Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **HFrEF** = heart failure with reduced ejection fraction; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **NT-proBNP** = N-terminal pro-B-type natriuretic peptide; **NYHA** = New York Heart Association; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **SGLT2** = sodium glucose co-transporter 2; **siRNA** = small interfering ribonucleic acid; **STEMI** = ST-elevation MI.

Welcome to the latest issue of Cardiology Research Review.

In this issue, the TRAVERSE study provides reassuring evidence of the cardiovascular safety of testosterone replacement therapy in men, a phase 2 trial reports promising results for the FGF21 analogue pegozafermin in patients with severe hypertriglyceridaemia, and the STOP-CA trial suggests that statins have a protective effect on LV function in patients receiving anthracycline-based chemotherapy. Also in this issue, a cost-effective analysis of the VICTORIA trial suggests that we should use vericiguat more often in patients with high-risk heart failure, and an analysis of the EMPHASIS-HF trial confirms that it's never too late to introduce mineralocorticoid receptor antagonists in patients with HFrEF.

We hope you find the selected studies interesting, and welcome your feedback.

Kind Regards,

Associate Professor John Amerena
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Cardiovascular safety of testosterone-replacement therapy

Authors: Lincoff AM et al., for the TRAVERSE Study Investigators

Summary: The TRAVERSE study investigated the cardiovascular safety of testosterone replacement therapy in middle-aged and older men with hypogonadism. 5246 men aged 45–80 years with hypogonadism (fasting testosterone level <300 ng/dl) and pre-existing or a high risk of cardiovascular disease were randomised to receive daily transdermal testosterone gel (dose adjusted to maintain testosterone level 350–750 ng/dl) or placebo gel. The primary cardiovascular safety end-point was major adverse cardiovascular events (MACE; a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke), and the secondary cardiovascular end-point was MACE + coronary revascularisation. Patients were treated for a mean 21.7 months, and followed up for a mean 33.0 months. A primary cardiovascular end-point event occurred in 7.0% of patients in the testosterone group and 7.3% in the placebo group (hazard ratio 0.96, 95% CI 0.78–1.17; p<0.001 for noninferiority), and the incidence of secondary end-point events appeared to be similar in the two groups.

Comment: There has been a lot of debate about the cardiovascular safety of testosterone replacement therapy with mixed results in the limited data available until now. Although there was a signal for increased AF, pulmonary embolism and acute kidney injury, the end-point of MACE + revascularisation was no different in the testosterone group compared with placebo. This study should give reassurance that testosterone replacement therapy is safe in patients with or at high risk for cardiovascular events, and presumably in patients with even lower cardiovascular risk.

Reference: N Engl J Med 2023;389(2):107-17
Abstract

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Dr Christopher Hammett reviews the HANON study

This study compared risk of bleeding associated with rivaroxaban and vitamin K antagonists in patients aged ≥80 years with non-valvular atrial fibrillation.

Click here to read the study review with Dr Hammett's interpretation and advice.

The FGF21 analog pegozafermin in severe hypertriglyceridemia

Authors: Bhatt DL et al., for the ENTRIGUE Principal Investigators

Summary: This phase 2 trial investigated the effects of the human fibroblast growth factor (FGF) 21 analogue pegozafermin in patients with severe hypertriglyceridaemia. Eighty-five patients with severe hypertriglyceridaemia (500–2000 mg/dl) were randomised to receive placebo or one of 5 different dosages of pegozafermin for 8 weeks. Pooled analysis showed that median triglyceride levels decreased significantly with pegozafermin compared with placebo (–57.3% vs –11.9%; p<0.001). Reductions in median triglycerides ranged from 36.4% to 63.4% across all treatment arms and were consistent regardless of background lipid-lowering therapy.

Comment: Elevated triglycerides are an underappreciated risk factor for cardiovascular disease. Until now, therapies to reduce triglyceride levels have been limited, as lifestyle modification, weight loss, reduction of alcohol intake and treatment of diabetes, and fibrates have been the only options. The REDUCE-IT trial, using the highly purified fish oil icosapent ethyl (a stable ester of eicosapentaenoic acid), showed that in patients with atherosclerotic cardiovascular disease and elevated triglycerides, treatment was associated with a significant reduction of cardiovascular events and cardiovascular death. This agent is currently with the TGA seeking approval for this indication in Australia. This study shows significant triglyceride reductions with pegozafermin, but outcome studies will need to be performed as time goes on.

