GP Research Review™

Making Education Easy

Issue 139 – 2018

In this issue:

Abbreviations used in this issue

BP = blood pressure
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
GI = gastrointestinal
HR = hazard ratio
ICS = inhaled corticosteroids
OR = odds ratio
PSA = prostate-specific antigen
RCT = randomised controlled trial
RR = relative risk
RTI = respiratory tract infection

Welcome to issue 139 of GP Research Review.

This issue reports data from two primary prevention trials of aspirin: ASPREE (Aspirin in Reducing Events in the Elderly) and ASCEND (A Study of Cardiovascular Events in Diabetes), both of which evaluated the risk associated with the use of aspirin for primary prevention in current practice. ASPREE demonstrated no benefit for the use of aspirin 100 mg/day over placebo for the composite primary endpoint of death, dementia, or persistent physical disability and neither was there any evidence of a CV benefit for aspirin. Moreover, the risk of major bleeding was higher with aspirin than with placebo. In ASCEND, aspirin was associated with a lower rate of serious vascular rates compared with placebo. However, this was offset by a higher rate of major bleeding events.

Evidence from one of the papers in the Natural Health section suggests that listening to self-selected music while undergoing pleural procedures lessens patients' anxiety. There was no change in state anxiety scores among the controls, who were not exposed to music. The study was small, however, with only 60 patients in total; it would be interesting to see if the results are replicated in larger samples.

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

Kind regards,
Jim

Assoc Professor Jim Reid
jimreid@researchreview.co.nz

Goodfellow Gems

Bisphosphonate holiday for some after 4 to 5 years

Patients on long-term alendronate/risedronate should be reassessed after 4 to 5 years:

- If their P1NP (bone turnover marker) is < 35 mcg/l and their femoral T-score is better than -2.5 and there are no new fractures, they can have a drug holiday (oral medication only) for 4 to 5 years.
- If T-score is worse than -2.5 or new fracture then continue treatment for 4-5 more years of oral medication and reassess (consider a 1-2 year drug holiday in this period).
- After 5 to 10 years of oral treatment, consider a 1-2 year holiday.

IV zoledronate is an alternative option, given every 18 to 24 months for 3-4 doses, then every 3 years if T-score remains worse than -2.5. In those on oral bisphosphonate with PINP > 35 µg/L, a change to IV is often indicated.

Bisphosphonates prevent fractures without the need for calcium supplements, though vitamin D should be provided to those at risk of deficiency (frail elderly, institutionalised etc).[1]

This Gem has been checked by Professor Ian Reid, University of Auckland.

Reference: Guidance on the Diagnosis and Management of Osteoporosis in New Zealand (2017) 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. www.goodfellowunit.org/gems

New evidence for the benefit of prostate-specific antigen screening: data from 400,887 Kaiser Permanente patients

Author: Alpert PF

Summary: This retrospective analysis examined the value of PSA screening in a cohort of 400,887 men aged <80 years without a history of prostate cancer, who underwent yearly PSA testing at Kaiser Permanente Northern California from 1998 through 2002 and were followed-up for 12–16 years. They were divided into 42 subgroups: 6 groups based on PSA intervals (12–18 months, 18–24 months, 2–3 years, 3–4 years, 4–9 years, or no prior PSA) and 7 age groups (<50, 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 years). Compared with no screening, PSA screening did not result in any clear benefits among the 154,125 men aged <55 years: χ^2 3.51 (p=0.62) for the 77,157 aged <50 years; χ^2 4.04 (p=0.54) for the 76,968 men aged 50–54 years. In contrast, the combined results for the 5 groups of men aged 55–75 years yielded a highly significant rate ratio of prostate cancer mortality between 12–18 months screening and no prior screening (cancer mortality, RR 0.36; 95% CI, 0.22 to 0.50; p<0.001; all-cause mortality, RR 0.76; 95% CI, 0.15 to 0.34; p<0.001).

Comment: I am indebted to Dr Ron Baker for bringing this paper to my attention. We all know the controversies surrounding PSA testing and the pros and cons from within the profession and from lay groups. The data comes from a very large Managed Health Consortium in the USA (Kaiser), which will have access to a large amount of quality data. This is one of the first studies that I have seen showing such a marked decrease in both prostate cancer deaths and all-cause mortality from annual PSA screening. The paper is unclear, however, about the comparator group – whether it was "usual care" referenced from national or regional statistics, or from the age grouping from within the study. These figures were reached after there was active surveillance for prevention of over-treatment. Perhaps food for thought????

Reference: Urology. 2018;118:119-26
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. **FOR FULL BIO CLICK HERE**

Effect of aspirin on cardiovascular events and bleeding in the healthy elderly

Authors: McNeil JJ et al.

