In this issue:

- Readmissions reduction programme reduces HF readmissions but increases mortality
- AF type and HFREF outcomes
- Serial ST2 measurements for acute HF prognosis
- Phenotype and clinical outcomes of TTN cardiomyopathy
- Mutation status and LV reverse remodelling in dilated cardiomyopathy
- Abdominal obesity increases all-cause mortality in HFPEF
- HF prognosis according to EF
- Stroke risk in congestive HF ±AF
- IL-1 blockade in recently decompensated systolic HF
- Impact of AF on rest/exercise haemodynamics in HF with midrange/preserved EF

Abbreviations used in this issue:

- AF = atrial fibrillation; CV = cardiovascular
- EF = ejection fraction; HF = heart failure;
- HFPEF/HFREF/HFRE/M = HF with borderline/preserved/reduced EF;
- HR = hazard ratio; IL = interleukin;
- LV = left ventricular;
- (NT-pro)BNP = (N-terminal prohormone of) brain natriuretic peptide;
- PCWP = pulmonary capillary wedge pressure; TTN = titin.

Welcome to issue 49 of Heart Failure Research Review.

The final issue for 2017 begins with research reporting that although a US hospital readmissions reduction programme for HF achieved the objective of fewer readmissions, there was an increase in mortality. Research from the Netherlands suggests that repeated ST2 level measurements strongly predict outcomes, independent of repeated NT-proBNP levels, in patients with acute HF. Despite the previously described obesity paradox in HF, an analysis of data from the TOPCAT trial has identified that abdominal obesity assessed by waist circumference is associated with increased mortality in patients with HFPEF. We conclude the year with research suggesting that adverse LV systolic function and peripheral oxygen kinetics might help explain the negative impact AF has in patients with HF with preserved or midrange EF.

I hope you find the selected papers and commentaries informative and helpful. I look forward to bringing you more interesting updates in HF research in 2018.

Kind Regards,

Dr. John Atherton
john.atherton@researchreview.com.au

Association of the hospital readmissions reduction program implementation with readmission and mortality outcomes in heart failure

Authors: Gupta A et al.

Summary: The impact of a US programme designed to reduce readmissions following hospitalisation for HF (the Hospital Readmissions Reduction Program) on readmission and mortality rates was explored for 115,245 Medicare patients from a prospective clinical registry. Compared with prior to implementation of the programme in April 2010, after the programme’s penalties came into effect in October 2012 (programme implementation lasted for the period between these months) the respective 30-day and 1-year risk-adjusted readmission rates decreased from 20.0% to 18.4% (HR 0.91 [95% CI 0.87–0.95]) and from 57.2% to 56.3% (0.92 [0.89–0.96]), but the respective 30-day and 1-year risk-adjusted mortality rates increased from 7.2% to 8.6% (1.18 [1.10–1.27]) and from 31.3% to 36.3% (1.10 [1.06–1.14]).

Comment: While the Hospital Readmissions Reduction Program appears to have been successful in reducing readmissions in patients with HF in the US, this study suggests there may have been unintended consequences with an increase in mortality observed during the same period. The findings were robust to various sensitivity analyses. While observational studies do not establish cause and effect, it is possible that gaming strategies aimed at reducing readmission may have adverse effects on patient outcomes. The question raised by this analysis is whether we should apply the same rigour required to establish the safety and clinical effectiveness of a new drug or technology to changes in administrative health policy.

Reference: JAMA Cardiol; Published online Nov 12, 2017

Abstract

Independent commentary by Dr. John Atherton. Director of Cardiology at the Royal Brisbane and Women’s Hospital, Associate Professor, University of Queensland and Adjunct Professor, Queensland University of Technology. He previously chaired the Asia-Pacific Acute Decompensated Heart Failure Registry SAC and the CSANZ Heart Failure Council. He has been an appointed member of the Australian Government Medical Services Advisory Committee and sat on the National Heart Foundation Heart Failure Guidelines executive writing group. Research interests include investigating novel methods to detect presymptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.
Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction

Authors: Mogereen UM et al., on behalf of the PARADIGM-HF and ATMOSPHERE Investigators and Committees.

