Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **CABG** = coronary artery bypass grafting; **HFrEF** = heart failure with reduced ejection fraction; **HFpEF** = heart failure with preserved ejection fraction; **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **MINOCA** = MI with nonobstructive coronary arteries; **NSTEACS** = non-ST-segment elevation ACS; **NSTEMI** = non-ST-segment elevation MI; **PCI** = percutaneous coronary intervention; **SGLT2** = sodium-glucose co-transporter-2; **STEMI** = ST-segment elevation MI; **TOE** = trans-oesophageal echocardiography.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, Danish investigators report that an anterolateral electrode position is better for AF cardioversion than an anteroposterior position, a systematic review finds that MINOCA is not as benign a condition as previously thought, and a meta-analysis indicates that routine pretreatment with oral P2Y12 inhibitors has no benefits in patients with NSTEACS who are scheduled for an invasive strategy. Also in this issue, an analysis of the EMPEROR-Preserved trial looks at the impact of empagliflozin on health-related quality of life, the FAME 3 trial supports preferential use of surgical revascularisation in patients with triple-vessel coronary artery disease, and an analysis of the VCOR-HF snapshot study provides further insight into the characteristics and clinical outcomes of patients with HFpEF.

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

Kind Regards,

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Anterior-lateral versus anterior-posterior electrode position for cardioverting atrial fibrillation

Authors: Schmidt AS et al.

Summary: This multicentre open-label study compared anterolateral and anteroposterior electrode positions for AF cardioversion. 468 patients with AF who were scheduled for elective cardioversion were randomised to either anterolateral or anteroposterior electrode position. The primary outcome (sinus rhythm after the first shock) occurred in 54% of patients assigned to anterolateral electrode position and 33% assigned to anteroposterior electrode position (risk difference 22 percentage points, 95% CI 13–30; p<0.001). Safety outcomes did not differ significantly between groups.

Comment: In patients undergoing direct current (DC) reversion for AF, an anterolateral paddle position is usually used unless the patient is markedly overweight or has a hyperinflated chest on the assumption that anteroposterior will deliver a greater electrical current to the heart and enhance the chances of reversion. This study would suggest that this is not correct and that overall, an anterolateral paddle position is associated with a greater chance of reversion than anteroposterior, and there were no differences in safety. Although the differences were small, the findings suggest that anterolateral should be the initial strategy for attempted DC conversion of AF to sinus rhythm.

Reference: Circulation 2021; published online Nov 24
Abstract

Survival in patients with suspected myocardial infarction with nonobstructive coronary arteries

Authors: Pasupathy S et al.

Summary: This systematic review and meta-analysis from the MINOCA Global Collaboration evaluated 12-month all-cause mortality in patients with MINOCA. A search of PubMed and Embase databases identified 23 eligible studies that were suitable for inclusion (55,369 patients with suspected MINOCA, 485,382 with MI and obstructive coronary artery disease [MI-CAD], and 33,074 without a history of MI [No-MI]). Meta-analysis of the data revealed an unadjusted 12-month all-cause mortality rate of 3.4% in patients with MINOCA (14 studies; n=30,733), and a reinfarction rate of 2.6% (10 studies; n=27,605). Patients with MINOCA had a lower 12-month all-cause mortality rate than those with MI-CAD (3.3% vs 5.6%; p<0.001) and a statistically nonsignificant trend toward worse 12-month all-cause mortality than those with No-MI (2.6% vs 0.7%; p=0.09).

Comment: MINOCA is not an uncommon clinical entity. Its prognosis has been unclear until this meta-analysis that suggests that 12-month all-cause mortality is 40% less than in patients with ASCVD and MI, but worse than in patients with no MI. This indicates that MINOCA is not a benign condition, but it is unknown whether the normal treatment strategies post ACS (aspirin, statin, ACE inhibitor and beta-blocker) affect the outcome in these patients, although most are usually treated the same as if they had an MI due to ASCVD.

Reference: Circ Cardiovasc Qual Outcomes 2021; published online Nov 16
Abstract

Assessment of pretreatment with oral P2Y12 inhibitors and cardiovascular and bleeding outcomes in patients with non-ST elevation acute coronary syndromes

Authors: Dawson LP et al.

