Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **CRP** = C-reactive protein; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **NSTEMI** = non-ST-elevation MI; **PCI** = percutaneous coronary intervention.

Welcome to the latest issue of Cardiology Research Review.

In this issue, a meta-analysis reinforces the health benefits of daily walking, the ARTESIA study finds that apixaban reduces stroke risk in patients with subclinical AF (albeit with an increased risk of bleeding), and an analysis of the CLEAR-Outcomes trial supports the use of colchicine in patients with coronary artery disease. Also in this issue, the ORBITA-2 trial finds that PCI is a viable treatment option in patients with stable angina, and the After Eighty study supports the use of an invasive strategy in elderly patients with NSTEMI.

We hope you find the selected studies interesting, and welcome your feedback.

Kind Regards,

Associate Professor John Amerena
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Relationship of daily step counts to all-cause mortality and cardiovascular events

Authors: Stens NA et al.

Summary: This meta-analysis examined the impact of daily step count on all-cause mortality and incident cardiovascular disease in the general population. A search of various databases identified 12 studies (n=111,309) that were suitable for inclusion. Meta-analysis of the data revealed that, compared with 2000 steps/day (reference), the risk of all-cause mortality decreased significantly at 2517 steps/day (adjusted HR [aHR] 0.92, 95% CI 0.84–0.999) and the risk of incident cardiovascular disease decreased significantly at 2735 steps/day (aHR 0.89, 95% CI 0.79–0.999). Risk reductions were optimal at 8763 steps/day for all-cause mortality (aHR 0.40, 95% CI 0.38–0.43) and at 7126 steps/day for incident cardiovascular disease (aHR 0.49, 95% CI 0.45–0.55).

Comment: It is often recommended that 10,000 steps per day improves health, but there is little evidence to support this advice. Many people now have smart watches that accurately measure steps per day, so the findings presented here are important, as they show that there is significant benefit from as little as 2600–2800 steps/day, with even greater risk reductions up to 8800 steps/day. We should thus encourage our patients to be active, especially those who have sedentary occupations, and emphasise the positive health benefits of this modest amount of exercise.

Reference: J Am Coll Cardiol. 2023;82(15):1483–94
Abstract

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Apixaban for stroke prevention in subclinical atrial fibrillation

Authors: Healey JS et al., for the ARTESIA Investigators

Summary: The ARTESIA study investigated the efficacy of apixaban for stroke prevention in patients with subclinical AF. 4012 patients (mean 76.8 years; mean CHA_2DS_2-VASc score 3.9) with subclinical AF lasting 6 min to 24h were randomised in a double-blind, double-dummy design to receive apixaban 5mg twice daily (or 2.5mg twice daily if indicated) or aspirin 81mg once daily. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major bleeding. During a mean follow-up of 3.5 years, stroke or systemic embolism occurred in 55 patients in the apixaban group and 86 patients in the aspirin group (HR 0.63, 95% CI 0.45–0.88; p=0.007). The rate of major bleeding was higher with apixaban (HR 1.80, 95% CI 1.26–2.57; p=0.001). Bleeding was fatal in five apixaban recipients and eight aspirin recipients.

Comment: Recent studies have shown that anticoagulation in patients in whom atrial high rate episodes are detected on implantable cardioverter defibrillators, cardiac resynchronisation therapy or permanent pacemaker does not improve outcomes unless AF is confirmed on ECG, Holter or implantable loop recorder. Previous studies have shown that subclinical AF for <6 min is not associated with stroke but AF duration >24h is, and anticoagulation is recommended if the stroke risk justifies. This study shows that subclinical AF for between 6 min and 24h is associated with an increased risk of stroke (but lower than if AF is >24h), and that anticoagulation with apixaban reduces stroke risk in these patients, albeit at increased risk of bleeding. It is important to note that the comparator was aspirin, presumably as many patients had an independent indication for it, such as ASCVD. These findings have significant clinical implications, as AF is not infrequently detected on routine device monitoring. If one accepts these findings, anticoagulation should be considered in patients with AF >6 min.

Reference: N Engl J Med. 2023; published online Nov 12
Abstract

Inflammation and cholesterol as predictors of cardiovascular events among 13970 contemporary high-risk patients with statin intolerance

Authors: Ridker PM et al.

