# Cardiology Research Review™

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## In this issue:


- Fractional flow reserve-guided PCI vs CABG for patients with triple vessel disease
- Safety of the oral factor Xla inhibitor asundexian in patients with AF
- Precarious employment and the risk of MI and stroke in middle-aged workers
- Coprescription of PDE5 inhibitors and oral nitrates in men with ischaemic heart disease
- Time to clinical benefit from intensive BP lowering in hypertensive patients
- The increasing role of rhythm control in patients with AF
- Management of ACS in patients in rural Australia
- Use of hs-cTnT in the ED to exclude acute myocardial injury and infarction
- Association between HDL cholesterol levels and adverse cardiovascular outcomes
- Long-term benefits of bariatric surgery on cardiovascular outcomes


**Abbreviations used in this issue:**

**ACS** = acute coronary syndrome; **AF** = atrial fibrillation; **BP** = blood pressure; **CABG** = coronary artery bypass grafting; **ED** = emergency department; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **hs-cTnT** = high-sensitivity cardiac troponin T; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **NOAC** = non-vitamin K antagonist oral anticoagulant; **PCI** = percutaneous coronary intervention; **PDE5** = phosphodiesterase type 5; **STEMI** = ST-segment elevation MI.



## Welcome to the latest issue of Cardiology Research Review.

In this issue, the FAME 3 study suggests that CABG is a better option than PCI for most patients with triple vessel disease, the PACIFIC-AF study determines the bleeding-related safety of asundexian (factor Xla inhibitor) in patients with AF, and a Swedish study highlights the deleterious effects of insecure employment on physical and psychological health. Also in this issue, a Danish observational study evaluates adverse events associated with coprescription of nitrates and PDE5 inhibitors in men with ischaemic heart disease, and an excellent review article explores the rationale for more widespread use of early rhythm control in the management of AF.

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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### Fractional flow reserve-guided PCI as compared with coronary bypass surgery

**Authors:** Fearon WF et al., for the FAME 3 Investigators


**Summary:** The multicentre non-inferiority FAME 3 trial investigated the use of fractional-flow reserve (FFR)-guided PCI compared with CABG in patients with triple vessel coronary artery disease. 1500 patients were randomised to undergo CABG or FFR-guided PCI with current-generation zotarolimus-eluting stents. The primary end-point was the occurrence of a major adverse cardiac or cerebrovascular event (MACCE) within 1 year, defined as death from any cause, MI, stroke, or repeat revascularisation. Non-inferiority of FFR-guided PCI to CABG was prespecified as an upper boundary of <1.65 for the 95% CI of the hazard ratio. The 1-year incidence of MACCE was 10.6% with FFR-guided PCI and 6.9% with CABG (HR 1.5, 95% CI 1.1–2.2).


**Comment:** This important study showed that multivessel FFR-guided PCI for revascularisation was not non-inferior to surgical revascularisation for patients with triple vessel coronary artery disease, despite the non-inferiority boundary being very generous (1.65), in that there was less death, MACE and revascularisation in patients who had surgery compared with PCI at 1 year. This suggests that surgery is a better option for most patients with triple vessel disease, and should guide our practice.


***Reference: N Engl J Med 2022;386:128-37***
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.

## Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF)

**Authors:** Piccini JP et al.

**Summary:** This multicentre phase 2 study evaluated the bleeding-related safety of the factor XIa inhibitor asundexian compared with apixaban in patients with AF. At 93 sites in 14 countries, 755 patients aged ≥45 years with AF, a $CHA_2DS_2$-VASc score of ≥2 (male) or ≥3 (female), and an increased bleeding risk were randomised 1:1:1 to receive asundexian 20mg or 50mg once daily or apixaban 5mg twice daily in a double-dummy design. The primary end-point was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least 1 dose of study medication. Ratios of incidence proportions for the primary end-point were 0.50 (90% CI 0.14–1.68) for asundexian 20mg (3 events), 0.16 (90% CI 0.01–0.99) for asundexian 50mg (1 event), and 0.33 (90% CI 0.09–0.97) for pooled asundexian (4 events) versus apixaban (6 events).

