Cardiology Research Review™

Making Education Easy

Issue 131 - 2021

In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **ACS** = acute coronary syndrome; **CAD** = coronary artery disease; **FFR** = fractional flow reserve; **HF** = heart failure; **HFpEF** = HF with preserved ejection fraction; **HFrEF** = HF with reduced ejection fraction; **HR** = hazard ratio; **LV** = left ventricular; **LVEF** = LV ejection fraction; **MACE** = major adverse cardiac events; **MI** = myocardial infarction; **NOAC** = non-vitamin K antagonist oral anticoagulant; **PCI** = percutaneous coronary intervention; **QOL** = quality of life; **SGLT2** = sodium-glucose transport protein 2.

Claim CPD/CME points Click here for more info.

Like us on Facebook
facebook.com/researchreviewau/

Welcome to the latest issue of Cardiology Research Review.

In this issue, an analysis of the RATE-AF study compares the effects of digoxin and bisoprolol on QOL in patients with AF and symptoms of HF, the findings of a Canadian study support the use of FFR thresholds to guide PCI in patients with CAD, and a secondary analysis of the STAR AF II study shows that catheter ablation improves QOL in AF patients. A study in Brazil finds that rivaroxaban may be suitable for use in AF patients with bioprosthetic mitral valves, the ALPHEUS trial supports clopidogrel as the standard of care for elective PCI, and an article discusses the use of a red yeast rice supplement for hypercholesterolaemia.

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

Kind Regards,

Associate Professor John Amerena

john.amerena@researchreview.com.au

Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life

Authors: Kotecha D et al.

Summary: This analysis of the RATE-AF study compared the effects of digoxin and bisoprolol on QOL in patients with AF and HF. 160 patients aged ≥60 years with permanent AF and symptoms of HF (New York Heart Association class II or higher) were randomised to receive digoxin 62.5–250 µg/day or bisoprolol 1.25–15 mg/day for heart rate control in an open-label design. The primary end-point of patient-reported QOL at 6 months (measured using the 36-Item Short Form Health Survey physical component summary score) did not differ significantly between groups. Fewer patients in the digoxin group than the bisoprolol group reported an adverse event during follow-up (25% vs 64%; p<0.001).

Comment: We traditionally used beta-blockers in preference to digoxin for rate control in patients with AF as beta-blockers are more effective at suppressing exercise-induced increases in heart rate than digoxin. There have also been concerns about digoxin toxicity, particularly in frail elderly populations especially if there is renal impairment. Conversely, there are data to suggest that beta-blockers do not confer the same survival benefit seen in patients with HF with AF compared with those in sinus rhythm. This study looked at patients with permanent AF and symptoms of HF predominantly due to HFpEF (>80% of participants had LVEF >50%). It showed little difference in the heart rate response to exercise in this population and a better QOL with digoxin when used for rate control rather than beta-blockers, as well as fewer adverse effects. Subgroup analysis showed no difference in this result whether the ejection fraction was above or below 50% but patients with HFrEF were underrepresented. This being the case it would seem that digoxin is a reasonable choice for rate control in patients with AF and HFpEF but I do not think the data are strong enough to support using it as an alternative to beta-blockers in patients with AF and reduced systolic function.

Reference: JAMA 2020;324(24):2497-2508
Abstract

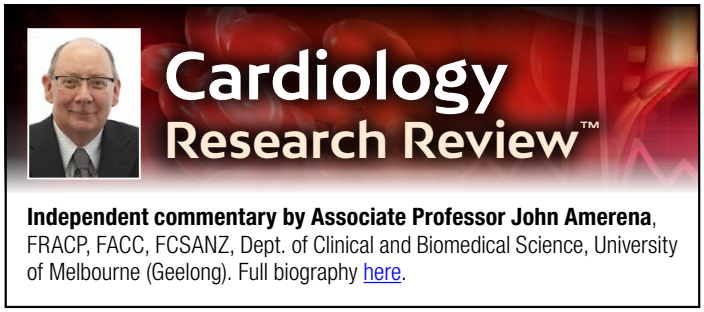
Association between adherence to fractional flow reserve treatment thresholds and major adverse cardiac events in patients with coronary artery disease

Authors: Sud M et al.

