Welcome to issue 32 of Heart Failure Research Review.

The year begins with a dose-finding phase 2 trial published in JAMA showing that while vericiguat, a soluble guanylate cyclase stimulator, did not statistically impact on NT-proBNP level in patients with worsening chronic HFREF, positive effects were seen, along with good tolerability, at the highest dose, suggesting further research is warranted. G-CSF (granulocyte colony-stimulating factor) plus bone marrow-derived cells improved cardiac function in patients with dilated cardiomyopathy. Two papers compare prognostic markers (NT-proBNP and FGF-23 [fibroblast growth factor 23]) between HFPEF versus HFREF. This issue concludes with research reporting on the benefits of a lateral sleeping position for patients with HF and CSA or OSA (central or obstructive sleep apnoea).

I hope the papers selected for this issue help to inspire you as we begin 2016. I appreciate your comments and suggestions, so please keep them coming.

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

Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction

Authors: Gheorghiade M et al., for the SOCRATES-REDUCED Investigators and Coordinators

Summary: Clinically stable patients with an LVEF <45% within 4 weeks of a worsening chronic HF event were randomised to receive oral vericiguat 1.25mg (n=91), 2.5mg (n=91), 5mg (n=91) or 10mg (n=91) or placebo (n=92) for 12 weeks. Change in baseline log-transformed NT-proBNP level at week 12 (primary endpoint; evaluable n=351) did not differ significantly between pooled vericiguat and placebo recipients (difference of means –0.122; ratio of geometric means 0.885 [p=0.15]). An exploratory secondary analysis suggested that higher vericiguat doses were associated with greater NT-proBNP level reductions (p<0.02). The respective adverse event rates in the vericiguat 10mg and placebo arms were 71.4% and 77.2%.

Comment: Whilst this study did not achieve its primary endpoint, vericiguat was well tolerated with some promising signals observed with the higher doses, including greater reductions in NT-proBNP level, larger increases in LVEF and numerically less cardiovascular deaths and HF hospitalisations. However, these results should be regarded as hypothesis-generating, and future studies will need to establish whether there is any additional benefit on top of standard care, which may be changing on the basis of the PARADIGM-HF study (especially given that neprilysin inhibition also augments cGMP).


Abstract

In this issue:

- Vericiguat and NT-proBNP levels in worsening chronic HFREF
- HF in Africa, Asia, the Middle East and South America
- G-CSF + bone marrow cells in nonischaemic dilated cardiomyopathy
- Adding point-of-care ultrasound to assess volume status in HF
- Prognostic value of NT-proBNP and FGF-23 in HFPEF vs. HFREF
- Restoring pulsatile flow via continuous-flow LVADs reduces sympathetic nerve activity
- Fully magnetically levitated LVAD for advanced HF
- HFREF, not HFPEF, benefits from NT-proBNP-guided therapy
- Lateral sleep position reduces CSA/OSA severity in HF

Abbreviations used in this issue:

AHI = apnoea-hypopnoea index;
C/OSA = central/obstructive sleep apnoea;
EF = ejection fraction;
G-CSF = granulocyte colony-stimulating factor;
HF = heart failure;
HF(P/R)EF = HF (with preserved/reduced) EF;
IVC = inferior vena cava;
LV = left ventricular;
LVAD = LV assist device;
NT-proBNP = N-terminal prohormone of brain natriuretic peptide;
NYHA = New York Heart Association;
RCT = randomised controlled trial.

Follow RESEARCH REVIEW Australia on Twitter now
@cardioreview
Visit https://twitter.com/cardioreviews
Heart failure in Africa, Asia, the Middle East and South America

Authors: Dokainish H et al., on behalf of the INTER-CHF Investigators

Summary: The INTER-CHF study prospectively enrolled 5813 consecutive ambulatory or hospitalised patients with HF (26% with HFPEF), including 1294 patients from Africa, 2661 from Asia, 1000 from the Middle-East and 858 from South America. Compared with patients from other regions, those from Africa, followed closely by those from Asia, were younger, had lower literacy levels and were less likely to have health or medication insurance or be receiving β-blockers, and were most likely to be NYHA class 4. South American patients were older, more literate, more likely to be insured and, along with those from the Middle East, more likely to be β-blocker recipients, and had the lowest proportion in NYHA class 4. The most common aetiology of HF was ischaemic heart disease among patients from all regions, with the exception of Africa where hypertensive heart disease was the most common aetiology.

