Welcome to the sixty-sixth issue of GP Research Review.

The New Zealand Medical Journal has published three case reports of New Zealand infants with potential renal complications including hypertension, renal failure and death following in utero ACE inhibitor exposure. This evidence demonstrates the importance of counselling women of child-bearing age regarding ACE inhibitors.

The prevailing concept is that the lower the BP, the better, in diabetic patients with hypertension. However, outcomes of two studies that we feature in this issue of GP Research Review challenge this assumption; an intensive BP-lowering strategy did not reduce the risk for mortality or myocardial infarction.

Our Natural Health section discusses the benefits of Qigong in fibromyalgia, and the efficacy of probiotics for the management of acute diarrhea in children.

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

Kind Regards
Jim

Associate Professor Jim Reid
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ACE inhibitor fetopathy: a case series and survey of opinion amongst New Zealand paediatricians, obstetricians, neonatologists, and nephrologists

Authors: Deva M, Kara T

Summary: Good epidemiological evidence demonstrates that angiotensin converting enzyme (ACE) inhibitors during pregnancy are associated with potential adverse effects to the developing foetus (fetopathy), yet women continue to receive ACE inhibitors both in New Zealand and overseas. This paper presents case details of three New Zealand infants with potential renal complications including hypertension, renal failure and death following in utero exposure to ACE inhibitors. Outcomes are also discussed from an email-based survey completed by relevant hospital-based specialists in New Zealand (paediatricians, neonatologists, maternal-foetal medicine obstetricians and nephrologists) that sought their experience and opinion on how to best counsel women regarding ACE inhibitors and pregnancy. Opinions varied amongst the respondents, reflecting differing experience and awareness. The paper suggests that the best way in which to counsel women regarding ACE inhibitors and pregnancy remains an area for further discussion in New Zealand.

Comment: It is not well known that ACE inhibitors are contraindicated in pregnancy, and these three case reports in the New Zealand Medical Journal are a sobering “wake up” call to all doctors and midwives.


Abbreviations used in this issue
ACE = angiotensin converting enzyme
BP = blood pressure
CV = cardiovascular

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Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes

Authors: Vamos EP et al

Summary: Data were retrospectively analysed from the UK General Practice Research Database to examine the effects of systolic and diastolic blood pressure (BP) on all-cause mortality in 126,092 adults (age ≥18 years) with newly diagnosed type 2 diabetes mellitus, with and without established cardiovascular disease. BP was determined during the first year after diagnosis of diabetes. After a median 3.5-year follow-up, 25,495 patients (20%) had died. In the 12,379 patients with established cardiovascular disease (myocardial infarction or stroke), tight control of systolic BP (<110 mm Hg) was associated with a significantly higher likelihood of death than was usual control of systolic BP (130–139 mm Hg) (HR, 2.79; p<0.001); similarly, the HRs for mortality were 1.32 (p=0.04) and 1.89 (p<0.01), respectively, for diastolic BPs at 70–74 mm Hg and <70 mm Hg compared to usual control of diastolic BP (80–84 mm Hg). Similar associations were found in patients without cardiovascular disease.

Comment: This is another study that threatens a sacred cow! The authors make two points. The first is that current BP recommendations (guidelines vary but in general recommend a systolic below 130 and diastolic below 80) do not reduce all-cause mortality, and further, low blood pressure actually demonstrated increased poor outcome risk. It may be that the latter group may have had some existing cardiovascular compromise, but the findings were similar for those with and without known cardiovascular disease. Food for thought!

Reference: BMJ 2012;345:e5567
http://www.bmj.com/content/345/bmj.e5567

Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus

Authors: McBrien K et al

Summary: Data were pooled from 5 randomised trials that investigated the safety and efficacy of intensive versus standard BP management in patients with type 2 diabetes. Intensive BP management used a target upper limit of 130 mm Hg systolic and 80 mm Hg diastolic; standard management was considered to be an upper limit of 140–160 mm Hg systolic and 85–100 mm Hg diastolic. The use of intensive BP targets was not associated with a significant decrease in the risk for mortality (relative risk difference, 0.76) or myocardial infarction (0.93) but was associated with a decrease in the risk for stroke (0.65). The pooled analysis of risk differences associated with the use of intensive BP targets demonstrated a small absolute decrease in the risk for stroke (absolute risk difference, −0.01) but no statistically significant difference in the risk for mortality or myocardial infarction.