Summary: This retrospective, population-based cohort study assessed the association between adherence to evidence-based FFR thresholds for PCI and major adverse cardiac events (MACE) in patients with CAD. 9106 patients who underwent single-vessel FFR assessment in 2013–2018 in Ontario, Canada, were grouped into 2 cohorts based on FFR thresholds: ≤0.80 (ischaemic) and >0.80 (non-ischaemic). Among 2693 patients with an ischaemic FFR, 75.3% received PCI and 24.7% received medical therapy only. In this cohort, PCI was associated with a significantly lower risk of MACE at 5 years compared with no PCI (31.5% vs 39.1%; HR 0.77, 95% CI 0.63–0.94). Among 6413 patients with a non-ischaemic FFR, 12.6% received PCI and 87.4% received medical therapy only. In this cohort, PCI was associated with a significantly higher risk of MACE at 5 years compared with no PCI (33.3% vs 24.4%; HR 1.37, 95% CI 1.14–1.65).

Comment: FFR is traditionally used as a guide to whether coronary stenoses are haemodynamically significant enough to warrant intervention. It is generally accepted that an FFR <0.80 is ischaemic and if this is the case intervention is reasonable. This retrospective study looked at differential effects between patients with ischaemic and non-ischaemic FFR who underwent PCI and found that at 5 years there was a reduction in MACE in patients who underwent appropriate PCI whereas patients who underwent inappropriate PCI on the basis of an FFR >0.8 had an increase in MACE. This study supports the current guidelines that FFR should be used to guide revascularisation strategies in patients with CAD.

Reference: JAMA 2020;324(23):2406-14
Abstract



Association between quality of life and procedural outcome after catheter ablation for atrial fibrillation

Authors: Terricabras M et al., for the STAR AF II Investigators

Summary: This secondary analysis of the STAR AF II trial investigated the impact of catheter ablation on QOL in patients with AF. 549 patients who underwent catheter ablation for AF at 35 centres in Europe, Canada, Australia, China, and Korea were assessed for QOL at baseline and at 6, 12, and 18 months using the 36-Item Short Form Health Survey and the EuroQol Health-Related Quality of Life 5-Dimension 3-Level questionnaire. Scores were converted to a physical health component score (PCS) and a mental health component score (MCS). AF burden significantly decreased from a mean 82% before ablation to 6.6% after ablation (p<0.001). Significant improvements in mean PCS and MCS were seen 18 months after ablation (both p<0.05).

Comment: Catheter ablation for AF is increasingly being used in patients with persistent AF who tolerate it poorly or have adverse effects to rhythm or rate control medication. This interesting study demonstrated that, regardless of which AF ablation technique was used, a reduction in AF burden was associated with an increase in QOL, with the greatest improvement in patients whose AF burden was reduced by >70%. This study supports our current strategy of using AF ablation as primarily a symptom control tool rather than having a mortality benefit (apart from in patients who have persistent AF and decreased LV systolic dysfunction, where an improvement in both EF and mortality has been demonstrated over a 5-year period with successful ablation).

Reference: JAMA Netw Open 2020;3(12):e2025473
Abstract

Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure

Authors: Teerlink JR et al., for the GALACTIC-HF Investigators

Summary: The GALACTIC-HF trial investigated the effects of the selective cardiac myosin activator omecamtiv mecarbil on cardiovascular outcomes in patients with HF. 8256 inpatients and outpatients with symptomatic chronic HF and LVEF ≤35% were randomised to receive omecamtiv mecarbil 25–50mg twice daily or placebo, in addition to standard HF therapy. The primary outcome was a composite of a first HF event (hospitalisation or urgent visit for HF) or death from cardiovascular causes. During a median follow-up of 21.8 months, a primary outcome event occurred in 37.0% of patients in the omecamtiv mecarbil group and 39.1% in the placebo group (HR 0.92, 95% CI 0.86–0.99; p=0.03). 19.6% and 19.4% of patients in the respective groups died from cardiovascular causes (p=NS).

