Cardiology Research Review™

Making Education Easy

Issue 161 - 2024

In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **CABG** = coronary artery bypass graft; **HFrEF** = heart failure with reduced ejection fraction; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **TAVI** = transcatheter aortic-valve implantation.

Welcome to the latest issue of Cardiology Research Review.

In this issue, a post-hoc analysis of ORION data supports the safety of inclisiran in patients with dyslipidaemia, a network meta-analysis finds that intravascular imaging-guided PCI is the best strategy for reducing the risk of cardiovascular events, a large US study confirms that better education (and presumably better health literacy) is associated with a reduced risk of cardiovascular events in the longer term, and an analysis of the CLEAR Outcomes trial finds that bempedoic acid is a promising alternative for statin-intolerant patients. Also in this issue, a report commissioned by European medical regulators found no association between semaglutide and suicidal ideation when used for obesity or type 2 diabetes.

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

Kind Regards,

Associate Professor John Amerena
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Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials

Authors: Wright RS et al.

Summary: This post hoc analysis of data from seven ORION trials investigated the long-term safety and tolerability of incliseran in patients with hypercholesterolaemia. The analysis included 3576 patients treated with inclisiran 300mg for up to 6 years and 1968 patients treated with placebo for up to 1.5 years. Kaplan-Meier analyses showed that serious treatment-emergent adverse events, hepatic/muscle/kidney events, incident diabetes, and elevations of creatine kinase were reported at comparable rates in each group for up to 1.5 years, with similar trends reported with inclisiran beyond this period. Fewer treatment-emergent major cardiovascular adverse events occurred with inclisiran during follow up. Treatment-induced antidrug antibodies were uncommon with inclisiran (4.6%).

Comment: The PCSK9 inhibitors lower LDL cholesterol by 50–60% on top of high-dose statin therapy. Evolocumab, a monoclonal antibody blocking PCSK, has been shown to reduce cardiovascular events in patients with ASCVD and elevated LDL while on maximally tolerated statin therapy, and there were no safety signals, even in patients with very low LDL levels (<0.5 mmol/L). Incliseran, another PCSK9 inhibitor, reduces PCSK9 production by blocking mRNA in hepatocytes, and is likely to become available in Australia soon. This study confirms its safety whilst we are awaiting the long-term outcome trials. Both agents lower LDL cholesterol to a similar extent (50–60%) but evolocumab can be administered by the patient every 2–4 weeks, whereas incliseran has to be given via SC injection by a healthcare professional every 6 months, indicating that patient preference may well play a role in which agent is used.

Reference: J Am Coll Cardiol. 2023;82(24):2251–61
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.

Comparison of intravascular imaging, functional, or angiographically guided coronary intervention

Authors: Kuno T et al.

Summary: This network meta-analysis evaluated clinical outcomes after imaging-guided PCI or functionally-guided PCI compared with conventional angiography-guided PCI. A search of PubMed and EMBASE identified 32 randomised controlled trials (n=22,684) that were suitable for inclusion. Meta-analysis of the data showed that intravascular imaging-guided PCI was associated with reduced risk of major adverse cardiovascular events (MACE; relative risk [RR] 0.72, 95% CI 0.62–0.82), cardiovascular death (RR 0.56, 95% CI 0.42–0.75), MI (RR 0.81, 95% CI 0.66–0.99), stent thrombosis (RR 0.48, 95% CI 0.31–0.73), and target lesion revascularisation (RR 0.75, 95% CI 0.57–0.99) compared with angiography-guided PCI. Functionally-guided PCI was also associated with reduced risk of MACE and MI compared with angiography-guided PCI. Intravascular imaging-guided PCI ranked first for MACE, cardiovascular death, stent thrombosis, and target lesion revascularisation outcomes, and the results were consistent between ACS and non-ACS cohorts.

Comment: In many centres the decision to do PCI is based on angiographic appearances, with intravascular ultrasound (IVUS) imaging or fractional flow reserve only performed on indeterminate lesions. This large meta-analysis shows that outcomes are significantly better with imaging and functionally-guided PCI than angiography alone across the board, but performing these procedures adds time and expense to PCI, and IVUS is currently not funded in Australia, so costs may be prohibitive. A cost-benefit analysis may help to prove that the extra upfront costs may reduce future costs in treating patients who undergo PCI.

Reference: J Am Coll Cardiol. 2023;82(23):2167–76
Abstract

Educational attainment and lifetime risk of cardiovascular disease

Authors: Magnani JW et al.

Summary: This study analysed data from six prospective cohort studies to evaluate the impact of education level on lifetime cardiovascular disease (CVD) risk. A total of 40,998 participants (56.2% female) were included. Individuals with less than high school or high school completion were found to have higher lifetime CVD risks than college graduates. Among middle-aged men, HRs for a CVD event were 1.58 (95% CI 1.38–1.80), 1.30 (95% CI 1.10–1.46), and 1.16 (95% CI 1.00–1.34) in those with less than high school, high school, and some college education, respectively, compared with those with college completion. Among women, corresponding HRs were 1.70 (95% CI 1.49–1.95), 1.19 (95% CI 1.05–1.35), and 0.98 (95% CI 0.83–1.15). Individuals with higher education had longer time to incident CVD.

