GP Research Review™

Making Education Easy

Issue 132 – 2018

In this issue:

Abbreviations used in this issue

BP = blood pressure
COPD = chronic obstructive pulmonary disease
DVT = deep vein thrombosis
HR = hazard ratio
ICS = inhaled cortiosteroid
OR = odds ratio
PAD = peripheral artery disease
PE = pulmonary embolism
PSA = prostate-specific antigen
RCT = randomised clinical trial
RR = relative risk
TCM = traditional Chinese medicine
VAS = visual analogue scale
VTE = venous thromboembolismn

Welcome to issue 132 of GP Research Review.

One of the papers in this issue proposes a very basic, highly reliable and objective clinical test to rule out underlying cardiac disease in children and avoid many unnecessary referrals to cardiologists. The paper demonstrates that the disappearance of a murmur on standing reliably predicts the absence of cardiac pathology.

Tuina therapy, a traditional Chinese massage technique, may provide meaningful relief in chronic neck pain. Tuina combines a manual therapeutic approach with anatomical and physiological principles, and emphasises the meridians and acupoints. As detailed in the last paper in our Natural Therapy section, just 6 treatment sessions over a 3-week period resulted in a clinically relevant reduction in mean neck pain intensity in patients with chronic neck pain. The therapy also improved function and physical quality of life compared to a no-intervention control group. Moreover, the sessions were relatively cost-effective.

I hope you enjoy this issue and I welcome your comments and feedback.

Kind regards,

Jim

Assoc Professor Jim Reid
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Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations

Authors: McKeever T et al.

Summary: This 1-year trial recruited 1,922 adolescents and adults with asthma who were receiving ICS, with or without add-on therapy, and who had had ≥1 exacerbation in the previous 12 months. They were randomised to a self-management plan that either quadrupled their ICS dose for 7–14 days when asthma control started to deteriorate or to a plan that continued their current dose. Data from 1,871 patients were included in the primary analysis (time to a first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or an unscheduled health care consultation for asthma). During the trial, 45% of participants in the quadrupling group and 52% of those in the non-quadrupling group had a severe asthma exacerbation, with an adjusted hazard ratio for the time to a first severe exacerbation of 0.81 (95% CI, 0.71 to 0.92; p=0.002). Quadrupling of the dose was associated with a higher rate of adverse effects, which were related primarily to local effects of inhaled glucocorticoids.

Comment: This study follows the concept of SMART (Single Inhaler and Maintenance Therapy), which uses a combination inhaler of a quick-acting long-acting bronchodilator (formoterol) in combination with an inhaled corticosteroid (budesonide). In this study, while the bronchodilator and steroid inhalers were used separately, nonetheless, fewer severe asthma exacerbations eventuated. In SMART use, if increased bronchodilator is required, there is "automatic" increase in inhaled steroid. Smart – patients do not have to make the decision as to which inhaler to increase. However, I emphasise, inhalers are horses for courses!!!!

Reference: N Engl J Med. 2018;378:902-10
Abstract

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Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial

Authors: Martin RM et al.

Summary: Data are reported for 408,825 men aged 50–69 years who participated in the UK Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) study. They were invited to undergo a single PSA test at a PSA testing clinic (n=189,386) or were allocated to standard (unscreened) practice (n=219,439). In the intervention group, 75,707 (40%) men attended the PSA testing clinic and 67,313 (36%) underwent PSA testing. Valid PSA test results were obtained for 64,436 men; 6,857 (11%) had a PSA level between 3 ng/mL and 19.9 ng/mL, of whom 5,850 (85%) had a prostate biopsy. At a median 10 years of follow-up, prostate cancer mortality did not differ significantly between the groups (0.30 per 1,000 person-years in the intervention group vs 0.31 per 1,000 person-years; rate difference, –0.013 per 1,000 person-years; RR 0.96; 95% CI, 0.85 to 1.08; p=0.50). More men were diagnosed with prostate cancer in the intervention group (4.3% vs 3.6%; RR 1.19; 95% CI, 1.14 to 1.25; p<0.001) and the intervention resulted in a higher rate of detection of prostate cancer tumours with a Gleason grade of ≤6 (1.7% vs 1.1%; p<0.001) compared with no screening. In an all-cause mortality analysis, 25,459 deaths occurred in the intervention group and 28,306 deaths in the control group (RR 0.99; 95% CI, 0.94 to 1.03; p=0.49). In an instrumental variable analysis for prostate cancer mortality, the adherence-adjusted causal RR was 0.93 (95% CI, 0.67 to 1.29; p=0.66).