Summary: This analysis of the multinational CLEAR-Outcomes trial evaluated high-sensitivity CRP (hsCRP) and LDL cholesterol levels as predictors of future adverse cardiovascular events in high-risk patients with statin intolerance. 13,970 patients were randomised to either oral bempedoic acid 180mg or matching placebo and were followed up for a median 40.6 months. Bempedoic acid reduced median hsCRP levels by 21.6% and mean LDL cholesterol levels by 21.1% compared with placebo at 6 months. Increasing baseline hsCRP quartiles were significantly associated with the primary composite end-point of major cardiovascular events, cardiovascular mortality, and all-cause mortality, but the association of increasing baseline LDL cholesterol quartiles was smaller in magnitude for the primary composite cardiovascular end-point and neutral for cardiovascular mortality and all-cause mortality. Risks were high for those with elevated hsCRP levels regardless of LDL cholesterol levels.

Comment: Previous work from this group has shown that elevated CRP is a stronger predictor of future cardiovascular events and mortality than LDL in patients with ASCVD treated with statins. This analysis of the CLEAR study, that showed the benefits of bempedoic acid in patients with ASCVD who were intolerant of statins, found that the relationship between elevated CRP and residual risk was the same as in statin-treated patients. These findings support the proven beneficial effects of colchicine in patients with coronary artery disease, but unfortunately hsCRP is not widely available in Australia. Ongoing studies with colchicine and interleukin-6 inhibition are underway which should help further clarify the role of anti-inflammatory therapies in ASCVD.

Reference: Circulation 2023; published online Nov 6
Abstract

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A placebo-controlled trial of percutaneous coronary intervention for stable angina

Authors: Rajkumar CA et al., for the ORBITA-2 Investigators

Summary: The ORBITA-2 trial evaluated the use of PCI in patients with stable angina. 301 patients (mean 64 years; 79% male) with stable angina stopped all antianginal medications before being randomised 1:1 to undergo PCI or a placebo procedure and were followed up for 12 weeks. The primary end-point was angina symptom score (higher scores indicating worse angina). At baseline, 80% of patients had ischaemia present in one cardiac territory, 17% had ischaemia in two territories, and 2% had ischaemia in three territories. At 12 weeks, the mean angina symptom score was 2.9 in the PCI group and 5.6 in the placebo procedure group (odds ratio 2.21, 95% CI 1.41–3.47; p<0.001). Four patients in the PCI group and six in the placebo group had an ACS event during follow up.

Comment: The ORBITA-1 study showed that PCI was no better than optimal medical therapy in symptom control in patients with stable angina, thus reducing the need for intervention in these patients. This study looked at patients with angina and proven ischaemia on no or minimal anti-ischaemic therapy, and showed that PCI not surprisingly reduced anginal symptoms and pill burden. This means it is valid to discuss treatment options with patients with angina, as some patients may prefer a procedure for symptom relief rather than long-term medical therapy, accepting the low risk of procedural complications.

Reference: N Engl J Med. 2023; published online Nov 11
Abstract

Long-term outcomes of invasive vs conservative strategies for older patients with non-ST-segment elevation acute coronary syndromes

Authors: Berg ES et al., for the After Eighty Study Investigators

Summary: The After Eighty study compared the efficacy of an invasive versus a conservative treatment strategy in elderly patients with NSTEMI. 457 patients aged ≥80 years with NSTEMI were randomised to an invasive strategy (early coronary angiography with immediate evaluation for revascularisation, and optimal medical therapy) or to a conservative strategy (optimal medical therapy alone). The primary end-point was a composite of MI, urgent revascularisation, stroke, and death. During a median follow up of 5.3 years, the invasive strategy significantly reduced the primary end-point compared with the conservative strategy (incidence rate ratio 0.76, 95% CI 0.63–0.93; p=0.0057). The invasive strategy also significantly improved event-free survival at 5 and 10 years compared with the conservative strategy.