Comment: This is the second study this month that challenges the blood pressure recommendations for diabetics. Close control did not reduce all-cause mortality or myocardial infarction, but did produce a small reduction in stroke. If we factor in the possibility of postural hypotension, especially in the elderly, maybe we should be thinking again about appropriate BP control. Again food for thought.


GP Research Review

Independent commentary by Associate Professor Jim Reid, Head of Department of General Practice at the Dunedin School of Medicine and Deputy Dean of the School.

For full bio CLICK HERE.

Research Review publications are intended for New Zealand health professionals.
Risk of coronary events in people with chronic kidney disease compared with those with diabetes

Authors: Tonelli M et al

Summary: This population-level cohort study sought to determine whether chronic kidney disease (CKD) is a coronary heart disease risk equivalent. Data were obtained from 1,268,029 individuals not currently on dialysis participating in the Alberta Kidney Disease Network (AKDN) and the National Health and Nutrition Examination Survey (NHANES). Baseline CKD was defined as an estimated glomerular filtration rate (eGFR) 15–59.9 mL/min per 1.73 m² (stage 3 or 4 disease). During a median 48-month follow-up, 11,340 participants (1%) were admitted to the hospital with myocardial infarction (MI). The unadjusted rate of MI was 18.5 per 1000 person-years in people with a previous MI, which was significantly higher than in subjects with diabetes but no CKD and in CKD without diabetes (5.4 per 1000 person-years and 6.9 per 1000 person-years, respectively; both p<0.0001). When using a more stringent definition of kidney disease, the rate of incident MI in diabetics was substantially lower than for those with CKD defined by an eGFR of <45 mL/min per 1.73 m² and severely increased proteinuria (6.6 per 1000 person-years vs 12.4 per 1000 person-years).

Comment: On the basis of this study, we should be factoring in renal function including eGFR when assessing cardiovascular risk. The original work for CV risk assessment came from the Framingham study and renal function is not included in that risk assessment. This study clearly shows that renal impairment significantly increases CV risk and is at least as (if not more) important as diabetes.

Reference: Lancet 2012;380(9844):807-14
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60572-8/abstract

Midlife fitness and the development of chronic conditions in later life

Authors: Willis BL et al

Summary: Patient data from 18,670 healthy middle-aged participants (median age 49 years) in the Cooper Center Longitudinal Study were linked with their Medicare claims filed in older age. Fitness was estimated by Balke treadmill time (analysed as metabolic equivalents) according to age- and sex-specific quintiles. During a median 26-year follow-up, men in the highest quintile of fitness had fewer chronic conditions (15.6 per 100 person-years) compared with men in the lowest quintile (28.2 per 100 person-years); corresponding rates for women were 11.4 vs 20.1 per 100 person-years. Further analysis suggested morbidity compression nearer the end of life, with the more-fit individuals living their final years of life with fewer chronic diseases. Among 2406 individuals who died during follow-up, higher fitness was associated with a lower risk of developing chronic conditions relative to survival (compression HR).

Comment: Even after correction for age, body mass index, blood pressure, lipids, glucose, smoking and alcohol use, physical fitness was important for reducing chronic disease outcomes in later life. If one is physically fit in midlife – then the chance of development of a chronic disease condition is at least deferred compared to those who are not fit! I am off to the gym!

Reference: Arch Intern Med 2012;1-8
http://tinyurl.com/8rx8g2s

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**Clostridium difficile-associated diarrhea and proton pump inhibitor therapy**

**Authors:** Janarthanan S et al

**Summary:** These US researchers examined the association between proton pump inhibitors (PPIs) and Clostridium difficile-associated diarrhoea (CDAD) among hospitalised patients. A systematic search of published literature on studies that investigated the association between PPIs and CDAD from 1990 to 2010 yielded 23 studies (17 case-control and 6 cohort studies) including close to 300,000 patients that met the inclusion criteria. A meta-analysis revealed a 65% (p<0.000) increase in the incidence of CDAD among PPI users. In a subgroup analysis by study design, there was still a significant increase in the incidence of CDAD among PPI users of 2.31 (p<0.001) and 1.48 (p<0.001) for cohort and case-control studies, respectively.

**Comment:** Proton pump inhibitors are currently the most prescribed medication in this country. While both patients and many doctors consider them to be benign therapy, they do have rare but possibly significant adverse effects, including community-acquired pneumonia, interstitial nephritis, increase in fracture in the elderly and erythema multiforme, to name a few. Now, added to these comes an increased risk of developing Clostridium difficile-related diarrhoea. Another thing to think about next time you write a prescription for a PPI.

