# Cardiology Research Review™

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**Abbreviations used in this issue:**

**AF** = atrial fibrillation; **BP** = blood pressure; **CV** = cardiovascular; **HF** = heart failure; **HFpEF** = HF with preserved ejection fraction; **HR** = hazard ratio; **KDC** = kidney age – chronological age difference; **LDL** = low-density lipoprotein; **LV** = left ventricular; **MI** = myocardial infarction; **NOAC** = non-vitamin K oral anticoagulant; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **SGLT2** = sodium glucose cotransporter-2.

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

In this issue, a study of the sugar substitute erythritol debunks the common misperception that diet drinks are healthier, the debate continues with respect to the cardiac effects of caffeine, and Swedish investigators confirm that some patients respond differently to different antihypertensive drug classes. Also in this issue, the BOAT-AF trial looks at the reasons why anticoagulants are not always prescribed for patients with nonvalvular AF, and a prespecified analysis of the DELIVER trial shows that it is never too late to start treatment with dapagliflozin in patients with HFpEF.

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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### The artificial sweetener erythritol and cardiovascular event risk

**Authors:** Witkowski M et al.


**Summary:** This study investigated the association between the sugar substitute erythritol and atherothrombotic disease risk. In initial untargeted metabolomics studies in 1157 patients undergoing cardiac risk assessment (discovery cohort), circulating levels of various polyol sweeteners (including erythritol) were associated with 3-year risk of incident major adverse CV events (MACE). Subsequent targeted metabolomics analyses in independent US (n=2149) and European (n=833) validation cohorts of stable patients undergoing elective cardiac evaluation confirmed the association. In a prospective pilot study in 8 healthy volunteers, erythritol ingestion induced marked and sustained increases in plasma erythritol levels well above thresholds associated with heightened platelet reactivity and thrombosis potential in *in vitro* and *in vivo* studies.


**Comment:** Diet soft drinks that contain no sugar are postulated to be healthier than their high sugar counterparts. These no-sugar drinks use artificial sweeteners and are often made more palatable by adding salt to attenuate the bitterness of many of these compounds. This study sounds alarm bells and suggests that erythritol, a widely used artificial sweetener, has long-lasting effects on platelet activation and increased risk of MACE. This certainly deserves more study, as if these findings are confirmed, the common perception that diet drinks are healthier may be incorrect, as the reduction in calories may be counterbalanced by an increased thrombotic risk.


***Reference: Nat Med 2023;29:710-8***

Abstract

### Self-screening for atrial fibrillation could reduce stroke

Atrial Fibrillation (AF) screening is recommended for people aged 65 and over, but only 11 per cent of eligible patients are screened by their GPs, often due to time constraints. This key paper by Prof Ben Freedman from the Heart Research Institute demonstrated that the use of AF self-screening stations in GP waiting rooms could improve AF screening and diagnosis rates, and reduce the number of AF-related strokes.

HRI HEART RESEARCH INSTITUTE

## Acute effects of coffee consumption on health among ambulatory adults

**Authors:** Marcus GM et al.

**Summary:** This prospective crossover trial examined the acute health effects of caffeinated coffee consumption. 100 adults (mean age 39 years, 51% female) were fitted with a continuously recording electrocardiogram device, a wrist-worn accelerometer, and a continuous glucose monitor, and downloaded a smartphone app to collect geolocation data. Text messages were sent to participants daily for 14 days to randomly instruct them to consume caffeinated coffee or avoid caffeine. The primary outcome was the mean number of daily premature atrial contractions. Caffeinated coffee consumption was associated with 58 premature atrial contractions daily, compared with 53 daily events on days when caffeine was avoided (p=ns).

**Comment:** The debate continues with respect to the cardiac effects of coffee consumption. Anecdotally, many people say that drinking coffee causes palpitations and tremor, especially if consumed in large quantities. This study shows there is no increase in atrial or ventricular ectopic activity induced by coffee drinking, with no difference between the days when coffee was consumed or avoided. This study still does not answer the question as to whether there is a dose-related increase in heart rate or ectopic activity with drinking coffee, and whether there are differences in sensitivity to coffee between patients, as many patients seem to tolerate 1–2 cups per day, but notice an increase in heart rate and tremor with excessive consumption.

