Welcome to the fortieth issue of Heart Failure Research Review.

This issue includes research reporting on the benefits of transvenous neurostimulation in patients with central sleep apnoea, including those with a history of HF. Other research found that patients with ischaemic heart disease and type 2 diabetes have a particularly poor prognosis, especially those who have not undergone revascularisation. Neither continuation of ACE inhibitors or ARBs at high doses nor uptitration was found to be related to adverse longer term renal function changes in patients with systolic chronic HF and stable stage III–IV CKD. Research comparing patients with HFPEF or HFREF from Singapore with those from Sweden found ethnic differences in the associations between EF and QRS duration.

As always, we welcome your comments and suggestions, so please keep them coming.

Kind Regards

Dr. John Atherton
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Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction

Authors: Margulies KB et al.

Summary: Recently hospitalised patients with established HF with reduced LVEF (median 25%) were randomised to receive subcutaneous liraglutide titrated to 1.8 mg/day over 30 days as tolerated (n=154) or placebo (n=146) for 180 days; the participants’ median NT-proBNP (N-terminal prohormone of brain natriuretic peptide) level was 2049 pg/mL and 271 completed the study. No significant difference was seen between liraglutide and placebo recipients for: i) the primary endpoint of mean global rank score in which all participants (regardless of treatment assignment) were ranked for time to death, time to HF rehospitalisation and time-averaged proportional change in NT-proBNP level from baseline to 180 days (p=0.31); ii) mortality rate (12% vs. 11% [p=0.78]); iii) HF rehospitalisation rate (41% vs. 34% [p=0.17]); and iv) exploratory secondary endpoints. There were also no significant between-group differences in the prespecified subgroup of patients with diabetes (n=178). The respective rates of investigator-reported hyperglycaemic events were 10% and 18% in the liraglutide and placebo arms, and the respective hypoglycaemic event rates were 1% and 3%.

Comment: Despite an earlier study demonstrating that recombinant GLP-1 was associated with improved myocardial function in HFREF patients, this study failed to achieve its primary endpoint in a high-risk HFREF cohort (two-thirds were NYHA 3–4). The authors speculated that enhancing endogenous insulin secretion or increasing insulin sensitivity may not be beneficial in HF (e.g. increased HF events with saxagliptin in SAVOR-TIMI-53 and with thiazolidinediones). Indeed, there were safety concerns with a nonsignificant increase in HF rehospitalisations, suggesting caution in considering initiation of GLP-1 agonists in HFREF.


Abstract

Liraglutide and clinical stability of advanced HFREF

Transvenous neurostimulation for central sleep apnoea

Type 2 diabetes and ischaemic/nonischaemic HF prognosis

ACC/AHA/HFSA guidelines update for HF

NGAL for acute kidney injury during acute HF hospitalisation

Complete left-sided reverse remodelling with CRT

Renal function changes with ACE inhibitor/ARB dosing in HF with CKD

Ethnic differences in association of QRS duration with EF and HF outcomes

Differential response to low-dose dopamine/resiniferide in acute HF/REF

Lung impedance-guided pre-emptive treatment of chronic HF

Abbreviations used in this issue:

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronisation therapy; EF = ejection fraction; GFR = glomerular filtration rate; HF = heart failure; HF/PEF = HF with preserved/reduced EF; HR = hazard ratio; LA/V = left atrial/ventricular; LBBB = left bundle branch block; NGAL = neutrophil gelatinase-associated lipocalin; NYHA = New York Heart Association.

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Transvenous neurostimulation for central sleep apnoea

Authors: Costanzo MR et al., for the remedee System Pivotal Trial Study Group

Summary: Medically stable adults with central sleep apnoea with an apnoea-hypopnoea index of ≥20 events per hour were implanted with a device that transvenously stimulates a nerve causing diaphragmatic contraction similar to normal breathing, and were randomised to device stimulation (n=73) or no stimulation (n=78) for 6 months. In an intent-to-treat analysis, a significantly greater proportion of the device stimulation group than control group had a reduction in apnoea-hypopnoea index of ≥50% at 6 months (51% vs. 11% [p<0.0001]), with similar procedure-related serious adverse event rates (8% vs. 9%). None of the seven deaths during the study were considered to be related to implantation, system or therapy. Therapy-related discomfort was reported by 37% of the device stimulation group, and this resolved with system reprogramming in all but one of the affected participants.