Summary: This systematic review and meta-analysis evaluated the effects of oral P2Y12 inhibitor pretreatment on cardiovascular and bleeding outcomes in patients with NSTEACS scheduled for an invasive strategy. A search of various databases identified 7 clinical trials involving 13,226 patients with NSTEACS who were randomised to either oral P2Y12 inhibitor pretreatment (prior to angiography) or no pretreatment (only given after angiography once coronary anatomy was known). Meta-analysis of the data showed that pretreatment with a P2Y12 inhibitor was not associated with a reduction in 30-day major adverse cardiovascular events, 30-day MI, or 30-day cardiovascular death, but was associated with an increased risk of 30-day major bleeding (odds ratio 1.51, 95% CI 1.16–1.97).

Comment: There is clear evidence that early treatment with aspirin and P2Y12 inhibitors improves outcomes in STEMI when administered early before the coronary anatomy is known. The ACCOAST study was the first to question whether pretreatment with dual antiplatelet therapy was beneficial in NSTEMI and showed that delaying the P2Y12 inhibitor until during or after angiography was not associated with any increase in recurrent ischaemia but there was significantly less bleeding. This meta-analysis from the Alfred/Baker group supports these findings. It suggests there is no ischaemic benefit with pretreatment in NSTEMI, but there is an increased risk of bleeding, and thus indicates it would be prudent to wait until the anatomy is known before adding a P2Y12 inhibitor to aspirin in NSTEMI.

Reference: JAMA Netw Open 2021;4(11):e2134322
Abstract

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

Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction

Authors: Butler J et al.

Summary: This analysis of the EMPEROR-Preserved trial evaluated the effects of empagliflozin on health-related quality of life in patients with HFpEF. Health-related quality of life was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 12, 32 and 52 weeks. Patients were classified into tertiles according to baseline KCCQ Clinical Summary Score (KCCQ-CSS), and the effect of empagliflozin on outcomes was compared across tertiles. Patients treated with empagliflozin had significant improvements in KCCQ-CSS versus placebo. The beneficial effects of the drug on the end-point of cardiovascular death or HF hospitalisation were consistent across KCCQ-CSS tertiles (HR 0.83 [95% CI 0.69–1.00], HR 0.70 [95% CI 0.55–0.88] and HR 0.82 [95% CI 0.62–1.08] for scores <62.5, 62.5–83.3 and ≥83.3, respectively; p trend=0.77).

Comment: Until the EMPEROR-Preserved study there was no treatment that improved the outcome of patients with HFpEF. Empagliflozin 10mg added to standard therapy in patients with HF and LVEF >40% had a reduction in HF hospitalisations and cardiovascular death as a combined end-point, driven primarily by a reduction in HF hospitalisation in patients with HFpEF with or without type 2 diabetes. This subanalysis shows that baseline KCCQ score (a measure of quality of life) did not influence the beneficial effect of this treatment in this population, and that patients felt better on active treatment than placebo irrespective of their baseline quality of life.

Reference: Circulation 2021; published online Nov 15
Abstract

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Fractional flow reserve-guided PCI as compared with coronary bypass surgery

Authors: Fearon WF et al., for the FAME 3 Investigators

Summary: This multicentre trial investigated the use of fractional-flow reserve (FFR)-guided PCI compared with CABG in patients with 3-vessel coronary artery disease. 1500 patients were randomised to undergo CABG or FFR-guided PCI with current-generation zotarolimus-eluting stents. The 1-year incidence of the composite primary end-point (death from any cause, MI, stroke, or repeat revascularisation) was 10.6% with FFR-guided PCI and 6.9% with CABG (HR 1.5, 95% CI 1.1–2.2).

Comment: In patients with triple-vessel coronary disease there has been intense discussion as to the benefits of multivessel PCI versus CABG. In patients with type 2 diabetes, surgical revascularisation has been shown to improve outcomes compared with PCI, but this has not been proven in patients without diabetes. This important study shows outcomes at 1 year are better with surgery than with FFR-guided PCI in multivessel coronary artery disease which would strongly support preferential use of surgical revascularisation in these patients.