**Comment:** The development of the NOACs changed the treatment paradigm for stroke prevention in AF as they were shown to be safer with respect to bleeding and as good as or better in reducing stroke compared with warfarin. The factor XIa inhibitors are the next evolution of antithrombotic therapy in this field, as they are said to be as effective as NOACs for stroke prevention but with even less bleeding. Large randomised controlled trials are about to start with these agents versus NOACs globally, and Australian research centres will be involved.

***Reference: Lancet 2022;399(10333):1383-90***
Abstract

## Trajectories of precarious employment and the risk of myocardial infarction and stroke among middle-aged workers in Sweden

**Authors:** Matilla-Santander N et al.

**Summary:** This register-based Swedish cohort study investigated the association between trajectories of precarious employment (PE) over time and the risk of MI and stroke. 1,583,957 individuals aged 40–61 years living in Sweden in 2003–2007 were included in the analysis. Adjusted estimates showed that constant PE and borderline PE trajectories increased the risk of MI (risk ratio [RR] 1.08, 95% CI 1.05–1.11; and RR 1.13, 95% CI 1.07–1.20, respectively) and stroke (RR 1.14, 95% CI 1.10–1.18; and RR 1.24, 95% CI 1.16–1.33, respectively) in males. Having constant low or very low income was associated with an increased risk of MI and stroke in both males and females.

**Comment:** With the increasing trend to insecure employment worldwide, there has been much debate about the deleterious effects of insecure (precarious) employment on physical and psychological health. This study shows that not having a secure job and reliable source of income translates into real health risks, indicating that the chronic stress of this lifestyle compromises patient health. What can be done about this is more difficult and contentious as providing secure long-term employment outside government-funded programmes is challenging in the current economic environment.

***Reference: Lancet Reg Health Eur 2022;15:100314***
Abstract

## Adverse events associated with coprescription of phosphodiesterase type 5 inhibitors and oral organic nitrates in male patients with ischemic heart disease

**Authors:** Holt A et al.

**Summary:** This Danish study evaluated adverse events associated with coprescription of oral nitrates and PDE5 inhibitors in males with ischaemic heart disease (IHD). 249,541 males in Denmark who were identified as having IHD in 2000–2018 were included. During this period, the prescription rate for PDE5 inhibitors in patients with IHD who were taking nitrates increased from an average of 0.9 prescriptions per 100 persons per year in 2000 to 19.5 prescriptions per 100 persons per year in 2018. Two composite outcomes were measured: 1) cardiac arrest, shock, MI, ischaemic stroke, or acute coronary arteriography; and 2) syncope, angina pectoris, or drug-related adverse event. No significant association was found between coprescription of nitrates and PDE5 inhibitors and either of the composite outcomes.

**Comment:** It has been traditionally thought that patients taking oral nitrates should not take PDE5 inhibitors, such as sildenafil, due to the risk of severe hypotension. This Danish observational study suggests that this may not be the case, although as it was an observational study, it was not able to report if patients on oral nitrates omitted them on the day they took PDE5 inhibitors. Even if they did not take the 2 drugs on the same day, this is an important observation as there was no increase in MACE, angiography or angina in patients prescribed the 2 medications. Therefore, we can be a bit more comfortable prescribing PDE5 inhibitors to patients with coronary artery disease who are on nitrates as long as they don't take the 2 drugs on the same day.

***Reference: Ann Intern Med 2022; published online Apr 19***
Abstract

## Time to clinical benefit of intensive blood pressure lowering in patients 60 years and older with hypertension

**Authors:** Chen T et al.

**Summary:** This meta-analysis investigated the time to clinical benefit of intensive BP lowering in older patients with hypertension. A search of PubMed identified 6 trials (original data from 2 trials and reconstructed data from 4 trials) with 27,414 participants (mean age 70 years, 56.3% female) that were suitable for inclusion. Meta-analysis of the data found that intensive BP treatment (systolic BP target <140mm Hg) was associated with a 21% reduction in MACE (HR 0.79, 95% CI 0.71–0.88; p<0.001). It was estimated that a mean 9.1 months of treatment were needed to prevent 1 MACE per 500 patients, 19.1 months were needed to prevent 1 MACE per 200 patients, and 34.4 months were needed to prevent 1 MACE per 100 patients.

