



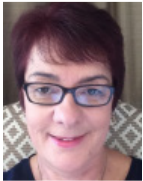
A RESEARCH REVIEW™
PRODUCT REVIEW

Sacubitril/Valsartan (Entresto®)

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2019

About the Reviewer



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Dr Raewyn Fisher, is an experienced general cardiologist working at Waikato DHB and Waikato Heart in Hamilton, with a special interest in echocardiography, hypertension and heart failure. Dr Fisher is the clinical director of the Waikato community-based Heart Failure Service and current chair of the Heart Failure Working Group of the NZ Cardiac Society. She has been involved in regional cardiology pathway development and is passionate about improving care for heart failure patients using new and established therapies.

ABOUT RESEARCH REVIEW

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This review discusses the evidence in support of the use of sacubitril/valsartan (Entresto®) for the treatment of patients with chronic heart failure and reduced ejection fraction. Sacubitril/valsartan is the first of a new class of agents, the angiotensin receptor neprilysin inhibitors, which have been designed to block the renin-angiotensin-aldosterone system and enhance natriuretic peptides, thereby improving neurohormonal balance in patients with heart failure.¹ Following New Zealand registration in November 2016, sacubitril/valsartan was approved for reimbursement by Pharmac in October 2018 for patients with NYHA/WHO functional class II, III or IV heart failure and a LVEF $\leq 35\%$, who are receiving concomitant optimal standard treatments for heart failure.^{2,3} This review is sponsored Novartis (NZ) Ltd.

Introduction

The prevalence of heart failure is approximately 1-2% of the population in developed countries, including New Zealand, rising to $\geq 10\%$ amongst those aged >70 years.^{4,5} Approximately 1 in 6 individuals aged >65 years presenting to primary care with breathlessness on exertion have unrecognised heart failure.⁶⁻⁸ At age 55 years, the lifetime risk of heart failure is 33% for men and 28% for women.⁵ Despite improvements in treatments and their implementation for heart failure, patient outcomes often remain unsatisfactory. Recent European data estimate 12-month all-cause mortality at 17% for hospitalised patients and 7% for stable/ambulatory patients.⁹ Corresponding 12-month hospitalisation rates were 44% and 32%, respectively.⁹

Sacubitril/valsartan for heart failure

Sacubitril/valsartan is the first in a new class of agents, the angiotensin receptor neprilysin inhibitors, which have been designed to block the renin-angiotensin-aldosterone system and enhance natriuretic peptides, thereby improving neurohormonal balance in patients with heart failure.¹ The landmark PARADIGM-HF trial, published in 2014, found that sacubitril/valsartan was superior to enalapril in reducing the risk of cardiovascular death and hospitalisation for heart failure.¹⁰ In 2018, the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand published updated guidelines for the management of chronic heart failure, recommending the use of sacubitril/valsartan in patients with heart failure and a LVEF $\leq 40\%$ despite receiving maximally tolerated or target doses of an ACE inhibitor or ARB and a β -blocker, with or without a mineralocorticoid antagonist.¹¹

In November 2016, sacubitril/valsartan was registered in New Zealand by Medsafe for the treatment of adult patients with chronic heart failure (NYHA functional class II-IV) and reduced ejection fraction.² In October 2018, sacubitril/valsartan was approved for reimbursement by Pharmac with the following special authority criteria:


- Patients must have NYHA/WHO functional class II, III or IV heart failure
- Patients must have documented LVEF $\leq 35\%$
- Patients must be receiving concomitant optimal standard chronic heart failure treatments
- Patients must be re-assessed after 12 months to ensure that sacubitril/valsartan remains appropriate and the patient is benefiting from this treatment
- Sacubitril/valsartan must not be co-administered with an ACE inhibitor or ARB.³

Prescribing is allowed by any relevant practitioner, however the data sheet states that sacubitril/valsartan should be initiated and up-titrated by a physician experienced with the treatment of heart failure.²

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Efficacy data from PARADIGM-HF

The PARADIGM-HF trial was a randomised, double-blind trial of 8442 patients with NYHA class II-IV heart failure, reduced ejection fraction and elevated NT-proBNP levels, who were treated with either sacubitril/valsartan or enalapril.¹⁰ At baseline, most patients were receiving standard heart failure therapies, consisting of β -blockers (93%), diuretics (80%), mineralocorticoid antagonists (56%), digitalis (30%), implantable cardioverter-defibrillator (15%) and cardiac resynchronisation therapy (7%).¹⁰ These treatments were continued throughout the study period.¹⁰ NYHA class was I in 5% of patients, II in 70% of patients, III in 24% of patients and IV in 1% of patients.¹⁰ Mean age of study participants was 64 years, 78% were male and 5% identified as Black. Mean LVEF was 29%.¹⁰