Reference: New Engl J Med 2021; published online Nov 4
Abstract

Angiotensin receptor-neprilysin inhibition in acute myocardial infarction

Authors: Pfeffer M et al., for the PARADISE-MI Investigators and Committees

Summary: The PARADISE-MI study investigated the efficacy of a fixed-dose combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan in patients with acute MI. 5661 patients with acute MI complicated by a reduced LVEF, pulmonary congestion, or both were randomised to receive either sacubitril/valsartan (97mg/103mg twice daily) or ramipril (5mg twice daily) in addition to recommended therapy. During a median 22 months of follow up, a primary outcome event (death due to cardiovascular causes or incident HF) occurred in 11.9% of patients in the sacubitril/valsartan group and 13.2% in the ramipril group (HR 0.90, 95% CI 0.78–1.04; p=ns). 357 patients (12.6%) in the sacubitril/valsartan group and 379 patients (13.4%) in the ramipril group discontinued treatment because of an adverse event.

Comment: We know that sacubitril/valsartan is associated with better outcomes and decreased mortality compared with enalapril in patients with HFrEF (LVEF <40%) who are 'stable' and in the community. Although there are many who would argue that there are no stable patients with HFrEF, there has been little research looking at initiation of this therapy earlier in the management of patients with HFrEF. The PIONEER study showed an improvement in surrogate outcomes (change in brain natriuretic peptide) in patients started on sacubitril/valsartan in hospital after an episode of decompensation, and this study looked at starting this therapy in patients with HF post MI. It showed no benefit compared with starting ramipril in this context, but no harm, so re-evaluation of LV function a few months after the index event before deciding to transition to sacubitril/valsartan would be reasonable, as many patients recover LV function over time.

Reference: New Engl J Med 2021;385:1845-55
Abstract

Characteristics and clinical outcomes in patients with heart failure with preserved ejection fraction compared to heart failure with reduced ejection fraction

Authors: Tan C et al.

Summary: This analysis of the Victorian Cardiac Outcomes Registry-Heart Failure (VCOR-HF) snapshot study determined the characteristics and outcomes of patients with HFpEF versus HFrEF. Of 1132 patients admitted with acute HF to 1 of 16 Victorian health services during the trial period, 436 were diagnosed with HFpEF. These patients were more likely to be female and older (81.5 vs 73.2 years) than those with HFrEF. They were also more likely to have hypertension, AF, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD), and less likely to have ischaemic heart disease with a history of previous MI, PCI or CABG. There were no significant differences in 30-day mortality and 30-day readmission rates between HFpEF and HFrEF patients.

Comment: This Australian study looked at patients admitted with acute HF in Victoria, and found that 38% of admissions were for patients with HFpEF. These patients were on average older and female, with more AF, hypertension, COPD and CKD than patients admitted with HFrEF who had more ischemic heart disease as the underlying cause of their HF. It is under appreciated that HFpEF has a similarly bad prognosis as HFrEF, but until recently (before the results of the EMPEROR-Preserved trial) we had no specific therapy to improve outcomes in HFpEF.

Reference: Heart Lung Circ 2021; published online Nov 3
Abstract

Mode of death in patients with heart failure and preserved ejection fraction: Insights from PARAGON-HF trial

Authors: Desai AS et al.

Summary: This analysis of the PARAGON-HF trial evaluated the mode of death in ambulatory patients with HFpEF. The trial compared clinical outcomes in 4796 patients with chronic HF and LVEF ≥45% who were randomised to sacubitril/valsartan or valsartan monotherapy. Of 691 deaths that occurred during the trial, 60% were due to cardiovascular causes, 32% to non-cardiovascular causes, and 8% to unknown causes. Cardiovascular deaths were due to sudden death (37%), heart failure (28%), stroke (8%), MI (6%), and other cardiovascular causes (20%). Rates of all-cause mortality, cardiovascular mortality, and sudden death were higher in patients with lower LVEF (all p<0.001), but rates of non-cardiovascular death were greater in patients with higher LVEF. Sacubitril/valsartan did not reduce overall death, cardiovascular death, or sudden death compared with valsartan, irrespective of baseline LVEF.

