Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction

Authors: Kotecha D et al., on behalf of the Beta-Blockers in Heart Failure Collaborative Group

Summary: This was a meta-analysis of individual patient data from 11 trials (n=13,833) of β-blockers in patients with HFREF (LVEF <0.45%) in sinus rhythm at baseline. Compared with placebo, β-blocker use was associated with lower mortality rates across age quartiles with median ages 50 years, 60 years, 68 years and 75 years (respective HRs 0.66 [95% CI 0.53–0.83], 0.71 [0.58–0.87], 0.65 [0.53–0.78] and 0.77 [0.64–0.92]). No significant interaction was apparent between β-blocker use and mortality when age was modelled as a continuous variable (p=0.1), and during median follow-up of 1.3 years, the absolute mortality reduction was 4.3% (number needed to treat, 23). β-blocker use also reduced hospital admissions, but the effect was attenuated as age increased (p=0.05 for interaction). Treatment effect did not interact with gender in any age group. There was no effect of treatment allocation, age or sex on drug discontinuation.

Comment: Elderly patients and women have been generally under-represented in the major HF RCTs. This individual patient data meta-analysis of the major HF RCTs comparing β-blockers and placebo in patients who were in sinus rhythm when enrolled confirms that both men and women benefit from β-blocker therapy. Whilst the SENIORS study demonstrated a significant reduction in the combined endpoint of all-cause mortality and CV hospitalisation in an elderly HF cohort, it was not powered to evaluate the effect of β-blockers on all-cause mortality alone. This individual patient data meta-analysis demonstrated that the beneficial effects on all-cause mortality and on HF hospitalisation were maintained in older patients (median age 75 years). Furthermore, tolerability and achieved doses were similar in the elderly.

Reference: BMJ 2016;353:i1855

Abstract
Establishing a pragmatic framework to optimise health outcomes in heart failure and multimorbidity (ARISE-HF): a multidisciplinary position statement

Authors: Stewart S et al.

Summary: These Australian and US authors reviewed the literature and prepared a position paper identifying the following five key steps (ARISE-HF) with the potential to improve clinical outcomes in patients with HF affected by multimorbidity when applied in a systematic manner: i) acknowledge multimorbidity as a clinical syndrome that leads to poor health outcomes; ii) use a standardised protocol adapted to the local healthcare system to routinely determine the extent of concurrent multimorbidity in all patients hospitalised with HF; iii) identify individualised priorities and person-centred goals according to the extent and nature of multimorbidity; iv) support individualised, home-based, multidisciplinary case management to supplement standard management of HF; and v) assess health outcomes beyond acute hospitalisation and encompass all-cause events and a person-centred perspective in affected patients.

Comment: Measures to prevent and treat CV disease have resulted in improved population survival accompanied by increasing multimorbidity. This paper describes a structured framework, with the aim being to increase clinician awareness of multimorbidity in their hospitalised HF patients and emphasise the importance of home-based, multidisciplinary case management, which was associated with a reduction in non-HF CV hospitalisation days in the WHICH? trial. This would include a postdischarge home visit to identify early signs of instability, evaluate potential environmental factors, support self-care and address polypharmacy. The authors also highlight the need to evaluate the impact of such interventions on both short-term and long-term all-cause outcome measures, and patient-centric measures such as QOL.

Reference: Int J Cardiol 2016;212:1–10

A comprehensive assessment of the association between anaemia, clinical covariates and outcomes in a population-wide heart failure registry

Authors: Jonsson A et al.

Summary: Haemoglobin levels were measured in 24,511 Swedish registry patients with HREF, including 8033 with anaemia, and associations between baseline characteristics and anaemia were explored. The most important independent predictors of anaemia were advanced age, male gender and renal dysfunction. Patients with anaemia had a lower 1-year survival rate than those without anaemia (75% vs. 81% [p<0.001]), with an increased risk of death from any cause in a Cox regression analysis with potential environmental factors, support self-care and address polypharmacy. The authors also highlight the need to evaluate the impact of such interventions on both short-term and long-term all-cause outcome measures, and patient-centric measures such as QOL.


Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy

Authors: Reant P et al.

Summary: Risk markers for predicting hypertrophic cardiomyopathy outcomes were identified in a retrospective cohort of 472 patients. The CV-related mortality rate over median 4.3 years of follow-up was 4.4%, with HF mortality, sudden cardiac death and stroke-associated death rates of 1.3%, 2.7% and 0.4%, respectively. Appropriate defibrillator shocks were delivered to 0.8% of the patients, and 2.7% were admitted for HF. Global longitudinal strain was associated with the primary endpoint of cardiac-related death, appropriate defibrillator shock or HF admission (-adjusted HR 0.90 [95% CI 0.83–0.98]) independent of age, maximal provoked LV outflow-tract gradient and LV end-systolic volume, and also the secondary endpoint of HF-related admission or death (0.82 [0.75–0.90]). Independent of age, previous AF, NYHA class III–IV, LV end-systolic volume, LVEF and outflow-tract gradient. Global longitudinal strain <15.6% was confirmed as a predictor of HF events on survival curves (p=0.0035).

