Welcome to issue 39 of Heart Failure Research Review.

Research selected for this issue includes a paper suggesting CRT in chronically RV-paced patients is associated with similar short-term benefits as those with new CRT implantations, which is followed by another paper on CRT reporting higher function and cognition after 6 months. Another CRT-related paper shows the clinical feasibility of LV endocardial pacing in patients who are unsuitable for conventional CRT. The latest ESC guidelines for diagnosing and treating acute and chronic HF are recommended reading, and are discussed in this issue. The issue concludes with a study assessing vagal nerve stimulation in patients with chronic HF.

I hope you have been finding your copies of Heart Failure Research Review informative and helpful in your everyday practice. Your feedback and suggestions are important, so please keep them coming.

Kind Regards,

Prof Peter Macdonald
peter.macdonald@researchreview.com.au

Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression

Authors: Angermann CE et al., for the MOOD-HF Study Investigators and Committee Members

Summary: The 24-month MOOD-HF trial randomised outpatients with NYHA class II–IV HF with LVEF <45% and depression to receive escitalopram 10–20mg or placebo added to optimal HF therapy. The trial was terminated early by the data and safety monitoring committee with median participation durations of 18.4 months for 185 escitalopram recipients and 18.7 months for 187 placebo recipients. The rate of primary outcome events (death or hospitalisation for any cause) was similar in the escitalopram versus placebo arm (63% vs. 64%; HR 0.99 [95% CI 0.76–1.27]), and there was no significant difference for improvements in mean Montgomery-Åsberg Depression Rating Scale sum scores between baseline and 12 weeks (from 20.2 to 11.2 vs. 21.4 to 12.5 [p=0.26]). The groups were also comparable for safety parameters.

Comment: Depression is common in patients with HF and is associated with increased morbidity and mortality. This is an important clinical trial that directly assessed the impact of the SSRI (selective serotonin reuptake inhibitor) antidepressant medication escitalopram on depression and clinical outcomes in patients with chronic HF. Overall, patients entered into the trial had improved mood over 3 months of treatment. While escitalopram performed no better than placebo, the trial demonstrated that escitalopram was safe over 18 months of treatment. The results mirror and extend those of an earlier trial of another SSRI, sertraline, in patients with chronic HF. In the SADHART trial, sertraline given for 3 months was also shown to be safe but not better than placebo. Together these studies suggest that there is little if any role for antidepressant medication in depressed patients with chronic HF.


Abstract
Short-term outcome of cardiac resynchronization therapy – a comparison between newly implanted and chronically right ventricle-paced patients

Authors: Lipar L et al.

Summary: These researchers compared CRT in patients with HF with previously implanted RV pacing systems (n=116) versus those with no prior pacing (n=165). Over mean follow-up of 290 days, the newly implanted versus prior implanted device groups had the same clinical response rates (both 65% [p=0.98] and improvements in NYHA class (both –0.7 [p=0.81]), and comparable echocardiographic response rates (84% vs. 62% [p=0.80]). LV ejection fraction (LVEF) increases (9.3% vs. 8.2% [p=0.53]) and LV end-systolic volume reductions (–34.5% vs. –25.7% [p=0.28]). QRS interval increased postimplantation in participants with newly implanted devices, whereas it decreased in those with prior implanted devices (+5 vs. –20.0 msec [p<0.001]).

Comment: It is well recognised that RV pacing induces an iatrogenic left bundle branch block, which is detrimental to LV function and may precipitate LV failure in patients with pre-existing LV dysfunction. There are limited published data on the impact of upgrading an existing RV pacing system to one that incorporates biventricular pacing. In this large observational series, US authors demonstrated similar echocardiographic and clinical improvements in patients being upgraded from RV to biventricular pacing to patients undergoing biventricular pacing for left bundle branch block. While this study is limited by its retrospective nonrandomised design, the findings provide strong support for upgrading RV to biventricular pacing in patients with congestive HF, LV dilatation and dysfunction during RV pacing.


Cardiac resynchronization therapy improves functional status and cognition

Authors: Fumagalli S et al.

