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Managing heart failure with reduced ejection fraction

Making Education Easy 2018

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Abbreviations used in this review

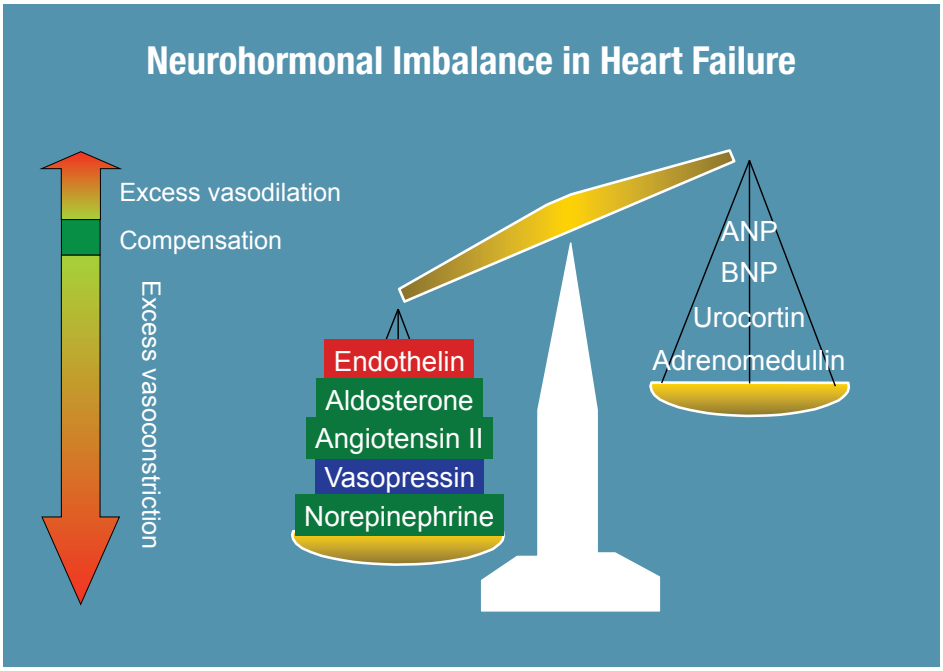
ACEI = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
AICD = automatic implantable cardioverter defibrillator
ANP = atrial natriuretic peptide
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor-neprilysin inhibitor
BB = β-blockers
BNP = brain/B-type natriuretic peptide
BP = blood pressure
CHF = chronic heart failure
CNP = C-type natriuretic peptide
CO = cardiac output
CRT = cardiac resynchronisation therapy
EF = ejection fraction
eGFR = estimated glomerular filtration rate
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
HR = heart rate
IDCM = idiopathic dilated cardiomyopathy
LV = left ventricle
LVEDD = left ventricular end diastolic diameter
LVEF = left ventricular ejection fraction
MRA = mineralocorticoid receptor antagonists
NEP = neutral endopeptidase
NP = natriuretic peptide
NPR = natriuretic peptide receptor
NYHA = New York Heart Association
PAW = pulmonary artery wedge
RA = renin-angiotensin
RAAS = renin-angiotensin-aldosterone system
RCT = randomised controlled trial
SNS = sympathetic nervous system

This review is a summary of presentations given by Professor Richard Troughton, Department of Medicine, University of Otago, Christchurch and Professor Peter Macdonald, Medical Director, Heart Transplant Unit, St Vincent's Hospital, Sydney, NSW, at a symposium at the recent 2018 CSANZ New Zealand Annual Scientific Meeting, held in Christchurch.

HFrEF AND NEUROHORMONAL SYSTEMS

– Professor Richard Troughton

Professor Troughton explained that under normal conditions the control of the circulation is regulated by a very finely balanced system where on one hand we have the sympathetic and renin-angiotensin-aldosterone systems (RAAS) that vasoconstrict and promote salt and water retention, and on the other hand, neurohormones that vasodilate and cause diuresis, modifying the activity of the vasoconstrictors. Between them, these systems allow our circulation to handle the everyday insults that we throw at it (posture change, exercise, dietary indiscretions) and maintain a stable perfusion of vital organs and a stable plasma volume. This is a very well-adapted system. In heart failure (HF), these systems become highly activated (particularly in systolic HF) and the dominant effect is overpowering of vasodilators by vasoconstrictors (**Figure 1**).



