Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ASCVD = atherosclerotic cardiovascular disease; **CKD** = chronic kidney disease; **ECG** = electrocardiogram; **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; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **SGLT2** = sodium-glucose co-transporter 2.

Welcome to the latest issue of Cardiology Research Review.

In this issue, Mayo Clinic investigators report that smartwatch ECGs acquired in nonclinical environments can be useful for identifying patients with cardiac dysfunction, pre-specified analyses of the DELIVER and EMPEROR-Preserved trials support the use of SGLT2 inhibitors across the full spectrum of ejection fraction in patients with heart failure, and a reanalysis of mortality data from the FOURIER trial ignites debate.

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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Prospective evaluation of smartwatch-enabled detection of left ventricular dysfunction

Authors: Attia ZI et al.

Summary: This prospective Mayo Clinic study investigated the use of a smartwatch to detect LV dysfunction. Patients were invited by email to download a Mayo Clinic iPhone application that sends smartwatch ECGs to a secure data platform; 2454 patients (mean age 53 years, 56% female) from 46 US states and 11 countries sent a total of 125,610 ECGs to the data platform between Aug 2021 and Feb 2022. 421 participants had at least one watch-classified sinus rhythm ECG within 30 days of an echocardiogram, of whom 16 (3.8%) had LVEF ≤40%. The artificial intelligence (AI) algorithm detected patients with low ejection fraction with an area under the curve of 0.885 (95% CI 0.823–0.946).

Comment: The role of AI in cardiology is rapidly expanding. There are published data concerning its role in diagnosis and management of aortic stenosis and pulmonary hypertension, and now it seems that there is the ability to diagnose LV dysfunction with a high degree of certainty by analysis of an ECG rhythm strip acquired from a watch linked to a smartphone. If this proves to be the case in larger validation studies, early detection of LV dysfunction in high-risk individuals, such as patients with type 2 diabetes, would allow early intervention and treatment, which could improve outcomes.

Reference: Nat Med 2022;28:2497-2503
Abstract

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Dapagliflozin in heart failure with improved ejection fraction: A prespecified analysis of the DELIVER trial

Authors: Vardeny O et al.

Summary: The DELIVER trial evaluated the efficacy of dapagliflozin in patients with symptomatic HF and mildly reduced or preserved LVEF. Patients were randomised to receive dapagliflozin 10mg or placebo daily and the primary outcome was a composite of cardiovascular death or worsening HF. This prespecified analysis investigated the efficacy of dapagliflozin in a subgroup of patients with HF with improved ejection fraction (HFimpEF; ejection fraction improved from ≤40% to >40%). 1151 of 6263 (18%) DELIVER participants had HFimpEF. Event rates in these patients were similar to those in patients with ejection fraction consistently greater than 40%.

Comment: In some patients who present with HFrEF, medical treatment results in an improvement or normalisation of LV function over time, but even if the LV function returns to normal it is recommended that guideline-directed medical therapy be continued as it is likely that LV function will deteriorate with treatment cessation. Patients with HFrEF that improve have usually been excluded from HFpEF studies, but they were included in the DELIVER trial of dapagliflozin versus placebo in patients with HF and ejection fraction >40%. The benefits in these patients whose LV function had been <40% was of the same magnitude as seen in those with HFpEF whose EF had always been above 40%. Taken together with the results of the DAPA-HF trial in patients with HFrEF, this indicates that dapagliflozin improves outcomes in patients with HFpEF and HFrEF independent of the ejection fraction.

Reference: Nat Med 2022;28:2504-11
Abstract

Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction: A pre-specified analysis of EMPEROR-Preserved

Authors: Anker SD et al.

Summary: The EMPEROR-Preserved trial reported that the SGLT2 inhibitor empagliflozin significantly reduced the risk of cardiovascular death or hospitalisation for heart failure in patients with HFpEF. This pre-specified analysis of the EMPEROR-Preserved trial investigated the effects of empagliflozin in patients with preserved LVEF (≥50%) or mid-range LVEF (41–49%). Empagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure (primary end-point) by 17% compared with placebo in patients with LVEF ≥50% (HR 0.83, 95% CI 0.71–0.98; p=0.024) and by 29% compared with placebo in patients with LVEF 41–49% (HR 0.71, 95% CI 0.57–0.88; p=0.002).