Comment: This study confirms what many of us see in day-to-day practice. Better education (and presumably better health literacy) is associated with a reduced risk of cardiovascular events in the longer term. Whether this is due to better adherence to medication, greater access to medical care and medication or healthier lifestyles in the more highly educated is unknown, but poor education is often associated with social deprivation, which is also known to increase lifetime cardiovascular events. Intervention in this domain would be difficult, but it seems likely that increasing education standards at a community level would reduce overall cardiovascular events, although this is still speculative.

Reference: JAMA Cardiol. 2024;9(1):45–54
Abstract

Impact of bempedoic acid on total cardiovascular events

Authors: Nicholls SJ et al.

Summary: This prespecified analysis of the CLEAR Outcomes trial investigated the effects of bempedoic acid on major adverse cardiovascular events (MACE) in patients with hypercholesterolaemia and high cardiovascular risk who were unable to take guideline-recommended statins. 13,970 patients (mean age 65 years, 51.8% male) were randomised to receive bempedoic acid or placebo daily, and the primary end-point was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularisation (MACE-4). Bempedoic acid reduced LDL cholesterol by 21% and high-sensitivity C-reactive protein (hsCRP) by 22% at 6 months. During a median follow-up of 3.4 years, treatment with bempedoic acid was associated with a reduction in risk of MACE-4 (HR 0.80, 95% CI 0.72–0.89; p<0.001), MACE-3 (HR 0.83, 95% CI 0.73–0.93; p=0.002), MI (HR 0.69, 95% CI 0.58–0.83; p<0.001), and coronary revascularisation (HR 0.78, 95% CI 0.68–0.89; p<0.001), but not stroke (HR 0.80, 95% CI 0.63–1.03).

Comment: The CLEAR study showed improved cardiovascular outcomes with bempedoic acid versus placebo in patients who were at high cardiovascular risk with elevated LDL who were intolerant of statins. There was a 21% reduction in LDL and a 22% reduction in hsCRP with this agent, and this subgroup analysis shows a significant reduction in total cardiovascular events, with greater risk reduction with recurrent events. This agent is a promising alternative for truly statin-intolerant patients, especially those who do not qualify for PCSK9 inhibitors. It is not available in Australia yet, but hopefully will be at some stage.

Reference: JAMA Cardiol. 2024; published online Jan 17
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 5-year outcomes after TAVI versus surgical aortic-valve replacement (SAVR) in low-risk patients. 1000 low-risk patients with severe, symptomatic aortic stenosis were randomised to undergo either TAVI or SAVR. 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 respective groups.

Comment: TAVI was first used successfully in patients with severe symptomatic aortic stenosis who were deemed inoperable, but since then lower and lower risk patients have had this performed, with good results compared with SAVR, as shown in this paper. There has always been concern about the durability of TAVI valves compared to SAVR, but this study and others have pretty much dispelled this concern, so that TAVI is increasingly being used for patients with severe symptomatic aortic stenosis irrespective of surgical risk, with SAVR probably now only being used in younger patients or those who require concomitant CABG or other valve replacements.

Reference: N Engl J Med. 2023;389:1949–60
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: While a low-salt diet is recommended for patients with hypertension, there has often been debate as to the benefits of a low-salt diet in patients without hypertension. This study shows that lowering salt intake does lower BP by up to 8mm Hg, independent of hypertension status, but it also showed that only half the patients studied were salt sensitive, as defined by a drop of >5mm Hg in MAP. Lowering salt intake has been shown to reduce cardiovascular events in a Chinese population with a history of hypertension and stroke in the Salt Substitute and Stroke Study (SSaSS), presumably due to a significant reduction in systolic and diastolic BP, but the benefits of lowering BP in healthy patients without hypertension and/or cardiovascular disease have not been demonstrated.

Reference: JAMA 2023;330(23):2258–66
Abstract

Long-term outcomes of resynchronization-defibrillation for heart failure

Authors: Sapp JL et al., for the RAFT Long-Term Study Team

Summary: This analysis of the RAFT trial compared the long-term impact of cardiac-resynchronisation therapy (CRT) versus implantable cardioverter-defibrillators (ICDs) in patients with heart failure. 1050 patients with NYHA class II or III heart failure and LVEF ≤30% were randomised to receive either an ICD alone or a CRT defibrillator (CRT-D); the primary outcome was death from any cause. During a median follow-up of 7.7 years, 76.4% of patients assigned to ICD and 71.2% assigned to CRT-D died. Time until death appeared to be longer for those assigned to CRT-D versus ICD (acceleration factor 0.80, 95% CI 0.69–0.92; p=0.002). Median duration of follow-up for those who survived was 13.9 years.

