Heart Failure Research Review™

Making Education Easy

Issue 63 - 2022

In this issue:

Abbreviations used in this issue:

6MWD = 6-minute walk distance; **ACE** = angiotensin converting enzyme; **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **CV** = cardiovascular; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **KCCQ** = Kansas City Cardiomyopathy Questionnaire; **LV** = left ventricular; **MI** = myocardial infarction; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide.

Welcome to issue 63 of Heart Failure Research Review.

This issue begins with research reporting the effectiveness and safety of starting real-world patients hospitalised for acute HF on sacubitril/valsartan therapy, followed by an evaluation of the effect of this treatment on NT-proBNP levels, 6MWD and quality of life, when compared with background medication-based individualised comparators, in patients with chronic HF with an LVEF of >40%. A simple score for predicting frailty in hospitalised patients with HF has also been described, as have their rehospitalisation and mortality rates. There are two papers reporting on temporal trends in HF, one from the US and the other from New Zealand. The issue concludes with research reporting benefits of metformin, but not sulfonylureas, for 12-month clinical outcomes in patients with comorbid HF and diabetes.

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

Kind Regards,

Professor Andrew Coats
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Clinical outcomes of sacubitril/valsartan in patients with acute heart failure

Authors: Chen D-Y et al.

Summary: These researchers reported on initiating sacubitril/valsartan compared with ACE inhibitors or ARBs for 3766 patients hospitalised for acute HF. Compared with ACE inhibitors/ARBs, a smaller proportion of sacubitril/valsartan recipients experienced rehospitalisation for HF or death over a mean 11.8 months of follow-up (22.9% vs. 32.6%; HR 0.71 [95% CI 0.52–0.97]), with lower risks of both these outcomes assessed individually (respective sub-HRs 0.83 [0.74–0.92] and 0.51 [0.27–0.94]) and no significant difference for worsening renal function or severe hyperkalaemia.

Comment: Recent guidelines have recommended sacubitril/valsartan as being superior to ACE inhibitors in patients with chronic HFREF. This is been supplemented in some guidelines with a similar or slightly weakened recommendation for initial treatment with sacubitril/valsartan in new-onset HFREF. In addition, the safety and efficacy of commencing to sacubitril/valsartan during an admission for acute HF has not been determined by any major clinical outcome trial, but has been evaluated in a moderate-size mechanistic trial – Prove-HF. This large well conducted registry analysis from Taiwan suggests that the acute initiation of sacubitril/valsartan during an acute hospital admission for HF is associated with fewer subsequent HF hospitalisations or deaths. Whilst there is always the possibility of unexpected confounding factors in such analyses even after propensity matching, the large scale and detail of this study is very reassuring that major outcomes are improved without any extra adverse risk of significant renal impairment or hyperkalaemia, with the strategy of initiating sacubitril/valsartan in preference to ACE inhibitors or ARBs during an admission for acute HF.

Reference: EClinicalMedicine 2021;41:101149
Abstract

Independent commentary by Professor Andrew Coats

Andrew was born and schooled in Melbourne and studied medicine at Oxford and Cambridge. He has more than 110,000 citations, and an H-index of 141. He served as Editor-in-Chief of the International Journal of Cardiology from 1999 to 2016. Andrew published the first randomised trial of exercise training for CHF. Andrew has been Chairman or Committee member of multiple major clinical trials. He has served as Head of Cardiology at Imperial College and Royal Brompton Hospital, London, as Dean of Medicine and Deputy Vice-President at the University of Sydney, and as Joint Academic Vice-President of the University of Warwick, UK, and Monash University, Australia. He is presently President of the Heart Failure Association of the ESC.