Summary: Fifty evaluable consecutive patients who had a CRT device implanted for HF were evaluated for cognition, disability, frailty and survival at baseline and again at 6 months in this research. Improvements were seen between baseline and 6 months for LVEF (from 28% to 35% [p<0.001]) and NYHA class (2.6 to 1.8 [p<0.001]), along with a decrease in LV end-systolic diameter (from 57 to 50mm [p<0.001]). Moreover, there was a significant improvement in SPPB (Short Physical Performance Battery) total score (from 9.1 to 10.3 [p<0.001]), including gait speed and strength and endurance subcores, with an associated improvement in MMSE (Mini-Mental State Examination) score (from 25.9 to 27.0 [p=0.009]). Improved functional performance and cognition was independently predicted by advanced age.

Comment: With the increased recognition that chronic HF is associated with comorbidity, physical frailty and cognitive impairment, particularly in the elderly, investigators have begun to focus more on these endpoints following therapeutic interventions. In this study of a relatively young cohort of patients with HFREF, undergoing implantation of a CRT device (pacing/ICD/pacemaker), the authors were able to demonstrate improvements not only in echocardiographic indices and physician-assessed clinical status, but also in cognition and functional performance across a number of physical domains including gait speed and strength – two core components of the physical frailty phenotype.

Reference: Int J Cardiol 2016;219:212–7

A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease

Authors: Filippatos G et al.

Summary: This phase 2b trial randomised 1066 patients with worsening HFREF and chronic kidney disease and/or diabetes to receive 90 days of treatment with finerenone 2.5mg, 5mg, 7.5mg or 15mg once daily, with the first four respective doses doubled and the 15mg dose increased to 20mg on day 30, or eplerenone 25mg every other day until day 29 then once daily, then increased to 50mg once daily on day 60. There were no significant differences between the finerenone versus eplerenone arms for decreases in NT-proBNP (N-terminal prohormone of brain natriuretic peptide) level of >30% over 90 days (primary endpoint; 30.9–38.8% vs. 37.2% [p=0.42–0.88]). The key exploratory composite endpoint of death from any cause, cardiovascular-related hospitalisation or emergency presentation for worsening HF over 90 days was numerically lower for finerenone recipients, except those in the lowest dose group, with nominal statistical significance reached in the recipients who received 10mg then 20mg (HR 0.56 [95% CI 0.35–0.90]). Potassium level increases to ≥5.6 mmol/L occurred in 4.3% of participants with a balanced distribution across groups.

Comment: Finerenone is a novel nonsteroidal mineralocorticoid receptor antagonist with higher selectivity for the mineralocorticoid receptor than spironolactone and higher affinity for the mineralocorticoid receptor than eplerenone. In this dose-ranging phase 2 study, finerenone was compared with eplerenone in patients with chronic HF requiring hospitalisation for worsening HF. In addition, patients needed to have either type 2 diabetes mellitus or chronic kidney disease of moderate severity to be eligible for the study. The primary efficacy endpoint of >30% decrease in NT-proBNP level was achieved in similar proportions of eplerenone and finerenone-treated patients regardless of the dose. Both drugs were well tolerated in this high-risk population. The authors’ observation that the second highest of the five dose levels of finerenone was associated with a markedly lower (adverse) clinical composite outcome compared with eplerenone is interesting, but should be interpreted with extreme caution. A larger phase 3 trial will be required to determine if there is any advantage of finerenone over alternative mineralocorticoid receptor antagonists.


Alternate Site Cardiac ResYNChronization (ALSYNC): a prospective and multicentre study of left ventricular endocardial pacing for cardiac resynchronization therapy

Authors: Morgan JM et al., on behalf of the ALSYNC Investigators

Summary: This paper reported on a prospective investigation of 138 patients with an indication for CRT but who were unsuitable for conventional CRT and underwent LV endocardial pacing with the lead implanted via a single pectoral access by a novel atrial trans-septal lead delivery system; the participants were followed for ≥12 months and required warfarin postimplantation. The procedure success rate was 89.4%. The 6-month rate of freedom from complications related to the lead delivery system, implant procedure or the lead (primary endpoint) was 82.2%, exceeding the study’s objective of ≥70%. There were 14 transient ischaemic attacks affecting nine participants, five participants experienced a nondisabling stroke and there were 23 deaths (none due to a primary endpoint complication). At 6 months, 59% of participants had an improved NYHA class and 55% had LV end-systolic volume reduction of ≥15%. Similar improvements with endocardial pacing were observed in participants enrolled after CRT nonresponse.

