 from other vitamin D metabolites may potentially overestimate neonatal 25(OH)D levels, but diagnostic misclassification in neonates is unlikely.

Risk of 'Coroner's clot' from the use of laryngeal mask airway during oropharyngeal surgery.

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Incidental internal acoustic meatus lipoma in a 68-year-old male.

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Inflammatory breast cancer (IBC) is an aggressive and rare form of breast cancer. At present, there are no established diagnostic, radiological, pathological or molecular diagnostic criteria for this entity. The aim of this study was to examine the patterns of presentation, treatment and outcomes of IBC in this institution over the course of a decade. This is a retrospective observational study using data from the Royal Perth Hospital from January 2001 to December 2010. Our results identified 57 women with IBC, representing 1.9% of all new breast cancer presentations. Human Epidermal Growth Factor Receptor 2 (HER2)-positive and triple negative tumors were overrepresented (41% and 18%, respectively). Forty-four (77%) patients had early disease at diagnosis, of whom 35 underwent surgery and 16 are relapse-free. All six patients achieving complete pathological response were relapse-free in contrast to 11 (38%) with lesser responses at a median follow-up of 59 months. Median survival in 13 patients with metastatic disease at diagnosis was 21.7 months, with two patients still in remission. Clearly, this small but important group continues to offer management challenges and warrants ongoing study, including better molecular and pathological profiling of tumors to allow improved diagnostic clarity and more effective targeted therapy.

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Angiographic progression of coronary atherosclerosis in patients with familial hypercholesterolaemia treated with non-statin diet and a resin.

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BACKGROUND AND AIMS: Familial hypercholesterolaemia (FH) profoundly increases the risk of coronary artery disease (CAD). We investigated whether diet and a bile-acid sequestrant decrease coronary atherosclerosis in patients with FH.

METHODS: We identified 26 men with FH and CAD, participating in the St Thomas’ Atherosclerosis Regression Study, who had been randomized to receive a fat-modified diet plus cholestryamine (8 g twice daily) (DC, n = 12) or usual care (UC, n = 14), and investigated the relative effects of these treatments on the angiographic progression of
coronary atherosclerosis over 39 months. FH was defined as probable/definite according to Dutch Lipid Clinic Network criteria; mean FH score was 8.7 (range 6-15) and mean baseline low-density lipoprotein cholesterol (LDL-Ch) concentration was 5.4 (SD 1.4) mmol/L. Coronary atherosclerosis was assessed by serial quantitative angiography as the global changes in mean and minimum absolute width of segments (MAWS and MinAWS, respectively).

RESULTS: Mean plasma LDL-Ch concentration fell by 35% with DC and remained significantly (p < 0.001) lower during the trial at 3.78 (SD 0.98) mmol/L compared with UC at 4.89 (1.04). MAWS decreased by 0.252 (SEM 0.072) mm in the UC group and by 0.001 (0.065) mm in the DC group (p = 0.007), with corresponding reductions in MinAWS of 0.290 (0.087) mm and 0.013 (0.058) mm (p = 0.009); these changes were significant after adjusting for baseline variables, including coronary luminal dimensions and lipoprotein(a). Progression was observed in 7 patients (50%) on UC and 3 (25%) on DC (p = 0.19), with regression in no patients (0%) and 3 patients (25%) (p < 0.05), respectively.

CONCLUSIONS: This investigation, carried out in the pre-statin era, demonstrates that a prudent diet and cholestyramine could improve the course of coronary atherosclerosis in men with phenotypic FH through sustained reductions in LDL-Ch.

BACKGROUND: There are conflicting reports concerning the outcome after anaesthesia guided by the surgical pleth index (SPI; GE Healthcare, Helsinki, Finland). One potential explanation may be the lack of evidence for the selection of SPI cut-off values. The aim of this trial was to investigate the correlation between SPI, arousal, and postoperative pain and to define a cut-off value for SPI to predict moderate-to-severe pain.

METHODS: After obtaining ethical approval and written informed consent, 70 patients undergoing non-emergency surgery were enrolled. Data relating to SPI, heart rate, mean arterial pressure, and state entropy were recorded every 10 s for the last 10 min of surgery (state entropy <60 at all times). Subsequently, recordings continued during the phase of arousal. After recovery room admission, pain scores (numerical rating scale 0-10) were obtained every 3 min for 15 min.

RESULTS: Data from 65 patients were analysed. Receiver-operating characteristic curve analysis revealed an optimal intraoperative cut-off SPI value of 30 to discriminate between numerical rating scale scores 0-3 and 4-10. For this value, the negative and positive predictive values to discriminate between numerical rating scale scores 0-3 and 4-10 were 50 and 89.7%, respectively. The SPI was significantly affected by arousal, and SPI scores obtained during this phase were not predictive of postoperative pain.

CONCLUSIONS: Surgical pleth index values are predictive of postoperative pain only if obtained before patient arousal. In contrast to previous studies, a relatively low SPI, >30, appears to predict pain with a high positive predictive value and may therefore be suggested for future studies of SPI-guided anaesthesia.

Clinical Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12615000804583.

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Baroreflex impairment and morbidity after major surgery.
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BACKGROUND: Baroreflex dysfunction is a common feature of established cardiometabolic diseases that are most frequently associated with the development of critical illness. Laboratory models show that baroreflex dysfunction impairs cardiac contractility and cardiovascular performance, thereby increasing the risk of morbidity after trauma and sepsis. We hypothesized that baroreflex dysfunction contributes to excess postoperative morbidity after major surgery as a consequence of the inability to achieve adequate perioperative tissue oxygen delivery.

METHODS: In a randomized controlled trial of goal-directed haemodynamic therapy (GDT) in higher-risk surgical patients, baroreflex function was assessed using the spontaneous baroreflex sensitivity (BRS) method via an arterial line placed before surgery, using a validated sequence method technique (one beat lag). The BRS was calculated during the 6 h postoperative GDT intervention. Analyses of BRS were done by investigators blinded to clinical outcomes. The primary outcome was the association between postoperative baroreflex dysfunction (BRS <6 mm Hg s(-1), a negative prognostic threshold in cardiovascular pathology) and early postoperative morbidity. The relationship between baroreflex dysfunction and postoperative attainment of preoperative indexed oxygen delivery was also assessed.

RESULTS: Patients with postoperative baroreflex dysfunction were more likely to sustain infectious (relative risk (RR) 1.75 [95% confidence interval (CI): 1.07-2.85], P=0.02) and cardiovascular morbidity [RR 2.39 (95% CI: 1.22-4.71), P=0.008]. Prolonged hospital stay was more likely in patients with baroreflex dysfunction [unadjusted hazard ratio 1.62 (95% CI: 1.14-2.32), log-rank P=0.004]. Postoperative O2 delivery was 36% (95% CI: 7-65) lower in patients with
baroreflex dysfunction in those not randomly assigned to GDT (P=0.02).

CONCLUSIONS: Baroreflex dysfunction is associated with excess morbidity, impaired cardiovascular performance, and delayed hospital discharge, suggesting a mechanistic role for autonomic dysfunction in determining perioperative outcome.

Clinical trial registration: iscrtn76894700.

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The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis.

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AIMS: Deprescribing is a suggested intervention to reverse the potential iatrogenic harms of inappropriate polypharmacy. The review aimed to determine whether or not deprescribing is a safe, effective and feasible intervention to modify mortality and health outcomes in older adults.

METHODS: Specified databases were searched from inception to February 2015. Two researchers independently screened all retrieved articles for inclusion, assessed study quality and extracted data. Data were pooled using RevMan v5.3. Eligible studies included those where older adults had at least one medication deprescribed. The primary outcome was mortality. Secondary outcomes were adverse drug withdrawal events, psychological and physical health outcomes, quality of life, and medication usage (e.g. successful deprescribing, number of medications prescribed, potentially inappropriate medication use).

RESULTS: A total of 132 papers met the inclusion criteria, which included 34,143 participants aged 73.8 +/- 5.4 years. In nonrandomized studies, deprescribing polypharmacy was shown to significantly decrease mortality (OR 0.32, 95% CI: 0.17-0.60). However, this was not statistically significant in the randomized studies (OR 0.82, 95% CI 0.61-1.11). Subgroup analysis revealed patient-specific interventions to deprescribe demonstrated a significant reduction in mortality (OR 0.62, 95% CI 0.43-0.88). However, generalized educational programmes did not change mortality (OR 1.21, 95% CI 0.86-1.69).

CONCLUSIONS: Although nonrandomized data suggested that deprescribing reduces mortality, deprescribing was not shown to alter mortality in randomized studies. Mortality was significantly reduced when applying patient-specific interventions to deprescribe in randomized studies.

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The Lower Limb Functional Index - A reliable and valid functional outcome assessment in burns.
Lower limb injuries account for up to 40% of all burns in Western Australia and affect physical function. Lower limb specific functional assessments are available to monitor recovery, yet no scale has been assessed for use in burns. The Lower Limb Functional Index (LLFI) which is validated in musculoskeletal patients was investigated for applicability in burn. Reliability was assessed using Cronbach’s alpha, principal components analysis and Rasch analysis. Validity was assessed using Spearman’s correlation coefficient with quality of life assessments (BSHS-B & SF-36) and physical assessments (TUG & ankle ROM). Regression analysis was performed with burn severity measures, time of recovery and location of the burn. The LLFI-10 was applied 1368 times on 739 patients at regular time points. It was internally consistent (alpha>0.8) and unidimensional. Associations were demonstrated with the BSHS-B and SF-36 (rho=-0.56 to -0.72, p<0.001), TUG (rho=0.41, p<0.001) and ankle ROM (rho=-0.31 to -0.35, p<0.001). The LLFI-10 also showed associations (p<0.001) with time since injury (rho=-0.29), age (rho=0.12) and TBSA (rho=0.12). The LLFI-10 is a reliable and valid tool to assess function in lower limb burns. This study supports the use of the LLFI-10 as part of a battery of assessment for lower limb burn recovery.