Comment: NSTEMI is not uncommon in very old patients (>80 years) but there is little evidence to demonstrate the benefits or harm of an invasive strategy in these patients. This being the case, we are often hesitant to treat these patients as aggressively as younger patients, especially as many are frail and have multiple comorbidities. This study suggests there are benefits of an invasive strategy in the very elderly, with a meaningful extension of event-free survival. Thus, age by itself should not be a barrier to an invasive approach in patients with NSTEMI if there are no contraindications to PCI with a view to intervention.

Reference: J Am Coll Cardiol. 2023;82(21):2021–30
Abstract

10-year cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus

Authors: Gyldenkerne C et al.

Summary: This Danish cohort study investigated sex- and age-specific 10-year cardiovascular disease risk in patients with newly diagnosed type 2 diabetes (T2D) compared with the general population. 142,587 Danish patients who were diagnosed with T2D in 2006–2013 were compared with 388,410 sex- and age-matched individuals from the general population; none of the participants had a history of ASCVD. Compared with the general population, the 10-year risk of cardiovascular disease (MI, stroke, and fatal cardiovascular disease) was higher in patients with T2D in both sexes and across all age groups. Patients aged 40–49 years had the largest difference in 10-year cardiovascular disease risk compared with the general population (6.1% vs 3.3%).

Comment: T2D is often labelled as a "coronary risk" equivalent, in that there is some data to suggest that the risk of a first MI in a patient with T2D is the same as the risk of a second MI in a patient with a background of ACS who does not have T2D. This Danish study would support this concept, as it shows that T2D is associated with an increased cardiovascular risk, and that clinical cardiovascular disease occurs up to 12 years earlier in these patients. Thus, aggressive risk factor modification should be implemented as soon as a diagnosis of T2D is made. Also, the younger a patient is at diagnosis, the greater the potential benefit.

Reference: J Am Coll Cardiol. 2023;82(16):1583–94
Abstract

Semaglutide and cardiovascular outcomes in obesity without diabetes

Authors: Lincoff AM et al., for the SELECT Trial Investigators

Summary: The SELECT trial investigated the effects of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide on cardiovascular risk in overweight or obese patients without diabetes. 17,604 patients aged ≥45 years with preexisting cardiovascular disease and BMI ≥27 kg/m^2 but no history of diabetes were randomised 1:1 to receive once-weekly subcutaneous semaglutide 2.4mg or placebo. Mean treatment duration was 34.2 months, and mean follow-up duration was 39.8 months. The primary cardiovascular end-point (a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) occurred in 6.5% of semaglutide recipients and 8.0% of placebo recipients (HR 0.80, 95% CI 0.72–0.90; p<0.001). Adverse events resulting in treatment discontinuation were reported in 16.6% of patients in the semaglutide group and 8.2% in the placebo group (p<0.001).

Comment: GLP-1 agonists have been shown to reduce cardiovascular events in patients with type 2 diabetes (T2D) and ASCVD but their benefits in patients with ASCVD without T2D was unknown until the SELECT study, which examined the effect of semaglutide 2.4mg weekly in overweight/obese patients (BMI >27) with ASCVD without T2D. This study showed a 20% reduction in the combined end-point of major adverse cardiovascular events and cardiovascular death, with strong trends to a reduction in cardiovascular mortality, hospitalisation for heart failure, and all-cause mortality. There was a weight loss of about 9% on average which plateaued at 12 months and was maintained at 24 months, and there were favourable effects on blood pressure, lipids, and CRP. Improvement in cardiovascular outcomes occurred well before the maximum weight loss, suggesting that these salutary effects were not due solely to weight loss. However, we are awaiting mediation analysis to help determine how much of the benefit was due to weight loss, rather than other factors. This study also has significant clinical implications, as many patients with ASCVD are overweight/obese and would benefit from this therapy, but it is not approved anywhere for this indication yet.

Reference: N Engl J Med. 2023;389:2221–32
Abstract

Natural history of echocardiographic changes in atrial fibrillation

Authors: Loring Z et al.

