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; **BP** = blood pressure; **HR** = hazard ratio; **MI** = myocardial infarction; **MRI** = magnetic resonance imaging; **NOAC** = non-vitamin K antagonist oral anticoagulant; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **PVD** = pulmonary vascular disease; **STEMI** = ST-segment elevation MI.

Welcome to the latest issue of Cardiology Research Review.

In this issue, the SODIUM-HF trial finds that reducing dietary sodium intake does not reduce clinical events in patients with heart failure, Korean investigators report that oral anticoagulants have clear benefits in frail patients, and a large Australian cohort study finds that oral anticoagulants may have protective effects against dementia. Also in this issue, an analysis of 2 large US cohorts supports the cardiovascular benefits of avocados, and a prespecified analysis of the SPYRAL HTN-ON MED study finds that renal denervation might be a useful adjunct to antihypertensive medication in patients with resistant hypertension.

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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Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF)

Authors: Ezekowitz JA et al.

Summary: The open-label SODUIM-HF trial investigated the impact of dietary sodium reduction on future clinical events in patient with heart failure. At 26 sites in 6 countries, 806 patients (median age 67 years) with chronic heart failure (New York Heart Association functional class 2–3) who were taking optimally tolerated guideline-directed medical treatment were randomised 1:1 to usual care according to local guidelines or to a low sodium diet (<1500 mg/day). The primary outcome was a composite of cardiovascular-related admission to hospital, cardiovascular-related emergency department (ED) visit, or all-cause death within 12 months. Between baseline and 12 months, median sodium intake decreased from 2286 mg/day to 1658 mg/day in the low sodium group and from 2119 mg/day to 2073 mg/day in the usual care group. By 12 months, the primary outcome had occurred in 15% of patients in the low sodium diet group and 17% in the usual care group (p=ns).

Comment: We usually recommend a low-salt diet to patients with heart failure on the assumption this will decrease fluid retention, improve symptoms, and reduce hospital admission. This admittedly small study showed that significant salt reduction did not improve outcomes (admission or ED visits or all-cause mortality) although patients tended to feel better. Some may argue that the numbers were too small to see small differences between the groups, or that the salt intake was still too high, but at present we do not have any other data, so perhaps we should be less emphatic about salt reduction in heart failure.

Reference: Lancet 2022;399(10333):1391-1400

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.

Effectiveness and safety of anticoagulation therapy in frail patients with atrial fibrillation

Authors: Kim D et al.

Summary: This retrospective population-based cohort study evaluated the effectiveness and safety of oral anticoagulants (OACs) in frail patients with AF. Medical records for 83,635 patients aged ≥65 years with AF and frailty (Hospital Frailty Risk Score ≥5) were extracted from the Korean National Health Insurance Service database for the period 2013–2016. During the study period, 14,968 net adverse clinical events, 3718 ischaemic strokes, 5536 major bleeding events, and 6188 cardiovascular deaths occurred. OAC use was associated with lower risks of net adverse clinical events (HR 0.78, 95% CI 0.75–0.82), ischaemic stroke (HR 0.91, 95% CI 0.86–0.97), and cardiovascular death (HR 0.52, 95% CI 0.49–0.55) compared with non-OAC use, but no difference was observed for major bleeding (HR 1.02, 95% CI 0.95–1.10). The associations of OAC use with favourable outcomes were more prominent in individuals with a CHA_2DS_2-VASc score ≥3.

Comment: Age and frailty are often used as reasons to withhold anticoagulation in the elderly and frail population in patients whose CHA_2DS_2-VASc is high enough to increase the risk of thromboembolic stroke. This paper shows that this logic is not correct and that there is net clinical benefit of OAC use in these elderly frail patients, with less stroke and less cardiovascular death but no increase in bleeding, perhaps because the non-OAC group was on aspirin for stroke prevention as this is perceived to be safer, which is not the case, and efficacious, which is also not true. NOACs were better than warfarin in all respects, so we should be less hesitant to prescribe NOACs in elderly frail patients who will clearly benefit from anticoagulation.

Reference: Stroke 2022; published online Feb 3
Abstract

Oral anticoagulant treatment and the risk of dementia in patients with atrial fibrillation

Authors: Bezabhe WM et al.

