Cardiology Research Review™

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Abbreviations used in this issue:

AF = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **ESC** = European Society of Cardiology; **HF** = heart failure; **HFpEF** = HF with preserved ejection fraction; **HFrEF** = HF with reduced ejection fraction; **HR** = hazard ratio; **MI** = myocardial infarction; **NOAC** = non-vitamin K oral anticoagulant; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **SGLT2** = sodium-glucose cotransporter-2; **siRNA** = small interfering ribonucleic acid; **STEMI** = ST-elevation MI; **SVT** = supraventricular tachycardia.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, the RAPID investigators report that self-administered etripamil nasal spray may be useful for acute conversion of paroxysmal SVT to sinus rhythm, a meta-analysis finds that monthly vitamin D supplements do not have cardioprotective effects, and an Australian study suggests that there is room for improvement in lipid management in high-risk patients. Also in this issue, we discuss some of the important studies presented at the recent ESC Congress.

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

Kind regards,

Associate Professor John Amerena

john.amerena@researchreview.com.au

Self-administered intranasal etripamil using a symptom-prompted, repeat-dose regimen for atrioventricular-nodal-dependent supraventricular tachycardia (RAPID)

Authors: Stambler BS et al., on behalf of the RAPID Investigators

Summary: The RAPID study investigated the efficacy and safety of self-administered etripamil nasal spray for acute conversion of atrioventricular-nodal-dependent paroxysmal SVT to sinus rhythm. 692 patients with a history of paroxysmal SVT were randomised 1:1 to use either intranasal etripamil or placebo if required. When prompted by symptoms of paroxysmal SVT, patients self-administered a first dose of intranasal etripamil 70mg or placebo, then repeated the dose if symptoms persisted beyond 10 min. Overall, 184 patients self-administered the study drug during follow-up. Kaplan-Meier estimates of conversion rates by 30 min were 64% with etripamil and 31% with placebo (HR 2.62, 95% CI 1.66–4.15; p<0.0001); median time to conversion was 17.2 min with etripamil and 53.5 min with placebo. Treatment-emergent adverse events occurred in 50% of etripamil recipients and 11% of placebo recipients; all of the events were transient and resolved without intervention.

Comment: Patients with symptomatic SVT often present to hospital and require adenosine for reversion but spend many hours in the A&E department to be assessed, treated and then discharged. This intranasal medication, etripamil, seems safe to be administered by patients outside a medical environment, and increases the chance of reversion without further intervention. If not too expensive this would seem to be a useful approach for patients with recurrent symptomatic atrioventricular nodal re-entrant tachycardia to reduce the need for hospital admission.

Reference: Lancet 2023;402(10396):118-28

Abstract

Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial

Authors: Thompson B et al.

Summary: The D-Health trial investigated the impact of monthly vitamin D supplementation on major cardiovascular events in older adults. 21,315 adults aged 60–84 years were randomised to receive oral vitamin D3 (60,000 IU/month) or placebo for up to 5 years; 80.2% of vitamin D recipients and 77.6% of placebo recipients completed the intervention period. A major cardiovascular event (MI, stroke, or coronary revascularisation) occurred in 6.0% of vitamin D recipients and 6.6% of placebo recipients during follow-up (HR 0.91, 95% CI 0.81–1.01). The rates of MI (HR 0.81, 95% CI 0.67–0.98) and coronary revascularisation (HR 0.89, 95% CI 0.78–1.01) were lower in the vitamin D group, but the stroke rate did not differ between groups (HR 0.99, 95% CI 0.80–1.23).

Comment: We know that low vitamin D levels are associated with increased cardiovascular events and vitamin D levels are often measured in older patients. If levels are low, supplementation is often recommended with the aim to make patients feel better, and reduce the risk of osteoporosis and cardiovascular disease. There is scant evidence for cardiovascular protection, and this meta-analysis suggests a neutral effect at best. On the current state of evidence, vitamin D should not be prescribed for cardiovascular protection, but can be considered for prevention of osteoporosis.

Reference: BMJ 2023;381:e075230

Abstract

Barriers to prescribing proprotein convertase subtilisin-kexin type 9 inhibitors after coronary revascularisation

Authors: Nguy J et al.