Comment: This is the largest study to date comparing characteristics of HF patients across Africa, Asia, the Middle East and South America, with a specific focus on countries that have been under-represented in previous epidemiological studies. The young age, low literacy rates and low β-blocker prescription rates in Africa compared with other regions stand out. The particularly high rates of obesity and diabetes in the Middle East are also noteworthy. Furthermore, these data suggest epidemiological transition in Africa and Asia, with an increasing proportion of cases due to ischaemic heart disease compared with previous registries, which suggests that the full health and economic burden of HF is yet to be realised.

Reference: Int J Cardiol 2016;204:133–41

Abstract

Randomized trial of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with non-ischaemic dilated cardiomyopathy

Authors: Hamshere S et al.

Summary: The phase 2 REGENERATE-DCM trial randomised 60 patients with dilated cardiomyopathy with no secondary cause (LVEF ≤45%, NYHA class ≥2) to receive peripheral G-CSF, G-CSF plus intracoronary serum, G-CSF plus intracoronary bone marrow-derived cells or placebo. G-CSF was administered for 5 days, and in the intracoronary arms this was followed by bone marrow-derived cells or serum on day 6. Participants in the peripheral G-CSF with intracoronary bone marrow-derived cell therapy arm had an increase in LVEF from 32.93% to 38.30% at 3 months (primary endpoint; p=0.0136), and this was maintained out to 1 year; there were also associated decreases in NYHA classification and NT-proBNP level and improvements in exercise capacity and quality of life. There were no significant changes in LVEF in the other groups.

Comment: The majority of studies evaluating the safety and efficacy of cell therapy in the setting of LV dysfunction have been conducted in patients with ischaemic heart disease, with variable results reported. This is the first randomised, placebo-controlled study evaluating the combination of cytokines (G-CSF) and cell therapy (intracoronary autologous bone marrow-derived cells) in the setting of dilated cardiomyopathy.

The study achieved its primary endpoint with a greater improvement in LVEF at 3 months, which was maintained for 1 year. This was accompanied by improvements in symptoms, exercise capacity and NT-proBNP reduction. Whilst these results are promising, they need to be confirmed in phase 3 studies powered for hard clinical outcomes.

Reference: Eur Heart J 2015;36(44):3061–9

Abstract

Adding point of care ultrasound to assess volume status in heart failure patients in a nurse-led outpatient clinic

Authors: Gundersen GH et al.

Summary: This research included 62 outpatients with HF who underwent laboratory testing, history recording and clinical examination by two nurses with and without an ultrasound examination of the pleural cavities and IVC (inferior vena cava) in random order. Diuretic dosing differed between the groups for 31/119 consultations, and dose adjustments at follow-up were predicted by weight change and volume status assessed clinically with and without ultrasound (p<0.05), but changes in oedema, NT-proBNP level, creatinine level and symptoms were not. Adjusted analyses showed that only volume status based on ultrasound was a significant predictor of diuretic dose adjustment at first visit and follow-up.

Comment: This group have previously demonstrated high agreement between nurse- and cardiologist-performed ultrasound evaluation of the IVC and pleural cavities. In this small study, they demonstrated that the presence of a pleural effusion or a dilated IVC with reduced collapsibility was associated with higher 2-year mortality. Furthermore, this led to changes in management with nurse-performed, point-of-care ultrasound estimation of volume status being a better predictor of diuretic dose adjustment than other clinical measures (including change in BNP levels). This implies that the treating clinicians placed more weight on the ultrasound findings. Future studies will need to determine whether this leads to better health outcomes.