Summary: This paper reports findings on major haemorrhage and CV disease (defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalisation for heart failure) from the ASPREE (Aspirin in Reducing Events in the Elderly) trial, which involved 19,114 community-dwelling men and women in Australia and the USA aged ≥70 years (or ≥65 years of age among blacks and Hispanics in the USA) free from CV disease, dementia, or disability at study entry. ASPREE evaluated the effect of enteric-coated aspirin 100 mg/day (n=9,525) compared with matching placebo (n=9,589). Recruitment began in March 2010 and ended in December 2014. At a median follow-up of 4.7 years, CV disease rates were not significantly different between the aspirin and placebo groups (10.7 events per 1,000 person-years of follow-up vs 11.3 events per 1,000 person-years, respectively; HR 0.95; 95% CI, 0.83 to 1.08). Notably, the rate of major haemorrhage was significantly higher in the aspirin group compared with the placebo group (8.6 events per 1,000 person-years vs 6.2 events per 1,000 person-years, respectively; HR 1.38; 95% CI, 1.18 to 1.62; p<0.001).

Comment: The conclusion to this study says it all. The risk/benefit ratio for the use of aspirin for primary prevention of CV disease is weighted against placebo in the ≥70-year age group (or ≥65 years of age among blacks and Hispanics in the USA). Basically, aspirin did not significantly reduce the risk of CV disease and was associated with increased risk of haemorrhage.

Reference: N Engl J Med. 2018;379(16):1509-18
Abstract

Effect of aspirin on all-cause mortality in the healthy elderly

Authors: McNeil JJ et al.

Summary: This analysis of the ASPREE trial reports all-cause mortality findings. During the median follow-up of 4.7 years, 1,052 deaths were recorded. The risk of death from any cause was higher in the aspirin group (12.7 events per 1,000 person-years vs 11.1 events per 1,000 person-years with placebo; HR 1.14; 95% CI, 1.01 to 1.29), with 1.6 excess deaths per 1,000 person-years in the aspirin group. Cancer-related death was the major contributor to the higher mortality with aspirin, occurring in 3.1% of the aspirin group compared with 2.3% of the placebo group (HR 1.31; 95% CI, 1.10 to 1.56).

Comment: There have been a number of previous studies that have had an alternative outcome with respect to the incidence of cancer (especially colon cancer). Although in a number of these there was an increase in bleeding with aspirin, the weighting was favourable towards cancer prevention and thus was positive towards aspirin. This study among older adults demonstrated that the group on aspirin had a higher all-cause mortality, mainly because of cancer. Which do you believe – I am not sure – both sides of the fence are pretty convincing, so the jury is still out!

Reference: N Engl J Med. 2018 Oct 18;379(16):1519-28
Abstract

Effect of aspirin on disability-free survival in the healthy elderly

Authors: McNeil JJ et al.

Summary: This analysis of ASPREE data reports on the primary endpoint of death, dementia, or persistent physical disability. The rate of the primary endpoint was 21.5 events per 1,000 person-years with aspirin and 21.2 per 1,000 person-years with placebo (HR 1.01; 95% CI, 0.92 to 1.11; p=0.79). In the final year of the trial, 62.1% of aspirin recipients and 64.1% of placebo recipients reported that they were still taking their assigned intervention. There were no marked between-treatment differences in the secondary individual endpoints of death, dementia, or persistent physical disability. However, major haemorrhage occurred in 3.8% of those on aspirin compared with 2.8% of those on placebo (HR 1.38; 95% CI, 1.18 to 1.62; p<0.001).

Comment: This is the same study of the elderly (70+ years) reported in the preceding articles who were studied for a median 4.7 years. This time, the authors looked at disability-free survival. In a nutshell, aspirin had no effect on this whatsoever and it had (as would be expected) an increase in bleeding. This time a win to placebo!

Reference: N Engl J Med. 2018;379(16):1499-508
Abstract

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our **CPD page**.

Effects of aspirin for primary prevention in persons with diabetes mellitus

Authors: ASCEND Study Collaborative Group

Summary: The ASCEND (A Study of Cardiovascular Events in Diabetes) trial randomised 15,480 adults with diabetes but no evident CV disease to receive aspirin 100 mg/day or matching placebo. During a mean 7.4 years of follow-up, serious vascular events (defined as myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial haemorrhage) occurred in 658 (8.5%) of the aspirin recipients and in 743 (9.6%) of the placebo recipients (rate ratio 0.88; 95% CI, 0.79 to 0.97; p=0.01), although the primary safety outcome, the first occurrence of any major bleeding event (defined as intracranial haemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or other serious bleeding), occurred in a significantly higher proportion of aspirin recipients compared with placebo recipients (314 [4.1%] vs 245 [3.2%]; rate ratio 1.29; 95% CI, 1.09 to 1.52; p=0.003); most of the excess was explained by GI bleeding and other extracranial bleeding. There were no significant between-group differences as to the numbers of patients who developed GI tract cancer (157 [2.0%] aspirin recipients vs 158 [2.0%] placebo recipients), or all cancers (897 [11.6%] vs 887 [11.5%], respectively).

