Cardiology Research Review™

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Issue 164 - 2024

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## Abbreviations used in this issue:

**ACS** = acute coronary syndrome; **BP** = blood pressure; **DAPT** = dual antiplatelet therapy; **HF** = heart failure; **HFpEF** = HF with preserved ejection fraction; **HFrEF** = HF with reduced ejection fraction; **HR** = hazard ratio; **Lp(a)** = lipoprotein(a); **LVEF** = left ventricular ejection fraction; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SGLT2** = sodium-glucose cotransporter 2.

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# Welcome to the latest issue of Cardiology Research Review.

In this issue, an Australian study reports the benefits of a culturally informed model of care for Indigenous patients with ACS, the High-STEACS and HiSTORIC investigators report that implementation of a uniform rule-out cardiac troponin threshold for MI is effective for both sexes, and the guideline-changing findings of the REDUCE-AMI trial indicate that beta-blockers are not mandatory after MI if LV function is normal and there is no residual disease. Also in this issue, an Italian case-control study finds that it is never too late to start BP-lowering treatment to reduce cardiovascular events and dementia risk in older patients, and the findings of the PREVENT trial support consideration to expand indications for PCI to include high-risk vulnerable plaques.

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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## Effects of a culturally informed model of care for Aboriginal and Torres Strait Islander patients with acute coronary syndrome in a tertiary hospital in Australia

**Authors:** Harrop DL et al.

**Summary:** This Australian study investigated whether implementation of a culturally informed model of care improved clinical outcomes for Aboriginal and Torres Strait Islander (Indigenous) patients hospitalised with ACS at Princess Alexandra Hospital in Brisbane. Outcomes for Indigenous patients (n=199) admitted with ACS before implementation of the model of care were compared with those in Indigenous patients (n=119) admitted after its implementation. Comparisons were also made with non-Indigenous cohorts across the same time-frames. The primary outcome was a composite of death, acute MI, unplanned revascularisation, and cardiac readmission within 90 days after index admission. Compared with the pre-implementation group, Indigenous patients admitted post-implementation had a significant reduction in the primary outcome (HR 0.60, 95% CI 0.40–0.90; p=0.012), which was driven by a reduction in unplanned cardiac readmissions (HR 0.55, 95% CI 0.35–0.85; p=0.006). No significant changes in the composite primary outcome were seen in non-Indigenous patients across the same time-frame. The primary outcome occurred more often in Indigenous than non-Indigenous patients pre-implementation (p<0.0001) but no between-group differences were seen after implementation of the model of care (p=ns).

**Comment:** Outcomes for patients with ACS who live in remote and regional areas are generally thought to be worse than those of their metropolitan counterparts and are even worse for Aboriginal community members. There are numerous reasons for this, but culturally insensitive models of care may contribute, as this paper suggests, when they demonstrated that outcomes improved after cultural factors were considered in the model of care. This may apply to other minorities as well.

***Reference: Lancet Glob Health 2024;12(4):e623–30***
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.

## Lipoprotein(a) blood levels and cardiovascular risk reduction with icosapent ethyl

**Authors:** Szarek M et al., for the REDUCE-IT Investigators

**Summary:** This post hoc analysis of the REDUCE-IT trial investigated the cardiovascular benefits of icosapent ethyl across a range of Lp(a) levels. 7026 patients with atherosclerotic cardiovascular disease who were taking statin therapy were randomised to receive icosapent ethyl 2g twice daily or matching placebo. Baseline Lp(a) level was found to be significantly associated with first and total MACE during follow-up (p<0.0001). Reductions in MACE reported with icosapent ethyl did not vary across the range of Lp(a) levels, with the drug reducing events in patients with Lp(a) levels <50 mg/dl and in patients with Lp(a) levels ≥50 mg/dl.

**Comment:** The REDUCE-IT study showed that in patients with atherosclerotic cardiovascular disease and elevated triglycerides who were on statins, icosapent ethyl reduced cardiovascular events and death. This substudy was instructive as it showed that elevated Lp(a) was associated with increased events (as expected), but that icosapent ethyl reduced events across the spectrum of Lp(a), indicating the beneficial effect was not attenuated by elevated Lp(a).