Reference: Nat Med 2023;29(7):1782-92
Abstract

Zilebesiran, an RNA interference therapeutic agent for hypertension

Authors: Desai AS et al.

Summary: This phase 1 study investigated the BP-lowering effects of subcutaneous zilebesiran, an siRNA agent that inhibits hepatic angiotensinogen synthesis. 107 patients with hypertension were randomised 2:1 to receive a single subcutaneous dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800mg) or placebo and were followed for 24 weeks. There were no reports of hypotension, hyperkalaemia, or worsening of renal function during follow-up, although five patients had mild, transient injection-site reactions. Zilebesiran administration decreased serum angiotensinogen levels in a dose-dependent manner. Single doses of zilebesiran ≥200mg were associated with decreases in systolic BP (>10mm Hg) and diastolic BP (>5mm Hg) by week 8; these changes were sustained at 24 weeks. The BP-lowering effects of zilebesiran 800mg were attenuated by a high-salt diet and augmented by coadministration with irbesartan.

Comment: We are entering a new era of therapeutics where agents are being developed to reduce production of proteins at a cellular level. We now have siRNAs that block PCSK9 production that are already in clinical practice (inclisiran), and new agents (antisense and siRNAs) that lower lipoprotein(a) are being studied (pelacarsen). This study uses an agent to reduce angiotensinogen at a hepatic cellular level, thus acting at a different level in the renin-angiotensin pathway from ACE inhibitors and ARBs. Dose-dependent reductions of angiotensinogen and BP were seen, with a prolonged duration of effect (24 weeks). Randomised controlled trials will need to be done but these therapies appear to be very effective, have a prolonged duration of action, and are safe with no off-target effects.

Reference: N Engl J Med 2023;389(3):228-38
Abstract

Phase 1 trial of antibody NI006 for depletion of cardiac transthyretin amyloid

Authors: Garcia-Pavia P et al.

Summary: This phase 1 trial investigated the safety of NI006 (a recombinant human anti- transthyretin amyloid [ATTR] antibody) in patients with ATTR cardiomyopathy and heart failure. 40 patients with ATTR cardiomyopathy and chronic heart failure were randomised 2:1 to receive intravenous infusions of either NI006 (0.3–60 mg/kg) or placebo every 4 weeks for 4 months. After four infusions, patients entered an open-label extension phase in which they received eight infusions of NI006 with stepwise dosage increases. Use of NI006 was not associated with any drug-related serious adverse events. At dosages ≥10 mg/kg, imaging-based surrogate markers of cardiac amyloid load appeared to decrease over a period of 12 months, as did median NT-proBNP and troponin T levels.

Comment: Our treatment for cardiac amyloidosis is primarily symptomatic, with limited agents available to actually interfere with the disease process and disease progression. Tafamidis, which works by stabilising the quaternary structure of the protein transthyretin, has shown improved outcomes in clinical trials in patients with TTR amyloidosis and is before the regulatory authorities awaiting approval. This interesting study reports on an agent that reduces markers of cardiac amyloidosis, perhaps due to depletion of the myocardial amyloid deposits, and may be another option in the future in this difficult-to-treat condition, which is more common than usually thought.

Reference: N Engl J Med 2023;389(3):239-50
Abstract

Atorvastatin for anthracycline-associated cardiac dysfunction

Authors: Neilan TG et al.

Summary: The STOP-CA trial investigated the impact of atorvastatin on anthracycline-associated cardiac dysfunction. At nine academic medical centres in the US and Canada, 300 patients with lymphoma who were scheduled to receive anthracycline-based chemotherapy were randomised to receive atorvastatin or placebo for 12 months. The primary outcome (≥10% decline in LVEF from before chemotherapy to a final value of <55% over 12 months) occurred in 22% of placebo recipients and 9% of atorvastatin recipients (odds ratio 2.9, 95% CI 1.4–6.4; p=0.002). Incident heart failure occurred in 3% of atorvastatin recipients and 6% of placebo recipients (p=ns) over 24 months of follow-up. The number of serious adverse events was low and did not differ significantly between groups.

