Cardiology Research Review™

Making Education Easy

Issue 149 - 2022

In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **BP** = blood pressure; **CV** = cardiovascular; **DOAC** = direct oral anticoagulant; **ECG** = electrocardiogram; **eGFR** = estimated glomerular filtration rate; **GLP-1** = glucagon-like peptide-1; **HR** = hazard ratio; **hs-cTnI** = high-sensitivity cardiac troponin I; **ICD** = implantable cardioverter defibrillator; **MI** = myocardial infarction; **NT-proBNP** = N-terminal pro-B-type natriuretic peptide; **VKA** = vitamin K antagonist.

Welcome to the latest issue of Cardiology Research Review.

In this issue, an analysis of the ARIC study finds that elevated NT-proBNP levels can serve as a "risk equivalent" for cardiovascular disease in high-risk adults, a retrospective cohort study suggests that patients with AF and elevated troponin should be assessed for myocardial injury, and an analysis of the ATLAS study reports promising evidence for subcutaneous ICDs. Also in this issue, a subanalysis of the SPRINT trial finds that intensive BP control does not have a legacy effect, and the SURMOUNT-1 trial investigates the use of once-weekly subcutaneous tirzepatide (another GLP-1 receptor agonist) for obesity.

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

Elevated NT-proBNP as a cardiovascular disease risk equivalent: Evidence from the Atherosclerosis Risk in Communities (ARIC) Study

Authors: Tcheugui JB et al.

Summary: This analysis of the ARIC study investigated whether elevated NT-proBNP levels can serve as a "risk equivalent" for CV disease in adults at high CV risk. 9789 patients (mean age 63.2 years, 55% women) who attended visit 4 of the ARIC study in 1996–1998 were included. Those without CV disease at baseline were grouped according to NT-proBNP level (<125, 125–449, and ≥450 pg/ml). 4562 patients died during a median 20.5 years of follow-up. Cox regression analysis showed that, in patients without a history of CV disease, those with NT-proBNP ≥450 pg/ml were at higher risk for all-cause mortality (HR 2.12, 95% CI 1.78–2.53), CV mortality (HR 2.92, 95% CI 2.15–3.97), incident total CV disease (HR 2.59, 95% CI 2.13–3.16), atherosclerotic CV disease (HR 2.20, 95% CI 1.72–2.80), and heart failure (HR 3.81, 95% CI 3.01–4.81) than those with NT-proBNP <125 pg/ml. The elevated CV risk in people with high NT-proBNP and no history of CV disease was similar to or higher than that in people with a history of CV disease.

Comment: We know that patients with chronic mild elevation of troponin from whatever cause have an increased risk of future CV events. This study shows that a chronically elevated NT-proBNP is also associated with an increased risk of CV events over 20 years in patients without clinically evident CV disease. The authors suggest that this is a risk equivalent that indicates these patients with elevated NT-proBNP without CV disease should be treated as if they did have CV disease. However, until clinical trials are done to prove a benefit with this approach, this strategy cannot be justified.

Reference: Am J Med 2022;135(12):1461-7

Abstract

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.

Structural cardiac abnormalities in patients with atrial fibrillation/flutter and myocardial injury

Authors: de Michieli L et al.

Summary: This retrospective observational cohort study determined the prevalence/significance of structural cardiac abnormalities in patients with AF/flutter and elevated high-sensitivity cardiac troponin T (hs-cTnT) levels. 1276 patients with an AF/flutter diagnosis, hs-cTnT measurements, echocardiograms, and coronary angiograms were included. Myocardial injury was defined as hs-cTnT >10 ng/L for women and >15 ng/L for men. 875 patients with definite causes for increased hs-cTnT were not evaluated further (common diagnoses were type 1 MI, critical illness, and known heart failure). Of the remaining 401 patients, 336 (84%) had increased hs-cTnT. Of these, 78% had non-ischaemic myocardial injury and 22% had type 2 MI. Patients with elevated hs-cTnT had greater left ventricular (LV) mass index, LV filling pressures, and right ventricular systolic pressure, and were more likely to have significant coronary artery disease (47% vs 31%; p=0.016). One-year mortality was higher in patients with myocardial injury.

Comment: As mentioned in the previous study, chronically elevated troponin not due to myocardial ischaemia is associated with adverse outcomes. This study looked at patients with AF and elevated troponin, presumably due to myocardial injury, and found that this was a common finding which was associated with a high prevalence of structural heart disease such as LV hypertrophy or elevated intra-cardiac pressures, and increased mortality. This being the case, these patients would probably have elevated NT-proBNP. These results suggest that investigation be undertaken in patients with elevated troponin and AF to determine if there are any potentially reversible causes of myocardial injury.