***Reference: J Am Coll Cardiol. 2024;83(16):1529–39***
Abstract

## Exercise therapy for chronic symptomatic peripheral artery disease: A clinical consensus document of the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases in collaboration with the European Society of Vascular Medicine and the European Society for Vascular Surgery

**Authors:** Mazzolai L et al.

**Summary:** A structure programme of exercise therapy yields optimal results in patients with lower extremity peripheral artery disease (PAD). This clinical consensus paper is intended as a guide for clinicians to promote and assist with the design of comprehensive exercise programmes to best suit patients with symptomatic chronic PAD. Different exercise training protocols specific for patients with PAD are outlined. The paper also highlights disparities in access to supervised exercise programmes across Europe, and the need for further research.

**Comment:** Cardiologists often see patients with PAD in association with coronary disease, as atherosclerosis is a diffuse vascular disease. This paper outlines a structured exercise programme to improve symptoms in patients with PAD, but this type of programme would be equally applicable to patients with coronary artery disease and angina, as exercise promotes angiogenesis and formation of collateral blood flow in the coronary circulation. Implementation of this type of structured programme would be difficult but perhaps could be incorporated as an extension of cardiac rehabilitation.

***Reference: Eur Heart J. 2024;45(15):1303–21***
Abstract



## Uniform or sex-specific cardiac troponin thresholds to rule out myocardial infarction at presentation

**Authors:** Li Z et al., for the High-STEACS and HiSTORIC Investigators

**Summary:** The implementation of a uniform rule-out threshold (<5 ng/L) for a high-sensitivity cardiac troponin I assay was evaluated in 16,792 consecutive patients (mean age 58 years, 46% female) presenting with possible MI. The threshold identified more female than male patients as low risk (73% vs 62%), but a similar proportion of female and male low-risk patients were discharged from the emergency department (both 81%), with <0.1% patients having a subsequent MI or cardiac death at 30 days. Compared with a uniform threshold of <5 ng/L, the investigators determined that use of sex-specific thresholds would increase the proportion of females identified as low risk and reduce the proportion of males identified as low risk.

**Comment:** There has been discussion as to whether sex-specific thresholds for troponin elevation should be used in the diagnosis of MI, as women have lower troponin levels than men and it is thought some MIs may be missed in women as their troponin does not go above the male threshold for an event. This paper acknowledges this but shows that a uniform threshold is safe and effective in diagnosing MI, suggesting one level fits all continues to be appropriate.

***Reference: J Am Coll Cardiol. 2024;83(19):1855–66***
Abstract

## Extended clopidogrel monotherapy vs DAPT in patients with acute coronary syndromes at high ischemic and bleeding risk

**Authors:** Li Y et al., for the OPT-BIRISK Investigators

**Summary:** The OPT-BIRISK trial investigated whether extended P2Y12 inhibitor monotherapy with clopidogrel was superior to ongoing DAPT with aspirin and clopidogrel after 9–12 months of DAPT in PCI patients who were at high risk for bleeding and ischaemia. 7758 patients (mean age 64.8 years, 59% male) with ACS and high bleeding and ischaemic risk who had completed 9–12 months of DAPT after drug-eluting stent implantation at 101 centres in China were randomised to either clopidogrel plus placebo or clopidogrel plus aspirin for an additional 9 months. The primary end-point (Bleeding Academic Research Consortium types 2, 3, or 5 bleeding within 9 months after randomisation) occurred in 2.5% of patients assigned to clopidogrel plus placebo and 3.3% of patients assigned to clopidogrel plus aspirin (HR 0.75, 95% CI 0.57–0.97; p=0.03). The incidence of major adverse cardiac and cerebral events was 2.6% and 3.5% in the respective groups (HR 0.74, 95% CI 0.57–0.96; p=0.02).

**Comment:** In patients who are at high ischaemic risk after PCI, it is tempting to continue DAPT for more than 12 months after the index event. The PEGASUS and DAPT studies with ticagrelor and clopidogrel did show a reduction in ischaemic events with continuation of DAPT but at the expense of excess bleeding. This study suggests continuation of clopidogrel monotherapy 12 months after PCI confers the same ischaemic benefit of ongoing DAPT with less bleeding, so this may be an attractive strategy in patients with high ischaemic and bleeding risk 12 months after PCI.

