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; **BP** = blood pressure; **DAPT** = dual antiplatelet therapy; **DOAC** = direct oral anticoagulant; **HF** = heart failure; **HR** = hazard ratio; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **NOAC** = non-vitamin K antagonist oral anticoagulant; **NT-proBNP** = N-terminal pro-B-type natriuretic peptide; **OR** = odds ratio; **SGLT2** = sodium-glucose cotransporter-2; **VKA** = vitamin K antagonist.

Welcome to the latest issue of Cardiology Research Review.

In this issue, the Fitbit Heart study finds that wearable devices may help identify individuals with undiagnosed AF, the SECURE trial reports that treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after MI is effective for secondary prevention, and the results of the INVICTUS study suggest that vitamin K antagonism remains the preferred strategy for stroke prevention in patients with rheumatic heart disease and 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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Detection of atrial fibrillation in a large population using wearable devices

Authors: Lubitz SA et al.

Summary: The Fitbit Heart study used a novel photoplethysmography (PPG)-based algorithm to detect undiagnosed AF using a wrist-worn device. 455,699 adults (median age 47 years, 71% female) without AF who were using a wearable Fitbit® device and had an Android or iOS smartphone (with an installed Fitbit® app) were included. PPG data were analysed using a novel algorithm that examined overlapping 5-min pulse windows (tachograms). Participants with an irregular heart rhythm detection (IHRD; defined as 11 consecutive irregular tachograms) were invited to schedule a telehealth visit and were mailed a 1-week ambulatory electrocardiogram (ECG) patch monitor. IHRDs occurred in 1% of participants (4% of those aged ≥65 years) during a median follow-up of 122 days. Among 1057 participants with an IHRD notification and subsequent analysable ECG patch monitor, 340 (32.2%) had AF. Of the 225 participants with another IHRD during ECG patch monitoring, 221 had concurrent AF on the ECG and 4 did not. The positive predictive value (PPV) of IHRD for AF was 98.2% overall and 97.0% in participants aged ≥65 years.

Comment: We know that AF is associated with an increase in cardiovascular events (particularly stroke) as patients get older. AF is often asymptomatic and sometimes the first recognition of AF is when a patient has a stroke. Wearable devices are becoming more and more prevalent and have the ability to detect abnormalities in the heart rate. This study involving more than 450,000 participants aged 22 years or over showed that overall 1% of participants had an IHRD but this increased to 4% of participants over the age of 65. If an IHRD was found, AF was present in about one-third of cases with a PPV of 98%. This being the case it would seem that the technology algorithms associated with wearable devices and subsequent analytical programmes are becoming more and more sensitive to detect AF, particularly in the older age group. Whether detecting AF on a wearable device translates into an increase in stroke is not clear. Also, whether anticoagulation if AF is detected on this type of wearable technology (if the CHADs-VA score is ≥2) would reduce the risk of stroke is not known as the burden of AF is not able to be determined by this technology.

Reference: Circulation 2022;146(19):1415-24
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.

Polypill strategy in secondary cardiovascular prevention

Authors: Castellano JM et al., for the SECURE Investigators

Summary: The SECURE trial investigated the efficacy of a polypill for secondary prevention of cardiovascular death and complications after MI. 2499 patients who had had an MI within the previous 6 months were randomised to a polypill-based strategy or usual care. The polypill treatment comprised aspirin 100mg, ramipril 2.5, 5, or 10mg, and atorvastatin 20 or 40mg. The primary composite outcome was cardiovascular death, nonfatal type 1 MI, nonfatal ischaemic stroke, or urgent revascularisation. During a median follow-up of 36 months, a primary-outcome event occurred in 9.5% of patients in the polypill group and in 12.7% in the usual-care group (HR 0.76, 95% CI 0.60–0.96; p=0.02).

Comment: There is published data showing that the low-dose quad-pill is effective at lowering high BP more rapidly with greater attainment of treatment targets in patients with hypertension. This study looking at a polypill consisting of aspirin, ramipril and atorvastatin showed that in patients with an acute MI less than 6 months before enrolment, this polypill reduced the risk of MACE and urgent revascularisation by 24% with an absolute risk reduction of 3.2% over an average of 3 years of follow up. This study is particularly relevant in lower- and middle- income countries where access to medication is less than ideal but will also be relevant to the developed world where anything that can be done to reduce pill burden will increase compliance and improve outcomes. My only concern with this approach is that it may encourage a set and forget attitude to patients who have had an MI, and that aggressive treatment of BP and lipids may not be undertaken in patients post MI to the same extent as if they were on the individual medications.

