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Welcome to issue 44 of Heart Failure Research Review.

This issue begins with research from JAMA reporting no improvements in exercise capacity with oral iron supplementation in patients with HFREF who are iron-deficient – intravenous iron therapy remains the appropriate treatment. A large study of US veterans exploring the relationship between HIV infection and HF provides data suggesting the association may be due to the virus itself, rather than drugs used for its treatment. While direct-acting anticoagulants may be safe and effective for systemic thromboembolism in patients with nonvalvular atrial fibrillation, researchers from the US have reported that dabigatran may be unsafe for patients with implanted mechanical valves or devices. This issue concludes with real-world data showing SGLT-2 inhibitors reduce the risks of hospitalisation for HF and death, building on the results of the EMPA-REG trial of empagliflozin in patients with type 2 diabetes and high risk of HF disease from 2 years ago.

I hope you find these and the other research selected for this issue interesting and helpful in your practice. Please let me know if you have any feedback or topics you would like to see covered in future issues.

Kind Regards,

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Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency

Authors: Lewis GD et al., for the NHLBI Heart Failure Clinical Research Network

Summary: The IRONOUT HF trial investigated the effects of oral iron supplementation on exercise capacity in 225 patients with HFREF and iron deficiency. The participants were randomised to receive oral iron polysaccharide 150mg twice daily or placebo for 16 weeks. The median baseline peak VO₂ was 1196 mL/min in the oral iron group and 1167 mL/min in the placebo group. The change in peak VO₂ at 16 weeks (primary endpoint) did not significantly differ between the iron versus placebo groups (+23 vs. –2 mL/min [p=0.46]), nor did 6MWD, NT-proBNP level or KCCQ score.

Comment: Many patients with advanced HF are iron deficient and several studies of intravenous iron therapy have demonstrated improvements in QOL and functional capacity (although evidence of benefit in terms of survival is still pending). This has raised the question of whether similar benefits could be obtained through oral iron replacement. This is an important negative study that clearly demonstrates that oral iron therapy is ineffective in this group of patients, probably due to poor gut absorption of the oral iron polysaccharide. If iron deficiency (as defined in this and other studies) is found in patients with chronic HF, it should be corrected with intravenous iron therapy.


Abstract

Effect of ularitide on cardiovascular mortality in acute heart failure

Authors: Packer M et al., for the TRUE-AHF Investigators

Summary: The TRUE-AHF study randomised 2157 patients with acute HF to receive a continuous intravenous infusion of ularitide 15 μg/kg/min or placebo for 48 hours in addition to accepted therapy. Treatment was started a median 6 hours after the initial clinical evaluation. There was no significant difference between the ularitide versus placebo arm for CV-related mortality rate during median follow-up of 15 months (21.7% vs. 21.0%) or for the hierarchical composite endpoint that evaluated the initial 48-hour clinical course.

Comment: Ularitide is a synthetic analogue of urodilatin, an endogenous vasodilator and natriuretic peptide. Earlier phase 2 trials of this drug administered intravenously to patients with acute decompensated HF demonstrated favourable haemodynamic and diuretic responses. TRUE-AHF was a large phase 3 clinical trial aimed at testing whether these favourable responses would lead to improved clinical outcomes. The results were disappointing. Despite more rapid and greater reductions in NT-proBNP level with ularitide, hospital length of stay and survival over the subsequent 6 months were no different between the groups. The results of this trial and the preliminary results of the larger RELAX2 trial (of another synthetic vasodilator serelaxin) have forced clinicians to rethink the use of acute vasodilator drug therapy in patients with acute decompensated HF, particularly as these drugs are associated with increased rates of symptomatic hypotension.


Abstract
Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era

Authors: Freiberg MS et al.

Summary: The association of HIV infection with future HFREF or HFPEF risk was assessed in a cohort of 98,015 participants without CV disease at baseline from the observational US Veterans Aging Cohort Study, which included veterans with HIV infection matched to uninfected veterans. There were 2636 HF events recorded during median follow-up of 7.1 years. 34.6% of which were HFREF (EF ≥50%), 15.5% were borderline HFREF (EF 40–49%), 37.1% were HFREF (EF <40%) and 12.8% were HF of unknown type. Compared with uninfected veterans, those with HIV infection were at increased risk of HFREF, borderline HFREF and HFREF (respectively HRs 1.21 [95% CI 1.03–1.41], 1.37 [1.09–1.72] and 1.61 [1.40–1.86]), particularly those aged <40 years at baseline (3.59 [1.95–6.58]). Among the veterans with HIV infection, a time-updated HIV-1 RNA viral load of ≥500 vs. <500 copies/mL increased the risk of HFREF, and a time-updated CD4-cell count <200 vs. >500 cells/mm³ increased the risk of both HFREF and HFPEF.

