Heart Failure Research Review™

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Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **AF** = atrial fibrillation; **ARB** = angiotensin receptor blocker; **ARNI** = angiotensin receptor neprilysin inhibitor; **CKD** = chronic kidney disease; **CRT/CRT-D** = cardiac resynchronisation therapy (with defibrillator); **CV** = cardiovascular; **EF/LVEF** = (left ventricular) ejection fraction; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **MRA** = mineralocorticoid receptor antagonist; **RAAS** = renin-angiotensin-aldosterone system; **SGLT** = sodium-glucose cotransporter; **SVC** = superior vena cava.

Welcome to issue 64 of Heart Failure Research Review.

This issue begins with the results of an analysis of the FIGARO-DKD trial demonstrating that finerenone was able to reduce new-onset HF and improve other HF outcomes in patients with CKD and type 2 diabetes regardless of HF history. This is followed by the long-term outcomes of the DANISH trial, which compared ICDs with usual clinical care in patients with nonischaemic systolic HF. In another analysis of trial data, this time from the EMPEROR-Reduced and EMPEROR-Preserved trials, the impact of the SGLT-2 inhibitor empagliflozin on HF outcomes was reported according to EF. The issue concludes with a propensity score-matched analysis of Japanese registry data assessing the time course of the renoprotective effect of tolvaptan in patients with acute decompensated HF.

We hope you enjoy this update in HF research, and we look forward to receiving comments and feedback.

Kind Regards,

Dr Mark Nolan
mark.nolan@researchreview.com.au

Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes

Authors: Filippatos G et al., on behalf of the FIGARO-DKD Investigators

Summary: This paper reported prespecified analyses of clinically important HF outcomes from the FIGARO-DKD trial, which investigated finerenone in patients with albuminuric CKD and type 2 diabetes. Of 7352 participants included in these analyses, 7.8% had a history of HF at baseline. Compared with placebo, finerenone recipients had a lower incidence of new-onset HF (1.9% vs. 2.8%; HR 0.68 [95% CI 0.50–0.93]). The incidences of all other HF outcomes analysed were also significantly lower among finerenone recipients compared with placebo recipients, including lower risks of CV-related death or first hospitalisation for HF (HR 0.82 [95% CI 0.70–0.95]), a first hospitalisation for HF (HR 0.71 [0.56–0.90]) and total hospitalisations for HF (rate ratio 0.70 [0.52–0.94]), without modification by HF history. The two groups were similar for treatment-emergent adverse events.

Comment: Finerenone is a nonsteroidal MRA, and is suggested to have higher selectivity for mineralocorticoid receptors than spironolactone, thus minimising noncardiac side effects with a more favourable heart:kidney distribution ratio, which explains the lower hyperkalaemia risk seen with finerenone in the ARTS trial. FIGARO-DKD demonstrated a 29% reduction in HF hospitalisation with finerenone compared with placebo in patients without symptomatic HFREF (i.e. stage A or B HF or HFPEF). This prespecified analysis confirms a 29% reduction in the novel outcome of hospitalisation for incident HF, and confirmed prior history of HF did not modify HF outcomes (p=0.81). This study further strengthens the case for using finerenone in stage A or B HF. Spironolactone has not to date been tested in this HF subpopulation. It may be reasonable to routinely measure urinary creatinine:albumin ratios for stage A and B HF and HFPEF patients to identify a potential cohort for when finerenone becomes available. At least one pharmaceutical company offers SGLT-2 inhibitor access through a product familiarisation scheme for CKD patients with UCR >23 mg/mmol; it is hoped that finerenone may one day also be similarly accessible.

Reference: Circulation 2022;145:437–47
Abstract

Heart Failure Research Review™

Independent commentary by Dr Mark Nolan

Mark Nolan is a Non-Invasive Cardiologist working at Western Health and the Peter Mac Cancer Centre in Melbourne, as well as a Post-Doctoral Researcher at the Baker Heart and Diabetes Institute. He has completed an Echocardiography Fellowship in Adelaide, Cardiac MRI and CT Fellowship in Toronto, and also a Cardio-Oncology Fellowship in Toronto. His PhD thesis examined the optimal use of cardiac imaging to guide treatment in cancer patients. He has first-author publications in Journal of American College of Cardiology: Cardiovascular Imaging, Journal of American College of Cardiology: CardioOncology and American Journal of Cardiology. His professional interests also include Cardio-Diabetology and Health Economics, and he has published in both of these fields. His recreational interests include bush walking in the Mornington Peninsula and reading about classical history. One of the things he likes most about medicine is the ability to both teach and learn.

