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Making Education Easy

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In this issue:

Abbreviations used in this issue
ACS = acute coronary syndrome
AF = atrial fibrillation
CV = cardiovascular
LV = left ventricular
MI = myocardial infarction
TIMI = Thrombolysis in Myocardial Infarction

Welcome to the first edition of NZ Cardiology Research Review for 2014.

I trust readers enjoyed a good summer break despite the rather variable weather – I'm writing this during a delayed vacation in glorious Nelson sunshine. This issue includes a few late-breaking studies presented at the American Heart Association meeting in November and published online or later in hard copy. While there has been little to grab major headlines in the past two months, a few papers of some interest have merited attention including a couple from New Zealand (a protocol for rapid processing of patients with low risk chest pain and data from ANZACS-QI on post-ACS statin use). We find a focus on the potential relevance of early intra-uterine life to later cardiovascular disease. There are two blows for intervention with a further analysis of COURAGE results not supporting intervention for prognostic reasons on the basis of either coronary anatomy or ischaemic burden and a lack of benefit for intervention for atherosclerotic renal artery stenosis. For those with AF, there's yet another novel anticoagulant showing benefit compared with warfarin and an audit of potential misuse of antiarrhythmic drugs. We do not neglect the surgeons faced with the dilemma of what to do about ischaemic mitral regurgitation and, finally, we examine the health benefits and hazards of laughter.

Kind regards,
Associate Professor Stewart Mann
stewartmann@researchreview.co.nz

Let's start at the very beginning

Authors: Jaddoe V et al.

Summary: This study investigated whether first trimester fetal growth restriction correlates with cardiovascular outcomes in childhood. 1184 children (aged 5.7–6.8 years) with first trimester fetal crown-to-rump length measurements were included. A 1-SD score greater first trimester fetal crown-to-rump length was associated with a lower total fat mass, android fat mass, android/gynoid fat mass ratio, diastolic blood pressure, total cholesterol and LDL cholesterol. Children with clustering of CV risk factors had a smaller first trimester fetal crown-to-rump length than children without clustering. In conclusion, impaired first trimester fetal growth is associated with an adverse CV risk profile in school age children, and may influence CV health in later life.

Comment: I suppose the very beginning is really the moment of cellular fusion determining our genetic nature but examination of nurture is beginning to focus more and more on our 'in utero' environment. Lower birth weight has previously been flagged as a possible risk factor for CV disease but it is unclear if this is correlated primarily with parental CV dysfunction or risk transmitted to offspring in other (genetic) ways. The correlation of first trimester growth with body shape at 6 years suggests early determination of body shape and raises speculation of whether any early intervention (and what sort) is worth exploring. There are possible cellular mechanisms by which trans-generational effects of environmental factors may be passed on and the accompanying leading article also speculates about the relevance of reproductive dysfunction. I expect a lot more research to come in this area although, where humans are the experimental subjects, studies will literally last a lifetime.

Reference: First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. BMJ 2014;348:g14
Abstract

Tools to help meet the ED time targets

Authors: Than M et al.

Summary: This study compared the effectiveness of a rapid versus standard-care diagnostic pathway for the assessment of patients with possible cardiac chest pain. 542 adults who presented to hospital with acute chest pain consistent with ACS for whom the attending physician planned further observation and troponin testing were randomised 1:1 to an accelerated diagnostic pathway (TIMI score, 0; electrocardiography; and 0- and 2-h troponin tests) or a standard-care pathway (troponin test on arrival at hospital, prolonged observation, and a second troponin test 6–12h after onset of pain). 19.3% of patients in the experimental group were successfully discharged within 6 hours compared with 11.0% of controls (odds ratio 1.92; 95% CI 1.18–3.13; p=0.008). It took 20 hours to discharge the same proportion of controls as was achieved in the experimental group in 6 hours. In conclusion, the accelerated diagnostic protocol in the experimental pathway almost doubled the proportion of patients with chest pain who were able to be discharged early.

Comment: Meeting the new politically driven targets for stay in the Emergency Department of patients with chest pain or possible ACS is a challenge for all of us. I sometimes wonder if we are too obsessed with the unattainable ideal of zero risk; indeed I previously reviewed a study where low-risk patients were presented with the actual risks and many chose to return home rather than have prolonged evaluation at the time of presentation. The Christchurch authors of this study have certainly taken a leading role in focusing on rapid triage and it has been fascinating to see how much risk can be determined by a profile alone (e.g. TIMI score). New highly sensitive troponin assays have also helped considerably but the natural history of evolution of coronary lesions will always prevent perfect prediction. Still, the move towards a default rapid triage protocol may help patients, reduce medical uncertainty and please managers and politicians.

