Cardiology Research Review™

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In this issue:

Welcome to the latest issue of Cardiology Research Review.

In this issue, Spanish investigators identify a promising new marker for detecting acute myocarditis, the PER DIEM study evaluates how to best screen for AF after an ischaemic stroke, and an analysis of the GARFIELD-AF trial answers the fundamental question of anticoagulation in AF. Also in this issue, a prespecified subanalysis of the DAPA-HF trial reports that the mortality benefits of dapagliflozin in patients with HFrEF occur regardless of sex, an analysis of the COMPASS trial reports the mortality benefits of rivaroxaban + aspirin in patients with chronic CAD or PAD, and a European cohort study reports that proton pump inhibitors reduce the risk of severe upper gastrointestinal bleeding in AF patients taking NOACs.

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

A novel circulating microRNA for the detection of acute myocarditis

Authors: Blanco-Domínguez R et al.

Summary: This Spanish study identified a novel microRNA for the diagnosis of acute myocarditis. Th17 cells were found to be a characteristic feature of myocardial injury in the acute phase of myocarditis in a murine model of experimental autoimmune myocarditis and MI. The human homologue (designated hsa-miR-Chr8:96) was then evaluated in patients with myocarditis. The area under the receiver-operating-characteristic curve for hsa-miR-Chr8:96 for distinguishing patients with acute myocarditis from those with MI was 0.927 (95% CI 0.879–0.975). The microRNA retained its diagnostic value after adjustment for age, sex, ejection fraction, and serum troponin level.

Comment: In patients presenting with chest pain and elevated troponin with a normal ECG, one often makes a presumptive diagnosis of MI with nonobstructive coronary arteries (MINOCA) or myocarditis once obstructive CAD has been ruled out on angiography. A more definitive diagnosis for myocarditis can be made with biopsy or MRI but this is generally not funded for this diagnosis in Australia. This new approach of detecting a microRNA in blood specific to myocarditis is extremely promising as it seems that this assay can distinguish myocarditis from ischaemia. If this technique can be validated, it should be widely adopted to make a definitive diagnosis of myocarditis without having to image the coronary arteries or myocardial tissue characteristics with MRI. This will be particularly important in patients labelled MINOCA based on nonobstructed coronary arteries on angiography as this invasive testing may be able to be avoided in patients with chest pain, elevated troponin and normal ECG if the specific mRNA for myocarditis is elevated.

Reference: N Engl J Med 2021;384:2014-27

Abstract

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **CAD** = coronary artery disease; **ECG** = electrocardiogram; **HFpEF** = heart failure with preserved ejection fraction; **HFrEF** = heart failure with reduced ejection fraction; **HR** = hazard ratio; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **MRI** = magnetic resonance imaging; **NOAC** = non-vitamin K antagonist oral anticoagulant; **PAD** = peripheral artery disease; **PCI** = percutaneous coronary intervention; **SCAD** = spontaneous coronary artery dissection.

Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke

Authors: Buck BH et al.

Summary: The PER DIEM trial investigated whether 12 months of monitoring with an implantable loop recorder detects more occurrences of AF than 30 days of conventional external loop recorder monitoring in patients with a recent ischaemic stroke. 300 patients without known AF who had an ischaemic stroke within the previous 6 months were randomised to ECG monitoring with either an implantable loop recorder (12 months) or an external loop recorder (30 days). The primary outcome (definite or highly probable AF) was observed in 15.3% of patients in the implantable loop recorder group and 4.7% of patients in the external loop recorder group (risk ratio 3.29, 95% CI 1.45–7.42; p=0.003).

Comment: Embolic stroke of unknown source (ESUS) is not uncommon and is often thought to be due to undetected AF. This study shows that the longer you monitor the heart rate post ESUS the more likely you are to detect AF, and thus anticoagulation can be started. Intuitively, anticoagulation should reduce recurrent ESUS but it is important to document AF in this patient population before starting anticoagulation, as 2 large studies with rivaroxaban and dabigatran were unable to demonstrate any benefit with anticoagulation in the absence of AF being diagnosed.