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CHF patients aged ≥ 70 years deserve an age-proven β-blocker[1,2]

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*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 years[1,2]

CHF = Chronic Heart Failure

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

NEBILET (nebivolol hydrochloride) tablets 1.25mg, 5mg, 10mg. Indication(s): Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. **Dose and Method of Administration:** Once daily dosing, can be given with or without meals, consistent approach is recommended. Indication 1 - 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 should be monitored closely. Indication 2 - CHF: The initial up titration should be done gradually at 1-2 weekly 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 medical supervision for at least 2 hours. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 micromol/L) is not recommended. **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 weeks. If 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; hepatic insufficiency or impaired liver functions; severe renal insufficiency; children and adolescents; pregnancy (Cat C); lactation; driving vehicles or operating machines. See approved PI. **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 antiarrhythmics; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine. For other combinations requiring careful consideration, see approved PI. **Adverse effects:** Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, hypertension, atrial fibrillation, angina pectoris, dyspnoea, oedema, slowed AV conduction/AV-block, bronchospasm. Post-marketing reports of hypersensitivity, angioneurotic oedema, abnormal hepatic function, acute pulmonary oedema, acute renal failure, myocardial infarction, Raynaud's phenomenon, thrombocytopenia. See approved PI. [mPI Version 8.0]

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 follow-up of DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality)

Authors: Yafasova A et al.

Summary: Four-year follow-up data were reported for the DANISH trial, which randomised patients with nonischaemic systolic HF to implantation of an ICD (n=556) or usual clinical care (n=560). Over a median 9.5 years of follow-up, there was no significant difference between the ICD versus usual care arm for all-cause mortality (37% vs. 40%; HR 0.89 [95% CI 0.74–1.08]) or CV-related death (26% vs. 29%; 0.87 [0.70–1.09]); however, these rates were significantly lower in ICD recipients aged ≤70 years (30% vs. 36%; 0.78 [0.61–0.99] and 22% vs. 28%; 0.75 [0.57–0.98], respectively) but not those aged >70 years (54% vs. 57%; HR 0.92 [0.67–1.28] and 36% vs. 35%; 0.97 [0.65–1.45]). The incidence of sudden CV-related death was significantly lower in the ICD arm than in the control arm (6% vs. 10%; HR 0.60 [95% CI 0.40–0.92]), and remained lower in participants aged ≤70 years (5% vs. 11%; 0.42 [0.24–0.71]), but not those aged >70 years (10% vs. 7%; 1.34 [0.56–3.19]).

Comment: In 2016, the DANISH trial failed to demonstrate mortality benefit in 1116 nonischaemic cardiomyopathy patients with LVEF < 35% at follow-up of 5.6 years. This longer-term study extended follow-up to 9.5 years with 100% patient follow-up. Once again no significant difference in all-cause mortality or CV death was seen, although a 22% reduction in all-cause mortality in the <70-year-old subgroup was observed (p=0.04). This study confirms the long-term stability of DANISH results but leaves unanswered questions. The study was underpowered for subgroup analyses and marginal significance would not withstand Bonferroni correction. The choice of 70 years as a threshold appears arbitrary, and the use of a ROC curve to investigate the optimal age threshold may have been helpful. Higher prevalences of hypertension and AF and a lower rate of mineralocorticoid use were seen in the >70-year age group – a multivariate analysis to see if ICD use remained an independent predictor of mortality after correction of these variables would have been interesting. The issue of ICD use in nonischaemic cardiomyopathy remains vexing, and ideally further randomised controlled trials with biomarkers other than LVEF (e.g. global longitudinal strain) could be undertaken.

Reference: Circulation 2022;145:427–36
Abstract

Trends in heart failure hospitalizations in the US from 2008 to 2018

Authors: Clark KAA et al.