Reference: A 2-hour diagnostic protocol for possible cardiac chest pain in the Emergency Department: a randomized clinical trial. JAMA Intern Med 2014;174(1):51-58
Abstract

Cardiology Research Review

Independent commentary by Stewart Mann, Associate Professor of Cardiovascular Medicine at the University of Otago, Wellington.

For full bio CLICK HERE.

More fuel to the intervention benefit debate

Authors: Mancini G et al.

Summary: This analysis of the COURAGE trial compared the prognostic utility of anatomic burden and ischaemic burden in patients with coronary artery disease (CAD). 621 patients with baseline quantitative nuclear single-photon emission computed tomography (SPECT) and quantitative coronary angiography were included. Regression analysis showed that anatomic burden and LV ejection fraction were consistent predictors of death, MI, and non–ST-segment elevation ACS (NSTE-ACS), whereas ischaemic burden and treatment assignment were not. Neither anatomy nor ischaemia interacted with therapeutic strategy to predict outcome. In conclusion, anatomic burden was a consistent predictor of death, MI, and NSTE-ACS in patients with CAD treated with optimal medical therapy, whereas ischaemic burden was not.

Comment: The results of the COURAGE trial remain a culture shock to those who focus on coronary angiograms and find it hard to believe that improving the plumbing does not automatically confer prognostic benefit independently of known effective medical therapy. Many have clung to the concept that the severity of either anatomical stenosis or consequent degree of ischaemia signals increase in risk which can be reversed. An earlier subgroup analysis of patients in COURAGE who had undergone perfusion scanning appeared to offer some hope but selection bias could not be eliminated. This current sub-analysis controls for bias more carefully and does confirm that both anatomical severity of stenosis and ischaemic burden confer an adverse prognosis. However, as with the results of the main study, results did not identify a prognostic benefit from intervention.

Reference: Predicting outcome in the COURAGE trial: coronary anatomy versus ischemia. J Am Coll Cardiol Intv 2014;7(2):195-201
Abstract

COR(R)AL the urge to stent renal arteries

Authors: Cooper C et al., for the CORAL Investigators

Summary: This study evaluated the usefulness of renal stenting for the prevention of major adverse renal and CV events in patients with renal artery stenosis. 947 patients with renal artery atherosclerosis and either systolic hypertension or chronic kidney disease were randomised to receive medical therapy plus renal-artery stenting or medical therapy alone. Patients were followed for the occurrence of adverse CV and renal events. The rate of the primary composite end-point did not differ significantly between groups during follow-up (median 43 months). There were also no significant between-group differences in the rates of the individual components of the primary end-point or in all-cause mortality during follow-up, but systolic blood pressure was consistently lower in the stent group (p=0.03). In conclusion, renal-artery stenting did not prevent clinical events when added to medical therapy in patients with renal artery atherosclerosis and hypertension or chronic kidney disease.

Comment: "The body is a series of tubes all waiting for stenting" is an epithet being subjected to some evidential challenge currently. This study (CORAL) carefully randomised patients with significant hypertension or chronic kidney disease along with renal artery atherosclerosis to medical therapy alone or supplemented by stenting. Despite nearly 1,000 patients being included, no difference in either cardiac or renal outcomes between groups could be observed although there was slight improvement in blood pressure levels.

Reference: Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 2014;370:13-22

Abstract

Now we are four

Authors: Giugliano R et al., for the ENGAGE AF-TIMI 48 Investigators

Summary: This study evaluated the efficacy and safety of once daily edoxaban compared with warfarin in patients with AF. 21,105 patients with moderate-to-high-risk AF were randomised to receive one of two edoxaban dosages, or warfarin for a median 2.8 years. The annualised rate of the primary end-point (stroke or systemic embolism) during treatment was 1.50% with warfarin, 1.18% with high-dose edoxaban (p<0.001 for noninferiority) and 1.61% with low-dose edoxaban (p=0.005 for noninferiority). The annualised rate of major bleeding was 3.43% with warfarin, 2.75% with high-dose edoxaban (p<0.001) and 1.61% with low-dose edoxaban (p<0.001), and the corresponding annualised rates of death from CV causes were 3.17%, 2.74% (p=0.01), and 2.71% (p=0.008). In conclusion, both edoxaban regimens were noninferior to warfarin with respect to the prevention of stroke or systemic embolism, and were associated with lower rates of bleeding and death from CV causes.

Comment: Global literature suggests that New Zealand has now considerable and leading experience with at least the first of the novel anticoagulants for which, I guess, we must thank PHARMAC for its almost unprecedented rapidity of reaching a funding agreement. Personal experience is mostly that the newer agent is popular with patients although a few have side effects. It is presumably good news for patients, clinicians and funders that there are several analogous products that have now proven their worth in comparison with warfarin for thrombo-embolic prophylaxis in AF. This will presumably mean a more competitive market for such products, further enhancing their cost-effectiveness when INR testing is obviated. Edoxaban now joins dabigatran, rivaroxaban and apixaban in this group with proven effectiveness. The individual comparisons with warfarin do not allow any reliable judgements about the superiority of any one of these over the others and it will be a brave company that submits its product to any such direct comparison.