Comment: Despite patients with HFrEF receiving optimal medical therapy there is still a frustratingly high risk of readmission to hospital with HF, progression of disease, and mortality. This study looked at a novel cardiac myosin activator omecamtiv mecarbil in patients with HF with reduced systolic function. This medication was added to conventional therapy and there was a high rate of adherence to optimal medical guideline-directed therapy. Patients who received this treatment had a reduction in admissions to hospital for HF or death but this was driven primarily by readmission rather than a reduction in mortality. However, this was a particularly sick group of patients who had a recent hospital admission, so this therapy may be particularly useful in patients who are on good medical therapy who have an episode of decompensation indicating a high risk of recurrent admissions. The other advantage of this medication over conventional HF treatment is that it has minimal or even a beneficial effect on blood pressure, which may make it attractive in patients with low blood pressure which precludes up-titration of standard medications to target levels.

Reference: N Engl J Med 2021;384(2):105-16
Abstract

Sotagliflozin in patients with diabetes and recent worsening heart failure

Authors: Bhatt DL et al., for the SOLOIST-WHF Trial Investigators

Summary: This study investigated the safety and efficacy of the SGLT2 inhibitor sotagliflozin when initiated soon after an episode of decompensated HF in patients with diabetes. 1222 patients with type 2 diabetes mellitus who were recently hospitalised for worsening HF were randomised to receive sotagliflozin or placebo. The first dose was administered before discharge in 48.8% of patients or soon after discharge in 51.2%. The primary end-point was a composite of deaths from cardiovascular causes, and hospitalisations and urgent visits for HF. During a median follow-up of 9 months, the rate (per 100 patient-years) of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs 76.3; HR 0.67, 95% CI 0.52–0.85; p<0.001). Diarrhoea was more common with sotagliflozin than placebo (6.1% vs 3.4%), as was severe hypoglycaemia (1.5% vs 0.3%).

Comment: The recent trials of SGLT2 inhibitors in patients with HFrEF with and without diabetes have shown significant benefits in reduction of readmission to hospital with HF, renal protection and (on meta-analysis) a reduction in cardiovascular and total mortality. In these studies the SGLT2 inhibitor was started remotely after an admission to hospital for HF and the question has been asked as to whether these agents could be used earlier in the course of HF management, and in particular in patients who are in hospital with or recently discharged after an episode of acute decompensated HF. Sotagliflozin is an SGLT 1 and 2 inhibitor and it was studied in patients with HFrEF who were admitted with acute HF. Patients were randomised to sotagliflozin or placebo, in addition to standard therapy, at the time of or soon after discharge. The results were impressive, showing that there was a reduction in hospitalisation for HF and urgent visits as well as a reduction in total mortality. The only downside is that the SGLT1 inhibition produced severe diarrhoea in 6% of patients. These findings suggest that SGLT2 inhibitors can be used earlier in the management of patients with systolic LV dysfunction and more acute HF, with no downside as the benefits were the same in the acute setting as in the chronic setting. Sotagliflozin is not available here but dapagliflozin has been approved for treatment of HFrEF with and without diabetes, but is not PBS subsidised yet.