Comment: Not all patients who meet clinical indications for CRT are able to undergo the procedure, e.g., due to inability to cannulate (or the absence of) a suitable tributary of the coronary sinus. This study reports the results of a pilot programme that evaluated the procedural success, risks and benefits of an alternative LV lead placement system. Patients undergoing the procedure had an endocardial LV lead placed via a steerable guiding catheter that was advanced into the left atrium after atrial trans-septal puncture then across the mitral valve into the LV cavity. The procedural success rate was lower than for conventional CRT, but still close to 90%. Despite all patients being treated with warfarin, (mainly transient) neurological complications presumably related to thromboembolism from the LV lead were common. Response rates (in terms of symptomatic improvement and LV remodelling) appear to be similar to conventional CRT. While more experience is needed, this report suggests that the ALSYNC procedure may be a reasonable alternative in selected patients who are unsuitable for conventional CRT.


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Independent commentary by Professor Peter Macdonald.

Peter Macdonald is a Conjoint Professor of Medicine in the University of New South Wales, senior staff cardiologist in the Heart & Lung Transplant Unit at St Vincent’s Hospital, Sydney and co-head of the Transplantation Research Laboratory at the Victor Chang Cardiac Research Institute. He is a past President of the Transplantation Society of Australia & New Zealand (TSANZ). His major research interests over the last 20 years have been in the areas of heart failure, pulmonary hypertension, transplant allograft rejection, donor management and organ preservation. He has published six national guidelines, 15 book chapters and over 250 peer-reviewed scientific papers.
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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Authors: Ponikowski P et al.

Summary: This paper summarised the ESC’s 2016 guidelines for diagnosing and treating acute and chronic HF, which were collated following a comprehensive review of relevant published diagnosis, treatment, prevention and rehabilitation evidence. It also covered estimates of expected health outcomes when possible and provides the corresponding level of evidence and strength of the recommendation for each of the particular management options. A useful list of ‘to do and not to do messages’ was also tabulated in the document, for which the complete manuscript is freely available via the ‘Abstract’ link below.

Comment: Guidelines provide clinicians with recommendations regarding assessment and management of a particular condition based on the best available evidence at the time of writing. There are many HF guidelines that have been produced by national and international bodies. Generally they are excellent documents; however, a major challenge for all guidelines (and their writing committees) is how to keep them up to date. (Our own national Heart Failure Guidelines are sadly out of date). The latest ESC Heart Failure Guidelines provide a comprehensive 71-page review of the current ‘state of the art’ in 2016, and are recommended reading for those who have the time. Unfortunately, many clinicians do not have the time and will no doubt be looking for the ‘pocket version’ or downloadable app to provide a ready reference guide.


Randomized, controlled trial of an advance care planning video decision support tool for patients with advanced heart failure

Authors: El-Jawahri A et al.

Summary: Patients aged ≥64 years with HF and an estimated likelihood of death of >50% within 2 years (n=246) were randomised to a verbal description for goals of care (life-prolonging care, limited care and comfort care) and CPR/intubation with or without a 6-minute video depicting the three levels of care, CPR/intubation and an advance care planning checklist. There were significant differences between the intervention versus control groups for chosen levels of care: 51% vs. 30% for comfort care (primary outcome); 22% vs. 41% for life-prolonging care; 25% vs. 30% for limited care; and 2% vs. 7% for undecided. Compared with controls, intervention participants were significantly more likely to choose to forgo CPR (68% vs. 35% [p=0.001]) and intubation (77% vs. 48% [p=0.001]) and had higher scores on a 6-point knowledge questionnaire (4.1 vs. 3.0 [p=0.001]).

Comment: Advance care planning is a process of shared decision making that informs and engages patients to ensure that the care delivered is consistent with their informed wishes. Advance care planning is an important but often overlooked component of chronic HF management. This interesting and important study demonstrates that when patients are provided with information in a clear and understandable format (in this case a video-assisted explanation and checklist regarding what advanced care treatment they would be prepared to accept), they are more likely to decide on a more palliative approach.

