Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **CRT** = cardiac resynchronisation therapy; **DOAC** = direct oral anticoagulant; **ECG** = electrocardiogram; **HOCM** = hypertrophic obstructive cardiomyopathy; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **NYHA** = New York Heart Association; **PCI** = percutaneous coronary intervention.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, the RADIANCE II trial revisits the use of renal denervation for resistant hypertension, the VALOR-HCM trial looks at the use of the cardiac myosin inhibitor mavacamten in patients with HOCM, and a meta-analysis of data from the DOAC registration trials evaluates their efficacy across the spectrum of kidney function. Also in this issue, the findings of two studies suggest that elevated HDL levels may not be as protective or benign as once thought.

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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Endovascular ultrasound renal denervation to treat hypertension

Authors: Azizi M et al., for the RADIANCE II Investigators and Collaborators

Summary: The RADIANCE II trial investigated the efficacy and safety of ultrasound renal denervation in patients with treatment-resistant hypertension. At 37 centres in the US and 24 centres in Europe, 1038 patients aged 18–75 years who had hypertension despite taking up to two antihypertensive medications and who had ambulatory blood pressure (BP) ≥135/85mm Hg and <170/105mm Hg after a 4-week medication washout were randomised 2:1 to undergo ultrasound renal denervation or a sham procedure, and abstained from antihypertensive medications for 2 months where possible. The reduction in daytime ambulatory systolic BP at 2 months (primary outcome) was greater with ultrasound renal denervation than with the sham procedure (mean –7.9 vs –1.8mm Hg; p<0.001).

Comment: Renal sympathetic denervation with radio frequency ablation has been shown to produce small but significant BP reduction in patients with resistant hypertension and in mildly hypertensive patients on no medication. This study uses an alternative means of ablating the renal sympathetic nerves and gives much the same BP reduction as radiofrequency ablation but whether the effect is durable is not clear, and whether it lowers BP on top of conventional antihypertensive medication remains to be seen.

Reference: JAMA 2023;329(8):651-61
Abstract

Self-screening for atrial fibrillation could reduce stroke

Atrial Fibrillation (AF) screening is recommended for people aged 65 and over, but only 11 per cent of eligible patients are screened by their GPs, often due to time constraints. This key paper by Prof Ben Freedman from the Heart Research Institute demonstrated that the use of AF self-screening stations in GP waiting rooms could improve AF screening and diagnosis rates, and reduce the number of AF-related strokes.

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Dose-blinded myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: Outcomes through 32 weeks

Authors: Desai MY et al.

Summary: The VALOR-HCM trial investigated the effect of 32 weeks' treatment with mavacamten on the need for septal reduction therapy (SRT) in patients with HOCM. At 19 US sites, 112 patients with HOCM who were taking maximally tolerated medical therapy and were due to undergo SRT were randomised in a double-blind design to receive mavacamten for 32 weeks or placebo for 16 weeks then mavacamten for 16 weeks. After 32 weeks, only 10.7% of patients in the original mavacamten group and 13.5% in the placebo crossover group still met SRT guideline criteria or elected to undergo SRT (primary outcome). In addition, 90.6% and 70% of patients in the respective groups improved by ≥1 NYHA class.

Comment: In patients with hypertrophic cardiomyopathy who have symptomatic outflow tract obstruction there are few therapeutic options. There is some evidence that disopyramide improves symptoms but it is hard to access in Australia. In patients who remain symptomatic on beta-blockers +/- disopyramide, septal myomectomy or alcohol ablation is the only other therapeutic option. Mavacamten has been shown to improve quality of life and symptoms in patients with symptomatic HOCM, and this study shows a significant reduction in septal thickness over 32 weeks, to the point where many patients who had been scheduled for surgery did not need it. Whether this effect is durable remains to be seen, but even if it delays the need for surgery this is an important finding.

Reference: Circulation 2023;147(11):850-63
Abstract

Cardiac resynchronization therapy improves outcomes in patients with intraventricular conduction delay but not right bundle branch block

Authors: Friedman DJ et al.