Comment: This is an interesting long-term observational study of a large population of US veterans, almost one third of whom had HIV infection treated with antiretroviral therapy. The take-home message is that HIV-infected patients on long-term antiretroviral therapy have a significantly increased risk of developing chronic HF of all types (HFREF, HF borderline and HFREF). Although the link between HIV infection and future chronic HF remains undefined, it is noteworthy that the risk of chronic HF was highest in those with less well-controlled infection (higher viral load and lower CD4-cell counts), suggesting that the link may be the virus rather than the treatment.


Use of risk models to predict death in the next year among individual ambulatory patients with heart failure

Authors: Allen LA et al.

Summary: This research sought to quantify how well the validated HF risk models SHFM (Seattle Heart Failure Model) and MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) estimate mortality among 10,930 ambulatory adults with HF from three integrated health systems. The 1-year posteroanterior mortality rate was 15.9%. At the population level, SHFM and MAGGIC predicted 1-year mortality rates of 9.7% and 17.5%, respectively (C statistics, 0.66 and 0.69). At the individual level, SHFM and MAGGIC predicted a >50% probability of dying in the next year for 48 and 52 of the 1661 patients who died, respectively (sensitivities, 0.5% and 3.1%), and for five and 63 patients who lived for >1 year (positive predictive values, 61.5% and 45.2%). SHFM estimated that 77.8% of patients had a <15% probability of dying at 1 year, but this lower risk end of the score range captured nearly two-thirds of deaths; similarly, MAGGIC estimated a probability of dying of <25% for most patients who died at 1 year.

Comment: This observational study of a large cohort of ambulatory patients with chronic HF provides a ‘reality check’ for proponents of the use of risk calculators in the management of individuals with chronic HF. Two risk calculators, SHFM and MAGGIC, were evaluated. When applied to the total population, they provided reasonable prediction of mortality risk over the subsequent 12 months, but when applied to individual patients with chronic HF, they identified few patients who died during the follow-up. A number of these risk calculators, e.g. the SHFM, are available as downloadable apps. While it is tempting for clinicians to apply them in the management of individuals with chronic HF, the results of this study suggests that they are of limited value in predicting mortality risk in individual patients.


Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease

Authors: Tseng W-C et al.

Summary: This nationwide population-based study explored the impact of spironolactone on CV mortality and morbidity in patients with predialysis stage 5 chronic kidney disease from a Taiwanese health insurance database; follow-up was 85,758 person-years. Compared with spironolactone nonusers (n=25,850), spironolactone users (n=19,863) had higher incidences of death from any cause (24.7 vs. 10.6 per 100 person-years; adjusted HR 1.35 [95% CI 1.24–1.46]), death due to infection (4.4 vs. 1.7 per 100 person-years; 1.42 [1.16–1.73]) and hospitalisation for HF (4.0 vs. 1.4 per 100 person-years; 3.15 [1.08–1.67]). CV-related mortality, major adverse CV events and hyperkalaemia-associated hospitalisation rates did not differ significantly between spironolactone users and nonusers. The results were consistent in comparisons of spironolactone users propensity-score matched to nonusers in a 1:3 ratio.

Comment: The mortality benefits of mineralocorticoid antagonists in patients with HFREF are well established; however, these studies excluded patients with advanced chronic renal disease (estimated glomerular filtration rate <30 mL/min), which is generally considered to be a contraindication to the use of these drugs. Nonetheless, there has been an interest in exploring the possibility that there may be benefits of spironolactone in treating patients with the combination of advanced heart and renal failure. This ‘big data’ analysis from Taiwan provides support for existing prescribing guidelines that spironolactone is safe in this population, its use being associated with increased risk of death and HF hospitalisation.

Reference: Int J Cardiol 2017;238:72–8

Pilot study of endothelin receptor blockade in heart failure with diastolic dysfunction and pulmonary hypertension (BADDHY-Trial)

Authors: Koller B et al.

Summary: Patients with HFPEF and pulmonary hypertension were randomised to receive 12 weeks of bosentan or placebo and then followed for a further 12 weeks off treatment. An interim analysis revealed that bosentan did not significantly affect baseline 6MWD (309.7m) at either the end of treatment (317.0m) or the 12-week post-treatment follow-up (307.0m). In contrast, placebo was associated with an increase in 6MWD that almost reached statistical significance, and also significant decreases in estimated systolic pulmonary artery pressure and right atrial pressure; the trial was terminated early.