Summary: This Australian study identified barriers to prescribing PCSK9 inhibitors in hospitalised patients with ASCVD. A retrospective 3-month, single-site, observational analysis was conducted involving 331 consecutive patients undergoing PCI (73.7%) or coronary artery bypass graft (CABG) surgery (26.3%). Lipid profiles were measured for 82.8% of patients undergoing PCI and 67.8% of patients undergoing CABG surgery. In 109 patients taking high-intensity statins on admission, 58.7%, 40.4% and 17.4% had low-density lipoprotein (LDL) cholesterol ≥1.4, ≥1.8 and >2.6 mmol/L, respectively. High-intensity statin prescribing at discharge was high (>80%), but none of the patients with LDL cholesterol ≥1.4 mmol/L were given ezetimibe. Variable advice was given by clinicians for LDL cholesterol targets, and none of the patients met the criteria for subsidised PSCK9 inhibitor therapy (largely due to lack of qualifying lipid levels after combined statin and ezetimibe therapy).

Comment: We have ample evidence that reducing LDL cholesterol to very low levels (<1.4 mmol/L) is associated with reduced cardiovascular events and is safe in patients with ASCVD. Australian lipid guidelines are decades out of date and suggest a 'one size fits all' approach of an LDL <1.8 mmol/L irrespective of whether the patient is at low-, intermediate-, or high-risk for cardiovascular events. It is recommended that maximum tolerated high-intensity statin be used initially, followed by addition of ezetimibe, and then PCSK9 inhibition if LDL is >1.8 mmol/L. This study shows that there is room for improvement in lipid management in high-risk patients, and that ezetimibe is underutilised. There is a role for PCSK9 inhibitors in these patients if LDL remains above 1.8 mmol/L despite maximally tolerated doses of statin and ezetimibe, with the monoclonal antibody evolocumab available through the PBS and the siRNA incliseran approved by the TGA but not reimbursed yet.

Reference: Intern Med J 2023;53(6):994-1001
Abstract

Ferric carboxymaltose in heart failure with iron deficiency

Authors: Mentz RJ et al., for the HEART-FID Investigators

Summary: The HEART-FID study investigated the clinical effects of ferric carboxymaltose in patients with HFrEF and iron deficiency. 3065 patients were randomised 1:1 to receive intravenous ferric carboxymaltose or placebo in addition to standard HF therapy. Ferric carboxymaltose or placebo was given every 6 months as needed, based on iron indices and haemoglobin levels. The primary outcome was a hierarchical composite of death within 12 months, hospitalisations for HF within 12 months, or change from baseline to 6 months in the 6-min walk distance. Death by month 12 occurred in 8.6% and 10.3% of patients in the ferric carboxymaltose and placebo groups, respectively; a total of 297 and 332 hospitalisations for HF occurred by month 12 in the respective groups; and the mean change from baseline to 6 months in 6-min walk distance was 8m and 4m, respectively (p=0.02). Repeated dosing of ferric carboxymaltose had an acceptable tolerability profile.

Comment: Iron infusion for patients with HFrEF (EF <40%) who have absolute (ferritin <100 mmol/L) or functional (ferritin <100–299 mmol/L and transferrin saturation <20%) iron deficiency has been widely used in Australia on the basis of the studies prior to this that showed a reduction in hospital admissions for HF and an improvement in functional status and quality of life, but mortality was not reduced. The HEART-FID trial recently presented at the ESC is the largest study performed in this area and although it showed improvements in mortality, hospitalisation for HF, and improvement in 6-min walk distance, the primary end-point was not significant as the p value for significance was set at <0.01 for regulatory approval in the US. If the p value was set at 0.05 the study would have been positive, so these results are unlikely to change practice in Australia, but probably won't convince cardiologists in the US to start using iron infusion in these patients.

Reference: New Engl J Med 2023; published online Aug 26
Abstract

Semaglutide in patients with heart failure with preserved ejection fraction and obesity

Authors: Kosiborod MN et al., for the STEP-HFpEF Trial Committees and Investigators

Summary: This analysis of the STEP-HFpEF trial investigated the efficacy and tolerability of subcutaneous semaglutide in patients with obesity-related HFpEF. 529 patients with HFpEF and a body mass index ≥30 kg/m^2 were randomised to receive once-weekly semaglutide 2.4mg or placebo for 52 weeks. The dual primary end-points were change from baseline in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; higher scores indicating fewer symptoms and physical limitations) and change in body weight. The mean change in KCCQ-CSS after 52 weeks was +16.6 points with semaglutide and +8.7 points with placebo (p<0.001), the mean percentage change in body weight was −13.3% with semaglutide and −2.6% with placebo (p<0.001), and the mean change in 6-min walk distance was +21.5m and +1.2m in the respective groups (p<0.001). Serious adverse events were reported in 13.3% of semaglutide recipients and 26.7% of placebo recipients.