Summary: These researchers reported trends across 11,692,995 hospitalisations due to HF between 2008 and 2018 in the US. They noted an increase in such hospitalisations during this period from 1,060,540 to 1,270,360, along with a significant decrease in the median age of patients hospitalised due to HF (from 76.0 to 73.0 years [p<0.001]), significant increases in the proportions of Black and Hispanic patients, and significant increases in comorbid diabetes, sleep apnoea and obesity across the entire HF cohort as well as in the HFREF and HFPEF subgroups. Compared with patients admitted due to HFREF, those admitted for HFPEF were more likely to be white and older, and their associated costs were lower. There was an overall reduction in inpatient mortality (from 3.3% to 2.6%), which persisted in the HFPEF subgroup (from 2.4% to 2.1%) but not the HFREF subgroup (no change from 2.8%). Inflation-adjusted hospital costs decreased for HF overall and for the HFPEF and HFREF subgroups, while length of stay remained relatively stable.

Comment: This well-designed retrospective study of over 11 million US HF hospitalisations confirms that the demands HF places on healthcare systems continue to evolve. Absolute hospitalisation numbers increased from 2008 to 2018, despite therapeutic advances due to population ageing and growth. These numbers are possibly underestimates of true HF hospitalisations, as ICD-10 codes have been reported to be only 69% sensitive and 99% specific for HF diagnosis compared with chart reviewing. Of particular concern in this study is the increasingly younger age of HF inpatients, often in context of cardiometabolic disease. Despite the recent addition of several novel drug classes for HFREF treatment, mortality disappointingly remains stable. Our current challenge is to grow our HF hospital services to meet demand, advocate for life-prolonging quadruple therapy in all eligible patients, and aggressively treat comorbidities in stage A and B HF, especially in the young.

Reference: J Card Fail 2022;28:171–80
Abstract

Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction

Authors: Butler J et al.

Summary: Data were pooled from the EMPEROR-Reduced and EMPEROR-Preserved trials to evaluate the impact of EF on the effect of empagliflozin on HF outcomes. These trials included 4860 participants with HF randomised to receive empagliflozin and 4858 to placebo, stratified by EF as follows: <25% (n=999), 25–34% (n=2230), 35–44% (n=1272), 45–54% (n=2260), 55–64% (n=2092) and ≥65% (n=865). CV-related mortality and HF hospitalisation rates declined progressively as EF increased, and empagliflozin reduced the risks of both these outcomes (mainly the latter). The reduced risk of HF hospitalisation with empagliflozin was ~30% across EF subgroups, but the effect was attenuated for EFs ≥65% (HRs 0.73 [95% CI 0.55–0.96], 0.63 [0.50–0.78], 0.72 [0.52–0.98], 0.66 [0.50–0.86], 0.70 [0.53–0.92] and 1.05 [0.70–1.58] for EFs <25%, 25–34%, 35–44%, 45–54%, 55–64% and ≥65%, respectively). Response patterns were similar for other HF outcomes and measures, including Kansas City Cardiomyopathy Questionnaire scores. The response to empagliflozin was not modified by sex.

Comment: The SGLT-2 inhibitor class has been an unexpected success story in CV medicine, and empagliflozin is to date the only agent demonstrated to change disease trajectory in HFPEF patients. This pooled analysis of 9718 patients in the EMPEROR-Reduced and EMPEROR-Preserved trials showed that empagliflozin benefits remained remarkedly consistent across the spectrum of LVEF values, with the exception of the LVEF >65% subgroup where little benefit was seen. No inter-gender difference was observed. One limitation is the relatively short follow-up of 21 months, which may underpower outcomes such as all-cause mortality. For comparison, the SOLVD study of enalapril in HFREF had follow-up of 41 months. This study supports the concept of using empagliflozin for HF regardless of LVEF value or gender. Optimal treatment of the LVEF >65% subgroup requires further study, and it is possible that this subgroup may contain a high proportion of undiagnosed infiltrative and genetic cardiomyopathies, which could influence treatment response. These findings suggest that LVEF should not limit access to SGLT-2 inhibitor treatment.

Reference: Eur Heart J 2022;43:416–26
Abstract

Treatment persistence of renin-angiotensin-aldosterone-system inhibitors over time in heart failure with reduced ejection fraction

Authors: Vaduganathan M et al.

