Cardiology Research Review™

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Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **BP** = blood pressure; **COVID-19** = coronavirus disease 2019; **CTCA** = computed tomography coronary angiography; **CV** = cardiovascular; **FFRCT** = fractional flow reserve derived from CTCA; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SBP** = systolic BP.

Welcome to the latest issue of Cardiology Research Review.

In this issue, a final report from the SPRINT trial reinforces the benefits of intensive BP-lowering (if tolerated) in hypertensive patients at risk for CV disease, and a large-scale meta-analysis finds that a 5-mm Hg reduction in SBP reduces the risk of major CV events by about 10%. Also in this issue, a nationwide cohort study in Korea shows that an initial rhythm control approach should be the preferred strategy in patients with AF, a US cross-sectional analysis finds that contrary to current recommendations many older diabetics are still taking low-dose aspirin for primary prevention, and an analysis of the ASPREE trial finds no association between statin therapy and cognitive decline or dementia in older adults.

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

Final report of a trial of intensive versus standard blood-pressure control

Authors: The SPRINT Research Group

Summary: The SPRINT trial compared outcomes associated with intensive or standard BP lowering in hypertensive patients at risk for CV disease. 9361 patients who were at increased risk for CV disease but did not have diabetes or previous stroke were randomised to an intensive treatment target (SBP <120mm Hg) or a standard treatment target (SBP <140mm Hg). The primary outcome was a composite of MI, other ACS, stroke, acute decompensated heart failure, or death from CV causes. This analysis of the SPRINT trial (after a median 3.33 years of follow-up) found that the rate of the primary outcome was significantly lower in the intensive-treatment group than in the standard-treatment group (1.77% vs 2.40% per year; HR 0.73, 95% CI 0.63–0.86), as was the rate of all-cause mortality (1.06% vs 1.41% per year; HR 0.75, 95% CI 0.61–0.92). However, serious adverse events (hypotension, electrolyte abnormalities, acute kidney injury or failure, and syncope) were significantly more common in the intensive-treatment group.

Comment: The SPRINT study was hailed as a landmark study that the authors hoped would change clinical practice, as it showed that lowering SBP to <120mm Hg improved outcomes compared with <140mm Hg in older hypertensive patients without diabetes. There was (and still is) controversy about the way BP was measured in the study, in that the BP recorded was the average of 3 automated readings over 15 min in a quiet darkened room unattended, which is very different from what happens in clinical practice. The original study and the follow up above both showed an excess of hypotension and adverse events in the intensive-treatment group, and the concern is that if this BP target is applied in routine clinical practice these rates would be unacceptably higher – the most current National Heart Foundation guidelines recommend SBP target of <140, but comment that lower is probably better if tolerated.

Reference: N Engl J Med 2021;384:1921-30

Abstract

Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure

Authors: The Blood Pressure Lowering Treatment Trialists' Collaboration

Summary: This meta-analysis investigated the effects of BP lowering for primary and secondary prevention of CV disease. Data for 344,716 patients in 48 randomised clinical trials were included. Mean baseline BP was 146/84mm Hg in patients with previous CV disease (19.8% had SBP <130mm Hg) and 157/89mm Hg in patients without previous CV disease (8.0% had SBP <130mm Hg). 12.3% of patients had at least 1 MACE during a median 4.15 years of follow-up. In patients without CV disease at baseline, the rate of MACE was 25.9 per 1000 person-years in the intervention group and 31.9 per 1000 person-years in the comparator group. In patients with CV disease at baseline, corresponding rates of MACE were 36.0 and 39.7 per 1000 patient-years. For a 5mm Hg reduction in SBP, the risk of MACE was reduced by 9% (HR 0.91, 95% CI 0.89–0.94) in patients without previous CV disease and by 11% (HR 0.89, 95% CI 0.86–0.92) in patients with previous CV disease.