Comment: This study was also presented at ESC and was met with great enthusiasm. Until recently there have been no treatments proven to improve the outcome of patients with HFpEF, but the SGLT2 inhibitors empagliflozin and dapagliflozin, based on the EMPEROR-Preserved and DELIVER studies, now have a class 1A recommendation in the recent ESC guidelines for management of HFpEF. The STEP study looked at obese patients with HFpEF and examined whether semaglutide 2.4mg once weekly would improve the combined end-point of change in weight and change in quality of life as measured by the KCCQ walk test over 1 year. As expected, patients lost approximately 10–15% of their body weight, and their KCCQ improved. It is interesting that the degree of obesity at baseline did not influence the amount of weight loss with semaglutide, and the greater the weight loss the greater the improvement in KCCQ and 6-min walk test. How much of these improvements were due to weight loss alone is unclear, but there were significant reductions in C-reactive protein and N-terminal prohormone of brain natriuretic peptide (NTproBNP) levels, indicating a reduction in inflammation and perhaps left ventricular remodelling. These results alone are probably not strong enough to get regulatory approval for semaglutide for HFpEF, and further outcome trials will need to be done.

Reference: New Engl J Med 2023; published online Aug 25
Abstract

Anticoagulation with edoxaban in patients with atrial high-rate episodes

Authors: Kirchhof P et al., for the NOAH-AFNET 6 Investigators

Summary: Device-detected atrial high-rate episodes (AHREs) are atrial arrhythmias detected by implanted cardiac devices. They resemble AF but are rare and brief. This study investigated whether the occurrence of AHREs in patients without AF justifies the initiation of anticoagulants. 2536 patients aged ≥65 years (mean 78 years, 37.4% female) who had AHREs lasting for ≥6 min and who had ≥1 additional risk factor for stroke were randomised 1:1 to receive edoxaban or placebo. The primary efficacy outcome was a composite of cardiovascular death, stroke, or systemic embolism, and the primary safety outcome was death or major bleeding. The trial was terminated early, after a median follow-up of 21 months, on the basis of futility and safety concerns. Prior to termination, a primary efficacy outcome event had occurred in 83 patients in the edoxaban group and 101 patients in the placebo group (HR 0.81, 95% CI 0.60–1.08; p=0.15), and a safety outcome event had occurred in 149 patients in the edoxaban group and 114 patients in the placebo group (HR 1.31, 95% CI 1.02–1.67; p=0.03).

Comment: This interesting study presented at ESC answers an important clinical question. We know that patients with CHADS-VASc score >2 and proven AF do better with anticoagulation. We often see AHREs on interrogation of pacemakers, cardiac resynchronisation therapy (CRT) and implantable cardioverter defibrillators (ICDs), and until now it has been unclear as to whether these AHREs increase stroke risk, and whether anticoagulation would be beneficial. This study looked at high-risk patients (CHADS-VASc score 4) and randomised them to anticoagulation versus placebo if AHREs of >6-min duration were detected on routine interrogation of their device. Aspirin was used if there was a specific indication (approximately 50% in both groups). Stroke rates were low in both groups (1%) despite the high CHADS-VASc score, and there was no stroke reduction with edoxaban, but there was a significant increase in bleeding, so the study was stopped early. This indicates that episodes of AHREs detected on interrogation of pacemakers, CRTs or ICDs do not indicate the need for anticoagulation even in patients with high risk scores, and that this therapy should be reserved for patients who have AF confirmed on electrocardiogram, Holter or implantable loop recorders.

Reference: New Engl J Med 2023; published online Aug 25
Abstract

Safety of switching from a vitamin K antagonist to a non-vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: Results of the FRAIL-AF randomized controlled trial

Authors: Joosten LPT et al.

Summary: The open-label FRAIL-AF trial investigated the safety of switching frail elderly patients with AF from vitamin K antagonists (VKAs) to NOACs. 1330 patients (mean age 83 years) with frailty and AF who were managed with VKAs were randomised to remain on the VKA or switch to a NOAC. The primary outcome was a major or clinically relevant non-major bleeding complication accounting for death; follow-up was 12 months. The trial was stopped for futility, after more primary outcome events (HR 1.69, 95% CI 1.23–2.32) and more thromboembolic events (HR 1.26, 95% CI 0.60–2.61) were reported in patients who switched to a NOAC.

Comment: We are often tempted to change elderly frail patients who are on warfarin to a NOAC to reduce the need for INRs and with the hope that this will reduce bleeding risk. Surprisingly, this study presented at ESC showed that frail elderly patients who were on warfarin with stable INRs had more bleeding when swapped to a NOAC rather than staying on warfarin with no difference in ischaemic events. This seems counterintuitive and possible explanations were that rivaroxaban was the most frequently used NOAC and perhaps appropriate dose reduction was not used, and that the time in therapeutic range was around 65% in the warfarinised patients, which is better than that seen in clinical practice. In any case, perhaps we should reconsider automatically changing frail elderly patients with stable INRs to a NOAC unless there is a specific reason to do so.