Summary: The frequency and independent predictors of treatment discontinuation were reported for new users of ACE inhibitors/ARBs (n=3509), ARNIs (n=1352) or MRAs (n=2129) entered in the CHAMP-HF registry. Over a median 18 months of follow-up, ACE inhibitor/ARB, ARNI and MRA discontinuation rates were 12.7%, 10.4% and 20.4%, respectively, and 11.0% of ARNI users switched to ACE inhibitors/ARBs, and 12.7% of ACE inhibitor/ARB users switched to ARNIs. The only factor significantly independently associated with a higher likelihood of RAAS inhibitor discontinuation was CKD. A higher Kansas City Cardiomyopathy Questionnaire overall summary score was a significant independent predictor of lower risk of discontinuation for ACE inhibitors/ARBs and ARNIs but not MRAs, whereas investigator clinical experience was a significant predictor of lower ACE inhibitor/ARB and MRA discontinuation risk but not ARNI discontinuation risk. All other independent discontinuation predictors were unique to individual classes.

Comment: The life-prolonging benefits of foundational HF therapies are incontrovertible. Despite this, there remains a gap between optimal HF pharmaceutical treatment and what is achieved in the community. This CHAMP-HF registry analysis confirms this by showing that by 18 months, 13% of HFREF patients had discontinued their ACE inhibitor or ARB agents, 10% had ceased their ARNI and 20% had ceased MRA agents. The rationale is unclear, although reduced renal function was a predictive factor. There was no significant difference in potassium levels between patients who continued and those who ceased. As CHAMP-HF entry required patient consent, it is possible that selection bias may have recruited patients less likely to discontinue, and true community discontinuation rates could be different. This study supports the need to provide patient monitoring, education and support throughout their HF journey to prevent nonindicated discontinuation by patients. Physicians should also be mindful of the risks of 'renalism', which is defined as underutilisation of beneficial therapies in kidney disease patients out of concerns (usually unsupported) of doing harm.

Reference: J Card Fail 2022;28:191–201
Abstract

Intermittent occlusion of the superior vena cava to improve hemodynamics in patients with acutely decompensated heart failure

Authors: Kapur NK et al.

Summary: Thirty patients with acutely decompensated HF were assigned to intermittent occlusion of the SVC with the preCARDIA system for 12 or 24 hours in the VENUS-HF early feasibility study. No participant experienced a device- or procedure-related major adverse event, and all but one had successful placement, activation and removal of the system after 12 (n=6) or 24 hours (n=23). Right atrial pressure decreased significantly from baseline by 34%, and pulmonary capillary wedge pressure decreased significantly by 27%, whereas urinary output and net fluid balance increased significantly by 130% and 156%, respectively, with ≥24 hours of treatment.

Comment: This thought-provoking phase 1 study showcased a first-in-human technique of using intermittent SVC occlusion to treat acute decompensated HFREF. Thirty patients with mean LVEF 28% and mean pulmonary wedge pressure of 31mm Hg had a balloon placed in the SVC. The balloon was periodically inflated for 5 minutes and deflated for 30 seconds over 12 hours. This could be done without compromising preload, as SVC return represents only 30% of total venous return. System placement showed 100% feasibility with only two minor side effects: facial flushing in one patient and a small haematoma in another. Anticoagulation was required. Substantial changes from baseline in cardiac pressures were seen, although there was no comparator class. Potential mechanisms of benefit could be increased transrenal flow due to reduced renal venous pressure, and it would be interesting to know if the creatinine level changed. Given the current dearth of effective treatments for acute decompensated HFREF beyond diuretics, it will be interesting to see the phase 2 results of this novel intervention.

Reference: Circ Heart Fail 2022;15:e008934
Abstract

Complications and mortality following CRT-D versus ICD implants in older Medicare beneficiaries with heart failure

Authors: Zeitler EP et al.

Summary: The comparative effectiveness of CRT-D versus ICD alone implantation was evaluated in US Medicare patients aged ≥65 years with HFREF. Compared with ICDs alone, patients with a CRT-D were older and more likely to be White, female and have left-bundle-branch block. Complications were 14–20% across age subgroups (65–74, 75–84 and ≥85 years) and the device groups, and all (sub)groups had a high 1-year mortality rate. Compared with ICDs only, CRT-Ds were associated with lower likelihoods of death in the 75- to 84-year and ≥85-year age groups (respective HRs 0.90 [95% CI 0.86–0.95] and 0.81 [0.72–0.90]) and hospitalisation for HF in the ≥85-year age group (0.82 [0.74–0.92]).