Comment: Although the EMPEROR-Preserved trial did not include patients with HFpEF with recovered ejection fraction, there was significant benefit of adding empagliflozin to standard therapy in patients with HFpEF whose ejection fraction was >40%. The magnitude of benefit was a little greater in patients with LVEF 40–49% compared with those whose LVEF was >50% but the p value for heterogeneity was not significant indicating no real difference in treatment effect. As with dapagliflozin, we can now confidently say that empagliflozin improves the outcome of patients with HF independent of LV function.

Reference: Nat Med 2022;28:2512-20
Abstract

Trends and real-world safety of patients undergoing percutaneous coronary intervention for symptomatic stable ischaemic heart disease in Australia

Authors: Hamilton GW et al., on behalf of the Melbourne Interventional Group (MIG) Registry

Summary: This registry study investigated the impact of PCI in patients with stable ischaemic heart disease (SIHD) refractory to medical therapy. Outcomes for 9421 consecutive patients undergoing PCI for SIHD in 2005–2018 were reviewed. Over the 14-year period, major bleeding rates after PCI decreased from 1.05% in 2005/06 to 0.29% in 2017/18 (p_{trend} <0.001), and other in-hospital and 30-day event rates remained low. Seven (0.07%) in-hospital deaths occurred, and five-year mortality was 10.3%. A subanalysis that compared proximal left anterior descending artery (prox-LAD) PCI to other-than-proximal LAD (non-LAD) PCI found no significant differences in outcomes.

Comment: These data from the MIG registry are reassuring as they show that over a 14-year period in Victorian Hospitals there was maintenance of procedural success and safety with lower rates of bleeding over time, despite increasing acuity of the patients undergoing PCI for SIHD symptoms. It is interesting that those with prox-LAD disease did no better or worse than those with non-LAD disease and that the major predictors of five-year mortality were non-cardiac comorbidities such as CKD and chronic obstructive pulmonary disease, as well as severe LV dysfunction.

Reference: Heart Lung Circ 2022;31(12):1619-29
Abstract

Comparative effects of low-dose rosuvastatin, placebo, and dietary supplements on lipids and inflammatory biomarkers

Authors: Laffin LJ et al.

Summary: This single-centre prospective trial investigated the effects of low-dose rosuvastatin compared with placebo and six common dietary supplements on low-density lipoprotein (LDL) cholesterol levels. 190 adults with LDL cholesterol 70–189 mg/dl and an increased 10-year risk of ASCVD were randomised to rosuvastatin 5 mg/day, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice extract for four weeks. The primary end-point was the percent change in LDL cholesterol level from baseline to day 28. Treatment with rosuvastatin significantly decreased LDL cholesterol levels compared with placebo (–35.2%; p<0.001) and all six supplements (p<0.001). None of the dietary supplements decreased LDL cholesterol levels compared with placebo.

Comment: Many patients have perceived or real statin intolerance and thus turn to "natural" therapies to reduce lipid levels in the hope this will improve outcomes. This study is interesting for two reasons, namely that there was a 35% reduction in LDL with a very small dose of rosuvastatin, and that none of the supplements, including red yeast rice extract, produced any meaningful reduction in LDL. Statin-intolerant patients may be able to cope with such a small dose of rosuvastatin, particularly if taken at night, and get a significant reduction in LDL, although perhaps not to target levels, but dietary supplements would seem to have no effect. Some of these patients may be candidates for PCSK9 inhibitors but criteria for reimbursement are still strict due to cost.

Reference: J Am Coll Cardiol 2023;81(1):1-12
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.

Restoring mortality data in the FOURIER cardiovascular outcomes trial of evolocumab in patients with cardiovascular disease: A reanalysis based on regulatory data

Authors: Erviti J et al.

Summary: The placebo-controlled FOURIER trial demonstrated the benefits of the PCSK9 inhibitor evolocumab on cardiovascular outcomes in patients with cardiovascular disease. However, there were inconsistencies between the information in the Clinical Study Report (CSR) and that in the 2017 primary trial results publication. This study reanalysed mortality data from the FOURIER trial, based on the information contained in the death narratives in the CSR. For 360 out of 870 (41.4%) deaths, the cause of death adjudicated by the FOURIER clinical events committee differed from that declared by the local clinical investigator. Deaths of cardiac origin were numerically higher in the evolocumab group than in the placebo group, suggesting possible cardiac harm.