ANP = atrial natriuretic peptide; BNP = brain/B-type natriuretic peptide

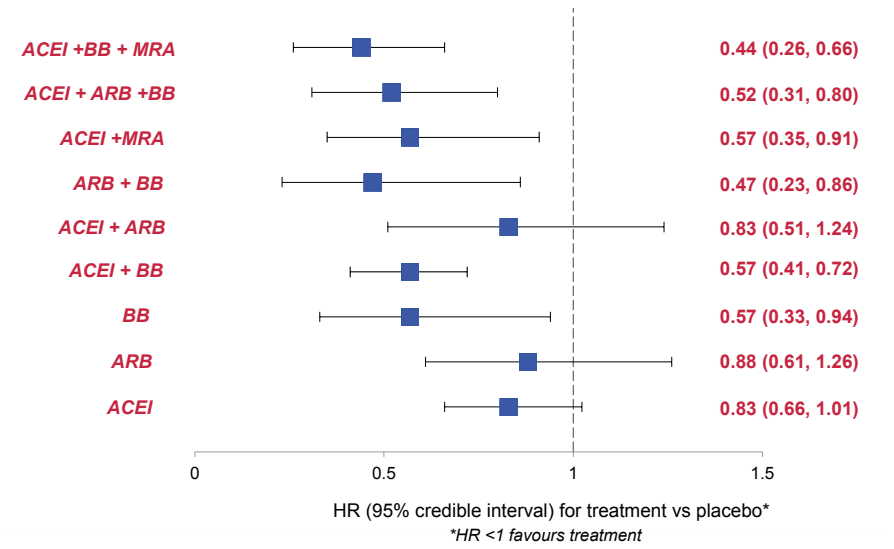
Figure 1. Neurohormonal imbalance in heart failure (Adapted from Shah et al 2001)[1]

HF is characterised by heightened sympathetic tone as a result of abnormal baroreceptor reflexes and angiotensin II-dependent sympathetic nervous system (SNS) activation.[2,3] These factors play a role in adverse haemodynamic and cardiac responses including increased heart rate (HR), increased contractility, increased sodium reabsorption, and increased renal and peripheral vascular resistance. While these mechanisms are good short-term adaptive responses, long-term, they may lead to hypertrophy, fibrosis and direct myocardial toxicity.

Landmark trials in HFrEF

Landmark trials in HF with reduced ejection fraction (HFrEF), included SOLVD-T[4] (enalapril), CIBIS-II[5] (bisoprolol), MERIT-HF[6] (metoprolol), CHARM-Alternative[7] (candesartan), CHARM-Added[8] (candesartan), SHIFT[9] (ivabradine) and EMPHASIS-HF[10] (eplerenone). These trials targeted the RA and sympathetic systems, and this approach was found to be very effective.

A 2017 meta-analysis of 57 RCTs assessing guideline-recommended drug classes (ACEI, ARB, BB and MRA) for HFrEF (**Figure 2**), revealed that combination therapy with RA system and sympathetic system inhibition, and mineralocorticoid receptor antagonism (ACEI + BB + MRA) was associated with a 56% reduction in mortality versus placebo (HR 0.44; 95% credible interval 0.26-0.66).[11] The combination of agents from these classes is now considered the cornerstone of therapy for HFrEF.



