Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ACE = angiotensin-converting enzyme; **ACS** = acute coronary syndrome; **ARB** = angiotensin receptor blocker; **CTCA** = computed tomography coronary angiography; **HFpEF** = heart failure with preserved ejection fraction; **HFrEF** = heart failure with reduced ejection fraction; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9.

Welcome to the latest issue of Cardiology Research Review.

In this issue, a US modelling study reports that sacubitril-valsartan has high economic value in the treatment of heart failure, an analysis of the PARTNER 3 trial suggests that transcatheter aortic-valve replacement is likely to become the preferred procedure for patients with severe symptomatic aortic stenosis, and a secondary analysis of the VALOR-HCM trial reports positive findings for mavacamten in patients with severely symptomatic hypertrophic obstructive cardiomyopathy. Also in this issue, a US study confirms the benefits of a low-salt diet in patients with hypertension, and the ADAPTABLE trial finds no difference in efficacy or serious gastrointestinal events between enteric-coated and uncoated aspirin in patients with cardiovascular disease.

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

Kind Regards,

Associate Professor John Amerena
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Health and economic evaluation of sacubitril-valsartan for heart failure management

Authors: Bhatt AS et al.

Summary: This modelling study used data from the PARADIGM-HF and PARAGON-HF trials to compare the cost-effectiveness of sacubitril-valsartan and other renin-angiotensin system (RAS) inhibitors across various upper-level cutoffs of LVEF. Data for a total of 13,264 patients were analysed, and calculations were based on a wholesale acquisition cost of sacubitril-valsartan of $US7092 per year. A 5-state Markov model projected that, compared with other RAS inhibitors, sacubitril-valsartan had an incremental cost-effectiveness ratio consistent with high economic value for patients with reduced (≤45%) and mildly reduced EF (≤50%), and at least intermediate value in patients with EF ≤60%.

Comment: Despite clinical trials showing significant benefits of sacubitril-valsartan compared with the ACE inhibitor enalapril in patients with heart failure, it is considerably more expensive than generic ACE inhibitors or ARBs, raising concerns about its cost-effectiveness in patients with HFrEF and mildly reduced EF (40–49%) or HFpEF (not approved for this in Australia). This paper looked at this from a US perspective (where everything is much more expensive than in Australia) and showed there was high economic value of sacubitril-valsartan in the treatment of heart failure, which is likely to be even greater in Australia, and that the lower the EF the greater the benefit. This supports the current recommendation that sacubitril-valsartan should be the preferred inhibitor of the RAS in patients with HFrEF.

Reference: JAMA Cardiol. 2023;8(11):1041–8
Abstract

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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.

Concomitant coronary atheroma regression and stabilization in response to lipid-lowering therapy

Authors: Biccirè FG et al.

Summary: The PACMAN-AMI trial investigated the effects of alirocumab on 'triple regression' in patients with acute MI. Patients who were already taking high-intensity statins were randomised to receive alirocumab or placebo and were followed up for 1 year. Triple regression was defined as atheroma volume reduction, maximum lipid core burden index within 4mm reduction, and minimal increase in fibrous cap thickness, and was measured using serial intravascular ultrasound, near-infrared spectroscopy, and optical coherence tomography. Overall, 40.8% of patients in the alirocumab group and 23.0% in the placebo group had triple regression (p=0.002). On-treatment LDL cholesterol levels were lower in patients with versus without triple regression (p<0.001). Triple regression was independently predicted by alirocumab treatment (odds ratio 2.83, 95% CI 1.57–5.16; p=0.001). The composite clinical end-point (death, MI, and ischaemia-driven revascularisation) occurred less frequently in patients with versus without triple regression (8.3% vs 18.2%; p=0.04).

Comment: We know that aggressive lipid lowering after ACS reduces recurrent events, and this study shows that structural changes in plaque composition can be produced by alirocumab (a PCSK9 inhibitor) after ACS, and that this is associated with a reduction in subsequent cardiovascular events. We know that statins can produce the same changes in the arterial wall, and improve outcomes, but this study demonstrates that even better outcomes can be attained by additional LDL reduction with PCSK9 inhibition on top of high-dose statin after ACS.

