Cardiology Research Review™

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Abbreviations used in this issue:

AF = atrial fibrillation; **COVID-19** = coronavirus disease 2019; **DOAC** = direct oral anticoagulant; **ESC** = European Society of Cardiology; **GLP-1** = glucagon-like peptide-1; **HFpEF** = heart failure with preserved ejection fraction; **HR** = hazard ratio; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **SGLT2** = sodium-glucose co-transporter-2; **STEMI** = ST-segment elevation MI; **TIA** = transient ischaemic attack.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, a meta-analysis of 6 cohort studies supports reducing dietary sodium intake and increasing potassium intake to reduce cardiovascular risk, a US study evaluates the association between COVID-19 diagnosis and in-hospital mortality in STEMI patients, and another US study finds disappointing rates of statin prescribing after lower extremity revascularisation procedures. Also in the issue, Danish researchers find that there is ongoing benefit in continuation of statin therapy in the elderly for both primary and secondary prevention, a case-crossover analysis reports that alcohol can trigger an AF episode within hours in people with paroxysmal AF, and a very large meta-analysis finds that fewer than 10% of patients have true statin intolerance.

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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24-Hour urinary sodium and potassium excretion and cardiovascular risk

Authors: Ma Y et al.

Summary: This meta-analysis investigated the association between 24-h urinary sodium and potassium excretion and cardiovascular risk. 10,709 healthy individuals (mean age 51.5 years) from 6 prospective cohort studies were included; sodium and potassium excretion was assessed using at least two 24-h urine samples per participant. 571 cardiovascular events (coronary revascularisation or fatal or nonfatal MI or stroke) occurred during a median follow-up of 8.8 years (incidence rate, 5.9 per 1000 person-years). Higher sodium excretion, lower potassium excretion, and a higher sodium-to-potassium ratio were all associated with higher cardiovascular risk ($p \leq 0.005$ for all comparisons) after adjustment for confounders. Each 1000 mg/day increment in sodium excretion was associated with an 18% increase in cardiovascular risk (HR 1.18, 95% CI 1.08–1.29), and each 1000 mg/day increment in potassium excretion was associated with an 18% decrease in risk (HR 0.82, 95% CI 0.72–0.94).

Comment: Data presented at the ESC Congress last year showed that a salt substitution strategy (75% NaCl and 25% KCl) improved cardiovascular outcomes and reduced death in Chinese patients who had hypertension and a history of stroke or were >60 years of age. This study supports these findings, as it showed that higher sodium and lower potassium in the diet (as measured by urinary analysis) was associated with adverse outcomes. Although the first of these studies was performed in China where there is generally a high salt consumption, the second was in a predominantly Western population so the results are generalisable. Thus, pressure should be put on salt manufacturers to change to the salt substitute preparation (which is indistinguishable in taste from 100% NaCl salt) as a public health initiative.

Reference: N Engl J Med 2022;386:252-63

Abstract

Association between COVID-19 diagnosis and in-hospital mortality in patients hospitalized with ST-segment elevation myocardial infarction

Authors: Saad M et al.

Summary: This retrospective cohort study evaluated the association between COVID-19 diagnosis and in-hospital mortality in patients hospitalised with STEMI. 80,449 consecutive adult patients hospitalised in 2019–2020 with out-of-hospital (n=76,434) or in-hospital (n=4015) STEMI at 509 US centres were included. In patients with out-of-hospital STEMI, in-hospital mortality rates were 15.2% in patients with COVID-19 and 11.2% in patients without COVID-19 (absolute difference 4.1%, 95% CI 1.1–7.0; p=0.007). In patients with in-hospital STEMI, in-hospital mortality rates were 78.5% in those with COVID-19 and 46.1% in those without COVID-19 (absolute difference 32.4%, 95% CI 29.0–35.9; p<0.001).

Comment: This article demonstrates the adverse interaction between acute MI and active COVID, in that outcomes were clearly worse in patients with STEMI and COVID, compared with patients without COVID, whether the MI occurred in or out of hospital. Whether COVID was the trigger for the MI is not clear, but I suspect it was, given the prothrombotic milieu that is associated with active COVID infection.

Reference: JAMA 2021;326(19):1940-52

Abstract

Prescribing of statins after lower extremity revascularization procedures in the US

Authors: Singh N et al.