Reference: Am J Med 2022;135(12):1488-96.e5
Abstract

Perioperative safety and early patient and device outcomes among subcutaneous versus transvenous implantable cardioverter defibrillator implantations

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

Summary: The ATLAS trial compared outcomes after standard single chamber transvenous ICD (TV-ICD) versus subcutaneous ICD (S-ICD). 503 patients with a primary or secondary prevention indication for an ICD who were aged <60 years, had a cardiogenetic phenotype, or had prespecified risk factors for lead complications were randomly assigned to S-ICD or TV-ICD and followed up for a mean 2.5 years. There were significantly fewer perioperative lead-related complications with S-ICD (0.4% vs 4.8%; p=0.001). There was a trend for more inappropriate shocks with the S-ICD (HR 2.37, 95% CI 0.98–5.77), but no increase in failed appropriate shocks. Patients in the S-ICD group had more ICD site pain on the day of implant (p<0.001) and 1 month later (p=0.035) than those in the TV-ICD group.

Comment: These early results from the ATLAS study comparing subcutaneous versus standard ICDs are promising. There were fewer lead-related issues (as S-ICDs are leadless), with similar appropriate shocks, but a trend towards more inappropriate shocks. Even if this is true, reprogramming may reduce this. The SC device was a bit more painful, but it would seem the advantages outweigh the disadvantages at present. We await with interest the results of the long-term follow up, and further clinical trials with this device.

Reference: Ann Intern Med 2022; published online Nov 8
Abstract

Longer-term all-cause and cardiovascular mortality with intensive blood pressure control

Authors: Jaeger BC et al.

Summary: This secondary analysis of the SPRINT trial evaluated the effects of intensive BP control on the long-term incidence of CV and all-cause mortality. In the SPRINT trial, 9361 patients aged ≥50 years (mean 67.9 years, 35.6% female) with hypertension and increased CV risk but without diabetes or history of stroke were randomised to an intensive treatment group (systolic BP [SBP] goal <120mm Hg) or a standard treatment group (SBP <140mm Hg). During a median intervention period of 3.3 years, intensive treatment was beneficial for both CV mortality (HR 0.66, 95% CI 0.49–0.89) and all-cause mortality (HR 0.83, 95% CI 0.68–1.01). However, at the median total follow-up of 8.8 years, there was no longer evidence of benefit for CV or all-cause mortality with intensive treatment. A subgroup analysis showed that the estimated mean SBP of patients randomised to intensive treatment increased from 132.8mm Hg at 5 years to 140.4mm Hg at 10 years.

Comment: The SPRINT study showed that lowering SBP to <120mm Hg in patients aged over 50 without a history of stroke or diabetes improved outcomes, but there has been much discussion as to the validity of this level of BP control as the study did not measure BP in the way it is measured in clinical settings. This subanalysis of the trial showed that there was no legacy effect of having been randomised to the lower BP group, as the benefits on CV and all-cause mortality did not persist after the trial was finished. We know that there is a legacy effect of lower cholesterol and better diabetic control in patients who participated in trials in these areas, but it appears this is not the case for hypertension. The reason for this is not clear.

Reference: JAMA Cardiol 2022;7(11):1138-46
Abstract

Management of older patients with unexplained, recurrent, traumatic syncope and bifascicular block: Implantable loop recorder versus empiric pacemaker implantation

Authors: Palmisano P et al.

Summary: This study compared the risk of syncope recurrence after empiric pacemaker implantation versus implantable loop recorder (ILR) monitoring. 309 consecutive patients with unexplained, recurrent, traumatic syncope and bifascicular block who underwent ILR monitoring or empiric pacemaker implantation were included. Propensity matching of the 309 patients yielded 89 matched pairs. During a median follow-up of 33 months, empiric pacemaker implantation was associated with a lower risk of syncope recurrence than ILR monitoring (19.1% vs 46.1%; p<0.001). 35 patients (39.3%) who underwent ILR monitoring developed bradyarrhythmias requiring pacemaker implantation during follow-up. The most frequent causes of syncope recurrence (excluding bradyarrhythmic syncope) in both study groups were reflex syncope and orthostatic hypotension.