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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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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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Effect of sacubitril/valsartan vs standard medical therapies on plasma NT-proBNP concentration and submaximal exercise capacity in patients with heart failure and preserved ejection fraction

Authors: Pieske B et al., for the PARALLAX Investigators and Committee members

Summary: The PARALLAX trial randomised patients with HFPEF (LVEF >40%) to receive sacubitril/valsartan (n=1286) or to a background medication-based individualised comparator control arm (n=1286); 87.1% of enrolled participants completed the trial. Compared with the control group, sacubitril/valsartan recipients achieved a greater reduction in NT-proBNP level by week 12 (adjusted geometric mean ratio 0.84 [p<0.001]), with no significant difference at week 24 for median change from baseline in 6MWD, mean change in the KCCQ clinical summary score or improvement in New York Heart Association class. The most frequent adverse events were hypotension (14.1% and 5.5% in the sacubitril/valsartan and control arms, respectively), albuminuria (12.3% and 7.6%) and hyperkalaemia (11.6% and 10.9%).

Comment: Sacubitril/valsartan has been a major advance in the treatment of many HF syndromes. The landmark PARADIGM–HF trial showed the benefit of sacubitril/valsartan in the treatment of HFREF, but subsequent trials in other HF syndromes unfortunately just fell short of statistical significance. These were two important trials – PARAGON-HF for the treatment of HFPEF and PARADISE-MI for the treatment of post-MI LV dysfunction. Thus any further evidence of the benefits of sacubitril/valsartan in other HF syndromes is of major interest. The PARALLAX trial was a large (n=2572) trial with two primary endpoints – NT-proBNP level reduction at 12 weeks and 6MWD at 24 weeks – in HF patients with a LVEF >40% therefore covering the HF with moderately reduced EF and HFPEF groups. It evaluated sacubitril/valsartan compared with whatever form of RAAS (renin-angiotensin-aldosterone system) inhibitor the patients were on prior to the trial, either an ACE inhibitor, an ARB or in a minority, no RAAS inhibitor. The NT-proBNP level was reduced significantly more by sacubitril/valsartan than comparator, but 6MWD showed no difference. In secondary endpoints there was no difference in KCCQ, but the trial did suggest the possibility of a lower rate of decline in estimated GFR slope, even though the adverse event of hyperkalaemia was actually numerically higher at 11.6% compared with 10.9% on comparator, which partly conflicts with previous evidence of a lower risk of hyperkalaemia with sacubitril/valsartan. Clearly further trials are of particular importance for understanding the role of sacubitril/valsartan in the treatment of HFPEF.

Reference: JAMA 2021;326:1919–29
Abstract

A simple risk score based on routine clinical parameters can predict frailty in hospitalized heart failure patients

Authors: Kałużna-Oleksy M et al.

Summary: These researchers developed a simple tool that used routine clinical parameters for predicting frailty in patients hospitalised for HF. The tool was developed using data from 153 hospitalised patients with HFREF in whom frailty syndrome was assessed using the SHARE-FI questionnaire and clinical and biochemical parameters were collected. The resultant proposed model included the following five variables with cutoff values, with one point assigned for each: age >50 years, systolic BP on admission <110mm Hg, total cholesterol level <4.85 mmol/L, bilirubin level ≥15.5 mmol/L and ALT level ≤34 U/L. A score of five points was considered high risk for frailty syndrome, with respective positive and negative predictive values of 83% and 72% and specificity of 97%. Frailty syndrome could be excluded by a score of ≤2 with a negative predictive value of 94%.

Comment: There is increasing interest in the concept of frailty in HF populations. The Fried analysis has become the standard for the assessment of frailty, but it requires assessment of five areas against population norms, and that is difficult to apply retrospectively to clinically acquired datasets. These include weight loss (subjective or objective), exhaustion (subjective), grip strength (objective), walking speed (subjective or objective) and physical activity (subjective). Many people have attempted to develop an HF-specific frailty assessment protocol or questionnaire. Ultimately frailty covers more than physical parameters, but rather includes psychosocial and comorbidity factors that are not easy to capture from routinely acquired clinical notes. Thus this paper that assessed a simple way to score hospitalised HF patients for the likelihood of formally defined frailty is of interest. It suggests that a model of five variables including age, systolic BP and cholesterol, bilirubin and ALT levels can be used as a reasonable screening test for the assessment of the likelihood of frailty. If the screening test suggests a reasonable probability, formal frailty can be assessed.

