Cardiology Research Review™

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Abbreviations used in this issue:

AF = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **BMI** = body mass index; **COVID-19** = coronavirus disease 2019; **HFpEF** = heart failure with preserved ejection fraction; **HFrEF** = heart failure with reduced ejection fraction; **HMG-CoA** = 3-hydroxy-3-methylglutaryl-coenzyme A; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **LVEF** = left ventricular ejection fraction; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **SGLT2** = sodium glucose co-transporter 2; **TAVI** = transcatheter aortic valve implantation.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, the EARLY-AF trial confirms the superiority of ablation over pharmacotherapy for rhythm control in patients with paroxysmal AF, a meta-analysis evaluates the occurrence of myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults, and the CLEAR Outcomes trial reports promising findings for the ATP citrate lyase inhibitor bempedoic acid in statin-intolerant patients.

We hope you find these and the other selected studies interesting, and welcome your feedback.

Kind Regards,

Associate Professor John Amerena
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Progression of atrial fibrillation after cryoablation or drug therapy

Authors: Andrade JG et al., for the EARLY-AF Investigators

Summary: This study investigated long-term outcomes after cryoablation or drug therapy for paroxysmal AF. 303 patients with untreated paroxysmal AF were randomised to undergo initial rhythm-control therapy with cryoablation or to receive antiarrhythmic drug therapy and were followed up for three years. During follow up, three patients (1.9%) in the cryoablation group and 11 (7.4%) in the drug therapy group had an episode of persistent AF (HR 0.25, 95% CI 0.09–0.70), and 87 (56.5%) and 115 (77.2%) of patients in the respective groups had recurrent atrial tachyarrhythmia (HR 0.51, 95% CI 0.38–0.67). Eight patients (5.2%) in the ablation group and 25 (16.8%) in the drug therapy group were hospitalised during the study (relative risk 0.31, 95% CI 0.14–0.66), and serious adverse events were reported in 4.5% and 10.1% of patients in the respective groups.

Comment: This study demonstrates the superiority of an ablative approach for rhythm control compared with pharmacotherapy in patients with paroxysmal AF. It is an important addition to the literature as there was less AF recurrence, AF burden, hospitalisations and adverse events during three years of follow up in patients who had ablation as their initial rhythm control strategy. This being the case, early ablation should be considered – especially in younger patients with paroxysmal AF. However, the availability of this procedure is not as great as it should be, especially in regional and remote locations.

Reference: N Engl J Med 2023;388:105-16
Abstract

New diet study could change clinical care for pregnant women globally

A new study by the Heart Research Institute is hoping to prove a Mediterranean diet for pregnant women can positively impact their babies' heart development as they investigate macro and micronutrients after ingestion. Dr Xiao Suo Wang explained 'these results will have huge implications and will change clinical care for pregnant women all over the world'.

HRI HEART RESEARCH INSTITUTE

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Myopericarditis after COVID-19 mRNA vaccination among adolescents and young adults

Authors: Yasuhara J et al.

Summary: This systematic review and meta-analysis investigated the clinical features and early outcomes associated with myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults. A search of PubMed and EMBASE identified 23 observational studies and case series that described COVID-19 vaccine-associated myopericarditis in a total of 854 individuals aged 12–20 years (90.3% male). Meta-analysis of the data showed that the incidence of myopericarditis was higher after the second dose than after the first dose, with 74.4% of events occurring after the second dose. Most patients (84.4%) had preserved left ventricular function. Of the 15.6% of patients with left ventricular systolic dysfunction (LVEF <55%), most cases were mild. Cardiac magnetic resonance imaging (MRI) revealed late gadolinium enhancement (LGE) in 87.2% of patients. 92.6% of patients were hospitalised and 23.2% needed intensive care unit admission, but only 1.3% of patients required inotropes and none of them died.

Comment: These data confirm what we see in clinical practice, namely that myocarditis post mRNA COVID vaccination is most common in young men within days of receiving it. Most cases were mild despite many being hospitalised. Of concern however was that nearly 90% of those studied had LGE on cardiac MRI indicating fibrosis which could increase the chances of arrhythmia and heart failure in the future. This being the case it is imperative these patients be followed up over time as they would appear to be at increased risk for cardiac disease as they age. It would be ideal to repeat the cardiac MRI several years after the initial scan to see if there is progression, but this is probably impractical in Australia as cardiac MRI is still not funded here, except to exclude arrhythmogenic right ventricular dysplasia.

Reference: JAMA Pediatr 2023;177(1):42-52
Abstract

Aortic stenosis progression: A systematic review and meta-analysis

Authors: Willner N et al.