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**Mucormycosis in Australia: contemporary epidemiology and outcomes.**

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Mucormycosis is the second most common cause of invasive mould infection and causes disease in diverse hosts, including those who are immuno-competent. We conducted a multicentre retrospective study of proven and probable cases of mucormycosis diagnosed between 2004-2012 to determine the epidemiology and outcome determinants in Australia. Seventy-four cases were identified (63 proven, 11 probable). The majority (54.1%) were caused by Rhizopus spp. Patients who sustained trauma were more likely to have non-Rhizopus infections relative to patients without trauma (OR 9.0, p 0.001, 95% CI 2.1-42.8). Haematological malignancy (48.6%), chemotherapy (42.9%), corticosteroids (52.7%), diabetes mellitus (27%) and trauma (22.9%) were the most common co-morbidities or risk factors. Rheumatological/autoimmune disorders occurred in nine (12.1%) instances. Eight (10.8%) cases had had no underlying co-morbidity and were more likely to have associated trauma (7/8; 87.5% versus 10/66; 15.2%; p <0.001).
Disseminated infection was common (39.2%). Apophysomyces spp. and Saksenaea spp. caused infection in immuno-competent hosts, most frequently associated with trauma and affected sites other than lung and sinuses. The 180-day mortality was 56.7%. The strongest predictors of mortality were rheumatological/autoimmune disorder (OR = 24.0, p 0.038 95% CI 1.2-481.4), haematological malignancy (OR = 7.7, p 0.001, 95% CI 2.3-25.2) and admission to intensive care unit (OR = 4.2, p 0.02, 95% CI 1.3-13.8). Most deaths occurred within one month. Thereafter we observed divergence in survival between the haematological and non-haematological populations (p 0.006). The mortality of mucormycosis remains particularly high in the immuno-compromised host. Underlying rheumatological/autoimmune disorders are a previously under-appreciated risk for infection and poor outcome. Copyright © 2016 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
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Renal denervation in hypertensive patients not on blood pressure lowering drugs.
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INTRODUCTION: Studies on the blood pressure lowering effect of renal denervation (RDN) in resistant hypertensive patients have produced conflicting results. Change in medication usage during the studies may be responsible for this inconsistency. To eliminate the effect of medication usage on blood pressure we focused on unmedicated hypertensive patients who underwent RDN.

METHODS AND RESULTS: Our study reports on a cohort of patients, who were not on blood pressure lowering drugs at baseline and during follow-up, from eight tertiary centers. Data of patients were used when they were treated with RDN and had a baseline office systolic blood pressure (SBP) >140 mmHg and/or 24-h ambulatory SBP >130 mmHg. Our primary outcome was defined as change in office and 24-h SBP at 12 months after RDN, compared to baseline. Fifty-three patients were included. There were three different reasons for not using blood pressure lowering drugs: (1) documented intolerance or allergic reaction (57 %); (2) temporary cessation of medication for study purposes (28 %); and (3) reluctance to take antihypertensive drugs (15 %). Mean change in 24-h SBP was -5.7 mmHg [95 % confidence interval (CI) -11.0 to -0.4; p = 0.04]. Mean change in office SBP was -13.1 mmHg (95 % CI -20.4 to -5.7; p = 0.001). No changes were observed in other variables, such as eGFR, body-mass-index and urinary sodium excretion.

CONCLUSION: This explorative study in hypertensive patients, who are not on blood pressure lowering drugs, suggests that at least in some patients RDN lowers blood pressure.

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Screening for obstructive sleep apnoea in cardiac rehabilitation: A position statement from the Australian
Obstructive sleep apnoea is highly prevalent in acute coronary syndrome patients eligible for enrolment in cardiac rehabilitation programmes. This condition is an independent predictor of increased morbidity and comorbid conditions in the general population and can lead to an increase in major adverse cardiac events such as revascularization, heart failure and hospital readmission in cardiac patients. There is convincing evidence that treatments such as continuous positive airway pressure or mandibular advancement devices can successfully treat obstructive sleep apnoea and these conditions can be improved or negated resulting in improved cardiac rehabilitation outcomes and improved health related quality of life. Given the potential benefits of obstructive sleep apnoea treatment it would make sense to screen for this condition upon entry to out-patient cardiac rehabilitation programmes. A two-stage approach to screening is recommended, where patients are initially evaluated for the probability of having obstructive sleep apnoea using a brief questionnaire (The STOP-Bang) and then followed up with objective evaluation (portable home monitor or polysomnography) where necessary. Potential barriers to further referral and treatment could be partly mitigated by the training of cardiac rehabilitation staff in sleep disorders and screening.

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Do polypills lead to neglect of lifestyle risk factors? Findings from an individual participant data meta-analysis among 3140 patients at high risk of cardiovascular disease.

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AIM: The aim of this study was to investigate whether polypill-based care for the prevention of cardiovascular disease (CVD) is associated with a change in lifestyle risk factors when compared with usual care, among patients with CVD or high calculated cardiovascular risk.

METHODS: We conducted an individual participant data meta-analysis of three trials including patients from Australia, England, India, Ireland, the Netherlands and New Zealand that compared a strategy using a polypill containing aspirin, statin and antihypertensive therapy with usual care in patients with a prior CVD event or who were at high risk of their first event. Analyses investigated any differential effect on anthropometric measures and self-reported lifestyle behaviours.

RESULTS: Among 3140 patients (75% male, mean age 62 years and 76% with a prior CVD event) there was no difference in lifestyle risk factors in those randomised to polypill-based care compared with usual care over a median of 15 months, either across all participants combined, or in a range of subgroups. Furthermore, narrow confidence intervals (CIs) excluded any major effect; for example differences between the groups in body mass index was -0.1 (95% CI -0.2 to 0.1) kg/m(2), in weekly duration of moderate intensity physical activity was -2 (-26 to 23) minutes and the proportion of smokers was 16% vs 17% (RR 0.98, 0.84 to 1.15) at the end of trial.

DISCUSSION: This analysis allays concern that polypill-based care may lead to neglect of lifestyle risk factors, at least among high-risk patients. Maximally effective preventive approaches should address lifestyle factors alongside pharmaceutical interventions, as recommended by major international guidelines.

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Predicting long-term neurological outcomes after severe traumatic brain injury requiring decompressive craniectomy: A comparison of the CRASH and IMPACT prognostic models.

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BACKGROUND: Predicting long-term neurological outcomes after severe traumatic brain (TBI) is important, but which prognostic model in the context of decompressive craniectomy has the best performance remains uncertain.

METHODS: This prospective observational cohort study included all patients who had severe TBI requiring decompressive craniectomy between 2004 and 2014, in the two neurosurgical centres in Perth, Western Australia. Severe disability, vegetative state, or death were defined as unfavourable neurological outcomes. Area under the receiver-operating-characteristic curve (AUROC) and slope and intercept of the calibration curve were used to assess discrimination and calibration of the CRASH (Corticosteroid-Randomisation-After-Significant-Head injury) and IMPACT (International-Mission-For-Prognosis-And-Clinical-Trial) models, respectively.

RESULTS: Of the 319 patients included in the study, 119 (37%) had unfavourable neurological outcomes at 18-month after decompressive craniectomy for severe TBI. Both CRASH (AUROC 0.86, 95% confidence interval 0.81-0.90) and IMPACT full-model (AUROC 0.85, 95% CI 0.80-0.89) were similar in discriminating between favourable and unfavourable neurological outcome at 18-month after surgery (p=0.690 for the difference in AUROC derived from the two models). Although both models tended to over-predict the risks of long-term unfavourable outcome, the IMPACT model had a slightly better calibration than the CRASH model (intercept of the calibration curve=-4.1 vs. -5.7, and log
CONCLUSIONS: Both CRASH and IMPACT prognostic models were good in discriminating between favourable and unfavourable long-term neurological outcome for patients with severe TBI requiring decompressive craniectomy, but the calibration of the IMPACT full-model was better than the CRASH model.
AIMS: To determine the numbers and outcomes of assessments for cognitive problems by the ACAT and hospital memory clinics for patients within a single ACAT catchment area.

METHODS: Data collected included patient demographics, diagnoses, referral and pharmacological treatment. Flow of referrals to the services that diagnose and manage dementia, and the number of incident dementia cases diagnosed in 2012 were determined.

RESULTS: The ACAT service assessed 1005 patients from the catchment, of which 241 patients already had a diagnosis of dementia. When compared with the estimated dementia prevalence in Australia, 19% of prevalent dementia cases (n=1260) within the catchment were reviewed by the ACAT. The two memory clinics saw a combined 186 new referrals (91 and 95 respectively) from within the catchment, with a total of 82 patients (22 and 60 respectively) receiving a new diagnosis of dementia. Using Australian estimates of dementia incidence, this would suggest 29% of 286 incident cases were managed through these memory clinics.

CONCLUSIONS: Geriatric services are responsible for the assessment and management of a large proportion of the estimated number of patients with dementia in this catchment area. Further resourcing and standardisation of the pathways to dementia assessment is required in Australia in order to diagnose and manage effectively people with dementia.
Curcumin Lowers Serum Lipids and Uric Acid in Subjects With Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial.

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most common hepatic diseases in the general adult population. Dyslipidemia, hyperuricemia, and insulin resistance are common risk factors and accompanying features of NAFLD. Curcumin is a dietary natural product with beneficial metabolic effects relevant to the treatment of NAFLD.

Aim: To assess the effects of curcumin on metabolic profile in subjects with NAFLD.

Methods: Patients diagnosed with NAFLD (grades 1-3; according to liver sonography) were randomly assigned to curcumin (1000 mg/d in 2 divided doses) (n = 50) or control (n = 52) group for a period of 8 weeks. All patients received dietary and lifestyle advises before the start of trial. Anthropometric measurements, lipid profile, glucose, insulin, glycated hemoglobin, and uric acid concentrations were measured at baseline and after 8 weeks of follow-up.

Results: Eighty-seven subjects (n = 44 and 43 in the curcumin and control group, respectively) completed the trial. Supplementation with curcumin was associated with a reduction in serum levels of total cholesterol (P < 0.001), low-density lipoprotein cholesterol (P < 0.001), triglycerides (P < 0.001), non-high-density lipoprotein cholesterol (P < 0.001), and uric acid (P < 0.001), whereas serum levels of high-density lipoprotein cholesterol and glucose control parameters remained unaltered. Curcumin was safe and well tolerated during this study.

Conclusion: Results of the present trial suggest that curcumin supplementation reduces serum lipids and uric acid concentrations in patients with NAFLD.

Os 19-01 Blood Pressure Independent Effects of Renal Denervation on the Decline of Kidney Function in Patients with Chronic Kidney Disease.
Hering D, Marusic P, et al.

Objective: Previous studies have shown that renal denervation has the potential to reduce blood pressure (BP) and slow the decline of renal function in chronic kidney disease (CKD) patients up to 12 months post procedure. The effects of RDN on estimated glomerular filtration rate (eGFR) and BP reduction beyond the first year remain unknown. This study investigated the effects of RDN on renal function and BP in CKD patients (eGFR < 60 ml/min/1.73 m) out to 24 months post procedure.