Comment: This interesting meta-analysis shows that lowering SBP reduces CV events, even in patients with high-normal (SBP 130–139) and normal (SBP 120–129) BP to a similar extent to patients with higher BP. In patients with high absolute CV risk (>15% over 5 years), lowering BP at these levels seems reasonable to reduce CV risk, but it is also reassuring to realise that lowering BP by any amount reduces risk at any level of initial BP, so that there is still benefit from BP reduction in patients who cannot get to target (SBP <140mm Hg).

Reference: Lancet 2021;397(10285):1625-36

Abstract

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation

Authors: Kim D et al.

Summary: This nationwide cohort study in Korea investigated whether the efficacy of a rhythm control strategy in patients with AF is affected by the timing of treatment initiation. 22,635 adults with AF and CV disease who were newly treated with rhythm control (antiarrhythmic drugs or ablation) or rate control strategies in 2011–2015 were followed up for a median 2.1 years. The primary outcome was a composite of death from CV causes, ischaemic stroke, admission to hospital for heart failure, or acute MI. Rhythm control reduced the risk of the primary composite outcome compared with rate control when initiated within 1 year of diagnosis (HR 0.81, 95% CI 0.71–0.93; p=0.002), but not when initiated more than 1 year after diagnosis (p=NS).

Comment: There is a commonly held belief that there is no advantage of a rhythm control strategy over rate control for AF based on the AFFIRM study which was published more than 20 years ago. More recent studies such as the EAST-AF study, and now this one, suggest that times have changed and that there are better outcomes with a rhythm control strategy, particularly if it is started early after AF has been diagnosed. Some of this is due to more judicious use of drugs to control AF, but also the advent of ablation must have played a part. Given these results, an initial rhythm control approach should be the preferred strategy, particularly in the non-elderly population.

Reference: BMJ 2021;373:n991
Abstract

Use of preventive aspirin among older US adults with and without diabetes

Authors: Liu EY et al.

Summary: This US study investigated the use of low-dose aspirin for primary prevention in older adults with and without diabetes. As part of the National Health and Nutrition Examination Survey 2011–2018, a total of 7103 individuals aged ≥60 years with or without diabetes completed a questionnaire on preventive use of low-dose aspirin. 61.7% of adults with diabetes and 42.2% of adults without diabetes reported using aspirin for primary prevention. Aspirin use increased with older age and higher CV disease risk in adults without diabetes, but was uniformly high among those with diabetes. Women with diabetes were less likely to be using aspirin for primary prevention than men (OR 0.63, 95% CI 0.48–0.83).

Comment: In the past, guidelines recommended that aspirin should be taken by patients with high CV risk and/or diabetes for primary prevention of CV events. Recent studies such as ASPREE, ARRIVE and ASCEND showed that risks outweighed benefits in patients without established CV disease, so that aspirin is no longer recommended for anyone for primary prevention. This study shows that many older patients in the US, and probably in Australia, who were presumably started on aspirin decades ago remain on it. We should consider actively deprescribing aspirin in these patients, especially as many complain of excessive bruising and minor bleeding.

Reference: JAMA Netw Open 2021;4(6):e2112210
Abstract

Factors that influence whether patients with acute coronary syndromes undergo cardiac catheterisation

Authors: Ayad M et al.

Summary: This retrospective analysis of the CONCORDANCE study evaluated factors influencing catheterisation rates in patients with ACS. 8245 patients admitted with ACS to 43 Australian hospitals in 2009–2018 were included; 5637 patients presented to catheterisation-capable hospitals and 2608 patients presented to hospitals without catheterisation facilities. More patients who presented to catheterisation-capable hospitals underwent catheterisation (81% vs 70%) or PCI (49% vs 35%). However, baseline characteristics of patients who underwent catheterisation were similar for both types of hospital, as were rates of MACE and all-cause mortality in hospital and during follow-up.

Comment: This Australian study is reassuring as it shows that there was appropriate referral of patients who presented with ACS from non PCI-capable hospitals, and that outcomes from ACS were similar independent of where the patient with ACS presented. It implies that similar ACS management algorithms are followed in smaller hospitals and regional centres, and that outcomes are not compromised by geographical considerations.

