Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **ASCVD** = atherosclerotic cardiovascular disease; **GLP-1** = glucagon-like peptide-1; **HF** = heart failure; **HFpEF** = HF with preserved ejection fraction; **HFrEF** = HF with reduced ejection fraction; **HR** = hazard ratio; **MI** = myocardial infarction; **SGLT2** = sodium-glucose cotransporter 2; **STEMI** = ST-elevation MI; **TAVI** = transcatheter aortic valve implantation; **T2D** = type 2 diabetes.

Welcome to the latest issue of Cardiology Research Review.

In this issue, the AEGIS-II investigators find that human apolipoprotein A1 infusions do not improve patient outcomes after acute MI and are unlikely to be investigated further, the ALIGN-AR trial reports the potential of a dedicated transcatheter heart valve in high-risk patients with moderate to severe native aortic regurgitation, and a population-based cohort study shows that GLP-1 agonists and SGLT2 inhibitors have additive benefits in patients with type 2 diabetes.

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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Apolipoprotein A1 infusions and cardiovascular outcomes after acute myocardial infarction

Authors: Gibson CM et al., for the AEGIS-II Committees and Investigators

Summary: This study investigated whether human apolipoprotein A1 (CSL112) infusions reduce the risk of recurrent cardiovascular events after acute MI. 18,219 patients with acute MI, multivessel coronary artery disease, and other cardiovascular risk factors were randomised to receive weekly infusions of either CSL112 (6g) or matching placebo for 4 weeks, with the first infusion administered within 5 days after acute MI. The primary end-point (a composite of MI, stroke, or death from cardiovascular causes) did not differ significantly between groups at 90 days (HR 0.93, 95% CI 0.81–1.05), 180 days (HR 0.91, 95% CI 0.81–1.01) or 365 days of follow up (HR 0.93, 95% CI 0.85–1.02).

Comment: Observational studies have shown that low HDL is associated with an increase in cardiovascular events and high HDL is protective. Studies using cholesterylester transfer protein (CETP) inhibitors to increase HDL have been disappointing with no benefit in patients with ASCVD and one was harmful (torcetrapib). This study looked at taking a different method of modulating HDL by using an infusion of human apolipoprotein A1 to increase HDL efflux after ACS, which theoretically should be a more physiological approach, but no benefit could be demonstrated even though efflux increased. It therefore seems that HDL is not a therapeutic target in patients with ASCVD, and I'd be surprised if further studies are conducted in this area.

Reference: N Engl J Med. 2024;390(17):1560–71
Abstract

Cardiology Research Review™

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.

Transcatheter aortic valve implantation in patients with high-risk symptomatic native aortic regurgitation (ALIGN-AR)

Authors: Vahl TP et al.

Summary: The ALIGN-AR trial investigated the use of transfemoral TAVI in patients with high-risk symptomatic native aortic regurgitation. At 20 US sites, 180 patients (mean age 75.5 years, 53% male) with symptomatic moderate-to-severe or severe aortic regurgitation who were considered to be at high risk for mortality and complications after surgical aortic valve replacement received the Trilogy transcatheter heart valve. Technical success was achieved in 95% of patients. Overall, 27% of patients had safety events, with new pacemaker implantation needed in 24% of patients. In the first 30 days, four patients died, two had disabling strokes, and two had non-disabling strokes. Fourteen patients (7.8%) died during 1 year of follow-up.

Comment: At present TAVI is reserved for patients with severe symptomatic aortic stenosis, and for patients with bioprosthetic valve failure, whether the valve is stenotic or regurgitant. Surgery is the only option for severe native valve regurgitation, but many patients are deemed not suitable due to age and/or comorbidities. This study looked at a new valve which can be used in native valve aortic regurgitation and showed promising procedural success and adverse event rates. Further work will need to be done but this is an area with a large treatment gap that needs to be addressed.

Reference: Lancet 2024;403(10435):P1451–9
Abstract

Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events

Authors: Simms-Williams N et al.