**Reference:** Am J Gastroenterol 2012;107(7):1001-10

http://www.nature.com/ajg/journal/v107/n7/abs/ajg2012179a.html

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**Patients who take their symptoms less seriously are more likely to have colorectal cancer**

**Authors:** Adelstein BA et al

**Summary:** This Australian group of researchers investigated whether serious disease is more likely to be present in patients who report that they take any symptoms less seriously than other people do, and to assess the reliability of a question which can be used to identify the extent to which patients take any symptom seriously. Data were used from the CRISP (Colonoscopy Research in Symptom Prediction) study, a cross-sectional study of 7736 patients aged >18 years scheduled to undergo colonoscopy for detection of colorectal cancer. Prior to colonoscopy, all patients completed a bowel symptom questionnaire, which contained an item relating to symptom perception: “Compared to other people of your age and sex, how seriously do you think you take any symptoms?” Logistic regression analyses determined that patients who reported taking symptoms less seriously were 3.28 times more likely to have colorectal cancer than patients who took symptoms more seriously than others. The effect was smaller (1.85), but remained statistically significant in models including symptoms and other predictors of colorectal cancer.

**Comment:** An interesting study with probably an obvious outcome. Patients who under-rate their symptoms are less likely to complain to a doctor until the condition becomes much more serious. These patients have a higher threshold for reporting symptoms, which would have rung alarm bells at a much earlier stage in others. GPs, who are responsible for continuing care, should be aware of the almost lack of past history in such patients, and should weigh complaints appropriately and have a low threshold for investigation. On the other hand, the frequent attender is also at risk, as doctors may be more dispersive of what may under other circumstances be alarming symptoms – often presented in dramatic fashion. There is a fine line between appropriate and under- and overinvestigation!

**Reference:** BMC Gastroenterology 2012;12:130

http://www.biomedcentral.com/1471-230X/12/130/abstract
Cauterization of the germinal nail matrix using phenol applications of differing durations: a histologic study

Authors: Becerro de Bengoa Vallejo R et al

Summary: This study sought to determine the optimal time required to perform phenol matricectomy for complete denaturation of the nail matrix to occur at a concentration of 88%. Using 30 cadaveric fresh specimens, the researchers applied 88% phenol solution for 1 to 6 minutes and applied haematoxylin-eosin staining to determine the presence or absence of the basal or germinal layer of the nail bed epithelium (NBE). The NBE was only superficially damaged and the basal layer remained primarily intact after a 1-minute application of 88% phenol solution. After a 2-minute application, the nail plate was avulsed with a thin basal layer remaining. A 3-minute application was associated with full-thickness necrosis of the NBE. After 4-, 5-, and 6-minute applications, full-thickness necrosis of the NBE was noted and the basal layer was completely destroyed in all 30 specimens.

Comment: Phenol ablation for ingrowing toenails is a common procedure undertaken in general practice. This is the first study I have seen attempting to quantify the length of time required to ablate the nail bed. The reviewer has undertaken such ablations for years, and has only used the application of phenol for two minutes. Even though the success rate is very high the time for the application of the phenol has been extended to five minutes before it is washed out with 95% alcohol. Time will tell if this reduces an already low recurrence rate.

http://www.jaad.org/article/S0190-9622(12)00470-7/abstract

Are patients with psoriasis being screened for cardiovascular risk factors? A study of screening practices and awareness among primary care physicians and cardiologists

Authors: Parsi KK et al

Summary: This US paper assessed cardiovascular (CV) risk factor screening practices in patients with psoriasis and assessed primary care physician (PCP) and cardiologist awareness of worse CV outcomes in patients with psoriasis. Of a total of 251 PCPs and cardiologists responded to a questionnaire between October 2010 and April 2011, 108 (43%) screened for hypertension, 27 (11%) screened for dyslipidaemia, 75 (30%) screened for obesity, and 67 (27%) screened for diabetes. Physicians who cared for a greater number of patients with psoriasis were more likely to screen for CV risk factors (hypertension p=0.0041, dyslipidaemia p=0.0143, and diabetes p=0.0065). Compared with PCPs, cardiologists were 3.5 times more likely to screen for obesity, and 67 (27%) screened for diabetes. Physicians who cared for a greater number of patients with psoriasis. Among primary care physicians and cardiologists