Comment: This is the last one on aspirin – I promise. This paper reports events for a group of diabetics of similar demographics (658 aspirin and 743 placebo) who were studied over 7.4 years. Those on aspirin had a positive outcome on CV disease prevention, but this was offset by the occurrence of major bleeding. In this study, there was no difference in either group in the incidence of GI cancer. The benefits of primary prevention were obviated by the increase in GI and intracranial bleeding. The result – a draw!

Reference: N Engl J Med. 2018;379(16):1529-39
Abstract

Impact of antibiotics for children presenting to general practice with cough on adverse outcomes: secondary analysis from a multicentre prospective cohort study

Authors: Redmond NM et al.

Summary: Outcomes are reported from a secondary analysis of data from a UK study involving 8,320 children aged 3 months to <16 years presenting to primary care with acute cough and other respiratory symptoms. The researchers sought to determine whether immediate or delayed antibiotic prescription affects the risk of adverse outcomes (subsequent hospitalisation or reconsultation for deterioration) within 30 days of initial consultation. Clinicians prescribed antibiotics to 3,084 children (37%); 2,313 (28%) were prescribed immediate and 771 (9%) delayed antibiotics. Sixty-five children (0.8%) were hospitalised for a respiratory tract infection (RTI) and 350 (4%) reconsulted for the same RTI with evidence of deterioration. Neither univariate nor multivariate analyses revealed any clear evidence that prescribing immediate or delayed antibiotics lessened the risk of being hospitalised within the 30 days of initial consultation, as compared with not prescribed an antibiotic (immediate antibiotic RR 0.83 and delayed RR 0.70; overall p=0.44). The evidence did suggest that delayed antibiotic prescribing reduced reconsultations for deterioration in the subsequent 30 days following the initial consultation, compared with not prescribing antibiotics (OR 0.55; 95% CI, 0.34 to 0.88); the point estimate for children prescribed an immediate antibiotic suggested a reduction, but as the article points out, the 95% CI does not rule out the absence of an effect (OR 0.82; 95% CI, 0.65 to 1.07; overall p=0.024).

Comment: There is often conflict between patient expectations and appropriate treatment. This study is interesting, insofar that the prescribing of antibiotics made no difference to the risk of hospitalisation of children presenting with cough and respiratory symptoms. It is therefore part of antimicrobial stewardship to restrict inappropriate antibiotic prescribing, and the "back pocket" prescription may be a mechanism that satisfies both parties.

Reference: Br J Gen Pract. 2018;68(675):e682-93
Abstract

Treatments for subacute cough in primary care: systematic review and meta-analyses of randomised clinical trials

Authors: Speich B et al.

Summary: These researchers systematically reviewed the evidence in RCTs published up to March 2017 that evaluated treatment outcomes of any drug or non-drug treatments (except for traditional Chinese and Asian medicines) in adult patients with subacute cough lasting 3–8 weeks following a non-specific viral infection. Six RCTs involving 724 patients were eligible and included in meta-analyses. Treatments included montelukast, salbutamol plus ipratropium bromide, gelatine, fluticasone propionate, budesonide, nociception opioid 1 receptor agonist therapy and codeine. Treatment effects on cough severity scores at various timepoints were reported in 5 studies. None of the treatments were clearly beneficial for cough recovery or other patient-relevant outcomes. Moreover, when the evidence on treatment effects was combined in random effects meta-analyses, there were no benefits for cough-related outcomes at 14 or 28 days.

Comment: Cough is a very common complaint in general practice and it certainly is in mine. Of course it is necessary to eliminate cause – infection, post-viral, COPD, asthma (rare – asthma sufferers wheeze, and cough is rare though it can happen), medication, sarcoidosis, interstitial lung disease, and numerous other canaries, but in many case investigation comes to zilch. There are many remedies for such coughs, but as this study says, most are ineffective. One is probably no better than the other, but mercifully for both patient and doctor, the condition is self-limiting.

Reference: Br J Gen Pract. 2018;68(675):e694-702
Abstract

Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: a randomized clinical trial

Authors: Devereux G et al.