Design and Method: eGFR from the previous 60 months were retrospectively collected from 46 CKD patients who were scheduled for RDN. eGFR and 24-hour ABPM was prospectively assessed at baseline, 3, 6, 12 and 24 months after RDN.

Results: A significant reduction in eGFR was noted from months 60 to 48 (-7.3 +/- 8.7), months 48 to 36 (-5.9 +/- 7.9 ml/min/1.73m) (P < 0.001), and from 12 months to baseline prior to RDN by -3.4 +/- 7.9 ml/min/1.73 m (P < 0.01). RDN improved eGFR at 3 months (+3.7 +/- 6.7 ml/min/1.73 m), 6 months (+2.7 +/- 9.0 ml/min/1.73m) and 12 months follow-up (+1.8 +/- 10.8 ml/min/1.73m) with only a small decline of -1.2 +/- 11.3 ml/min/1.73 m at 24 months follow-up (P < 0.05). There was no significant change in daytime SBP between visits from baseline to 12 months after RDN for the entire cohort. Patients with baseline daytime SBP > 135 mmHg (n = 12) experienced a significant reduction in daytime SBP 24 months post procedure (P = 0.009). Changes in daytime BP were unrelated to the changes in eGFR at 6 months (r = 0.033, P =
0.84), 12 months (r = 0.01, P = 0.93) and 24 months (r = -0.42, P = 0.17) follow-up.

CONCLUSIONS: Our findings indicate that RDN slows further progression of renal function irrespective of BP lowering effects in patients with CKD. The improvement in eGFR post procedure may be associated with alterations of intrarenal and glomerular haemodynamics achieved with RDN via inhibition of sympathetic outflow to the renal vasculature.

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Young people have a new vision for essential medicines.
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Impact of statin therapy on plasma resistin and visfatin concentrations: A systematic review and meta-analysis of controlled clinical trials.

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The beneficial effects of statin therapy in reducing cardiovascular morbidity and mortality is not merely explained by the lipid-modulating effects. Although adipokines levels have been associated with cardiometabolic disorders, a few studies have explored the effect of statin on resistin and visfatin. We aimed to evaluate the impact of statin therapy on levels of resistin and visfatin through a meta-analysis of published studies. A systematic literature search in Medline and SCOPUS databases was conducted up to January 2015 to identify controlled trials assessing changes in plasma concentrations of visfatin and resistin during treatment with statins. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. 12 eligible studies with 14 treatment arms were included. Overall, 844 participants were studied. No significant change in plasma resistin concentrations was observed following statin therapy (WMD: -0.11ng/mL, CI: -1.94,1.73, p=0.909). This effect was robust and not affected by statin type, treatment duration and LDL-cholesterol concentrations. With respect to visfatin concentrations, there was a marginally significant reduction following statin therapy (WMD: -2.40ng/mL, CI: -4.79,-0.002, p=0.050). However, this effect size was weak and sensitive to three of the trials included in the analysis. This meta-analysis did not suggest any effect of statin therapy on plasma resistin levels, while a slight reduction in visfatin levels was found. The effect of statins on visfatin levels may represent a novel pleiotropic characteristic of these drugs.


A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials investigating the effects of statin therapy on plasma lipid concentrations in HIV-infected patients.

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Statin therapy may lower plasma lipid concentrations, but the evidence in HIV-infected patients is still unclear. Therefore, we aimed to investigate the impact of statin therapy on plasma lipid concentrations through a systematic review of the literature and meta-analysis of available randomized controlled trials (RCTs). The literature search included PUBMED, SCOPUS, Web of Science and Google Scholar up to October 30, 2015. The meta-analysis was performed using either a fixed-effects or random-effect model according to I(2) statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Two investigators independently reviewed the title or abstract, further reviewed the full-texts and extracted information on study characteristics and study outcomes. Meta-analysis of 12 RCTs with 697 participants suggested significant reductions in plasma concentrations of low density lipoprotein (LDL) cholesterol (WMD: -0.72mmol/L [-27.8mg/dL], 95%CI: -1.04, -0.39, p<0.001; I(2)=85.7%), total cholesterol (WMD: -1.03mmol/L [-39.8mg/dL], 95%CI: -1.42, -0.64, p<0.001; I(2)=94.7%) and non-high density lipoprotein cholesterol (non-HDL-C) (WMD: -0.81mmol/L [-31.3mg/dL], 95%CI: -1.32, -0.30, p=0.002; I(2)=76.5%), and elevations in HDL-C (WMD: 0.072mmol/L [2.8mg/dL], 95%CI: 0.053, 0.092, p<0.001; I(2)=0%) following treatment with statins (mostly of moderate-intensity). No significant alteration in plasma triglycerides (TG) concentrations was found (WMD: -0.16mmol/L [-14.2mg/dL], 95%CI: -0.61, 0.29, p=0.475; I(2)=90.2%). All these effects were robust in sensitivity analysis, suggesting that the computed effect is not driven by any single study. In subgroup analysis, no significant difference was found among different statins in terms of changing plasma concentrations of LDL-C, HDL-C and TG. However, atorvastatin was found to be more efficacious in reducing plasma total cholesterol concentrations (p<0.001). In conclusion, the meta-analysis suggested significant reductions in plasma concentrations of LDL-C, total cholesterol and non-HDL-C, and elevations in HDL-C, but no significant alteration in plasma TG following treatment with statins.

A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control.

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A systematic review and meta-analysis was conducted to evaluate the effect of oral magnesium supplementation on insulin sensitivity and glucose control in both diabetic and non-diabetic individuals. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched (from inception to November 25, 2015) to identify RCTs evaluating the effect of magnesium on insulin sensitivity and glucose control. A random-effects model and generic inverse variance method were used to compensate for the heterogeneity of studies. Publication bias, sensitivity analysis, and meta-regression assessments were conducted using standard methods. The impact of magnesium supplementation on plasma concentrations of glucose, glycated hemoglobin (HbA1c), insulin, and HOMA-IR index was assessed in 22, 14, 12 and 10 treatment arms, respectively. A significant effect of magnesium supplementation was observed on HOMA-IR index (WMD: -0.67, 95% CI: -1.20, -0.14, p=0.013) but not on plasma glucose (WMD: -0.20mmol/L, 95% CI: -0.45, 0.05, p=0.119), HbA1c (WMD: 0.018mmol/L, 95% CI: -0.10, 0.13, p=0.756), and insulin (WMD: -2.22mmol/L, 95% CI: -9.62, 5.17, p=0.556). A subgroup analysis comparing magnesium supplementation durations of <4 months versus >4 months, exhibited a significant difference for fasting glucose concentrations (p<0.001) and HOMA-IR (p=0.001) in favor of the latter subgroup. Magnesium supplementation for >4 months significantly improves the HOMA-IR index and fasting glucose, in both diabetic and non-diabetic subjects. The
present findings suggest that magnesium may be a beneficial supplement in glucose metabolic disorders.

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**Fibrate therapy and flow-mediated dilation: A systematic review and meta-analysis of randomized placebo-controlled trials.**

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Flow-mediated dilation (FMD) of the brachial artery reflects endothelium-dependent vasodilator function; since it correlates with coronary endothelial function, its reduction could predict cardiovascular events. Several studies have investigated the potential impact of fibrates therapy on endothelial function, but clinical findings have not been fully consistent. We aimed to conduct a meta-analysis of randomized placebo-controlled trials in order to clarify whether fibrate therapy could improve endothelial function. A systematic search in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases was performed to identify randomized placebo-controlled trials investigating the effect of fibrates on endothelial function as estimated by FMD. A random-effects model and generic inverse variance method were used for meta-analysis. Sensitivity analysis, risk of bias evaluation, and publication bias assessment were carried out using standard methods. Random-effects meta-regression was used to evaluate the impact of treatment duration on the estimated effect size. Fifteen trials with a total of 556 subjects met the eligibility criteria. Fibrate therapy significantly improves FMD (weighted mean difference [WMD]: 1.64%, 95% CI: 1.15, 2.13, p<0.001) and the result was confirmed in both subgroups with treatment durations <8 weeks (WMD: 1.35%, 95% CI: 0.85, 1.86, p<0.001) and >8 weeks (WMD: 2.55%, 95% CI: 1.21, 3.89, p<0.001). When the analysis was stratified according to the fibrate type, a significant effect was observed with fenofibrate but not with gemfibrozil, though difference between the two subgroups was not significant. Meta-analysis of data from trials where nitrate mediated dilation (NMD) was available did not suggest a significant change in NMD following treatment with fibrates. The results of this meta-analysis suggest that fibrates may exert beneficial effects on endothelial function, even over a short-term treatment course.

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**Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial.**


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Non-alcoholic fatty liver disease (NAFLD) is a global health problem. Although many aspects of NAFLD pathogenesis have been understood, there is a paucity of effective treatments to be used as the second line when lifestyle modification is insufficient. Curcumin, a natural polyphenol from turmeric, has been shown to be effective against development of hepatic steatosis and its progression to steatohepatitis, yet these beneficial effects have not been explored in clinical practice. The aim of this study is to investigate the effects of curcumin on hepatic fat content as well as biochemical and anthropometric features of patients with NAFLD. In this randomized double-blind placebo-controlled trial, patients with ultrasonographic evidence of NAFLD were randomly assigned to receive an amorphous dispersion curcumin formulation (500mg/day equivalent to 70-mg curcumin) or matched placebo for a period of 8 weeks. Liver fat content (assessed through ultrasonography), glycemic and lipid profile, transaminase levels, and anthropometric indices were evaluated at baseline and at the end of follow-up period. The clinical trial protocol was registered under the Iranian Registry of Clinical Trials ID: IRCT2014110511763N18. Compared with placebo, curcumin was associated with a significant reduction in liver fat content (78.9% improvement in the curcumin vs 27.5% improvement in the placebo group). There were also significant reductions in body mass index and serum levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, glucose, and glycated hemoglobin compared with the placebo group. Curcumin was safe and well tolerated during the course of trial. Findings of the present proof-of-concept trial suggested improvement of different features of NAFLD after a short-term supplementation with curcumin. Copyright © 2016 John Wiley & Sons, Ltd. PMID:27270872 DOI: https://dx.doi.org/10.1002/ptr.5659

Prostaglandins Leukotrienes & Essential Fatty Acids. 2016; 112: 50-5. Prenatal omega-3 fatty acid supplementation does not affect offspring telomere length and F2-isoprostanes at 12 years: A double blind, randomized controlled trial. See VH, Mas E, et al. See, V H L. School of Medicine and Pharmacology, Royal Perth Hospital, University of Western Australia, Perth, Australia. Mas, E. School of Medicine and Pharmacology, Royal Perth Hospital, University of Western Australia, Perth, Australia. Burrows, S. School of Medicine and Pharmacology, Royal Perth Hospital, University of Western Australia, Perth, Australia. O'Callaghan, N J. Commonwealth Scientific and Industrial Research Organization (CSIRO) Food, Nutrition and Bioproducts Flagship, Adelaide, South Australia, Australia. Fenech, M. Commonwealth Scientific and Industrial Research Organization (CSIRO) Food, Nutrition and Bioproducts Flagship, Adelaide, South Australia, Australia. Prescott, S L. Telethon Kid's Institute, University of Western Australia, Perth, Australia; School of Paediatrics and Child Health, Princess Margaret Hospital, University of Western Australia, Perth, Australia. Beilin, L J. School of Medicine and Pharmacology, Royal Perth Hospital, University of Western Australia, Perth, Australia. Huang, R C. Telethon Kid's Institute, University of Western Australia, Perth, Australia. Mori, T A. School of Medicine and Pharmacology, Royal Perth Hospital, University of Western Australia, Perth, Australia. Electronic address: trevor.mori@uwa.edu.au.