Summary: These authors analysed data for 15,415 participants with HFREF from the PARADIGM-HF and ATMOSPHERE trials to assess outcomes according to AF type: 5481 participants had a history of AF at randomisation, 1645 of whom had paroxysmal AF. Compared with participants without AF, those with paroxysmal AF at randomisation had greater likelihoods of experiencing a primary composite endpoint event (CV-related death or hospitalisation for HF; HR 1.20 [95% CI 1.09–1.32]), hospitalisation for HF (1.34 [1.19–1.51]) and stroke (1.34 [1.02–1.76]), whereas no increase in these risks or mortality was evident for participants with persistent or permanent AF. Participants with new-onset AF during the trials had increased risks of a primary endpoint event (HR 2.18 [95% CI 1.80–2.21]). HF hospitalisation (2.11 [1.58–2.81]), stroke (2.20 [1.25–3.88]) and death from any cause (2.26 [1.86–2.74]) compared with participants without AF. Lower proportions of participants with paroxysmal and new-onset AF received anticoagulants compared with those with persistent or permanent AF (53% and 16%, respectively, vs. 71%).

Comment: There is controversy regarding whether AF is an independent prognostic risk factor in HF. The strength of this study was the consistent approach taken to document covariates including BNP levels in all patients and endpoint adjudication to allow adjusted analyses. The findings may seem somewhat counterintuitive, suggesting greater risk in new-onset and paroxysmal AF compared with persistent or permanent AF. The lower rates of anticoagulation in paroxysmal AF may partly contribute to this. These findings support applying the same thresholds to management (including anticoagulation) regardless of the type of AF in patients with HFREF.

Reference: J Am Coll Cardiol 2017;70(20):2490–500

Prognostic value of serial ST2 measurements in patients with acute heart failure

Authors: van Vark LC et al., for the TRIUMPH investigators.

Summary: The prognostic value of ST2 level measurements was evaluated in 496 participants with acute HF from the TRIUMPH cohort study; the median ST2 level at baseline was 71 ng/mL. The study’s primary endpoint event rate (death from any cause or HF rehospitalisation) was 40% over median follow-up of 325 days. The risk of a primary endpoint was increased by each standard deviation increase in baseline ST2 level on the log scale (adjusted HR 1.30 [95% CI 1.08–1.56]), and the risk increased when repeated ST2 level measurements during follow-up were taken into account (1.85 [1.02–3.33]). ST2 levels also appeared to rise several weeks prior to a primary endpoint event.

Comment: This study confirms the independent, prognostic utility of ST2 in HF (with most patients having a reduced LVEF), and further demonstrates the incremental utility of repeated measurements of serum ST2 level, even in models that adjusted for repeated measurements of plasma NT-proBNP level. Given the disappointing results reported from the GUIDE-IT study with serial monitoring of NT-proBNP levels, the current study results coupled with the lower biological variability of ST2 supports investigating the clinical utility of monitoring ST2 levels (with or without NT-proBNP level). However, while we may be able to identify those patients at the highest risk, it remains unclear how we should change management to avoid adverse events.

Reference: J Am Coll Cardiol 2017;70(19):2378–88

Phenotype and clinical outcomes of titin cardiomyopathy

Authors: Tayal U et al.

Summary: Relationships among TTN truncating variant genotypes, cardiac phenotype and dilated cardiomyopathy outcomes were explored in a prospective observational cohort of 716 patients, 83 of whom had TTN truncation variants. Patients with versus without TTN truncation variants were younger at enrolment (49.0 vs. 54.1 years [p=0.002]) and had a 5.1 g/m2 lower indexed LV mass (p=0.03), but biventricular EF did not differ significantly, and moreover, neither did rate of primary endpoint events (CV-related death, major arrhythmia or major HF; 12.7% vs. 12.9% [p=0.82]).

Comment: TTN truncating variants are the most common known genetic cause of dilated cardiomyopathy. Identifying the genetic cause then allows predictive genetic testing in family members. Noncarriers (and their offspring) can be reassured, and clinical surveillance may then focus on the carriers. However, it is less clear whether identifying a TTN truncating variant confers a higher risk of an adverse outcome in a patient with known dilated cardiomyopathy. This study reported that neither the presence nor position of TTN truncating variants provided independent risk prediction over and above clinical variables. While this was the largest study to date to address this question, there were only nine events in the 71 patients with TTN truncating variants, so larger studies are required to confirm or refute these findings.

Reference: J Am Coll Cardiol 2017;70(18):2264–74

Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy

Authors: Dal Ferro M et al.