***Reference: JAMA Cardiol. 2024; published online Apr 17***
Abstract

## Beta-blockers after myocardial infarction and preserved ejection fraction

**Authors:** Yndigegn T et al., for the REDUCE-AMI Investigators

**Summary:** Most trials showing a benefit of beta-blockers post MI included patients with large MIs and were conducted in an era before modern biomarker-based diagnosis of MI and treatment with PCI, antithrombotics, high-intensity statins, and renin-angiotensin-aldosterone system antagonists became available. This analysis of REDUCE-AMI data investigated the efficacy of beta-blockers in patients with acute MI who had undergone PCI and had preserved LVEF (≥50%). 5020 patients were randomised to receive either long-term treatment with a beta-blocker (metoprolol or bisoprolol) or no beta-blocker treatment. The primary end-point was a composite of all-cause mortality or new MI. During a median follow-up of 3.5 years, a primary end-point event occurred in 7.9% of patients in the beta-blocker group and 8.3% of patients in the no beta-blocker group (HR 0.96, 95% CI 0.79–1.16; p=ns).

**Comment:** Guideline-directed medical therapy recommends beta-blockers be given to all patients who suffer an MI but the evidence for this strategy was derived from studies conducted before contemporary treatment of MI was introduced (revascularisation, statins and ACE inhibitors). Despite this, in Australia there has been a growing trend to discontinue beta-blockers a year or two after MI if LV function is normal and there is no residual stenotic coronary disease. This study looked at whether beta-blockers started in the acute phase after MI (once the anatomy and LV function was known) had any benefits compared with placebo, and found there was no improvement in outcomes. These findings are highly relevant clinically, and should change guidelines, and indicate that beta-blockers after MI are not mandatory if LV function is normal and there is no residual disease.

***Reference: N Engl J Med. 2024;390(15):1372–81***
Abstract

## Risk of dementia during antihypertensive drug therapy in the elderly

**Authors:** Rea F et al.

**Summary:** This nested case-control study in Italy determined the impact of antihypertensive drug therapy on the risk of dementia in older patients. Patients who were aged ≥65 years and had started taking antihypertensive drugs in 2009–2012 were included. Cases (n=13,812) were patients who developed dementia or Alzheimer disease during follow-up through to 2019. For each case, five controls matched for sex, age, and clinical status were selected. Exposure to antihypertensive drug therapy was found to be inversely associated with the risk of dementia. Compared with patients with very low exposure to antihypertensive therapy, those with low, intermediate, and high exposure exhibited a 2%, 12%, and 24% risk reduction, respectively. The same associations were seen in very old and frail patients.

**Comment:** There is good evidence that treating hypertension reduces cardiovascular events, heart failure, arrhythmias and cardiovascular death, but there is little evidence of the benefits on dementia in the elderly. This study shows that BP lowering in older and very old patients reduces the risk of developing cognitive impairment over time, even in frail elderly patients. This implies that it is never too late to start BP-lowering treatment to reduce cardiovascular events and dementia in older patients, although care needs to be taken not to lower BP too much too quickly, as this increases the risk of falls and trauma.

***Reference: J Am Coll Cardiol. 2024;83(13):1194–1203***
Abstract

## Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials

**Authors:** Cholesterol Treatment Trialists' (CTT) Collaboration

**Summary:** This meta-analysis of individual participant data from randomised controlled trials of statin therapy investigated the effects of statins on the risk of new-onset diabetes or worsening glycaemia. Long-term randomised controlled trials of statin therapy that participated in the CTT Collaboration were included. Nineteen trials compared statin versus placebo (n=123,940), and four trials compared more- versus less-intensive statin therapy (n=30,724). Meta-analysis of the data showed that allocation to low- or moderate-intensity statin therapy resulted in a 10% proportional increase in new-onset diabetes compared with placebo (rate ratio [RR] 1.10, 95% CI 1.04–1.16), and allocation to high-intensity statin therapy resulted in a 36% proportional increase (RR 1.36, 95% CI 1.25–1.48). In participants without diabetes at baseline, mean glucose level increased by 0.04 mmol/L with low-, moderate- and high-intensity statins, and mean HbA1c increased by 0.06% (95% CI 0.00–0.12) with low- or moderate-intensity statins and 0.08% (95% CI 0.07–0.09) with high-intensity statins. Among patients with diabetes at baseline, the RRs for worsening glycaemia were 1.10 (95% CI 1.06–1.14) for low- or moderate-intensity statin therapy and 1.24 (95% CI 1.06–1.44) for high-intensity statin therapy compared with placebo.