Reference: Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-2104

Abstract

Post-ACS statin adherence in New Zealand

Authors: Grey C et al.

Summary: This NZ study examined patterns of statin use in the 3-year period after an ACS. National hospitalisation, mortality and pharmaceutical dispensing data were linked for all 11,348 patients aged 35–84 years who were discharged from a NZ public hospital with an ACS in 2007. A Medication Possession Ratio (MPR) was calculated for each patient; adequate maintenance was defined as an MPR ≥80%. Within 90 days of hospital discharge, 83% of patients had received a statin. 66% of patients were adequately maintained on a statin during follow-up (69% in the first year, 67% in the second year and 66% in the third year). Patients who were taking statins prior to admission and those who underwent a coronary procedure were 20–50% more likely than others to be adequately maintained on a statin over the 3-year period. Patients aged 35–45 years and those of Maori or Pacific ethnicity were 13–25% less likely to have an MPR ≥80% than those aged 55–64 years and Europeans. In conclusion, these findings identify groups who may benefit from efforts to improve statin use after ACS.

Comment: A fall-off in adherence to statin therapy after initial prescription is widespread and well known as with any preventive therapy. Despite the shock of an acute coronary event and, one would imagine a strong desire to avoid a repeat, this still occurs in the years after an admission. It is not helped of course when prominent politicians claim that changes to their lifestyle have obviated the need to take medication. This study demonstrates the power of comprehensive databases, this one based on the New Zealand NHI system, now popularly known as "big data" and it is gratifying to see the ANZACS-QI database exerting its research potential. One's perspective depends on previous expectation and in some respects I found the results rather better than anticipated although there is still a major deficiency from the ideal goal.

Reference: Maintenance of statin use over 3 years following acute coronary syndromes: a national data linkage study (ANZACS-QI-2). Heart 2014; published online 16 Jan

Abstract

Could beta blockers be safe in asthma

Authors: Short P et al.

Summary: This study assessed the safety and tolerability of acute dosing with the beta blockers esmolol and propranolol in patients with asthma. 12 patients with mild-to-moderate asthma who were taking inhaled corticosteroids underwent a 6- to 8-week dose titration of oral propranolol (tiotropium was given concurrently), and a subgroup received an IV bolus dose of esmolol (0.5 mg/kg). Measurements were recorded before and after the esmolol dose, and after the first dose of 10mg, 20mg, and 80mg propranolol. IV esmolol had no adverse effects on forced expiratory volume in 1s (FEV_1), and no bronchoconstriction was seen after the first dose of 10mg, 20mg or 80mg propranolol in the presence of tiotropium. In conclusion, IV esmolol had no adverse effects on pulmonary function in patients with mild to moderate asthma, and tiotropium prevented propranolol-induced bronchoconstriction.

Comment: I have always been intrigued by this question having (as a student) seen a patient with mild previous asthma go into status and eventual brain death after a single dose of beta blocker, contrasting with later seeing a number of severe asthmatics inadvertently put on beta blockade with no obvious ill effects. Clearly there are idiosyncratic factors at work. A recent theory has also been voiced that, like in heart failure, beta blockers may actually be helpful, for example by upregulating adrenergic receptors. This study appears to verify that many asthmatic patients can indeed tolerate acute and initial doses of beta blockers but caution must remain a watchword.

Reference: Effects of intravenous and oral β-blockade in persistent asthmatics controlled on inhaled corticosteroids. Heart 2014;100(3):219-23

Abstract

For more information, please go to http://www.medsafe.govt.nz

Do you REALISE if your antiarrhythmic prescribing for AF matches the guidelines?

Authors: Chiang C et al., on behalf of the RealiseAF Survey Investigators

Summary: The RealiseAF survey investigated the extent to which prescribing for patients with AF complies with international guidelines (2006 ACC/AHA/ESC AF guidelines). Patients from 26 countries who had ≥1 AF episode in the last 12 months were surveyed. Participating physicians were randomly selected during 2009–10 from lists of office-based or hospital-based cardiologists and internists. Overall, 4947 patients with paroxysmal (n=2606) or persistent AF (n=2341) were included. Class Ic drugs were prescribed in 589 patients, but in 20.0% of these patients the indication was not consistent with published guidelines. 219 patients were prescribed sotalol, but 16.0% of these patients were treated for an indication that deviated from the published guidelines. Amiodarone was prescribed as first-line therapy in 1268 patients, but 49.9% of these patients did not have heart failure or hypertension with significant LV hypertrophy. In conclusion, the use of antiarrhythmic drugs for persistent or paroxysmal AF showed deviation from international guidelines.