***Reference: N Engl J Med 2023;388(12):1092-1100***
Abstract

## Prediction of cardiovascular death and non-fatal cardiovascular events by the kidney age–chronological age difference (KCD) score in men and women of different ages in a community-based cohort

**Authors:** Campbell DJ et al.

**Summary:** This analysis of the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) cohort investigated the utility of the KCD score, an age-adapted measure of kidney function, to predict CV death or non-fatal CV events. 11,180 community-based individuals aged 23–95 years from urban and nonurban areas across Australia who had serum creatinine levels measured at baseline were included in the analysis. 308 CV deaths or non-fatal CV events were reported during 5 years of follow-up. Penalised spline curve analysis showed similar progressive increase in CV death or non-fatal CV event risk with increasing KCD score in males and females, and in participants aged <50 years to ≥80 years. Receiver operating characteristic curve analysis showed optimal discrimination at a KCD score ≥20 years (KCD20) for all participants.

**Comment:** We know that renal dysfunction is an under-recognised risk factor for CV disease, and that mortality in patients with advanced renal disease is predominantly from CV disease rather than renal. This Australian study looked at CV outcomes in the AusDiab study related to markers of renal dysfunction. It showed that the KCD20 score predicted CV events in patients aged 50–80 years, but it was particularly effective in patients <70 years old, as it was a stronger predictor of events than decreased estimated glomerular filtration rate. This score may identify higher risk patients for targeted intervention and allow earlier initiation of therapies to reduce renal and CV risk.

***Reference: BMJ Open 2023;13:e068494***
Abstract



## Heterogeneity in blood pressure response to 4 antihypertensive drugs

**Authors:** Sundström J et al.

**Summary:** This randomised crossover trial in Sweden investigated the heterogeneity in BP response to four antihypertensive drug classes. 280 patients (mean age 64 years, 54% male) with grade 1 hypertension who were at low risk for CV events were scheduled for treatment in random order with four different classes of BP-lowering drugs: angiotensin-converting enzyme inhibitor (lisinopril), angiotensin-receptor blocker (candesartan), thiazide diuretic (hydrochlorothiazide), and calcium channel blocker (amlodipine). Median duration of treatment was 56 days. The BP response to different treatments varied considerably between individuals (p<0.001), specifically for lisinopril versus hydrochlorothiazide, lisinopril versus amlodipine, candesartan versus hydrochlorothiazide, and candesartan versus amlodipine. It was estimated that personalised treatment had the potential to provide a mean additional 4.4mm Hg decrease in ambulatory daytime systolic BP.

**Comment:** This interesting study demonstrates what we frequently see in clinical practice, in that some patients respond to BP-lowering medication differently. The reasons for this could be related to factors such as high or low renin levels, activation of the sympathetic nervous system and volume status, but it is likely that there are genetic factors that are unknown at present. I think it is likely that as time goes on these genetic determinants of response to BP-lowering medications will be discovered, and that in the future we will be able to tailor antihypertensive medication according to the genetic and haemodynamic profile of the individual patient.

***Reference: JAMA 2023;329(14):1160-9***
Abstract

## Patients and their physician's perspectives about oral anticoagulation in patients with atrial fibrillation not receiving an anticoagulant

**Authors:** Cannon CP et al., for the BOAT-AF Investigators and Research Coordinators

**Summary:** The BOAT-AF study investigated the perceptions of untreated AF patients and their physicians about the risk of stroke associated with AF and the benefits and risks of anticoagulation. 817 patients with nonvalvular AF and a $CHA_2DS_2$-VASc score ≥2 who were not receiving anticoagulation were enrolled from the PINNACLE Registry. Each patient completed a survey, and their treating physician then conducted a clinical review of their care. The top five reasons the physicians cited for no anticoagulation were low AF burden or successful rhythm control (34.0%), patient refusal (33.3%), perceived low risk of stroke (25.2%), falls risk (21.4%), and high bleeding risk (20.4%). Of the 647 patients (79.2%) who were adjudicated to be (or may be) appropriate for anticoagulation, physicians said they would reconsider anticoagulation for only 21.2% of them, while 64.5% of the patients said they would either agree to starting anticoagulation or were neutral to the idea. At follow-up, 14.6% of patients had been prescribed an anticoagulant.