Reference: Circulation 2016;134(1):52–60

Underutilization of coronary artery disease testing among patients hospitalized with new-onset heart failure

Authors: Doshi D et al.

Summary: Patterns of testing for ischaemic CAD and revascularisation in patients with new-onset HF were investigated using retrospective data from a cohort of 67,161 inpatients with new HF. Testing for ischaemic CAD was performed in 17.5% during the index hospitalisation and in 27.4% by day 90, and the respective values were 2.1% and 4.3% for revascularisation; among tests for ischaemic CAD, the respective rates were 7.9% and 14.6% for stress testing and 11.1% and 16.5% for coronary angiography. Compared with patients without CAD at baseline, those with CAD at baseline were significantly more likely to undergo noninvasive ischaemic testing (odds ratio 1.25 [95% CI 1.17–1.33]) or invasive ischaemic testing (1.93 [1.83–2.05]) during their index hospitalisation.

Comment: This retrospective analysis of a large cohort of patients with new-onset HF found that only a low proportion of patients underwent noninvasive or invasive testing for underlying CAD — about 20% during the acute admission increasing to about 30% during the next 90 days. Given the frequency of CAD in the community and its role in the causation of HF (particularly HFREF), the authors expressed surprise at the low utilisation of these tests; however, at present we have little evidence that identification of CAD or revascularisation improves the prognosis of patients presenting with new-onset HF (in the absence of overt ischaemia or infarction) who are commenced on evidence-based medications.

Reference: J Am Coll Cardiol 2016;68(5):450–8

High-output heart failure: a 15-year experience

Authors: Reddy YNV et al.

Summary: This was a retrospective analysis of consecutive patients referred for haemodynamic assessment, comparing 120 patients with definite HF according to Framingham criteria with 24 matched controls, to characterise the aetiologies, pathophysiology, clinical and haemodynamic characteristics and outcomes of high-output HF. Obesity was the most frequent high-output HF aetiology at 31%, followed by liver disease and arteriovenous shunts each at 23%, lung disease at 16% and myeloproliferative disorders at 8%. Compared with controls, patients with high-output HF had eccentric LV remodelling and increased natriuretic peptide activation, filling pressures, pulmonary hypertension and cardiac output, despite similar EFs. Among patients with high-output HF, relationships were seen between elevated cardiac output and both lower arterial afterload (decreased systemic vascular resistance) and higher metabolic rate. Patients with high-output HF had a higher mortality risk than controls (HR 3.4 [95% CI 1.6–7.6]), and those with the lowest systemic vascular resistance had the worst haemodynamics and outcomes.

Reference: J Am Coll Cardiol 2016;68(5):473–82

Vagus nerve stimulation for the treatment of heart failure

Authors: Gold MR et al.

Summary: Patients with HF with EF ≤40% and NYHA functional class III symptoms were randomised to vagal nerve stimulation provided by an implanted device (n=436) or continued medical therapy (n=271) in the INOVATE-HF trial; mean follow-up was 16 months. There was no significant difference between the vagal nerve stimulation versus medical therapy arms for the primary efficacy outcome event rate (composite of death from any cause or first event for worsening HF; 30.3% vs. 25.8% [p=0.37]) or the estimated annual mortality rate (9.3% vs. 7.1% [p=0.19]). Vagal nerve stimulation was associated with favourable outcomes for quality of life, NYHA functional class and 6-minute walk distance (p=0.05), but not LV end-systolic volume index (p=0.49).

Comment: This large international clinical trial tested the hypothesis that enhanced vagal nerve stimulation (using an implantable device similar to a pacemaker) would reduce the composite endpoint of mortality and HF hospitalisation in HFREF. The trial failed to demonstrate any benefit on the primary endpoint (indeed the trend was for worse outcomes in the intervention group). A number of more subjective endpoints were favourably influenced by vagal nerve stimulation, but the significance of these improvements is doubtful in the absence of a sham control group.

Reference: J Am Coll Cardiol 2016;68(2):149–58

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