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blockers; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; MRA = mineralocorticoid receptor antagonists

Figure 2. Random effects network meta-analysis of 57 RCTs assessing guideline-recommended drug classes (ACEI, ARB, BB, MRA) for HFrEF versus placebo; Hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals (Adapted from Burnett et al. 2017).[11]

Augmenting natriuretic peptides

While the major focus of research has been on antagonising the detrimental effects of the vasoconstrictor systems, the other side of the balance, augmenting the activity of beneficial peptides has, to an extent, been ignored. The most well-known peptides are the natriuretic peptides (atrial natriuretic peptide [ANP], brain or B-type natriuretic peptide [BNP] and C-type natriuretic peptide [CNP]). ANP and BNP are mainly secreted by cardiomyocytes, primarily in response to increased wall stretch, while CNP is largely secreted via vascular endothelial cells in response to vascular shear stress.[12] These peptides produce highly beneficial effects. ANP and BNP work through natriuretic peptide receptor (NPR)-A and result in vasodilation, diuresis, renin secretion inhibition and reduced sympathetic tone, all helpful effects in the setting of HF.[12-15] CNP, acting through NPR-C, is a powerful vasodilator, antifibrotic and antihypertrophic peptide.[12,13]

A study by Lainchbury and colleagues from Christchurch, published in 1999, demonstrated that short-term augmentation of BNP and the hormone adrenomedullin (excreted from vascular tissue) within the pathophysiological range in patients with HFrEF, resulted in beneficial reductions in BP and significant inhibition of aldosterone secretion.[16] Unfortunately it is not pragmatic to infuse such peptides and studies examining short-term infusions did not demonstrate any long-term benefits on mortality or hospitalisation. Another approach has been to inhibit the clearance of natriuretic peptides, which are cleared by two pathways in approximately equal proportions (via NPR-C and through neprilysin).[14] Neprilysin, also called neutral endopeptidase (NEP), is a membrane-bound, zinc-dependent endopeptidase widely present in the kidneys, heart, brain, gut and lungs.[17] Another study by Lainchbury and colleagues investigated the effects of inhibition of NEP in LV impairment and found significant increases in BNP, ANP and second messenger cGMP levels, as well as a late rebound increase in aldosterone levels.[18] Based on the potential for NEP inhibition to be used to increase NP levels long-term, oral NEP inhibitors, such as candoxatril and ecadotril, were developed.[19-22] However, such therapy failed to demonstrate significantly beneficial clinical efficacy in HF, with ecadotril leading to numerically more deaths, and the development of these agents for HF was discontinued.[21] The lack of efficacy with NEP inhibition monotherapy appears to be partly due to increased angiotensin II levels offsetting the beneficial effects of enhancing the NP system.[23] Neprilysin inhibition must therefore be accompanied by simultaneous RAAS blockade and vasopeptidase inhibitors (dual NEP and ACE inhibition) showed promise in HFrEF.

The IMPRESS study comparing the efficacy and safety of the vasopeptidase inhibitor omapatrilat with that of the ACEI lisinopril in 573 patients with HFrEF over 24 weeks found that omapatrilat exhibited a trend towards reducing death or hospital admission for HF and improved NYHA class in patients who were NYHA class III or IV, compared with lisinipril.[24] However, the larger OVERTURE study (n = 5770) comparing omapatrilat with the ACEI enalapril, showed that omapatrilat reduced the risk of death and hospitalisation in CHF, but was no more effective than ACEI monotherapy in reducing the risk of a primary clinical event; furthermore, significant safety concerns were raised, with a significantly higher risk of angioedema with omapatrilat.[25] The observed angioedema was subsequently attributed to the simultaneous inhibition of neprilysin and ACE by omapatrilat resulting in elevated levels of bradykinin.[26,27]

In further studies, the selective inhibition of NEP, coupled with an ARB, was found to enhance the beneficial effects of the NP system while inhibiting the RAAS with minimal effect on bradykinin degradation.[26] Developed by Novartis, the first-in-class dual NEP inhibitor and AT1 receptor blocker, sacubitril/valsartan [Entresto®], was designed to inhibit vasoconstrictors and their harmful effects, while augmenting ANP, BNP and CNP and their beneficial effects.[28,29]