Comment: As the authors report, the response to the questionnaire was modest (less than 20%) and because of this one wonders how much credence should be placed on the outcome. Such questionnaires tend to attract polarised responses. In addition, it is not surprising that cardiologists would probably screen most patients that they see for cardiac risk factors, whether they have psoriasis or not. The important point that the paper makes is that doctors should be aware of the increase in cardiovascular risk carried by psoriasis sufferers.

http://www.jaad.org/article/S0190-9622(12)00470-7/abstract

Current asthma control predicts future risk of asthma exacerbation

Authors: Wei HH et al

Summary: This study explored the ability of the baseline asthma control test (ACT) score to predict future risk of asthma exacerbation, using data from a 12-month follow-up prospective cohort study in 290 patients with asthma. Based on ACT score at baseline, patients were classified as having either uncontrolled (n=128), partly-controlled (n=111), or well-controlled (n=51) asthma. In adjusted analyses, lower ACT scores at baseline in the uncontrolled and partly-controlled groups were associated with an increased probability of asthma exacerbations (ORs of 3.65 and 5.75, respectively), unplanned visits (8.03 and 8.21, respectively) and emergency visits (20.00 and 22.60, respectively) over a 12-month follow-up period. In addition, patients in the uncontrolled and partly-controlled groups had a shorter time to the first asthma exacerbation (all p<0.05). Further analysis of the baseline ACT for screening the patients at high risk of asthma exacerbations identified that it had an increased sensitivity of over 90.0% but a lower specificity of about 30.0% and a lower AUC of 0.40.

Comment: The asthma control test (ACT) is a valuable tool in assessing how well the patient’s asthma is controlled. In general, many patients are notoriously bad at assessing both the severity and control (and these are different) of their condition. The ACT can provide the doctor or nurse with valuable information about the appropriateness of current medication. Some patients, when asked if their asthma is well controlled, will reply in the affirmative and then reveal that they need their reliever inhaler up to 6 times a day. The ACT is quick, can be completed in the waiting room and, as shown in this paper, provide real change in disease management.

Reference: Chin Med J (Engl) 2012;125(17):2986-93
http://tinyurl.com/8up2o6m

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A randomized controlled trial of qigong for fibromyalgia

Authors: Lynch M et al

Summary: In this study, 100 patients with fibromyalgia were randomised to either immediate Qigong training or to a delayed practice group receiving training at the end of the control period. Qigong training (level 1 Chaoyi Fanhuan Qigong, CFQ), given over 3 half-days, was followed by weekly review/practice sessions for 8 weeks; participants were also asked to practice at home for 45 to 60 minutes per day over this time. In both the immediate and delayed treatment groups, CFQ demonstrated significant improvements in pain, impact, sleep, physical function and mental function when compared to the wait-list/usual care control group at 8 weeks, with benefits extending beyond this time. Analysis of combined data indicated significant changes for all measures (pain, impact, sleep, physical function and mental function) at all times for 6 months, with only one exception.

Comment: The evidence for alternative therapies in fibromyalgia is growing. One such therapy is Qigong, an ancient Chinese practice which incorporates breathing techniques, meditation and movement. This study from Canada showed that one particular type of Qigong resulted in long-lasting improvements in fibromyalgia symptoms, such as sleep and mental and physical function. My guess is that even non-fibromyalgia sufferers would benefit from this therapy!

http://arthritis-research.com/content/14/4/R178

Randomised clinical trial: Lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea

Authors: Francavilla R et al

Summary: Seventy-four children (6–36 months) hospitalised in Italy for acute diarrhoea with clinical signs of dehydration were randomised to receive either Lactobacillus reuteri DSM 17938 (dose of 4 × 10⁸ colony-forming units/day) or placebo, as an adjunct to rehydration therapy. L. reuteri significantly reduced the duration of watery diarrhoea as compared with placebo (mean 2.1 days vs 3.3 days; p<0.03); on day 2 and 3 of treatment, watery diarrhoea persisted in 82% and 74% of the placebo and 55% and 45% of the L. reuteri recipients, respectively (both p<0.03). Finally, children receiving L. reuteri had a significantly lower relapse rate of diarrhoea (15% vs 42%; p<0.03). Length of hospital study did not differ significantly between the groups. No adverse events were recorded.

Comment: Probiotic L. reuteri has been the subject of several studies, showing positive results in conditions such as infant colic, gingivitis and H. pylori infection. Here we see that the duration of diarrhoea in children was significantly shorter in the L. reuteri group compared to placebo. No doubt many worried parents will be interested in this treatment option.


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