Abstract

Prognostic value of NT-proBNP in heart failure with preserved versus reduced EF

Authors: Kang S-H et al., on behalf of the KorHF Registry

Summary: These researchers evaluated NT-proBNP levels in a prospective cohort of consecutive patients hospitalised for acute HF syndrome, including 528 with LVEF ≤50% (HFPEF; n=528) and LVEF ≤40% (HFREF; n=1142). Compared with patients with HFREF, those with HFPEF had a significantly lower median NT-proBNP level (2723 vs. 5644 ng/L [p<0.001]), but there was no between-group difference for death from any cause (88.4% vs. 86.9%, p=0.471) or the composite of death or HF readmission at 1 year (73.8% vs. 70.6%, p=0.225). Although a significant association was seen between high NT-proBNP level and poor outcomes, there was no significant difference between patients with HFPEF versus HFREF.

Reference: Heart 2015;101(23):1881–8

Abstract

Fibroblast growth factor 23 is an independent and specific predictor of mortality in patients with heart failure and reduced ejection fraction

Authors: Koller L et al.

Summary: The prognostic impact of FGF-23 on HF mortality was assessed in 511 study participants with HFREF and 469 with HFPEF followed for a median 8.6 years and a second cohort of 320 patients with advanced HFREF. Participants with HFREF showed a significant independent association between each standard deviation increase in FGF-23 level and mortality (adjusted hazard ratio 1.30 [95% CI 1.14–1.48]), which was confirmed on external validation (1.23 [1.02–1.60]), but no such association was evident in patients with HFPEF (p=0.043 for interaction). FGF-23 level provided increased discriminatory power for mortality in addition to NT-proBNP level (C-statistic 0.59 vs. 0.63) and a 39.6% improvement in the net reclassification index (p<0.001).


Abstract

Comment: The independent prognostic utility of NT-proBNP in HF is well established. Kang et al. confirmed in an acute HF cohort that this applies whether the LVEF is reduced or preserved. Furthermore, despite the patients with acute HFPEF having lower NT-proBNP levels than the patients with HFREF, their 12-month mortalities were similar. Conversely, Koller et al. reported that FGF-23 was independently associated with increased mortality in HFREF, but not in HFPEF, with modest additional discriminatory power and individual risk stratification over NT-proBNP level. Whilst it is likely that combined biomarker panels will soon allow better risk prediction, future studies will need to establish whether this has any clinical utility.

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 SA2 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.
In post-MI heart failure protection comes as standard

† In patients with heart failure and left ventricular impairment within 3–14 days of acute myocardial infarction, in combination with standard therapy.

PBS Information: Authority required (STREAMLINED - 2637).
Refer to PBS Schedule for full authority information.

BEFORE PRESCRIBING, PLEASE REVIEW FULL PRODUCT INFORMATION AT www.pfizer.com.au

INSPIRA® (eplerenone) 25 mg and 50 mg Tablets. Indications: Risk reduction of CV death in combination with standard therapy in patients with evidence of heart failure and left ventricular impairment within 3–14 days of an acute myocardial infarction; Risk reduction of CV mortality and morbidity in adults with NYHA Class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30% or LVEF ≤35% in addition to QRS duration of > 130 msec), in addition to standard optimal therapy.

Contraindications: Hypersensitivity to eplerenone or any of the excipients, clinically significant hyperkalaemia, chronic kidney disease stages 4 and 5*, severe hepatic insufficiency, co-administration of potassium-sparing diuretics or strong inhibitors of CYP3A4.

