Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **CABG** = coronary artery bypass grafting; **DPP-4** = dipeptidyl peptidase 4; **GLP-1** = glucagon-like peptide 1; **HFrEF** = heart failure with reduced ejection fraction; **HR** = hazard ratio; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **NSTEMI** = non-STEMI; **PCI** = percutaneous coronary intervention; **SGLT2** = sodium-glucose cotransporter 2; **SSRI** = selective serotonin reuptake inhibitor; **STEMI** = ST-elevation MI.

Welcome to the latest issue of Cardiology Research Review.

In this issue, we report concerning evidence that nanoplastic particles found in carotid plaques may be associated with an increased risk of cardiovascular events, the KARDIA-1 trial investigates the antihypertensive efficacy of the RNA interference agent zilebesiran, a Swedish cohort study reinforces the need for close observation of patients with AF post CABG, and an analysis of the GRADE study suggests that early use of GLP-1 agonists should be considered in patients with type 2 diabetes in preference to sulphonylureas and DPP-4 inhibitors.

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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Microplastics and nanoplastics in atheromas and cardiovascular events

Authors: Marfella R et al.

Summary: This study investigated the presence of microplastics and nanoplastics (MNPs) in carotid plaque specimens from patients undergoing carotid endarterectomy for asymptomatic carotid artery disease. Excised carotid plaque specimens from 304 patients were analysed using pyrolysis-gas chromatography-mass spectrometry, stable isotope analysis, and electron microscopy. 257 patients completed a mean 33.7 months of follow-up. 150 of them (58.4%) had polyethylene detected in carotid artery plaque and 31 (12.1%) had measurable amounts of polyvinyl chloride. Electron microscopy revealed visible foreign particles among plaque macrophages and in the external debris, and radiographic examination showed that some of these particles included chlorine. Patients who had MNPs detected within the atheroma were at higher risk for a primary end-point event (MI, stroke, or all-cause mortality) than those in whom MNPs were not detected (HR 4.53, 95% CI 2.00–10.27; p<0.001).

Comment: There have been reports that cardiovascular events are increased in patients who are exposed to air pollution but the mechanism is not clear. This interesting study showed that when nanoplastic particles were detected in plaques from carotid endarterectomy, there was an increased risk of subsequent cardiovascular events. If this association is confirmed it has profound implications as micro- and nanoplastic particles are used in many cosmetics and skin creams, and potentially could be a contaminant in foods.

Reference: N Engl J Med. 2024;390:900–10
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.

RNA interference with zilebesiran for mild to moderate hypertension

Authors: Bakris GL et al., for the KARDIA-1 Study Group

Summary: The multinational phase 2 KARDIA-1 trial investigated the efficacy and safety of the RNA interference agent zilebesiran in patients with mild to moderate hypertension. 394 patients with daytime mean ambulatory systolic BP (SBP) of 135–160mm Hg after antihypertensive washout were randomised to 1 of 4 subcutaneous zilebesiran regimens (150, 300, or 600mg once every 6 months or 300mg once every 3 months) or placebo (once every 3 months) for 6 months. Least-squares mean differences in SBP change from baseline at 3 months (compared with placebo) were –14.1mm Hg with zilebesiran 150mg once every 6 months ($p<0.001$); –16.7mm Hg with zilebesiran 300mg once every 3 or 6 months ($p<0.001$); and –15.7mm Hg with zilebesiran 600mg once every 6 months ($p<0.001$). Adverse events were reported in 60.9% of zilebesiran recipients and 50.7% of placebo recipients.

Comment: Therapies using mRNA modification are becoming more common in cardiovascular medicine (incliseran for LDL reduction and the lipoprotein(a)-reducing agents) and have been shown to be effective, durable and safe. This agent blocks angiotensinogen production in the liver and appears to be effective in reducing BP with no serious adverse effects to date. Further studies will need to be done but given the safety of the other agents which work by a similar mechanism, there are unlikely to be off-target effects, and if sustained BP reduction can be shown this will be an attractive antihypertensive therapy.

Reference: JAMA 2024;331(9):740–9
Abstract

Recurrence of atrial fibrillation in patients with new-onset postoperative atrial fibrillation after coronary artery bypass grafting

Authors: Herrmann FEM et al.

