Cardiology Research Review™

Making Education Easy

Issue 144 - 2022

In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **BP** = blood pressure; **CABG** = coronary artery bypass grafting; **CAC** = coronary artery calcium; **CAD** = coronary artery disease; **CTCA** = computed tomography chest angiography; **HF** = heart failure; **HR** = hazard ratio; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SGLT2** = sodium-glucose co-transporter-2.

Welcome to the latest issue of Cardiology Research Review.

In this issue, a real-world study supports the adoption of early rhythm-control therapy as part of the management of new-onset AF (in line with EAST-AFNET 4 findings), an analysis of the ARIC study suggests that targeting diabetes early in the HF process is critical for reducing HF progression, and an analysis of the REGARDS study reinforces the importance of staying active rather than adopting a sedentary lifestyle.

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

Kind Regards,

Associate Professor John Amerena
john.amerena@researchreview.com.au

Generalizability of the EAST-AFNET 4 trial: Assessing outcomes of early rhythm-control therapy in patients with atrial fibrillation

Authors: Dickow J et al.

Summary: The EAST-AFNET 4 trial demonstrated the clinical benefits of early rhythm-control (ERC) therapy in patients with new-onset AF and concomitant cardiovascular conditions. This study evaluated the generalisability of the EAST-AFNET 4 findings in routine practice. 109,739 patients with newly diagnosed AF were identified from a US administrative database and classified as receiving ERC (AF ablation therapy or antiarrhythmic drug therapy) within the first year after AF diagnosis (n=27,106) or not receiving ERC (control group, n=82,633). 72.9% of patients met inclusion criteria for EAST-AFNET 4. Cox proportional hazards regression analysis showed that ERC was associated with a reduced risk of the primary composite outcome of all-cause mortality, stroke, or hospitalisation for HF or MI (HR 0.85, 95% CI 0.75–0.97; p=0.02). Results were largely consistent between patients who were eligible for EAST-AFNET 4 trial inclusion and those who were not.

Comment: The EAST-AFNET 4 trial showed that an ERC strategy had advantages over a rate control approach, which is usually adopted initially in asymptomatic patients based on the AFFIRM study, which showed no benefit of a rhythm control approach over rate control. This evidence is more than 20 years old and was before AF ablation was routinely performed and was thought to reflect toxicity of the antiarrhythmic drugs at that time negating any benefits from rhythm control. This real-world study supports the EAST-AFNET 4 results and showed that an ERC strategy was associated with less all-cause mortality, stroke, or hospitalisation for HF or MI as a combined end-point. Unfortunately, the availability of AF ablation is limited in Australia, particularly in the public sector, so many of our patients will not be able to benefit from an ERC strategy, despite its advantages.

Reference: J Am Heart Assoc 2022;11(11):e024214
Abstract

Diabetes and progression of heart failure: The Atherosclerosis Risk In Communities (ARIC) study

Authors: Echouffo-Tcheugui JB et al.

Summary: This analysis of the ARIC study evaluated the influence of diabetes on the progression of HF. 4774 adults with preclinical HF (1551 with stage A HF and 3223 with stage B HF) who attended visit 5 of the ARIC study in 2011–2013 were included. 470 HF events were reported during 8.6 years of follow-up. Stage B participants with HbA1c ≥7% developed clinical HF at a younger age than those with controlled diabetes or without diabetes (mean age 80 vs 83 vs 82 years; p<0.001). Patients with stage B HF and HbA1c ≥7% were at increased risk for HF progression than those with stage A HF without diabetes (HR 7.56, 95% CI 4.68–12.20).

Comment: We know that there is an increased incidence of HF in patients with type 2 diabetes, but traditionally cardiologists have focussed on the cardiac issues after HF becomes apparent rather than glycaemic control. This study shows that poor glycaemic control in the elderly with stage B pre-HF (no symptoms or signs of HF but evidence of structural heart disease, abnormal left ventricular function or elevated biomarkers) is associated with a more rapid development of symptomatic and clinical HF at an earlier age, so it is imperative that diabetologists and cardiologists work together to decrease the risk of HF developing in these patients with pre-clinical HF.