Precautions: Hyperkalaemia, chronic kidney disease, impaired hepatic function, pregnancy, lactation, paediatric use, use in elderly, driving and use of machinery*. See PI for details. Interactions with other Medicines: Inhibitors/inducers of CYP3A4; ACE inhibitors*; angiotensin receptor blockers*; thiazide, cyclopenthiazide, indapamide; beta-blockers; NSAIDs. See PI for details. Adverse Effects: Common - hyperkalaemia, myocardial infarction, diarrhoea, nausea, constipation*, infection*, dehydration*, musculoskeletal pain*, dizziness, hypotension, syncope*, renal impairment, cough*, pruritis*; Serious but not common - left sided cardiac failure, tachycardia*, hypothyroidism*, cholecystitis*, blood glucose increased*. Serious post-marketing: angioedema, rashes. See PI for details. Dosage and Administration: Initiate treatment at 25 mg once daily and titrate to the target dose of 50 mg once daily within 4 weeks, taking into account serum potassium levels. Patients with baseline eGFR 30–50 mL/min/1.73m2, initial dose should be 25mg every other day, titrated to maximum of 25 mg daily. Serum potassium should be measured before initiating and during INSPIRA therapy, particularly in patients with chronic kidney disease, and the dose adjusted as required*. See PI for details.

* Registered trademark. PFZ3700. P9858 03/15.

† Please note change(s) to Product Information.


Pfizer Australia Pty Ltd. 38-42 Wharf Road, West Ryde, NSW 2114.
Medical information 1800 675 229. www.pfizer.com.au

© Registered trademark. PFZ3700. P9858 03/15.
Restoration of pulsatile flow reduces sympathetic nerve activity among individuals with continuous-flow left ventricular assist devices

Authors: Cornwell WK III et al.

Summary: This research conducted in ten men and three women with continuous-flow LVADs sought to determine if restoring pulsatile flow via pump speed modulation would reduce muscle sympathetic nerve activity through the arterial baroreceptor reflex. Steady-state responses of beat-to-beat BP, carotid ultrasonography at the level of the arterial baroreceptors and muscle sympathetic nerve activity were recorded for stepped reductions in pump speed from 10,480 to 8500 revolutions per minute. Compared with high pump speed, low speed was associated with a significantly higher pulse pressure (26 vs. 17mm Hg [p<0.01]), significantly increased carotid artery distension and carotid arterial wall tension and decreased muscle sympathetic nerve activity (33 vs. 41 bursts per minute [p<0.01]), despite a reduction in mean arterial pressure; muscle sympathetic nerve activity was inversely related to pulse pressure (p=0.037).

Comment: This intriguing ‘back-to-the-future’ study utilised a cohort of patients with Heartmate II continuous axial-flow LVADs to confirm observations made in physiological experiments conducted in animals over two decades ago. The authors have previously reported that muscle sympathetic nerve activity is much higher in patients with continuous-flow LVADs compared with older generation pulsatile LVADs. By altering pump speed, they were able to induce pulsatile arterial flow, which resulted in a reduction in muscle sympathetic nerve activity, which the authors suggest is due to arterial baroreceptor-mediated inhibition of sympathetic outflow. Future studies will need to determine whether these findings are specific for axial-flow LVADs and the effect of longer term changes in pump speed on sympathetic outflow (perhaps estimated using total body noradrenaline [norepinephrine] spillover) and clinical outcomes.


Abstract

Fully magnetically levitated left ventricular assist system for treating advanced HF

Authors: Nötuka I et al.

Summary: The performance and safety of the HeartMate III LVAD was reported for 50 adults with EF ≤25%, cardiac index ≤2.2 L/min/m² without inotropes or inotrope-dependent on optimal medical management, or listed for transplant; indications for LVAD support were bridge to transplantation in 54% or destination therapy in 46%. Six-month outcomes included continued LVAD support in 88% of patients, transplantation in 4% and death in 8%, giving a 6-month survival rate of 92%, which exceeded the performance goal of 88%. Compared with the Seattle Heart Failure Model, mortality risk was reduced by 66% with the HeartMate III LVAD (p=0.0093), and steady-state reductions were seen for NIVH conditional means, 6-minute walk tests and quality of life scores. Reoperation for bleeding occurred in 14% of patients, atrioventricular infection in 10%, gastrointestinal bleeding in 8% and debilitating stroke in 8%; there were no pump exchanges, malfunctions or thromboses or haemolytic events.