Summary: These researchers used next-generation sequencing to examine the genetic landscape of a cohort of 152 registry patients with dilated cardiomyopathy and explore potential relationships between various genotypes and LV reverse remodelling (defined as normalisation of LVEF or an increase of ≥10% associated with normalisation in indexed LV end-diastolic diameter or a relative decrease of ≥10% at 24 months follow-up). Identified pathogenic disease-related gene variants affected TTN in 18%, LMNA in 5%, structural cytoskeleton Z-disk genes in 11%, desmosomal genes in 6%, motor sarcomeric genes in 12% and other genes in 6%; variants were identified in 57% of the overall cohort. The different genotypes did not differ significantly for baseline clinical features. Compared with other gene cluster subgroups, structural cytoskeleton Z-disk gene mutations were associated with a significantly lower rate of LV reverse remodelling (p<0.05), with rare variants independently, inversely associated with LV reverse remodelling (adjusted odds ratio 0.065 [95% CI 0.008–0.535]).

Comment: Treatment-related LV reverse remodelling is associated with a favourable prognosis in patients with HFREF. This study explored whether there was a correlation between reverse remodelling and the underlying genetic cause of dilated cardiomyopathy in the Trieste Heart Muscle Disease Registry. A higher than expected proportion (57%) had a pathogenic variant identified, which likely reflects referral bias. The authors identified that patients with mutations in genes encoding structural cytoskeleton Z-disk proteins were less likely to develop reverse remodelling. Despite this being a major referral centre, this study was underpowered with only 16 patients having structural cytoskeleton Z-disk gene mutations. Larger, multicentre studies will be required to further evaluate this and other genotype-phenotype correlations.

Reference: Heart 2017;103(21):1704–10

Abdominal obesity is associated with an increased risk of all-cause mortality in patients with HfPEF

Authors: Tsujimoto T & Kajio H

Summary: Data from TOPCAT trial participants with HfPEF were used to compare mortality rates between those with (n=2413) and those without (n=897) abdominal obesity, which was assessed by waist circumference measurements: there were 500 deaths over mean follow-up of 3.4 years. Compared with participants with waist circumference measurements <102cm in men and <88cm in women, those with greater waist circumference measurements had significantly higher risks of all-cause mortality (461 vs. 40.7 events per 1000 person-years; adjusted HR 1.52 [95% CI 1.16–1.99]), CV-related mortality (1.50 [1.08–2.00]) and non-CV-related mortality (1.38 [1.02–1.85]).

Comment: While obesity is a well-recognised risk factor for the development of HF (especially HfPEF), previous studies have reported the ‘obesity paradox’, with lower mortality in patients with either an increased body mass index or waist circumference in the setting of HFREF. Similarly, this study reported a lower mortality associated with a higher body mass index in the setting of HfPEF. However, patients with a larger waist circumference as a measure of abdominal obesity had a higher mortality rate in adjusted analyses. While it remains unclear whether interventions aimed at decreasing waist circumference will improve outcomes in HfPEF, these findings provide support for advice weight reduction (if obese) in HfPEF.

Reference: J Am Coll Cardiol 2017;70(22):2739–49
CHF patients aged ≥ 70 years
deserve an age-proven β-blocker¹,²

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of CHF patients aged ≥ 70 years*¹,²

*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

NEBILET: Age proven in CHF patients aged ≥ 70 years¹²

CHF = Chronic Heart Failure

PBS Information: Restricted benefit. Moderate to severe heart failure. Refer to PBS Schedule for full restricted benefit information.

Please review full Product Information before prescribing. The Product Information can be accessed at www.menarini.com.au/pi