Reference: J Am Coll Cardiol 2022;79(23):2285-93
Abstract

Association of accelerometer-measured sedentary time and physical activity with risk of stroke among US adults

Authors: Hooker SP et al.

Summary: This analysis of the REGARDS study investigated the associations of sedentary time and physical activity with the risk of incident stroke. Accelerometer data were collected from 7607 black and white adults aged ≥45 years in the US in 2009–2013. During a mean 7.4 years of follow-up, 286 incident stroke cases (85.3% ischaemic) occurred. Fully adjusted HRs for incident stroke in the highest tertile compared with the lowest tertile were 0.74 (95% CI 0.53–1.04; p=0.08) for light-intensity physical activity, 0.57 (95% CI 0.38–0.84; p=0.004) for moderate- to vigorous-intensity physical activity, and 1.53 (95% CI 1.10–2.12; p=0.008) for sedentary lifestyle.

Comment: We often recommend an active lifestyle for patients with cardiovascular disease, on the assumption that it will be beneficial, with very little evidence to support this recommendation. This study showed that a sedentary lifestyle was associated with an increased risk of stroke, and that the longer the duration of exercise and the greater intensity, the greater the risk reduction. This is also likely to apply to patients with coronary disease, and reinforces the importance of staying active rather than adopting a sedentary lifestyle.

Reference: JAMA Netw Open 2022;5(6):e2215385
Abstract

Thromboembolic risk in patients with pneumonia and new-onset atrial fibrillation not receiving anticoagulation therapy

Authors: Søgaard M et al.

Summary: This population-based study in Denmark investigated the risk of thromboembolism in patients with pneumonia and new-onset AF. Among 274,196 patients hospitalised with incident community-acquired pneumonia in 1998–2018, 6553 patients (mean 79.1 years, 52.0% female) developed new-onset AF. The 1-year risk of thromboembolism was 0.8% in patients without AF versus 2.1% in patients with new-onset AF without anticoagulation. Among patients with new-onset AF, 32.9% had a new hospital contact because of AF, and 14.0% started anticoagulation therapy in the 3 years after AF diagnosis. 49.8% of patients with new-onset AF died during 3 years of follow-up compared with 25.7% of those without AF.

Comment: It is not common practice to anticoagulate patients who have an episode of triggered AF, such as after surgery (especially CABG), infection (e.g. pneumonia) or ACS if the patient reverts to sinus rhythm, even if the CHADS-VASc score is >/= 2. It is thought that many if not all the patients who have triggered AF have an underlying substrate for AF and that the trigger reveals it. This study shows that there is an increased risk of future AF in patients who had AF after pneumonia, and that the higher the risk score the higher the risk of stroke. This indicates we need to be particularly diligent in screening patients who have a history of triggered AF, but we don't yet have enough evidence to recommend routine anticoagulation after an episode of triggered AF if the patient reverts to sinus rhythm, even if the CHADS-VASc score is >/= 2.

Reference: JAMA Netw Open 2022;5(5):e2213945
Abstract

Mortality among patients with early-onset atrial fibrillation and rare variants in cardiomyopathy and arrhythmia genes

Authors: Yoneda ZT et al.

Summary: This prospective cohort study evaluated the association between mortality and rare variants in cardiomyopathy and arrhythmia genes in patients with early-onset AF. Among 1293 patients with AF diagnosed before 66 years of age who underwent whole-genome sequencing, 131 (10%) were found to have rare genetic variants associated with cardiomyopathy or arrhythmias. Univariable analysis showed that the genetic variants were associated with an increased risk of mortality (HR 1.5, 95% CI 1.0–2.1; p=0.05), and the association remained significant in multivariable modelling after adjustment for confounding factors. Disease-associated variants were associated with a higher risk of mortality compared with no disease-associated variant in patients who had AF diagnosed at a younger age (p=0.008). Higher body mass index and lower left ventricular ejection fraction were also associated with higher mortality risk.

