Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **AMI** = acute MI; **BP** = blood pressure; **CPAP** = continuous positive airway pressure; **DOAC** = direct oral anticoagulant; **HFrEF** = heart failure with reduced ejection fraction; **HFpEF** = heart failure with preserved ejection fraction; **HR** = hazard ratio; **MI** = myocardial infarction; **NT-proBNP** = N-terminal pro-brain natriuretic peptide; **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 TALOS-AMI study reports that de-escalating to clopidogrel/aspirin after 1 month of ticagrelor/aspirin post PCI is an effective treatment strategy in patients with ACS, the LIFE study suggests that there may come a time where heart failure is too advanced to respond to new therapies such as sacubitril/valsartan (arguing for their earlier introduction), and an analysis of the DAPA-HF trial finds that dapagliflozin provides clinically meaningful survival benefits in patients with HFrEF. Also in this issue, an analysis of data from the GARFIELD-AF registry suggests that attempting a rhythm control strategy is reasonable in most patients with recently diagnosed AF, and an interesting crossover study shows that beta-blockers compromise exercise tolerance in patients with HFpEF.

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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Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI)

Authors: Kim CJ et al.

Summary: The TALOS-AMI trial investigated the efficacy of an unguided de-escalation strategy from ticagrelor to clopidogrel after PCI in patients with AMI. 2697 patients at 32 institutes in South Korea who had been taking aspirin and ticagrelor without major ischaemic or bleeding events for 1 month after index PCI were randomised to a de-escalation group (clopidogrel plus aspirin) or an active control group (ticagrelor plus aspirin). The primary end-point was a composite of cardiovascular death, MI, stroke, or bleeding type 2, 3, or 5 according to Bleeding Academic Research Consortium criteria. At 12 months, the primary end-point had occurred in 4.6% of patients in the de-escalation group compared with 8.2% in the active control group (HR 0.55, 95% CI 0.40–0.76; p=0.0001).

Comment: In patients with ACS the risk of recurrent ischaemic events is highest in the first 30 days after index presentation, and then diminishes over the next 12 months, whereas the incidence of bleeding tends to be much the same over this period. This study tested the hypothesis that more intensive antiplatelet therapy (with ticagrelor/aspirin) for 1 month post ACS followed by de-escalation to less intense antiplatelet therapy (with clopidogrel/aspirin) would not compromise ischaemic outcomes but would reduce bleeding. The results showed that this was the case as there was no difference in major adverse cardiovascular events with this regimen, but significantly less bleeding. This makes it an attractive strategy, particularly in countries where the cost of ticagrelor is prohibitive.

Reference: Lancet 2021;398(10308):1305-16
Abstract

Effect of treatment with sacubitril/valsartan in patients with advanced heart failure and reduced ejection fraction

Authors: Mann DL et al., for the LIFE Investigators

Summary: The LIFE study investigated the efficacy of sacubitril/valsartan compared with valsartan in patients with advanced HFrEF and recent NYHA class IV symptoms. 335 patients with advanced heart failure were randomised in a double-blind design to receive sacubitril/valsartan (target dose 97/103mg twice daily) or valsartan (target dose 160mg twice daily) in addition to recommended therapy. The primary outcome was area under the curve (AUC) for the ratio of NT-proBNP compared with baseline measured through 24 weeks of therapy. The median NT-proBNP AUC did not differ significantly between the valsartan and sacubitril/valsartan treatment arms (1.19 and 1.08, respectively). Treatment with sacubitril/valsartan did not improve the clinical composite end-point (number of days alive out of hospital and free from heart failure events) compared with valsartan. There was a significant increase in hyperkalaemia in the sacubitril/valsartan arm (17% vs 9%; p=0.04), but no other safety concerns.

Comment: Sacubitril/valsartan has become standard therapy for patients with HFrEF with an ejection fraction <40%, as this therapy was shown to be superior to enalapril in the PARADIGM-HF study. Most of the patients enrolled in PARADIGM-HF had NYHA class II–III symptoms with very few having advanced heart failure. This randomised study looked at the benefits of using sacubitril/valsartan in patients with advanced heart failure compared with valsartan alone and was unable to demonstrate any benefit, with no significant changes in NT-proBNP levels, number of days alive out of hospital, and heart failure events. These results are concordant with the results of the VICTORIA study using the guanylate cyclase stimulator vericiguat, which showed that the benefits of reduction in hospitalisation and cardiovascular death seen in less severe heart failure were not seen in patients with the most advanced disease on top of standard background heart failure therapy. These results suggest that there may come a time where heart failure is too advanced to respond to these new therapies and this argues for the earlier introduction of both sacubitril/valsartan and vericiguat in patients with less advanced disease to prevent progression and improve outcomes.