KEY RESULTS FROM THE PARADIGM-HF STUDY

– Professor Peter Macdonald

About PARADIGM-HF

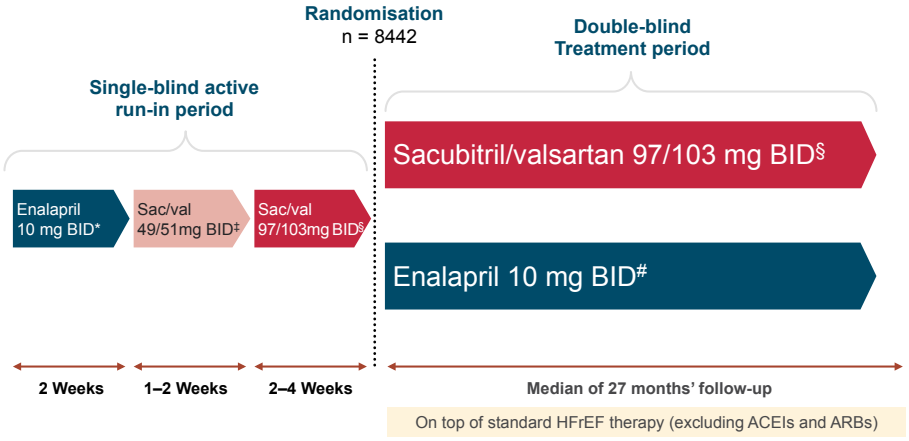
PARADIGM-HF was the landmark study comparing ARNI with ACEI and was specifically designed to determine whether sacubitril/valsartan could replace ACEIs as the cornerstone of HFrEF treatment.[29,30] The study was a world-wide (although not including NZ and Australia) multicentre, randomised, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril on morbidity and mortality in patients with chronic HFrEF. PARADIGM-HF, involving 8442 patients, is the largest mortality/morbidity trial to date in HFrEF.

Enalapril was chosen as the comparator to sacubitril/valsartan as it was the only ACEI shown to reduce mortality in a broad spectrum of HFrEF patients; the SOLVD-T study demonstrated a significantly reduced risk of mortality with enalapril versus placebo in patients with NYHA class I-IV HFrEF.[4] Enalapril at 10mg twice daily is the regulatory `gold standard' ACEI based upon SOLVD-T and CONSENSUS trial data, and this dose was chosen as the comparator dose in the PARADIGM-HF study.[4,29-31] The mean daily enalapril dose achieved in PARADIGM-HF (18.9mg) was higher than, or similar to, mean daily doses received in SOLVD-T (16.6mg) and CONSENSUS (18.4mg), respectively.[4,29,31]

A 200mg twice daily dose of sacubitril/valsartan was chosen as this dosing is considered essential to obtain 24-hour NEP inhibition.[25,30] Furthermore, twice daily dosing mitigates the risk of post-dose hypotension, such as that seen in the OVERTURE study with a larger once-daily dose of omapatrilat.[25,30]

Study design

The PARADIGM-HF study design is depicted in **Figure 3**.[30] A total of 10,513 patients entered the enalapril run-in phase and 9419 carried on to enter the sacubitril/valsartan run-in phase. Only those who had tolerated treatment during the run-in phase (n = 8442) were randomised to double-blind treatment; 4187 patients received sacubitril/valsartan and 4212 received enalapril.[29] Key study inclusion criteria for PARADIGM-HF included NYHA class II-IV HF, LVEF ≤40% (later amended to ≤35%), ability to tolerate enalapril 10 mg/day for >4 weeks, on guideline-endorsed treatment with BBs and MRAs, systolic BP ≥100 mmHg at baseline or systolic BP ≥95 mmHg after enalapril run-in, eGFR >30 mL/min/m^2 and K+ ≤5.4 mmoL/L at randomisation. The mean age was approximately 64 years, the majority of patients were male, approximately 70% were NYHA functional class II, BP was well preserved, 80% were receiving diuretics, over 90% were receiving BBs and over half were receiving MRAs. Professor Macdonald pointed out that patients with NYHA functional class II are the sort of patients that come into ones medical practice doing reasonably well on an ACEI and BB.



ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; BID = twice daily; HFrEF = heart failure with reduced ejection fraction; Sac/val = sacubitril/valsartan

*Enalapril 5mg twice-daily (10mg total daily dose) for 1-2 weeks followed by enalapril 10mg twice-daily (20mg total daily dose) as an optional starting run-in dose for those patients who were treated with ARBs or with a low dose of ACEI; ‡98/102mg total daily dose; §194/206 total daily dose; #20mg total daily dose.

Figure 3. PARADIGM-HF study design.[30]

Study results

The primary endpoint in PARADIGM-HF was the composite of death from cardiovascular causes or first hospitalisation for HF. The study was stopped early after a median follow-up of 27 months, because the boundary for an overwhelming benefit with sacubitril/valsartan had been crossed.[29] At that time, the primary outcome had occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1117 patients (26.5%) in the enalapril group (hazard ratio 0.80; 95% CI 0.73-0.87; p < 0.001) and the benefit with sacubitril/valsartan was evident for over 3 years of follow-up (**Figure 4**). Analysis of the individual components of the primary endpoint revealed a 20% reduction in risk of death from cardiovascular causes (hazard ratio 0.80; 95% CI 0.71-0.89, p < 0.001) and a 21% reduction in risk of first hospitalisation for HF (hazard ratio 0.79; 95% CI 0.71-0.89, p < 0.001) with sacubitril/valsartan compared with enalapril.[29] Strikingly, the benefit seen with sacubitril/valsartan with regard to reduction in HF hospitalisation was evident within the first 30 days after randomisation (hazard ratio 0.60; 95% CI 0.38-0.94, p = 0.027).[32]

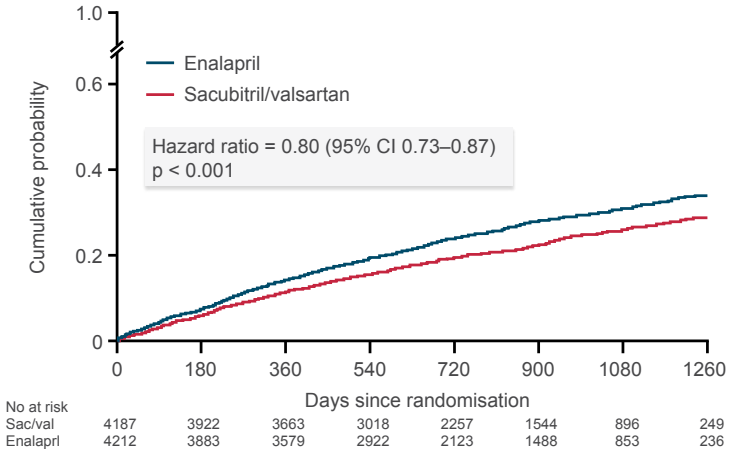


Figure 4. Primary endpoint (composite of death from cardiovascular causes or first hospitalisation for HF) in the PARADIGM-HF study.[29]

The results of pre-specified subgroup analyses for the primary endpoint are shown in **Figure 5**. Professor Macdonald explained that the benefit with sacubitril/valsartan tended to favour the younger and less symptomatic patients (NYHA class I or II).[29] There was consistent benefit with sacubitril/valsartan over enalapril regardless of baseline eGFR, diabetic status, systolic BP, median EF or AF.

All-cause mortality, sudden cardiac death and worsening HF were significantly reduced in sacubitril/valsartan recipients compared with enalapril recipients (**Figure 6**); the majority (>80%) of deaths had a cardiovascular cause.[33] The distribution of cause of death in PARADIGM-HF is comparable to recent HFrEF trials.[34] Among secondary endpoints investigated were new-onset AF and decline in renal function which showed no significant difference between the two treatment groups, and systolic BP during run-in and after randomisation, which showed a mean decrease of 3.2mmHg from the value at randomisation with sacubitril/valsartan compared with enalapril ($p < 0.001$).[29]

Adverse events leading to drug discontinuation

Fewer patients in the sacubitril/valsartan group than in the enalapril group discontinued study drug due to an adverse event (10.7% vs 12.3%, $p = 0.03$).[29] Adverse events leading to permanent study drug discontinuation included hypotension (sacubitril/valsartan 0.9% vs enalapril 0.7%, $p = 0.38$), renal impairment (0.7% vs 1.4%, $p = 0.002$) and hyperkalaemia (0.3% vs 0.4%, $p = 0.56$).[29]

Where does sacubitril/valsartan fit within current HFrEF guidelines?