Reference: N Engl J Med 2022;387(11):967-77
Abstract

Rivaroxaban in rheumatic heart disease-associated atrial fibrillation

Authors: Connolly SJ et al., for the INVICTUS Investigators

Summary: The INVICTUS study investigated the efficacy of rivaroxaban in patients with rheumatic heart disease-associated AF. 4531 patients (mean age 50.5 years, 72.3% female) with AF and echocardiographically-documented rheumatic heart disease were randomised to receive standard doses of rivaroxaban or a dose-adjusted VKA. The primary efficacy outcome was a composite of stroke, systemic embolism, MI, and death. In the intention-to-treat analysis, 560 patients in the rivaroxaban group and 446 in the VKA group had a primary-outcome event. Survival curves were nonproportional, with rivaroxaban recipients having a shorter mean survival time (1599 vs 1675 days; p<0.001). No significant between-group differences in major bleeding events were reported. Permanent discontinuation of trial medication was more common with rivaroxaban than with VKA therapy.

Comment: Rheumatic heart disease is still common in the developing world and is a major source of morbidity and mortality particularly when it affects the mitral valve. Anticoagulation with VKAs is difficult in many countries in the developing world due to poor access to INR monitoring so this study was performed to determine whether rivaroxaban would be an alternative to VKA treatment in patients with AF with rheumatic mitral valve disease. Unfortunately it showed that there was an increase in cardiovascular events and death in patients who received rivaroxaban over a VKA, with no decrease in bleeding. The reasons for this are unclear but at the present time it would seem that vitamin K antagonism is the preferred strategy for stroke prevention in patients with rheumatic mitral valve disease and AF. It is worthy of comment however that the time in therapeutic range in the patients in this study was 64% which is much higher than one would expect to see in clinical practice. Despite this it does not explain why there was an increase in cardiovascular events and mortality in the patients who received rivaroxaban so I do not think that further studies with NOACs in this population will be undertaken.

Reference: N Engl J Med 2022;387:978-88
Abstract

Association of ischemic and bleeding events with mortality among patients in Sweden with recent acute myocardial infarction receiving antithrombotic therapy

Authors: Simonsson M et al.

Summary: This cohort study in Sweden compared the association of ischaemic events and bleeding events with mortality in patients with a recent MI. 86,736 patients (median age 71 years, 66.0% male) who were discharged after MI in 2012–2017 and were prescribed antithrombotic therapy (antiplatelet therapy or oral anticoagulation) were included in the analysis. Patients were assessed for a first ischaemic event (hospitalisation for MI or ischaemic stroke) or bleeding event (hospitalisation with bleeding) up to 1 year after discharge; mortality risk up to 1 year after each type of event was also assessed. 4039 patients had an ischaemic event (5.7 per 100 person-years) and 3399 had a bleeding event (4.8 per 100 person-years) during 1 year of follow up. Cox proportional hazards regression models showed that the risk of 1-year mortality was higher after an ischaemic event (adjusted HR [aHR] 4.16, 95% CI 3.91–4.43) than after a bleeding event (aHR 3.43, 95% CI 3.17–3.71) compared with no event.

Comment: We worry about increasing the risk of bleeding in patients discharged on antithrombotic therapy after ACS/MI, as they are usually on DAPT with some patients requiring triple therapy (DAPT + anticoagulant), at least in the short term after an event. This study shows that recurrent ischaemic events are more common than bleeding events in patients within the first 12 months after ACS, and that ischaemic events are associated with a higher 12-month mortality than if the patient bleeds. This suggests that appropriate antithrombotic therapy should be given to patients post ACS, even if bleeding risk is high, as recurrent ischaemia has a worse outcome than a bleeding event.

Reference: JAMA Netw Open 2022;5(8):e2220030
Abstract

Aspirin for primary prevention of cardiovascular events in relation to lipoprotein(a) genotypes

Authors: Lacaze P et al.

Summary: This analysis of ASPREE data investigated the effects of aspirin on primary prevention in the elderly with regard to lipoprotein(a) genotypes. 12,815 genotyped individuals aged ≥70 years without prior cardiovascular disease events who were randomised to aspirin 100 mg/day or placebo in the ASPREE trial were included. Lipoprotein(a)-associated genotypes were defined using rs3798220-C carrier status and quintiles of a lipoprotein(a) genomic risk score (LPA-GRS). During a median 4.7 years of follow-up, 435 MACE occurred. Cox proportional hazards models showed that rs3798220-C carrier status was associated with increased MACE risk in the placebo group (HR 1.90, 95% CI 1.11–3.24) but not in the aspirin group (HR 0.54, 95% CI 0.17–1.70). Similarly, high LPA-GRS (versus low) was associated with increased MACE risk in the placebo group (HR 1.70, 95% CI 1.14–2.55) but not in the aspirin group (HR 1.41, 95% CI 0.90–2.23).