Effects on cardiovascular death and hospitalisations for heart failure

At the time of study closure after a median follow-up of 27 months, the primary composite endpoint of cardiovascular death or heart failure hospitalisation had occurred in 21.8% of patients in the sacubitril/enalapril group and 26.5% of patients in the enalapril group (see **Figure 1**), giving a hazard ratio (HR) of 0.80 (95% CI 0.73-0.87; $p < 0.001$) with sacubitril/valsartan.¹⁰

In contrast to several previous trials of ACE inhibitors and ARBs in heart failure, which have shown a more marked effect on hospitalisation for worsening heart failure than for cardiovascular death,¹²⁻¹⁵ sacubitril/valsartan had a similar degree of benefit on both outcomes (HR 0.80; 95% CI 0.71-0.89; $p < 0.001$) for cardiovascular death and (HR 0.79; 95% CI 0.71-0.89; $p < 0.001$) for heart failure hospitalisations vs enalapril.¹⁰

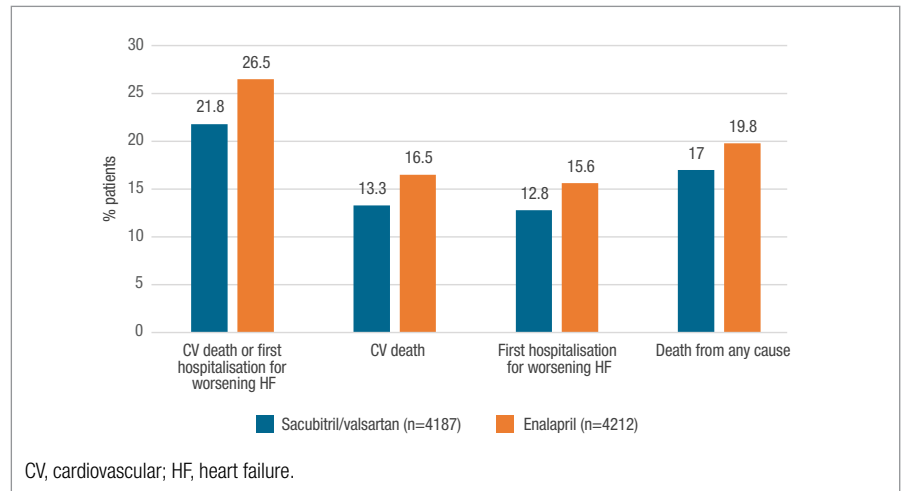
The reduced risk of cardiovascular death with sacubitril/valsartan vs enalapril was largely attributable to reductions in the risks for both sudden cardiac death (HR 0.80; 95% CI 0.68-0.94; $p < 0.01$) and death due to worsening heart failure (HR 0.79; 95% CI 0.64-0.98; $p < 0.05$).¹⁶ The risk of death from any cause was also significantly lower in the sacubitril/valsartan vs enalapril group (HR 0.84; 95% CI 0.76-0.93; $p < 0.001$).¹⁰

The reduced rate of heart failure hospitalisation with sacubitril/valsartan vs enalapril was statistically significant after only 30 days of treatment.¹⁷

Effects across age categories

When patients were analysed according to age < 55 years, 55-64 years, 65-74 years or ≥ 75 years, the superiority of sacubitril/valsartan compared with enalapril for the primary composite outcome of cardiovascular death or hospitalisation for heart failure was consistent across all age categories.¹⁸ Although risk of cardiovascular death was slightly higher with sacubitril/valsartan compared with enalapril in the most elderly patients, there was no significant interaction between age and treatment effect on this variable.¹⁸ The incremental benefit of sacubitril/valsartan compared with enalapril on hospitalisation for heart failure and all-cause mortality was consistent across all age categories.¹⁸