Summary: This population-based cohort study investigated the effects of combined use of GLP-1 receptor agonists and SGLT2 inhibitors on major adverse cardiovascular events (MACE) and serious renal events in patients with type 2 diabetes, compared with either drug class alone. Using data extracted from the UK Clinical Practice Research Datalink (2013–2020), two new-user cohorts were assembled, with follow-up through Mar 2021. Patients in the first cohort started on GLP-1 receptor agonists and added SGLT2 inhibitors (n=6696), and patients in the second cohort started on SGLT2 inhibitors and added GLP-1 agonists (n=8942). Combination users were matched 1:1 to patients prescribed the same background drug. Cox proportional hazards models showed that the SGLT2 inhibitor + GLP-1 agonist combination was associated with a 30% lower risk of MACE (HR 0.70, 95% CI 0.49–0.99) and a 57% lower risk of serious renal events (HR 0.43, 95% CI 0.23–0.80) than GLP-1 agonists alone. In addition, the GLP-1 agonist + SGLT2 inhibitor combination was associated with a 29% lower risk of MACE (HR 0.71, 95% CI 0.52–0.98) and a nonsignificant 33% decrease in serious renal events (HR 0.67, 95% CI 0.32–1.41) compared with SGLT2 inhibitors alone.

Comment: SGLT2 inhibitors and GLP-1 agonists have both been shown to improve outcomes in patients with T2D, as well as having salutatory effects in patients with and without diabetes with HF (SGLT2s) and in obese patients with ASCVD without diabetes (semaglutide). This study shows that there are additive beneficial effects when using the two agents together in patients with T2D, although the PBS does not subsidise this combination for patients with T2D without HF. However, if HF is present (HFrEF or HFpEF), an SGLT2 inhibitor can be prescribed for a HF indication and a GLP-1 agonist can be used for treatment of T2D if appropriate.

Reference: BMJ 2024;385:e078242
Abstract

Cardiovascular effects of oral ketone ester treatment in patients with heart failure with reduced ejection fraction

Authors: Berg-Hansen K et al.

Summary: This randomised, double-blind, crossover study investigated whether oral ketone ester treatment improves resting and exercise haemodynamics and exercise capacity in patients with HFrEF. Twenty-four nondiabetic patients (mean age 65 years, 71% male) with HFrEF received 14-day regimens of either oral ketone ester or an isocaloric non-ketone ester comparator, separated by a 14-day washout period. Each treatment was administered in four daily doses. The primary end-point was resting cardiac output (CO). Resting CO at trough levels was higher during ketone ester administration compared with the isocaloric comparator (5.2 vs 5.0 L/min), and pulmonary capillary wedge pressure was lower (8 vs 11mm Hg). These changes were amplified after ketone ester dosing. Across all exercise intensities, ketone ester treatment was associated with lower mean exercise pulmonary capillary wedge pressure and higher mean CO.

Comment: One of the postulated mechanisms by which SGLT2 inhibitors improve outcomes in patients with T2D with and without HF, is that these agents induce a mild ketotic state which favours production of 3-hydroxybutyrate which is then used as a more effective energy source by myocardial tissue. This study supports this hypothesis, as it showed that administration of ketone ester improved myocardial performance with higher CO at rest and lower filling pressures, cardiac volumes, and N-terminal pro-B-type natriuretic peptide levels compared with an isocaloric comparator in patients with HF and without T2D. This mechanism is likely to be even more relevant in patients with T2D treated with SGLT2s, and it would be interesting to see if these results could be replicated in non-diabetic patients who were taking an SGLT2 for HF.

Reference: Circulation 2024;149(19):1474–89
Abstract

Impact of statin adherence and interruption within 6 months after ST-segment elevation myocardial infarction (STEMI): Results from the real-world regional registry FAST-STEMI

Authors: Giacobbe F et al.

Summary: This real-world study investigated the impact of statin adherence versus interruption (poor adherence or discontinuation) within 6 months after STEMI. A total of 6043 STEMI patients enrolled in the FAST STEMI registry were followed up for a mean 4.7 years; adherence to statin therapy was assessed using pharmacy registries. Overall, 7.2% of patients interrupted statin therapy within 6 months after STEMI, whereas 58.1% had optimal (>80%) adherence. Optimal statin adherence was found to be protective against cardiovascular mortality (adjusted HR [aHR] 0.025, 95% CI 0.008–0.079; p<0.001), all-cause mortality (aHR 0.032, 95% CI 0.018–0.059; p<0.001), and ischaemic stroke (p=0.001) at 1 year. Statin discontinuation within 6 months after STEMI was associated with an increase in both cardiovascular (aHR 2.23, 95% CI 1.37–3.65; p=0.001) and all-cause mortality (aHR 2.32, 95% CI 1.73–3.11; p<0.001) at 1 year.