**Comment:** Statins have been associated with an increased risk of increasing glucose levels and triggering diabetes, but the magnitude of this risk has not been clear. This meta-analysis suggests that the risk is small but greater with intensive statin therapy compared with low-moderate intensity dosing, in that mean HbA1c increased by 0.06% with low-intensity or moderate-intensity statins and 0.08% with high-intensity statins. Development of type 2 diabetes occurred mostly in patients who were pre-diabetic, but the risk-benefit was still clearly in favour of statin therapy.

***Reference: Lancet Diabetes Endocrinol. 2024;12(5):306–19***
Abstract

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## Efficacy and safety of dapagliflozin in patients with acute heart failure

**Authors:** Cox ZL et al.

**Summary:** This multicentre, open-label study (DICTATE-AHF) investigated the diuretic efficacy and safety of early dapagliflozin initiation in patients with acute HF. 240 patients were randomised within 24h of hospitalisation for acute HF to dapagliflozin 10mg once daily or structured usual diuretic care. The primary outcome was diuretic efficiency at day 5 or hospital discharge, expressed as cumulative weight change per cumulative loop diuretic dose. Diuretic efficiency did not differ significantly between dapagliflozin and usual care groups (OR 0.65, 95% CI 0.41–1.02; p=0.06). Dapagliflozin was associated with reduced loop diuretic doses (p=0.006) and fewer intravenous diuretic up-titrations (p≤0.05) to achieve equivalent weight loss as usual care. It was also associated with improved median 24-h natriuresis and urine output during hospitalisation, and did not increase diabetic, renal, or cardiovascular adverse events.

**Comment:** This study looked at whether dapagliflozin affected the degree of diuretic dosing required in patients admitted with acute HF (HFrEF or HFpEF). It showed that the total dose of diuretics needed was reduced in patients who received dapagliflozin, and there were no safety signals. The results are in keeping with those of the SOLOIST and EMPULSE studies, which looked at similar populations. Taken together, these results show it is safe and effective to start SGLT2s in hospital in patients with acute HF, although PBS criteria for reimbursement are a bit uncertain in this area.

***Reference: J Am Coll Cardiol. 2024;83(14):1295–1306***
Abstract

## Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT)

**Authors:** Park SJ et al., for the PREVENT Investigators

**Summary:** The PREVENT study investigated whether preventive PCI of vulnerable plaques improved clinical outcomes compared with optimal medical therapy alone. At 15 research hospitals in four countries (South Korea, Japan, Taiwan, and NZ), 1606 adult patients (73% male) with non-flow-limiting vulnerable coronary plaques identified by intracoronary imaging were randomised 1:1 to either PCI plus optimal medical therapy or optimal medical therapy alone. The primary outcome was a composite of death from cardiac causes, target-vessel MI, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina. At 2 years, the primary outcome had occurred in 0.4% of patients in the PCI group compared with 3.4% of patients in the medical therapy alone group (p=0.0003). The incidence of serious clinical or adverse events did not differ between groups.

**Comment:** Traditionally, non-flow-limiting coronary lesions are not stented and intensive medical therapy is recommended. This study looked at whether PCI of coronary lesions with fractional flow reserve >80 (non-flow-limiting) that had characteristics of vulnerability on imaging was better than ongoing medical therapy, and showed that although event rates were low, there was a 3% absolute risk reduction at 2 years, with reductions in all the components of the primary end-point. If these data are confirmed they will be a game changer, as it will mean all non-flow-limiting plaques should be interrogated with intravascular ultrasound or optical coherence tomography, and if features of vulnerability are identified, PCI should be performed followed by optimal medical therapy.

***Reference: Lancet 2024;403(10438):1753–65***
Abstract

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