BACKGROUND: Oxidative stress and nutritional deficiency may influence the excessive shortening of the telomeric ends of chromosomes. It is known that stress exposure in intrauterine life can produce variations in telomere length (TL), thereby potentially setting up a long-term trajectory for disease susceptibility.

OBJECTIVE: To assess the effect of omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) supplementation...
during pregnancy on telomere length and oxidative stress in offspring at birth and 12 years of age (12y).

DESIGN: In a double-blind, placebo-controlled, parallel-group study, 98 pregnant atopic women were randomised to 4g/day of n-3 LCPUFA or control (olive oil [OO]), from 20 weeks gestation until delivery. Telomere length as a marker of cell senescence and plasma and urinary F2-isoprostanes as a marker of oxidative stress were measured in the offspring at birth and 12y.

RESULTS: Maternal n-3 LCPUFA supplementation did not influence offspring telomere length at birth or at 12y with no changes over time. Telomere length was not associated with F2-isoprostanes or erythrocyte total n-3 fatty acids. Supplementation significantly reduced cord plasma F2-isoprostanes (P<0.001), with a difference in the change over time between groups (P=0.05). However, the differences were no longer apparent at 12y. Between-group differences for urinary F2-isoprostanes at birth and at 12y were non-significant with no changes over time.

CONCLUSIONS: This study does not support the hypothesis that n-3 LCPUFA during pregnancy provides sustained effects on postnatal oxidative stress and telomere length as observed in the offspring.

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Awareness of Pre-diabetes or Diabetes and Associated Factors in People With Psychosis.

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OBJECTIVE: To estimate awareness of pre-diabetes or type 2 diabetes and associated factors in people with psychosis, a known high-risk group.

METHODS: Cross sectional analysis of a national sample with psychosis who were aged 18-64 years, gave a fasting blood sample (n = 1155), had pre-diabetes or diabetes based on testing (n = 359) and reported if they knew they had high blood sugar or diabetes at survey (n = 356). Logistic regression was used to identify factors associated with awareness of pre-diabetes or diabetes prior to testing.

RESULTS: The prevalence of pre-diabetes (19.0% 219/1153) or type 2 diabetes (12.1%, 140/1153) was 31.1% (359/1153); 45% (160/356) were known prior to testing. Factors associated with detection were higher fasting blood glucose, older age, a perception of poor health, severe obesity, dyslipidaemia or treatment with a lipid regulating drug, a family history of diabetes, Aboriginal or Torres Strait Islander descent, decreased cognitive functioning, regional economic disadvantage, treatment with an antihypertensive drug, and an elevated 5-year risk for cardiovascular disease. The prevalence of undiagnosed pre-diabetes/diabetes was highest in those aged 25-34 years at 34.2%.

CONCLUSIONS: Clinical detection of pre-diabetes or diabetes in people with psychosis was strongly dependent on established risk factors for type 2 diabetes in the population but not on current antipsychotic drug treatment or psychiatric case management which should ensure regular screening. Screening must become a clinical priority and should not wait until age 40.

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Paravalvular leakage (PVL) is an important complication of transcatheter aortic valve implantation (TAVI). It contributed to the erosion of the clinical benefits of TAVI and confidence of its adoption as a default therapy in low surgical-risk patients. Newer TAVI technologies are provided with effective paravalvular sealing as well as retrieval/reposition mechanisms that are believed to considerably lower the risk of PVL. Meanwhile, developments in timely detection and accurate quantitation of PVL remain lagging behind those technological advances. The Valve Academic Research Consortium-standardized criteria of PVL assessment are based on echocardiography and are, according to experts' opinion, not adequately validated. Peri-procedural diagnosis, based on angiographic, haemodynamic, and/or echocardiographic methods, is so far without standardization of acquisition or interpretation. The aim of this report is to review the strengths and limitations of the current technologies used for PVL adjudication. Understanding this strengths/limitations ratio is important to define an appropriate scheme for detection and quantitation of PVLs both in clinical trials and in routine clinical practice.

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Brown SG, Ball EL, et al.

Study protocol for a randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax.
Brown SG, Ball EL, et al.

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INTRODUCTION: Current management of primary spontaneous pneumothorax (PSP) is variable, with little evidence from randomised controlled trials to guide treatment. Guidelines emphasise intervention in many patients, which involves chest drain insertion, hospital admission and occasionally surgery. However, there is evidence that conservative management may be effective and safe, and it may also reduce the risk of recurrence. Significant questions remain regarding the optimal initial approach to the management of PSP.

METHODS AND ANALYSIS: This multicentre, prospective, randomised, open label, parallel group, non-inferiority study will randomise 342 participants with a first large PSP to conservative or interventional management. To maintain allocation concealment, randomisation will be performed in real time by computer and stratified by study site. Conservative management will involve a period of observation prior to discharge, with intervention for worsening symptoms or physiological instability. Interventional treatment will involve insertion of a small bore drain. If drainage continues after 1 hour, the patient will be admitted. If drainage stops, the drain will be clamped for 4 hours. The patient will be discharged if the lung remains inflated. Otherwise, the patient will be admitted. The primary end point is the proportion of participants with complete lung re-expansion by 8 weeks. Secondary end points are as follows: days in hospital, persistent air leak, predefined complications and adverse events, time to resolution of symptoms, and pneumothorax recurrence during a follow-up period of at least 1 year. The study has 95% power to detect an absolute non-inferiority margin of 9%, assuming 99% successful expansion at 8 weeks in the invasive treatment arm. The primary analysis will be by intention to treat.

ETHICS AND DISSEMINATION: Local ethics approval has been obtained for all sites. Study findings will be disseminated by publication in a high-impact international journal and presentation at major international Emergency Medicine and Respiratory meetings.

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BACKGROUND: Few studies have evaluated the clinical outcomes of transcatheter aortic valve replacement (TAVR) in patients with bicuspid aortic valve stenosis (AS). Particularly, limited data exist comparing the results of TAVR with new-generation devices versus early-generation devices.

OBJECTIVES: This study sought to evaluate the clinical outcomes of TAVR for bicuspid AS with early- and new-generation devices.

METHODS: The Bicuspid TAVR Registry is an international multicenter study enrolling consecutive patients with bicuspid AS undergoing TAVR between April 2005 and May 2015.

RESULTS: Of 301 patients, 199 patients (71.1%) were treated with early-generation devices (Sapien XT [Edwards Lifesciences Corporation, Irvine, California]: n = 87; CoreValve [Medtronic, Minneapolis, Minnesota]: n = 112) and 102 with new-generation devices (Sapien 3 [Edwards Lifesciences Corporation]: n = 91; Lotus [Boston Scientific Corporation, Marlborough, Massachusetts]: n = 11). The mean Society of Thoracic Surgeons score was 4.7 +/- 5.2 without significant differences between groups (4.6 +/- 5.1 vs. 4.9 +/- 5.4; p = 0.57). Overall, all-cause mortality rates were 4.3% at 30 days and 14.4% at 1 year. Moderate or severe paravalvular leak was absent and significantly less frequent with new-generation compared to early-generation devices (0.0% vs. 8.5%; p = 0.002), which resulted in a higher device success rate (92.2% vs. 80.9%; p = 0.01). There were no differences between early- and new-generation devices in stroke (2.5% vs. 2.0%; p > 0.99), life-threatening bleeding (3.5% vs. 2.9%; p > 0.99), major vascular complication (4.5% vs. 2.9%; p = 0.76), stage 2 to 3 acute kidney injury (2.5% vs. 2.9%; p > 0.99), early safety endpoints (15.1% vs. 10.8%; p = 0.30), and 30-day all-cause mortality (4.5% vs. 3.9%; p > 0.99).

CONCLUSIONS: The clinical outcomes of TAVR in patients with bicuspid AS were favorable. New-generation devices were associated with less paravalvular leak and, hence, a higher device success rate than early-generation devices.

(The Bicuspid Aortic Stenosis Following Transcatheter Aortic Valve Replacement Registry [Bicuspid TAVR]: NCT02394184).
BACKGROUND: The PCSK9 antibody alirocumab (75 mg every 2 weeks; Q2W) as monotherapy reduced low-density lipoprotein-cholesterol (LDL-C) levels by 47%. Because the option of a monthly dosing regimen is convenient, ODYSSEY CHOICE II evaluated alirocumab 150 mg Q4W in patients with inadequately controlled hypercholesterolemia and not on statin (majority with statin-associated muscle symptoms), receiving treatment with fenofibrate, ezetimibe, or diet alone.

METHODS AND RESULTS: Patients were randomly assigned to placebo, alirocumab 150 mg Q4W or 75 mg Q2W (calibrator arm), with dose adjustment to 150 mg Q2W at week (W) 12 if W8 predefined LDL-C target levels were not met. The primary efficacy endpoint was LDL-C percentage change from baseline to W24. Mean baseline LDL-C levels were 163.9 mg/dL (alirocumab 150 mg Q4W, n=59), 154.5 mg/dL (alirocumab 75 mg Q2W, n=116), and 158.5 mg/dL (placebo, n=58). In the alirocumab 150 mg Q4W and 75 mg Q2W groups (49.1% and 36.0% of patients received dose adjustment, respectively), least-squares mean LDL-C changes from baseline to W24 were -51.7% and -53.5%, respectively (placebo [+4.7%]; both groups P<0.0001 versus placebo). In total, 63.9% and 70.3% of alirocumab-treated patients achieved their LDL-C targets at W24. Treatment-emergent adverse events occurred in 77.6% (alirocumab 150 mg Q4W), 73.0% (alirocumab 75 mg Q2W), and 63.8% (placebo) of patients, with injection-site reactions among the most common treatment-emergent adverse events.