Reference: JAMA 2021;325(21):2160-8
Abstract

Clinical outcomes in asymptomatic and symptomatic atrial fibrillation presentations in GARFIELD-AF

Authors: Gibbs H et al., for the GARFIELD-AF Investigators

Summary: This analysis of the GARFIELD-AF trial compared clinical characteristics, treatment, and 2-year outcomes in patients with asymptomatic versus symptomatic AF. Of 52,032 eligible patients, 25.4% had asymptomatic AF and 74.6% had symptomatic AF. Asymptomatic patients were slightly older (72 vs 70 years), more likely to be male (64.2% vs 52.9%), and more likely to be taking anticoagulants ± antiplatelets (69.4% vs 66.0%). No between-group differences in non-haemorrhagic stroke/systemic embolism, all-cause mortality, or bleeding were observed. Anticoagulation was associated with comparable reductions in non-haemorrhagic stroke/systemic embolism and all-cause mortality in the 2 groups.

Comment: Many patients with AF have no symptoms, and it is only detected when they present with a stroke, which can have devastating effects on the patient and their families. This study shows that the stroke risk and benefit of anticoagulation is independent of symptomatic status, so that even if the patient is asymptomatic, anticoagulation should be started if the CHADS-VA justifies. Screening for AF when patients have a medical contact should be part of routine practice, as feeling the radial pulse for irregularity is easy, and although sometimes the irregular heart rate will be due to ectopic activity on ECG or Holter, it is better to be cautious given the implications for the patient. An irregular heart rate detected on a smart watch is more problematic, as studies have shown that there is a low incidence of AF detection using this technology, and even if it is AF the burden to justify anticoagulation is still contentious, as is what to do when AF is picked up on a routine permanent pacemaker or implantable cardioverter defibrillator check.

Reference: Am J Med 2021;134(7):893-901
Abstract

Efficacy and safety of dapagliflozin in men and women with heart failure with reduced ejection fraction

Authors: Butt JH et al.

Summary: This prespecified analysis of the DAPA-HF trial compared the efficacy and safety of dapagliflozin in males and females with HFrEF. In DAPA-HF, 4744 patients (23.4% female) with HFrEF were randomised to receive dapagliflozin 10mg or placebo once daily. Compared with placebo, dapagliflozin reduced the risk of worsening HF events or cardiovascular mortality to a similar extent in both males (HR 0.73, 95% CI 0.63–0.85) and females (HR 0.79; 95% CI 0.59–1.06). Compared with placebo, dapagliflozin increased the proportion of patients with a meaningful improvement in symptoms and decreased the proportion with worsening symptoms, irrespective of sex. Tolerability profiles of dapagliflozin did not differ between sexes.

Comment: Women are traditionally underrepresented in large cardiovascular outcome trials. The DAPA-HF trial is no exception, as only 23.4% of participants were female (although this is a reasonable number to evaluate). This prespecified subanalysis of the DAPA-HF trial (patients with ejection fraction <40% with and without diabetes), shows that the benefits of dapagliflozin in reducing heart failure and death, and improving quality of life were the same in men and women, and is reassuring that gender does not influence outcome with this therapy. In contrast, there was a signal that women did better with sacubitril/valsartan than valsartan when used in patients with HFpEF in another contemporary trial.

Reference: JAMA Cardiol 2021;6(6):678-89
Abstract

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM)

Authors: Koo B-K et al.

Summary: The HOST-EXAM trial compared the efficacy and safety of aspirin and clopidogrel monotherapy during the chronic maintenance period after coronary stenting. At 37 sites in South Korea, 5438 patients who received dual antiplatelet therapy (DAPT) without clinical events for 6–18 months after PCI with a drug-eluting stent were randomised to receive monotherapy with either clopidogrel 75mg once daily or aspirin 100mg once daily for a further 24 months. The primary end-point was a composite of all-cause death, non-fatal MI, stroke, readmission for ACS, and Bleeding Academic Research Consortium (BARC) bleeding type 3 or greater. During follow-up, the primary outcome occurred in 152 (5.7%) patients in the clopidogrel group and 207 (7.7%) in the aspirin group (HR 0.73, 95% CI 0.59–0.90; p=0.0035).