Comment: The benefits of bosentan and other endothelin antagonists in primary pulmonary arterial hypertension are well established. On the other hand, bosentan has been found to be ineffective in left HF due to HFREF as confirmed by the primary outcomes analysis of the ENABLE trials, published in JACC Heart Failure in May. Indeed, in patients with advanced HFREF, bosentan was associated with increased fluid retention and worsening symptomatic HF; particularly in the first month after starting treatment. Patients enrolled in the ENABLE trials were not screened for pulmonary hypertension, and there has been ongoing speculation that bosentan may have a role in treating patients with pulmonary artery hypertension secondary to left HF. In the BADDHY trial, investigators explored the therapeutic potential of bosentan in patients with pulmonary hypertension secondary to HFREF. The results were disappointing. The study was of limited size and duration, and was terminated early as an interim analysis of a number of surrogate endpoints favoured the placebo group.

Elderly (≥70 years) CHF patients deserve an age-proven β-blocker¹,²

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of elderly CHF patients¹,²

* vs placebo P= 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

PBS Information: Restricted benefit. Moderate to severe heart failure.
Refer to PBS Schedule for full restricted benefit information.

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

Nebilet® (nebivolol hydrochloride) tablets 1.25 mg, 5 mg, 10 mg. INDICATIONS: Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. 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; 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 wks; refer to full PI. 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; driving vehicles or operating machines. Pregnancy (Cat C), Lactation, Children and adolescents. Renal and hepatic insufficiency – see Dosage and Administration.

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 antiarrhythmic drugs; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine; for other combinations requiring careful consideration, see full PI. ADVERSE EFFECTS: Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, 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, others see full PI. DOSAGE AND ADMINISTRATION: Once daily dosing, can be given with or without meals, consistent approach is recommended. 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 monitored closely. Chronic Heart Failure: The initial up titration should be done gradually at 1-2 wk 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 supervision for at least 2 h. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 µmol/L) is not recommended. Date prepared 17 December 2015. References: 1. Nebilet Approved Product Information, 14 December 2015. 2. Flather MD et al. Eur Heart J 2005; 26: 215–25.
Increased thromboembolic events with dabigatran compared with vitamin K antagonism in left ventricular assist device patients

Authors: Andreas M et al.

Summary: This pilot trial randomised patients with LVADs to receive phenprocoumon or dabigatran 110mg (normal renal function) or 75mg (glomerular filtration rate 30–80 mL/min) twice daily added to aspirin for long-term anticoagulation. Planned treatment duration was 1 year or until a primary endpoint event occurred. The study was stopped early due to safety concerns, at which time 16 participants had been randomised. The thromboembolic event rates in the respective dabigatran and phenprocoumon were 50% and 13% (p<0.28). There were no major bleeds or deaths during the study. Dabigatran recipients terminated treatment in a significantly shorter median time than phenprocoumon recipients (8.5 vs. 12.0 months [p<0.015]).

Comment: Patients with advanced left HF who are supported with implanted LVADs require lifelong anticoagulation, usually in combination with antiplatelet therapy to prevent potentially life-threatening pump thrombosis. Vitamin K antagonists like warfarin have been the oral anticoagulant used in all reported LVAD trials to date. In this study of patients implanted with the HeartWare LVAD, investigators compared the clinical efficacy and safety of the direct-acting thrombin inhibitor dabigatran with warfarin. The study was terminated prematurely due to safety concerns with four of eight patients randomised to dabigatran developing thromboembolic complications. This study commenced before the publication of the RE-ALIGN trial that compared dabigatran to warfarin in patients with mechanical heart valves (N Engl J Med, Sept 2013), but serves to reinforce the findings reported in that trial; in RE-ALIGN, dabigatran was associated with increased rates of thromboembolism and bleeding compared with warfarin. While dabigatran and other direct acting anticoagulants are safe and effective in preventing systemic thromboembolism in patients with nonvalvular atrial fibrillation, they are inferior to warfarin and unsafe in patients with implanted mechanical valves or devices.

Reference: Circ Heart Fail 2017;10(5):e003709 Abstract

Patient-reported outcomes in the SOLuble guanylate Cyclase stimulatoR in heArT failurePatiENTS with PRESERVED Ejection fraction (SOCRATES-PRESERVED) study

Authors: Filipatos G et al.