CONCLUSIONS: Alirocumab 150 mg Q4W can be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C.


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Phase I Clinical Trial of Marizomib (NPI-0052) in Patients with Advanced Malignancies Including Multiple Myeloma: Study NPI-0052-102 Final Results.

Harrison SJ, Mainwaring P, et al.

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PURPOSE: Marizomib (NPI-0052) is an irreversible proteasome inhibitor, derived from a marine actinomycete, with activity and specificity that is distinct from other proteasome inhibitors.

EXPERIMENTAL DESIGN: Phase I study (NPI-0052-102) evaluated the MTD, pharmacokinetics, and pharmacodynamics of marizomib intravenously on two dosing schedules.

RESULTS: Forty-two patients with advanced malignancies received Schedule A (0.1-0.9 mg/m(2) over 1-10 minutes on days 1, 8, 15 in 4-week cycles); 44 patients with relapsed and/or refractory multiple myeloma (RRMM) and other hematologic malignancies received Schedule B (0.075-0.6 mg/m(2) over 1 minute to 2 hours on days 1, 4, 8, 11, in 3-week cycles). The Schedule A recommended phase II dose was 0.7 mg/m(2) over 10 minutes; Schedule B was 0.5 mg/m(2) over 2 hours. The most common (>25% of patients) related adverse events were fatigue, nausea, diarrhea, and infusion site pain (Schedule A); and fatigue (Schedule B). Overall response rate of 11% was seen in 27 efficacy-evaluable RRMM Schedule B patients (1 very good partial response, 3 partial responses, 4 minimal responses,
and 12 stable disease). One Schedule A patient with transformed marginal zone lymphoma had complete response. Marizomib has a short half-life (<30 minutes), with high volume of distribution (~15-416 L) and clearance (~0.9-22 L/minutes).

CONCLUSIONS: Marizomib does not exhibit the severe peripheral neuropathy or hematologic toxicity observed with other proteasome inhibitors. Marizomib was generally well tolerated with low-dose dexamethasone, demonstrated activity in heavily pretreated RRMM patients, and warrants further evaluation. Clin Cancer Res; 22(18); 4559-66. ©2016 AACR.

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**Structural and electrical cardiac abnormalities are prevalent in asymptomatic adults with myotonic dystrophy.**

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OBJECTIVE: Cardiac disease accounts for a large burden of premature mortality and morbidity in patients with type 1 myotonic dystrophy (MD). However, little is known about structural cardiac abnormalities particularly in asymptomatic patients with MD. We sought to describe the prevalence and extent of structural cardiac abnormalities in patients with MD and to assess their association with functional, electrical, biochemical and genetic disturbances.

METHODS: In this case-control study, 40 adults with MD who had no contraindications to cardiac MRI (CMR) were identified from the Grampian region genetic database. Forty-one age-and-gender-matched healthy volunteers were also recruited. All subjects underwent detailed assessment including CMR, echocardiography, electrocardiography, signal-averaged electrocardiography, Holter monitoring and quantification of serum B-type natriuretic peptide (BNP).

Genetic testing of patients with MD was performed with quantification of CTG trinucleotide repeat sequences. Results of clinical, electrical, genetic and biochemical investigations were correlated with cardiac structural and functional abnormalities detected on CMR.

RESULTS: Electrical disturbances including prolongation of PR (187+/-29 vs 156+/-23 ms, p<0.001) and QRS intervals (99+/-11 vs 89+/-9 ms, p<0.001) were the most prevalent abnormality. Patients with MD had a significantly lower left ventricular (LV) mass (142+/-44 vs 172+/-73 g, p=0.03) and lower right ventricular (RV) ejection fraction (46+/-9 vs 50+/-7%, p=0.02) compared with controls, although LV ejection fraction was similar between the groups (58+/-8 vs 59+/-6%, p=0.34). LV non-compaction was also significantly more prevalent in the MD cohort (35% vs 12%, p=0.019).

Late gadolinium enhancement was present in 13% of patients with MD. Muscular disability scores correlated with electrical changes (r=0.529, p<0.001); however, the number of CTG repeat sequences did not correlate with either electrical or structural abnormalities.

CONCLUSIONS: Patients with MD have a high prevalence of both electrical and structural abnormalities. These include reduced LV mass, impaired RV contractility, a high prevalence of LV non-compaction and myocardial fibrosis. These findings illustrate the potential utility of CMR detecting subclinical disease in otherwise asymptomatic patients with MD.

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MBOAT7 rs641738 increases risk of liver inflammation and transition to fibrosis in chronic hepatitis C.


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Cirrhosis likely shares common pathophysiological pathways despite arising from a variety of liver diseases. A recent GWAS identified rs641738, a polymorphism in the MBOAT7 locus, as being associated with the development of alcoholic cirrhosis. Here we explore the role of this variant on liver inflammation and fibrosis in two cohorts of patients with chronic hepatitis C. In 2,051 patients, rs641738 associated with severe hepatic inflammation and increased risk of fibrosis, as well as fast fibrosis progression. At functional level, rs641738 associated with MBOAT7 transcript and protein levels in liver and blood, and with serum inflammatory, oxidative stress and macrophage activation markers. MBOAT7 was expressed in immune cell subsets, implying a role in hepatic inflammation. We conclude that the MBOAT7 rs641738 polymorphism is a novel risk variant for liver inflammation in hepatitis C, and thereby for liver fibrosis.

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OBJECTIVE: To capture the clinical patterns, timing of key milestones and survival of patients presenting with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) within Australia.
METHODS: Data were prospectively collected and were timed to normal clinical assessments. An initial registration clinical report form (CRF) and subsequent ongoing assessment CRFs were submitted with a completion CRF at the time of death.
DESIGN: Prospective observational cohort study.
PARTICIPANTS: 1834 patients with a diagnosis of ALS/MND were registered and followed in ALS/MND clinics between 2005 and 2015.

RESULTS: 5 major clinical phenotypes were determined and included ALS bulbar onset, ALS cervical onset and ALS lumbar onset, flail arm and leg and primary lateral sclerosis (PLS). Of the 1834 registered patients, 1677 (90%) could be allocated a clinical phenotype. ALS bulbar onset had a significantly lower length of survival when compared with all other clinical phenotypes (p<0.004). There were delays in the median time to diagnosis of up to 12 months for the ALS phenotypes, 18 months for the flail limb phenotypes and 19 months for PLS. Riluzole treatment was started in 78-85% of cases. The median delays in initiating riluzole therapy, from symptom onset, varied from 10 to 12 months in the ALS phenotypes and 15-18 months in the flail limb phenotypes. Percutaneous endoscopic gastrostomy was implemented in 8-36% of ALS phenotypes and 2-9% of the flail phenotypes. Non-invasive ventilation was started in 16-22% of ALS phenotypes and 21-29% of flail phenotypes.

CONCLUSIONS: The establishment of a cohort registry for ALS/MND is able to determine clinical phenotypes, survival and monitor time to key milestones in disease progression. It is intended to expand the cohort to a more population-based registry using opt-out methodology and facilitate data linkage to other national registries.

Auditory verbal hallucinations (AVHs) and related psychotic phenomena in mood disorders: analysis of the 2010 Survey of High Impact Psychosis (SHIP) data.

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BACKGROUND: Auditory verbal hallucinations (AVHs) are known to occur in mood disorders, but there has been scant research in the area. This paper aimed to explore the presence of hallucinations, and AVHs in particular, across affective disorders (with non-affective disorders serving as clinical reference groups). Specific attention was given to i) running commentary, ii) voices conversing, and iii) negative voices. A secondary aim was to examine patterns of associated delusional themes.

METHOD: Participants were 1550 Australians, aged 18-64 years, assigned to one of four groups on the basis of diagnosis: i) bipolar disorder (BD), ii) depressive psychosis (DP), iii) schizophrenia (SCZ), and iv) schizoaffective disorder (SAD). Relevant data collected from the 2010 Australian Survey of High Impact Psychosis (SHIP) was analysed.

RESULTS: Current prevalence of hallucinations was such that BD<DP; severity of hallucinations, and AVHs in particular, was in the order BD=DP<SAD=SCZ. These results were statistically significant. Negative voices, and concomitantly, persecutory delusions, were prominent across all clinical groups.

DISCUSSION: Future research should examine age of AVH onset as well as other forms of AVHs, whilst taking into account participants’ specific mood states.

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Mycophenolate mofetil is an effective and safe option for the management of systemic sclerosis-associated interstitial lung disease: results from the Australian Scleroderma Cohort Study.

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OBJECTIVES: To report the efficacy and tolerability of mycophenolate mofetil (MMF) and azathioprine (AZA) in the management of systemic sclerosis-associated interstitial lung disease (SSc-ILD).

METHODS: Patients in the Australian Scleroderma Cohort Study treated with at least 3 months of MMF or AZA for SSc-ILD confirmed on high resolution computed tomography (HRCT) chest were identified and their pulmonary function tests (PFTs) retrieved. Individuals with available results for T-1 (12 months prior to treatment commencement), T0 (date of treatment commencement) and at least one subsequent time point were included in the drug efficacy analysis. The Wilcoxon signed-rank test was used to compare absolute FVC at T1, T0, 12 months (T1), 24 months (T2) and 36 months (T3). Analysis of drug tolerability included all identified patients treated with MMF or AZA.

RESULTS: 18/22 patients treated with MMF and 29/49 treated with AZA had adequate PFTs for inclusion in the drug efficacy analysis. Median absolute FVC at T1 for MMF treatment was 2.50L, declining to 2.12L at T0 (p=0.02). Following MMF therapy, FVC results were stable at T1 (2.13L, p=0.86), T2 (2.17L, p=0.65) and T3 (2.25L, p=0.78). In the AZA group, a statistically significant decline did not occur prior to treatment, however FVC results remained stable at T1, T2 and T3.Adverse events leading to early discontinuation (<12 months treatment) were less common in the MMF group (4/22 vs. 13/49). Gastrointestinal complications were the main cause of discontinuation in both groups.

