In this issue:

- Prediabetes and cardiovascular risk
- Evolocumab has additional benefits in statin-treated patients
- Calcium intake and cardiovascular risk
- Caffeine does not induce arrhythmias
- Tranexamic acid in patients undergoing cardiac surgery
- Cardiovascular safety of celecoxib
- Intensity of statin dose affects mortality risk
- Renal denervation in patients with ISH
- Long-term follow-up of carriers of HCM mutations
- Symptom-to-balloon time is important

Welcome to the latest issue of Cardiology Research Review.

This month we report the risks associated with prediabetes, the benefits of the PCSK9 inhibitor evolocumab in statin-treated patients, and evidence that high calcium intake does not cause cardiovascular disease in healthy individuals. We also report that patients with heart disease do not need to reduce their caffeine intake, and present reassuring evidence of the cardiovascular safety of the COX-2 inhibitor celecoxib. The issue finishes with a study from Canberra that reinforces the importance of educating patients to present to hospital quickly if they develop chest pain.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,
Associate Professor John Amerena
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Association between prediabetes and risk of cardiovascular disease and all cause mortality

Authors: Huang Y et al.

Summary: This systematic review and meta-analysis evaluated the associations between different definitions of prediabetes and the risk of cardiovascular disease and all-cause mortality. A search of electronic databases identified 53 prospective cohort studies (n=1,611,339) that were suitable for inclusion. Prediabetes was defined as impaired fasting glucose according to the criteria of the American Diabetes Association (IFG-ADA; fasting glucose 5.6–6.9 mmol/L), the WHO expert group (IFG-WHO; fasting glucose 6.1–6.9 mmol/L), impaired glucose tolerance (IGT; 2-h plasma glucose concentration 7.8–11.0 mmol/L during an oral glucose tolerance test), or raised haemoglobin A1c (HbA1c) according to ADA criteria (39–47 mmol/mol) or the National Institute for Health and Care Excellence (NICE) guideline (42–47 mmol/mol). During a median follow-up of 9.5 years, prediabetes was associated with an increased risk of composite cardiovascular disease (relative risk 1.13, 1.18, and 1.20, respectively), stroke (1.06, 1.17, and 1.20, respectively), and all-cause mortality (1.13, 1.13 and 1.32, respectively) compared with normoglycaemia. Increases in HbA1c to 39–47 mmol/mol or 42–47 mmol/mol were both associated with an increased risk of composite cardiovascular disease and coronary heart disease, but not stroke or all-cause mortality.

Comment: Many patients with prediabetes, as defined by IFG or IGT, develop diabetes as time goes on, and thus become at increased risk for cardiovascular disease, which is the leading cause of morbidity/mortality in this population. This study shows that even prediabetes has an increase in cardiovascular risk, but we do not have any evidence yet that intervention, in particular lowering blood pressure and lipids, has the same benefit as in established diabetes. Despite this, it is still reasonable to recommend lifestyle interventions in prediabetic patients to reduce the risk of evolving to diabetes.

Reference: BMJ 2016;355:i5953

Abstract

Cardiology Research Review

Independent commentary by Associate Professor John Amerena, FRACP, FACC, FCSANZ, Dept. of Clinical and Biomedical Science, University of Melbourne (Geelong).

Unexplained breathlessness, fatigue, syncope and/or signs of right ventricular dysfunction

COULD IT BE PULMONARY ARTERIAL HYPERTENSION (PAH)?


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Effect of evolocumab on progression of coronary disease in statin-treated patients

**Authors:** Nicholls S et al.

**Summary:** The GLAGOV trial determined the effects of the PCSK9 inhibitor evolocumab on progression of coronary atherosclerosis in statin-treated patients. 968 patients with angiographic coronary disease were randomised 1:1 to receive subcutaneous injections of evolocumab 420mg or placebo monthly for 76 weeks, in addition to statins. The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasound (IVUS) imaging. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL cholesterol levels (p<0.001). Evolocumab also decreased PAV and total atheroma volume compared with placebo (both p<0.001), and induced plaque regression in a greater percentage of patients than placebo.

**Comment:** The PCSK9 inhibitors lower LDL cholesterol markedly when given with background statin therapy. LDL levels <1 mmol/L are consistently achieved, with no signal of harm even at extremely low levels. The GLAGOV study with evolocumab showed that plaque atheroma volume decreases with these very low LDL levels, and we eagerly await the results of the FOURIER trial that will be presented at the ACC in March. A recent press release reported that the outcome of this trial was positive with a reduction in cardiovascular events in the patients who received evolocumab, but the magnitude of the benefit is unknown at present, and whether there was a decrease in all-cause mortality will be revealed when the study is presented.