Summary: This US cross-sectional study evaluated longitudinal trends in statin use in patients with peripheral artery disease (PAD) undergoing lower extremity revascularisation. 125,791 patients undergoing a total of 172,025 procedures in 2014–2019 were included. Overall, rates of statin prescription at discharge improved from 75% of patients in 2014 to 87% of patients in 2019. However, only 30% of 42,020 patients not already taking a statin at the time of revascularisation were newly discharged with a statin medication. New statin prescription rates were substantially lower after endovascular intervention (26%) than after lower extremity bypass (41%). Body mass index ≥30, diabetes, smoking, hypertension, and coronary heart disease were associated with an increased likelihood of new statin prescription after endovascular intervention, whereas female sex, older age, antiplatelet use, and prior peripheral revascularisation were associated with a decreased likelihood.

Comment: This study identifies a large treatment gap in prescribing guideline-directed therapy in patients with PAD who receive revascularisation in the US, in that only 30% of patients who were not on a statin before intervention were started on one during their admission, despite good evidence that lowering cholesterol improves outcomes in this high-risk population. I would hope Australian figures would be better than this, as lipid lowering is one of the most important treatments in patients with PAD, along with smoking cessation and controlling hypertension and diabetes.

Reference: JAMA Netw Open 2021;4(12):e2136014
Abstract

Statin discontinuation and cardiovascular events among older people in Denmark

Authors: Thompson W et al.

Summary: This Danish cohort study evaluated the association between statin discontinuation and MACE rates among patients aged ≥75 years. All adults in Denmark aged ≥75 years who had been treated with statins for at least 5 consecutive years as of Jan 1, 2011 were followed up through 2016. The main outcome was rate of occurrence of MACE and its components (MI, ischaemic stroke or TIA, coronary revascularisation, and death due to MI or ischaemic stroke) in patients continuing statins compared with those discontinuing statins. 67,418 long-term statin users were included, comprising 27,463 in a primary prevention analysis (median age 79 years, 66% female) and 39,955 in a secondary prevention analysis (median age 80 years, 47% female). In both the primary and secondary prevention analyses, the rate of MACE was higher among those who discontinued statins compared with those who continued statins. Adjusted sub-hazard ratios were 1.32 (95% CI 1.18–1.48) in the primary prevention cohort and 1.28 (95% CI 1.18–1.39) in the secondary prevention cohort.

Comment: We are often tempted to deprescribe medication in the elderly to reduce pill burden and polypharmacy. These data suggest that there is ongoing benefit in continuation of statin therapy in the elderly for both primary and secondary prevention, as cardiovascular event rates over 5 years were higher in patients who discontinued statins for whatever reason. We should thus encourage our elderly patients to continue statin therapy as they get older, and only consider discontinuation for real intolerance or adverse reactions.

Reference: JAMA Netw Open 2021;4(12):e2136802
Abstract

Independent commentary by Associate Professor John Amerena, FRACP, FACC, FCSANZ, Dept. of Clinical and Biomedical Science, University of Melbourne (Geelong). Full biography here.

Acute consumption of alcohol and discrete atrial fibrillation events

Authors: Marcus GM et al.

Summary: This prospective case-crossover analysis investigated whether alcohol consumption increases the risk of an AF episode in patients with paroxysmal AF. 100 ambulatory patients (mean age 64 years, 79% male) with paroxysmal AF were fitted with a continuous electrocardiogram (ECG) monitor and an ankle-worn transdermal ethanol sensor for 4 weeks. Real-time documentation of alcoholic drink consumption was self-recorded using a button on the ECG recording device, and fingerstick blood tests were used to corroborate drinking events. 56 participants had at least 1 episode of AF during the 4-week study period. An AF episode was twice as likely after 1 alcoholic drink in the preceding 4 hours (odds ratio [OR] 2.02, 95% CI 1.38–3.17) and more than 3 times as likely after ≥2 drinks (OR 3.58, 95% CI 1.63–7.89) compared with no alcohol. Episodes of AF were also associated with higher peak blood alcohol concentration and the total area under the curve of alcohol exposure in the preceding 12h.

