Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **ASCVD** = atherosclerotic CVD; **BP** = blood pressure; **ACS** = acute coronary syndrome; **CVD** = cardiovascular disease; **HFrEF** = heart failure with reduced ejection fraction; **MI** = myocardial infarction; **PBS** = Pharmaceutical Benefits Scheme; **PCI** = percutaneous coronary intervention; **SGLT2** = sodium-glucose cotransporter 2; **STEMI** = ST-segment elevation MI; **TGA** = Therapeutic Goods Administration.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, an analysis of data from the SWEDEHEART registry highlights the need for evidence-based pharmacotherapy in the immediate post-infarct period in all STEMI patients irrespective of perceived risk, a cohort study finds that most patients hospitalised for heart failure in the US will be candidates for dapagliflozin treatment, and an analysis of the EMPEROR-Reduced trial finds that the clinical benefits of SGLT2 inhibitors in patients with HFrEF are not entirely related to diuresis. Also in this issue, an Australian study reinforces the importance of using as many evidence-based therapies as possible after ACS, and the HOST-EXAM study finds that clopidogrel is superior to aspirin in patients requiring indefinite antiplatelet monotherapy after PCI.

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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Mortality in STEMI patients without standard modifiable risk factors

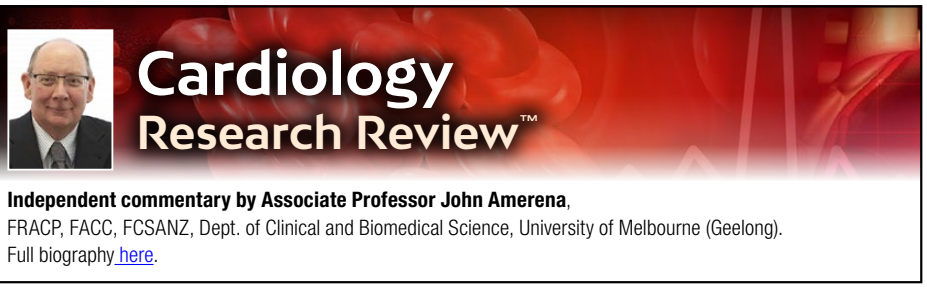
Authors: Figtree GA et al.

Summary: This analysis of SWEDEHEART registry data evaluated mortality risk in STEMI patients without standard modifiable risk factors (SMuRFs; hypertension, diabetes, hypercholesterolaemia, and smoking). Between Jan 2005 and May 2018, 62,048 patients in the registry were hospitalised with STEMI; 9228 (14.9%) of them had no SMuRFs that reached diagnostic thresholds. Median age in patients with SMuRFs was similar to that in patients without SMuRFs (68 vs 69 years). Patients without SMuRFs had a similar rate of PCI to those with SMuRFs, but were significantly less likely to receive a statin, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), or beta-blocker at discharge. By 30 days after presentation, all-cause mortality was significantly higher in patients without SMuRFs (HR 1.47, 95% CI 1.37–1.57; p<0.0001). The increased mortality remained significant after adjustment for age, sex, left ventricular ejection fraction, creatinine, and BP, but was attenuated after inclusion of pharmacotherapy prescription (ACE inhibitor/ARB, beta-blocker, or statin) at discharge.

Comment: It is not infrequent to see patients with ACS/MI who have no traditional risk factors for coronary artery disease, and this study showed this was the case in 15% of Swedish patients who presented with STEMI. It showed a significant increase in mortality at 30 days and up to 12 years post ACS in these patients, especially in women, but this increased risk was attenuated when adjusted for use of guideline-based ACS therapy, which was underused in these patients. This underscores the importance of using evidence-based guideline-recommended treatment post ACS in all patients irrespective of their gender and risk factor profile at presentation.

Reference: Lancet 2021;397(10279):1085-94

Abstract



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

Applicability of US Food and Drug Administration labeling for dapagliflozin to patients with heart failure with reduced ejection fraction in US clinical practice

Authors: Vaduganathan M et al.

Summary: This US cohort study determined the proportion of patients hospitalised with HFrEF who would be candidates for initiation of dapagliflozin treatment based on the FDA label. 154,714 patients with HFrEF who were hospitalised at 406 sites in the Get With the Guidelines-Heart Failure (GWTG-HF) registry in 2014–2019 were included. 81.1% of them were found to be candidates for dapagliflozin according to the FDA label. This proportion was similar across all study years and was higher in patients without versus with type 2 diabetes (85.5% vs 75.6%). Among GWTG-HF participants, the most frequent reason for not meeting FDA label criteria was estimated glomerular filtration rate <30 ml/min/1.73m^2 at discharge.

