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Welcome to issue 35 of Heart Failure Research Review.

Among the research selected for this issue, there is a paper showing no association between incretin-based agents and hospitalisation for HF. This is followed by two papers from the same Lancet issue investigating shunting devices for HFPEF and HFREF. US researchers have reported on complications associated with home IV inotrope therapy when used for patients with intractable chronic HF, and others have presented data suggesting that bariatric surgery is safe and effective in obese patients with LV systolic dysfunction. I have concluded this issue with an extension of the STICH trial reporting sustained benefits of CABG for patients with ischaemic cardiomyopathy.

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

Kind Regards,

Prof Peter Macdonald
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Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure

Authors: Ong MK et al., for the Better Effectiveness After Transition – Heart Failure (BEAT-HF) Research Group

Summary: Patients aged ≥50 years hospitalised for decompensated HF were randomised to a care transition intervention of health coaching telephone calls and telemonitoring of blood pressure, heart rate, symptoms and bodyweight data (n=715) or usual care (n=722), and were followed for 180 days, in BEAT-HF (Better Effectiveness After Transition – Heart Failure) study. There was no difference between the intervention and usual care arms for the primary outcome of readmission for any cause within 180 days of discharge (50.8% vs. 49.2%; adjusted HR 1.03 [95% CI 0.88–1.20]), or for 30-day readmission or 180-day mortality, but QOL at 180 days was significantly different. There were no adverse events reported.

Comment: There is widespread acceptance that patients with acute decompensated HF benefit from referral to a multidisciplinary service to facilitate transition to community care and reduce the risk of readmission or mortality. While there is strong evidence for home-based and clinic-based multidisciplinary services, the benefit of remote telephone support with or without noninvasive monitoring remains unclear. The BEAT-HF study is one of the largest prospective randomised studies to compare remote telephone monitoring with usual care. The overall results were disappointing, with the intervention providing no mortality or rehospitalisation benefit over 6 months of follow-up. One possible explanation is the relatively poor adherence of the intervention group to the telephone support.


Abstract

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PBS Information:
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For patients with chronic heart failure who meet the clinical criteria set out in the PBS schedule.
A multicenter observational study of incretin-based drugs and heart failure

Authors: Filion KB et al., for the CNODES Investigators

Summary: These authors applied a common protocol for analyzing healthcare data from four Canadian provinces, the US and the UK on patients hospitalised for HF, each matched with ≤20 controls from the same cohort. A total of 1,499,650 patients with diabetes were included, including 29,741 hospitalised for HF (incidence rate 9.2 events per 1,000 persons per year). There was no difference between incretin-based drug versus oral antidiabetic drug combination use for the HF hospitalisation rate among patients with a history of HF (HR 0.86 [95% CI 0.62–1.19]) or among those without a history of HF (0.82 [0.67, 1.05]; similar results were seen for DPP (dipeptidyl peptidase)-4 inhibitors and GLP (glucagon-like peptide)-1 analogues.

Comment: There is ongoing uncertainty regarding the safety of incretin-based drugs (DPP-4 inhibitors and GLP-1 analogues) in patients with type 2 diabetes who are at risk of HF – so much so that the US FDA has mandated that all novel drugs developed for type 2 diabetes are required to be subjected to large-scale clinical trials to prove CV safety. The results of this ‘big data’ registry analysis drawn from almost 1.5 million individuals from multiple countries suggest that these drug classes do not increase the risk of chronic HF admissions compared with other oral drug combinations. While the results provide some reassurance, caution is recommended with use of these drug classes in diabetic patients with established HF.


Abstract

Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction

Authors: Del Trigo M et al.

