Welcome to issue 34 of Heart Failure Research Review.

This issue begins with a systematic overview of the effect of DPP (dipeptidyl peptidase)-4 inhibitors on HF risk in patients with type 2 diabetes, which remains uncertain. Researchers from Hong Kong demonstrated that CCM (cardiac contractility modulation) associated with improved survival in patients with HF, especially those with LVEF 25–40%. This is followed by an analysis of TOPCAT trial data reporting variation in participant characteristics and outcomes according to LVEF, although the efficacy of spironolactone appeared to be at its best in the lower end of the LVEF spectrum. To conclude this issue, researchers report on the feasibility and prognostic value of frailty assessments in patients with advanced HF.

I hope you enjoy reading this issue’s selection, and that you find the comments helpful.

Kind Regards,

Dr. John Atherton
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Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes

Authors: Li L et al.

Summary: This was a systematic review and meta-analysis of 43 trials (n=6775) and 12 observational studies (n=1777,358) comparing DPP-4 inhibitors against placebo in adults with type 2 diabetes and reporting HF outcomes. Data pooled from 38 trials reported with low-quality evidence that compared with controls, DPP-4 inhibitor users had a similar risk of HF (odds ratio 0.97 [95% CI 0.61–1.56]); observational study data were generally in agreement, but with very low quality evidence. Data from five trials reporting HF admission showed with moderate quality evidence that DPP-4 inhibitor users had an increased risk of this outcome over controls (odds ratio 1.13 [95% CI 1.00–1.26]), and this was supported by adjusted estimates from observational studies, with very low quality evidence, in which DPP-4 inhibitor recipients were treated exclusively with sitagliptin (1.41 [0.95–2.09]).

Comment: This is the most rigorous systematic review to date to address whether DPP-4 inhibitors increase the risk of HF. This study suggests there may be an increased risk of HF hospitalisation in patients with type 2 diabetes who are at high CV risk; however, the effect size is small and overlaps with unity, and the signal in RCTs is largely driven by one study. Clinicians may consider this in their choice of glucose-lowering therapies in patients at high CV risk, especially with recent RCTs (EMPA-REG OUTCOME, LEADER) reporting beneficial effects on overall CV outcomes with other glucose-lowering therapies, namely sodium-glucose cotransporter 2 inhibition and glucagon-like peptide-1 receptor agonist treatment.

Reference: BMJ 2016;352:i610

Abstract
Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy

Authors: Abraham WT et al., for the CHAMPION Trial Study Group

Summary: This paper reported complete follow-up results from the CHAMPION RCT in which patients with NYHA class III HF symptoms and a previous admission to hospital had been randomised by centre in blocks sizes of four to either medical therapy either guided (n=270) or not (n=280) by pulmonary artery pressure. Compared with controls, participants who received pulmonary artery pressure guidance were less likely to require hospital admission for HF during an average 18 months of follow-up (HR: 0.67 [95% CI 0.55–0.80]). After the randomised treatment phase, 374 participants entered an extension phase in which pulmonary artery pressure guidance was available for everyone over an average of 13 months follow-up. The HF admission rate among former control participants decreased by 48% compared with the prior rate without pulmonary artery pressure guidance for this group (HR 0.52 [95% CI 0.40–0.69]). There were eight device- or system-related complications and seven procedure-related adverse events.

Comment: The CHAMPION study evaluated patients with NYHA class III HF. All patients received an implantable, wireless haemodynamic sensor, and were then randomised to an active treatment group (daily uploaded pulmonary artery pressure used to guide treatment) or a control group. The current study reports that the beneficial effect on HF hospitalisation was maintained over 18 months during the randomised phase, with similar benefits seen in patients in the former control group when the pulmonary artery pressures were made available to the treating investigator. Importantly, a reduction in all-cause hospitalisation was also seen. This suggests that in the context of organised HF programmes, the beneficial effects of pulmonary artery pressure monitoring may be realised in a ‘real-world’ setting.


Improvement of long-term survival by cardiac contractility modulation in heart failure patients

Authors: Liu M et al.

Summary: These researchers compared consecutive patients with HF with LVEF <40% treated with CCM with 41 matched control registry patients with HF; mean follow-up durations were 75 months and 69 months in the respective groups. Compared with controls, participants treated with CCM had a lower all-cause mortality rate (39% vs. 71% [p = 0.001]), with a greater difference in participants with EF ≥25–40% (36% vs. 80% [p<0.001]) than those with EF <25% (50% vs. 56% [p=0.05]). CCM was also associated with superior quality of care-related death and the composite outcome of death and HF hospitalisation. While there was no significant between-group difference overall for HF hospitalisation, this was lower in CCM recipients with EF ≥25–40% (36% vs. 64% [p = 0.005]).