Reference: JAMA Cardiol 2021; published online Nov 3
Abstract

Extrapolating long-term event-free and overall survival with dapagliflozin in patients with heart failure and reduced ejection fraction

Authors: Docherty KF et al., for the DAPA-HF Investigators and Committees

Summary: This analysis of the DAPA-HF trial estimated the long-term treatment effects of dapagliflozin in patients with HFrEF over the duration of a patient's lifetime. In DAPA-HF, 4744 patients (mean age 66.3 years) with NYHA class II–IV heart failure and elevated plasma NT-proBNP levels were randomised to receive dapagliflozin 10mg once daily or placebo in addition to standard therapy, and were followed up for a mean 17.6 months. The extrapolated mean event-free survival for an individual aged 65 years from a primary composite end-point event (first hospitalisation for heart failure, urgent heart failure visit requiring intravenous therapy, or cardiovascular death) was 6.2 years for placebo and 8.3 years for dapagliflozin, representing an event-free survival time gain of 2.1 years (p=0.002).

Comment: The seminal trials that have demonstrated benefits of dapagliflozin and empagliflozin in patients with HFrEF were conducted over a relatively short time-frame of 2 years or so. In both studies the curves were diverging at the end of the study period but we have no real information as to the long-term benefit of these agents and assume the benefits will continue over the longer term use. This study looked at extrapolating the data to a longer time-frame and suggested that, if the benefits seen in the study continue, that at around 9–10 years there would be a survival gain of 1.7 years with dapagliflozin if it was continued in patients with HFrEF. These results provide meaningful information to patients when considering adding this therapy to standard background therapy in HFrEF, and may help convince patients that the extra pill burden is worth it both in terms of symptomatic improvement and of extension of life.

Reference: JAMA Cardiol 2021;6(11):1298-1305
Abstract

Association of statin treatment with progression of coronary atherosclerotic plaque composition

Authors: van Rosendael AR et al.

Summary: This cohort study evaluated the effect of statin treatment on progression of coronary atherosclerotic plaque composition. 857 patients in 7 countries who underwent serial coronary computed tomography angiography (CCTA) 2 or more years apart and had quantitative measurements of coronary plaques throughout the entire coronary artery tree were included. Six plaque composition types were defined on a voxel-level basis according to the plaque attenuation (expressed in Hounsfield units): low attenuation (–30 to 75HU), fibro-fatty (76–130HU), fibrous (131–350HU), low-density calcium (351–700HU), high-density calcium (701–1000HU), and 1K (>1000 HU). In total, 2458 coronary lesions in 857 patients were evaluated. Untreated coronary lesions increased in volume over time for all 6 compositional types. Statin therapy was associated with volume decreases in low-attenuation plaque and fibro-fatty plaque, and greater progression of high-density calcium plaque and 1K plaque. When analyses were restricted to lesions without low-attenuation plaque or fibro-fatty plaque at baseline, statin therapy was not associated with a change in overall calcified plaque volume, but was associated with a transformation toward more dense calcium.

Comment: A high coronary calcium score is associated with an increased risk of future cardiac events in the general population, and I am often asked by patients if lowering their cholesterol will reduce coronary calcification. This study looked at patients who had serial CCTA and coronary calcium score (CCS) and showed that lowering LDL with statins improves plaque characteristics and volume, but paradoxically increases calcium density in the plaque, potentially making them more stable and less inflammatory. Patients therefore need to be reassured that although statins are likely to increase coronary calcification, this is probably a good thing, as it indicates transformation of plaques to more stability, and less risk of cardiovascular events. However, there is no clinical trial evidence yet showing that lipid lowering improves outcomes in asymptomatic patients on the basis of a positive CCS.

Reference: JAMA Cardiol 2021;6(11):1257-66
Abstract

Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction

Authors: AbouEzzeddine OF et al.

Summary: This US population-based cohort study determined the prevalence of transthyretin amyloid cardiomyopathy (ATTR-CM) in patients with HFpEF and ventricular wall thickening. 1235 consecutive patients with HFpEF aged ≥60 years with ventricular wall thickness ≥12mm were included. The cohort comprised 2 subcohorts: a community cohort without systematic screening (n=949) and a community cohort that underwent systematic screening with technetium Tc-99m pyrophosphate scintigraphy and reflex testing (n=286). The prevalence of ATTR-CM was 1.3% in the cohort without screening (2.5% in males and 0% in females) and 6.3% in the screening cohort (10.1% in males and 2.2% in females). The prevalence increased with age, from 0% in patients aged 60–69 years to 21% in patients aged ≥90 years (p<0.001).