Summary: Ten adults with NYHA class III chronic HFREF underwent implantation of a unidirectional left-to-right interatrial shunt after trans-septal catheterisation with transoesophageal echocardiography guidance under general anaesthesia in this safety and proof-of-principle study. All device implantations were completed successfully, and there were no device- or procedure-related adverse events during follow-up. Ali shunts were patent with no thrombosis or migration on transoesophageal echocardiography at 1 month. At 3 months follow-up, improvements were seen in:

i) NYHA classification from class III to II in seven participants

ii) 6-minute walk distance from 244 to 318m (p=0.016)

iii) Mean pulmonary capillary wedge pressure from 23 to 17mm Hg (p=0.035).

There were no changes in right atrial pressure, pulmonary arterial pressure or pulmonary resistance, and there were no hospitalisations for worsening HF. One participant was hospitalised with GI bleeding at 1 month, and one died after incessant ventricular tachycardia storm led to terminal HF at 2 months.

Comment: This is another proof-of-concept study of the use of a percutaneously delivered interatrial stent to create an interatrial shunt – this time in patients with HFREF. The investigators reported a significant reduction in pulmonary wedge pressure and improved functional class after 3 months. In addition, the death of a patient 2 months postimplant from intractable ventricular tachycardia (despite the presence of an automated ICD) does raise a question about the safety of the procedure. Further studies are needed.


Abstract

Infections, arrhythmias, and hospitalizations on home intravenous inotropic therapy

Authors: Acharaya D et al.

Summary: Data on arrhythmias, infections and hospitalisations from 197 patients with stage D HF discharged on IV inotropes were collected until death, transplant or LVAD receipt, inotropic weaning or study end; 30% had a baseline history of ventricular tachycardia, 71% had a history of cardiac arrest and 39% had a history of atrial fibrillation. During follow-up, ≥1 ICS shock was needed by 17% of the patients, and 82% of these had appropriate shocks for ventricular tachycardia/ventricular fibrillation, 9% had inappropriate shocks and 9% had both appropriate and inappropriate shocks.

There was an increase in ICD shock and inotrope dose. Infections (≥1) occurred in 29% of the patients during follow-up, with bacteremia the most common type; there was no evidence that implanted electrophysiology devices increased infection risk. Hospitalisations (≥1) during follow-up were needed for 57% of the patients, commonly for worsening HF symptoms (41%), infections (20%) and arrhythmias (12%).

Comment: The use of home IV inotropic therapy to manage patients with intractable chronic HF (stage D) has largely been superseded by the use of long-term mechanical support devices (VADs); however, a small proportion of this group are either unsuitable for VAD implantation or opt for home inotropic therapy while waiting for heart transplantation. This report from a single US centre is one of the largest to date examining the outcomes of home IV inotropic therapy. The absence of a control group makes it difficult to judge the efficacy of home IV inotropic therapy; however, the high rate of readmission for worsening HF raises questions regarding the efficacy and durability of this approach. In addition, the high rates of ICD shocks and line sepsis experienced by these patients point to the limitations of this approach.


Abstract

A transcatheater intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF)

Authors: Hasenfuß G et al., on behalf of the REDUCE LAP-HF study investigators

Summary: Patients aged >40 years from a number of countries, including Australia, with HFPEF symptoms despite pharmacological therapy and a raised pulmonary capillary wedge pressure (n=68) underwent transcatheater interatrial shunt device implantation in the open-label, phase 1 REDUCE LAP-HF trial. The devices were successfully implanted in 64 participants, with no periprocedural or major adverse cardiac or cerebrovascular events or need for cardiac surgery intervention for device-related complications during 6 months follow-up. Pulmonary capillary wedge pressure was reduced at rest in 52% of the participants and during exertion in 58%, with 39% fulfilling both these criteria. There were also significant reductions from baseline in mean exercise pulmonary capillary wedge pressure at 6 months at 20W and peak workloads (32 vs. 29mm Hg [p=0.0124] and 34 vs. 32mm Hg [p=0.0255], respectively), despite an increase in mean exercise duration (7.3 vs. 8.2 min [p=0.03]). Device patency was sustained, with a reduction in baseline pulmonary/systemic flow ratio at 6 months (1.06 vs. 1.27 [p=0.0044]).