Comment: Two recently published audits of antiarrhythmic drug use in AF (the other is at http://www.ahjonline.com/article/S0002-8703%2813%2900538-3/abstract) have reached similar conclusions with deviations of practice from internationally agreed guidelines in a significant proportion of patients. The reference point for the RealiseAF was 2006 guidelines which have of course been modified since with a rise and fall in recommendations for dronedarone. The most common "fault" appears to be an undue fondness for amiodarone where other drugs have not been tried or are not contraindicated by other pathology. There is still debate over the acceptable tolerance limits of higher heart rates to protect against the risk of rate-related cardiomyopathy and how much rate control should be determined by symptoms alone so it is perhaps too easy to find fault where sensible individual choice has been exercised.

Reference: Inappropriate use of antiarrhythmic drugs in paroxysmal and persistent atrial fibrillation in a large contemporary international survey: insights from RealiseAF. Europace 2013;15(12):1733-1740
Abstract

Is ending better than mending for leaky mitral valves with an ischaemic basis?

Authors: Acker M et al.

Summary: This study compared the use of mitral valve repair and mitral valve replacement in patients with severe ischaemic mitral regurgitation. 251 patients were randomised to undergo either a repair or replacement procedure. After 12 months, the primary end-point of mean LV end-systolic volume index (LVESVI) among surviving patients was 54.6 ml/m^2 in the repair group and 60.7 ml/m^2 in the replacement group. The mortality rate was 14.3% in the repair group and 17.6% in the replacement group. There was no significant between-group difference in LVESVI after adjustment for mortality. The rate of moderate or severe recurrence of mitral regurgitation at 12 months was higher in the repair group than in the replacement group (32.6% vs 2.3%, p<0.001) but there were no significant between-group differences in functional status or quality of life. In conclusion, there was no significant difference in LV reverse remodelling or survival at 12 months between patients who underwent mitral-valve repair and those who underwent mitral-valve replacement.

Comment: Ischaemic mitral regurgitation generally occurs following a significant myocardial infarction and may be due to a variety of mechanisms. Both the explanations and therapies have been controversial although one constant is that prognosis is often poor. There is clearly a spectrum from the acute and often disastrous immediate regurgitation following infarction to the more frequent chronic situation resulting from ventricular remodelling. Direct ischaemic involvement of papillary muscles is controversial and variable. Surgical options include revascularisation alone, valve repair and valve replacement. This paper tends to favour repair although clinical outcomes were similar to replacement and its conclusion echoes that of a non-randomised study published in 1987.

Reference: Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23-32
Abstract

ODDSPOT

MIRTH wins best acronym of the month, even if effects are mixed

Authors: Ferner R and Aronson J

Summary: This study reviewed the beneficial and harmful effects of laughter. Medline (1946–2013) and Embase (1974–2013) were searched for reports of the benefits or harms associated with laughter in humans. The reported benefits of laughter included reduced anger, anxiety, depression, stress and tension; increased pain threshold; reduced risk of MI (hearty laughter presumably); improved lung function; increased energy expenditure; and reduced blood glucose levels. The reported dangers of laughter included syncope, cardiac and oesophageal rupture, protrusion of abdominal hernias (from side splitting laughter or laughing fit to burst), asthma attacks, cataplexy, headaches, jaw dislocation, and stress incontinence (laughing like a drain). Infectious laughter can disseminate real infection, which may be prevented by laughing up your sleeve.

Comment: At least one previous study has shown that laughter can reduce the risk of myocardial infarction ("hearty laughter"?) and there have been advocates for taking a light-hearted approach to the administration of cardiovascular and other medical treatment. On the other hand I remember an otherwise healthy medical student colleague cracking a couple of ribs while laughing. As this review testifies, there are both benefits and hazards. So it's up to you whether to read the Christmas British Medical Journal or book tickets for Billy Connolly's upcoming tour if either of those tickle your funny bone. You could start by reading this wittily written article.

Reference: Laughter and MIRTH (Methodical Investigation of Risibility, Therapeutic and Harmful): narrative synthesis. BMJ 2013;347:f7274
Abstract

References: 1. Wallentin L, et al. N Engl J Med 2009;361:1045-57. **2.** Hamer A, et al. NZMJ 2012;125(1357):1-26. **3.** Hamm CW, et al. European Heart J 2011;doi:10.1093/eurheartj/ehr236. **4.** Steg G, et al. European Heart J 2012;doi:10.1093/eurheartj/ehs215. **5.** Wright RS, et al. Circulation 2011;123:2022-2060.