Comment: There are limited treatment options for patients with persistent symptomatic HF with a reduced LVEF and a narrow QRS duration despite medical therapy. Previous RCTs evaluating CCM have reported improved symptoms, quality of life and exercise parameters up to 12 months, although the durability of this treatment effect is uncertain. The current study reports a survival benefit, which was seen over a longer term period. However, given the observational study design, one cannot exclude the possibility of residual confounding. Larger RCTs are required to confirm whether CCM decreases mortality and hospitalisation.

Reference: Int J Cardiol 2016;206:122–6

Heart Failure Research Review

Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction

Authors: Solomon SD et al., on behalf of the TOPCAT Investigators

Summary: This analysis of data from 3444 TOPCAT participants with HF with preserved EF (LVEF 44–85%) found that those with higher LVEFs were older, more likely to be female, less likely to have prior myocardial infarction and more likely to have prior hypertension or diabetes. Participants with lower LVEFs had a higher incidence of the primary endpoint (CV-related death, HF hospitalisation or aborted cardiac arrest) and CV-related death. The treatment effect of spironolactone in TOPCAT was modified by LVEF (particularly for participants from the Americas), with greater effects for LVEF <50% vs. ≥60% for the primary outcome (HR 0.72 [95% CI 0.50–1.05] vs. 0.97 [0.76–1.23]) and HF hospitalisation (0.76 [0.46–1.27] vs. 0.98 [0.74–1.30]).

Comment: The benefits of mineralocorticoid receptor antagonists have been clearly established in patients with HF associated with a reduced LVEF. However, spironolactone failed to achieve its primary endpoint in patients with HF associated with a preserved LVEF in the TOPCAT study. A prespecified, dichotomised, subgroup analysis showed no significant treatment effect with the underlying LVEF. However, the current post hoc analysis demonstrated a significant interaction when LVEF was treated as a continuous variable, and suggests that spironolactone may be beneficial in HF patients with an intermediate LVEF (LVEF 45–50%). Given the limited treatment options, one might consider spironolactone in patients with persistent symptomatic HF associated with an intermediate LVEF; however, these findings should be regarded as hypothesis-generating.


Comparison of right ventricular septal pacing and right ventricular apical pacing in patients receiving cardiac resynchronization therapy defibrillators

Authors: Leclercq C et al., on behalf of the SEPTAL CRT Study investigators

Summary: Noninferiority of RV septal over RV apical pacing on LV reverse remodelling was investigated in the SEPTAL CRT study; 131 patients receiving a CRT-defibrillator were randomised to RV septal and 132 to RV apical pacing. There was no significant difference between the RV septal and RV apical pacing groups for LV end-systolic volume reduction at 6 months (∼25.3 vs. ∼29.3 mL [p = 0.79; p = 0.006 for noninferiority]), the proportion of those with a reduction in LV end-systolic volume of >15% at 6 months, time to first HF hospitalisation or death (p=0.532) or procedural or device-related serious adverse event rates (p=0.401).

Comment: Isolated RV apical pacing has been associated with adverse outcomes in HF; however, the benefits of CRT have only recently been obtained with the RV lead positioned at the RV apex. The current study demonstrated similar effects on CRT-induced LV reverse remodelling and a number of secondary endpoints (including implantation success rate) for RV septal and apical pacing. This suggests that RV lead position may not be important in achieving reverse remodelling with CRT; however, other studies have suggested that the maximal electrical separation between the LV and RV leads may be important, which was not evaluated in the current study.