Summary: Approximately 30% of patients undergoing CABG develop new-onset post-operative AF (POAF). This Swedish nationwide cohort study investigated whether early AF recurrence in patients with POAF after CABG is associated with worse outcomes. Data were collected from the SWEDEHEART registry and three other mandatory national registries for 10,609 patients (median age 71 years; 81.6% male) who developed POAF after undergoing isolated first-time CABG in 2007–2020. Early AF recurrence was defined as an episode of AF requiring hospital care within 3 months after discharge; the primary outcome was all-cause mortality. During a median follow-up of 7.1 years, 6.7% of patients had early AF recurrence. Event rates per 100 patient-years in patients with versus without early AF recurrence were 2.21 vs 2.03 for all-cause mortality, 3.94 vs 2.79 for heart failure hospitalisation, and 3.97 vs 2.74 for major bleeding. There was no association between early AF recurrence and all-cause mortality.

Comment: We know that AF post CABG is common, and that these patients are more likely to have recurrent AF, so should be followed closely. This study showed that about 6% of patients with post-op AF had recurrence within 3 months of discharge, and that during extended follow up this was not associated with excess mortality, but there was increased risk of hospitalisation for AF and serious bleeding, presumably due to anticoagulation. This study reinforces the need for close observation of patients who have AF post CABG.

Reference: JAMA Netw Open 2024;7(3):e241537
Abstract

Cardiovascular outcomes in GRADE (Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study)

Authors: Green JB et al., for the GRADE Study Research Group

Summary: The GRADE study investigated cardiovascular outcomes in patients with type 2 diabetes (T2D) treated with insulin glargine, glimepiride, liraglutide, or sitagliptin, on top of baseline metformin. 5047 patients (mean age 57.2 years; diabetes duration 4 years; and low baseline prevalence of cardiovascular disease) were randomised to the various treatment groups and followed up for a median 5 years. Outcomes included MACE-3 (a composite of cardiovascular death, MI, and stroke), MACE-4 (MACE-3 + unstable angina), MACE-5 (MACE-4 + coronary revascularisation), MACE-6 (MACE-5 + hospitalisation for heart failure), and the individual components. There were no significant between-group differences in the incidences of first MACE-3, MACE-4, MACE-5, or MACE-6 outcomes, or their individual components. However, when compared with the other treatment groups combined, the liraglutide group had a significantly lower risk of MACE-5, MACE-6, and hospitalisation for heart failure. In addition, the groups treated with glimepiride or sitagliptin had significantly higher rates of recurrent MACE-6 events than the liraglutide group.

Comment: The LEADER study showed that liraglutide reduced MACE in patients with T2D and atherosclerotic cardiovascular disease, and similar results were seen with semaglutide in the SUSTAIN study in the same patient population. This study suggests that this benefit is also seen in patients with T2D without atherosclerotic cardiovascular disease, as well as reducing hospitalisation for heart failure. A decrease in heart failure hospitalisations was not seen in LEADER and SUSTAIN, but was demonstrated in the STEP-HF study which showed semaglutide reduced heart failure hospitalisations in patients with heart failure and preserved ejection fraction who had a BMI >30. Given these results, early use of GLP-1 agonists should be considered in patients with T2D in preference to sulphonylureas and DPP-4s, which in this study had worse outcomes than patients who received liraglutide, and at best have a neutral effect on cardiovascular events.

Reference: Circulation 2024;149(13):993–1003
Abstract

Direct oral anticoagulants for stroke prevention in patients with device-detected atrial fibrillation: A study-level meta-analysis of the NOAH-AFNET 6 and ARTESiA trials

Authors: McIntyre WF et al.

Summary: This systematic review and meta-analysis investigated the efficacy and safety of direct oral anticoagulants for stroke prevention in patients with device-detected AF. A search of MEDLINE and Embase identified two randomised controlled trials that compared oral anticoagulation with antiplatelet or no antithrombotic therapy in adults with device-detected AF: the NOAH-AFNET 6 trial of edoxaban (n=2536) and the ARTESiA trial of apixaban (n=4012). Meta-analysis of the data from these two trials demonstrated that oral anticoagulation with edoxaban or apixaban significantly reduced the risk of ischaemic stroke (relative risk [RR] 0.68, 95% CI 0.50–0.92). Oral anticoagulation also reduced a composite of cardiovascular death, all-cause stroke, peripheral arterial embolism, MI, or pulmonary embolism (RR 0.85, 95% CI 0.73–0.99), but did not reduce cardiovascular or all-cause mortality. Oral anticoagulation was associated with an increase in major bleeding (RR 1.62, 95% CI 1.05–2.50).

Comment: This meta-analysis demonstrates that AF detected on devices (implantable loop recorder, permanent pacemaker, implantable cardioverter defibrillator, and cardiac resynchronisation therapy device) is clinically important as there is an increased risk of stroke that can be attenuated with oral anticoagulation in patients whose CHADSVA score is high enough to justify anticoagulation. The AF burden that justifies anticoagulation has become a lot clearer lately with the publication of the ARTESiA study, which showed device-detected AF of >6 min but <24h duration was associated with increased stroke risk which could be reduced with anticoagulation, albeit at the cost of increased bleeding.