Comment: HFPEF remains a syndrome of untreatable need. Multiple drugs have been tested, but so far none have been shown to improve survival. A characteristic feature of HFPEF is raised left atrial pressure secondary to LV diastolic dysfunction. In this proof-of-concept international multicentre trial, investigators tested the concept that a novel percutaneously delivered stent to create an interatrial shunt between the left and right atria would relieve left atrial pressure and symptoms of pulmonary congestion. The procedure was well tolerated and overall the trial demonstrated a modest fall in resting and exercise pulmonary pressures and improvements in QOL and exercise duration at 6 months follow-up. A potential adverse effect of the intervention was an increase in right heart chamber diameters and right atrial pressure. This may explain the lack of any improvement in NT-proBNP levels during the trial. While the overall results are encouraging, longer term follow-up and further studies ideally with sham controls are needed.


Abstract

The effect of increasing inspired oxygen on exercise performance in patients with chronic heart failure

Authors: Koshy A et al.

Summary: Thirty-one patients with chronic HF completed three maximal incremental exercise tests in a randomised crossover manner, each with a different FiO2 (fraction of inspired oxygen; 20.9% [room air], 28% or 40%); participants rested for >4 days between tests. Compared with room air, FiO2 values of 28% and 40% were associated with significant increases in:

i) Mean exercise time (525 and 536, respectively, vs. 501 sec [p values 0.042 and p<0.001]);

ii) Maximal metabolic equivalents (3.67 and 3.70 vs. 3.47 [p values 0.002 and <0.001]); and

iii) Maximal workload (82.6 and 84.2 vs. 78.4W [p values 0.021 and 0.002]). Mean oxygen saturation values during exercise increased as FiO2 increased. An FiO2 of 28% was also associated with a decrease in mean heart rate, but it did not fall further at an FiO2 of 40%. Blood pressure was not affected by changes in FiO2.

Comment: Although reduced exercise tolerance is one of the cardinal symptoms of HF, the pathophysiological basis for this symptom remains unclear. A number of studies have tested the hypothesis that administration of supplemental oxygen during exercise will increase exercise duration in patients with chronic HF – with conflicting results. This carefully conducted study is the largest to date to examine this hypothesis. The authors demonstrated a dose-dependent increase in exercise capacity in patients with HFREF who were administered supplemental oxygen during exercise. While the results are encouraging, further mechanistic studies are needed to determine how supplemental oxygen is improving exercise capacity and whether the response is sustained with repeated administration.


Abstract

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Acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure

Authors: Teerlink JR et al.
Summary: Patients hospitalised with acute HF with LVEF ≤40%, dyspnoea and elevated plasma natriuretic peptide levels (n=606) were randomised to receive 48-hour IV infusions of placebo or omecamtiv mecarbil in three sequential, escalating-dose cohorts in the ATOMIC-AHF study. There was no significant improvement over placebo for the primary endpoint of dyspnoea relief with any of the omecamtiv mecarbil doses (42–51% vs. 41% [p=0.33]) or for any of the secondary outcomes assessed. However, supplemental, prespecified analyses showed that compared with placebo, the highest omecamtiv mecarbil dose was associated with greater dyspnoea relief at 48 hours (51% vs. 37% [p=0.034]), which lasted out to day 5 (p=0.038). Omeamcmtiv mecarbil was also associated with plasma concentration-related increases in LV systolic ejection time (p<0.0001) and decreases in end-systolic dimensions (p<0.05). There were no notable differences in adverse events between omecamtiv mecarbil and placebo, with no increase in ventricular or supraventricular tachyarrhythmia. Omecamtiv mecarbil recipients did have a 0.004 ng/mL higher median plasma creatinine level elevations (4.1% vs. 2.7% [p=0.001]) and potassium level elevations (7.7% vs. 12.5% [p<0.001]).