Summary: This systematic review and meta-analysis determined the rate of progression of aortic stenosis (AS). A search of Medline, Embase, and the Cochrane Central Register of Controlled Trials identified 24 prospective studies (n=5450) that evaluated the progression of AS using echocardiography (mean gradient [MG], peak velocity [PV], peak gradient [PG], and aortic valve area [AVA]) or computed tomography (calcium score [AVC]). Meta-analysis of pooled data showed that the rate of annualised progression was +4.10mm Hg for MG, −0.08cm^2 for AVA, +0.19 m/s for PV, +7.86mm Hg for PG, and +158.5 AU for AVC. Increasing baseline severity of AS was predictive of higher rates of progression for MG, PV, and AVC, but not for AVA or PG. Only four studies reported AS progression stratified by sex; in these studies no difference between sexes was observed for PV or AVC, but the level of confidence was low.

Comment: The life expectancy of our Western society is increasing, so the diseases associated with age are also increasing. Hypertension, type 2 diabetes and AF are on the rise as is the awareness and detection of AS. Timing of intervention in AS is controversial, as most wait for the development of symptoms before aortic valve replacement (surgical or TAVI), but there is some data to suggest early intervention in severe AS (even in the absence of symptoms) improves outcomes. This study suggests that the average rate of progression of AS is about 4mm per year, which may help predict when it will become severe, and help plan management strategies once AS has been detected.

Reference: JACC Cardiovasc Imaging 2023;16(3):314-28
Abstract

Metformin can be safely used in patients exposed to contrast media

Authors: Qiao H et al.

Summary: This systematic review and meta-analysis investigated the association between metformin use and contrast-induced acute kidney injury (AKI) in patients exposed to contrast media. A search of Medline, PubMed, Embase, and Web of Science databases identified seven studies (n=2325) that were suitable for inclusion. Meta-analysis of the data revealed no significant increase in the risk of contrast-induced AKI in patients who were taking metformin regularly.

Comment: Metformin has traditionally been withheld around the time of non-urgent coronary angiography or PCI on the assumption that there would be an increased risk of AKI and lactic acidosis if it is continued. This meta-analysis suggests that this is not the case, which is what we see clinically in patients with type 2 diabetes on metformin who need an urgent procedure. Adequate volume status and minimising contrast volume are the best means of avoiding renal dysfunction in patients undergoing invasive angiography. We used to think that N-acetylcysteine and bicarbonate infusions reduced contrast-induced nephropathy but this has been refuted, and it appears that metformin discontinuation has suffered the same fate.

Reference: Cardiology 2022;147(5-6):469-78
Abstract

Bempedoic acid and cardiovascular outcomes in statin-intolerant patients

Authors: Nissen SE et al., for the CLEAR Outcomes Investigators

Summary: The CLEAR Outcomes trial investigated the effects of bempedoic acid (an ATP citrate lyase inhibitor) on cardiovascular outcomes in statin-intolerant patients. 13,970 patients who were unable or unwilling to take statins due to unacceptable adverse effects ("statin-intolerant" patients) and had or were at high risk for cardiovascular disease were randomised to receive oral bempedoic acid 180 mg/day or placebo. The primary end-point was major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation. During a median follow-up of 40.6 months, the primary end-point occurred significantly less often with bempedoic acid than with placebo (11.7% vs 13.3%; HR 0.87, 95% CI 0.79–0.96; p=0.004). Bempedoic acid was associated with a higher incidence of gout (3.1% vs 2.1%) and cholelithiasis (2.2% vs 1.2%) than placebo.

Comment: Many patients with ASCVD, or at high risk of developing it, are unable to take statins for real or perceived intolerance, generally related to myalgia or arthralgia. Until now, ezetimibe monotherapy and non-drug therapy such as sterol-containing margarine, psyllium and lipoplex (a red yeast rice extract) were all we had to offer, but none of these achieve significant reductions in LDL, and certainly nowhere near target levels in most patients. PCSK9 inhibitors can be used in some patients but their use is markedly restricted in Australia. This new agent bempedoic acid blocks ATP citrate lyase and reduces cholesterol production at a higher level than statins (which block HMG-CoA reductase). ATP citrate lyase is not present in skeletal muscle, whereas HMG-CoA reductase is, making it potentially more tolerable in statin "intolerant" patients. This study shows that this is the case, and that it produces meaningful LDL reductions and improves outcome compared with placebo, but with a slight increase in gall stones. This agent is not available in Australia yet, but we are hopeful it will be soon, to help in the management of the difficult group of high-risk patients who can't take statins.

Reference: N Engl J Med 2023; published online Mar 4
Abstract

Association of dapagliflozin use with clinical outcomes and the introduction of uric acid-lowering therapy and colchicine in patients with heart failure with and without gout

Authors: Butt JH et al.