Reference: Circulation 2024;149(13):981–8
Abstract

Angiotensin receptor-neprilysin inhibition in patients with STEMI vs NSTEMI

Authors: Mann DL et al.

Summary: The PARADISE-MI trial compared the cardiovascular effects of sacubitril/valsartan with those of ramipril in patients with acute MI (either STEMI or NSTEMI). A total of 5661 patients with acute MI complicated by LV dysfunction and/or pulmonary congestion and at least 1 risk-enhancing factor were randomised to either sacubitril/valsartan or ramipril. Three-quarters (75.8%) of patients had STEMI, and these patients were younger and had fewer comorbidities and cardiovascular risk factors than NSTEMI patients. After adjustment for potential confounders, the risk of the primary outcome (cardiovascular mortality or incident heart failure) was slightly higher in NSTEMI versus STEMI patients (adjusted HR 1.19, 95% CI 1.00–1.41; p=0.05). The primary composite outcome occurred at similar rates in patients randomised to sacubitril/valsartan versus ramipril in STEMI (10% vs 12%; p=ns) and NSTEMI patients (17% vs 17%; p=ns).

Comment: Sacubitril/valsartan has largely replaced ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for chronic renin-angiotensin-aldosterone system inhibition in patients with HFrEF and EF <40%, whether the aetiology is ischaemic or non-ischaemic, as outcomes were demonstrated to be better than enalapril in the pivotal PARADIGM study. The PARADISE study examined whether early administration of sacubitril/valsartan after MI with heart failure improved outcomes compared to ramipril but it showed no benefit in either STEMI or NSTEMI. Importantly there was no harm. In Australia, sacubitril/valsartan is PBS reimbursed for patients with HFrEF with EF<40% after stabilisation with ACEIs or ARBs, so initiation soon after an MI would be problematic, although there is no guidance as to the definition of stability (days, weeks, months?) so perhaps it could be considered in this context in high-risk patients who had a few days of ACEI/ARB post MI.

Reference: J Am Coll Cardiol. 2024;83(9):904–14
Abstract

No effect of remoteness on clinical outcomes following myocardial infarction: An analysis of 43,729 myocardial infarctions in Victoria, Australia

Authors: Livori AC et al.

Summary: This study in Victoria, Australia, investigated the impact of remoteness on 1-year clinical outcomes after MI. 43,729 post-MI patients discharged from hospitals in Victoria in 2012–2017 were included. The relationship between remoteness (determined using the Accessibility/Remoteness Index of Australia), MACE, and all-cause mortality over 1-year was evaluated using adjusted Poisson regression. Adjusted rates of MACE after NSTEMI were 77.5 per 1000 person-years for the most remote area versus 83.4 per 1000 person-years for the least remote area, and rates of MACE after STEMI were 28.5 versus 33.5 per 1000 person-years, respectively. Rates of all-cause mortality after NSTEMI were 82.2 and 100.8 per 1000 person-years for the most versus least remote area, and after STEMI were 24.7 versus 22.3 per 1000 person-years, respectively.

Comment: In the past, remote and regional communities had worse outcomes compared with their metropolitan counterparts after ACS. It was postulated that this was due to delay in presentation and diagnosis, as well as transport issues when transferring to PCI-capable centres. This paper shows that this problem has largely been overcome in Victoria in that rates of recurrent MACE and all-cause mortality were not different between remote, regional and metropolitan areas after ACS. Victoria is a small state however, so it would be interesting to see if these findings are similar in large states such as WA, Queensland and NSW.

Reference: Int J Cardiol. 2024:398:131593
Abstract

Use of secondary prevention medications in metropolitan and non-metropolitan areas: An analysis of 41 925 myocardial infarctions in Australia

Authors: Livori AC et al.

Summary: This study in Victoria, Australia, investigated whether remoteness affects the use of secondary prevention medications after MI. A total of 41,925 post-MI patients who were alive for at least 90 days after discharge from hospitals in Victoria in 2012–2017 were included (10,819 STEMI admissions and 31,106 NSTEMI admissions). The dispensing of P2Y12 inhibitors, statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers within 90 days after discharge was assessed according to remoteness (determined using the Accessibility/Remoteness Index of Australia). None of the medication classes dispensed in the 90-day post-discharge period differed significantly between the least remote and the most remote areas. The largest difference between the least versus most remote areas for medication use after NSTEMI was seen for ACEIs/ARBs (71% vs 80%), and after STEMI was seen for statins (89% vs 95%). Predicted 12-month medication use after STEMI and NSTEMI did not differ significantly according to remoteness. The largest difference between the least versus most remote areas in medication use after NSTEMI was seen for P2Y12 inhibitors (48% vs 55%), and after STEMI was seen for ACEI/ARBs (68% vs 76%).