Comment: The trials demonstrating the efficacy and safety of CRT and CRT-D have been of relatively short duration. This long-term follow up of patients in the RAFT study which studied patients with HFrEF and indications for CRT ± ICD shows that CRT-ICD decreases mortality moreso than ICD alone over an extended period of time after implantation (median 14 years). It also reinforces that congestive heart failure is a condition with high mortality despite optimal medical therapy, as >70% of patients died over the period of follow up.

Reference: N Engl J Med. 2024;390:212–20
Abstract

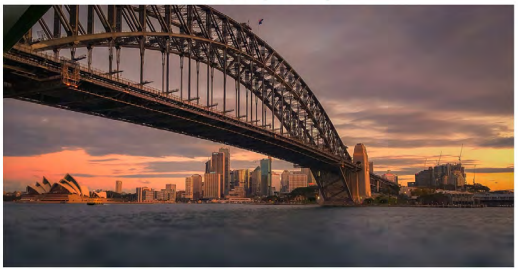
Incidences, risk factors, and clinical correlates of severe QT prolongation after the use of quetiapine or haloperidol

Authors: Wang C-L et al.

Summary: This study in Taiwan examined the risk of severe QT prolongation in patients taking quetiapine or haloperidol. Electronic medical records from a healthcare hospital system in Taiwan were analysed for 8832 patients taking quetiapine and 2341 patients taking haloperidol. Among these patients, 13.0% and 14.2%, respectively, developed severe QT prolongation. Common risk factors included old age, heart failure, hypokalaemia, concomitant amiodarone use, and baseline QTc interval. In quetiapine users, severe QT prolongation was significantly associated with ventricular arrhythmias (odds ratio 2.84, 95% CI 1.95–4.13) and sudden cardiac death (2.29, 95% CI 1.44–3.66).

Comment: Many typical and atypical antipsychotic agents can cause prolongation of the QTc, especially clozapine, and it appears haloperidol and quetiapine, although this is often not appreciated in the cardiac community. Despite this, it is uncommon to see ventricular arrhythmias with these agents when used in isolation, but the risk increases substantially if other therapies are used in conjunction with these antipsychotic agents, such as sotalol, amiodarone and macrolide antibiotics. It is therefore important to recognise potential drug interactions in patients who are on antipsychotic medications, and thus it would be prudent to check for interactions before starting concomitant treatments in patients on these agents.

Reference: Heart Rhythm 2024; published online Jan 24
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 in sinus rhythm. A convolutional neural network using 12-lead ECGs from two VA hospital networks was trained to predict the presence of AF within 31 days of sinus rhythm ECGs. The model was tested on ECGs held out from training at the two VA networks as well as four additional VA networks and one large non-VA academic medical centre. The deep learning model predicted the presence of AF within 31 days of a sinus rhythm ECG on held-out test ECGs at 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: Clinical predictors of AF are well recognised (hypertension, coronary artery disease, heart failure etc) but this study looked at ECG predictors of AF analysed by deep learning AI modelling. It showed that this model, when applied to ECGs in sinus rhythm, was extremely accurate in predicting AF within 31 days of the ECG being taken (78–87% accuracy) which was not influenced by gender, age, race or stroke risk score, but was more accurate in higher-risk individuals. This technology could be a useful adjunct to early diagnosis and treatment of AF, especially in high-risk individuals, with the potential to reduce some of the morbidity and mortality associated with AF.

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

Association of semaglutide with risk of suicidal ideation in a real-world cohort

Authors: Wang W et al.

Summary: This retrospective cohort study assessed the risk of suicidal ideation with semaglutide compared with non-GLP-1 agonists for obesity or diabetes. Electronic health records from the TriNetX Analytics Network were analysed for 240,618 patients who were prescribed semaglutide or non-GLP-1 agonists for obesity, and for 1,589,855 patients who were prescribed semaglutide or non-GLP-1 agonists for type 2 diabetes. Semaglutide was found to be associated with lower risk for incident (HR 0.27, 95% CI 0.20–0.60) and recurrent (HR 0.44, 95% CI 0.32–0.60) suicidal ideation compared with non-GLP-1 agonist anti-obesity medications in patients with overweight or obesity (mean age 50.1 years, 72.6% female). Similar findings were observed in patients with type 2 diabetes (mean age 57.5 years, 49.2% female).

Comment: There have been some case reports suggesting that there was an increased risk of suicidal ideation with semaglutide, but this has not been reported in clinical trials. This retrospective report, commissioned by the European medical regulators, found no association with suicidal ideation with semaglutide when used for obesity or management of type 2 diabetes in 1.8 million patients. If anything, there was less suicidal ideation in patients on semaglutide, so we can be confident that excess suicidal ideation is not triggered by semaglutide therapy.

Reference: Nat Med. 2024;30:168–76
Abstract

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