Nebilet® (nebivolol hydrochloride) tablets 1.25 mg, 5 mg, 10 mg. INDICATIONS: Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. CONTRAINDICATIONS: Hypersensitivity to the active or any of the excipients; liver insufficiency or liver function impairment; acute heart failure; cardiogenic shock or episodes of heart failure decompensation requiring IV inotropic therapy; sick sinus syndrome, including sino-atrial block; second and third degree heart block (without a pacemaker); history of bronchospasm (e.g. including COPD) and/or asthma; untreated phaeochromocytoma; metabolic acidosis; bradycardia (HR < 60 bpm prior to starting therapy); hypotension (systolic BP < 100 mmHg); severe peripheral circulatory disturbances. PRECAUTIONS: Avoid abrupt cessation unless clearly indicated – reduce dosage gradually over 1-2 wks, refer to full PI. It must be withdrawn abruptly, close observation is required. Anaesthesia: untreated congestive heart failure, unless stabilised; bradycardia; peripheral circulatory disorders (e.g. Raynaud’s disease, intermittent claudication); first degree heart block; Prinzmetal’s or variant angina; lipid and carbohydrate metabolism – does not affect glucose levels in diabetic patients, but may mask symptoms of hypoglycaemia. Hyperthyroidism; COPD/asthma; phaeochromocytoma; various skin rashes; conjunctival xerosis; oculomucocutaneous syndrome; psoriasis; increased sensitivity to allergens and severity of anaphylactic reactions; galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption; driving vehicles or operating machines. Pregnancy (Cat C). Lactation. Children and adolescents. Renal and hepatic insufficiency – see Dosage and Administration. INTERACTIONS: Combination not recommended: Class I antiarrhythmics; calcium channel antagonists (verapamil/diltiazem); centrally-acting antihypertensives; other beta-blockers (incl. eye drops). Combination to be used with caution: Class III antiarrhythmic drugs; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine; for other combinations requiring careful consideration, see full PI. ADVERSE EFFECTS: Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, dyspnoea, oedema, slowed AV conduction/AV-block, bronchospasm. Post-marketing reports of hypersensitivity, angio-neurotic oedema, abnormal hepatic function, acute pulmonary oedema, acute renal failure, myocardial infarction, others see full PI. DOSAGE AND ADMINISTRATION: Once daily dosing, can be given with or without meals, consistent approach is recommended. Hypertension: 5 mg daily. Renal insufficiency: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 65 years: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 75 years: caution must be exercised and these patients monitored closely. Chronic Heart Failure: The initial up titration should be done gradually at 1-2 wk intervals based on patient tolerability starting at 1.25 mg once daily, increased to 2.5 mg, then to 5 mg and then to 10 mg once daily. Initiation of therapy and every dose increase should be done under close supervision for at least 2 h. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 µmol/L) is not recommended. Date prepared 17 December 2015. References: 1. Nebilet Approved Product Information, 14 December 2015. 2. Flather MD et al. Eur Heart J 2005; 26: 215–25. A. Menarini Australia Pty Ltd. ABN 62 116 935 758, Level 8, 67 Albert Avenue, Chatswood NSW 2067 Medical Information 1800 644 542 • NEB-AU-0718 October 2017 • MN2042/10/17

www.researchreview.com.au

a RESEARCH REVIEW publication
Heart failure with preserved, borderline, and reduced ejection fraction

Authors: Shah KS et al.

Summary: Longitudinal data from the US Get With The Guidelines – Heart Failure programme and Medicare were linked to compare 5-year outcomes for patients hospitalised with HFREF (EF ≥50%; n=18,299), HFMBF (HF with borderline EF; EF 41–49%; n=2285) and HFHREF (EF ≤40%; n=18,398). Median survival duration was 2.1 years. Five-year mortality rates were similar for the groups with HFREF and HFMBF versus HFHREF (75.3% and 75.7%, respectively, 95% CI 74.9–76.1% and 75.1–76.5%, respective HRs 0.99 [95% CI 0.958–1.022] and 0.99 [0.947–1.046]), as were rates of the composite of mortality or rehospitalisation; however, CV-related and HF-related readmission rates were higher in patients with HFHREF or HFMBF. Median survival duration was lower for patients with HF regardless of age and EF when compared with US population data.

Comment: This analysis from the Get With The Guidelines – HF registry reported similar mortality and rehospitalisation rates over 5-year follow-up following HF hospitalisation, regardless of the underlying LVEF. There were cause-specific differences with a larger proportion of deaths being due to CV causes in patients with a reduced LVEF. Nonetheless, outcomes were poor with substantial 4- to 15-year reductions in lifespan compared with the general population. A major limitation of this analysis is that it does not consider subsequent changes in LVEF following treatment. Nonetheless, these findings suggest that while LVEF is currently used to guide treatment decisions, we need better methods to risk stratify our patients, especially once they have been hospitalised with HF.

Reference: J Am Coll Cardiol 2017;70(20):2476–86

Risk of stroke in congestive heart failure with and without atrial fibrillation

Authors: Kang S-H et al.

Summary: This analysis of insurance data reported stroke and thromboembolism risks for 4533 patients with congestive HF, 1213 with congestive HF plus AF and 90,277 controls from the Republic of Korea. Patients with congestive HF had a significantly increased ischaemic stroke risk in adjusted models. The respective annualised stroke rates for the congestive HF, AF, congestive HF plus AF and control groups were 2.00, 2.27, 2.67 and 0.54 per 100 person-years. CHA2DS2-VASc scores had moderate discriminative value for stroke risk in patients with congestive HF as well as in AF. The stroke risks for the congestive HF and AF groups were comparable when stratified by CHA2DS2-VASc scores; patients with HF or AF whose CHA2DS2-VASc scores were 0 or 1 were at low risk for stroke.