Summary: This retrospective Australian study evaluated the impact of oral anticoagulants (OACs) on dementia risk in primary care patients with AF. 18,813 patients (mean age 71.9 years, 47.1% female) with newly diagnosed AF in 2010–2017 and with no recorded history of dementia or stroke were included. During a mean follow-up of 3.7 years, 2.3% of patients had a documented diagnosis of dementia. After propensity score matching, the incidence of dementia was significantly lower in OAC users (HR 0.59, 95% CI 0.44–0.80; p<0.001) than nonusers. Direct-acting oral anticoagulant users had a lower incidence of dementia than non-OAC users (HR 0.49, 95% CI 0.33–0.73; p<0.001) and warfarin users (HR 0.46, 95% CI 0.28–0.74; p=0.002), but there was no significant difference in dementia incidence between warfarin users and non-OAC users.

Comment: We know that AF is associated with an increased risk of dementia, presumably on the basis of micro thromboembolism, but there have been variable reports as to the efficacy of OACs in reducing dementia. This large Australian retrospective population-based cohort study showed that the incidence of dementia was low (6.1 per 1000 patient-years, 2.3%) and that OACs reduced its development compared with no anticoagulation and warfarin, which was no better than patients who received no anticoagulation. The majority of patients studied were on NOACs rather than warfarin (47% vs 14%), so this apparent lack of benefit of warfarin may reflect less than ideal time in therapeutic range, in association with the lower numbers studied, rather than a true difference between OACs. In any case, it is comforting to know that NOACs reduce dementia as well as reducing stroke more than warfarin, so they should be the anticoagulant of choice in patients with AF whose CHA_2DS_2-VASc score justifies OAC use.

Reference: J Am Heart Assoc 2022;11(7):e023098
Abstract

Prophylactic rivaroxaban therapy for left ventricular thrombus after anterior ST-segment elevation myocardial infarction

Authors: Zhang Z et al.

Summary: This study investigated the use of rivaroxaban for left ventricular (LV) thromboprophylaxis in patients with anterior STEMI. 279 patients with anterior STEMI who had undergone primary PCI were randomised 1:1 to receive low-dose rivaroxaban 2.5mg twice daily plus dual antiplatelet therapy (DAPT) or DAPT alone for 30 days. The addition of low-dose rivaroxaban to DAPT reduced LV thrombus formation within 30 days compared with DAPT alone (0.7% vs 8.6%; HR 0.08, 95% CI 0.01–0.62; p=0.015). Net clinical adverse events within 30 days were lower in the rivaroxaban group and remained relatively low throughout the 180-day follow-up period. Bleeding events did not differ significantly between groups during follow-up, although 1 case of intracranial haemorrhage occurred in the rivaroxaban group within 30 days.

Comment: Patients who have large anterior MI have an increased risk of LV thrombus, even if they undergo intervention. This was traditionally thought to be mediated by at least transient akinesis/hypokinesis or dyskinesis of the anterior wall, providing a substrate for thrombus formation. In this study, adding low-dose rivaroxaban to DAPT reduced thrombus formation without increasing bleeding significantly, which is the same dose regimen that has been shown to be beneficial in the ATLAS study (with DAPT post ACS) and the COMPASS trial (with aspirin in chronic atherosclerotic cardiovascular disease). The incidence of LV thrombus was surprisingly high at 8.6% in the DAPT alone group, especially when the average ejection fraction was >50%. This may indicate that LV thrombus is underdiagnosed in Australia, as patients with suspicious or nonconclusive echos in this study underwent contrast echo or MRI to confirm LV thrombus, which are infrequently used here for this indication. However, we seldom see strokes in patients with anterior infarcts on DAPT, so whether diagnosing LV thrombus more accurately or using prophylactic therapy will affect outcomes is not known.

Reference: JACC Cardiovasc Interv 2022;15(8):861-72
Abstract

Avocado consumption and risk of cardiovascular disease in US adults

Authors: Pacheco LS et al.

Summary: This analysis of 2 large prospective US cohorts investigated the relationship between avocado intake and long-term cardiovascular disease. 68,786 women from the Nurses' Health Study and 41,701 men from the Health Professionals Follow-up Study who were free of cancer, coronary heart disease, and stroke at baseline were included. Diet was assessed using food frequency questionnaires at baseline and then every 4 years. 14,274 incident cases of cardiovascular disease (9185 coronary heart disease events and 5290 strokes) were reported during 30 years of follow-up. After adjusting for lifestyle and other dietary factors, individuals with higher avocado intake (≥2 servings/week) had a 16% lower risk of cardiovascular disease (pooled HR 0.84, 95% CI 0.75–0.95) and a 21% lower risk of coronary heart disease (pooled HR 0.79, 95% CI 0.68–0.91) than nonconsumers. No significant associations were observed for stroke. Replacing half a serving per day of margarine, butter, egg, yogurt, cheese, or processed meats with the equivalent amount of avocado was associated with a 16–22% lower risk of cardiovascular disease.