**Comment:** Lowering BP improves cardiovascular outcomes irrespective of age. This meta-analysis confirms this, but also shows that the beneficial effects of BP reduction take time to accrue, so that in patients whose life expectancy is less than 1 year the risk of side effects outweighs the benefits, indicating that aggressive BP lowering is not appropriate in this population.

***Reference: JAMA Intern Med 2022; published online May 9***
Abstract

## The increasing role of rhythm control in patients with atrial fibrillation: *JACC* state-of-the-art review

**Authors:** Camm AJ et al.

**Summary:** Evidence supports early rhythm control in patients with AF, but current clinical practice and guidelines do not yet fully reflect this change. Early rhythm control has the potential to halt AF progression and potentially save patients from years of symptomatic AF, and should therefore be offered more widely. This review article explored the rationale and evidence for more widespread adoption of early rhythm control in the management of AF.

**Comment:** This excellent review examines the evidence for initiating an early rhythm control strategy in patients with AF, as recent data suggest this approach improves outcomes, quality of life and pill burden in patients with relatively recent-onset AF. It has traditionally been thought that there was no benefit of a rhythm control approach over rate control, but this was based on data more than 20 years old, and these new studies effectively debunk this old way of thinking. Rhythm control should now be considered the optimal treatment for most patients with recent-onset AF.

***Reference: J Am Coll Cardiol 2022;79(19):1932-48***
Abstract

## Management of acute coronary syndromes in patients in rural Australia

**Authors:** Dee F et al.

**Summary:** This randomised clinical trial evaluated the impact of a MORACS (management of rural ACS) intervention on STEMI diagnoses in rural Australia. 29 hospital EDs in rural Australia with no emergency medicine specialists were cluster randomised to provide usual care or the MORACS intervention for patients presenting with ACS symptoms. For the intervention, triage of a patient with ACS symptoms triggered an automated notification to a tertiary hospital coronary care unit; electrocardiogram and point-of-care troponin results were reviewed remotely and the rural hospital physician was assisted (via telephone) with the diagnosis and initiation of treatment. Of 7474 ED presentations with suspected ACS, STEMI accounted for 2.0% of presentations in usual care hospitals and 1.3% of presentations in MORACS hospitals. Missed diagnosis of STEMI occurred in 35% of suspected ACS presentations in usual care hospitals and 0% of presentations in MORACS hospitals (p<0.001). Patients with missed STEMI diagnoses had a mortality of 25.9% compared with 2.0% for those with accurately diagnosed STEMI (relative risk 13.2, 95% CI 1.71–102.00; p=0.001).

**Comment:** This Australian study shows that a diagnostic support service from a tertiary referral hospital for rural hospitals improves the rate and appropriate management of MI, compared with usual care, and that this approach reduced the rate of mortality from MI. This is a relatively low tech area of innovation, but its implementation may be challenging over a 24h period, as during the working day there is plenty of registrar /fellow and consultant cover but this is more limited after hours.

***Reference: JAMA Cardiol 2022; published online May 25***
Abstract



## Rapid exclusion of acute myocardial injury and infarction with a single high sensitivity cardiac troponin T in the emergency department

**Authors:** Sandoval Y et al.

**Summary:** This US cohort study investigated whether a single hs-cTnT level <6 ng/L is a safe cutoff for identifying patients in the ED who are at low-risk for acute myocardial injury and infarction. The cohort comprised 85,610 patients who presented to an ED with chest pain, 24,646 (29%) of whom had a hs-cTnT level <6 ng/L. Women were more likely than men to have hs-cTnT <6 ng/L (38% vs 20%; p<0.0001). Of 11,962 patients with hs-cTnT <6 ng/L in the ED followed by serial measurements, only 1.2% developed acute myocardial injury (negative predictive value 98.8% and sensitivity 99.6%). In an adjudicated cohort, a non-ischaemic electrocardiogram with hs-cTnT <6 ng/L identified 33% of patients as low-risk, with a 30-day rate of MI or death of 0.2%.