Reference: N Engl J Med 2021;384:117-28
Abstract

Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve

Authors: Guimarães HP et al., for the RIVER Trial Investigators

Summary: 1005 patients with AF and a bioprosthetic mitral valve were randomised to receive either rivaroxaban 20mg once daily or dose-adjusted warfarin (target international normalised ratio, 2–3) at 49 sites in Brazil. A primary outcome event (death, MACE or major bleeding) occurred at a mean 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (p<0.001 for non-inferiority). Death from cardiovascular causes or thromboembolic events occurred in 3.4% of patients in the rivaroxaban group and 5.1% in the warfarin group (HR 0.65, 95% CI 0.35–1.20), and the incidence of stroke in the corresponding groups was 0.6% and 2.4% (HR 0.25, 95% CI 0.07–0.88). Major bleeding occurred less often with rivaroxaban (1.4% vs 2.6%; HR 0.54, 95% CI 0.21–1.35).

Comment: In the seminal studies demonstrating the benefits of NOACs over warfarin in patients with non-valvular AF, there was a small percentage of patients who had bioprosthetic mitral valves. There was no difference in the outcome between these patients and those with native mitral valves but the numbers were small and there has been residual doubt as to the appropriateness of using NOACs in this situation. This study looked at more than 1000 patients with bioprosthetic mitral valves and showed that rivaroxaban was a reasonable alternative to warfarin, in that it was not inferior with respect to death, MACE or bleeding. These results support what is commonly done in clinical practice in Australia. However, the findings do not answer the question of optimal anticoagulation strategy immediately after implantation of a bioprosthetic valve, and whether rivaroxaban can be used in this context, or whether there should be a 3-month period of anticoagulation with warfarin before swapping to a NOAC as is common practice in Australia.

Reference: N Engl J Med 2020;383:2117-26
Abstract

Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS)

Authors: Silvain J et al.

Summary: The ALPHEUS study compared the effects of ticagrelor and clopidogrel on periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI. At 49 hospitals in France and the Czech Republic, 1910 patients with stable CAD and an indication for PCI were randomised to receive either ticagrelor (180mg loading dose then 90mg twice daily for 30 days) or clopidogrel (300–600mg loading dose then 75mg daily for 30 days). Within 48h of PCI, the primary outcome (a composite of PCI-related type 4 MI or major myocardial injury) was observed in 35% of patients in the ticagrelor group and 36% in the clopidogrel group (p=NS). The primary safety outcome of major bleeding did not differ significantly between groups, but minor bleeding events were more common with ticagrelor than clopidogrel at 30 days (11% vs 8%; p=0.007).

Comment: In the PLATO and TRITON studies, ticagrelor and prasugrel were shown to improve outcomes in patients presenting with ACS undergoing a PCI. These agents have been widely used in this setting in preference to clopidogrel but this study examined whether there was any significant difference in the context of elective PCI rather than after ACS. It demonstrated that there was no difference in periprocedural MI between patients who received ticagrelor versus clopidogrel but there was a slight excess of bleeding. This may indicate that more aggressive antiplatelet regimens are necessary in the context of ACS where inflammatory vulnerable plaques have ruptured, as opposed to the chronic setting where plaques are much more likely to be stable and less inflammatory, so that less intensive antiplatelet therapy may suffice.

Reference: Lancet 2020;396(10264):1737-44
Abstract

Red yeast rice for hypercholesterolemia

Authors: Cicero AFG et al.

Summary: This article discussed the use of red yeast rice as a cholesterol-lowering supplement. The cholesterol-lowering effectiveness of red yeast rice is directly related to its monacolin K content, and daily consumption of monacolin K can reduce low-density lipoprotein (LDL) cholesterol levels by 15–25% within 6–8 weeks. Decreases in LDL cholesterol are accompanied by similar reductions in total cholesterol, plasma apolipoprotein B, matrix metalloproteinases 2 and 9, and high-sensitivity C-reactive protein. The lipid-lowering effect of red yeast rice is also associated with significant improvements in pulse wave velocity and endothelial function. Its mechanism of action is similar to that of statins, but a daily dose of 3–10mg monacolin K has only minimal associated risks (mild myalgias are seen only in the most frail patients).