Comment: The DAPA-HF and EMPEROR-Reduced trials showed that SGLT2 inhibition with dapagliflozin and empagliflozin, respectively, improved outcomes in patients with HF, with a reduction in HF admission and mortality (on meta-analysis) in patients with HFrEF with or without type 2 diabetes. This US study suggests that most patients hospitalised for HF in the US are candidates for this intervention, and it is likely this will also be the case here. Use of these agents has not been incorporated in the Australian HF guidelines yet but has been recommended by our US and European colleagues. Dapagliflozin has been approved by the TGA for this indication but not subsidised by the PBS yet, but is available through a patient familiarisation programme. Empagliflozin is working its way through the regulatory process, and hopefully these agents will become more widely available for treating patients with HFrEF given the strength of the results of clinical trials.

Reference: JAMA Cardiol 2021;6(3):267-75
Abstract

Empagliflozin in patients with heart failure, reduced ejection fraction, and volume overload

Authors: Packer M et al., for the EMPEROR-Reduced Trial Committees and Investigators

Summary: This analysis of the EMPEROR-Reduced trial evaluated the effects of the SGLT2 inhibitor empagliflozin on symptoms, health status, and major outcomes in HF patients with and without recent volume overload. The EMPEROR-Reduced trial randomised 3730 patients with HFrEF (with or without diabetes) to receive empagliflozin or placebo; approximately 40% of patients had volume overload in the 4 weeks before study enrolment. Compared with placebo, empagliflozin reduced the composite risk of cardiovascular death or hospitalisation for HF, decreased total HF hospitalisations, and improved health status and functional class. The magnitude of these benefits in patients with recent volume overload was no greater than that in patients without recent volume overload.

Comment: Sceptics suggest that the benefits of SGLT2 inhibitors in HFrEF are solely due to the mild diuretic effect of these agents by promoting natriuresis in patients with and without type 2 diabetes. This analysis suggests that this is not the case and that markers of volume status were not consistently affected by these agents. The beneficial effects are more likely to be due to the inhibition of the intracellular Na^+/H^+ exchanger with an alteration in mitochondrial energy production, and changing the myocardial and renal fuel substrate, particularly in diabetic patients. Ongoing studies are trying to clarify this, but there are emerging data showing that empagliflozin improves left ventricular remodelling and reduces pulmonary artery pressure in patients with HFrEF independent of diuretic use, supporting these hypotheses.

Reference: J Am Coll Cardiol 2021;77(11):1381-92
Abstract

Effect of marine omega-3 fatty acid and vitamin D supplementation on incident atrial fibrillation

Authors: Albert CM et al.

Summary: This randomised clinical trial in the US investigated the effects of long-term administration of marine omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) and vitamin D on incident AF. 25,119 adults aged ≥50 years without prior CVD, cancer, or AF were randomised to receive EPA-DHA (460 mg/day and 380 mg/day) and vitamin D3 (2000 IU/day); EPA-DHA and placebo; vitamin D3 and placebo; or 2 placebos. During a median 5.3 years of treatment and follow-up, the primary end-point of incident AF occurred in 3.6% of the study population; no significant between-group differences were reported.

Comment: The two largest trials of fish oil in prevention of CVD (REDUCE IT and STRENGTH) both showed an increase in incidence of AF in participants compared with placebo, but only REDUCE IT showed a benefit in reduction of cardiovascular events using icosapent ethyl. This large study looked at the relationship between fish oil and vitamin D and AF in patients with no history of ASCVD or AF and found that there was no effect on the incidence of AF with either intervention. This suggests the increase in AF in the other studies may well have been due to an interaction between fish oil and the underlying CVD in the populations studied, as most if not all patients in REDUCE IT and STRENGTH had to have CVD to be enrolled. This being the case, and the fact that icosapent ethyl is not available here, there is no evidence to support the use of fish oil for secondary prevention in Australia at the present time.

Reference: JAMA 2021;325(11):1061-73
Abstract

Association of socioeconomic status with risk factor target achievements and use of secondary prevention after myocardial infarction

Authors: Ohm J et al.

Summary: This study investigated whether socioeconomic status affects risk factor target achievements and risk-modifying activities during the first year after MI. 30,191 one-year survivors of first-ever MI aged 18–76 years who were residing in the general community in Sweden were included. Overall, higher socioeconomic status was associated with better target achievements and use of most secondary prevention. The highest (vs lowest) income quintile was associated with achieved smoking cessation (odds ratio [OR], 2.05), target BP levels (OR, 1.17), target glycated haemoglobin levels (OR, 1.57), participation in physical training programmes (OR, 2.28) and cardiac rehabilitation educational sessions (OR, 2.29). The highest (vs lowest) income quintile was also associated with more monitoring of lipid profiles (OR, 1.20) and intensification of statin therapy (OR, 1.22) during the first year after MI.