Comment: Reducing alcohol consumption has been shown to reduce risk of recurrent AF after successful ablation. This study shows that AF can be triggered by alcohol consumption within hours, and that the more consumed the greater the risk of an acute attack of AF in predisposed individuals. Thus, recommending minimal or no alcohol intake is a reasonable strategy in patients with paroxysmal AF to reduce the frequency of episodes of AF, which may avoid the need for medication. It also implies that alcohol may have an acute direct toxic effect on atrial myocytes, although this has not been definitively proven.

Reference: Ann Intern Med 2021;174(11):1503-9
Abstract

Sodium-glucose cotransporter-2 inhibitors versus glucagon-like peptide-1 receptor agonists and the risk for cardiovascular outcomes in routine care patients with diabetes across categories of cardiovascular disease

Authors: Patorno E et al.

Summary: This population-based cohort study compared the cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus, with or without cardiovascular disease. Propensity score-matched pairs of adult type 2 diabetics with and without cardiovascular disease (52,901 and 133,139 matched pairs, respectively) initiating SGLT2 inhibitors or GLP-1 agonists were included. Compared with initiation of GLP-1 receptor agonist therapy, the initiation of SGLT2 inhibitors was associated with a slightly lower risk of MI or stroke in patients with cardiovascular disease (HR 0.90, 95% CI 0.82–0.98), a similar risk in those without cardiovascular disease (HR 1.07, CI 0.97–1.18), and a lower risk of hospitalisation for heart failure in patients with or without cardiovascular disease (HR 0.71, 95% CI 0.64–0.79 and HR 0.69, 95% CI 0.56–0.85, respectively).

Comment: This cohort study is concordant with the results of the large clinical trials of SGLT2 inhibitors and GLP-1 agonists in patients with type 2 diabetes mellitus. The greatest benefit of SGLT2 inhibition over GLP-1 agonists was in reduction in heart failure, particularly in patients with established cardiovascular disease, although there was also a small but significant reduction in MI and stroke. Individualisation of therapy in the management of type 2 diabetes according to patient characteristics is becoming more and more important with the advent of these new therapies, particularly as weight loss is likely to be greater with GLP-1 agonists compared with SGLT2 inhibitors.

Reference: Ann Intern Med 2021;174(11):1528-41
Abstract

Prevalence of statin intolerance

Authors: Bytyçi I et al.

Summary: This large meta-analysis investigated the true prevalence of statin intolerance. A search of various databases identified 176 studies (112 randomised controlled trials and 64 cohort studies) involving 4,143,517 patients that were suitable for inclusion. The overall prevalence of statin intolerance (9.1%) was similar regardless of whether it was defined using National Lipid Association, International Lipid Expert Panel, or European Atherosclerosis Society criteria. The prevalence of statin intolerance in randomised controlled trials (4.9%) was significantly lower than that in cohort studies (17%). In a meta-regression model, age, female sex, Asian and black race, obesity, diabetes mellitus, hypothyroidism, chronic liver failure, and renal failure were all significantly associated with statin intolerance.

Comment: Statin intolerance is perceived to be common by patients and doctors, but this huge meta-analysis (>4 million patients) shows that there is true intolerance in <10% of patients who take statins. Many patients blame musculoskeletal aches and pains on statins, especially as they get older, but the study did identify risk factors for intolerance which is helpful. Strategies such as having a drug holiday, alternate day treatment, adding ezetimibe to allow reduction of statin dose, and using sterol-containing food substitutes, psyllium and lipoplex (a red rice yeast extract) can help patients attain target lipid levels in truly intolerant patients. However, every effort should be made to keep patients on statins, especially in secondary prevention, given their large benefit in reducing recurrent events.

Reference: Eur Heart J 2022; published online Feb 16
Abstract

Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II)

Authors: Shah SJ et al., on behalf of the REDUCE LAP-HF II Investigators

Summary: The multicentre sham-controlled REDUCE LAP-HF trial investigated the effects of an atrial shunt device in patients with HFpEF. 626 patients (aged ≥40 years) with HFpEF were randomised to receive either a shunt device or sham procedure at one of 89 centres; patients and outcome assessors were masked to randomisation. The primary end-point was a hierarchical composite of cardiovascular death or non-fatal ischaemic stroke at 12 months, rate of total heart failure events up to 24 months, and change in Kansas City Cardiomyopathy Questionnaire overall summary score at 12 months. There were no between-group differences in the primary composite end-point or in its individual components. Prespecified subgroups that demonstrated a differential effect of atrial shunt device treatment on heart failure events were pulmonary artery systolic pressure at 20W of exercise (>70mm Hg was associated with worse outcomes), right atrial volume index (≥29.7 ml/m^2 was associated with worse outcomes), and sex (men had worse outcomes).