Comment: Unilateral, phrenic nerve stimulation is a novel approach to treating central sleep apnoea, with previous single-arm studies reporting safety and clinical efficacy. This randomised controlled trial met its primary efficacy and safety endpoints, and the treatment was well tolerated. Approximately two-thirds of the patients had a prior history of HF with similar benefits reported in these patients. Future larger studies will need to determine whether this approach improves hard clinical outcomes.

Reference: Lancet 2016;388(10,048):974–82

Prognostic implications of type 2 diabetes mellitus in ischemic and nonischemic heart failure

Authors: Johansson I et al.

Summary: The effects of ischaemic versus nonischaemic HF and previous revascularisation on long-term prognosis in the presence versus absence of type 2 diabetes were explored in 35,163 Swedish HF registry patients; 90% of the patients had ≥1 associated comorbidity; 62% and 47% had ischaemic heart disease with and without type 2 diabetes, respectively, of whom 53% and 48% had previously undergone revascularisation. The presence of type 2 diabetes was associated with an increased likelihood of death in patients with and without ischaemic heart disease (respective adjusted HRs 1.40 [95% CI 1.33–1.46] and 1.30 [1.22–1.39]). The mortality risk was greatest in patients with both type 2 diabetes and ischaemic heart disease, but was lowered by revascularisation, even after propensity score adjustment (HR 0.87 [95% CI 0.78–0.96]). The presence of type 2 diabetes increased mortality risk in patients who had and not undergone revascularisation (respective HRs 1.36 [95% CI 1.24–1.48] and 1.45 [1.33–1.56]).

Comment: This study confirms that diabetes is an independent, adverse prognostic marker in HF. Sixty-two percent of HF patients with diabetes had ischaemic heart disease, with these patients having a particularly high mortality, which was partially offset by prior revascularisation. Given the lower mortality observed at 10 years follow-up in patients randomised to receive coronary artery bypass surgery in the STICH trial, this reinforces the need to consider investigations to rule out significant coronary artery disease in HF patients, especially in those with diabetes.

Reference: J Am Coll Cardiol 2016;68(13):1404–16

Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations

Authors: Maisel AS et al.

Summary: The prospective AKINESI study enrolled 927 patients presenting with acute HF requiring intravenous diuretic agents to assess if plasma NGAL (neutrophil gelatinase-associated lipocalin) levels were able to predict worsening renal failure (increase in plasma creatinine level of 0.5 mg/dL or ≥50%) within the first 5 days of hospitalisation, which occurred in 72 participants. Although peak NGAL level was more predictive than the first NGAL level, neither added significant diagnostic utility to first creatinine level (respective areas under ROC curves 0.656, 0.647 and 0.652). Similarly, first creatinine level was similar to first and peak NGAL levels for predicting in-hospital adverse events (respective areas under the ROC curves 0.686, 0.691 and 0.653), of which there were 235 events affecting 144 participants. A post hoc analysis of participants with an estimated GFR of <60 mL/min/1.73m² revealed that a first NGAL level of <150 ng/mL was indicative of a low likelihood of adverse events.

Comment: Given that serum creatinine level increases 1–3 days after renal injury, this large multicentre study evaluated whether the tubular marker NGAL would be a more reliable marker of subsequent worsening renal failure in acute HF patients receiving (or about to receive) intravenous diuretics. The failure of plasma NGAL level to provide incremental risk prediction beyond serum creatinine level may reflect the multifactorial contributors to both worsening renal failure and plasma NGAL level itself (including renal and nonrenal production), and also questions whether increases in serum creatinine level in this setting actually represent worsening renal function in most patients. Meanwhile the results for urinary NGAL are awaited.

Reference: J Am Coll Cardiol 2016;68(13):1420–31

2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Authors: Yancy CW et al.

Summary: This is a report on the ACC (American College of Cardiology)/AHA (American Heart Association) Task Force on Clinical Practice Guidelines and the HFSAs’s (Heart Failure Society of America) updated guideline recommendations for HF. This update was submitted to a similar degree of rigorous, multilevel review and approval as full guidelines are typically subjected to, and has focused on use of inhibitors of the angiotensin-renin system and ivabradine for HFREF. The authors noted that further updates are forthcoming.