Reference: J Clin Med 2021;10:5963
Abstract

Clinical risk prediction model for 30-day all-cause re-hospitalisation or mortality in patients hospitalised with heart failure

Authors: Driscoll A et al.

Summary: Analysis of individual-level data pooled from two cohort studies in patients with acute HF followed for 30 days after discharge from hospitals in Victoria (n=1380) identified 58 candidate predictors, often recorded in electronic medical records, of 30-day rehospitalisation, from which ten were included in a risk prediction model. These included two available on admission, namely estimated GFR and prescription of anticoagulants and thiazide diuretics, and eight available at discharge, namely length of stay >3 days, systolic BP, heart rate, sodium level <135 mmol/L, >10 prescribed medications and prescription of ACE inhibitors, ARBs or anticoagulants. The model was found to have moderate discrimination (C-statistic 0.684; optimism estimate 0.062) and good calibration.

Comment: Multiple risk models have been developed for HF. Some are in regular use, and others are restricted to clinical trials or detailed registry analysis only. It is interesting to note this Australian study looks at a contemporary risk model in patients following an admission for HF from Victorian hospitals. It evaluated clinical parameters routinely collected and showed that of 58 candidates, the ten most important variables were mainly ones that we may have predicted such as estimated GFR, length of stay, BP, heart rate, serum sodium level and the use of certain medications. Such a simple model would be used to evaluate the risk profile at a population level to direct follow-up resources in a more targeted fashion.

Reference: Int J Cardiol 2022;350:69–76
Abstract

Trends in hospitalizations for heart failure, acute myocardial infarction, and stroke in the United States from 2004 to 2018

Authors: Salah HM et al.

Summary: Trends in US hospitalisations for HF, acute MI and stroke were reported in this retrospective study. Data on 33.4 million hospitalisations among adults with a primary discharge diagnosis of HF (48%), acute MI or stroke showed that after an initial decline from 5.3 to 4.0 HF hospitalisations per 1000 between 2004 and 2013 (p<0.001), they progressively increased to 4.9 per 1000 in 2018 (p<0.001). Hospitalisations for acute MI decreased from 3.1 to 2.5 per 1000 between 2004 and 2010 (p<0.001) and remained stable thereafter out to 2018. Hospitalisations for stroke were the same in 2004 and 2011 (2.3 per 1000), after which there was a small, significant increase to 2.5 per 1000 in 2018. After adjustments, length of stay and in-hospital mortality declined for HF, acute MI and stroke hospitalisations over the evaluation period.

Comment: Those of us who read many HF manuscripts are struck by the sometimes conflicting summaries of the population trends of HF. Most quote an increased prevalence of HF as the populations of the world age, particularly in the realm of HFPEF. However, estimates of the incidence of HFREF in younger populations are sometimes conflicting. Thus this very large analysis of the National Inpatient Sample of the US is of particular interest. It evaluated over 30 million hospitalisations subdivided into HF, which formed nearly half, and acute MI and stroke. In contrast to the other two CV conditions, the incidence of HF hospitalisation showed varying trends over time. HF hospitalisations significantly decreased from 2004 to 2013 by nearly 25%, but thereafter (2013–2018) showed a subsequent increase of nearly the same magnitude. Thus the temporal trends in heart for the hospitalisation as a healthcare burden are complicated and likely to increase in the next decade.

Reference: Am Heart J 2022;243:103–9
Abstract

Contrasting trends in heart failure incidence in younger and older New Zealanders, 2006–2018

Authors: Chan DZL et al.

Summary: Age-specific trends in HF incidence in New Zealand were reported in this research, which included 116,113 incident HF hospitalisations recorded during 2006–2018. There was a significant decrease in the age-standardised incidence of HF from 403 to 323 per 100,000 between 2006 and 2013, after which it plateaued out to 2018. Analyses by age range revealed that for individuals aged 20–49 years, the HF rate increased by 1.5% per year, whereas it decreased in individuals aged ≥80 years by 1.2% per year. For the 50- to 79-year age group, the HF rate initially declined between 2006 and 2013, and then remained stable or increased over the 2013–2018 period. There was a decrease in the proportion of HF hospitalisations associated with ischaemic heart disease from 35.1% to 28.0% over the entire evaluation period.