Comment: The increasing use of suicide death risk stratification in hypertrophic cardiomyopathy has altered the natural history of this disease, with more patients surviving to develop subsequent HF. Whilst progression to the so-called dilated phase of disease is associated with a measured reduction in LVEF, this represents an advanced stage in the disease process, given that decreased afterload secondary to LV hypertrophy is associated with a higher LVEF. This single-centre study suggests that global longitudinal strain may be a more sensitive marker to identify hypertrophic cardiomyopathy patients at high risk of developing subsequent HF.


A systematic review of the main mechanisms of heart failure management interventions

Authors: Clark AM et al.

Summary: These authors undertook a systematic review of 33 studies (n=3355), including 18 RCTs, three mixed methods studies, six pretest–posttest studies and six qualitative studies, reporting data related to mechanisms of effect of HF management programmes. The main mechanisms identified were associated with greater patient understanding of HF and its links to self-care, greater involvement of other individuals in this self-care, better psychosocial well-being and support from health professionals to use technology.

Comment: The variable results reported in previous studies evaluating the efficacy of HF disease management have often been attributed to patient selection, evolving trends in the comparator (i.e. improvements in the standard of care), and the difficulty in delivering a consistent intervention. This systematic review of selected studies evaluating HF disease management identified features of these programmes that were associated with improved outcomes. It was not entirely clear to me how the studies were selected. Nonetheless, this could be used to provide HF disease management services with a ‘tick-box’ to ensure they meet these requirements, and does overlap with the previous toolkit developed by the Australian Heart Foundation (National Heart Foundation of Australia. Multidisciplinary care for people with chronic HF. Principles and recommendations for best practice. 2010).

Reference: Heart 2016;102(9):707–11

Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients

Authors: Platz E et al.

Summary: These researchers analysed routine lung ultrasonograms from eight chest zones, obtained with a pocket device, in 185 evaluable outpatients with NYHA class II–IV HF. The sum of B-lines in all zones (vertical lines on the lung ultrasonograms) ranged between 0 and 13, and B-line tertiles were associated with clinical and laboratory markers of congestion. Three or more B-lines on lung ultrasonograms were present in 32% of the patients, despite low to moderate levels of congestion as well as in 81% of these patients. The 6-month hospitalisation/mortality rate (primary outcome) was 27%. Compared with patients in the lowest B-line tertile, those in the third tertile (≥3 B-lines) were at increased risk of a primary outcome event (adjusted HR 4.08 [95% CI 1.95–8.54]) and spent significantly fewer days and out of hospital (125 vs. 165 [p<0.001]).

Comment: Previous studies have demonstrated the diagnostic utility of lung ultrasonography to detect pulmonary congestion in patients with undifferentiated dyspnea. This study demonstrated the prognostic utility of lung ultrasonography in an ambulatory HF population. Future studies are required to determine whether the eight-region approach is the best method to detect pulmonary congestion and whether this can be reliably performed by less experienced staff. Finally, controlled studies should evaluate whether adjusting therapy on the basis of lung ultrasound findings leads to better outcomes.


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Reference: Heart 2016;102(9):707–11

Independent commentary by Dr. John Alberton. Director of Cardiology at the Royal Brisbane and Women’s Hospital and Head of the newly formed University of Queensland and Adjunct Professor at QIMR Berghofer Medical Research Institute 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 pre-symptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.

Reference: Int J Cardiol 2016;211:124–31

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†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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Dosage and Administration: Initiate 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 m² 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.

Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device

Authors: Di Biase L et al.

Summary: The open-label AATAC trial randomised patients with persistent AF and a dual-chamber implantable cardioverter defibrillator or cardio-resynchronisation therapy defibrillator (NYHA class II–III, LV EF <40% within the prior 6 months) to undergo catheter ablation (n=102) or receive amiodarone (n=101), and followed them for ≥24 months; participants in the catheter ablation arm underwent an average of 1.4 procedures each, and single-procedure success rates were 29–61% across participating centres. Compared with amiodarone, catheter ablation was associated with: i) a significantly greater proportion of patients who were free of AF recurrence (primary endpoint) at the end of follow-up (70% vs. 34% [p<0.001]), with amiodarone associated with a greater likelihood of ‘failure’ (adjusted HR 2.5 [95% CI 1.5–4.3]); ii) a lower 2-year unplanned hospitalisation rate (31% vs. 57%; relative risk 0.55 [0.39–0.76]); and iii) a lower mortality rate (8% vs. 18% [p=0.037]).