CONCLUSIONS: In patients with SSc-ILD with declining pulmonary function, MMF therapy was associated with stability for up to 36 months. Early adverse events leading to discontinuation occurred less frequently in patients treated with MMF than in AZA treated patients.

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The role of asymmetric dimethylarginine alone and in combination with N-terminal pro-B-type natriuretic peptide as a screening biomarker for systemic sclerosis-related pulmonary arterial hypertension: a case control study.

Thakkar V, Stevens W, et al.
OBJECTIVES: Asymmetric dimethylarginine (ADMA) is a novel biomarker of endothelial cell dysfunction. In this proof of concept study, we sought to evaluate the role of ADMA as a screening biomarker for incident systemic sclerosis-related pulmonary arterial hypertension (SSc-PAH).

METHODS: ADMA levels were measured using high performance liquid chromatography in 15 consecutive treatment-naive patients with newly-diagnosed SSc-PAH and compared with 30 SSc-controls without PAH. Logistic regression models were used to evaluate the independent association of ADMA with PAH. The optimal cut-point of ADMA for SSc-PAH screening was determined. NT-proBNP levels were previously measured in the same patients and the optimal cut-point of NT-proBNP of >210ng/mL was coupled with the optimal cut-point of ADMA to create a screening model that combined the two biomarkers.

RESULTS: The PAH group had significantly higher mean ADMA levels than the control group (0.76+/-0.14 μM versus 0.59+/-0.07 μM; p<0.0001). ADMA levels remained significantly associated with PAH after the adjustment for specific disease characteristics, cardiovascular risk factors and other SSc-related vascular complications (all p<0.01). An ADMA level >0.7 μM had a sensitivity of 86.7%, specificity of 90.0% and AUC of 0.86 for diagnosing PAH. A screening model that combined an NT-proBNP >210ng/mL and/or ADMA >0.7 ng/mL resulted in a sensitivity of 100% and specificity of 90% for the detection of SSc-PAH.

CONCLUSIONS: In this small study, use of ADMA in combination with NT-proBNP produced excellent sensitivity and specificity for the non-invasive identification of SSc-PAH. The role of ADMA as a screening biomarker for SSc-PAH merits further evaluation.

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A Descriptive Study of the Temporal Patterns of Volume and Contents Change in Human Acute Burn Edema: Application in Evidence-Based Intervention and Research Design.
Edgar DW, Fear M, et al.

Edema after burn contributes significantly to burn wound depth conversion. In humans after burn injury, there is a lack of detailed understanding of the contents and temporal changes in volume of acute tissue edema. The novel findings of these studies relate to the collection of edema fluid after partial-thickness burn injury. Edema volume peaks on day 1 after burn without formal fluid resuscitation. The studies indicated that the peak was on day 2 for a resuscitated burn. In contrast, animal studies suggest that the peak of edema occurs by or before day 1 after injury.
The findings confirm the pitfalls of evidence derived from animal models and assuming direct transference to humans. Postburn edema was demonstrated to be a high-protein fluid (ie, >10g/L) for the duration of the inflammatory period. The presence of high-protein edema presents greater challenges to clinicians developing novel treatment options. The rate of volume change over time tapered to insignificant levels after day 4 following burn. Greater than 98% of the edema contents was fluid. However, the size of particulate matter did not preclude it passing through patent lymphatic collectors. The results indicate a necessity for urgent postburn intervention, which should incorporate the active stimulation of the lymphatic system to improve efficacy of edema removal.

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Rescue therapy with PCSK9 inhibitors for patients with delayed diagnosis of heterozygous familial hypercholesterolemia: Redressing the balance of missed opportunities.
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Ten years of lipoprotein apheresis for familial hypercholesterolemia in Malaysia: A creative approach by a cardiologist in a developing country.
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BACKGROUND: Familial hypercholesterolemia (FH) leads to premature coronary artery disease and aortic stenosis, with undertreated severe forms causing death at a young age. Lipoprotein apheresis (LA) is often required for lowering low-density lipoprotein cholesterol levels in severe FH.

OBJECTIVES: The objective of this study was to present the first experiences with LA in Malaysia, between 2004 and 2014.

METHODS: We retrospectively collected data from patient records to assess the effectiveness, adverse effects, patient quality of life, and costs associated with an LA service for genetically confirmed homozygous and heterozygous FH.

RESULTS: We treated 13 women and 2 men aged 6 to 59 years, 10 with homozygous and 5 with heterozygous FH, all on maximally tolerated cholesterol-lowering drug therapy, for a total of 65 patient-years. Acute lowering of low-density lipoprotein cholesterol post apheresis was 56.3 +/- 7.2%, with time-averaged mean lowering of 34.9 +/- 13.9%. No patients experienced any cardiovascular events during the period of receiving LA. Patients receiving LA experienced few side effects and enjoyed reasonable quality of life, but inability to continue treatment was frequent because of cost.

CONCLUSION: LA for severe FH can be delivered effectively in the short term in developing nations, but costs are a
major barrier to sustaining this mode of treatment for this high-risk group of patients. New drug therapies for FH, such as the proprotein convertase subtilisin/kexin type 9 inhibitors, microsomal triglyceride transfer protein inhibitors, and apolipoprotein B-100 antisense oligonucleotides may allow improved care for these patients, but costs and long-term safety remain as issues to be addressed.

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**Usage of rectus sheath catheters: A service evaluation project.**

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Rectus sheath catheters have several benefits for postoperative analgesia after abdominal surgeries. They provide a viable alternative to epidural analgesia, can decrease the usage of opioids with less nausea, vomiting, ileus, confusion and in addition contribute to improved mobility with no motor block of legs and early removal of urinary catheters [1, 2]. Methods We performed a study of the usage and efficacy of rectus sheath catheters for postoperative analgesia in our hospital as a part of service evaluation project. We collected data for 32 cases retrospectively. All of our cases had bilateral rectus sheath catheters inserted surgically at the end of the procedure followed by bolus dose of 20-60 ml 0.25% chirocaine. Postoperatively, patient-controlled analgesia (morphine, fentanyl or diamorphine) was supplemented in 91% of cases in addition to local anaesthetic infusion of 0.1% bupivacaine and 2 mcg/ml of fentanyl through the rectus sheath catheters. Results Laparotomies formed about 75% of the cases in which the catheters were used. The other cases in which they were used were liver resections, open cholecystectomies and radical cystectomies. The main cohort of surgical patients in whom they were used was emergency surgeries (41%) and malignant colorectal surgeries (31%). Intra-operative analgesia was supplemented by remifentanil infusion in 50% of cases. In the postoperative recovery unit, 69% of the cases did not require further analgesia and 19% required intravenous morphine analgesia. A total of 40% of the patients had a pain score of 0, both at rest and on movement in the recovery unit. Of the rest, 26.7% had pain scores at rest of < 5 and 33.3% had scores > 5. On movement, 20% had pain scores on < 5 and 40% had scores > 5. Further, 93% had oral intake established by day 1 postoperatively, 84% were mobilised by day 2 and 87% had their rectus sheath catheters removed by day 4 postoperatively. There were neither local anaesthetic complications nor catheter-related complications in any of the cases. Discussion Our results show rectus sheath catheters to be a useful mode of postoperative analgesia in many types of surgeries, both in elective and non-elective cases. Opiate supplementation is essential while using rectus sheath catheters to treat visceral pain, and a majority of our cases were prescribed a patient-controlled analgesic opiate. Usage of rectus sheath catheters minimised opiate requirements and proved effective for earlier mobilisation, gastrointestinal uptake of food and overall recovery of patients.

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**Predicting long-term neurological outcomes after severe traumatic brain injury requiring decompressive craniectomy: A comparison of the crash and impact prognostic models.**

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Background & Objectives: Predicting long-term neurological outcomes after severe traumatic brain (TBI) is important, but which prognostic model has the best performance remains uncertain. Materials & Methods: This retrospective cohort study included all patients who had severe TBI requiring decompressive craniectomy, between 2004 and 2014,
in two neurosurgical centres in Western Australia. Severe disability requiring help with daily living, vegetative state, or death were defined as unfavourable neurological outcomes. Area under the receiver-operating-characteristic curve (AUROC) and slope and intercept of the calibration curve were used to assess discrimination and calibration. of the CRASH (Corticosteroid-Randomisation-After-Significant-Head injury) and IMPACT (International-Mission-For-Prognosis-And-Clinical-Trial) models, respectively. Results: Of the 319 patients included in the study, 118 (37%) had unfavourable neurological outcomes at 18-month after decompressive craniectomy for severe TBI. Both CRASH (AUROC 0.86, 95% confidence interval 0.81-0.90) and IMPACT (AUROC 0.85, 95%CI 0.80-0.89) models were similarly good in distinguishing between favourable and unfavourable neurological outcome at 18-month after surgery (p=0.690 for the difference in AUROC derived from the two models). Although both models tended to over-predict the risks of long-term unfavourable outcome, the IMPACT model had a slightly better calibration than the CRASH model (intercept of the calibration curve = -4.1 vs. -5.7, respectively), especially when the predicted risks of unfavourable outcome were <80%. Conclusion: Both CRASH and IMPACT prognostic models were good in discriminating between favourable and unfavourable long-term neurological outcome for patients with severe TBI requiring decompressive craniectomy, but the calibration of the IMPACT full-model was better than the CRASH model. These results suggest that both prognostic models can be used for risk adjustments in randomised controlled trials but the better calibration of the IMPACT model makes it as the preferred model for risk adjustment in observational studies and in providing objective prognostic outcome prediction.

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Comparison of pre-oxygenation with high-flow humidified nasal oxygen compared to standard facemask technique in healthy volunteers.