Summary: This case-control study investigated the frequency and timing of AF-associated echocardiographic changes. Patients within the Duke University Health System who had two or more transthoracic echocardiograms (TTEs) in 2005–2018 were evaluated. 727 patients with AF were compared with patients without AF matched for year of TTE, age, and CHA_2DS_2-VASc score. During 5 years of follow-up, patients with AF had higher rates of left atrial enlargement (HR 1.53, 95% CI 1.27–1.85; p<0.001), left ventricular systolic dysfunction (HR 1.80, 95% CI 1.00–3.26; p=0.045), left ventricular diastolic dysfunction (HR 1.51, 95% CI 1.08–2.10; p=0.01) and moderate or greater mitral regurgitation (HR 2.09, 95% CI 1.27–3.43; p=0.003) than patients without AF. Rates of atrial enlargement, systolic dysfunction, and mitral regurgitation in patients with AF surpassed rates in patients without AF within 6–12 months; differences in diastolic dysfunction emerged at 24 months.

Comment: It is often difficult to determine if structural cardiac changes are due to AF or are the cause of AF. This interesting study looked at cardiac remodelling in patients with normal echos at the time of diagnosis of AF, and showed that significant remodelling occurred over 6–24 months. It did not report on whether these changes could be attenuated by restoration of sinus rhythm, but it would be reasonable to speculate that an early rhythm control approach may prevent these changes occurring.

Reference: Heart Rhythm 2023; published online Sep 15
Abstract

Atrial fibrillation recurrence in patients with transient new-onset atrial fibrillation detected during hospitalization for noncardiac surgery or medical illness

Authors: McIntyre WF et al.

Summary: This matched cohort study estimated the risk of AF recurrence in patients with new-onset AF detected during a hospitalisation for noncardiac surgery or medical illness. 139 patients with transient new-onset AF were compared with age- and sex-matched control patient from the same hospital ward with no history of AF. All patients left the hospital in sinus rhythm, and were assessed by 14-day ECG monitor at 1 and 6 months and via telephone at 1, 6, and 12 months. During 1 year of follow up, recurrent AF >30 s was detected in 33.1% of patients in the transient new-onset AF group and 5.0% of matched controls. After adjustment for baseline clinical differences and the number of ECG monitors worn, the adjusted relative risk was 6.6 (95% CI 3.2–13.7).

Comment: It is commonly thought that if patients have transient triggered AF, i.e. AF that occurs in the context of a surgical procedure or medical illness, there is an increased risk of subsequently developing clinical AF. This has been postulated to be due to the acute stress triggering AF in patients who have the underlying substrate for AF. This study quantifies this increased risk at about 30% over 12 months and indicates that close monitoring for AF is important in patients who have had triggered AF, as they are generally not anticoagulated after the index event even if their CHADSVA score is ≥2.

Reference: Ann Intern Med. 2023;176(10):1299–1307
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.

Cost-effectiveness and diagnostic accuracy of focused cardiac ultrasound in the pre-participation screening of athletes

Authors: Halasz G et al.

Summary: The SPORT-FoCUS study evaluated the use of focused cardiac ultrasound in the pre-participation screening of athletes for cardiac abnormalities. 2111 athletes (mean age 24.9 years; 77.4% male) underwent a physical examination, standardised medical history collection, resting ECG, focused cardiac ultrasound (10 min/5 views protocol), comprehensive echocardiography, and an exercise stress test. Three incremental pre-participation screening models were compared: Model A – standardised medical history and physical examination; Model B – Model A plus resting and stress ECG; and Model C – Model B plus focused cardiac ultrasound. Overall, 30 athletes were found to have a cardiac condition associated with sudden cardiac death (three were identified by Model A, 14 by Model B, and 13 by Model C). The introduction of focused cardiac ultrasound (i.e. Model C) increased the sensitivity of pre-participation screening compared with Model A and Model B (94%, 19% and 58%, respectively) without changing specificity. The incorporation of focused cardiac ultrasound into the screening process was shown to be cost-effective.

Comment: Sudden cardiac death is very uncommon in athletes, but when it occurs it is devastating. Intensive screening for cardiac abnormalities associated with sudden cardiac death in athletes will identify those at risk, but this would be a massive undertaking, and the resources needed to screen at a population level would be prohibitive in an Australian setting. More investigation of athletes who have clinical indicators of increased risk (e.g. family history of sudden death) would be reasonable, but the Australian medical system which is already struggling with increased demand for services would not cope with a more generalised screening programme.

Reference: Eur J Prev Cardiol. 2023;30(16):1748–57
Abstract