Comment: There are an increasing number of genetic abnormalities that have been found to be associated with arrhythmia and cardiomyopathy. This study suggests that around 10% of patients who have AF at an early age have a genetic abnormality, and that this is associated with an increased risk of mortality. AF may also be the first indication of incipient cardiomyopathy, so patients with AF at a younger age should be worked up, and have genetic testing, although this is problematic in Australia as it is not funded and there is a substantial out of pocket cost.

Reference: JAMA Cardiol 2022; published online May 11
Abstract

The prognostic value of CAC zero among individuals presenting with chest pain

Authors: Agha AM et al.

Summary: This meta-analysis investigated the utility of CAC assessment for ruling out obstructive CAD in patients with stable or acute chest pain. A search of various databases identified 19 studies in patients with stable chest pain undergoing CAC (n=79,903), and 13 studies in patients with acute chest pain undergoing simultaneous CAC and CTCA (n=12,376) that were suitable for inclusion. Overall, 45% of patients with stable chest pain and 58% with acute chest pain had a CAC score of zero. The negative predictive values for a CAC score of zero ruling out obstructive CAD were 97% in patients with stable chest pain and 98% in patients with acute chest pain. 13% of patients with stable chest pain who had a CAC score of zero had nonobstructive CAD, compared with 9% of those with acute chest pain who had a CAC score of zero. A CAC score of zero predicted a low annual incidence of major adverse cardiac events in patients with stable or acute chest pain (0.5% and 0.8%, respectively).

Comment: This meta-analysis looked at the predictive value of a negative CAC score in patients with stable or acute chest pain. It found that it had a very good negative predictive value, in that if the score was zero there was an extremely low risk of having significant obstructive disease or having a major cardiovascular event. This is valuable information, and suggests that if the CAC score is zero no further coronary imaging is needed, and other mechanisms for chest pain should be considered if there are recurrent symptoms.

Reference: J Am Coll Cardiol Img 2022; published online Jun 15
Abstract

Rivaroxaban monotherapy vs combination therapy with antiplatelets on total thrombotic and bleeding events in atrial fibrillation with stable coronary artery disease

Authors: Naito R et al., for the AFIRE Investigators

Summary: This post hoc secondary analysis of the AFIRE trial evaluated the use of rivaroxaban alone or in combination with antiplatelet therapy in patients with AF and CAD. 2215 patients with AF and stable CAD who had undergone PCI or CABG at least 1 year earlier or who had angiographically confirmed CAD not requiring revascularisation were randomised to receive rivaroxaban monotherapy or combined with antiplatelet therapy. 12.2% of patients in the rivaroxaban monotherapy group and 19.2% in the combination-therapy group had a thrombotic, bleeding, or fatal event during a median follow-up of 24.1 months. Mortality rates were 3.7% and 6.6% in the respective groups. Rivaroxaban monotherapy was associated with a lower risk of total events compared with combination therapy (HR 0.62, 95% CI 0.48–0.80; p<0.001).

Comment: Cardiologists are often concerned about the recommendation that patients with AF and coronary disease stop antiplatelet therapy 12 months after an ACS, PCI or CABG and continue anticoagulation alone. This post hoc analysis of the AFIRE study showed there was an increased risk of bleeding and thrombotic events in those who stayed on dual therapy (rivaroxaban and an antiplatelet therapy) compared with monotherapy with rivaroxaban alone, as well as a trend to decreased mortality. This should give confidence to the cardiology community that anticoagulation alone is sufficient 12 months after an ACS or revascularisation procedure in patients with AF, as dual therapy increases event rates and perhaps mortality.

Reference: JAMA Cardiol 2022; published online Jun 15
Abstract

Sodium-glucose co-transporter-2 inhibitors and cardiac outcomes among patients treated with anthracyclines

Authors: Gongora CA et al.