Comment: It has been postulated that avocados have beneficial cardiovascular effects and this analysis from the Nurses' Health Study supports this. It found that there were significant reductions in cardiovascular and coronary disease with ≥2 servings per week, and that the benefits were even greater when avocado replaced margarine, butter, egg, yogurt, cheese, or processed meats. These benefits were comparable to the benefits seen with increased olive oil intake in the same population, and these observations reinforce the benefits of the Mediterranean diet and replacing animal-derived fat and protein with foods like avocado.

Reference: J Am Heart Assoc 2022; published online Mar 30
Abstract

Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED)

Authors: Mahfoud F et al.

Summary: This prespecified analysis of the SPYRAL HTN-ON MED study evaluated the long-term efficacy and safety of renal denervation in the presence of antihypertensive medication. At 25 centres in the US, Germany, Japan, the UK, Australia, Austria, and Greece, 80 patients with uncontrolled hypertension despite taking up to 3 antihypertensive drugs were randomised 1:1 to radiofrequency renal denervation or a sham control procedure. Mean ambulatory systolic and diastolic BP were significantly reduced from baseline in the renal denervation group, and were significantly lower than the sham control group at 24 and 36 months. The pill burden at 36 months was 2.13 medications in the renal denervation group and 2.55 medications in the sham control group (p=ns). At 36 months, the ambulatory systolic BP reduction was –18.7mm Hg in the renal denervation group and –8.6mm Hg in the sham control group (p=0.0039). There were no short- or long-term safety issues associated with renal denervation.

Comment: Renal denervation was an evolving procedure for treating resistant hypertension until the SYMPLICITY HTN-3 trial failed to demonstrate significant BP reduction in patients who received the denervation compared with placebo. There were criticisms of this study however, with concerns that the inexperience of many of the proceduralists who had done few or no procedures prior to the study resulted in incomplete denervation. Since then the ablation catheters have improved, and the anatomy of the renal nerves is more defined so there has been renewed interest in the technique. This study does show meaningful and sustained BP reduction with renal denervation over placebo in patients receiving antihypertensive therapy, with a reduced pill burden. If these results can be reproduced in patients with mild hypertension, there is the potential to use this as a primary treatment and avoid or delay the need for medication.

Reference: Lancet 2022;399(10333):1401-10
Abstract

Renal artery stenting in consecutive high-risk patients with atherosclerotic renovascular disease

Authors: Reinhard M et al.

Summary: This study evaluated the effects of renal artery stenting in patients with severe atherosclerotic renal artery stenosis and high-risk clinical presentations (severe renal artery stenosis with true resistant hypertension, rapidly declining kidney function, or recurrent heart failure/sudden pulmonary oedema).102 consecutive patients were included in the analysis. At baseline, mean 24-hour ambulatory systolic BP was 166.2 mm Hg and estimated glomerular filtration rate was 41.1 ml/min/1.73m^2. In 96 patients with 3-month follow-up data after renal artery stenting, mean 24-hour ambulatory systolic BP decreased by 19.6 mm Hg (p<0.001), the defined daily dose of antihypertensive medication was reduced by 52% (p<0.001), and estimated glomerular filtration rate increased by 7.8 ml/min/1.73m^2 (p<0.001). All changes were maintained through 24 months of follow-up.

Comment: Significant renal artery stenosis is often detected in older patients with vascular disease and hypertension. Early studies have shown that routine revascularisation is not beneficial for BP reduction in most patients, with no reduction in pill burden. The traditional indications for intervention have been, and still are, truly resistant hypertension and deteriorating renal function, or recurrent acute pulmonary oedema (APO). This study shows that in these types of patients who underwent stenting, BP was lower, renal function improved and there were fewer admissions with APO after revascularisation. These findings support the current guidelines for renal artery stenting.