Comment: HFpEF is an increasing clinical problem as patients get older and is a frequent cause of hospital admission. Cardiac amyloidosis has received a lot more interest in recent times due to the discovery of the disease-modifying agent tafamidis, which inhibits formation of the transthyretin amyloid-forming protein and has been shown to improve outcomes. However, the proportion of patients with HFpEF who have underlying cardiac amyloidosis as the cause of their clinical syndrome is not clear. This cohort study looked at patients with HFpEF and found that around 2% of patients had cardiac amyloidosis on clinical grounds but this diagnosis increased in frequency to around 6% in patients who underwent screening with technetium pyrophosphate scintigraphy, and that the prevalence of this condition increased with advancing age. These results infer that cardiac amyloidosis is not an uncommon cause of HFpEF in patients, particularly in the elderly, and argue that scintigraphy should be considered as a diagnostic procedure for patients with HFpEF, although at the present time tafamidis is not available even if this diagnosis is made.

Reference: JAMA Cardiol 2021;6(11):1267-74
Abstract

Long-term medication adherence trajectories to direct oral anticoagulants and clinical outcomes in patients with atrial fibrillation

Authors: An J et al.

Summary: This study evaluated the association between different patterns of adherence to DOACs and clinical outcome in patients with non-valvular AF. 18,920 adults with non-valvular AF who initiated a DOAC between 2012 and 2018 in Kaiser Permanente Southern California were included. Three long-term DOAC adherence trajectories were identified: consistently adherent (85.2%), early discontinuation within 6 months (10.6%), and gradually declining adherence (4.2%). Predictors of early discontinuation and gradually declining adherence trajectories included lower CHA_2DS_2-VASc score and previous injurious falls. Early discontinuation of DOAC therapy was associated with a higher risk of thromboembolism (rate ratio, 1.40; 95% CI 1.05–1.86) but a lower risk of major bleeding (rate ratio, 0.48; 95% CI 0.30–0.75) than consistent adherence. A gradual decline in adherence to DOACs did not increase the risk of thromboembolism outcomes compared with consistent adherence.

Comment: Large studies have shown that in patients with a CHADS-VASc score of ≥2 for men and ≥3 for women, anticoagulation reduces the risk of stroke substantially. This real-world study looked at the consequences of early discontinuation and declining adherence with anticoagulation in patients who had been commenced on DOAC therapy in the US. They found that overall there was good adherence to ongoing anticoagulant therapy, but that early discontinuation (within 12 months) and declining adherence over time was associated with an increased risk of stroke but less risk of bleeding. The predictors for early discontinuation were relatively low stroke risk (CHADS-VASc ≤1) and the patient having injuries from falls. The increased risk of stroke was particularly marked if discontinuation was for more than 12 months whereas bleeding was reduced particularly in the first 12 months after discontinuation which is not surprising. These results reinforce that long-term anticoagulation is essential to reduce stroke risk in patients with elevated CHADS-VASc scores. If patients do discontinue treatment it would be prudent to examine different strategies such as dose reduction (if criteria are met) or alternative agents which may have less bleeding risk, as well as discontinuation of other therapies that increase bleeding risk, such as aspirin.

Reference: J Am Heart Assoc 2021;10(21):e021601
Abstract

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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NEBILET: Age proven in CHF patients aged ≥ 70 years[1,2]

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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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Long-term effect of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea

Authors: Shirahama R et al.

Summary: This study in Japan investigated the longitudinal effects of CPAP therapy adherence on BP and bodyweight in patients with obstructive sleep apnoea (OSA). 918 patients with OSA who were undergoing CPAP therapy at a Kanagawa-area sleep clinic were assessed for CPAP adherence, BP, and bodyweight over a 24-month period. Patients with good CPAP adherence during the 24-month follow-up period had a significant reduction in diastolic BP compared with patients with poor CPAP adherence (p=0.03), but no significant association was found between CPAP adherence and bodyweight.

Comment: OSA is a frequent trigger for hypertension, and if OSA is untreated elevated BP is often difficult to control. Large outcome studies have shown use of CPAP improves symptoms in patients with OSA but does not improve cardiovascular outcomes. Anecdotally, use of CPAP in hypertensive patients with OSA makes BP easier to control, but most patients still require BP-lowering medication unless there is significant weight loss, which is the exception rather than the rule. This study showed that using CPAP lowered diastolic BP but not systolic BP and did not affect weight, which is important to recognise, as most of our patients with OSA are older and overweight, and systolic BP is a much greater risk factor than diastolic BP. It is thus important to emphasise that treatment of OSA will help patients feel better, but will not necessarily decrease their pill burden.

Reference: Sci Rep 2021;11:19101
Abstract

Cardioversion in patients with newly diagnosed non-valvular atrial fibrillation

Authors: Pope MK et al.