Summary: This pooled analysis of two phase 3 clinical trials (DAPA-HF and DELIVER) investigated the effects of dapagliflozin in patients with heart failure, with and without gout. Both trials compared the effects of dapagliflozin 10mg once daily and placebo in patients with heart failure (LVEF ≤40% in DAPA-HF and >40% in DELIVER). Among 11,005 patients for whom gout history was available, 10.1% had a history of gout. The prevalence of gout was 10.3% in those with LVEF ≤40% and 10.1% in those with LVEF >40%. Patients with gout were more often male (80.3%), and had a higher BMI, more comorbidities, lower estimated glomerular filtration rate, and were more often treated with a loop diuretic. Compared with placebo, dapagliflozin reduced the risk of the primary end-point (a composite of worsening heart failure or cardiovascular death) to the same extent in patients with gout (HR 0.84, 95% CI 0.66–1.06) and without a history of gout (HR 0.79, 95% CI 0.71–0.87). Dapagliflozin recipients were less likely to require initiation of uric acid-lowering therapy (HR 0.43, 95% CI 0.34–0.53) or colchicine (HR 0.54, 95% CI 0.37–0.80) compared with placebo recipients.

Comment: We know that elevated uric acid is a risk factor for worse outcomes in HFrEF and that several heart failure treatments lower uric acid, although this has not been demonstrated to independently improve outcomes. SGLT2 inhibitors lower uric acid and this pooled analysis of DAPA-HF (HFrEF) and DELIVER (HFpEF) looked at the relationship between symptomatic gout, treatment with dapagliflozin, and need for uric acid-lowering therapy. As expected, gout was common in patients with heart failure, and was associated with worse outcomes. However, the beneficial effects of dapagliflozin were not modified by the presence of gout, despite presumably lowering uric acid in some, as there was less need for initiation of uric acid-lowering therapy. This may indicate that elevated uric acid is an epiphenomenon in heart failure rather than a cause of worse outcomes.

Reference: JAMA Cardiol 2023; published online Feb 22
Abstract

Sodium-glucose cotransporter-2 inhibitors and cancer outcomes

Authors: Spiazzi BF et al.

Summary: This systematic review and meta-analysis examined the association between SGLT2 inhibitors and cancer risk. A search of PubMed, Embase and CENTRAL databases identified 76 randomised controlled trials of SGLT2 inhibitors with a minimum 48-week follow-up that were suitable for inclusion (n=116,375). Meta-analysis of the data revealed that SGLT2 inhibitors did not increase or decrease the overall risk of cancer or cancer mortality (including breast and bladder cancer).

Comment: The SGLT2 inhibitors are being increasingly used for management of type 2 diabetes and heart failure independent of ejection fraction. Postmarketing surveillance has not shown any signal for increased malignancy with these therapies and it is reassuring to see that this large analysis of trials with these agents did not detect any increase in risk of breast and/or bladder cancer. This should give us confidence to continue to use them to improve the outcome of patients with type 2 diabetes and patients with heart failure (whether they have type 2 diabetes or not).

Reference: Diabetes Res Clin Pract 2023; published online Mar 12
Abstract

Overweight or obesity increases the risk of cardiovascular disease among older Australian adults, even in the absence of cardiometabolic risk factors: A Bayesian survival analysis from the Hunter Community Study

Authors: Opio J et al.

Summary: This analysis of data from the Hunter Community study estimated the risk of cardiovascular disease (CVD) in older adults with overweight or obesity without metabolic risk factors. 2313 community-dwelling older men and women without known CVD and with BMI ≥18.5 kg/m^2 were stratified by BMI and metabolic risk to create six BMI-metabolic health categories. During a median follow-up of 9.7 years, 283 incident CVD events, 58 CVD-related deaths and 277 deaths from any cause occurred. In an adjusted Bayesian survival model, the risk of CVD was increased in metabolically healthy overweight participants (HR 1.52, 95% CI 0.96–2.36) and metabolically healthy obese participants (HR 1.86, 95% CI 1.14–3.08) compared with metabolically healthy normal weight participants.

Comment: It has often been debated as to whether obesity increases cardiovascular risk independent of other risk factors common in overweight and obese people, such as obstructive sleep apnoea, hypertension, type 2 diabetes and hyperlipidaemia. This study in Newcastle with nearly 10 years of follow up showed that there was a greater risk of cardiovascular events and death in overweight/obese subjects who had no associated risk factors for CVD, indicating that being overweight is a risk factor in its own right and should be addressed as well as the more conventional risk factors. There is no evidence to date however that losing weight will improve outcomes, but studies are underway to examine whether glucagon-like peptide-1 agonists (that often produce significant weight loss) are associated with a reduction in cardiovascular events in obese/overweight patients with established ASCVD, which should be instructive.