Reference: J Am Coll Cardiol. 2023;82(18):1737–47
Abstract

Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome

Authors: Hong S-J et al., on behalf of the T-PASS Investigators

Summary: The open-label T-PASS trial investigated whether stopping aspirin within a month and reducing to ticagrelor monotherapy is noninferior to 12 months of ticagrelor-based dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation for ACS. 2850 patients with ACS who received a DES at 24 centres in South Korea were randomised 1:1 to receive either ticagrelor monotherapy (90mg twice daily) after <1 month of DAPT or 12 months of ticagrelor-based DAPT. The primary end-point (a composite of all-cause death, MI, definite or probable stent thrombosis, stroke, and major bleeding at 1 year) occurred in 2.8% of patients receiving ticagrelor monotherapy after <1-month DAPT compared with 5.2% of patients receiving ticagrelor-based DAPT for 12 months (HR 0.54, 95% CI 0.37–0.80; p<0.001 for noninferiority and p=0.002 for superiority). Major bleeding occurred less often with ticagrelor monotherapy than with DAPT (1.2% vs 3.4%; p<0.001).

Comment: Current guidelines recommend DAPT for 12 months after PCI, whether this be in patients with stable coronary artery disease or after ACS. The majority of benefit for reduction of recurrent ischaemic events with DAPT is in the first 30 days post ACS, whereas bleeding rates are evenly distributed over the 12-month period. This being the case, shorter durations of DAPT have been studied, and this paper suggests there is no price to pay in stopping aspirin 1 month after PCI for ACS, with no increase in ischaemic events in those who received ticagrelor alone 1 month after ACS but significantly less bleeding. Event rates were low, suggesting that many of these patients were not high risk, but even so, cessation of aspirin at 1 month with continuation of monotherapy with ticagrelor is appealing in lower-risk patients after ACS. However, this would be problematic in Australia as ticagrelor is only approved and reimbursed for use with aspirin.

Reference: Circulation 2023; published online Oct 25
Abstract

High-risk plaques on coronary computed tomography angiography: Correlation with optical coherence tomography

Authors: Kinoshita D et al.

Summary: This study investigated the correlation between high-risk plaque features on CTCA and plaque characteristics on optical coherence tomography (OCT). 448 patients (median 67 years, 79.7% male) who underwent both CTCA and OCT before coronary intervention were included. High-risk plaque was defined as a plaque with ≥2 of the following features: positive remodelling, low-attenuation plaque, napkin-ring sign, and spotty calcification. A total of 1075 high-risk plaques identified by CTCA were evaluated by OCT. Positive remodelling was found to be associated with all OCT features of plaque vulnerability; low-attenuation plaque was associated with lipid-rich plaque, macrophage, and cholesterol crystals; napkin-ring sign was associated with cholesterol crystals; and spotty calcification was associated with microvessels. All four high-risk plaque features were associated with thin-cap fibroatheroma. During up to 3 years' follow-up, the composite end-point (target vessel revascularisation and cardiac death) occurred significantly more often in patients with versus without high-risk plaques (4.7% vs 0.5%; p=0.01).

Comment: Intravascular ultrasound and OCT have been thought to be superior to CTCA in defining plaque morphology, but this study shows that high-risk features can be detected on CTCA and it correlates well with OCT indicators of vulnerability after ACS. This being the case, it is tempting to speculate that if high-risk plaque features are detected on CTCA in the absence of ACS, aggressive lipid lowering will improve plaque morphology and subsequent events. This has not been proven yet, but is likely given the results of this study.

Reference: J Am Coll Cardiol Img. 2023; published online Sep 13
Abstract

Transcatheter aortic-valve replacement in low-risk patients at five years

Authors: Mack MJ et al., for the PARTNER 3 Investigators

Summary: This analysis of the PARTNER 3 trial compared long-term (5-year) outcomes after transcatheter aortic-valve implantation (TAVI) versus surgical aortic-valve replacement (SAVR). 1000 low-risk patients with severe, symptomatic aortic stenosis were randomised to undergo either TAVI or surgery. The first primary end-point (a composite of death, stroke, or rehospitalisation related to the valve, the procedure, or heart failure) occurred in 22.8% of patients in the TAVI group and 27.2% of patients in the surgery group during 5 years of follow-up (p=ns). Failure of the bioprosthetic valve occurred in 3.3% and 3.8% of patients in the TAVI and surgery groups, respectively.