Comment: Patients with ACS who are treated with PCI traditionally receive 12 months of DAPT with aspirin plus a P2Y12 inhibitor such as clopidogrel or ticagrelor. At 12 months the P2Y12 inhibitor is generally stopped and aspirin is continued as monotherapy indefinitely on the basis of vascular protection in patients with established cardiovascular disease. The CAPRI study demonstrated many years ago that clopidogrel was superior to aspirin in preventing recurrent events in patients with pre-existing vascular disease and this effect was particularly strong in patients with a history of MI or PAD. Although the benefits were statistically significant they were clinically less impressive, as there was only an 8.7% relative risk reduction in events with clopidogrel compared with aspirin, and given the cost differential of clopidogrel at that time, it was only used in aspirin-intolerant patients or aspirin failures. This subsequent analysis has shown that there was a significant 2% absolute risk reduction in MACE and readmission with ACS in patients receiving clopidogrel monotherapy rather than aspirin for maintenance antiplatelet therapy post PCI for ACS. This translates to needing to treat 100 patients for 1 year to achieve this effect and now that clopidogrel is off patent and much cheaper, using it in this way becomes more attractive although it is not subsidised by the PBS in Australia for this indication.

Reference: Lancet 2021;397(10293):2487-96
Abstract

Mortality benefit of rivaroxaban plus aspirin in patients with chronic coronary or peripheral artery disease

Authors: Eikelboom JW et al.

Summary: This analysis of the COMPASS trial investigated the impact of low-dose rivaroxaban + aspirin on mortality in patients with chronic CAD or PAD. The COMPASS trial randomised 18,278 patients with CAD or PAD to receive rivaroxaban 2.5mg twice daily + aspirin 100mg once daily (n=9152) or aspirin alone (n=9126). During a median 23 months of follow-up, 3.4% of patients receiving combination therapy and 4.1% receiving aspirin alone died (HR 0.82, 95% CI 0.71–0.96; p=0.01). Compared with aspirin alone, the rivaroxaban + aspirin combination reduced cardiovascular death (HR 0.78, 95% CI 0.64–0.96; p=0.02) but not non-cardiovascular death. The absolute mortality benefits increased with increasing baseline risk.

Comment: The COMPASS trial in patients with CAD or PAD (or both) showed a reduction in the combined end-point of MACE and cardiovascular death in those who received low-dose rivaroxaban and aspirin compared with aspirin alone. This subanalysis confirms a reduction for both total and cardiovascular mortality in the patients who received dual pathway inhibition. Although this was statistically significant, about 280 patients would need to be treated for a year to save 1 event, making the clinical significance of this therapy debatable.

Reference: J Am Coll Cardiol 2021;78(1):14-23
Abstract

Risk stratification of cardiovascular complications using CHA_2DS_2-VASc and $CHADS_2$ scores in chronic atherosclerotic cardiovascular disease

Authors: Sen J et al., for the COMPASS Trial Investigators

Summary: This analysis of the COMPASS trial evaluated the accuracies of the CHA_2DS_2-VASc and $CHADS_2$ scores for predicting MACE in patients with chronic ASCVD randomised to rivaroxaban + aspirin (n=9152) or aspirin alone (n=9126). Overall, high CHA_2DS_2-VASc (6–9) or $CHADS_2$ (3–6) scores were associated with more than 3-fold greater absolute risk of MACE compared with CHA_2DS_2-VASc score of 1–2 or $CHADS_2$ score of 0. The effects of rivaroxaban + aspirin compared with aspirin alone were consistent across CHA_2DS_2-VASc and $CHADS_2$ score categories for MACE, bleeding and net clinical benefit.

Comment: As seen in the previous study, there are demonstrable benefits with dual pathway inhibition (DPI) in patients with CAD, PAD or both. The mortality benefits are relatively small, although the greater the baseline risk, the greater the benefit. This analysis of the COMPASS trial shows that the CHA_2DS_2-VASc and $CHADS_2$ scores can be used to select out the highest risk patients that would benefit from DPI. It showed that the higher the risk score, the higher the risk of MACE and the greater the net clinical benefit of DPI. This may be a useful tool when considering in whom to use this treatment strategy.