Summary: Outcomes are reported from the multicentre UK TWICS (theophylline with inhaled corticosteroids) trial, which enrolled 1,578 patients (mean age 68.4 years) with COPD, all of whom had a baseline FEV_1/FVC of <0.7 and had experienced ≥2 exacerbations (treated with antibiotics, oral corticosteroids, or both) in the 12 months before study entry and were on ICS. They were randomly assigned to either low-dose theophylline (200 mg once or twice daily to provide plasma concentrations of 1–5 mg/L determined by ideal body weight and smoking status; n=791) or placebo (n=787) for 1 year. Primary outcome (exacerbation) data were available for 772 theophylline-treated patients and 764 placebo-treated patients. A total of 3,430 exacerbations were reported during the 1-year treatment period: 1,727 with theophylline (mean, 2.24 exacerbations/year) and 1,703 with placebo (mean, 2.23 exacerbations/year); the adjusted incidence rate ratio was 0.99 (95% CI, 0.91 to 1.08). Serious adverse events noted in the theophylline and placebo groups respectively included cardiac events (2.4% vs 3.4%) and GI events (2.7% vs 1.3%). Respective rates of other adverse reactions included nausea (10.9% vs 7.9%) and headache (9.0% vs 7.9%).

Comment: Theophylline is still widely used in some countries – it is tricky to use but is cheap. There is some evidence that it has intrinsic anti-inflammatory effects and these can be additive with ICS. This study looked at unwanted effects and the incidence of exacerbations in COPD patients who were all using ICS and using additional theophylline vs those on placebo. There was an across the board increase in unwanted effects in those on theophylline (GI, nausea and headache) and it did not confer any reduction in exacerbations. In this country, it remains very much a second-line medication.

Reference: JAMA. 2018;320(15):1548-59
Abstract

EVIDENCE-BASED NATURAL HEALTH
by Dr Chris Tofield

Music reduces state anxiety scores in patients undergoing pleural procedures: a randomised controlled trial

Authors: Mackintosh J et al.

Summary: This study randomised 60 patients undergoing therapeutic pleural procedures to music therapy (self-selection of music using ear-bud headphones for the duration of the procedure) or no music (controls) and compared baseline with post-procedure scores on the State Trait Anxiety Inventory. In the music group, state anxiety scores were significantly improved from baseline following the procedure ($p<0.001$), whereas no such change occurred in the control group ($p=0.51$). Music therapy was also associated with significant improvements after the procedure in heart rate, systolic and diastolic BP ($p\leq0.04$ for all comparisons), whereas there were no such changes from baseline in the control group. No significant between-group differences were observed for patient pain scores, willingness to repeat the procedure, satisfaction with the performance of the pleural procedure, or with its duration.

Comment: We have previously reported on research that showed calming effects of music preoperatively. In this Australian study, however, music was listened to during an entire procedure, and resulted in improvements in anxiety score as well as in physiological parameters of anxiety (e.g. BP, heart rate). It makes one wonder whether music during a GP consult may have similar beneficial effects – on both the patient as well as the GP?

Reference: Intern Med J. 2018;48(9):1041-8
Abstract

Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis

Authors: Garcia-Larsen L et al.

Summary: This systematic review included observational studies published between January 1946 and July 2013 and intervention studies published between 1946 and until December 2017 that evaluated associations between diet during pregnancy, lactation, or the first year of life and future risk of allergic or autoimmune disease. The researchers identified 260 original studies (964,143 participants) of milk feeding, including 1 intervention trial of breastfeeding promotion, and 173 original studies (542,672 participants) of other maternal or infant dietary exposures, including 80 trials of maternal (n=26), infant (n=32), or combined (n=22) interventions. A high risk of bias was found in 125 (48%) milk feeding studies and 44 (25%) studies of other dietary exposures. Data from 19 intervention trials indicated that oral probiotic supplementation during late pregnancy and lactation could reduce eczema risk (RR 0.78; 95% CI, 0.68 to 0.90; absolute risk reduction [ARR] 44 cases per 1,000) and 6 trials suggested that fish oil supplementation during pregnancy and lactation may reduce risk of allergic sensitisation to egg (RR 0.69; 95% CI, 0.53 to 0.90; ARR 31 cases per 1,000). Grading of Recommendations Assessment, Development and Evaluation (GRADE) domains defined the certainty of the evidence as moderate. GRADE domains rated the certainty of evidence as low for the hypotheses that breastfeeding promotion reduces risk of eczema during infancy (1 intervention trial), that prolonged exclusive breastfeeding reduces risk of type 1 diabetes (28 observational studies), and that probiotics reduce risk of allergic sensitisation to cow's milk (9 intervention trials). Other dietary exposures, including prebiotic supplements, maternal allergenic food avoidance, vitamin, mineral, fruit, and vegetable intake, did not apparently influence risk of allergic or autoimmune disease. Data were inconclusive or inconsistent for many dietary exposures.

Comment: There is a whole lot we still don't know about the effects of maternal immune processes on the fetus. For now, this meta-analysis looking at maternal diet (including probiotics and fish oils) did not produce any 'hard' findings, and that may not be surprising seeing that so many different factors affect outcomes in unborn babies. I suspect we'll be seeing much more research in this area.

Reference: PLoS Med. 2018;15(2):e1002507
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.**