Heart Failure Research Review

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.
Protection in post-MI heart failure\textsuperscript{1,2†}

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

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\section*{INSPRA\textsuperscript{®} \textit{eplerenone}} 25 mg and 50 mg Tablets. \textbf{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. \textbf{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. \textbf{Precautions:} Hyperkalaemia, potassium supplements or salt substitutes containing potassium, chronic kidney disease, impaired hepatic function, pregnancy, lactation, paediatric use, use in elderly, driving and use of machinery. See PI for details. \textbf{Interactions with Other Medicines:} Inhibitors/inducers of CYP3A4; ACE inhibitors; angiotensin receptor blockers, lithium; cyclosporin; tacrolimus; trimethoprim; alpha-1-blockers; tricyclic anti-depressants; neuroleptics; amifostine; baclofen; NSAIDs. See PI for details. \textbf{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, hyperthyroidism, cholecystitis, blood glucose increased. \textbf{Dosage and Administration:} Initial 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/1.73 m\textsuperscript{2}; initial dose should be 25 mg every other day, titrated to maximum of 25 mg daily. Serum potassium should be measured before initiating and during INSPRA therapy, particularly in patients with chronic kidney disease, and the dose adjusted as required. See PI for details. © Registered trademark. V10216.
N-terminal pro-brain natriuretic peptide and heart failure risk among individuals with and without obesity
Authors: Ndumele CE et al.
Summary: These researchers analysed NT-proBNP level data for 12,230 participants from the ARIC study who were free of prior HF at baseline and with BMI ≥18.5 kg/m². There were 1681 HF events over median 20.6 years of follow-up. Baseline BMI was weakly, inversely associated with NT-proBNP level (r = -0.10), despite increased risk HF in obesity and an association between higher baseline NT-proBNP level and increased HF risk across all BMI categories. HF risk prediction was improved with NT-proBNP level, even in patients with BMI ≥35 kg/m² (C statistic improvement 0.032 [95% CI 0.011–0.053]). However, considering the higher HF rates among those with obesity, higher BMI was associated with greater absolute HF risk at each NT-proBNP level; e.g. NT-proBNP levels 100–<200 pg/mL were associated with an average 10-year HF risk of <5% among individuals of normal bodyweight, but of >10% among those who were very obese.
Reference: Circulation 2016;133(7):631–8
Abstract

Body mass index, abdominal fatness, and heart failure incidence and mortality
Authors: Aune D et al.
Summary: This systematic review and meta-analysis explored the relationships between general and abdominal adiposity and HF risk. Among 647,388 participants from 23 prospective studies, there were >15,905 incident HF cases; four studies comprised 3 MOCA items, to evaluate the sensitivity and specificity of NINDS-CSN. Cognitive impairment (MOCA score <26) was identified in 62% of the participants. NINDS-CSN screen scores were 3–11, and the tool had an area under the receiver operating characteristic curve of 0.88 (p<0.01), indicating good accuracy. Respective sensitivity and specificity values of 89% and 71% were seen with a NINDS-CSN score cutoff of <9.
Comment: This Australian study firstly identified that cognitive impairment was common, affecting 62% of elderly HF patients enrolled in two HF disease management programmes. The authors tested a number of screening protocols, and demonstrated reasonable diagnostic utility to screen for cognitive impairment in elderly HF patients. These findings should be prospectively validated against comprehensive neuropsychological assessment in an independent cohort, and compared with other cognitive impairment screening tools. Such a screening tool could be applied in clinical practice either during clinic visits or over the telephone to allow clinicians to identify those patients who should undergo formal cognitive assessment, tailor disease management, and allow risk adjustment for outcome measures in clinical studies.
Abstract

Frailty assessment in advanced heart failure
Authors: Madan SA et al.
Summary: Forty consecutive patients aged ≥65 years with HF (LVEF ≤35%, NYHA class 3 or 4 and 6-minute walk distance <300m) were assessed for frailty using the five-item MOCA, NINDS-CSN (National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network) screens, which comprised 3 MOCA items, to evaluate the sensitivity and specificity of NINDS-CSN. Cognitive impairment (MOCA score <26) was identified in 62% of the participants. NINDS-CSN screen scores were 3–11, and the tool had an area under the receiver operating characteristic curve of 0.88 (p<0.01), indicating good accuracy. Respective sensitivity and specificity values of 89% and 71% were seen with a NINDS-CSN score cutoff of <9.
Comment: This single-centre study adds to the body of evidence that frailty is an important marker of adverse clinical outcomes in HF. The investigators used a validated frailty assessment tool (a modified version of the Fried Frailty Index) and demonstrated its prognostic utility in an elderly advanced HF cohort. Although based on small numbers, it is interesting that frailty appeared to be a stronger marker for non-HF hospitalisation (as opposed to HF hospitalisation), which probably reflects the prevalence of comorbidities in an elderly HF cohort.
Reference: J Card Fail; Published online Feb 13, 2016
Abstract

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