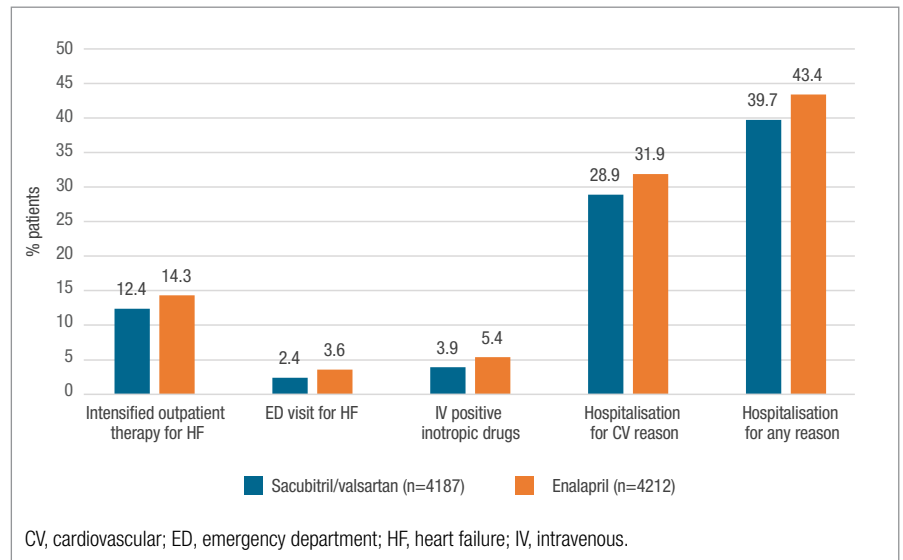
Figure 1. Cardiovascular death, hospitalisation for worsening heart failure and death from any cause in the PARADIGM-HF trial.¹⁰



Effects on clinical progression in surviving patients

Fewer patients treated with sacubitril/valsartan than enalapril required intensification of medical treatment for heart failure (12.4% vs 14.3%; HR 0.84; 95% CI 0.74-0.94; $p < 0.01$) (see **Figure 2**).¹⁷ Sacubitril/valsartan also reduced the risk of an emergency department visit for worsening heart failure (HR 0.66; 95% CI 0.52-0.85; $p = 0.001$), of requiring intravenous positive inotropic drugs (HR 0.69; 95% CI 0.57-0.85; $p < 0.001$), of hospitalisation for a cardiovascular reason (HR 0.88; 95% CI 0.82-0.94; $p < 0.001$) and of hospitalisation for any reason (HR 0.84; 95% CI 0.78-0.91; $p < 0.001$).¹⁷

Figure 2. Measures of clinical progression in surviving patients in the PARADIGM-HF trial.¹⁷