**Comment:** Most patients presenting to EDs in Australia have an initial and 6h troponin to rule out MI, which often jams up ED beds. This study looked at the risk of ischaemia in patients whose initial troponin estimation was negative and found that only 1.2% of these patients subsequently had an ischaemic event. Implementing this strategy could allow earlier discharge of these very low-risk patients for outpatient follow up, with an acceptable and small risk of a subsequent ischaemic event.

***Reference: Circulation 2022; published online May 10***
Abstract

## Association between high-density lipoprotein cholesterol levels and adverse cardiovascular outcomes in high-risk populations

**Authors:** Liu C et al.

**Summary:** This multicentre cohort study investigated the association between very high HDL cholesterol levels (>80 mg/dl) and mortality in patients with coronary artery disease. 14,478 patients with coronary artery disease who were registered with UK Biobank (UKB) and 5467 patients in Atlanta, Georgia, who were registered with Emory Cardiovascular Biobank (EmCAB) were included. Over a median follow-up of 8.9 years (UKB) and 6.7 years (EmCAB), a U-shaped association with mortality outcomes was observed, with higher risk in patients with both low and very high HDL cholesterol levels compared with those with mid-range values. In the UKB, a very high HDL cholesterol level (>80 mg/dl) was associated with increased risk of all-cause death (HR 1.96, 95% CI 1.42–2.71; p<0.001) and cardiovascular death (HR 1.71, 95% CI 1.09–2.68; p=0.02) compared with those with HDL cholesterol levels 40–60 mg/dl, after adjustment for confounding factors. Similar results were found with EmCAB data.

**Comment:** It has been shown in older large observational studies that low HDL increases the risk of cardiovascular disease and that a high HDL is protective, so much so that high LDL levels in older women are often not treated if they have no overt cardiovascular disease and have a high HDL. Population data have raised concerns that high HDL may not be as protective as previously thought, and this has been confirmed in this large cohort study, where an HDL >2.1 was associated with worse outcomes. This suggests that low-density lipoprotein cholesterol should be the primary focus in both primary and secondary prevention, and that HDL levels should not influence the decision to treat or not.

***Reference: JAMA Cardiol 2022; published online May 18***
Abstract

## Long-term cardiovascular outcomes after bariatric surgery in the Medicare population

**Authors:** Mentias A et al.

**Summary:** This study evaluated long-term cardiovascular outcomes after bariatric surgery in the Medicare population. Medicare beneficiaries who underwent bariatric surgery in 2013–2019 were propensity-score matched 1:1 to a control group of patients with obesity who did not undergo bariatric surgery. The study cohort comprised 189,770 patients (94,885 in each group). By study design, the 2 groups had similar age, sex, and degree of obesity, and were well balanced on all clinical variables. After a median 4-year follow-up, bariatric surgery was associated with a lower risk of mortality (HR 0.63, 95% CI 0.60–0.66), new-onset heart failure (HR 0.46, 95% CI 0.44–0.49), MI (HR 0.63, 95% CI 0.59–0.68), and stroke (HR 0.71, 95% CI 0.65–0.79).

**Comment:** Obesity is increasing in epidemic proportions globally and is associated with greater rates of hypertension, type 2 diabetes, obstructive sleep apnoea and cardiovascular disease. This study shows that weight loss induced by bariatric surgery in morbidly obese patients significantly improves cardiovascular outcomes and should be considered in these patients. The availability of this in Australia is limited and patients' characteristics increasing the chances of success have yet to be clearly defined. Whether weight loss with the GLP1 agonists will produce similar results is not clear yet, but studies are underway.

***Reference: J Am Coll Cardiol 2022;79(15):1429-37***
Abstract



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