Reference: Med J Aust 2021;214(7):310-7
Abstract

Effect of statin therapy on cognitive decline and incident dementia in older adults

Authors: Zhou Z et al., on behalf of the ASPREE Investigator Group

Summary: This analysis of the ASPREE trial investigated the neurocognitive effects of statins in older adults. 18,846 patients aged ≥65 years participating in a randomised trial of aspirin who had no prior CV events, major physical disability, or dementia were followed up for 4.7 years. During follow-up, statin use versus nonuse was not associated with incident dementia or mild cognitive impairment, or with changes in cognitive function scores over time. No differences were found between users of hydrophilic or lipophilic statins.

Comment: The anti-statin lobby has long claimed that statin use has been associated with neurocognitive decline and type 2 diabetes. While there is certainly a very small increase in the rate of developing diabetes with statin use, it is generally in patients who are at increased risk for type 2 diabetes and have impaired glucose tolerance and/or the metabolic syndrome. This analysis of the ASPREE study (which examined whether aspirin was beneficial in older patients without CV disease), and other contemporary analyses show that statin use is not associated with cognitive decline in older individuals, and in fact may even be protective against its development. We can reassure our patients that the benefits of statins outweigh the risks, particularly in secondary prevention.

Reference: J Am Coll Cardiol 2021;77(25):3145-56
Abstract

Effectiveness of blood lipid management in patients with peripheral artery disease

Authors: Hess CN et al.

Summary: This study used MarketScan data to investigate the use of lipid-lowering therapy in 250,103 patients with peripheral artery disease (PAD). At baseline, 20.5% of patients were taking high-intensity lipid-lowering therapy (high-dose statin, statin plus ezetimibe, or PCSK9 inhibitor), 39.5% were taking low-intensity lipid-lowering therapy (any other lipid-lowering regimen), and 40.0% were not taking any lipid-lowering therapy. Median LDL cholesterol was 91 mg/dl at baseline, and 24.5% of patients had LDL cholesterol <70 mg/dl. After a median 15.1 months of follow-up, use of high-intensity lipid-lowering therapy increased by 3.7%, median LDL cholesterol decreased by 4.0 mg/dl, and an additional 4.1% of patients had LDL cholesterol <70 mg/dl. Use of high intensity lipid-lowering therapy was greater after MACE (55.0%) or major adverse limb events (41.0%) during follow up than after no ischaemic event (26.1%).

Comment: Atherosclerosis is a diffuse vascular disease, and it has been shown that many patients with PAD have occult coronary artery disease (CAD) and cerebrovascular disease. Patients with symptomatic or asymptomatic PAD have a high rate of CV events such as MI and stroke and should be treated as aggressively as patients with CAD, but as this study shows, aggressive lipid lowering is often not undertaken. Many patients with asymptomatic PAD are not diagnosed, and thus not treated aggressively, and symptomatic patients are often managed by vascular surgeons for acute intervention (revascularisation and amputation) and then followed in community based practice, where the benefits of lowering lipids may be underappreciated. Aggressive lipid lowering in patients with PAD improves outcomes, but it needs to be in conjunction with smoking cessation, exercise, treatment of hypertension and diabetes, and consideration of low-dose rivaroxaban with aspirin if they also have proven CAD, diabetes or heart failure.

Reference: J Am Coll Cardiol 2021:77(24)3016-27
Abstract

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References: 1. NEBILET® Approved Product Information, 13 November 2020.
2. Flather MD *et al. Eur Heart J* 2005; 26: 215–25.

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Patients with acute myocarditis following mRNA COVID-19 vaccination

Authors: Kim HW et al.