Comment: The benefits of CRT have largely been extrapolated from large randomised controlled trials to elderly populations, which have been under-represented in these trials. This real-world assessment of patients aged ≥65 years found that patients treated with CRT-D had lower 12-month mortality rates and HF rehospitalisations compared with patients treated with ICDs alone. All patients had at least one prior HF hospitalisation, so this represented a reasonably high-risk subgroup, supported by the finding of 18% 12-month mortality in the 65- to 74-year-old group and 33% 12-month mortality in the >85-year-old group. This was a nonrandomised study, so confounding variables may account at least in part for observed differences. Patients without left-bundle-branch-block were included. Patient-level data were missing that might account or exclude confounders. Although this registry study has limitations, it does offer support that age alone need not exclude patients from receiving the benefits of CRT implantation.

Reference: JACC Heart Fail 2022;10:147–57
Abstract

Risk and predictors of heart failure in sarcoidosis in a population-based cohort study from Sweden

Authors: Rossides M et al

Summary: These researchers reported on risk factors for HF in 8574 Swedish registrants with sarcoidosis, with a first visit between 2006 and 2013, matched to 84,192 comparators from the general population. HF occurred at a higher rate among the patients with sarcoidosis than in the general population during follow-up (2.2 vs. 0.7 per 1000 person-years; HR 2.43 [95% CI 2.06–2.86]) with no variation by age, sex or treatment status, and greater likelihoods during the first 2 years after diagnosis (HR 3.7 vs. 1.9) and in individuals with no history of ischaemic heart disease (HR 2.7 vs. 1.7). The strongest independent clinical predictors of HF were diabetes and AF/other arrhythmias.

Comment: This Swedish national registry study followed patients with noncardiac sarcoidosis for 4.8 years. It reported that 2.4% of patients had developed HF by study end with an HR of 2.43 (95% CI 2.06–2.86) compared with the general population. Risk factors for HF in this population were similar to the general population and included ischemic heart disease, diabetes and AF. No information regarding type of HF or presentation was available. Information of anti-inflammatory treatments that could contribute to HF, e.g. infliximab, was not available. The finding that any arrhythmia predisposes to HF in sarcoidosis patients raises the question of whether some patients had unrecognised cardiac sarcoidosis at study entry with later development of the HF phenotype. The Heart Rhythm Society 2014 guidelines recommend screening noncardiac sarcoidosis patients annually, with history, physical examination and ECG, with echocardiography reserved for select cases. This paper raises the possibility that routine echo screening of sarcoidosis patients may be beneficial.

Reference: Heart 2022;108:467–73
Abstract

Temporal change in renoprotective effect of tolvaptan on patients with heart failure

Authors: Nishino M et al.

Summary: The time course of the renoprotective effect of tolvaptan and prognoses were reported for registrants (AURORA; n=911) with acute decompensated HF; 58 patients who had initiated tolvaptan ≥2 days after hospitalisation were propensity score matched with 58 who had not. Compared with patients who did not start tolvaptan after hospitalisation, those who did experienced significantly greater changes in creatinine level and estimated glomerular filtration rate 5 days after admission, with the between-group differences gradually diminishing thereafter. The 1-year survival and rehospitalisation rates were similar between the tolvaptan recipients and nonrecipients.

Comment: The clinical significance of worsening renal function in the context of decongestion of acute decompensated HF is uncertain, with several studies suggesting it counterintuitively portends an improved prognosis. However, it likely leads to under-zealous diuretic treatment, with up to half of acute decompensated HF patients remaining congested at time of discharge. Tolvaptan, an aquaretic drug that blocks vasopressin-2 receptors, failed to reduce mortality in the EVEREST trial, although it did cause short-term improvements in dyspnoea, weight loss and oedema. This Japanese propensity-matched observational study showed reduced rates of worsening renal function in tolvaptan-treated patients (17% vs. 38%) with no difference in hard outcomes of mortality or rehospitalisation. It is unclear whether the reduction in worsening renal function with tolvaptan represents prevention of acute kidney injury or alteration in glomerular haemodynamics. Limitations of this study include the nonrandomised nature, small patient numbers, short follow-up and lack of ancillary data that would tease out the mechanism of creatinine alterations, such as NGAL (neutrophil gelatinase-associated lipocalin) screening for acute kidney injury. To date, no long-term benefit of vasopressin antagonists has been demonstrated in HF.

Reference: J Clin Med 2022;11:977
Abstract