Comment: Omeamcmtiv mecarbil is a novel positive inotropic agent with a unique mode of action that involves direct activation of cardiac myosin. In this phase 2b multicentre clinical trial of patients admitted to hospital with acute decompensated HF and low LVEF, three different doses of IV omecamtiv mecarbil were compared with placebo. Overall, the trial failed to meet its primary endpoint of dyspnoea relief, although there appeared to be a benefit for the highest dose of omecamtiv mecarbil tested. Omeamcmtiv mecarbil appeared to be well-tolerated; however, a small but significant increase in plasma troponin levels in the omecamtiv mecarbil-treated patients raises concerns about the possibility of subclinical ischaemia induced by the drug.

Reference: J Am Coll Cardiol 2016;67(12):1444–55

Coronary-artery bypass surgery in patients with ischemic cardiomyopathy

Authors: Velazquez EJ et al., for the STICHES Investigators
Summary: Patients with LVEF ≤35% and coronary artery disease amenable to CABG were randomised to medical therapy with (n=610) or without (n=602) CABG; median follow-up in this extended follow-up of the STICH study was 9.8 years. Compared with medical therapy alone, the inclusion of CABG was associated with significantly lower rates of all-cause mortality (primary outcome; 58.9% vs. 66.1%; HR 0.84 [95% CI 0.73–0.97]), CV-related mortality (40.5% vs. 49.3%; 0.73 [0.66–0.83]) and the composite of all-cause mortality and CV-related hospitalisation (76.6% vs. 87.0%; 0.72 [0.64–0.82]).

Comment: The STICH study compared CABG surgery to optimal medical therapy in patients with coronary artery disease and severe LV dysfunction (LVEF ≤35%). Most of the patients entered into the trial had symptomatic HF (mainly NYHA class II or III) and all were receiving evidence-based medical therapy. The initial trial results were published in N Engl J Med in 2011 and demonstrated a nonsignificant beneficial trend of CABG surgery on the primary endpoint of all-cause mortality after median follow-up of 56 months. The STICH Extension Study (STICHES) reports the 10-year outcomes of the STICH trial. The authors report a 16% relative and 6% absolute reduction in all-cause mortality risk in patients assigned to surgery. Furthermore, if the analysis was limited to patients who received the assigned treatment (rather than intention to treat), the relative risk reduction was closer to 25%. The STICH trial provides convincing evidence for a long-term benefit of CABG surgery for this group of patients in the modern era.


Clinical and echocardiographic outcomes after bariatric surgery in obese patients with left ventricular systolic dysfunction

Authors: Vest AR et al.
Summary: This research compared outcomes and efficacy of 42 obese bariatric surgical patients with LV systolic dysfunction versus 2588 without known LV systolic dysfunction. Compared with patients without known LV systolic dysfunction, those with LV systolic dysfunction had more comorbid conditions at baseline and a slight increase in early postoperative HF and myocardial infarction, but a mean 22.6% reduction in bodyweight with no excess mortality at 1 year. A review was also undertaken of pre- and postoperative echocardiographic images from an overlapping cohort of 38 patients with LV systolic dysfunction and matched nonsurgical controls. LVEF improved significantly by 5.1% between images from an overlapping cohort of 38 patients with LV systolic dysfunction and matched nonsurgical controls. LVEF improved significantly by 5.1% between images from an overlapping cohort of 38 patients with LV systolic dysfunction and matched nonsurgical controls. The presence of morbid obesity (body mass index >35 kg/m²) is regarded as a contraindication to heart transplantation in most jurisdictions due to the higher post-transplant morbidity and mortality experienced by these patients. Previous reports of bariatric surgery in morbid obesity chronic HF patients have been limited to small case series. This US series is the largest reported to date. Consistent with previous series, the authors found that bariatric surgery was generally well-tolerated with low operative mortality and excellent weight reduction at follow-up. In addition, they observed a significant increase in LVEF, suggesting an improvement in chronic HF status.

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Reference: Circ Heart Fail 2016;9:e002260

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Heart Failure Research Review

Independent commentary by Professor Peter Macdonald.

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