Comment: Anthracyclines are commonly used to treat lymphomas and have a high rate of success. Unfortunately, this class of effective chemotherapeutic agents often causes a decrease in LV function that necessitates treatment cessation, and may cause irreversible cardiac dysfunction. There has been some preliminary evidence suggesting that statins have a protective effect on LV function in anthracycline-treated patients, and this larger randomised trial shows that there was significantly less decline in LV function in patients treated with atorvastatin. Given that this is a relatively safe and inexpensive drug, I would suggest that it start to be used as a preventative therapy in patients receiving anthracycline-based chemotherapy.

Reference: JAMA 2023;330(6):528-36
Abstract

Mortality trends after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Authors: Thrane PG et al.

Summary: This study evaluated temporal trends in mortality after STEMI in Western Denmark, where PCI has been the national reperfusion strategy since 2003. Using the Western Denmark Heart Registry, 19,613 patients (median age 64 years, 74% male) who were undergoing primary PCI for STEMI in 2003–2018 were identified. Patients were divided into four time-interval groups according to the year of primary PCI (2003–2006, 2007–2010, 2011–2014, and 2015–2018) and were followed up using Danish national health registries. One-year mortality after STEMI decreased gradually over time, from 10.8% in 2003–2006, 10.4% in 2007–2010, and 9.1% in 2011–2014 to 7.7% in 2015–2018. The largest absolute decline in mortality occurred in the first 30 days after STEMI.

Comment: This study showed that there was a significant reduction in mortality in patients with STEMI treated with primary PCI over a 15-year period (from 10.8% to 7.7%; absolute risk reduction [ARR], 3.1%). The biggest decrease in mortality was in the first 30 days post STEMI (2.3% ARR) but the benefit continued up to one year. Primary PCI is commonly used in Australia in PCI-capable hospitals, so the results are likely to be similarly good, but many patients with STEMI are still treated with fibrinolysis due to distance from primary PCI centres, so outcomes may not be as good in these patients.

Reference: J Am Coll Cardiol 2023;82(10):999-1010
Abstract

Cost-effectiveness of vericiguat in patients with heart failure with reduced ejection fraction

Authors: Chew DS et al., for the VICTORIA Study Group

Summary: In the VICTORIA trial, vericiguat significantly reduced cardiovascular death and heart failure hospitalisations compared with placebo in patients with high-risk heart failure. In a prespecified analysis, the treatment effects of vericiguat varied substantially as a function of baseline NT-proBNP levels, with survival benefits in the lowest three NT-proBNP quartiles but not in the highest quartile. This analysis of the VICTORIA trial investigated the cost-effectiveness of vericiguat in patients with HFrEF. Life expectancy modelling results varied according to whether the observed heterogeneity of treatment effect by baseline NT-proBNP values was incorporated into the modelling. When the interaction term was included, life expectancy was 4.56 quality-adjusted life-years (QALYs) in the vericiguat arm and 4.13 QALYs in the placebo arm. When the treatment heterogeneity/interaction term was not included, life expectancy was 4.50 and 4.33 QALYs in the respective groups. Incremental cost-effectiveness ratios were also sensitive to whether the analysis accounted for observed NT-proBNP treatment effect heterogeneity ($US66,509 per QALY when allowing for treatment heterogeneity and $124,512 without heterogeneity).

Comment: The VICTORIA study, using the guanylate cyclase stimulator vericiguat in patients who had a recent admission to hospital with heart failure, showed a reduction in the combined end-point of hospitalisation for heart failure and cardiovascular death, but all-cause mortality was not reduced. Somewhat paradoxically the patients with the highest NT-proBNP had the least benefit, perhaps suggesting that their heart failure was too advanced for this intervention to work. This study suggests that this treatment (which is underutilised in Australia), was in the intermediate range for cost effectiveness, especially in patients with lower NT-proBNP levels, so we should start to use it more in these high-risk patients.

Reference: Circulation 2023; published online Sep 6
Abstract

Underutilization of mineralocorticoid antagonists in patients with heart failure with reduced ejection fraction

Authors: Matsumoto S et al.