Comment: This multicentre, international study describes the first-in-man study describes which HeartMate III LVADs. While the results are promising, further studies are needed to confirm the clinical benefits of this technology.

Reference: J Am Coll Cardiol 2015;66(23):2579–89

Abstract

Which heart failure patients profit from natriuretic peptide guided therapy?

Authors: Brunner-La Rocca H-P et al.

Summary: This was a meta-analysis of data from 1731 patients with HFREF versus 301 with HFPEF from eight randomised NT-proBNP guidance trials. Compared with symptom-guided therapy, NT-proBNP-guided therapy was associated with lower mortality risk and fewer HF admissions in patients with HFREF (respectively hazard ratios 0.78 [95% CI 0.62–0.97] and 0.80 [0.67–0.97], but not in patients with HFPEF (1.22 [0.76–1.96] and 1:01 [0.67–1.53]; p<0.02 for interactions). An interaction was seen between age and treatment strategy independent of EF for mortality (p=0.02) but not HF admission (p=0.54), with the age-mortality interaction explained by the interaction of treatment strategy allocation with comorbidities. Among comorbidities, the strongest interaction for treatment allocation was seen for renal failure (i.e. increased risk of NT-proBNP-guided therapy if present) in patients with HFPEF (p<0.01), whereas in patients with HFREF, the strongest interaction was seen for the presence of ≥2 comorbidities (i.e. NT-proBNP-guided therapy beneficial only if ≤1 of chronic obstructive pulmonary disease, diabetes, cardiovascular insult or peripheral vascular disease was present; p<0.01). In patients with HFPEF without hypertension, NT-proBNP-guided therapy was harmful (p=0.02).

Comment: The current patient data and other aggregate meta-analyses of RCTs have previously reported a mortality benefit and reduced HF hospitalisation in HF patients whose treatment was adjusted according to NT-proBNP levels. The current analysis seeks to clarify which patients are more likely to benefit. The benefit was mainly seen in HFREF, with no benefit in HFPEF. No survival benefit was seen in HFREF patients with ≥2 of four specific comorbidities (chronic obstructive pulmonary disease, diabetes, cerebrovascular accident/transient ischaemic attack or peripheral vascular disease), which largely explained why there was no mortality reduction in the elderly. Whilst this should be regarded as hypothesis-generating, the findings are biologically plausible given that the HFREF patients enrolled in the RCTs that informed our treatment guidelines were generally younger with fewer comorbidities than the real-world HF population.

Reference: Eur J Heart Fail 2015;17(12):1252–61

Abstract

Differential impact of body position on the severity of disordered breathing in heart failure patients with obstructive vs. central sleep apnoea

Authors: Pinna GD et al.

Summary: These researchers assessed and compared sleep position on sleep apnoea severity in patients with moderate-to-severe HF and systolic dysfunction who also had OSA (n=29) or CSA (n=91). Compared with the supine position, the lateral (right and left side combined) position was associated with a marked decrease in median AH1 (apnoea-hypopnoea index) in participants with OSA and CSA (10.4 vs. 50.3 and 19.3 vs. 47.4 events per hour, respectively), with the decrease significantly greater in participants with OSA (p=0.027); similar reductions were seen in oxygen desaturation and the apnoea ratio (p<0.0001). Positional sleep apnoea (>50% AH1 reduction between the supine and lateral positions) was more common among participants with OSA than CSA (76% vs. 53% [p=0.028]).

Comment: This study reports that a high proportion of both OSA (76%) and CSA (53%) are positional (based upon having a >50% reduction in AH1 in the lateral compared with the supine position) in a cohort of consecutive chronic HFREF patients. Whilst this finding is not unique for HF given the results of SERVE-HF (admittedly in a HFREF cohort with predominant CSA), it would seem reasonable to trial positional approaches (i.e. avoiding the supine sleeping position) in such patients.

Reference: Eur J Heart Fail 2015;17(12):1302–9

Abstract

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government dept., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists.
Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.

www.researchreview.com.au a RESEARCH REVIEW publication © 2016 RESEARCH REVIEW