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Background & Objectives: High flow humidified nasal oxygen (HFHNO) administration has been recently used in difficult airway management and rapid sequence induction (1). There has not been close investigation into the efficacy of HFHNO for pre-oxygenation and its correct application. We designed a pilot study in healthy volunteers to compare HFHNO to the standard facemask technique using end-tidal oxygen fraction (ETO<sub>2</sub>) and transcutaneous oxygen concentration (TcPO<sub>2</sub>) as markers of efficacy. We also compared the effect of mouth open and mouth closed breathing techniques with HFHNO on efficacy of overall pre-oxygenation. Materials & Methods: 10 healthy volunteers were positioned sitting at 45 degrees. Subjects were randomised to either start with facemask or HFHNO for pre-oxygenation. Pre-oxygenation with HFHNO was performed with a flow rate of 60L/min. Subjects were asked to breath normally for 3min. At the end of 3min the subject was asked to breath out maximally into a mouthpiece connected to the gas analyser. Pre-oxygenation with HFHNO was performed with a flow rate of 60L/min. Subjects were asked to breath normally for 3min with their mouth closed. At the end of 3min the subjects were again asked to breath out maximally into a mouthpiece connected to the gas analyser. Pre-oxygenation with HFHNO was also performed and studied similarly with subject breathing with their mouth open for 3min. Between each part of testing ETO<sub>2</sub> and TcPO<sub>2</sub> were allowed to return to baseline. Results: There was no significant difference in ETO<sub>2</sub> and TcPO<sub>2</sub> after 3min pre-oxygenation with HFHNO using the closed mouth technique and the standard facemask technique. The was a significantly lower ETO<sub>2</sub> (p=0.001) and TcPO<sub>2</sub> (p=0.033) after using HFHNO with the open mouth technique (OMO) when compared with the closed mouth technique (CMO). Conclusion: Our pilot study shows that HFHNO with closed mouth technique is as effective for pre-oxygenation at 3min tidal breathing as the standard facemask technique. However, we highlight the significant effect of the method of breathing on the efficacy of pre-oxygenation with HFHNO. Pre-oxygenation efficacy is difficult to monitor during HFHNO and optimal time, flow rate and technique needs to be defined. We caution the use of HFHNO for pre-oxygenation without adequate monitoring of efficacy of the technique. (Table Presented).

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A comparison of resistance to deformation in common brands of spinal needles: The effect of different methods of testing.

Background & Objectives: The deformation of spinal needles during clinical use can affect the safe and timely conduct of anaesthesia. The strength profile of needles is measured by industry standard tests, which do not necessarily reflect clinical use (1). Testing is done by individual manufacturers and there are few objective, comparative studies of different needle brands (2). We aimed to compare the resistance to deformation in commonly used brands of spinal needles of a set length and gauge (27G 90mm) using both industry standard approaches and our own. Materials & Methods: We designed a testing rig incorporating a force transducer which measured the registered force during calibrated deflection of a sensor tip. A horizontal three-point bend test (A) was performed as a common industry standard test and a separate vertical test was designed by the group (B). During horizontal testing the sensor was pushed onto the needle shaft and in the vertical test the sensor was pushed onto the needle tip. Final needle deformation was measured (C). 27G 90mm luer spinal needles were tested from 4 popular, global brands. Each needle brand was tested 8 times in random order. Results: Only the vertical testing showed a significant difference in the deformation of the needles where Brand C showed significantly greater deformation than the other brands (p<0.05). Conclusion: Currently employed manufacturer tests may not identify differences in needle strength that could be clinically relevant. Our study identified differences between manufacturers in our specially designed test of axial strength but not in the standard industrial test. An awareness of such differences is important for clinicians when using or purchasing needles from different manufacturers. (Figure Presented).

A comparison of strong ion gap and other markers of acid-base status in predicting mortality of critically ill patients.
Ho KM, Lan NS, et al.

Background & Objectives: Acid-base disorders are common in critically ill patients and patients after major surgery. This cohort study compared the prognostic significance of Strong Ion Gap (SIG) with other acid-base markers in the critically ill. Materials & Methods: The relationships between SIG, lactate, anion gap (AG), anion gap albumin-corrected (AG-corrected), or Strong Ion Difference-effective (SIDe), all obtained within the first hour of intensive care unit (ICU) admission, and hospital mortality of 6878 patients were analysed. The prognostic significance of each acid-base marker, both alone and in combination with the Admission Mortality Prediction Model (MPM<inf>0</inf>) III predicted mortality, were assessed by the area under the receiver-operating-characteristic curve (AUROC). Results: Of the 6878 patients included in the study, 924 patients (13.4%) died after ICU admission. Except plasma chloride concentrations, all acid-base markers were significantly different between the survivors and non-survivors. Arterial lactate concentrations, both by itself (AUROC 0.701, 95% confidence interval [CI] 0.682-0.721) and in combination with the MPM<inf>0</inf> III predicted risks (AUROC 0.824, 95%CI 0.809-0.839), had the strongest ability to differentiate between survivors and non-survivors. Adding AG-corrected or SIG to a combination of lactate and MPM<inf>0</inf> III predicted risks did not substantially improve the latter's ability to differentiate between hospital survivors and non-survivors. Conclusion: Arterial lactate concentration had a better ability than SIG to predict mortality of the
critically ill. Lactate should always be considered regardless which acid-base approach is used to manage acid-base
disorders.
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GE=fulltext&D=emed18b&AN=612648496

How should i treat this unusual anterolateral ST-elevation myocardial infarction with recurrent ventricular
fibrillation and cardiac arrest?
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Background: A 51-year-old man with recurrent chest pain admitted with NSTEMI developed acute anterolateral STEMI
with recurrent VF and prolonged cardiac arrest. Investigation: Coronary angiography. Diagnosis: Anterolateral STEMI. Management: Percutaneous coronary intervention. Copyright © 2016 Europa Digital & Publishing. All rights reserved.
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GE=fulltext&D=emed18b&AN=612686823

Certolizumab pegol and methotrexate in DMARD-naive patients with active, severe, rheumatoid arthritis:
Results from C-EARLY Period 1 including Australian patients.
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Background: C-EARLY (NCT01519791) was a Phase 3 study in DMARD-naive patients with active, severe RA and negative prognostic factors, assessing efficacy and safety of certolizumab (Figure Presented) pegol (CZP)+optimized MTX versus placebo (PBO)+optimized MTX in inducing and sustaining clinical response and inhibiting radiographic progression. Results are presented for the total study population (TSP) and Australian patients (AP) from Period 1. Methods: Patients in this multicenter, double-blind, randomized study had RA <1 year since diagnosis at baseline (2010 ACR/EULAR criteria); >4 swollen and >4 tender joints; DAS28 (ESR)>3.2; CRP > 10 mg/L and/or ESR>28 mm/h and RF or ACPA positivity. 879 patients were randomized 3:1 to CZP (400 mg at Weeks 0, 2, 4, 200 mg Q2W to Week 52)+MTX or PBO Q2W+MTX: 37 Australian patients were included in the 879 randomized patients. Due to low patient numbers, inferential statistics are not presented for AP. Results: Baseline characteristics were generally balanced
between arms (Table A). In the TSP, statistically significant changes in favor of CZP+MTX were reported for all endpoints (Table B). Australian patients receiving CZP+MTX generally reported better outcomes than PBO+MTX patients. AE incidence rates were similar for both treatment arms. Infections were higher with CZP+MTX versus PBO+MTX (TSP: 71.8 versus 52.7/100 patient-years; AP: 160.1 vs. 103.9), but similar for serious infections (TSP: 3.3 vs. 3.7/100 patient-years; AP: 0 vs. 10.5). There were no new CZP safety signals. Conclusion: DMARD-naive patients from all regions including Australia, with active, severe, RA and negative prognostic factors, treated with CZP+MTX had higher sREM and sLDA rates, greater improvements in RA signs and symptoms and lower radiographic progression than PBO+MTX patients.

Sunitinib induced acute interstitial nephritis-a case report.
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Background: Sunitinib, tyrosine kinase inhibitor is used in treatment of metastastic renal cell carcinoma (mRCC) is rarely associated with renal adverse effects. Case Report: We report the only case of Sunitinib provoking biopsy proven acute interstitial nephritis (AIN), that resolved with drug withdrawal and steroid therapy. RS, 78 year, male with pre-existing stage IV chronic kidney disease secondary to diabetic and hypertensive nephrosclerosis was initiated on Sunitinib in July 2015 for mRCC in pleural lesions with baseline serum creatinine of 271 umol/L (eGFR 18 ml/min/1.73 m<sup>2</sup>). Other comorbidities include Type 2 diabetes, gout, vascular disease and polymyalgia rheumatica in remission. Erythromycin 400 mg BD for suspected respiratory infection leads to increased serum levels. Oral ulcers, elevated hepatic enzymes and increased serum creatinine were noted. He presented 4 weeks after initiation of Sunitinib, with serum creatinine of 860 umol/L with eGFR 4ml/min/1.73 m<sup>2</sup>, stable proteinuria, negative autoimmune and vasculitic screen. Renal biopsy (No 1) confirmed the diagnosis of severe eosinophilic acute interstitial nephritis, with eosinophilic casts, background diabetes with mild nephrosclerotic vascular changes. Sunitinib was ceased and was treated IV methylprednisolone followed by prednisolone over next 6 weeks; with adjustment to diabetic medications. Renal Biopsy (No 2) 6 weeks following the initial biopsy showed marked resolution of the infiltrates with stable chronic changes, with decline in Serum Creatinine to 418 umol/L (eGFR 11 ml/min/1.73m<sup>2</sup>). He remains dialysis free as of April 2016. Conclusions: It is important that nephrologists be aware of the potential renal adverse effects of Sunitinib (and its class), so that appropriate surveillance strategies can be implemented.

Weekly Kt/V targets do not describe PD adequacy in patients with residual renal function.
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Aim: We hypothesised that conventional target levels of Kt/V are an indiscriminate marker of dialysis adequacy in PD patients with significant residual renal function. Background: Objective measurement of small solute clearance is a prominent component of peritoneal dialysis (PD) adequacy though the minimum 'adequate' dialysis dose is unknown. Method: Records were reviewed from a prevalent cohort of patients who had PD adequacy assessed between September 2015 and March 2016. Total weekly Kt/V, dialysate and residual renal subcomponents, and creatinine-clearance (CrCl) were compared according to minimal Kt/V thresholds being achieved through residual function alone. Time-coincident haemoglobin, serum calcium, phosphate, parathyroid hormone, albumin, bicarbonate and urea levels were compared as surrogate adequacy markers. Results: 94 PD patients (65 M:29 F) had an adequacy
assessment in the 6-month window. The cohort median total Kt/V was 2.25 (IQR 1.94-2.76), and the median CrCl was 71.47 (IQR 59.02-122.33). 84 patients (89%) had total Kt/V> 1.6 with 27 patients (29%) having residual Kt/V> 1.6. A total weekly Kt/V-centric assessment was a relatively meaningless guide to managing PD where native renal Kt/V exceeded 1.6. Of these 27 patients, 5 patients were on CAPD and 22 patients on APD. The median total Kt/V was 3.66 (IQR 3.11- 4.27) with median residual Kt/V was 2.69 (IQR 2.19-3.42) and median CrCl 157.29 (IQR 127.75-212.91). All biochemical surrogate markers of treatment adequacy were within CARI recommendation thresholds. Conclusion: Nearly one-third of PD patients had residual function with native Kt/V and creatinine clearances already well above recommended targets. In the context of other markers of clinical wellbeing, conventional thresholds of solute clearance traditionally applied across all-comers are insensitive descriptors of PD adequacy in this group.