Comment: As in the previous study, patients from remote, regional and metropolitan areas were studied 90 days after ACS to determine if their place of residence influenced use of secondary prevention therapies. It showed there were no differences in use of secondary prevention treatments at 90 days between remote, regional and metropolitan patients. I suspect this is due to initiation of these therapies (aspirin, P2Y12 inhibitors, statins, ACE/ARBs and beta-blockers) in hospital, rather than having to be initiated by community-based doctors post discharge. Attainment of target levels of BP and lipids is less than ideal in these high-risk patients, and it would be interesting to see if there are differences in achieving targets depending on geographical location.

Reference: Eur J Prev Cardiol. 2024;31(5):580–8
Abstract

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Concomitant use of selective serotonin reuptake inhibitors with oral anticoagulants and risk of major bleeding

Authors: Rahman AA et al.

Summary: This population-based, nested case-control study investigated the risk of bleeding associated with the concomitant use of SSRIs and oral anticoagulants. Patients with AF who initiated oral anticoagulants in the UK in 1998–2021 were included. Cases with major bleeding during follow-up (n=42,190) were each matched with up to 30 controls according to age, sex, cohort entry date, and follow-up duration (n=1,156,641). Comparison of cases and controls showed that concomitant use of SSRIs and oral anticoagulants was associated with an increased risk of major bleeding compared with oral anticoagulants alone (incidence rate ratio [IRR] 1.33, 95% CI 1.24–1.42). The risk peaked during the first 30 days of concomitant use and persisted for up to 6 months, and did not vary with age, sex, history of bleeding, chronic kidney disease, or potency of SSRIs.

Comment: This analysis suggests that there is an increased risk of bleeding when SSRIs are started in patients taking non-vitamin K oral anticoagulants (NOACs), especially in the first 6 months after starting them. This does not seem to be a problem in clinical practice however, and although the numbers in this study are large these findings could be just the play of chance. This association was not specifically looked at in the pivotal trials demonstrating that NOACs reduced bleeding compared with warfarin for stroke prevention in AF, but it would still be prudent to pay particular attention to modifying bleeding risk factors in patients who need SSRIs and NOACs.

Reference: JAMA Netw Open 2024;7(3):e243208
Abstract

Left ventricular function, congestion, and effect of empagliflozin on heart failure risk after myocardial infarction

Authors: Udell JA et al.

Summary: This analysis of the EMPACT-MI trial evaluated the influence of LVEF and congestion on post-MI outcomes, and the effects of empagliflozin on heart failure risk post-MI. A total of 6522 patients were randomised within 14 days of acute MI complicated by either newly reduced LVEF <45%, congestion, or both, to empagliflozin 10 mg/day or placebo and were followed up for a median 17.9 months. At baseline, 2648 patients (40.6%) had LVEF <45% alone, 1483 (22.7%) had congestion alone, and 2181 (33.4%) had both. In placebo recipients, multivariable adjusted risk for each 10-point reduction in LVEF included all-cause death or heart failure hospitalisation (HR 1.49, 95% CI 1.31–1.69; p<0.0001), first heart failure hospitalisation (HR 1.64, 95% CI 1.37–1.96; p<0.0001), and total heart failure hospitalisations (rate ratio [RR] 1.89, 95% CI 1.51–2.36; p<0.0001). Congestion was also associated with an increased risk of each of these outcomes (HR 1.52, HR 1.94, and RR 2.03, respectively). Empagliflozin reduced the risk of first heart failure hospitalisation (HR 0.77, 95% CI 0.60–0.98) and total heart failure hospitalisations (RR 0.67, 95% CI 0.50–0.89) irrespective of the presence of LVEF or congestion or both.

Comment: The EMPACT study was unable to show benefit of empagliflozin added to standard therapy in patients post MI who had EF <45% or congestion or both, as although the primary end-point of hospitalisation for heart failure and all-cause mortality was slightly less than placebo, it was not significant. This analysis looking at the effect of empagliflozin on hospitalisation for heart failure alone, showed not surprisingly that the lower the EF post MI and the presence of congestion were adverse prognostic markers, and that empagliflozin significantly reduced this end-point and had no adverse effects compared with placebo. These data, as well as the SOLOIST, EMPULSE and DICTATE studies, support the safety and efficacy of starting SGLT2s in patients with acute heart failure while the patient is still in hospital or soon after.

Reference: J Am Coll Cardiol. 2024; published online Apr 1
Abstract

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