Comment: This initial focused update of the 2013 ACCF/AHA Heart Failure Guidelines (developed concurrently and independently of the 2016 ESC Heart Failure Guidelines) refers to the ARNI (angiotensin receptor-neprilysin inhibitor), sacubitril/valsartan (new for both guidelines), and the sinus-node inhibitor, ivabradine (new for the ACC/AHA/HFSA guidelines). Whilst largely concordant, there are some minor differences. In chronic HFREF patients who tolerate an ACE inhibitor or an ARB, the ACC/AHA/HFSA recommends replacement with an ARNI, whereas the ESC recommends replacement with an ARNI in HFREF patients who remain symptomatic despite optimal treatment with an ACE inhibitor, ß-blocker and a mineralocorticoid receptor antagonist.


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.

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Protection in post-MI heart failure$^{1,2,+}$

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

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**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, 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.

**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.

**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, hyperkalaemia, cholecystitis, blood glucose increased. *Serious post-marketing:* angioedema, rash. See PI for details.

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References:
2. INSPIRA Product Information.
Clinical implications of complete left-sided reverse remodelling with cardiac resynchronization therapy

**Authors:** Mathias A et al.

**Summary:** This was an analysis of data from MADIT-CRT study participants who had a CRT defibrillator device and LBBB, 212 of whom had complete left-sided reverse remodelling (above-median change in both LA volume and LV end-systolic volume), 115 with discordant reverse remodelling (above-median change in only LA volume or LV end-systolic volume) and 206 with lesser reverse remodelling (below-median LA volume and LV end-systolic volume volume). Compared with participants with discordant reverse remodelling, those with complete left-sided reverse remodelling had a significantly lower rate of HF or death (p<0.001). Multivariate Cox proportional hazard models revealed that the risk of HF or death was consistently lower in patients with complete reverse remodelling than in those with discordant reverse remodelling or lesser reverse remodelling (HR 0.66 [95% CI 0.50–0.85]; similar findings were seen for HF alone and death alone.

**Comment:** This landmark analysis conducted in a subgroup of patients from the MADIT-CRT trial with LBBB who received a CRT defibrillator device highlights the importance of both LV and LA reverse remodelling in response to CRT. Predictors of 'complete', 'left-sided', reverse remodelling included female sex, absence of prior myocardial infarction, small indexed LA volume, wider baseline QRS duration (>150 msec) and better renal function. Whether these findings apply to broader populations (e.g. non-LBBB, atrial fibrillation, NYHA III/IV) will require further study. Furthermore, these post-treatment observations don’t allow better patient selection for CRT.

**Reference:** J Am Coll Cardiol 2016;68(12):1269–76

Long-term changes of renal function in relation to ACE inhibitor/angiotensin receptor blocker dosing in patients with heart failure and chronic kidney disease

**Authors:** Fröhlich H et al.

**Summary:** These authors reported on 722 retrospective, consecutive outpatients with systolic chronic HF and stable stage III/IV CKD (estimated GFR 15–60 mL/min/1.73m²) receiving chronic ACE inhibitor/ARB treatment. No significant relationship was seen between change in estimated GFR and baseline ACE inhibitor/ARB dose or relative or absolute change of ACE inhibitor/ARB dose during follow-up. Similar results were seen when renal function was expressed as a categorical variable (improved/stable/decreased) or in subgroup analyses with respect to age, sex, NYHA functional class, LVEF, diabetes, concomitant aldosterone antagonists, CKD stage, hypertension, ACE inhibitor versus ARB use and congestion status. Neither ACE inhibitor/ARB dose nor dose change was associated with worsening CHF or hyperkalaemia.

**Comment:** Randomised controlled trials evaluating the efficacy of ACE inhibitors/ARBs in HFREF excluded patients with severe CKD. This study provides some reassurance that neither the dose of ACE inhibitor/ARB nor up titration of these agents was associated with longer term worsening of renal function in HFREF patients with stage III/IV CKD. However, important caveats are that the patients selected had all been on treatment for at least 1 month, and that they were closely monitored in an HF clinic setting.