Comment: HFpEF is a common cause of HF and is characterised by elevated left atrial pressure, which rises dramatically with exertion, as does pulmonary artery pressure. Given the limited number of proven therapies for patients with HFpEF, this study looked at whether offloading the left atrium in patients with HFpEF by creating a small atrial left to right shunt to reduce the rise in left atrial pressure with exertion would improve outcomes. Although the haemodynamics improved, this did not translate into an improvement in symptoms or a reduction in HF events, so I doubt whether this procedure will be used clinically, especially as some patients with high pulmonary pressure with exercise or with large right atrial volume index seemed to do worse after shunting than those who had a sham procedure.

Reference: Lancet 2022; published online Feb 1
Abstract

Flu vaccine and mortality in hypertension

Authors: Modin D et al.

Summary: This nationwide Danish cohort study investigated the impact of the influenza vaccine on mortality in patients with hypertension. 608,452 patients with hypertension during 9 consecutive influenza seasons from 2007–2016 who were prescribed at least 2 different classes of antihypertensive agents (renin-angiotensin system inhibitors, diuretics, calcium antagonists, or beta-blockers) were included. Exposure to influenza vaccination was assessed before each influenza season. Vaccine coverage ranged from 26–36% per season during a median follow-up of 5 seasons (975,902 person-years of follow-up). 3.5% of patients died of all-causes during follow-up, 2.0% died of cardiovascular causes, and 0.6% died of acute MI or stroke. After adjusting for confounders, vaccination was significantly associated with reduced risks of all-cause death (HR 0.82; p<0.001), cardiovascular death (HR 0.84; p<0.001), and death from acute MI or stroke (HR 0.90; p=0.017).

Comment: In the COVID era the incidence of influenza has declined dramatically, as the same measures that reduce transmission of COVID reduce the transmission of influenza. The IAMI study showed that influenza vaccination post MI reduced recurrent cardiovascular events, and this large study shows that mortality and cardiovascular events were reduced by vaccinating hypertensive patients. Now that COVID restrictions are being relaxed, as the new variants seem less serious, it is imperative that we are not complacent with respect to flu vaccination rates and that we keep them high to reduce the significant morbidity and mortality associated with influenza A.

Reference: J Am Heart Assoc 2022; published online Feb 8
Abstract

Practical "1-2-3-4-day" rule for starting direct oral anticoagulants after ischemic stroke with atrial fibrillation

Authors: Kimura S et al., for the SAMURAI, RELAXED, RAF, RAF-NOAC, CROMIS-2, NOACISP LONGTERM, Erlangen Registry and Verona Registry Investigators

Summary: This cohort study used data from various prospective Japanese and European registries to investigate the optimal timing of DOAC initiation after acute ischaemic stroke or TIA in patients with nonvalvular AF. 1797 patients were divided into a TIA subgroup and 3 stroke subgroups based on the National Institutes of Health Stroke Scale score: mild (0–7), moderate (8–15), and severe (≥16). DOACs were started a median 2 days after TIA and 3, 4, and 5 days after mild, moderate, and severe strokes, respectively. Subsequent stroke or systemic embolism was less common in those who initiated DOAC treatment early (within 1, 2, 3, and 4 days in the respective subgroups) compared with those who initiated DOAC treatment later (1.9% vs 3.9%; adjusted HR 0.50, 95% CI 0.27–0.89). Ischaemic stroke was also less common in those who initiated DOAC treatment early (1.7% vs 3.2%; adjusted HR 0.54, 95% CI 0.27–0.999). Major bleeding rates were similar in the 2 groups.

Comment: The timing of starting oral anticoagulation post ischaemic stroke in patients with AF has been contentious. In general, the more severe the stroke, the longer anticoagulation has been delayed for fear of causing haemorrhagic transformation. This study suggests it is safe to anticoagulate patients with a DOAC much earlier than common practice and that this is associated with a decreased rate of recurrent events with no excess of bleeding complications. These findings need to be confirmed in a large randomised controlled trial.

Reference: Stroke 2022; published online Feb 2
Abstract

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