**Comment:** There are a substantial number of patients who are eligible for and would benefit from anticoagulation for stroke prevention in nonvalvular AF who are not prescribed therapy. This study looked at this cohort of patients and found that there were physician-related reasons for not prescribing anticoagulation, more so than patient-related factors. Given the safety and efficacy of the NOACs we should readdress anticoagulation every time we see these patients, as excess bleeding and falls risk are not good reasons to withhold therapy, and this study shows that many patients who have initially refused anticoagulation change their mind over time.

***Reference: JAMA Netw Open 2023;6(4):e239638***
Abstract

## Association between achieved low-density lipoprotein cholesterol levels and long-term cardiovascular and safety outcomes

**Authors:** Gaba P et al.

**Summary:** This analysis of the FOURIER open-label extension (OLE) investigated the association between achieved LDL cholesterol levels and long-term CV and safety outcomes in patients with stable atherosclerotic CV disease. 6559 patients who had received open-label evolocumab in the FOURIER-OLE for a median 5 years after finishing the double-blind trial were included. 24%, 40%, 16%, 7%, and 12% of them achieved LDL cholesterol levels of <20, 20 to <40, 40 to <55, 55 to <70, and ≥70 mg/dl, respectively. There was a monotonic relationship between lower achieved LDL cholesterol levels down to <20 mg/dl (<0.5 mmol/L) and a lower risk of the primary efficacy end-point (a composite of CV death, MI, stroke, hospital admission for unstable angina or coronary revascularisation). No significant associations were seen between lower achieved LDL cholesterol levels and increased risk of safety outcomes.

**Comment:** Despite the large clinical trials with PCSK9 inhibitors showing that very low LDL levels (<0.5 mmol/L) were not associated with risk, there has always been residual doubt as these were relatively short-term trials. This analysis of the FOURIER-OLE that studied patients who were on evolocumab for at least 7 years, showed that the lower the LDL, the better the outcome, with no hint of a safety signal. This being the case there is no justification for reducing lipid-lowering therapies on the basis that LDL is too low.

***Reference: Circulation 2023;147(16):1192-1203***
Abstract

## Prevalence and prognostic significance of bradyarrhythmias in patients screened for atrial fibrillation vs usual care

**Authors:** Diederichsen SZ et al.

**Summary:** This post hoc analysis of the LOOP trial investigated the prevalence and prognostic significance of bradyarrhythmias in individuals screened for AF using an implantable loop recorder (ILR). 6004 patients aged ≥70 years without known AF but diagnosed with hypertension, diabetes, heart failure, or prior stroke were randomised to ILR screening for AF (ILR group) or to usual care. During a median follow-up of 65 months, bradyarrhythmia was diagnosed in 20.8% of patients in the ILR group compared with 3.8% of controls (p<0.001); these bradyarrhythmias were asymptomatic in 249 (79.8%) and 41 (23.8%) participants, respectively. Sinus node dysfunction was the most common bradyarrhythmia, followed by high-grade atrioventricular block. Risk factors for bradyarrhythmia included older age, male sex, and prior syncope. A pacemaker was implanted in 4.5% and 2.9% of patients in the ILR and control groups, respectively (HR 1.53, 95% CI 1.14–2.06; p<0.001), but syncope and sudden CV death rates did not differ significantly between groups.

**Comment:** This study not surprisingly showed that there is a higher detection rate of bradyarrhythmias when older patients are continuously monitored with ILR compared with standard care, but 80% of these were asymptomatic. There was a significant increase in pacemaker implantation in the ILR group, but this did not reduce the rate of syncope or death. This being the case I wonder if it is appropriate to pace patients with asymptomatic bradyarrhythmias, as it would seem that prophylactic pacing does not reduce hard event rates, so perhaps pacing should be mainly used for symptomatic bradyarrhythmia?

***Reference: JAMA Cardiol 2023;8(4):326-34***
Abstract

## Patient characteristics, outcomes, and effects of dapagliflozin according to the duration of heart failure

**Authors:** Kondo T et al.

**Summary:** This prespecified analysis of the DELIVER trial compared patient characteristics, outcomes, and effects of dapagliflozin according to HF duration in patients with mildly reduced or preserved ejection fraction. HF duration was categorised as ≤6 months (n=1160), >6 to 12 months (n=842), >1 to 2 years (n=995), >2 to 5 years (n=1569), or >5 years (n=1692). Patients with longer-duration HF were older and had more comorbidities with worse symptoms. The primary outcome was a composite of worsening HF or CV death. The rate of the primary outcome (per 100 person-years) increased with HF duration, from 7.3 for a duration ≤6 months to 10.6 for a duration >5 years. The benefit of dapagliflozin was consistent across HF duration categories. The absolute benefit was greatest in longest-duration HF: the number needed to treat was 24 for HF duration >5 years versus 32 for HF duration ≤6 months.