Summary: This meta-analysis of randomised controlled trials investigated the benefits of CRT in patients with differing QRS characteristics. Patient-level data from the pivotal CRT trials (MIRACLE, MIRACLE-ICD, MIRACLE-ICD II, REVERSE, RAFT, BLOCK-HF, COMPANION, and MADIT-CRT) were analysed using Bayesian Hierarchical Weibull survival regression models to assess CRT benefit by QRS morphology and duration. Patients had left bundle branch block (LBBB; n=4549), right bundle branch block (RBBB; n=691), and intraventricular conduction delay (IVCD; n=1024). Overall, 61% of patients received CRT with or without an implantable cardioverter defibrillator. Meta-analysis of the data showed that CRT was associated with a lower risk of heart failure hospitalisation or death overall (HR 0.73, credible interval [CrI] 0.65–0.84), and in subgroups of patients with QRS ≥150ms and either LBBB (HR 0.56, CrI 0.48–0.66) or IVCD (HR 0.59, CrI 0.39–0.89), but not RBBB (HR 0.97, CrI 0.68–1.34). No significant association of CRT with heart failure hospitalisation or death was observed when QRS was <150ms, regardless of QRS morphology.

Comment: CRT is indicated in patients with wide QRS on ECG and ejection fraction <35%. This study further defines patients who will get the most benefit and suggests that those with RBBB do not have reduced hospitalisation for heart failure or death after CRT, even if their QRS is >150ms. This being the case, RBBB should be a contraindication for CRT, and careful consideration should be given with intraventricular conduction defect and QRS >150ms as patients with LBBB clearly have the greatest benefit from CRT.

Reference: Circulation 2023;147:812-23
Abstract

U-shaped relationship between apolipoprotein A1 levels and mortality risk in men and women

Authors: Faaborg-Andersen CC et al.

Summary: Apolipoprotein A1 (ApoA1) is the principal protein component of HDL. This UK Biobank study investigated the association between serum ApoA1 levels and survival outcomes. 402,783 individuals without coronary artery disease at baseline were followed up for a median of 12.1 years. After adjustment for traditional cardiovascular risk factors, there was a U-shaped relationship between ApoA1 levels and both cardiovascular mortality and all-cause mortality. Individuals in the highest decile of ApoA1 levels had higher cardiovascular mortality (HR 1.21, 95% CI 1.07–1.37; p<0.0022) and all-cause mortality (HR 1.14, 95% CI 1.07–1.21; p<0.0001) than those in the lowest risk eighth decile. The U-shaped relationship was present for both sexes, but more pronounced in males.

Comment: Observational studies such as Framingham showed that low HDL was associated with an increased rate of cardiovascular events, whereas high HDL was protective. Randomised trials of cholesterylester transfer protein (CETP) blockers that reduce the breakdown of HDL and thus increase its levels have generally been disappointing, with any benefits thought to be primarily due to LDL reduction rather than increased HDL. This large analysis from the UK Biobank confirms that low HDL is associated with increased risk, but also shows high HDL is associated with increased mortality. However, the fact that very high HDL was not associated with increased mortality casts doubt on this relationship, as although this finding could be due to low numbers, there seems to be no obvious mechanism as to why this should be.

Reference: Eur J Prev Cardiol 2023;30(4):293-304
Abstract

Association of plasma high-density lipoprotein cholesterol level with risk of fractures in healthy older adults

Authors: Hussain SM et al.

Summary: This post hoc analysis of data from the ASPREE trial and the ASPREE-Fracture substudy investigated whether higher HDL cholesterol levels are associated with fracture risk in healthy older adults. Of the 16,262 participants who had a plasma HDL cholesterol measurement at baseline, 1659 had at least 1 fracture during a median 4-year follow-up. Cox regression analysis adjusted for confounding factors showed that each 1-SD increment in HDL cholesterol was associated with a 14% higher risk of fracture (HR 1.14, 95% CI 1.08–1.20). Results were similar when analyses were stratified by sex.