Reference: JAMA 2016;316(22):2373-84

Calcium intake and cardiovascular disease risk

**Authors:** Chung M et al.

**Summary:** This systematic review and meta-analysis examined the effects of calcium intake on cardiovascular disease in healthy adults. A search of electronic databases identified 4 randomised controlled trials and 27 observational studies that reported dietary or supplemental calcium intake and cardiovascular outcomes. Meta-analysis of the data found no differences in risk of cardiovascular disease events or mortality between groups receiving supplements of calcium (or calcium plus vitamin D) and those receiving placebo. There were no consistent dose-response relationships between total, dietary, or supplemental calcium intake levels and cardiovascular mortality, total stroke or stroke mortality.

**Comment:** Calcium supplementation is commonly used to reduce the risk of osteoporosis in older females, but has been associated with increased cardiovascular risk in some studies. This meta-analysis shows that high dietary or supplemental calcium intake is not associated with cardiovascular disease in healthy individuals, but does not address whether there is increased risk in patients with established cardiovascular disease.


Short-term effects of high-dose caffeine on cardiac arrhythmias in patients with heart failure

**Authors:** Zuchinali P et al.

**Summary:** This double-blind crossover study evaluated the effects of high-dose caffeine on cardiac arrhythmias in patients with heart failure. 51 patients with predominantly moderate to severe left ventricular systolic dysfunction were randomised to receive caffeine (total dose 500mg) or placebo during a 5-hour protocol. After a 1-week washout period, the protocol was repeated. No significant differences between the caffeine and placebo groups were observed in the number of ventricular and supraventricular premature beats, couplets, bigeminal cycles, or nonsustained tachycardia during continuous electrocardiographic monitoring. Exercise test-derived variables (ventricular and supraventricular premature beats, exercise duration, estimated peak oxygen consumption, and heart rate) were not influenced by caffeine ingestion.

**Comment:** Many patients say they are more aware of their heart beating faster and harder after drinking strong coffee, but there are few data about the potential arrhythmic effects of caffeine. This study suggests that caffeine does not induce arrhythmia, even in at risk patients with heart failure, so it appears that caffeine reduction is not necessary in patients with heart disease, unless there is a clear relationship between palpitations and coffee ingestion, such as in some patients with supraventricular tachycardia or atrial fibrillation.


IN PAH, VASCULAR DAMAGE AND FUNCTIONAL DETERIORATION OCCUR EARLY¹

Prompt diagnosis and treatment offers the best chance to delay progression and it may improve outcomes²⁻⁵


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Tranexamic acid in patients undergoing coronary-artery surgery

Authors: Myles P et al., for the ATACAS Investigators of the ANZCA Clinical Trials Network

Summary: This study examined the use of tranexamic acid in patients undergoing cardiac surgery. 4631 patients who were scheduled to undergo coronary artery surgery and were at risk for perioperative complications were randomised in a 3×2 factorial design to receive aspirin or placebo and tranexamic acid or placebo. A primary outcome event (composite of death and thrombotic complications within 30 days after surgery) occurred in 16.7% of patients in the tranexamic acid group and 18.1% in the placebo group (relative risk, 0.92; p=0.22). The number of units of blood products that were transfused during hospitalisation was lower in the tranexamic acid group than in the placebo group (4331 vs 7994; p<0.001). The tranexamic acid group had a lower rate of major haemorrhage or cardiac tamponade leading to reoperation (1.4% vs 2.8%; p=0.001), but a higher rate of seizures (0.7% vs 0.1%; p=0.002).

Comment: Tranexamic acid potentially reduces bleeding after surgery but its use has been sporadic, as there have been mixed reports as to its overall benefit. This large Australian study shows that routine use after coronary artery graft surgery does result in a clinically meaningful reduction in bleeding but at the expense of increased seizures. This being the case, perhaps its use should be reserved for patients who have risk factors for postoperative bleeding.


Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis

Authors: Nissen S et al., for the PRECISION Trial Investigators

Summary: The multicentre PRECISION trial used a 3-arm parallel group design to compare the cardiovascular effects of celecoxib, ibuprofen and naproxen in patients with osteoarthritis or rheumatoid arthritis with established cardiovascular disease or at high risk for cardiovascular disease. 24,081 patients were randomised in a double-blind design to receive celecoxib 100–200mg twice daily, ibuprofen 600–800mg three times daily or naproxen 375–500mg twice daily. Aspirin 75–100mg daily was allowed according to local guidelines, and patients were randomised in a double-blind design to receive celecoxib, ibuprofen and naproxen in patients with osteoarthritis or rheumatoid arthritis with established cardiovascular disease or at high risk for cardiovascular disease.

Comment: After the Vioxx® scandal, there has been concern that other COX-2 inhibitors may have excess cardiovascular risk compared with other nonsteroidal anti-inflammatories (NSAIDs). This study is reassuring with no increase in cardiovascular risk and less bleeding with a conventional dose of celecoxib compared with relatively high dose ibuprofen and a reasonable dose of naproxen. It is not definitive evidence of safety however, as more than two-thirds of patients stopped study medication and more than a quarter were lost to follow up. This is the only evidence we have however, so if it is necessary to use an NSAID in patients with established cardiovascular disease, celecoxib would be acceptable, particularly if bleeding risk is increased.


Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease

Authors: Rodríguez F et al.

Summary: This study examined the association between all-cause mortality and intensity of statin therapy in patients with atherosclerotic cardiovascular disease (ASCVD). A retrospective cohort analysis was conducted of patients aged 21–84 years with ASCVD treated in the Veterans Affairs health care system from April 2013 to April 2014. Intensity of statin therapy was defined by the 2013 American College of Cardiology/American Heart Association guidelines, and use was defined as a filled prescription in the previous 6 months. 509,766 eligible adults were included. 29.6% of them were taking high-intensity statin therapy, 45.6% were taking moderate-intensity statin therapy, 6.7% were taking low-intensity statin therapy, and 18.2% were not taking any statins. During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% for those taking high-intensity statin therapy, 4.8% for those taking moderate-intensity statin therapy, and 6.6% for those not taking a statin (p<0.001).

Comment: This study clearly demonstrates that there is a relationship between intensity of statin dose and cardiovascular outcomes, presumably mediated by a greater reduction in LDL cholesterol. These data bode well for the trials of cardiovascular outcomes with the PCSK9 inhibitors, and reinforce the importance of using the maximal tolerated dose of a statin to attempt to get patients with cardiovascular disease to low LDL levels.

Reference: JAMA Cardiol 2017;2(1):47-54

Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension

Authors: Mahfoud F et al.

Summary: This study pooled data from the SYMPLICITY HTN-3 and the global SYMPLICITY registry to determine the blood pressure-lowering effects of catheter-based renal denervation in patients with ISH. Data for 1103 patients were included (429 patients had ISH and 674 had combined systolic-diastolic hypertension [CH]). Patients with ISH were significantly older than those with CH, had a higher incidence of type 2 diabetes mellitus, and had a lower mean estimated glomerular filtration rate. Six months after renal denervation, systolic blood pressure had decreased by 18.7mmHg in CH patients and 10.9mmHg in ISH patients (p<0.001). The presence of ISH at baseline was associated with less pronounced blood pressure changes after the procedure.

Comment: Although renal denervation has largely been abandoned after the randomised double-blind SYMPLICITY HTN-3 study failed to show benefit of the procedure over placebo, the global registry continues to accumulate patients and follow them up. These data from SYMPLICITY HTN-3 and the registry suggest that there is a meaningful reduction in blood pressure in patients with systolic/diastolic hypertension more so than in patients with ISH, but until there are more consistent results and a method of evaluating extent of denervation, health care providers are unlikely to fund it.

Reference: Eur Heart J 2017;38(2):93-100
A long term follow-up study of carriers of hypertrophic cardiomyopathy mutations

Authors: McTaggart D et al.

Summary: This Australian study evaluated long-term outcomes in carriers of HCM mutations. 14 genotype positive/left ventricular hypertrophy (LVH) negative patients with HCM were identified, 7 of which were children when first diagnosed as gene carriers. Ten patients were followed up for a total of 18 years, two for a total of 17 years, one for 11 years and one for 8 years. Eleven participants carried a mutation for the MYBPC3 gene and three carried a mutation for the MYH7 gene. One patient developed phenotypic features of HCM on echocardiography and magnetic resonance imaging (MRI), one had an increase in wall thickness diagnostic for HCM only on MRI, and another was found to be borderline for HCM on MRI.

Comment: As HCM is genetically mediated, it is common practice to screen family members of patients after the index case has been diagnosed. Genetic testing is often used in addition to imaging, and it has been increasingly recognised that there are gene positive-phenotype negative patients. This study shows that some of these patients may develop characteristic left ventricular changes over time, so ongoing surveillance would seem sensible in these gene positive patients who have no characteristics of the disease when initially assessed.


Abstract

Symptom-to-balloon time is a strong predictor of adverse events following primary percutaneous coronary intervention

Authors: Chandrasekhar J et al.

Summary: This Australian Capital Territory PCI registry study analysed the impact of symptom-to-balloon (STB) time on major adverse cardiovascular events (MACE) after primary percutaneous coronary intervention (PCI). Data for 1002 consecutive patients who underwent primary PCI in 2008–2014 were analysed. STB time was available for 893 patients; 65.8% had STB ≤240 min and 34.2% had STB >240 min. The incidence of 1-year MACE increased significantly in a stepwise manner with increasing STB time (p for trend=0.003). STB time was an independent predictor of 1-year MACE.

Comment: We traditionally consider door-to-balloon time as a parameter to evaluate performance of PCI centres. This study from Canberra shows what one would intuitively expect, i.e. the longer between onset of symptoms and reperfusion, the worse the outcome. It reinforces the ongoing education of patients to present quickly if they develop chest pain, and for non PCI capable hospitals to transfer early. It also supports the growing trend in large cities for ambulances to take STEMI patients only to PCI capable centres that are staffed 24 hours a day.


Abstract