Comment: There is never a month goes by without a number of conflicting papers appearing in various journals about prostate cancer. This study sums up what is stated in a number of others. A single PSA test needs to be taken with a grain of salt, but serial testing (one every 2 years – the jury is still out) can be enlightening. This study demonstrated that single testing, while it turned up more low-risk cancer cases, did not result in a mortality difference between testing or no testing, after 10 years. The study did not report on anxiety, or operative complications in such low-risk cases.

Reference: JAMA. 2018;319(9):883-95
Abstract

Goodfellow Gems

The triple whammy of (ACE/ARB) + (diuretic) + (NSAID) is a dangerous trio

This common combination of medication is considered a dangerous trio and is also known as the triple whammy.[1] There are 4 key points:

1. Avoid this combination if possible.
2. Be aware of the risk factors for renal failure e.g. older patients with CHF or liver disease or volume depletion from vomiting/diarrhoea or low fluid intake on hot days.
3. Take care with older i.e. 75 years patients - check renal function yearly at least.
4. Advise patients not to self-medicate with NSAIDs when prescribing angiotensin converting enzyme receptor/ angiotensin II receptor antagonist (ACE/ARB) and diuretics.[2]

When volume depletion occurs consider stopping any (prescribed or OTC) NSAIDs and monitor renal function and serum potassium levels.[1]

There is also the double whammy i.e. NSAID with either diuretics or ACE/ARB, with the numbers needed to harm for one year 300 versus 158 for triple whammy.[3]

References:

1. SaferX (2017) Click here
2. SaferX Patient Information Guide (2016) Click here
3. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/ or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury (2015). Click here

Gems are chosen by the Goodfellow director Dr. Bruce Arroll to be either practice changing or practice maintaining. The information is educational and not clinical advice.

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Association of varicose veins with incident venous thromboembolism and peripheral artery disease

Authors: Chang SL et al.

Summary: This retrospective analysis used claims data from Taiwan's National Health Insurance program to identify 212,984 patients aged ≥20 years with varicose veins enrolled between 1 January 2001 and 31 December 2013; a control group of 212,984 patients without varicose veins was matched by propensity score. The varicose vein cohort was followed-up for a median 7.5 years for deep vein thrombosis (DVT), 7.8 years for pulmonary embolism (PE), and 7.3 years for peripheral artery disease (PAD); corresponding periods in the control cohort were 7.6 years, 7.7 years for PE and 7.4 years for PAD. Incidence rates in the varicose veins group were higher than those in the control group for DVT (6.55 vs 1.23 per 1,000 person-years; absolute risk difference [ARD] 5.32; 95% CI, 5.18 to 5.46), PE (0.48 vs 0.28 per 1,000 person-years, respectively; ARD 0.20; 95% CI, 0.16 to 0.24), and for PAD (10.73 vs 6.22 per 1000 person-years, respectively; ARD 4.51; 95% CI, 4.31 to 4.71). In Cox proportional hazards analysis, hazard ratios for the varicose veins group compared with the control group were 5.30 (95% CI, 5.05 to 5.56) for DVT, 1.73 (95% CI, 1.54 to 1.94) for PE, and 1.72 (95% CI, 1.68 to 1.77) for PAD.

Comment: This is an interesting paper, the concept of which clearly requires expansion with further research. It seems that those with DVT had a 5-fold increase in incidence over a 13-year period (? decreased flow in deep venous system) in the varicose vein group as compared with controls. However, the findings for pulmonary embolism and peripheral artery disease was not so clear-cut because of confounding factors. Food for thought – and further research. An ideal topic for general practice to pick up.

Reference: JAMA. 2018;319(8):807-17
Abstract

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Authors: Papi A et al.

Summary: This multinational trial recruited 1,532 patients with symptomatic COPD, severe or very severe airflow limitation and ≥1 moderate or severe exacerbation in the previous year, despite maintenance therapy. After a 2-week run-in period with one inhalation per day of indacaterol plus glycopyrronium (IND/GLY) (85 µg/43 µg), patients were randomly assigned to receive 52 weeks of treatment with two inhalations of extra-fine beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) (87 µg/5 µg/9 µg) twice per day (n=764) or one inhalation of IND/GLY (85 µg/43 µg) per day (n=768). Moderate-to-severe exacerbation rates were 0.50 per patient per year for BDP/FF/G and 0.59 per patient per year for IND/GLY, giving a rate ratio of 0.848 (p=0.043) in favour of BDP/FF/G. Similar proportions of adverse events were reported by each group (64% in the BDP/FF/G arm vs 67% in the IND/GLY arm). Pneumonia occurred in 4% of patients in each group and one treatment-related serious adverse event occurred in each group: dysuria with BDP/FF/G and atrial fibrillation with IND/GLY.