Comment: As opposed to the previous study, this analysis from the ASPREE trial did show a relationship between higher HDL and fractures, even after adjustment for confounders. Why this should be is not clear, but perhaps we should be more diligent in screening for osteoporosis in women with high HDL.

Reference: JAMA Cardiol 2023;8(3):268-72
Abstract

Direct oral anticoagulants versus warfarin across the spectrum of kidney function

Authors: Harrington J et al.

Summary: This meta-analysis of data from the COMBINE AF database as well as the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials evaluated the safety and efficacy of DOACs versus warfarin across the spectrum of kidney function. 71,683 patients (mean age 70.6 years, 37.3% female, median follow-up 23.1 months) were included in the analysis. The incidence of stroke and systemic embolism, major bleeding, intracranial haemorrhage (ICH) and death increased significantly with worsening kidney function. Compared with warfarin, standard-dose DOAC was associated with a significantly lower risk of ICH at CrCl levels <122 ml/min, a significantly lower risk of stroke and systemic embolism at CrCl <87 ml/min, and a significantly lower risk of death at CrCl <77 ml/min. Use of lower-dose DOACs was not associated with a significant difference in incident bleeding or ICH in patients with reduced kidney function but was associated with a higher incidence of death and stroke or systemic embolism.

Comment: It is tempting to use low-dose DOACs in patients with renal dysfunction on the assumption that stroke prevention efficacy will be maintained with less bleeding and ICH. This study looking at pooled data from the large registration trials of DOACs showed that this is not the case. Stroke, systemic embolism, major bleeding, ICH and death increased with decreasing renal function (as expected) but the benefits of DOACs over warfarin for these outcomes was maintained independent of renal function. Moreover, with inappropriate low dosing in patients with impaired renal function there was no benefit in terms of bleeding risk, but there was an increased risk of stroke and death. This emphasises the importance of only using lower dose DOACs when dose reduction criteria are met.

Reference: Circulation 2023; published online Apr 12
Abstract

Aspirin vs clopidogrel for long-term maintenance after coronary stenting in patients with diabetes

Authors: Rhee T-M et al., for the HOST-EXAM Investigators

Summary: This post hoc analysis of the HOST-EXAM trial investigated the long-term use of clopidogrel versus aspirin after coronary stenting in patients with and without diabetes. 5438 patients who received dual antiplatelet therapy for 6–18 months after PCI with drug-eluting stents were randomised 1:1 to receive clopidogrel or aspirin monotherapy and followed up for 24 months. The primary outcome was a composite of all-cause death, nonfatal MI, stroke, readmission for ACS, and major bleeding. The rate of the primary composite end-point at 24 months was significantly lower with clopidogrel than with aspirin in patients with diabetes (6.3% vs 9.2%; HR 0.69, 95% CI 0.49–0.96; p=0.03) and in patients without diabetes (5.3% vs 7.0%; HR 0.76, 95% CI 0.58–1.00; p=0.046).

Comment: This Korean study looked at using either aspirin or clopidogrel as monotherapy after dual antiplatelet therapy had been discontinued in patients 6–18 months after PCI. It showed a reduction in major adverse cardiovascular events and recurrent ACS when clopidogrel was continued as monotherapy compared with aspirin in patients independent of diabetic status. This is concordant with the CHARISMA study which also showed clopidogrel was superior to aspirin for cardiovascular event prevention in patients with atherosclerotic cardiovascular disease. Now that clopidogrel is off authority perhaps we should consider using it more frequently in this context.

Reference: JAMA Cardiol 2023; published online Apr 12
Abstract

Blinded, randomized trial of sonographer versus AI cardiac function assessment

Authors: He B et al.