Reference: J Am Heart Assoc 2022;11(7):e024421
Abstract

Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction

Authors: Räber L et al., for the PACMAN-AMI Collaborators

Summary: The PACMAN-AMI study investigated the effect of the PCSK9 inhibitor alirocumab on plaque burden and composition when added to high-intensity statin therapy in patients with coronary atherosclerosis. 300 patients undergoing PCI for acute MI at 9 academic European hospitals were randomised 1:1 to receive biweekly subcutaneous alirocumab 150mg or placebo (initiated within 24h after urgent PCI of the culprit lesion) for 52 weeks in addition to high-intensity statin therapy (rosuvastatin 20mg). Intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography were serially performed in 2 non–infarct-related coronary arteries at baseline and after 52 weeks. At 52 weeks, mean change in percent atheroma volume was –2.13% with alirocumab and –0.92% with placebo (p<0.001), mean change in maximum lipid core burden index within 4mm was –79.42 with alirocumab and –37.60 with placebo (p=0.006), and mean change in minimal fibrous cap thickness was 62.67µm with alirocumab and 33.19µm with placebo (p=0.001).

Comment: This study supports the concept that aggressive lipid lowering can favorably change plaque characteristics, with a reduction in plaque volume and lipid content and a thicker fibrous cap in the patients who received alirocumab on top of high-dose statin. Patients with recent ACS are particularly at risk of recurrent events, so the strategy of early, intense lipid lowering after an event is appealing, but outcome studies will need to be done before adding a PCSK9 to guideline-directed medical therapy for ACS will be recommended.

Reference: JAMA 2022; published online Apr 3
Abstract

Latent pulmonary vascular disease may alter the response to therapeutic atrial shunt device in heart failure

Authors: Borlaug BA et al., on behalf of the REDUCE LAP-HF-II Investigators

Summary: This analysis of the REDUCE LAP-HF II trial compared outcomes after implantation of an atrial shunt device in heart failure patients with latent PVD versus patients without PVD. Latent PVD was defined as pulmonary vascular resistance ≥1.74 WU during peak exercise (highest tertile). Compared to patients without PVD (n=382), those with latent PVD (n=188) were older, had more AF and right heart dysfunction, and were more likely to have elevated left atrial pressure at rest. Shunt treatment was associated with worse outcomes in patients with latent PVD (p=0.005) and with evidence of clinical benefit in patients without PVD (p=0.038).

Comment: The overall results of the REDUCE LAP-HF study were disappointing, as left atrial decompression by insertion of an atrial shunt device did not improve outcomes or symptoms. This subgroup analysis showed that patients with marked PVD induced by exercise did not benefit but those who did not have latent PVD did. To me this suggests that if this procedure is to be of benefit, left atrial decompression needs to be performed early in the course of management of heart failure with preserved ejection fraction (HFpEF) before pulmonary vascular changes become established. Further clinical trials are likely to be done in patients with HFpEF without latent PVD so watch this space.

Reference: Circulation 2022; published online Mar 31
Abstract

Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome

Authors: Watanabe H et al., for the STOPDAPT-2 ACS Investigators

Summary: The multicentre STOPDAPT-2 ACS trial compared the effects of 1–2 months of DAPT (aspirin + clopidogrel) followed by clopidogrel monotherapy versus 12 months of DAPT in patients with ACS. 4169 patients with ACS who underwent successful PCI at 96 centres in Japan in 2015–2020 were randomised 1:1 to receive either 1–2 months of DAPT followed by clopidogrel monotherapy, or 12 months of DAPT. The primary end-point was a composite of cardiovascular events (cardiovascular death, MI, stroke, or stent thrombosis) or bleeding events at 12 months. A total of 4107 patients completed the 1-year follow-up. One to 2 months of DAPT was not noninferior to 12 months of DAPT for the primary end-point, which occurred in 3.2% and 2.8% of patients in the respective groups (p=0.06 for noninferiority).

Comment: This trial tested the hypothesis that 12 months of DAPT with clopidogrel and aspirin after ACS was no better than 1–2 months of DAPT followed by 10–11 months of clopidogrel alone. The truncated DAPT regimen showed less bleeding but more major adverse cardiovascular events and stent thrombosis and was not noninferior to the standard 12 months of DAPT. Whether the result would have been different with ticagrelor, as was tested in the GLOBAL LEADERS study, is doubtful as this study was also unable to show benefit of early discontinuation of DAPT. Therefore, the current guidelines should be followed and ideally DAPT should be given for 12 months after ACS.

Reference: JAMA Cardiol 2022;7(4):407-17
Abstract

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