**Reference:** Am Heart J 2016;178:28–36

Ethnic differences in the association of QRS duration with ejection fraction and outcome in heart failure

**Authors:** Gissibels CM et al.

**Summary:** Associations of QRS duration with EF and outcomes were compared between 839 Asian patients with HF from Singapore and 11,221 white patients from Sweden from prospective population-based HF studies. Compared with white patients, those of Asian ethnicity were younger (62 vs 74 years [p<0.001]), were shorter height (163 vs 171cm [p<0.001]), weighed less (70 vs 80kg [p<0.001]), were more likely to have an EF of <30% (47% vs. 28%) and had a shorter unadjusted QRS duration (101 vs. 104 msec [p<0.001]). The relationship seen between EF and longer QRS duration (<0.001) was steeper among Asian patients than white patients (p<0.001 for interaction). Asian and white patients in HFREF had similar adjusted QRS durations when those with LBBB were excluded, but for HFREF, QRS duration was significantly longer in the Asian patients. Compared with QRS durations ≥120 msec, greater durations were associated with a greater likelihood of HF hospitalisation or death events over 2 years (52% vs. 40%), with each 10 msec incremental increase significantly increasing the likelihood (HR 1.04 [p<0.001]), but with no interaction by ethnicity.

**Comment:** Our current approach to treating HFREF is largely based on clinical trials with a predominance of middle-aged, white men. This study based on two population-based HF registries reports that Asian (compared with white) HF patients had slightly shorter QRS duration (as expected); however in adjusted analyses, Asian (compared with white) HFREF patients had longer QRS duration with a steeper inverse relationship between LVEF and QRS duration. While these findings are hypothesis-generating, they nonetheless highlight the limitations of our current simplistic approach to categorising HF management based on variables such as LVEF and QRS duration, which vary according to age, sex and ethnicity.

**Reference:** Heart 2016;102(18):1464–71

Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction

**Authors:** Wan S-H et al.

**Summary:** This post hoc analysis of 360 ROSE AHF trial participants with acute HF and renal dysfunction evaluated interactions between treatment effect and EF. Variations were seen for the effects of dopamine and nesiritide on urine volume according to EF (respectively p values for interaction 0.001 and 0.039), with HFREF and HFP EF patients having greater and lower urine volumes, respectively, with active treatment versus placebo. There were also variations by EF for the effects of dopamine and nesiritide on bodyweight change, sodium excretion and incidence of acute HF treatment failure (p<0.05 for all interactions), but no interaction on change in cystatin-C level. Dopamine was associated with better clinical outcomes in HFREF and worse ones in HFP EF compared with placebo, whereas for nesiritide versus placebo, no differences in clinical outcomes were seen between participants with HFREF and those with HFP EF.

**Comment:** Given that the ROSE AHF trial did not achieve its primary endpoint, these results should be regarded as hypothesis-generating. The opposing effects of low-dose dopamine in HFREF (benefit) and HFP EF (harm) could represent the play of chance, although are biologically plausible. Pending further investigation, this suggests that low-dose dopamine may have a role in acute HF patients with a reduced LVEF, renal dysfunction and persisting congestion despite intravenously (preferably high-dose) diuretic therapy. However, clinicians should bear in mind that even at this so-called ‘low-dose’, patients experienced higher rates with dopamine (reported in the original study publication), suggesting a β-agonist effect (and therefore the potential for proarrhythmia).

**Reference:** Circ Heart Fail 2016;9:e002593

Non-invasive lung IMPEDANCE-guided preemptive treatment in chronic heart failure patients

**Authors:** Shohat MK et al.

**Summary:** Patients with NYHA class II–IV chronic HF and LVEF <35% who had been admitted for acute HF within the prior 12 months (n=296) were randomised to receive lung impedance-assisted therapy and monitoring or a control group in the IMPEDANCE-HF trial. Compared with the control group, the lung impedance monitoring was associated with fewer hospitalisations for acute HF during the first year (67 vs. 158 [p<0.001]) and during the entire follow-up of 48 vs. 39 months (211 vs. 386 [p<0.001]), and fewer deaths (HR 0.52 [95% CI 0.35–0.78]) including those due to HF (0.30 [0.15–0.58]); the noncardiovascular-related death rates were similar.

**Comment:** This single-blind study demonstrated a significant reduction in the primary endpoint (acute HF hospitalisations) as well as significant reductions in all-cause mortality (driven by reductions in HF death) associated with treatment adjusted according to noninvasive measurement of lung impedance performed by technicians at outpatient clinics. These findings contrast with the DOT-HF and OptiLink HF studies, which used OptiVol to measure intrathoracic impedance. The authors suggest that their technique is more sensitive given that it measures intrathoracic impedance. Whist this technology is promising, the intervention was resource-intensive with scheduled monthly outpatient hospital clinic visits. These findings require confirmation, and ideally better delineation of which patients will gain most benefit from this technology.

**Reference:** J Card Fail 2016;22(9):713–22

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