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Hospitalisation, treatment delay and the use of imaging in peritoneal dialysis related peritonitis: Outcomes from the prompt study.

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Aim: To determine predictors of hospitalisation and the impact of radiological investigations on treatment delay in the management of peritoneal dialysis-related peritonitis (PDRP). Background: Peritonitis has significant adverse consequences for patients and health providers. Identifying risks for hospitalisation and barriers to effective antibiotic treatment may improve outcomes. Methods: Retrospective review of patients presenting with presumed PDRP in Western Australia between 2012 and 2014. We determined the risks of hospitalisation and the use and value of radiology investigations in the management of patients and the impact on treatment times. Results: In 157 episodes of PDRP, 54% were admitted with an average LOS of 3 days (Q1-Q3 1-6). In a multivariable model, significant predictors of admission were abnormal exit-site (OR 7.7), presentation to a hospital facility (OR 4.1), absence of cloudy bag (OR 5.8), female (OR 3.4) and antibiotic treatment >4 hours after presentation (OR 3.4) but not diabetes or indigenous race. Imaging was performed in 45% of presentations to a tertiary hospital (n = 72). Plain films (91%) were the commonest imaging modality; 82.2% of imaging procedures were either normal or clinically unhelpful. Episodes involving imaging had a median time to antibiotic treatment of 3.1 hours vs 2.8 without imaging (p = 0.22). In episodes with contact to treatment time >4 hours, 65% had imaging performed prior to treatment. Treatment failure occurred in 34.4% of episodes where imaging was performed, versus 23.7% where no imaging was performed (p=0.322). Conclusions: Hospitalisation at presentation with PDRP was more likely in those with significant treatment delay. Half of presentations to a hospital also included an imaging test, most of which had no clinical benefit. Strategies to reduce unnecessary imaging and reduce treatment delays are warranted.

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Comparison of case mix in tertiary and secondary centre nephrology clinics-does the current activity allotment reflect need?

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Aim: To compare the characteristics of patients currently under active follow up by nephrologists in tertiary and secondary referral settings in metropolitan WA. Background: Allocation of clinicians’ time to nephrology outpatients is based on estimates of budgeted activity and anticipated occasions of service. Actual patient numbers, the severity of chronic kidney disease (CKD) or comorbidities are not considered. Methods: Outpatient lists for one tertiary care nephrologist (Centre 1, n = 408) and both nephrologists at a secondary centre (Centre 2, n = 307) were obtained.
Clinic letters and blood results were reviewed to determine primary renal diagnosis, age, sex and most recent stage of CKD. Each nephrologist reported their full time equivalent (FTE) allocated to outpatient care. Results: Patients at Centre 2 averaged 10 years older (69.98 years versus 58.79), with more Stage 3b-5 (69 versus 37%), but fewer patients receiving renal replacement therapy (0.33% versus 13%). Haemodialysis is not available at Centre 2. The most frequent diagnoses at Centre 2 were hypertensive and diabetic nephropathy, whilst common Centre 1 diagnoses included diabetic nephropathy, post-transplant follow up and disorders of mixed aetiology. Centre 2 has 0.2 FTE consultants allocated to renal clinic; Centre 1 has 0.3 FTE including consultants and junior staff, with a further 0.1 FTE to review letters. Conclusions: In the population studied, secondary centre nephrologists provide outpatient care for an older group with more severe CKD, but fewer dialysis or transplant patients, without junior staff to assist. Neither overall numbers nor patient acuity is currently reflected in allocated FTE. Future workforce modelling could include these more relevant methods of determining demand.

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Validation of escalation criteria and adult dialysis observation and response chart in dialysis unit.
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Aim: Validation and assessment of clinical utility of the newly designed "Observation and Response Charts" for the dialysis. Background: The Australian commission on safety and quality in health care Standard 9 requires a system for recognising and responding to clinical deterioration. An innovative dialysis- specific chart was composed to ensure the dialysis patient's deterioration is recognised promptly and appropriate action is taken. Methods: The colour-coded chart records clinical vital signs and technical dialysis data for each dialysis. Specific scoring system (ADDS score) and intervention indications are documented. Episodes of escalation of care from 6 weeks prior and 6 months after the introduction of new chart were reviewed. Escalation triggers were reviewed with clinical outcomes. All adverse outcomes are also reviewed within the departmental meetings. Staff feedback was obtained at monthly intervals. Results: The number of escalations of care pre- and post-chart implementation was 5 in 926 treatments and 31 in 3785 treatments, respectively. However, the results of the number of escalations per trigger showed only 19% of escalations were triggered by the ADDS score while 81% escalations were from clinical assessments. There was no increase in escalations following introduction of ADDS score. Event rates were low. Resistance to change and need to manually input by staff were challenges for introduction. Conclusions: The chart gives an easy trend view analysis on patient's dialysis parameters and vital signs. The study results showed while the ADDS scoring system is useful in escalation of care, clinical assessment and examinations remains vital in determining and recognising the patients deterioration.

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Pure red cell aplasia due to anti erythropoietin antibodies and/ or parvoirus B19 in a peritoneal dialysis patient.
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Background: Acquired pure red cell aplasia (PRCA) is a rare cause of severe anaemia with very low reticulocyte count and absence of erythropoiesis in bone marrow, due to autoimmune, post-viral, genetic or idiopathic causes. PRCA was described in 1998-2002 due to cross-reactive anti-Epexx antibodies induced by syringe lubricant methionine contamination (Boven, NDT 2005), but unreported since changed manufacturing procedures. Batches of Epexx were recalled in mid-2015 in Australia due to high levels of methionine contamination again. Case Report: A 69-year-old Chinese male with focal and segmental glomerulosclerosis, on Peritoneal Dialysis for 8 months and subcutaneous
Eprex (epoetin alfa) 4000 Unit weekly for nearly 11 months, presented in August 2015 with fatigue, Hb fall from 106 to 51 g/dl and absent reticulocytes 2 x 10<sup>9</sup>/L (N 20-130). Bone marrow biopsy confirmed absent erythropoiesis. He had antibodies to both EPO (per Janssen-Cilag) and Parvovirus B19 IgM. Eprex was immediately ceased, but he required two units packed red cells monthly to maintain Hb>60 g/dl and was not responsive to both IV immunoglobulin 150 g monthly (50 g once daily for 3 days) for 3 months and Rituximab. As of April 2016, he remains transfusion dependent receiving total 24 units of PRBC, with iron overload (serum ferritin 4030, transferrin saturation 94%), planned for iron chelation (oral Desferriox 500 mg alternate day). Conclusions: Pure red cell aplasia can be due to combination of anti-EPO antibodies, Parvovirus and exposure to Eprex Methionine. The treatment can be challenging with multiple blood transfusions causing iron overload, use of iron chelating agent in a renal failure patient and uncertain response of intravenous immunoglobulin and rituximab.

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Pyroglutamic acidosis: An uncommon condition with common risk factors.
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Background: Accumulation of pyroglutamic acid (5-oxoproline), a by-product of the gamma-glutamyl cycle involved in glutathione synthesis, results in pyroglutamic acidosis (PGA), a high anion gap metabolic acidosis (HAGMA). Although considered rare, with only approximately 50 reported cases, the true incidence is unknown. The commonest known association of therapeutic paracetamol administration, and other risk factors including older age, female gender, liver disease and flucloxacinil, are all common in hospitalised patients, possibly suggesting significant underreporting. We describe three cases identified in a single hospital over a 10-month period. Case Report: Case 1. 72-year-old woman with Staphylococcus aureus bacteraemia from an epidural abscess, well treated with decompression and receiving intravenous flucloxacinil and paracetamol, presented with acute delirium. Secondary causes of delirium were ruled out. Investigations revealed HAGMA (pH7.28, bicarbonate 8, anion gap 22, lactate 0.7, Cr 60). Elevated urinary 5-oxoproline was detected. Repeat urine analysis following acidosis resolution showed negative 5-oxoproline. Case 2. 74-year-old woman with cirrhosis and Staphylococcus aureus prosthetic joint infection receiving flucloxacinil and paracetamol developed a persistent HAGMA. Once other causes were ruled out, urine analysis confirmed elevated 5-oxoproline. Case 3. 70-year-old female with alcoholic liver disease with disproportionate HAGMA in the setting of pneumococcal sepsis complicated by acute kidney injury was tested for urine 5-oxoproline which was elevated. In all cases acidosis resolved following paracetamol cessation. Conclusions: Our experience of diagnosing 3 patients over 10 months suggests that PGA is probably more common than thought. Given that paracetamol is a common over the counter medication and other risk factors are highly prevalent in hospitalised patients, physicians need to consider PGA as a differential for unexplained HAGMA.

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Affective disorders, psychosis and dementia in a community sample of older men with and without parkinson's disease.
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Background and Aims: Patients receiving dual anti-platelet therapy often present for emergency surgery. Co-morbidities are common and general anaesthesia can pose unacceptable risks for perioperative complications. Central neuraxial blockade is contraindicated as per guidelines. Although peripheral nerve blockade (PNB) is relatively contraindicated, it can represent a safe anaesthetic option but success and complication rates remain under-reported.

Methods: A 54-year-old obese female presented with a confirmed knee infection requiring emergency surgery in the presence of aspirin and clopidogrel. Comorbidities included ischaemic heart disease, cardiomyopathy (NYHA III), severe pulmonary hypertension, interstitial lung disease from bleomycin therapy and chronic renal impairment. Perioperative cardio-respiratory risks with general anaesthesia or spinal haematoma with neuraxial techniques were deemed to outweigh the risks of bleeding associated with PNB. Results: Femoral, sciatic and obturator nerve blocks were performed under ultrasound guidance and a low dose remifentanil infusion for conscious sedation achieved good surgical conditions. The patient was followed up where nerve function and haematoma formation assessed. A second washout 4 days later was conducted with the same anaesthetic approach with no complications. Conclusions: Case reports of haemorrhagic complications after PNB are informative but many predate the ultrasound era. Our experience highlights issues when performing PNB in the presence of dual antiplatelet therapy, it can represent a safe anaesthetic option. The literature may be useful for refining existing guidelines but there is a danger of reporting bias - only good outcomes get reported. A national audit project or online reporting system would increase our understanding in this area of regional anaesthesia. (Figure Presented).

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