Comment: There is a word missing in the conclusion. The word is "just" and the conclusion should read – "In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G **just** significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia." The p value was 0.043 and probably one or two patients could have made the difference between significance and non-significance.

Reference: Lancet. 2018;391(10125):1076-84
Abstract

Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial

Authors: McManus RJ et al.

Summary: This UK study included 1,182 hypertensive primary care patients aged >35 years with BP >140/90 mm Hg, who were willing to self-monitor their BP. They were randomly assigned to a self-monitoring BP group (n=395), to self-monitoring BP with telemonitoring (n=393), or to usual care (clinic BP; n=394). A total of 1,003 participants were included in the primary analysis (clinic-determined systolic BP at 12 months from randomisation). After 12 months, systolic BP was lower in both intervention groups compared with usual care (self-monitoring, 137.0 mm Hg and telemonitoring, 136.0 mm Hg vs usual care, 140.4; adjusted mean differences vs usual care: self-monitoring alone, –3.5 mm Hg; telemonitoring, –4.7 mm Hg). There was no between-group difference for the self-monitoring and telemonitoring groups. Results were similar in sensitivity analyses including multiple imputation. Adverse events were similar between the groups.

Comment: This study demonstrates that "white-coat" hypertension is alive and well. We all know that when the patient relaxes after some casual distracting conversation the 2nd and 3rd BP readings in the surgery are lower. This is why a single normotensive reading in the consulting room is highly significant, whereas a single elevated reading needs repeating and perhaps 24-hour monitoring before commencement of long-term treatment.

Reference: Lancet. 2018;391(10124):949-59
Abstract

Prevalence of pulmonary embolism in patients with syncope

Authors: Costantino G et al.

Summary: This analysis obtained administrative data from 5 databases in Canada, Denmark, Italy, and the USA concerning 1,671,944 adults (aged ≥18 years) who presented to the emergency department (ED) for evaluation of syncope between 1 January 2000 and 30 September 2016. The prevalence of PE ranged from 0.06% to 0.55% for all patients and from 0.15% to 2.10% for hospitalised patients. Corresponding rates at 90 days of follow-up ranged from 0.14% to 0.83% and from 0.35% to 2.63%, respectively. The 90-day prevalence of VTE ranged from 0.30% to 1.37% for all patients and from 0.75% to 3.86% for hospitalised patients.

Comment: The stats of the study actually show that PE was a rare cause of syncope, but it is a diagnosis that, along with others, should be considered, especially in the elderly.

Reference: JAMA Intern Med. 2018;178(3):356-62
Abstract

Renal function monitoring in patients prescribed dabigatran in the Compass Health Primary Health Organisation: a quality improvement audit

Authors: McBain L, Kyle A

Summary: Outcomes are reported from two audits performed by the Compass Health Primary Health Organisation (PHO) throughout the Wellington, Porirua, Kapiti and Wairarapa regions – the first included data from July 2013 to May 2014 and the second from May 2014 to October 2016 – reviewing annual renal function monitoring and clinical indications for use in patients prescribed dabigatran. The first audit involved 941 patients; the second involved 1,564 patients. At the time of the second audit, renal function monitoring improved from 88% to 90%, and dabigatran was prescribed for an approved indication in 96% of patients.

Comment: The introduction of funding for dabigatran on the prescribing of GPs met with not insignificant resistance from some medical vocations in NZ. I have always been interested in such opposition – it happened years ago with β-blockers, with inhaled steroids, and from my pharmacy days I remember when prednisone was "hospital only" and was "committee approved" after specialist prescribing. There was a similar fuss about releasing isotretinoin. I wonder if digoxin was introduced in 2018, would it get approval for general prescribing? This study demonstrates that best practice and guidelines for dabigatran are being followed.

Reference: N Z Med J. 2018;131(1471):40-7
Abstract

Independent commentary by Associate Professor Jim Reid.
Jim Reid has a private family medicine practice at the Caversham Medical Centre, Dunedin, New Zealand. He is a Distinguished Fellow of the Royal New Zealand College of General Practitioners and is also a Fellow of the American College of Chest Physicians.

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Auscultation while standing: A basic and reliable method to rule out a pathologic heart murmur in children

Authors: Lefort B et al.