Comment: This provocative article received a lot of attention after publication, as it accused the management committee of the FOURIER study of misrepresenting and misreporting the results particularly with respect to cardiovascular mortality and called for a reanalysis of the results. Unfortunately, the response from the senior management committee of the trial did not attract the same attention. I must confess to a conflict of interest as I was the Australian National Lead Investigator with Prof. Anthony Keech, but we are both confident of the integrity of the trial and the accuracy of the results. This analysis did not have access to the information required to make an evaluation as the cause of an event and given it is a post hoc analysis, little credence can be given to its conclusions. They were also under the impression that the trial was stopped early, which is not the case, as it was stopped when the prespecified number of trial end-points was attained. The FOURIER study was conducted according to the established protocols for randomised controlled trials and had an experienced, blinded end-point committee adjudicating events, which is not the case with the analysis leading to this flawed paper. The US Food and Drug Administration, European Medicines Agency, and Therapeutic Goods Administration have not raised concerns on the basis of this data, and physicians should feel confident to continue to prescribe PCSK9 inhibitors to eligible patients to improve outcomes.

Reference: BMJ Open 2022;12(12):e060172
Abstract

Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease

Authors: O'Donoghue ML et al., for the OCEAN(a)-DOSE Trial Investigators

Summary: This randomised controlled trial investigated the effects of olpasiran (a small interfering RNA; siRNA) on lipoprotein(a) (Lp[a]) levels in patients with ASCVD. 281 patients with established ASCVD and Lp(a) concentrations >150 nmol/L were randomised to receive one of four subcutaneous doses of olpasiran (10mg every 12 weeks, 75mg every 12 weeks, 225mg every 12 weeks, or 225mg every 24 weeks) or matching placebo. The primary end-point was the percentage change in Lp(a) concentration from baseline to week 36. At baseline, 88% of patients were also taking a statin, 52% were taking ezetimibe, and 23% were taking a PCSK9 inhibitor. At 36 weeks, the Lp(a) concentration had increased by a mean 3.6% in the placebo group, whereas significant and dose-dependent decreases were seen with olpasiran therapy. Placebo-adjusted mean percent changes were –70.5%, –97.4%, –101.1%, and –100.5% with olpasiran 10mg every 12 weeks, 75mg every 12 weeks, 225mg every 12 weeks, and 225mg every 24 weeks (all p<0.001 vs baseline). The overall incidence of adverse events was similar across trial groups.

Comment: Lp(a) has been recognised as a risk factor for premature cardiovascular disease and aortic stenosis but until recently it was not given much attention as there was no way to reduce its levels. It has been proposed that elevated Lp(a) imparts a residual risk in patients who have ASCVD, particularly in patients whose LDL levels are at target but who continue to have cardiovascular events. Current guidelines recommend that Lp(a) be measured at least once in the general population, as its level is stable over time, and it is elevated in about 20% of Caucasian populations. Both observational studies and Mendelian randomisation have confirmed the strong association between elevated levels and cardiovascular disease, so measurement of Lp(a) is especially important in high-risk individuals. We now have siRNA therapies that target mRNA transcription of Lp(a) specifically in hepatic cells, and this study shows that reductions of >90% can be achieved with little in the way of short-term adverse events. Large randomised controlled trials are underway to determine whether this improves outcomes.

Reference: N Engl J Med 2022;387(20):1855-64
Abstract

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Value of screening for the risk of sudden cardiac death in young competitive athletes

Authors: Sarto P et al.

Summary: This article reported long-term findings from the Italian programme of cardiovascular preparticipation screening (PPS) in young, competitive athletes. The PPS was repeated annually in Italian children aged 7–18 years and included medical history, physical examination, resting ECG, and stress testing. Over an 11-year period, 22,324 children (mean age 12 years, 62% male) underwent a total of 65,397 annual evaluations. 69 (0.3%) children were identified as having cardiovascular disease that placed them at risk of sudden cardiac death, including congenital heart disease, channelopathies, cardiomyopathies, and non-ischaemic LV scar with ventricular arrhythmias. At-risk cardiovascular diseases were identified more frequently in children aged ≥12 years and on repeat evaluation. The estimated cost per diagnosis was €73,312. During 7.5 years of follow up, one child with normal PPS findings had an episode of resuscitated cardiac arrest during sports activity (event rate 0.6/100,000 athletes/year).