Summary: This analysis of the EMPHASIS-HF trial investigated the efficacy of the mineralocorticoid receptor antagonist (MRA) eplerenone according to disease duration in patients with HFrEF. 2732 patients with HFrEF (NYHA class II) who were randomised to receive eplerenone or placebo in addition to standard heart failure therapy were grouped according to duration of HFrEF: <1 year, 1 to <5 years, and ≥5 years. The primary outcome was a composite of heart failure hospitalisation or cardiovascular death. Patients with longer-duration heart failure were older and more likely to have cardiovascular and noncardiovascular comorbidities. Despite this, the benefits of eplerenone were consistent across heart failure durations: hazard ratios for the primary outcome were 0.57 (95% CI 0.42–0.79) for <1 year, 0.81 (95% CI 0.60–1.10) for 1 to <5 years, and 0.61 (95% CI 0.48–0.78) for ≥5 years (p=ns).

Comment: MRAs are one of the cornerstone and foundational therapies for patients with HFrEF, in addition to ACE inhibitors/ARBs/angiotensin receptor neprilysin inhibitors, beta-blockers and SGLT2 inhibitors. This study looked at whether the duration of heart failure affected the efficacy of the MRA eplerenone in patients with HFrEF. Not surprisingly, it found that event rates increased with the duration of heart failure but the benefit of this MRA was maintained whether the patient had recent onset or long-standing heart failure, and in fact the absolute benefit was in the patients who had the longest duration of heart failure. This suggests it's never too late to introduce MRAs in patients with HFrEF, but in Australia spironolactone is the only MRA approved for this, as eplerenone has very strict and restrictive criteria for PBS reimbursement.

Reference: J Am Coll Cardiol 2023;82(11):1080-91
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.

Phenotyping coronary plaque by computed tomography in premature coronary artery disease

Authors: Rahoual G et al.

Summary: This study used computed tomography coronary angiography (CTCA) to compare the characteristics of coronary plaques in individuals with premature coronary artery disease (CAD) with those of incidental plaques found in matched individuals without overt cardiovascular disease. 106 individuals with a history of acute or stable obstructive CAD aged ≤45 years were matched by age, sex, smoking status, cardiovascular heredity, and dyslipidaemia with 106 controls. CTCA showed that individuals with premature CAD had a higher prevalence of non-calcified plaques (65.1% vs 30.2%; p<0.001), spotty calcification (42.5% vs 17.9%; p<0.001), positive remodelling (41.5% vs 9.4%; p<0.001), low attenuation (24.5% vs 3.8%; p<0.001), and napkin-ring sign (1.9% vs 0.0%). They also had more high-risk plaque (HRP) features than controls (mean 2.2 vs 0.4; p<0.001). During a median follow-up of 24 months, individuals with premature CAD and ischaemic recurrence had more HRP features than those without ischaemic recurrence.

Comment: This study documents that persons with premature coronary disease have different plaque characteristics from older patients. There was less calcification and more high-risk features in the younger patients, which was a strong predictor of recurrent events. Intuitively, if this type of plaque morphology on CTCA was detected before an event, aggressive lipid lowering may stabilise and attenuate the plaque, making it less vulnerable, and reduce ischaemic events, but this has not been proven.

Reference: Eur Heart J Cardiovasc Imaging 2023; published online Aug 19
Abstract

Stroke risk in women with atrial fibrillation

Authors: Buhari H et al.

Summary: This population-based cohort study in Ontario evaluated disparities in cardiovascular care and stroke risk between males and females with AF. 354,254 individuals aged ≥66 years who were diagnosed with AF in 2007–2019 were included. Females were more likely than males to be diagnosed in the emergency department, and were less likely to be assessed by a cardiologist, receive a statin, or have their low-density lipoprotein cholesterol levels measured. Cause-specific hazard regression showed that females with AF were at higher risk for stroke than males over a 2-year follow-up (adjusted hazard ratio 1.27, 95% CI 1.21–1.32). However, adjusting for markers of cardiovascular care and multimorbidity decreased the hazard ratio, so that female sex was not associated with increased stroke risk in patients aged ≤80 years.

Comment: The CHADSVASc score includes female gender as a risk factor for stroke, whereas our local CHADSVA risk score does not include gender, as our guidelines include female sex as a risk modifier rather than risk factor. This interesting cohort study suggests that the apparent increase in stroke in women is driven primarily by age and inadequate treatment rather than gender, supporting the Australian guidelines and risk scoring tool.

Reference: Eur Heart J 2023; published online Aug 30
Abstract