Comment: High-dose statin therapy is guideline recommended treatment in patients who have ACS (STEMI or NSTEMI). Patients are generally discharged on high-dose statin, in addition to other guideline-directed medical therapy, but this study and Australian data show that adherence to statin treatment wanes as time goes on and that this has implications with an increase in stroke and mortality at 12 months in patients who are non-adherent 6 months after their event. This poor adherence may be due to a combination of adverse drug effects, cost of medication and tablet burden, but it is essential that patients be followed up after an ACS and the importance of adherence emphasised to both the patient and their treating physician.

Reference: Int J Cardiol. 2024;405:131933
Abstract

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

Transcatheter or surgical treatment of aortic-valve stenosis

Authors: Blankenberg S et al., for the DEDICATE-DZHK6 Trial Investigators

Summary: This German study investigated whether low-risk patients with severe, symptomatic aortic stenosis (AS) should undergo TAVI or surgical aortic valve replacement (SAVR). 1414 patients (mean age 74 years, 57% male) with severe AS who were at low or intermediate surgical risk were randomised to TAVI or SAVR; the primary outcome was a composite of all-cause mortality or stroke at 1 year. The Kaplan–Meier estimate of the primary outcome at 1 year was 5.4% in the TAVI group and 10.0% in the SAVR group (HR 0.53, 95% CI 0.35–0.79; p<0.001 for non-inferiority). The incidence of all-cause mortality was 2.6% in the TAVI group and 6.2% in the SAVR group (HR 0.43, 95% CI 0.24–0.73), and the incidence of stroke was 2.9% and 4.7% in the respective groups (HR 0.61, 95% CI 0.35–1.06).

Comment: TAVI has generally been reserved for patients with symptomatic severe AS who are deemed too high risk or unsuitable for surgery, but there are many patients who are at low-intermediate surgical risk who would prefer a percutaneous procedure rather than open heart surgery. This paper shows that TAVI was non-inferior to SAVR in this type of patient, with death, MI and stroke all in favour of TAVI at 1 year. Given the shorter hospital stay and quicker recovery with TAVI, it is likely that this will become the procedure of choice in most cases of symptomatic AS, especially those who would be candidates for a bioprosthetic surgical valve.

Reference: N Engl J Med. 2024;390:1572–83
Abstract

Empagliflozin after acute myocardial infarction

Authors: Butler J et al.

Summary: This study investigated the safety and efficacy of empagliflozin in patients with acute MI. 6522 patients who had been hospitalised for acute MI and were at risk for HF were randomised 1:1 to receive empagliflozin 10 mg/day or placebo in addition to standard care within 14 days after admission. During a median follow-up of 17.9 months, the primary end-point (first hospitalisation for HF, or death from any cause) occurred in 8.2% of patients in the empagliflozin group and 9.1% in the placebo group (HR 0.90, 95% CI 0.76–1.06; p=ns). Adverse events were similar in each group and were consistent with the known safety profile of empagliflozin.

Comment: This study that looked at prevention of HF in patients at high risk for HF post MI failed to show superiority over placebo for the primary end-point of all-cause mortality and first hospitalisation for HF, but a prespecified analysis did demonstrate a significant reduction in first admission for HF. Adverse events were low in patients who received empagliflozin, with no adverse safety signals. Empagliflozin can be used to prevent HF in patients with T2D, as demonstrated in the EMPA-REG study, and this study shows it is safe to do so even in the context of an acute MI in patients with diabetes. However, in Australia it is not reimbursed for HF prevention in patients without diabetes.

Reference: N Engl J Med 2024;390:1455–66
Abstract

Deep learning of electrocardiograms in sinus rhythm from US veterans to predict atrial fibrillation

Authors: Yuan N et al.