Summary: This report examined the association between COVID-19 vaccination and acute myocarditis. Seven patients were diagnosed with acute myocarditis at Duke University Medical Centre in the 3-month period between February 1 and April 30, 2021; 4 of them developed myocarditis within 5 days of COVID-19 vaccination. Three were younger males (age 23–36 years) and 1 was an older female (age 70 years). All 4 had received the second dose of an mRNA vaccine (2 received the Moderna vaccine and 2 received the Pfizer vaccine), and all of them presented with severe chest pain and had biomarkers for myocardial injury. Cardiac magnetic resonance imaging findings were typical for myocarditis, and other tests provided no alternative explanation.

Comment: There has been a lot of adverse publicity about the risks of the AstraZeneca COVID-19 vaccine in younger patients, with very low rates of thrombotic complications and mortality, which have been overemphasised by the social and mainstream media. This case report suggests that both mRNA vaccines may be associated with a small increase in the risk of myocarditis in younger patients, but this association needs to be confirmed by larger observational studies. It is worrisome, however, and if there does prove to be an association the general population will have to accept that there is no perfect risk-free vaccine and that the benefits far outweigh the risks both at an individual and population level.

Reference: JAMA Cardiol 2021; published online Jun 29
Abstract

Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain

Authors: Curzen N et al.

Summary: The FORECAST trial investigated whether an evaluation strategy based on FFRCT has better economic and clinical outcomes than standard care in patients with stable chest pain. 1400 patients with stable chest pain were randomised to initial testing with CTCA with selective FFRCT (intervention group) or standard clinical care pathways (controls). 439 (63%) controls and 674 (96%) patients in the intervention group underwent initial CTCA; 254 patients in the intervention group then underwent FFRCT. Mean total cardiac costs at 9 months were 8% higher in the intervention group than the control group (p=NS). Major adverse cardiac and cerebrovascular events during 9 months' follow-up did not differ significantly between groups, and angina and quality of life improved to a similar degree in both groups. The need for invasive angiography was reduced significantly in the intervention group (19% vs 25%; p=0.01).

Comment: Assessing the functional significance of coronary stenosis detected on CTCA has been the Holy Grail of this form of imaging. This approach has been validated in the past but has been prohibitively expensive in Australia and slow due to the complex algorithms and the computing power needed to generate information from them. This paper looking at using this approach in patients with stable angina suggests that this hurdle has been overcome and that using this technology in selected patients now is not significantly more expensive than a standard approach. Invasive angiography rates were reduced by 20%, but rates of PCI and short- and medium-term MACE were the same. I'm not sure whether this technology is available in Australia at present, but inevitably it will be if costs are reasonable.

Reference: Eur Heart J 2021; published online Jul 16
Abstract

Clinical strategy for the diagnosis and treatment of immune checkpoint inhibitor-associated myocarditis

Authors: Lehmann LH et al.

Summary: This narrative review discussed the diagnosis and management of myocarditis associated with use of immune checkpoint inhibitors (ICIs). Clinical presentation and cardiac pathological findings are highly variable in patients with ICI-associated myocarditis. Endomyocardial biopsy is the standard diagnostic test but a complete history of recent cancer treatments and physical examination in combination with cardiac biomarkers (particularly troponin) and cardiac imaging assist with diagnosis. The risk of ICI-associated myocarditis is increased by use of a cytotoxic T-lymphocyte–associated protein 4 inhibitor with a programmed cell death protein 1 or programmed death-ligand 1 inhibitor.

Comment: Cardiac complications of new therapies for cancer and arthritides are becoming more common as these drugs are increasingly used. Most cardiologists don't know much about the potential cardiac problems with these drugs, and although cardio-oncology is becoming a recognised area of subspecialisation, physicians with expertise in this area are not widely available. This review discusses the issues relevant to diagnosis and management of cardiac complications of ICIs, to provide a framework for assessment and supervision of care in these unwell patients.

Reference: JAMA Cardiol 2021; published online Jul 7
Abstract

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Independent commentary by Associate Professor John Amerena,
FRACP, FACC, FCSANZ, Dept. of Clinical and Biomedical Science, University of Melbourne (Geelong).
Full biography here.

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