Reference: Int J Cardiol 2021;337:9-15
Abstract

Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry

Authors: Cerrato E et al., for the DISCO Collaborators

Summary: This European registry study investigated the use of antiplatelet drugs in medically treated SCAD patients, and the relationship between single (SAPT) and dual (DAPT) antiplatelet therapy and 1-year patient outcomes. 199 patients (89% female, mean age 52.3 years) with conservatively managed SCAD were divided into 2 groups according to treatment with SAPT (33.7%) or DAPT (66.3%); the primary end-point was 12-month incidence of MACE. DAPT comprised aspirin + clopidogrel (62.9%) or aspirin + ticagrelor (36.4%). Overall, the rate of MACE was 14.6% during 12 months of follow-up. The MACE rate was higher with DAPT versus SAPT (18.9% vs 6.0%; HR 2.62, 95% CI 1.22–5.61; p=0.013), driven by an early excess of non-fatal MI or unplanned PCI. Multiple regression analysis showed that type 2a SCAD (odds ratio 3.69, 95% CI 1.41–9.61; p=0.007) and DAPT regimen (odds ratio 4.54, 95% CI 1.31–14.28; p=0.016) were independently associated with a higher risk of 12-month MACE.

Comment: Most patients admitted with SCAD are treated as though they have NSTEMI, although the underlying pathophysiology is a vasculopathy rather than atherosclerosis. This being the case, DAPT, statins and beta-blockers are frequently used. This interesting study suggests that DAPT is associated with worse outcomes than SAPT over 12 months with higher rates of MACE and unplanned PCI. This may be due to more potent antiplatelet therapy causing more intramural haematoma formation and events. These data need confirmation but will change clinical practice if verified.

Reference: Eur Heart J 2021; published online Aug 2
Abstract

Non-vitamin K antagonist oral anticoagulants, proton pump inhibitors and gastrointestinal bleeds

Authors: Komen J et al.

Summary: This cohort study investigated whether proton pump inhibitors (PPIs) reduce the risk of upper gastrointestinal (GI) bleeding in AF patients treated with NOACs. 164,290 patients in Stockholm, Denmark and the Netherlands were included. 806 severe upper GI bleeding events occurred during 272,570 patient-years of follow-up. After inverse probability weighting, Poisson regression analysis showed that use of PPIs was associated with lower rates of severe upper GI bleeding (incidence rate ratio 0.75, 95% CI 0.59–0.95). The protective effect was greatest in high-risk patients (age ≥75 years, HAS-BLED score ≥3, or taking concomitant antiplatelet therapy).

Comment: There have been conflicting reports about the benefits of using PPIs to reduce upper GI bleeding in patients on anticoagulation. This cohort study confirms what one would intuitively expect, and showed that PPI use in patients with AF on NOACs reduces severe upper GI bleeding, indicating that they should probably be used as preventative therapy in patients with high bleeding risk (perhaps HAS-BLED ≥3).

Reference: Heart 2021; published online Aug 2
Abstract

Early rhythm control therapy in patients with atrial fibrillation and heart failure

Authors: Rillig A et al.

Summary: This prespecified subanalysis of the EAST-AFNET 4 trial assessed the effect of systematic, early rhythm control therapy (antiarrhythmic drugs or catheter ablation within 1 year of AF diagnosis) compared to usual care (allowing rhythm control therapy to improve symptoms) in AF patients with signs or symptoms of heart failure (HF). 798 patients (37.6% female, median age 71 years) were included in the analysis. Most patients (n=442) had HFpEF, 211 had HF with mid-range ejection fraction, and 132 had HFrEF. Over the 5.1-year median follow-up, the composite primary outcome of cardiovascular death, stroke, or hospitalisation for worsening HF or for ACS occurred less often with early rhythm control therapy than with usual care (HR 0.74, 95% CI 0.56–0.97; p=0.03), and was not affected by HF status. The primary safety outcome (death, stroke, or serious adverse events related to rhythm control therapy) also occurred less often with early rhythm control therapy (HR 0.85, 95% CI 0.62–1.17; p=0.33).

Comment: The EAST-AFNET 4 trial recently showed there was a small but significant benefit of an early rhythm control strategy in patients with AF. This subanalysis looked at patients with HF in this study and found that the efficacy and safety of an early rhythm control approach (ablation or antiarrhythmic therapy) in patients with HF had an even greater benefit than that in patients without HF. This approach is reinforced by the earlier CASTLE trial, in which similar results were found. This being the case, an early rhythm control strategy should be preferred in patients with AF, especially in patients with HF.

Reference: Circulation 2021; published online Jul 30
Abstract