Comment: Similarly to the US National Inpatient Survey study just quoted previously, this report from New Zealand shows similar if not identical trends, but extends the data to age-standardised rates. Using age-standardised data from a national data linkage study, the authors reported that the rate of HF hospitalisation in patients aged between 20 and 49 years old increased by 1.5% per year between 2006 and 2018, but it decreased in those aged over 80 years by 1.2% per year. Rates in the middle-age band of 50 to 79 years initially declined and then remained stable. Interestingly, the proportion of HF hospitalisations associated with ischaemic heart disease (most notably associated with younger patients) decreased from 35% to 28%. Thus we are seeing an increase in the burden of HF, but the demographics and clinical features of admitted patients has not been stable.

Reference: Heart 2022;108:300–6
Abstract

Clinical outcomes with metformin and sulfonylurea therapies among patients with heart failure and diabetes

Authors: Khan MS et al.

Summary: The impact of metformin and sulfonylurea agents on the clinical outcomes of patients with comorbid HF and diabetes was explored in US Medicare beneficiaries hospitalised for HF between 2006 and 2014. The 5852 patients had not been prescribed metformin or a sulfonylurea prior to admission, with 454 (7.8%) and 504 (8.6%) newly prescribed metformin and a sulfonylurea, respectively, within 90 days of discharge, with the remainder prescribed neither. Patients prescribed metformin had an independent reduction in the risk of the composite endpoint of death or hospitalisation for HF (adjusted HR 0.81 [95% CI 0.67–0.98]); although the endpoint's individual components were not statistically significant overall, patients with an EF >40% had lower risks of the composite endpoint (0.68 [0.52–0.90]) and also for hospitalisation for HF (0.58 [0.40–0.85]; p≤0.04 for interaction). In contrast, patients who started a sulfonylurea had increased risks of mortality (HR 1.24 [95% CI 1.00–1.52]) and hospitalisation for HF (1.22 [1.00–1.48]), with the associations consistent regardless of EF. Neither metformin nor sulfonylurea initiation were associated with negative control endpoints (namely, hospitalisation for urinary tract infection, hospitalisation for gastrointestinal haemorrhage and influenza vaccination).

Comment: The treatment of type two diabetes mellitus has changed quite significantly over the last 5–10 years. In the past, the major treatment aim was to normalise glucose control with increasing efforts to find drugs that are effective at reducing HbA_{1c} level. The finding of an unexpected series of adverse outcomes associated with some treatments, in particular thiazolidinediones (glitazones), led to regulatory authorities requiring large CV outcome trials to be conducted for any new hypoglycaemic agent. Whilst this was seen initially as a safety feature to identify any new drug that would increase CV hazard, one such trial, the EMPA-REG outcome trial, suggested a significant benefit including a reduction in CV-related mortality with empagliflozin. Subsequent trials of this drug class, the SGLT-2 (sodium glucose cotransporter-2) inhibitors, showed a consistent benefit in reducing the risk of HF in patients with type 2 diabetes and increased CV risk, or with established CV disease, along with efficacy as a treatment for HF itself. What we don't have however are similar trials for established agents, because there is no commercial interest in funding such trials. Therefore comparing the CV safety and efficacy of older agents requires different approaches. This report is one such, looking at US HF registry data coupled with Medicare data, and looking at real-world evidence of two older drug classes – metformin and sulfonylureas. With all the caveats about the possible confounding factors inherent in such studies, it does suggest a clear preference for metformin over a sulfonylurea for both mortality and the risk of HF hospitalisation when treating type 2 diabetes in the setting of HF.

Reference: JACC Heart Fail; Published online Dec 8, 2021
Abstract