Comment: The ASPREE study showed us that using aspirin for primary prevention in an elderly population without overt ASCVD did not improve cardiovascular outcomes but did increase the risk of bleeding significantly. There is currently a focus on Lp(a) as a factor that mediates residual cardiovascular risk in patients with ASCVD who have recurrent cardiovascular events despite BP and lipid targets being attained. Studies are currently underway with agents that lower Lp(a) in patients with established ASCVD, but these results are of great interest as they suggest that a high-risk group of patients with elevated Lp(a) but without clinical ASCVD may benefit from aspirin without an increased risk of bleeding. Unfortunately, estimation of Lp(a) is not funded in Australia at present, so many patients will opt not to have it checked, and it is hard to press patients to pay for it when there is only suggestive but not definitive evidence that intervention in patients with elevated levels will improve outcomes.

Reference: J Am Coll Cardiol 2022;80(14):1287-98
Abstract

Early rhythm control therapy for atrial fibrillation in low-risk patients: A nationwide propensity score-weighted study

Authors: Kim D et al.

Summary: The EAST-AFNET 4 study found that early rhythm control is associated with lower risk for adverse cardiovascular outcomes compared with usual care in patients with recent-onset AF and a CHA_2DS_2-VASc score of approximately 2 or greater. This population-based cohort study in Korea investigated whether the EAST-AFNET 4 findings can be generalised to patients with low stroke risk. Data for 54,216 patients with AF who initiated rhythm control (antiarrhythmic drugs or ablation) or rate control therapy within 1 year of an AF diagnosis were extracted from the Korean National Health Insurance Service database. Overall, 69.3% of patients met eligibility criteria for the EAST-AFNET 4 trial (median age 70 years; median CHA_2DS_2-VASc score 4). In these patients, early rhythm control was associated with lower risk of the primary composite outcome compared with rate control (HR 0.86, 95% CI 0.81–0.92). In the 30.7% of patients who did not meet inclusion criteria for EAST-AFNET 4 (median age 54 years; median CHA_2DS_2-VASc score 1), early rhythm control was also associated with a lower risk of the primary outcome (HR 0.81, 95% CI 0.66–0.98).

Comment: There is increasing evidence that an early rhythm control approach in patients with recent-onset AF is associated with better outcomes than an initial rate control strategy. The EAST-AFNET 4 study and more recent data from the American Heart Association show that outcomes are better with an early rhythm control strategy (primarily with ablation) and that this translates into a lower risk of transition to persistent or permanent AF with an improvement in quality of life, less drug burden and less utilisation of healthcare resources. It is becoming clear that this strategy is advantageous to patients with AF even if they are at low risk from a stroke perspective. However, the availability of AF ablation in Australia is limited, so by the time many of these patients get an ablation, left atrial dilatation and fibrosis may be present which will decrease the short- and long-term success of an ablative procedure. Unfortunately, there still continues to be discrepancies with respect to the availability of AF ablation between the public and private sectors so we should encourage our hospital and government administrators to improve the access to this procedure in the public hospital system to provide equitable care.

Reference: Ann Intern Med 2022;175(10):1356-65
Abstract

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study)

Authors: Mackenzie IS et al., on behalf of the TIME Study Group

Summary: The TIME study investigated whether evening dosing of antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension. 21,104 adults (mean age 65.1 years) with hypertension who were taking at least one antihypertensive medication were randomised 1:1 to take all of their usual antihypertensive medications in the morning (0600–1000h) or in the evening (2000–0000h). The composite end-point was vascular death or hospitalisation for non-fatal MI or non-fatal stroke. During a median follow-up of 5.2 years, a primary end-point event occurred in 3.4% of patients in the evening dosing group compared with 3.7% in the morning dosing group (unadjusted HR 0.95, 95% CI 0.83–1.10; p=ns).

Comment: There has been ongoing debate about the optimal time to take BP-lowering medication, as some studies have suggested nocturnal dosing is better than morning to prevent the early morning surge in BP and perhaps reduce cardiovascular events which are most common in the first few hours after wakening. However, there is concern that if BP-lowering medications are taken at night diastolic BP may be lowered too much and coronary artery flow may be compromised and increase the risk of ischaemia in patients with underlying coronary artery disease. This study showed that timing of BP medication had no influence on outcomes, so that patients should take their medications at a convenient time on a regular basis without concern about affecting outcomes.