Summary: This study investigated whether deep learning models applied to ECGs for outpatients in sinus rhythm can predict AF. 907,858 ECGs from patients across six US Veterans Affairs (VA) hospitals were included in the analysis; all patients had 12-lead ECGs taken while in sinus rhythm. A convolutional neural network using ECGs from two VA hospital networks was trained to predict the presence of AF within 31 days of a sinus rhythm ECG. The model was tested on ECGs from all six VA networks as well as one large non-VA academic medical centre. The deep learning model predicted the presence of AF within 31 days of a sinus rhythm ECG at the VA sites, with an area under the receiver operating characteristic curve (AUROC) of 0.86, accuracy of 0.78, and F1 score of 0.30. At the non-VA site, AUROC was 0.93, accuracy was 0.87, and F1 score was 0.46. Model performance was similar regardless of ethnicity, sex, age or CHA_2DS_2-VASc score.

Comment: Artificial intelligence is increasingly being used in cardiology and this study shows how it can be used as a screening tool to identify patients at high risk of developing AF by examining patients' ECGs while in sinus rhythm. If this type of technology becomes available it will allow high-risk patients to be targeted for more intensive monitoring, and it would appear to be an extremely effective tool as fewer than three patients deemed to be high risk needed to be screened to detect a case of AF.

Reference: JAMA Cardiol. 2023;8(12):1131–9
Abstract

Earn CPD

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Aspirin vs clopidogrel for long-term maintenance after coronary stenting in patients with diabetes

Authors: Rhee T-M et al., for the HOST-EXAM Investigators

Summary: This post hoc analysis of the HOST-EXAM trial investigated the long-term use of clopidogrel versus aspirin after coronary stenting in patients with and without diabetes. 5438 patients who received dual antiplatelet therapy (DAPT) for 6–18 months after PCI with drug-eluting stents were randomised 1:1 to receive clopidogrel or aspirin monotherapy and followed up for 24 months. The primary outcome was a composite of all-cause death, nonfatal MI, stroke, readmission for ACS, and major bleeding. The rate of the primary composite end-point at 24 months was significantly lower with clopidogrel than with aspirin in patients with diabetes (6.3% vs 9.2%; HR 0.69, 95% CI 0.49–0.96; p=0.03) and in patients without diabetes (5.3% vs 7.0%; HR 0.76, 95% CI 0.58–1.00; p=0.046).

Comment: Conventional practice is to treat patients with ACS with DAPT for at least 12 months after the event and then discontinue the P2Y12 inhibitor (clopidogrel or ticagrelor). This study suggests that monotherapy with clopidogrel rather than aspirin when DAPT is discontinued may be a better strategy, as there were fewer recurrent ischaemic events and less bleeding with clopidogrel monotherapy. It also showed that diabetes did not affect the benefits. These results are consistent with the CAPRIE study, published many years ago, which showed a similar benefit of clopidogrel monotherapy over aspirin in patients with chronic ASCVD. Although not approved in Australia for this indication, clopidogrel is off-patent and a private script would not be expensive.

Reference: JAMA Cardiol. 2023;8(6):535–44
Abstract

Excess apolipoprotein B and cardiovascular risk in women and men

Authors: Johannesen CDL et al.

Summary: This analysis of the Copenhagen General Population Study investigated whether excess apolipoprotein B (apoB) is associated with an increased risk of MI, ASCVD, and all-cause mortality. 53,484 females and 41,624 males who were not taking statins were included in the analysis. Excess apoB levels were defined as the value of apoB above that contributed by LDL cholesterol levels alone. During a median 9.6 years of follow up, 2048 patients had an MI, 4282 had an ASCVD event, and 8873 died. Excess apoB was dose-dependently associated with risk of MI and ASCVD in both females and males, and with the risk of all-cause mortality in women.

Comment: We know that LDL and apoB are closely linked and that elevated levels of both are associated with increased risk of developing cardiovascular disease. We also know that in the CURE study, apoB was the strongest predictor of coronary artery disease in patients with ACS, compared with matched controls without ACS. This study shows that measuring apoB is worthwhile and that it adds incremental value to assessment of LDL alone. This may help select patients who require more intensive lipid lowering, especially in primary prevention, but reduction of LDL should still be the parameter that guides treatment.

Reference: J Am Coll Cardiol. 2024;83(23):2262–73
Abstract

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