Comment: Blackouts in the elderly are not uncommon, and when bifascicular block is present on the resting ECG it is tempting to assume that more advanced heart block is likely to be the cause. In these circumstances some physicians will implant a pacemaker whereas others will want definitive evidence of heart block before inserting a device. Not surprisingly this study showed that there was less syncope in the group that had a pacemaker first up, but what is interesting was that only 40% of the patients who had an initial ILR had documentation of a bradyarrhythmia, meaning that if all these patients had been given a pacemaker as their initial treatment strategy, 60% would have been unnecessary. Hypotension and vagally-mediated syncope were common, so I feel that an initial ILR strategy is still the best option.

Reference: Heart Rhythm 2022;19(10):1696-1703
Abstract

Single high-sensitivity point of care whole blood cardiac troponin I measurement to rule out acute myocardial infarction at low risk

Authors: Apple FS et al., on behalf of the SAMIE Investigators

Summary: This study investigated whether a rapid, point-of-care, whole-blood hs-cTnI assay at presentation can identify patients at low risk of index MI. The derivation cohort comprised 1086 consecutive emergency department (ED) patients with suspected ACS in the US (SEIGE study) and the validation cohort comprised 1486 consecutive ED patients with suspected ACS in Australia (SAMIE study). A derivation whole blood point-of-care hs-cTnI concentration of <4 ng/L had a sensitivity of 98.9% and a negative predictive value (NPV) of 99.5% for ruling out MI. In the validation cohort, sensitivity was 98.8% and NPV was 99.8%. 17.8% and 41.8% of patients in the respective cohorts were defined as low risk and suitable for early discharge. The primary outcome (cardiac adverse events at 30 days) occurred in 0.1% of SEIGE participants and 0.8% of SAMIE participants.

Comment: Standard practice is to do serial troponins in patients who present with chest pain, and if there are two negative tests 6h apart an MI is ruled out. This delay in diagnosis often jams up A&E beds so a rapid assessment and rule-out for MI would be of great benefit. This study from Australia and the US shows that if a point-of-care hs-cTnI is negative at presentation, the patient can be deemed low risk and discharged early, with a very low risk of adverse cardiac events in the next 30 days, before which outpatient investigations for the cause of chest pain (e.g. stress test) should be undertaken.

Reference: Circulation 2022; published online Oct 31
Abstract

Tirzepatide once weekly for the treatment of obesity

Authors: Jastreboff AM et al., for the SURMOUNT-1 Investigators

Summary: The SURMOUNT-1 trial investigated the efficacy and safety of the GLP-1 receptor agonist tirzepatide in individuals with obesity. 2539 adults with BMI ≥30 kg/m^2 (or ≥27 kg/m^2 and ≥1 weight-related complication, excluding diabetes) were randomised 1:1:1:1 to receive once-weekly subcutaneous tirzepatide (5mg, 10mg, or 15mg) or placebo for 72 weeks (including a 20-week dose-escalation period). The mean percentage change in weight at week 72 was −15.0% with tirzepatide 5mg, −19.5% with tirzepatide 10mg, −20.9% with tirzepatide 15mg, and −3.1% with placebo (all p<0.001 vs placebo). The percentage of participants who had ≥5% weight reduction was 85%, 89%, and 91% with tirzepatide 5mg, 10mg, and 15mg, respectively, and 35% with placebo. 50% and 57% of participants in the tirzepatide 10mg and 15mg groups had ≥20% weight reduction, compared with 3% in the placebo group (all p<0.001 vs placebo). The most commonly reported adverse events with tirzepatide were gastrointestinal (most were mild to moderate and occurred primarily during dose escalation).

Comment: There is a global shortage of the GLP-1 agonists such as semaglutide and dulaglutide at present as they have been avidly prescribed for weight loss in non-diabetic patients and the manufacturers can't keep up with demand. The STEP study with semaglutide showed that most patients lost up to 15% of body weight at 12 months and this weight loss was sustained with ongoing therapy. This new agent tirzepatide, which blocks GLP-1 and gastric inhibitory peptide, seems to be even more effective in promoting weight loss and outcome studies are underway. Many patients suffer gastrointestinal side effects when treatment is started, but these adverse effects often wane with ongoing therapy. These agents will revolutionise the management of obesity as they are safe and effective, and with time will become more affordable.

Reference: N Engl J Med 2022;387(3):205-16
Abstract

Direct oral anticoagulants vs vitamin-K antagonists in thrombotic antiphospholipid syndrome

Authors: Khairani CD et al.