Summary: This case-control study investigated the cardiac efficacy and overall safety of SGLT2 inhibitors in patients with diabetes mellitus and cancer who were being treated with anthracyclines. All of the participants had diabetes and were taking an anthracycline for cancer. Cases (n=32) were also taking an SGLT2 inhibitor whereas controls (n=96) were not. The primary cardiac outcome was a composite of cardiac events (HF incidence, HF admissions, new cardiomyopathy, and clinically significant arrhythmias). During a median follow-up of 1.5 years, cases had a lower incidence of cardiac events (3% vs 20%; p=0.025), mortality (9% vs 43%; p<0.001) and sepsis/neutropenic fever (16% vs 40%; p=0.013).

Comment: Chemotherapy-induced cardiomyopathy is associated particularly with anthracycline use and can often limit optimal treatment choices for patients with malignancy that is sensitive to these agents. Preventative therapies with inhibitors of the renin-angiotensin system in patients with breast cancer have been disappointing (PRADA study) but this small study showed large potential benefits from SGLT2 inhibitors with a reduction in events and mortality in patients with type 2 diabetes and cancer treated with anthracyclines who were on them. The findings are promising but large randomised controlled trials will need to be carried out before these agents can be used as preventative therapy.

Reference: JACC Heart Fail 2022; published online Jun 8
Abstract

Impact of blood pressure in the early 40s on left atrial volumes in the mid-60s: Data from the ACE 1950 study

Authors: Rønningen PS et al.

Summary: This study evaluated the impact of BP levels in patients' early 40s on left atrial volumes later in life. Data were linked for 2591 individuals born in the 1950s who participated in both the Age 40 Program (mean age 40.1 years) and the ACE 1950 study (mean age 64.0 years). The proportion of individuals with an enlarged left atrium in the ACE 1950 study increased across quartiles of systolic BP in the Age 40 Program (p=0.001). Systolic BP was independently associated with left atrial volumes; end-systolic volume increased by 0.09ml for every 1-mm Hg increase in systolic BP.

Comment: We know that hypertension is associated with the risk of cardiovascular events, particularly stroke and HF, as well as AF. We also know that treating hypertension reduces these cardiovascular events, but there is little evidence that treating hypertension reduces the risk of future AF. This interesting longitudinal analysis shows that left atrial dimensions increase over time (20 years) more in patients whose BP was higher in their 40s, than in those in whom it was well controlled. These structural changes could be the link between hypertension and AF, perhaps indicating an atrial myopathy induced by higher BP. It appears that treatment makes little if any difference in reducing the rate of AF but does indicate a need for diligent screening in patients whose left atrium is dilated in the context of hypertension, whether it is well controlled or not.

Reference: J Am Heart Assoc 2022;11(11):e023738
Abstract

Enrollment of female participants in United States drug and device phase 1–3 clinical trials between 2016 and 2019

Authors: Sosinsky AZ et al.

Summary: This study characterised the enrolment of female participants in recent clinical trials. Data for 1433 US-based phase 1–3 clinical trials were extracted from ClinicalTrials.gov for the 4-year period from 2016 to 2019. Of the 302,664 participants, 41.2% were female. Compared with their proportion of the disease population, females were underrepresented in cardiovascular disease trials (41.9% female participants versus 49% female population with cardiovascular disease), psychiatry trials (42.0% vs 60%), and cancer trials (41.0% vs 51%). For each therapeutic area analysed, female participation in clinical trials fell short of the benchmark derived from national prevalence data.

Comment: Historically there has been under representation of women in clinical trials, but the results of many studies predominantly in males have been extrapolated to females. In many areas there are clear differences in treatment effect (or lack of) and toxicity according to gender, so it is imperative to have female representation that reflects the population prevalence of the disease being studied. Although things have improved, there is still a gap that needs to be addressed, but strategies to encourage more female participation in clinical trials remain elusive.

Reference: Contemp Clin Trials 2022;115:106718
Abstract

Cardiology Research Review™

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.

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.