Comment: We are all concerned when we see athletes collapse, and even die, on the sporting field, presumably due to unrecognised underlying cardiac disease. To avoid this, prescreening of all school-age children prior to participating in sport has been suggested. This is commonplace in Italy but not in most other countries. This study showed that the yield for finding a potentially life-threatening condition on prescreening was very low (0.3%) and increased slightly with repeat screening and age. When abnormalities were detected it was recommended that there be no participation in sport, and only one child with normal screening had a cardiac arrest. The estimated cost per diagnosis was more than $AU100,000, making the benefit/risk ratio unlikely to be acceptable in an Australian context.

Reference: Eur Heart J 2023; published online Feb 10
Abstract

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Phase 2 trial of baxdrostat for treatment-resistant hypertension

Authors: Freeman MW et al., for the BrigHTN Investigators

Summary: The multicentre phase 2 BrigHTN trial investigated the efficacy of the selective aldosterone synthase inhibitor baxdrostat in patients with treatment-resistant hypertension. 248 patients who were taking stable doses of at least three antihypertensive agents (including a diuretic) were randomised to received placebo or baxdrostat (0.5mg, 1mg, or 2mg) once daily for 12 weeks. The primary end-point was the change in systolic blood pressure (SBP) from baseline to week 12. Dose-dependent changes in SBP of –12.1mm Hg, –17.5mm Hg, and –20.3mm Hg were observed with baxdrostat 0.5mg, 1mg and 2mg, respectively, compared with –9.4mm Hg with placebo. The placebo-adjusted decrease in mean SBP at week 12 was –11.0mm Hg with baxdrostat 2mg (p<0.001) and –8.1mm Hg with baxdrostat 1mg (p=0.003).

Comment: Mineralocorticoid receptor antagonists (MRAs) such as spironolactone are beneficial in the management of resistant hypertension, but are often not tolerated due to oestrogenic side effects such as gynaecomastia or due to hyperkalaemia. This interesting new agent blocks aldosterone at a different level by inhibiting aldosterone synthesis at an enzymatic level. This study shows that it lowers BP quite effectively, and it did not have the same side effect profile as the MRAs. Further study needs to be done in management of hypertension but also in heart failure where MRAs have also been shown to be effective.

Reference: N Engl J Med 2023;388(5):395-405
Abstract

Major cardiovascular events and subsequent risk of kidney failure with replacement therapy: A CKD Prognosis Consortium study

Authors: Mark PB et al.

Summary: This analysis of the CKD Prognosis Consortium determined the impact of cardiovascular disease on future risk of kidney failure requiring replacement therapy (KFRT). 25,903,761 individuals (mean 53 years) from the CKD Prognosis Consortium with known baseline estimated glomerular filtration rate (eGFR) were included. 15% of participants had diabetes and 8.4% had urinary albumin-to-creatinine ratio available (median 13 mg/g); 9.5% had prevalent coronary heart disease (CHD), 3.2% had prior stroke, 3.3% had HF, and 4.4% had prior atrial fibrillation (AF); mean eGFR was 89 ml/min/1.73m^2. During follow-up, both prevalent and incident cardiovascular disease were associated with subsequent KFRT. After adjustment for potential confounders, HRs for KFRT were 3.1 (95% CI 2.9–3.3) for incident CHD, 2.0 (95% CI 1.9–2.1) for incident stroke, 4.5 (95% CI 4.2–4.9) for incident HF, and 2.8 (95% CI 2.7–3.1) for incident AF. HRs were highest in the first 3 months after the cardiovascular event and declined to baseline levels after 3 years. Incident HF hospitalisations had the strongest association with KFRT within 3 months (HR 46, 95% CI 43–50) after adjustment for other cardiovascular disease subtypes.

Comment: This study of a huge number of patients with CKD (>25,000,000) looked at the impact of cardiovascular disease on progression of CKD. They found that HF, CHD, AF and stroke all increased the need for renal replacement therapy, especially in the first 3 months after a cardiovascular event. This being the case we should have a lower threshold for seeking renal input when patients with CKD are admitted under cardiology with an acute event, to try to decrease the chances of deterioration in renal function.

Reference: Eur Heart J 2023; published online Jan 24
Abstract

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