Summary: This analysis of data from the GARFIELD-AF registry compared clinical outcomes in patients with recent onset non-valvular AF who did or did not undergo cardioversion. 52,057 adults with newly diagnosed AF (up to 6 weeks' duration) and at least 1 stroke risk factor were included. Comparisons were made between patients who received cardioversion at baseline and those who did not, and between patients who received direct current cardioversion and those who had pharmacological cardioversion. 44,201 patients were included in the analysis of cardioversion (14.9%) versus no cardioversion (85.1%) at baseline. The propensity score-weighted HR for all-cause mortality in the cardioversion group was 0.74 (95% CI 0.63–0.86) from baseline to 1 year, and 0.77 (95% CI 0.64–0.93) from 1 year to 2 years. 7175 patients were assessed in the analysis of direct current cardioversion (66.2%) versus pharmacological cardioversion (33.8%). During 1 year of follow-up, event rates for all-cause mortality were 1.36 (95% CI 1.13–1.64) and 1.70 (95% CI 1.35–2.14) per 100 patient-years in patients who received direct current and pharmacological cardioversion, respectively.

Comment: This interesting analysis of the GARFIELD study showed that the majority of patients with recently diagnosed AF were treated with a rate rather than rhythm control approach (85% vs 15%). Those who did have an early rhythm control strategy (whether it be direct cardioversion or pharmacological) did better with respect to mortality, which is concordant with recently presented data from the EAST-AF study. These data in totality suggest that an attempt at a rhythm control strategy is reasonable in most patients with recently diagnosed AF irrespective of symptoms (which was also reported in a recent subanalysis of the EAST-AF study), and that the mode of cardioversion does not affect the improvement in outcome.

Reference: BMJ 2021;375:e066450
Abstract

Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction

Authors: Palau P et al.

Summary: This crossover study evaluated the effect of beta-blocker withdrawal on peak oxygen consumption (peak Vo_2) in patients with HFpEF and chronotropic incompetence. Patients with stable HFpEF, NYHA class II–III, previous treatment with beta-blockers, and chronotropic incompetence were first randomised to withdraw the beta-blocker treatment (arm A; n=26) or continue beta-blocker treatment (arm B; n=26) and then crossed over to receive the opposite intervention. Each treatment period was for 2 weeks, separated by a 2-week washout period. At baseline, mean peak Vo_2 and peak Vo_2% were 12.4 ml/kg/min and 72.4%, respectively. After beta-blocker withdrawal, both peak Vo_2 and peak Vo_2% increased significantly (+2.1 ml/kg/min, p<0.001; and +11.7%, p<0.001, respectively).

Comment: Until the recently published EMPEROR-Preserved study using empagliflozin, there has been no specific treatment that has improved outcomes in patients with HFpEF. Beta-blockers are frequently used in these patients with little evidence of benefit. This interesting crossover study of patients with HFpEF showed that exercise tolerance is actually compromised by beta-blocker use, due to limiting the heart rate rise with exercise, and that peak Vo_2 and peak Vo_2% increased significantly after beta-blocker withdrawal. This being the case, it would seem reasonable to have a trial of beta-blocker withdrawal in patients with HFpEF to see if exercise tolerance improves (and if BP goes up, using an antihypertensive agent that does not limit heart rate response to exercise). Given the results of EMPEROR-Preserved however, empagliflozin is likely to become the preferred treatment in these patients, but this does not negate the importance of these findings.

Reference: J Am Coll Cardiol 2021;78(21):2042-56
Abstract

Left atrial appendage closure versus non-warfarin oral anticoagulation in atrial fibrillation: 4-year outcomes of PRAGUE-17

Authors: Osmancik P et al.

Summary: The PRAGUE-17 trial demonstrated that left atrial appendage closure (LAAC) was non-inferior to non-warfarin oral anticoagulants (NOACs) for preventing major neurological, cardiovascular or bleeding events in high-risk patients with AF. This report described pre-specified long-term outcomes in 402 PRAGUE-17 participants (mean age 73.3 years, 65.7% male). During a median follow-up of 3.5 years, LAAC was non-inferior to NOACs for the primary composite end-point of cardioembolic events, cardiovascular death, clinically-relevant bleeding, or procedure/device-related complications (p for non-inferiority=0.006). LAAC decreased non-procedural clinically-relevant bleeding compared with NOACs (subdistribution HR 0.55, 95% CI 0.31–0.97; p=0.039), but none of the other individual components of the composite end-point differed significantly between groups.

Comment: LAA occlusion is often used in Australia in patients with AF at risk of stroke in whom anticoagulants are contraindicated. Short-term studies in patients suitable for anticoagulation with warfarin (PREDICT and PROTECT) and NOACs (PRAGUE-17), have shown non-inferiority of LAA occlusion in terms of stroke reduction but with less bleeding, and registries in patients with AF who cannot take anticoagulants (EWOLUTION) have shown lower stroke rates compared with no anticoagulation. This longer-term follow up of patients in the PRAGUE-17 study is reassuring as it shows that these benefits are maintained over at least 4 years, and there is no reason to expect they will diminish over time.

Reference: J Am Coll Cardiol 2021; published online Nov 5
Abstract

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