Comment: This study demonstrated that catheter ablation resulted in greater freedom from AF recurrence (primary endpoint), improved QOL, increased LV EF and exercise capacity, and reduced unplanned hospitalisation and mortality in HF patients with persistent AF compared with amiodarone. The complication rate was remarkably low, which likely reflects the level of expertise in the operators. It should be noted that repeat ablation procedures (approximately 40% of patients) were not included in the unplanned hospitalisation endpoint. Also, the reduction in mortality was based on small numbers and compared with a treatment with significant toxicity. Whilst the results are promising, larger studies with different comparators will determine whether AF ablation improves long-term clinical outcomes in HF (CASTLE-AF).

Reference: Circulation 2016;133(17):1637–44

Abstract

Impact of spironolactone on longitudinal changes in health-related quality of life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial

Authors: Lewis EF et al., for the TOPCAT Investigators

Summary: Patients aged ≥50 years with symptomatic HF and LV EF ≥45% were randomised to receive spironolactone or placebo in the TOPCAT trial; this paper reported changes in health-related QOL according the study group assignment in 3445 participants for whom paired KCCQ (Kansas City Cardiomyopathy Questionnaire) data were available. The mean change in KCCQ score at 4 months was 7.7 and the mean change in EQ5D visual analogue scale score was 4.7. Compared with placebo recipients, spironolactone recipients had significantly superior adjusted mean changes in KCCQ score at 4 months, 12 months and 36 months, whereas there were no significant between-group differences for changes in EQ5D visual analogue scale scores or McMaster Overall Treatment Evaluation scores. Associations were seen between declines in KCCQ scores and older age, obesity, current smoking, NYHA class III/IV and comorbid illnesses, and spironolactone use was an independent predictor of improved KCCQ score.

Comment: The TOPCAT study did not achieve its primary endpoint; therefore, these results should be considered hypothesis-generating. The improvements in HF-specific QOL were relatively modest, but were similar to those seen with other beneficial treatments in HFREF. Nonetheless, given the limited treatment options for HFPEF and the previously reported regional variations in event rates, treatment effects and side effects in TOPCAT, one could consider spironolactone for patients with persistent symptomatic HFPEF despite diuretic therapy and standard treatment of risk factors including hypertension.

Reference: Circ Heart Fail 2016;9(3):e001937

Abstract

Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction

Authors: Solomon SD et al.

Summary: The PARADIGM trial randomised 8399 patients with NYHA class II–IV HFREF (mean LV EF 29.5%) to receive sacubitril/valsartan 97mg/103mg twice daily or enalapril 10mg twice daily; median follow-up was 27 months. In this paper, LV EF was related to study outcomes (the primary endpoint was CV-related death or HF hospitalisation) and the effectiveness of sacubitril/valsartan across the LV EF spectrum was assessed. Each 5-point decrease in LV EF was associated with increased risks of a primary endpoint event (adjusted HR 1.01 [95% CI 1.05–1.13]), CV-related mortality (1.09 [1.04–1.14]), and all-cause mortality (1.07 [1.03–1.12]). Efficacy of sacubitril/valsartan was evident across the LV EF spectrum when modelled in tertiles or continuously, with no evidence of heterogeneity.

Comment: A consistent reduction in CV death and HF hospitalisation for sacubitril/valsartan compared with enalapril was seen across the full range of LV EFs for the patients enrolled in PARADIGM-HF, including a significant benefit in the upper tertile (LV EF ≥33%). This is important, given that during the study, a decision was made to change the LV EF cutoff criterion from <40% to <35% to ensure a sufficiently high event rate to achieve sufficient power for the CV-related death endpoint. Meanwhile, the efficacy of sacubitril/valsartan is being evaluated in HFPEF in the PARAGON-HF trial.

Reference: Circ Heart Fail 2016;9(3):e002744

Abstract

Chronic subcutaneous brain natriuretic peptide therapy in asymptomatic systolic heart failure

Authors: McKie PM et al.

Summary: Patients with asymptomatic systolic HF were randomised to receive 12 weeks of SC BNP 10 µg/kg (n=22) or placebo (n=12) twice daily. Compared with placebo, BNP treatment was associated with significantly greater increases in urinary sodium excretion (primary endpoint; 166 vs. 15 mEq/min [p=0.02]) and urine flow (p<0.01) at 12 weeks, and there was also a trend for a differential response in glomerular filtration rate (p=0.08).

Comment: This short-term, proof-of-concept study demonstrated increased natriuresis and diuresis in response to volume expansion following the administration of twice-daily SC BNP. This is interesting given the favourable results of the PARADIGM-HF study were likely at least partly due to augmentation of natriuretic peptides. However, it may be difficult to convince asymptomatic HF patients to take regular, SC injections. Whether this translates into a mortality/morbidity benefit and how this compares with SC furosamide should be evaluated in future studies. Furthermore, the same benefits may not be seen on top of angiotensin receptor neprilysin inhibition, which is also associated with augmentation of natriuretic peptides.


Abstract