Comment: In a population-based cohort, the CHA2DS2-VASc scoring system provided similar thromboembolism risk prediction in subjects with a diagnosis of HF (without AF) and AF. This study confirms earlier reports from other groups (reported in Heart Failure Research Review issue 28 and issue 29). Meanwhile, there is an ongoing, randomised, controlled trial evaluating the clinical efficacy of a non-vitamin K oral anticoagulant in patients with HF.


Interleukin-1 blockade in recently decompensated systolic heart failure

Authors: Van Tassell BW et al.

Summary: REDHART (Recently Decompensated Heart Failure Anakinra Response Trial) randomised 60 patients with HFREF and C-reactive protein levels ≥2 mg/L to receive subcutaneous anakinra 100 mg/day for 2 weeks or 12 weeks or placebo commencing within 14 days of hospital discharge. Although 12 weeks of anakinra was associated with a significant improvement in peak VO2, from 14.5 to 16.1 ml/kg/min (p=0.009), there was not to significant difference when compared against the 2-week anakinra or placebo group, neither of which resulted in a significant within-group improvement. No improvements in ventilatory efficiency (VE/VCO2 slope) were seen. The respective 24-week incidences of death or rehospitalisation for HF were 6%, 31% and 30% in the 12-week anakinra, 2-week anakinra and placebo arms (p=0.10).

Comment: These findings build on previous phase 2 studies conducted in patients with chronic HF demonstrating the safety and tolerability of the IL-1 blocker, anakinra. While the between-group differences were not significant for peak VO2, there were promising signals. Furthermore, the sustained reductions in C-reactive protein levels seen with anakinra were not observed with previous anti-inflammatory therapies (including infliximab and etanercept) evaluated in patients with chronic HF. These findings suggest that the benefits of targeting the IL-1 pathway recently reported in the Canakinumab Anti-Inflammatory Thrombosis Outcome study conducted in patients with previous myocardial infarction may also apply in HF; however, larger studies are required.

Reference: Circ Heart Fail 2017;10(11):e004373

Impact of atrial fibrillation on rest and exercise haemodynamics in heart failure with mid-range and preserved ejection fraction

Authors: Kaye DM et al.

Summary: Central haemodynamics were invasively measured at rest and during symptom-limited supine cycle exercise in patients with HF with preserved or reduced EF, including 35 in sinus rhythm and 20 in AF with matched LVEF. Patients with versus without AF had significantly increased PCWP (pulmonary capillary wedge pressure) and lower cardiac index and LV stroke work index values at rest, despite similar resting heart rates. There was also no significant between-group difference for calculated oxygen consumption or systemic arteriovenous oxygen gradient at rest. The patients with AF experienced a reduced capacity to increase their oxygen consumption during supine cycling, accompanied by persistent impairment in cardiac index and LV stroke work index.

Comment: This is a very nice study that explored haemodynamic contributors to poorer outcomes in patients with HF and (relatively) preserved LVEF associated with AF. A smaller increase in VO2 was observed during exercise in patients with AF accompanied by persistently impaired cardiac index. It is tempting to speculate that diastolic ventricular interaction may play a role, given the higher resting mean pulmonary arterial pressure accompanied by larger exercise-induced increases in right atrial pressure (despite similar increases in PCWP) in patients with AF. Hence, there was a smaller increase in true filling pressure (estimated PCWP-right atrial pressure) during exercise, which may at least partly explain the smaller increase in stroke volume observed in patients with AF.

Reference: Eur J Heart Fail; Published online Oct 11, 2017

Heart Failure Research Review is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health.

Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Research content is created independently of sponsor companies with assistance from leading local specialists. Research Review Australia Pty Ltd are prepared with an independent commentary from relevant specialists. To become a reviewer please email submit@researchreview.com.au

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email review@researchreview.com.au.

Research Review subscriptions are the Australian perspective since 2007. Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Research content is created independently of sponsor companies with assistance from leading local specialists. Research Review Australia Pty Ltd are prepared with an independent commentary from relevant specialists. To become a reviewer please email submit@researchreview.com.au

Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Research content is created independently of sponsor companies with assistance from leading local specialists. Research Review Australia Pty Ltd are prepared with an independent commentary from relevant specialists. To become a reviewer please email submit@researchreview.com.au

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.