Reference: Lancet 2022;400(10361):1417-25
Abstract

Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF)

Authors: Mebazaa A et al.

Summary: The multinational, open-label STRONG-HF trial investigated the safety and efficacy of up-titration of guideline-directed medical therapies for acute HF. 1078 patients (mean age 63 years, 39% female) who were admitted to hospital with acute HF but not treated with full doses of guideline-directed drug treatment were recruited from 87 hospitals in 14 countries. Before discharge, they were randomised 1:1 to either usual care or high-intensity care. High-intensity care comprised up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits in the 2 months after discharge to monitor clinical status, laboratory values, and NT-proBNP levels. By day 90, more patients in the high-intensity care group had been up-titrated to full doses of prescribed drugs (renin-angiotensin blockers 55% vs 2%; beta-blockers 49% vs 4%; and mineralocorticoid receptor antagonists [MRAs] 84% vs 46%). HF readmission or all-cause death up to day 180 (primary end-point) occurred less often in the high-intensity care group (15.2% vs 23.3%; risk ratio 0.66, 95% CI 0.50–0.86). More adverse events occurred with high-intensity versus usual care, but the incidence of serious or fatal adverse events did not differ significantly between groups.

Comment: Current guidelines recommend that the foundational therapies for patients with HF with reduced ejection fraction (HFrEF) be started within one month of the initial diagnosis, and that up-titration to maximally tolerated doses be undertaken as soon as possible. Despite this, many patients with HFrEF are not on guideline-directed medical therapy months after diagnosis. This study showed that early initiation and rapid up-titration of renin angiotensin system blockers (ACE inhibitors/angiotensin receptor blockers or angiotensin receptor neprilysin inhibitors), MRAs, beta-blockers and SGLT2 inhibitors resulted in better outcomes and quality of life for patients with HFrEF. Although this approach consumes more resources than the standard method, this study shows real benefits with the intensive treatment regimen that should now become standard of care.

Reference: Lancet 2022; published online Nov 4
Abstract

Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation

Authors: Lau WCY et al.

Summary: This multinational population-based cohort study compared the effectiveness of four DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) in routine clinical practice. Data for 527,226 patients who were newly diagnosed with AF in 2010–2019 and received a DOAC prescription were extracted from electronic healthcare databases in France, Germany, the UK, and the US. A Cox regression model showed that apixaban was associated with a lower risk of gastrointestinal bleeding than dabigatran (HR 0.81, 95% CI 0.70–0.94), edoxaban (HR 0.77, 95% CI 0.66–0.91), and rivaroxaban (HR 0.72, 95% CI 0.66–0.79), but no substantial differences were seen between the DOACs for ischaemic stroke/systemic embolism, intracranial haemorrhage (ICH), or all-cause mortality.

Comment: This real-world study of more than half a million patients showed results similar to the pivotal trials of the DOACs. It showed similar efficacy between all the agents with respect to reduction in stroke, ICH and all-cause mortality but less risk of gastrointestinal bleeding with apixaban, even in the elderly and those with impaired renal function. Although consistent with the clinical trials, real-world data are inherently subject to selection bias, so caution must be taken when translating the results to clinical practice.

Reference: Ann Intern Med 2022;175(11):1515-24
Abstract

Blood pressure lowering and prevention of dementia

Authors: Peters R et al., for the DIRECT Collaboration

Summary: This meta-analysis of five seminal randomised double-blind placebo-controlled trials (ADVANCE, HYVET, PROGRESS, SHEP, and SYST-EUR) investigated the effects of BP-lowering treatment for the prevention of dementia. Overall, data for 28,008 patients in 20 countries were included. 861 cases of incident dementia occurred during a median follow-up of 4.3 years. Meta-analysis of individual patient data showed that antihypertensive treatment was associated with a reduction in incident dementia (adjusted OR 0.87, 95% CI 0.75–0.99).

Comment: There has been much debate about whether lowering BP in the elderly reduces dementia, as it is quite common to see multiple small lacunar infarcts in older patients with so called "vascular" dementia. This study looked at patient level data and showed that treating hypertension in middle-aged and elderly patients reduced the risk of dementia. Target BP in these age groups is still <140/90mm Hg (<150/90 if >80 years) but recent studies have shown that lower BP (if tolerated) is associated with better cardiovascular outcomes.

Reference: Eur Heart J 2022; published online Oct 25
Abstract