Comment: The indications for TAVI have been progressively liberalised over time so that in many countries, low-risk patients who would be suitable for SAVR are now having TAVI. This study shows no difference in outcomes 5 years after TAVI versus SAVR in low-risk patients, and there is increasing evidence that percutaneously implanted valves are as durable as or better than surgically implanted bioprosthetic valves. This being the case, it is likely that TAVI will become the preferred procedure for severe symptomatic aortic stenosis, and that SAVR will only be done on patients who need coronary artery grafts as well.

Reference: N Engl J Med. 2023; published online Oct 24
Abstract

Mavacamten in patients with hypertrophic cardiomyopathy referred for septal reduction: Week 56 results from the VALOR-HCM randomized clinical trial

Authors: Desai MY et al.

Summary: This analysis of the VALOR-HCM trial examined the effects of mavacamten on the need for septal reduction therapy (SRT) in patients with severely symptomatic hypertrophic obstructive cardiomyopathy (HOCM). Patients with HOCM (New York Heart Association class III/IV) who were referred for SRT were randomised to receive mavacamten or placebo for 16 weeks, at which time those taking placebo crossed over to mavacamten for 40 weeks and those initially assigned to mavacamten continued with the drug through week 56. The composite end-point (proportion of patients undergoing SRT, remaining guideline eligible or having unevaluable SRT status at week 56) was met by 8.9% of patients in the original mavacamten group and 19.2% in the placebo crossover group. Overall, 11.1% of patients had LVEF <50% at week 56, and 75% continued with treatment.

Comment: Management of symptomatic HOCM with LV outflow tract obstruction has largely been focussed on symptom relief, rather than disease modification. Beta-blockers or heart rate-slowing calcium channel blockers are used, as is disopyramide, but mavacamten has now been shown to improve outcomes in patients with symptomatic HOCM. In this study, the beneficial effect on reduction of LV outflow tract obstruction was still present 12 months after starting treatment compared with placebo. There was a reduced need for surgical myomectomy but whether this will be sustained needs longer-term follow up. It is a step forward as this is the only agent that has ever been shown to have beneficial effects in this condition, by modifying LV hypertrophic changes. This agent is TGA approved, and hopefully will soon be PBS reimbursed.

Reference: JAMA Cardiol. 2023;8(10):968–77
Abstract

LDL-C reduction with lipid-lowering therapy for primary prevention of major vascular events among older individuals

Authors: Andersson NW et al.

Summary: This Danish cohort study evaluated the use of lipid-lowering therapy for primary prevention in older individuals. 65,190 individuals aged ≥50 years who had commenced lipid-lowering therapy in 2008–2017 and had no history of atherosclerotic cardiovascular disease were included. The risk of major vascular events among elderly individuals (≥70 years) was compared with that in younger individuals (<70 years). In both age-groups the median LDL cholesterol reduction was 1.7 mmol/L. Each 1-mmol/L decrease in LDL cholesterol in older individuals was associated with a 23% lower risk of major vascular events (HR 0.77, 95% CI 0.71–0.83), which was comparable to that seen in younger participants (HR 0.76, 95% CI 0.71–0.80).

Comment: Trials of statins in primary prevention have shown benefit, although the magnitude of effect is less than that for patients who have had a cardiovascular event (secondary prevention). Most of these primary prevention trials excluded the elderly, so doubt remains as to whether there is benefit with statin therapy in the elderly for primary prevention. This interesting observational study from Denmark suggests that the benefits of LDL reduction for prevention of cardiovascular events is independent of age, so it is never too late to start LDL reduction therapy. Things should be clearer with the results of the Australian STAREE study, which is a randomised controlled trial looking at atorvastatin versus placebo in a healthy elderly cohort to determine if there is a reduction in major adverse cardiovascular events and an increase in disability-free survival with this intervention.

Reference: J Am Coll Cardiol. 2023;82(14):1381–91
Abstract

Clinical implementation of partial oral treatment in infective endocarditis

Authors: Pries-Heje MM et al.