**Comment:** It is often thought that the longer the duration of HF, the less benefit there may be with therapy, due to the development of irreversible structural changes in the myocardium. This study showed that in patients with HFpEF in the DELIVER trial, the greater the duration of HF the greater the rate of worsening HF and death, but it also demonstrated that the benefits of dapagliflozin were maintained irrespective of the duration of HF, so it is never too late to start this therapy. Whether this applies to patients with HFrEF has not been reported, but is likely to be the case.

***Reference: Circulation 2023;147(14):1067-78***
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.

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## The association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in anthracycline-treated patients with cancer

**Authors:** Abdel-Qadir H et al.

**Summary:** This population-based cohort study investigated the impact of SGLT2 inhibitors on the risk of anthracycline-associated cardiotoxicity. 933 patients aged >65 years with treated diabetes (99 were taking an SGLT2 inhibitor) and no prior HF who received anthracycline-containing chemotherapy in 2016–2019 were included. During a median follow-up of 1.6 years, there were 31 hospitalisations for HF (none in patients taking an SGLT2 inhibitor), 93 new HF diagnoses, and 74 hospitalisations with documented CV disease. Compared with patients not taking an SGLT2 inhibitor, SGLT2 inhibitor exposure significantly decreased HF hospitalisations (HR, 0.00; p<0.001), but did not decrease incident HF diagnoses, CV disease diagnoses, or mortality.

**Comment:** We know that anthracyclines cause LV dysfunction in most patients who receive them for treatment of malignancy, and that recent data from the American College of Cardiology showed that atorvastatin reduced the risk of LV dysfunction in patients treated with anthracyclines for lymphoma. We also know that in patients with type 2 diabetes, SGLT2 inhibitors reduce the risk of hospitalisation for HF. This study shows that in patients with type 2 diabetes without overt HF who receive anthracyclines, the reduction in hospitalisations for HF with SGLT2 inhibition was similar to that seen in the earlier studies. This suggests that SGLT2 inhibitors could be used as preventative therapy in patients with type 2 diabetes who require anthracycline therapy, but whether this protective effect is present in patients without type 2 diabetes who receive anthracyclines has yet to be studied. The beneficial effects of SGLT2 inhibitors on HF were seen in HF patients with and without type 2 diabetes, so this is a promising area to be researched.

***Reference: J Am Coll Cardiol CardioOnc 2023; published online May 9***
Abstract

## Association of beta-blockers beyond 1 year after myocardial infarction and cardiovascular outcomes

**Authors:** Ishak D et al.

**Summary:** This nationwide cohort study in Sweden investigated the role of beta-blockers beyond one year post MI. 43,618 patients who had an MI in 2005–2016 were included. Overall, 78.5% of them were still taking a beta-blocker one year post MI and 21.5% were not. Patients were followed up until 31 Dec 2017; those with HF or LV systolic dysfunction were excluded. In the intention-to-treat analysis, the unadjusted rate of the primary outcome (a composite of all-cause mortality, MI, unscheduled revascularisation and hospitalisation for HF) during follow-up was lower among patients who were taking a beta-blocker beyond one year post MI (3.8 vs 4.9 events/100 person-years; HR 0.76, 95% CI 0.73–1.04). However, after inverse propensity score weighting and multivariable adjustment, the risk of the primary outcome did not differ according to beta-blocker treatment (HR 0.99, 95% CI 0.93–1.04).

**Comment:** Early studies showed beneficial effects of 1–2 years' beta -blockade after MI, but this was before there was routine revascularisation and before guideline-directed medical therapy was available. Although most contemporary guidelines recommend lifelong beta-blockers after MI, many physicians stop them at 12 months if LV function is normal and there is no other indication for continuation, such as residual coronary artery disease that can't be fixed, AF or LV dysfunction. This study supports this practice as it showed no difference in outcomes if the beta-blocker was discontinued at 12 months post MI compared with ongoing use, if there was no compelling reason for continuation.

***Reference: Heart 2023; published online May 2***
Abstract



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