Professor Macdonald discussed the new European Guidelines for the diagnosis and treatment of acute and chronic HF (**Figure 7**) and explained where the ARNI sacubitril/valsartan fits into the treatment algorithm.[35] The guidelines recommend that patients with HFrEF should initially receive an ACEI plus a BB and if they remain symptomatic with an LVEF ≤35%, an MRA should be added. If these patients continue to be symptomatic with an LVEF ≤35% and are able to tolerate an ACEI (or ARB), then they should be switched from the ACEI to an ARNI (sacubitril/valsartan).

Professor Macdonald pointed out that the Australian and New Zealand Guidelines are in the process of being rewritten to incorporate the use of ARNIs in patients with HFrEF. He concluded that ARNI are now starting to replace ACEI/ARB as the cornerstone of HFrEF therapy. He believes that for the time being, patients starting therapy will still be placed on ACEIs and ARBs, but once they are stabilised they will tend to be switched to ARNIs.

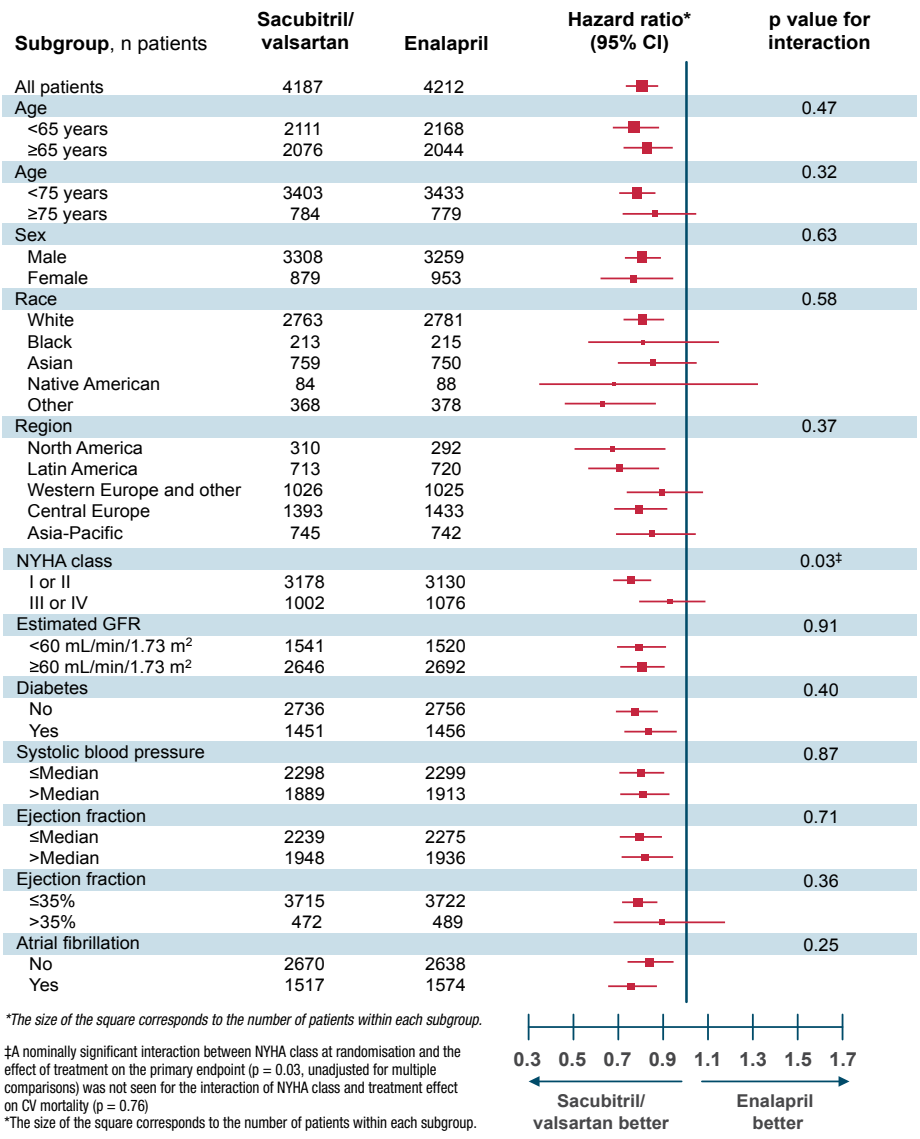
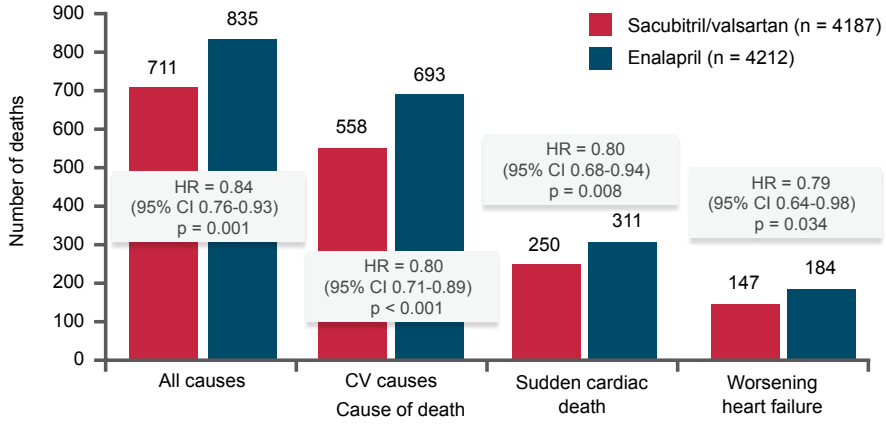
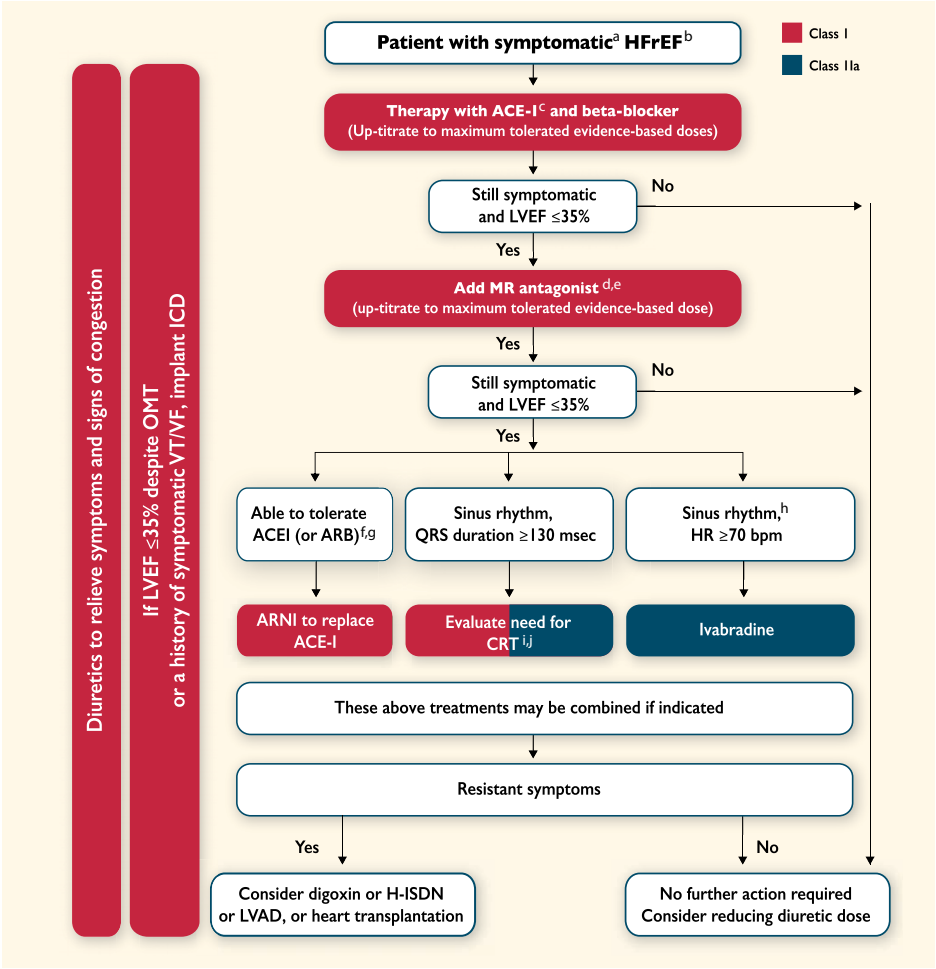