Summary: This systematic review and meta-analysis compared the use of DOACs and VKAs in patients with thrombotic antiphospholipid syndrome. A search of PubMed, EMBASE, and Cochrane Central Register of Controlled Trials identified four open-label randomised controlled trials (n=472) that were suitable for inclusion. Meta-analysis of the data revealed that use of DOACs compared with VKAs was associated with increased odds of subsequent arterial thrombotic events (odds ratio [OR] 5.43, 95% CI 1.87–15.75; p<0.001), especially stroke and a composite of arterial thrombotic events or venous thromboembolism (OR 4.46, 95% CI 1.12–17.84; p=0.03). The odds of subsequent venous thromboembolism or major bleeding did not differ significantly between the two groups.

Comment: DOACs have replaced warfarin and Clexane® as antithrombotic therapy in many conditions such as stroke prevention in AF, treatment and prevention of deep vein thrombosis/pulmonary embolism post orthopaedic surgery and in medically unwell patients. Warfarin has recently been shown to be superior to rivaroxaban in patients with AF and rheumatic mitral stenosis, with an excess of death and bleeding in the DOAC group. This study also shows that warfarin is preferable to DOACs for prevention of thrombosis in patients with antiphospholipid syndrome, particularly with respect to arterial thrombosis. Thus a VKA should continue to be the preferred anticoagulant in patients with moderate to severe rheumatic mitral valve disease, metallic heart valves, and in patients with antiphospholipid syndrome, as well as patients with severe renal dysfunction (eGFR <30 ml/min for dabigatran, <25 ml/min for apixaban and <15 ml/min for rivaroxaban), as well as patients on dialysis.

Reference: J Am Coll Cardiol 2022; published online Oct 31
Abstract

Sodium restriction in patients with heart failure

Authors: Colin-Ramirez E et al.

Summary: This systematic review and meta-analysis evaluated the effects of sodium restriction on clinical outcomes in patients with heart failure (HF). A search of Cochrane Central, MEDLINE, Embase Ovid, and CINAHL Plus databases identified 17 randomised controlled trials (n=1705) that were suitable for inclusion. Meta-analysis of the data revealed that sodium restriction did not reduce the risk of all-cause mortality, hospitalisation, or the composite of mortality/hospitalisation in patients with HF compared with controls. Among trials that reported New York Heart Association (NYHA) change, two trials (accounting for two-thirds of the data) showed an improvement in NYHA class with sodium restriction.

Comment: It has been common practice to recommend salt restriction in patients with HF, on the assumption that a reduction in salt intake will result in a reduction in intravascular volume and less congestive symptoms. This meta-analysis shows that the latter is true, but this did not translate into an improvement in hard outcomes (death or hospitalisation). This may be because volume depletion may cause reflex activation of the renin-angiotensin system which may negate some of the benefits of ACE inhibitors/angiotensin receptor blockers or angiotensin receptor neprilysin inhibitors, but this is speculative. In any case it appears we should focus less on salt intake in HF but total fluid intake is still important.

Reference: Circ Heart Fail 2022; published online Nov 14
Abstract

Reduction in blood pressure for people with isolated diastolic hypertension and cardiovascular outcomes

Authors: Suzuki Y et al.

Summary: This retrospective study investigated the relationship between BP reduction and incident CV disease in patients with isolated diastolic hypertension (IDH; systolic BP [SBP] <140mm Hg and diastolic BP [DBP] ≥90mm Hg). 71,297 patients with IDH (median age 48 years, 83.1% male, median DBP 92mm Hg) who were not taking BP-lowering medications at baseline and did not have a history of CV disease were included. BP was measured at baseline and again at the 1-year follow-up, and participants were categorised into two groups based on DBP at one year (≥90mm Hg or <90mm Hg). During a mean follow-up of 1100 days, 1317 composite CV disease end-points were recorded. Participants with DBP <90mm Hg at 1 year were at lower risk for composite CV disease events during follow-up than those with DBP ≥90mm Hg (HR 0.75, 95% CI 0.67–0.83).

Comment: We know that in Western countries SBP tends to rise and DBP falls with age, presumably due to progressive arteriosclerosis making our arteries stiffer. The focus has usually been on lowering SBP to reduce CV risk, with DBP thought to play a less important role. IDH is more commonly seen in young and middle-aged hypertensive patients and this analysis suggests that IDH is associated with excess CV risk, and that reducing it improves outcomes. The optimal level of DBP is around 80mm Hg (as shown in the HOT study) as there may be an increase in CV events above or below this level – the so-called J-curve phenomenon.

Reference: Eur J Prev Cardiol 2022; published online Nov 22
Abstract