Comment: Actual or perceived statin intolerance is a real issue in many developed countries and many patients who would benefit from lipid lowering are unable to take sufficient doses of statins to achieve target levels. Red yeast rice is a substance that is extracted from rice that has been fermented with a type of yeast called *Monascus purpureus* and is an alternative "natural" therapy that can produce meaningful reductions in total and LDL cholesterol in the order of 15–25%. When taken in conjunction with ezetimibe (if tolerated) and other non-traditional lipid-lowering therapy (sterol margarine, porridge, psyllium) patients may be able to lower lipids to near target, but in any case the lower the LDL the better, irrespective of how it is attained, although there are no outcomes data with these therapies. Red yeast rice is available in Australia but depending on local regulations can be over the counter/internet or require a prescription.

Reference: J Am Coll Cardiol 2021;77(5):620-8
Abstract

The acute effects of an ultramarathon on biventricular function and ventricular arrhythmias in master athletes

Authors: Cavigli L et al.

Summary: This study evaluated the acute effects of an ultramarathon on biventricular function and ventricular arrhythmias in master athletes aged ≥40 years. 68 healthy, non-professional master athletes (mean age 47.9 years) participating in a 50km ultramarathon were included. A single-lead electrocardiogram (ECG) was recorded continuously from the day before the race until the end of the race, and echocardiography and 12-lead resting ECG were performed before and after the race. R-wave amplitude in V1 and QTc duration were higher after the race compared with baseline (p<0.001). 7% of athletes had exercise-induced isolated premature ventricular beats, but none showed non-sustained ventricular tachycardia before or during the race. LVEF and global longitudinal strain did not change significantly during the race.

Comment: There has been much debate about the safety of older men engaging in endurance sports, as ventricular arrhythmias and dilatation has been seen, as well as troponin elevation and myocardial oedema in participants after marathon running. This study looked at trained master athletes and found no indication of adverse cardiac effects with endurance exercise, with no significant changes in LV size and function (apart from those expected with volume depletion) and no worrisome arrhythmias. This information gives reassurance that it is safe for trained older athletes to compete in endurance events, but whether this can be extrapolated to untrained or elite athletes is not clear.

Reference: Eur Heart J Cardiovasc Imaging 2021; published online Feb 5
Abstract

Empagliflozin effects on pulmonary artery pressure in patients with heart failure

Authors: Nassif ME et al.

Summary: The EMBRACE-HF trial evaluated the effects of empagliflozin on pulmonary artery (PA) pressure in patients with HF. At 10 centres in the US, 65 patients with HF (with or without type 2 diabetes mellitus) and a previously implanted PA pressure sensor were randomised to receive empagliflozin 10 mg/day or placebo for 12 weeks. The primary end-point was change in PA diastolic pressure (PADP) from baseline to end of treatment. Empagliflozin significantly reduced PADP during the study period. Effects were apparent from week 1 and amplified over time. Mean PADP at week 12 was 1.7mm Hg lower with empagliflozin than with placebo (p=0.02).

Comment: SGLT2 inhibitors have been shown to reduce HF admissions and mortality in patients with HFrEF with or without diabetes. These effects are postulated to be due to effects on the Na^+/H^+ exchanger that are independent of the effect of glucose-lowering by blockade of the SGLT2 receptor in the renal tubule in diabetics. This small study shows a marked decrease in pulmonary pressure in patients with HFrEF with empagliflozin that were not produced by diuresis, probably mediated by the same mechanism. Improvements in LV function and structure have also been documented with SGLT2 inhibitors, and these data taken in conjunction with the clinical benefits seen in the outcome trials make these agents appealing to use as add-on therapy to standard treatment for HFrEF. Dapagliflozin has been approved by the TGA for use in HFrEF in diabetics and non-diabetics but is not PBS funded yet, and empagliflozin is still awaiting approval.

Reference: Circulation 2021; published online Feb 8
Abstract

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 60 credits per year in Category One – Educational Activities) **for reading and evaluating Research Reviews.**
Please CLICK HERE to download CPD Information

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