Reference: Int J Obes (Lond) 2023;47(2):117-25
Abstract

Independent commentary by Associate Professor John Amerena

Associate Professor John Amerena trained in Melbourne before spending four years in the United States at the University of Michigan. Over that period of time he worked in the fields of hypertension and hyperlipidemia, before returning to Australia where he is now a Cardiologist at Barwon Health. He currently has a joint appointment in the Department of Clinical and Biomedical Sciences at the University of Melbourne and the Department of Epidemiology and Preventive Medicine at Monash University. He is the director of the Geelong Cardiology Research Unit, which is currently involved in many phase II-III clinical trials. While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also the Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.

Efficacy and safety of the oral PCSK9 inhibitor MK-0616: A phase 2b randomized controlled trial

Authors: Ballantyne CM et al.

Summary: This multicentre study evaluated the efficacy and safety of the oral PCSK9 inhibitor MK-0616 in patients with hypercholesterolaemia. 381 patients (49% female, median age 62 years) with a wide range of ASCVD risk were randomised 1:1:1:1:1 to receive MK-0616 (6, 12, 18, or 30mg once daily) or matching placebo for 8 weeks. All doses of MK-0616 caused significant (p<0.001) reductions in LDL cholesterol from baseline to week 8 compared with placebo: –41.2% (6mg), –55.7% (12mg), –59.1% (18mg), and –60.9% (30mg). Adverse events were reported in similar proportions of MK-0616 (39.5–43.4%) and placebo (44.0%) recipients during the study.

Comment: In recent years, new lipid-lowering therapies have been introduced after years of stagnation. The injectable PCSK9 inhibitors (evolocumab and alirocumab) have been shown to be safe, very effective and well tolerated as well as improving outcomes in patients with ASCVD and LDL >1.8 mmol/L. Others are on the way, with results of the ORION studies showing that inclisiran (an siRNA inhibitor) is also safe and effective in lowering LDL with outcome studies in progress. The CLEAR study (pg 2 of this issue) showed that the ATP citrate lyase inhibitor bempedoic acid is effective in lowering LDL and improves outcome compared to placebo in statin-intolerant patients, and studies with lipoprotein(a)-lowering agents are also underway. This study shows promising results for an oral PCSK9 inhibitor, so watch out for phase 3 efficacy and outcome trials with it.

Reference: J Am Coll Cardiol 2023; published online Mar 6
Abstract

Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: A collaborative analysis of three randomised trials

Authors: Ridker PM et al., for the PROMINENT, REDUCE-IT, and STRENGTH Investigators

Summary: This analysis of data from the PROMINENT, REDUCE-IT, and STRENGTH trials evaluated the relative importance of high-sensitivity C-reactive protein (hsCRP) and LDL cholesterol as determinants of risk for major adverse cardiovascular events (MACE), cardiovascular death, and all-cause death in patients taking statins. Overall, 31,245 patients with (or at high risk for) ASCVD who were taking a statin were analysed. Residual inflammatory risk was found to be significantly associated with incident MACE (highest vs lowest hsCRP quartile, adjusted HR 1.31, 95% CI 1.20–1.43; p<0.0001), cardiovascular mortality (2.68, 95% CI 2.22–3.23; p<0.0001), and all-cause mortality (2.42, 95% CI 2.12–2.77; p<0.0001). However, the association of residual cholesterol risk was neutral for MACE (highest vs lowest LDL cholesterol quartile, adjusted HR 1.07, 95% CI 0.98–1.17; p=0.11), and of low magnitude for cardiovascular death (1.27, 95% CI 1.07–1.50; p=0.0086) and all-cause death (1.16, 95% CI 1.03–1.32; p=0.025).

Comment: Many patients with ASCVD have recurrent events despite good control of conventional risk factors, including LDL cholesterol. It has been postulated that this residual risk may be mediated by inflammation as evidenced by an elevated CRP, or by elevated lipoprotein(a). This analysis of three large lipid-lowering trials with fish oils, showed that in >30,000 patients (all on statins), elevated CRP was a stronger predictor of future events than LDL. This supports the hypothesis that, if CRP is elevated, specific therapies to reduce inflammation should be helpful, as well as aggressive LDL reduction. This has been shown with canakinumab (an interleukin [IL]1 inhibitor) and colchicine, and is currently being tested with IL6 inhibition (ziltivekimab). Unfortunately hsCRP is still not funded or widely available in Australia so using it for risk stratification is underutilised here.

Reference: Lancet 2023; published online Mar 3
Abstract