Comment: Psychiatric illness and low socioeconomic status have been shown to increase the risk of initial and recurrent CVD compared to patients with higher status. This is commonly seen in clinical practice here, and it appears also to be the case in Sweden. Both countries have good public health systems and access to subsidised medications, so the difference in outcomes probably reflects other factors commonly seen in lower socioeconomic populations, namely poor education, poor health literacy, and higher rates of obesity, smoking and alcohol intake and less active lifestyles, as well as less compliance with medication. Frequent and regular contact with allied health professionals post discharge from hospital can help in all these respects but this intervention is costly and unable to be implemented in most health systems.

Reference: JAMA Netw Open 2021;4(3):e211129
Abstract

Prognostic significance of suboptimal secondary prevention pharmacotherapy after acute coronary syndromes

Authors: Yudi MB et al., on behalf of the Melbourne Interventional Group

Summary: This Australian study evaluated the prognostic significance of suboptimal pharmacotherapy in ACS survivors. 9375 consecutive ACS patients from the Melbourne Interventional Group registry who were alive 30 days after their index PCI were divided into 3 categories based on the number of secondary prevention medications prescribed. The optimal medical therapy (OMT), near-optimal medical therapy (NMT), and suboptimal medical therapy (SMT) groups were prescribed 5, 4 and ≤3 medications, respectively. 60.6% of patients received OMT, 31.0% received NMT and 8.5% received SMT. Patients receiving SMT were older, more likely to be female and had a higher burden of comorbidities. Long-term mortality during follow-up (median 3.9 years) was lower in the OMT group than in the NMT and SMT groups (8.2% vs 10.5% and 16.5%, respectively; p<0.001).

Comment: This Australian study reinforces the importance of using as many evidence-based therapies as possible post ACS, as it showed that suboptimal medical therapy was associated with an increased mortality over time. Paradoxically, it still appears that the highest risk patients and women are more likely to receive suboptimal treatment, which we documented in the ACACIA study more than 10 years ago. It is imperative that we address this long-standing issue and try to get all our ACS patients on as many guideline-directed therapies as possible to improve outcomes, and examine why there still continues to be gender differences in ACS treatment.

Reference: Intern Med J 2021;51(3):366-74
Abstract

Antihypertensives and statin therapy for primary stroke prevention

Authors: Bosch J et al., for the HOPE-3 Investigators

Summary: The HOPE-3 trial reported the benefits of antihypertensive therapy combined with a statin for prevention of a first stroke in patients at intermediate cardiovascular risk. This secondary analysis of the trial evaluated outcomes according to stroke subtype. 12,705 patients from 21 countries with vascular risk factors but without overt CVD were randomised in a 2-by-2 factorial design to receive candesartan 16 mg/day + hydrochlorothiazide 12.5 mg/day or candesartan + placebo, as well as rosuvastatin 10 mg/day or placebo. Baseline BP (138/82mm Hg) was reduced by 6.0/3.0mm Hg and low-density lipoprotein (LDL) cholesterol (3.3 mmol/L) was reduced by 0.90 mmol/L on active treatment. During 5.6 years of follow-up, 169 strokes occurred. BP lowering did not significantly reduce total stroke, ischaemic stroke, or haemorrhagic stroke, but rosuvastatin significantly reduced total stroke (HR, 0.70; 95% CI 0.52–0.95), mainly due to reductions in ischaemic stroke (HR, 0.53; 95% CI 0.37–0.78). The combination of both interventions significantly reduced total stroke (HR, 0.56; 95% CI 0.36–0.87) and ischaemic stroke (HR, 0.41; 95% CI 0.23–0.72) compared with double placebo.

Comment: This interesting analysis of the HOPE-3 trial surprisingly showed that in normotensive patients with normal lipids, a small reduction in BP (–6/3mm Hg) did not reduce stroke risk, but that lowering lipids did (–0.9 mmol/L). Lowering both BP and lipids was associated with the best stroke reduction (44%), driven mainly by LDL reduction. This challenges the commonly held belief that stroke is more related to BP than lipids and suggests that lipid lowering should be an integral component of strategies to reduce stroke, both for primary and secondary prevention.

Reference: Stroke 2021; published online May 14
Abstract

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM)

Authors: Koo B-K et al.

Summary: The HOST-EXAM trial compared the efficacy and safety of aspirin and clopidogrel monotherapy during the chronic maintenance period after coronary stenting. At 37 sites in South Korea, 5438 patients who received dual antiplatelet therapy (DAPT) without clinical events for 6–18 months after PCI with a drug-eluting stent (DES) were randomised to receive monotherapy with either clopidogrel 75mg once daily or aspirin 100mg once daily for a further 24 months. The primary end-point was a composite of all-cause death, non-fatal MI, stroke, readmission for ACS, and Bleeding Academic Research Consortium (BARC) bleeding type 3 or greater. During follow-up, the primary outcome occurred in 152 (5.7%) patients in the clopidogrel group and 207 (7.7%) in the aspirin group (HR 0.73, 95% CI 0.59–0.90; p=0.0035).