Summary: This French investigation included 194 paediatric patients aged 2–18 years referred for heart murmur evaluation to paediatric cardiologists between January 2014 and January 2015. All patients underwent heart murmur recordings while supine and then while standing, as well as an echocardiogram. Abnormal echocardiogram readings identified a pathologic (organic) heart murmur in 30 (15%) patients. Half (n=100) of the cohort had a murmur that was present while they were supine but completely disappeared when they stood up; a pathologic murmur was identified in only 2 of these patients, and only 1 of them needed further evaluation. The complete disappearance of murmur on standing excluded a pathologic murmur with a high positive predictive value of 98% and specificity of 93%, and a sensitivity of 60%.

Comment: Fascinating. This is a message that I have taken on board. If you hear a murmur when a child is lying – stand them up and listen again. This study shows that if the murmur disappears it is most likely to be benign. How much anxiety and needless referral can be saved by this simple procedure.

Reference: Ann Fam Med. 2017;15(6):523-8
Abstract

EVIDENCE-BASED NATURAL HEALTH
by Dr Chris Tofield

Effect of vitamin D and calcium supplementation on cancer incidence in older women: A randomized clinical trial

Authors: Lappe J et al.

Summary: In this US trial, 2,303 healthy postmenopausal women aged ≥55 years with a mean baseline serum 25-hydroxyvitamin D level of 32.8 ng/mL received daily dietary supplementation with either vitamin D_3 (2,000 IU) and calcium (1,500 mg; n=1,156) or identical placebos (n=1,147) for 4 years. 2,064 (90%) women completed the study. In an intention-to-treat analysis, a new diagnosis of cancer was confirmed in 3.89% women in the vitamin D_3 + calcium group and 5.58% in the placebo group (p=0.06). Similarly, there was no significant between-group difference in Kaplan-Meier survival analysis; the incidence of all-type cancer (excluding nonmelanoma skin cancers) over 4 years was 0.042 in the vitamin D_3 + calcium group and 0.060 in the placebo group (p=0.06). Proportional hazards modelling yielded a hazard ratio of 0.70 (95% CI, 0.47 to 1.02). Adverse events potentially related to the study included renal calculi (16 women in the vitamin D_3 + calcium group and 10 in the placebo group) and an increase in serum calcium levels (6 in the vitamin D_3 + calcium group and 2 in the placebo group).

Comment: Nice to see a randomised trial on vitamin D rather than yet another observational study. Although at first all hyped up, there has been a cooling off on the vitamin D front, with several studies now showing limited usefulness. This US study adds to that, failing to show any benefit of vitamin D and calcium in terms of cancer prevention in women.

Reference: JAMA. 2017;317(12):1234-43
Abstract

Effectiveness and cost-effectiveness of Tuina for chronic neck pain: A randomized controlled trial comparing Tuina with a no-intervention waiting list

Authors: Pach D et al.

Summary: Outcomes are reported for 92 outpatients with chronic neck pain attending a single German university clinic specialising in Integrative Medicine. The participants were randomised to receive 6 Tuina (also known as Tui Na; traditional Chinese massage) treatments over a 3-week period (n=46), or no intervention (n=46). At baseline, the mean VAS score was 57.7 mm on a scale of 0–100 mm (0 = no pain, 100 = worst imaginable pain). Tuina treatment was associated with a clinically meaningful reduction in neck pain intensity: the between-group differences were –22.8 mm at 4 weeks (p<0.001) and –17.9 mm at 12 weeks (p<0.001). There were no serious adverse events. Neither total costs nor quality-adjusted life years (QALYs) differed significantly between the groups. In an analysis that accounted for group differences independently from their statistical significance, costs per QALY gained (incremental cost-effectiveness ratio) ranged within a cost-effective area from €7,566 (cost €10.28 per session) to €39,414 (cost €35 per session).

Comment: I recall a young adult once with chronic neck pain, who had undergone every investigation and medical treatment in the book, but without success. And yet he was not interested in any 'natural' treatment options. According to this paper, he might have been well advised to trial Tui Na, a traditional Chinese body work treatment modality. With 92 participants in this study, there were just enough to confer some statistical credibility of the results that showed just six sessions to be effective.

Reference: J Altern Complement Med. 2017 Oct 26. [Epub ahead of print]
Abstract

Dr Christopher Tofield
Dr Tofield completed his medical training at St Bartholomew's and the Royal London Hospital in London. He now works part time in general practice in Tauranga, is involved with clinical research, has published several medical papers and a textbook on pharmacology, and is clinical advisor to Bay of Plenty District Health Board.
For full bio CLICK HERE.