Figure 5. Pre-specified subgroup analysis for the primary endpoint (composite of death from cardiovascular causes or first hospitalisation for HF) in the PARADIGM-HF study.
(Adapted from McMurray et al 2014[29]).



CV = cardiovascular; HR = hazard ratio

Figure 6. Distribution of cause of death and worsening HF in the PARADIGM-HR study.[33]



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronisation therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a]Symptomatic = NYHA Class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contraindicated, use ARB. [d]If MR antagonist not tolerated/contra-indicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/mL or NTproBNP > 500 pg/mL in men and 750 pg/mL in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalisation within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g]In doses equivalent to enalapril 10 mg b.i.d. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥ 130msec and LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥130msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualised decision). Red indicates a class I recommendation, blue indicates a class IIa recommendation.

Figure 7. Therapeutic algorithm for the treatment of HFrEF.[35]

Take-home messages:

- Consider sacubitril/valsartan in HFrEF patients after they are stabilised on an ACEI or ARB
- Initial dose of sacubitril/valsartan will depend on tolerated dose of ACEI or ARB
- The NYHA Class II patient is the ideal candidate to make the change to sacubitril/valsartan
- Allow 36 hours between last dose of ACEI and first dose of ARNI.

Case report supporting the use of sacubitril/valsartan

Professor Macdonald presented the following case as an example of the type of patient he believes is suitable for treatment with sacubitril/valsartan.

A relatively young man (aged 47 years) was diagnosed in 2012 with idiopathic dilated cardiomyopathy (IDCM) after presenting with a chest infection and acute decompensated HF. At that time, he was working as a large-vehicle mechanic and had been well prior to this presentation. A chest x-ray revealed marked cardiomegaly, an ECG showed sinus rhythm with left bundle branch block and a dilated LV (LVEDD 85mm), with a very low LVEF (15%) evident upon echocardiography. At that time, he was referred for potential consideration for heart transplantation. A right heart catheter was placed and a very low cardiac output (3.0) and cardiac index (1.4) were recorded. A coronary angiogram revealed normal findings.

The man was started on therapy with bisoprolol, ramipril, frusemide, spironolactone and warfarin, and underwent a primary prevention CRT/AICD. He demonstrated a marked improvement and was able to return to work, performing mainly administration duties. He swam 500m a day and was classified as NYHA Class I-II. He was uptitrated to a full dose of ramipril, bisoprolol and spironolactone, and was continuing to take warfarin. Despite his improvement, echocardiography revealed an LVEDD of 89mm and an LVEF of 15-20%. A repeat right heart catheterisation revealed an improved wedge pressure and a cardiac index of 2.3.

In February 2017, the man felt that he was doing well, however, echocardiography findings revealed an LVEDD of 96mm and a LVEF of 15-20%. He was subsequently switched from ramipril to sacubitril/valsartan, initially at a dose of 49/51mg twice daily and 2 weeks later to a dose of 97/103mg twice daily. In February 2018, he remained symptomatically well with an LVEDD of 87mm and an LVEF of 20-25%.

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