Summary: The Danish POETry study investigated the efficacy of oral step-down antibiotic therapy in stabilised patients with left-sided infective endocarditis. 562 patients with infective endocarditis caused by *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus spp.* or coagulase-negative staphylococci were included. All patients initially received conventional intravenous antibiotic treatment for ≥10 days (or ≥7 days after heart surgery). Once stabilised, 322 patients continued with intravenous antibiotics and 240 patients were switched to oral antibiotic therapy. More patients in the intravenous group had infective endocarditis caused by *S. aureus* or had an intra-cardiac abscess or a pacemaker, and more of them were surgically treated. The primary outcome (embolic events, unplanned cardiac surgery, relapse of bacteraemia and all-cause mortality within 6 months) occurred in 13% of patients who switched to oral antibiotics and 18% of those who continued with intravenous antibiotics (p=0.051). Patients who switched to oral antibiotics had a shorter median length of stay (24 vs 43 days; p<0.001) and a lower mortality rate (8% vs 14%; p=0.024).

Comment: Standard treatment for subacute bacterial endocarditis involves 6 weeks of intravenous antibiotics. Depending on the regimen, some of this can be delivered through a 'hospital in the home' programme rather than 6 weeks as an inpatient, both of which are labour intensive. This study suggests that the duration of intravenous antibiotics can be shortened in selected stable low-risk patients and that many can be transitioned to oral antibiotics with no difference in relapsed bacteraemia, need for surgery, embolic events or death at 6 months. More study will need to be done before this can be recommended as routine practice, but it is an appealing concept.

Reference: Eur Heart J. 2023; published online Oct 25
Abstract

Effect of dietary sodium on blood pressure

Authors: Gupta DK et al.

Summary: This crossover trial in the US investigated blood pressure (BP) responses to dietary sodium. A total of 213 community-based individuals aged 50–75 years with normotension (25%), controlled hypertension (20%), uncontrolled hypertension (31%), and untreated hypertension (25%) were included. Participants attended a baseline visit while consuming their usual diet, then completed 1 week of a high-sodium diet (approximately 2200 mg/day sodium added to usual diet) and a low-sodium diet (approximately 500 mg/day total) in a crossover design. While consuming usual, low-sodium, and high-sodium diets, participants' median systolic BP levels were 125, 119, and 126mm Hg, respectively. The median within-individual change in mean arterial pressure (MAP) between high- and low-sodium diets was 4mm Hg, which was not affected by hypertension status. Compared with the high-sodium diet, the low-sodium diet decreased MAP in 73.4% of participants.

Comment: This study shows that there is a relationship between dietary salt consumption and BP in patients with and without hypertension. An extremely low-salt diet (<500 mg/day) induced a BP reduction comparable to what you would expect to see with antihypertensive monotherapy, but sticking to this degree of salt restriction outside of a clinical trial environment would be extremely difficult. Thus, this reinforces that we should advise our patients who are being treated for hypertension to keep salt intake as low as possible to try and achieve targets with as few medications as possible.

Reference: JAMA 2023; published online Nov 11
Abstract

Effectiveness and safety of enteric-coated vs uncoated aspirin in patients with cardiovascular disease

Authors: Sleem A et al.

Summary: This secondary analysis of the ADAPTABLE trial compared the efficacy and safety of enteric-coated versus uncoated aspirin in patients with atherosclerotic cardiovascular disease. Baseline aspirin formulation used in the trial was self-reported for 10,678 participants, of whom 69.0% took enteric-coated aspirin and 31.0% took uncoated aspirin. The primary effectiveness end-point was a composite of MI, stroke, or death from any cause, and the primary safety end-point was major bleeding events. No significant differences in efficacy or safety outcomes were reported in patients taking enteric-coated versus uncoated aspirin.

Comment: We often recommend enteric-coated aspirin to patients with cardiovascular disease, on the assumption it will reduce gastrointestinal side effects whilst maintaining efficacy. This study showed there was no difference between enteric-coated and uncoated aspirin with respect to efficacy or serious gastrointestinal events, although there was a nonsignificant trend to more bleeding with uncoated aspirin. The use of proton pump inhibitors (PPIs) did not affect efficacy or safety but they did not report the frequency of symptomatic gastro-oesophageal reflux disease (GORD), as symptoms often increase when aspirin is started in patients with pre-existing GORD. Enteric-coated aspirin probably should be recommended in these patients, but if still symptomatic, adding a PPI or changing to clopidogrel could be considered. There is little evidence however that using PPIs prophylactically in patients on aspirin is beneficial in reducing gastrointestinal bleeding or symptoms.

Reference: JAMA Cardiol. 2023;8(11):1061–9
Abstract

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