Summary: This blinded, non-inferiority clinical trial compared the accuracy of a cardiac sonographer versus artificial intelligence (AI) for the assessment of LVEF. 3495 transthoracic echocardiograms were randomised 1:1 to be evaluated by AI or one of 25 cardiac sonographers (mean 14.1 years' practise). The echocardiograms were then assessed by one of ten cardiologists (mean 12.7 years' practise). The primary outcome was the change in LVEF between initial AI or sonographer assessment and final cardiologist assessment, defined as the proportion of echocardiograms with substantial (>5%) change. Substantial change between the initial and final assessments occurred in 16.8% of studies in the AI group and 27.2% in the sonographer group (between-group difference, –10.4%; p<0.001 for non-inferiority).

Comment: This blinded study showed that AI estimation of left ventricular function on echo was non-inferior to assessment by sonographers and cardiologists, which saved time for both. Good image acquisition is essential for this to work, but this would seem to be a reasonable step forward. Whether AI will be able to report other aspects of echocardiography in the future has not been determined, but even if so, clinical judgement in interpretation will always be essential.

Reference: Nature 2023;616:520-24
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.

Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk

Authors: Karam G et al.

Summary: This systematic review and meta-analysis compared the impact of structured dietary programmes on mortality and major cardiovascular events in patients at increased risk for cardiovascular disease. A search of AMED, CENTRAL, Embase, Medline, CINAHL, and ClinicalTrials.gov identified 40 trials (n=35,548) of seven dietary programmes (low fat; Mediterranean; very low fat; modified fat; combined low fat and low sodium; Ornish; and Pritikin) that were suitable for inclusion. Based on moderate certainty evidence, Mediterranean dietary programmes were superior to minimal intervention for the prevention of all-cause mortality (odds ratio [OR] 0.72, 95% CI 0.56–0.92), cardiovascular mortality (OR 0.55, 95% CI 0.39–0.78), stroke (OR 0.65, 95% CI 0.46–0.93), and non-fatal MI (OR 0.48, 95% CI 0.36–0.65) in patients at intermediate risk, and low fat programmes were superior to minimal intervention for prevention of all-cause mortality (OR 0.84, 95% CI 0.74–0.95) and non-fatal MI (OR 0.77, 95% CI 0.61–0.96). The effects of these dietary programmes were more pronounced in high-risk patients. The other dietary programmes had little or no benefit compared with minimal intervention.

Comment: This study looked at popular dietary regimens to determine if there were demonstrable benefits on cardiovascular health. Yet again, the Mediterranean diet showed a significant benefit with a reduction in all-cause mortality and non-fatal MI in patients at increased cardiovascular risk, as did a low fat diet, whereas the other interventions had minimal effect. Physical activity seemed not to influence the results of any of these interventions but should still be encouraged as there are non-cardiovascular benefits of staying physically active.

Reference: BMJ 2023;380:e072003
Abstract

Clinical validation of 5 direct-to-consumer wearable smart devices to detect atrial fibrillation

Authors: Mannhart D et al.

Summary: The BASEL Wearable Study evaluated the accuracies of five commercially available smart devices in identifying atrial fibrillation (AF) in a real-world cohort. 201 patients (31% female, median age 66.7 years) with AF who presented to a cardiology service at the University Hospital Basel were included. 31% of them had AF according to a physician-interpreted 12-lead ECG. Sensitivity and specificity for the detection of AF were comparable between devices: 85% and 75% for the Apple Watch 6®, 85% and 75% for the Samsung Galaxy Watch 3®, 79% and 69% for the AliveCor KardiaMobile®, 66% and 79% for the Fitbit Sense®, and 58% and 75% for the Withings Scanwatch®, respectively. The rate of inconclusive tracings was 18%, 17%, 26%, 21% and 24% with the respective devices. The Apple Watch was ranked highest (39% of participants) for patient acceptability.

Comment: Smart devices are increasingly being used to detect AF in the general population. This study shows reasonable sensitivity and specificity with common smart devices, but uninterpretable readings were common (17–26%) depending on the device, although most of these could be classified by physician review. Detection of AF with this technology is important, but the burden and threshold for instituting anticoagulation for stroke prevention when AF is detected in this way has not been determined.

Reference: JACC Clin Electrophysiol 2023;9(2):232-42
Abstract

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