Reference: Circulation 2023; published online Aug 27
Abstract

Muvalaplin, an oral small molecule inhibitor of lipoprotein(a) formation

Authors: Nicholls SJ et al.

Summary: Muvalaplin is an orally administered small molecule inhibitor of lipoprotein(a) (Lp[a]) formation. This phase 1 study investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of muvalaplin in 114 healthy individuals. Muvalaplin was not associated with tolerability concerns or clinically significant adverse effects. Oral doses of 30–800mg for 14 days resulted in increasing muvalaplin plasma concentrations, with a half-life of 70–414h. The drug decreased plasma Lp(a) levels within 24h after the first dose, with further Lp(a) reductions on repeated dosing; maximum Lp(a) reduction was 63–65%.

Comment: Lp(a) is attracting more and more attention as it is proposed that some of the residual risk in patients with ASCVD and well-controlled lipids is mediated through this lipid moiety. Outcome studies are currently underway with antisense and siRNA injectable agents that lower Lp(a) by more than 90%, but this oral agent lowers levels by 65% which is still pretty good. Whether lowering Lp(a) improves outcomes in patients with ASCVD and elevated levels is still to be demonstrated, and what magnitude of reduction and target levels are needed to achieve benefit are not clear, but hopefully the clinical trials will address this.

Reference: JAMA 2023; published online Aug 28
Abstract

CASTLE-HTx: Catheter ablation versus medical therapy to treat atrial fibrillation in end-stage heart failure

Speaker: Christian Sohns, Germany

Summary: The CASTLE-HTx trial investigated whether AF ablation is superior to medical therapy in patients with AF and end-stage HF. 194 patients (mean age 64 years, 19% female) with symptomatic AF and end-stage HF who were eligible for heart transplantation were randomised 1:1 to receive either first-time catheter ablation or medical therapy for AF (rate or rhythm control). Both groups received guideline-directed HF therapy. The primary end-point (a composite of all-cause death, worsening HF requiring urgent heart transplantation, or implantation of a left ventricular assist device) occurred in 8 (8.2%) patients in the ablation group and 29 (29.9%) patients in the medical therapy group during 1 year of follow-up (HR 0.24, 95% CI 0.11–0.52; p<0.001).

Comment: We often assume that when patients with severe HF are referred for assessment for transplantation, all avenues of therapy and intervention have taken place. This study shows that meaningful improvement in mortality, worsening of HF and transplantation can be obtained in these severely unwell patients, if they have AF and undergo successful ablation. This suggests that patients with severe HF may still benefit from restoration of sinus rhythm, which may delay or obviate the need for transplantation – ergo "it's never too late to ablate" in HFrEF.

Hot Line 6 session, ESC Congress 2023

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.

MULTISTARS AMI: Multivessel immediate versus staged revascularization in STEMI

Speaker: Barbara Elisabeth Stahli, Switzerland

Summary: The MULTISTARS AMI trial investigated whether immediate complete revascularisation at the time of primary PCI is non-inferior to staged multivessel PCI in haemodynamically stable patients with STEMI and multivessel coronary artery disease. 840 patients (mean age 65 years, 21.2% female) with acute STEMI and multivessel coronary artery disease who were haemodynamically stable after successful primary PCI of the infarct-related coronary artery were randomised 1:1 to immediate or staged (within 19–45 days) PCI of the non-culprit lesions. The primary end-point (a composite of all-cause death, non-fatal MI, stroke, unplanned ischaemia-driven revascularisation, or hospitalisation for HF within 1 year) occurred in 35 (8.5%) patients in the immediate group and 68 (16.3%) patients in the staged group (risk ratio 0.52, 95% CI 0.38–0.72; p<0.001 for non-inferiority and p<0.001 for superiority).

Comment: This study provides confirmation of the COMPLETE study results that showed that complete revascularisation post STEMI is beneficial compared with intervention on the infarct-related artery alone if there is significant bystander disease. The optimal timing of revascularisation of the non-culprit lesion(s) was not defined but this MULTISTARS study showed that immediate revascularisation at the time of the initial procedure was non-inferior to a staged approach. Both these studies show that complete revascularisation is beneficial, but the outcome is similar whether it is done at the index procedure, or a staged approach is undertaken.

Hot Line 6 session, ESC Congress 2023