Summary: Patients with chronic HF and EF ≤45% (n=477) were randomised within 4 weeks of decompensation to receive titrated-dose vericiguat 1.25mg, 2.5mg, 5mg and 10mg or placebo once daily for 12 weeks. Compared with placebo, vericiguat 10mg was associated with a greater proportion of participants achieving clinically meaningful improvements in KCCO clinical summary score (82.0% vs. 59.0% [p=0.0052]), and greater increases in the mean physical limitations domain score (17.2 vs. 4.5 [p=0.0009]) and the EQ-5D US index score (0.064 vs. –0.009 [p=0.0461]). The improvements in KCCO and EQ-5D scores were paralleled by physician-assessed New York Heart Association class and clinical congestion.

Comment: SOCRA-TES-PRESERVED was a large phase 2 placebo-controlled dose-ranging study of the direct guanylate cyclase stimulator vericiguat in patients with HFPEF. Study drug was administered for 12 weeks. The main trial results were published separately and more or less simultaneously in Eur Heart J. Vericiguat in doses up to 10mg daily had no significant impact on NT-proBNP levels or left atrial volume, the two primary endpoints of the trial, however, as demonstrated in this report there were significant and dose-dependent improvements in two QOL measures. Considering the two publications together, the results are mixed; however, the improvements in patient reported QOL measures and the lack of alternative therapies suggest that further evaluation of this drug in HFPEF is warranted.


Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure

Authors: Matsuo Y et al.

Summary: The relationship between time-to-diuretic treatment and clinical outcome was explored in REALITY-AHF, a prospective, multicentre, observational cohort study in 1291 patients with acute HF who received intravenous furosemide within 24 hours of ED presentation. The median time between ED arrival and furosemide administration was 90 minutes. Compared with patients who received intravenous furosemide >1 hour after ED arrival, those who received it within 60 minutes (n=481) were more likely to arrive by ambulance, had more signs of congestion and had a lower in-hospital mortality rate (2.3% vs. 6.0%; adjusted odds ratio 0.39 [95% CI 0.20–0.79]).

Comment: In this fascinating prospective observational study from Japanese investigators, the authors assessed the impact of time from ED presentation with acute decompensated HF to first intravenous dose of furosemide (which they called door-to-furosemide time or D2F) on subsequent mortality. Just over one-third of patients received furosemide within 60 minutes of arrival. Mortality for these patients was less than half that of patients with a door-to-furosemide time >60 minutes. Despite differences in baseline characteristics, the lower mortality in the early treatment group persisted after adjustment for these differences. If this finding is confirmed in follow-up studies, it is conceivable that like ‘door-to-balloon time’ in the setting of acute myocardial infarction, door-to-furosemide time may become a key performance indicator for EDs.


Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs

Authors: Kosiborod M et al., and on behalf of the CVD-REAL Investigators and Study Group

Summary: The CVD-REAL study compared hospitalisation for HF and death in real-world patients newly initiated on any SGLT-2 inhibitor (n=154,528) versus propensity score-matched patients starting other glucose-lowering drugs (n=154,528). Medical claims, primary care/hospital record and national registry data from the US, Norway, Denmark, Sweden, Germany and the UK were analysed; mortality data for Germany were not available. Canagliflozin, dapagliflozin and empagliflozin accounted for 53%, 42% and 5%, respectively, of the SGLT-2 inhibitor total exposure time. Over 190,164 person-years of follow-up, the respective incidence rates for HF hospitalisation, death and HF hospitalisation or death were 0.51, 0.87 and 1.38 per 100 person-years. Compared with other glucose-lowering drugs, SGLT-2 inhibitor use was associated with reduced risk of CV disease, death or hospitalisation or death (respective HRs 0.61 [95% CI 0.51–0.73], 0.49 [0.41–0.57] and 0.54 [0.48–0.60]) with no significant heterogeneity by country.

Comment: This large real-world experience builds on the results of the phase 3 EMPA-REG trial of empagliflozin in patients with type 2 diabetes mellitus at high risk of CV disease (published in N Engl J Med in 2015 and reviewed in Heart Failure Research Review, issue 29). In the EMPA-REG trial, treatment with the SGLT-2 inhibitor empagliflozin compared with placebo was associated with reduced mortality and HF hospitalisation. In this large data linkage study of >300,000 patients collected from six countries, those treated with one of three SGLT-2 inhibitors had significantly lower mortality and HF hospitalisations compared with other glucose-lowering drugs. The results of the recently published CANVAS trial with canagliflozin (N Engl J Med, June 2017) provide yet further evidence of the CV benefits of SGLT-2 inhibitors.


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