Comment: HF is associated with an increase in mortality but the modes of death may be different between HFrEF and HFpEF, which is primarily sudden death and progressive HF in patients with HFrEF. The PARAGON trial examined whether sacubitril/valsartan improved outcomes compared to valsartan alone in patients with HFpEF and LVEF >45%, and overall showed no benefit in reducing events or mortality but this subanalysis found that as LVEF rose above 45%, there were relatively more deaths from non-cardiovascular causes, which is not surprising given that it is thought that patients with mildly reduced LVEF (40–49%) behave more like patients with HFrEF than HFpEF (>50%), and that there are increased non-cardiovascular morbidities in patients with HFpEF.

Reference: Circ Heart Fail 2021; published online Nov 22
Abstract

Cardiac computed tomography versus transesophageal echocardiography for the detection of left atrial appendage thrombus

Authors: Yu S et al.

Summary: This systematic review and meta-analysis investigated the diagnostic accuracy of cardiac computed tomography (CCT) compared with trans-oesophageal echocardiography (TOE) for detection of left atrial appendage (LAA) thrombus. A search of PubMed, Embase, and Cochrane Library databases identified 27 studies (n=6960) that were suitable for inclusion. Early imaging studies with CCT had sensitivity of 0.95 (95% CI 0.79–0.99) and specificity of 0.89 (95% CI 0.85–0.92) for detecting LAA thrombus. The positive posterior probability was 19.11%, and the negative posterior probability was 0.16%. Delayed imaging studies improved both the sensitivity (1.00 vs 0.89; p<0.05) and the positive posterior probability (95.76% vs 19.11%; p<0.05).

Comment: In patients with AF, cardioversion is not recommended if LAA thrombus is detected. Many centres routinely perform a TOE before direct current reversion (DCR) to rule out LAA thrombus, but many others do DCR 'blind' after 3–4 weeks of therapeutic anticoagulation on the assumption that if LAA thrombus had been present it would have dissolved or organised over this period of anticoagulation and would not embolise and cause stroke. This meta-analysis suggests that delayed CCT is a sensitive and specific investigation to rule out LAA thrombus with high negative and positive predictive value. This may be a way of enabling DCR to be performed earlier in centres with limited access to TOE, and avoids the rare but often serious complications of TOE such as perforation.

Reference: J Am Heart Assoc 2021;10(23):e022505
Abstract

Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose co-transporter-2 inhibition use in type 2 diabetes

Authors: Lam CSP et al.

Summary: This analysis of the AMPLITUDE-O trial evaluated the cardiovascular effects of the glucagon-like peptide-1 (GLP-1) receptor agonist efpeglenatide when used with or without a concomitant SGLT2 inhibitor in patients with type 2 diabetes. In the AMPLITUDE-O trial, once weekly injections of efpeglenatide reduced a number of outcomes, including major adverse cardiovascular events (MACE), MACE, coronary revascularisation or unstable angina hospitalisation (expanded MACE), a renal composite outcome, and MACE or death compared with placebo in patients with type 2 diabetes and cardiovascular and/or renal disease. This analysis of AMPLITUDE-O trial data found that the effects of efpeglenatide on MACE, expanded MACE, the renal composite outcome, and the outcome of MACE or death were not affected by baseline SGLT2 inhibitor use.

Comment: We know that SGLT2 inhibitors and GLP-1 agonists improve cardiovascular outcomes in patients with type 2 diabetes but there is little data about their combined use with respect to safety and efficacy. The AMPLITUDE-O trial showed a 26% reduction in MACE with efpeglenatide (a GLP-1 agonist) in patients with type 2 diabetes, and a subanalysis showed that this benefit was even greater in patients receiving concomitant SGLT2 inhibition, with no safety signals. Use of SGLT2 inhibitors and GLP-1 agonists together is not reimbursed by the PBS at present, but hopefully this will change as the combination seems to be particularly attractive in patients with type 2 diabetes and ASCVD.

Reference: Circulation 2021; published online Nov 14
Abstract

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