Comment: It is standard practice for patients to receive at least 12 months of DAPT after ACS with or without PCI, or after elective PCI with DES. When the decision is made to revert to monotherapy, in most cases clopidogrel is stopped and aspirin is continued, unless there is a specific indication to continue clopidogrel. This study should make us re-evaluate this strategy as long-term outcomes were better with ongoing clopidogrel compared with aspirin as monotherapy. This is not surprising as the CHARISMA study demonstrated the superiority of clopidogrel over aspirin in patients with ASCVD more than 20 years ago. Unfortunately, the PBS criteria for reimbursement of clopidogrel in Australia do not reflect this, but now that clopidogrel is off patent there should be a push to allow us to use it for long-term maintenance antiplatelet therapy to improve outcomes.

Reference: Lancet 2021; published online May 16
Abstract

Total ischemic event reduction with rivaroxaban after peripheral arterial revascularization in the VOYAGER PAD trial

Authors: Bauersachs RM et al., for the VOYAGER PAD Committees and Investigators

Summary: The VOYAGER PAD trial evaluated the effects of low-dose rivaroxaban on vascular events after lower extremity revascularisation in patients with peripheral artery disease (PAD). 6564 patients were randomised to receive rivaroxaban 2.5mg twice daily + aspirin, or aspirin alone for a median 2.5 years. The primary end-point was first event of acute limb ischaemia, major amputation of a vascular cause, MI, ischaemic stroke, or cardiovascular death. This analysis of the trial considered all events (first and subsequent) of the primary end-point as well as additional vascular events including peripheral revascularisation and venous thromboembolism. During follow-up, rivaroxaban + aspirin reduced total primary end-point events (HR 0.86, 95% CI 0.75–0.98; p=0.02) and total vascular events (HR 0.86, 95% CI 0.79–0.95; p=0.003) compared with aspirin alone.

Comment: The COMPASS trial showed that low-dose rivaroxaban 2.5mg twice daily with low-dose aspirin (100mg) reduced cardiovascular events and mortality in patients with ASCVD, and major adverse limb events (MALE) such as revascularisation and amputation in patients with PAD. The VOYAGER study showed that this strategy reduced the first event of acute limb ischaemia, major amputation of a vascular cause, MI, ischaemic stroke, or cardiovascular death in patients undergoing revascularisation for PAD. This subsequent analysis showed that as well as reducing the first event, subsequent events were also reduced, driven mainly by a reduction in repeat revascularisation, but there was also a reduction in major adverse cardiovascular events. This being the case we should strongly consider using this strategy in all patients with PAD, as there are no other medical therapies that have been shown to reduce MALE in this population.

Reference: J Am Coll Cardiol 2021; published online May 7
Abstract

Left atrial appendage occlusion during cardiac surgery to prevent stroke

Authors: Whitlock RP et al., for the LAAOS III Investigators

Summary: This study in Canada investigated the use of left atrial appendage (LAA) occlusion during cardiac surgery to prevent stroke in patients with AF. 4770 patients with AF and a CHA_2DS_2-VASc score of ≥2 who were scheduled to undergo cardiac surgery for another indication were randomly assigned to undergo or not undergo occlusion of the LAA during surgery. All patients were expected to receive usual care, including oral anticoagulation, during a mean 3.8 years of follow-up. Stroke or systemic embolism occurred in 4.8% of patients in the occlusion group and 7.0% in the no-occlusion group during follow-up (HR 0.67, 95% CI 0.53–0.85; p=0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between groups.

Comment: Percutaneous occlusion of the LAA has been shown to provide stroke protection in patients with AF who are unable to take anticoagulants due to a prior history of intracerebral haemorrhage or bleeding into critical organs. The initial studies were done in patients who were able to take oral anticoagulants, but in Australia and the US LAA occlusion is predominantly performed in AF patients at risk of stroke who can't take oral anticoagulants. This study showed that occlusion of the LAA during thoracotomy for coronary artery graft surgery and or valve replacement in patients with AF and an indication for oral anticoagulants reduced the risk of stroke significantly over 3.8 years, despite fewer patients in the LAA occlusion group being on oral anticoagulants at the end of the study. This was more pronounced after the initial surgery, and the benefit increased over time. It is essential that the surgical technique must ensure complete occlusion or amputation of the LAA, as even a small residual pocket could act as a substrate for thrombus formation and subsequent stroke. At present it is recommended that oral anticoagulation continue after surgical occlusion of the LAA if the CHA_2DS_2-VASc score justifies it, but given the low rates of stroke and bleeding with surgical closure this advice will probably change over time.

Reference: N Engl J Med 2021; published online May 15
Abstract

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