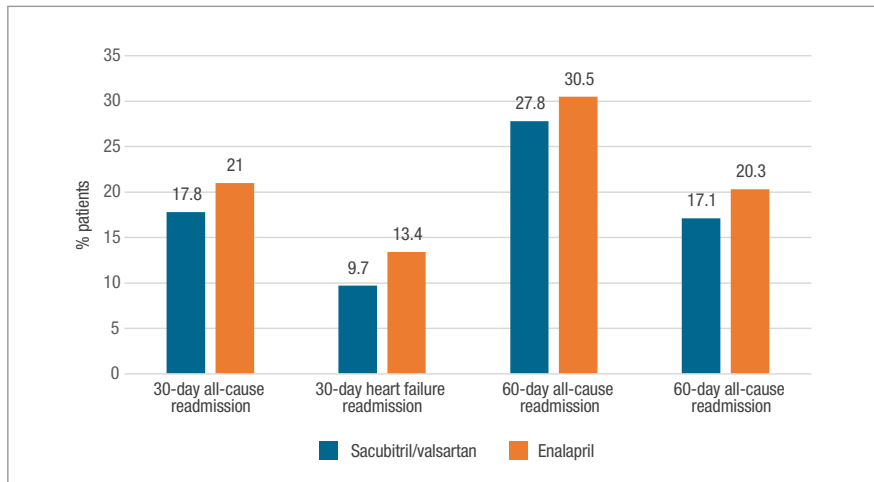


Effects on 30-day hospital readmission

Readmission for heart failure is being increasingly used as a metric for quality of care. Since 2010, US hospitals with higher than expected 30-day readmission rates have been at risk for substantial financial penalties as part of the Hospital Readmission Reduction Program.¹⁹ In PARADIGM-HF, there were 1076 heart failure hospitalisations in the sacubitril/valsartan group, and 1307 in the enalapril group.²⁰ The 30-day rate of hospital readmission for any cause was 17.8% in the sacubitril/valsartan group and 21.0% in the enalapril group (see **Figure 3**), giving an odds ratio for sacubitril/valsartan of 0.74 (95% CI 0.56-0.97; $p = 0.031$).²⁰ Corresponding rates of readmission for heart failure at 30 days were 9.7% and 13.4%, respectively (OR 0.62; 95% CI 0.45-0.86; $p = 0.006$).²⁰ The benefit of sacubitril/valsartan persisted at 60 days, with significantly lower rates of all-cause readmission and heart failure readmission.²⁰ Benefits were also apparent when the analysis was restricted to patients with adjudicated heart failure hospitalisations, patients enrolled in the US and Medicare-eligible patients aged > 65 years.²⁰



Figure 3. Readmission after heart failure hospitalisation in the PARADIGM-HF trial.²⁰



Expert comment

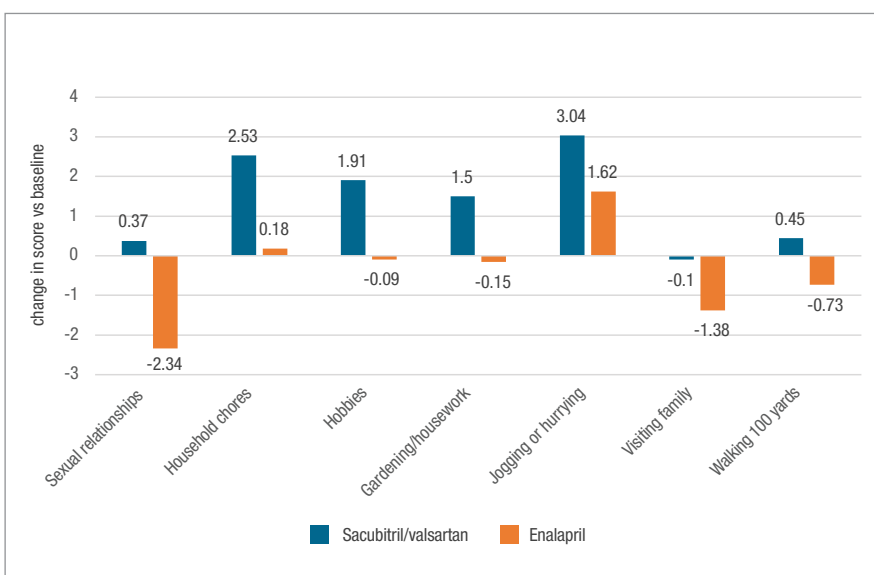
Rehospitalisation contributes to a large proportion of the health burden of chronic heart failure. Although avoiding first hospitalisation with prevention, early diagnosis and instituting appropriate therapy for heart failure (especially heart failure with reduced ejection fraction) is the ideal goal, managing those with established disease is far from a lost cause. The outlook for patients with a diagnosis of heart failure is more optimistic these days, and with our heart failure management teams along with our early experience of sacubitril/valsartan we are already seeing patients spending more time well and at home.

Effects on quality of life

Improving health-related quality of life, rather than simply prolonging life, is an important outcome for many patients with heart failure.²¹ Health-related quality of life was a prespecified secondary outcome measure of the PARADIGM-HF trial.²²

At 8 months, both Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score and KCCQ overall summary score were significantly improved with sacubitril/valsartan compared with enalapril (0.64 vs -0.29, $p=0.008$ and 1.13 vs -0.14, $p<0.001$, respectively).²² Furthermore, significantly fewer patients had a ≥ 5 -point decrease on both KCCQ scores with sacubitril/valsartan vs enalapril (27% vs 31%; $p=0.01$).²² Consistent improvements in KCCQ-CS and KCCQ-OS scores with sacubitril/valsartan vs enalapril were observed through to 36 months.²²

Figure 4. Change in KCCQ physical and social activity scores at 8 months in the PARADIGM-HF trial.²³



A further analysis of PARADIGM-HF data investigated individual physical and social activity items in the KCCQ domains that are particularly important to patients with heart failure.²³ Items measured were dressing yourself, showering or having a bath, walking 100 yards on level ground, doing gardening or housework or carrying groceries, climbing a flight of stairs without stopping, jogging or hurrying, hobbies and recreational activities, working or doing household chores, visiting family or friends and intimate or sexual relationships.²³

At baseline, jogging and sexual relationships has the lowest mean scores on the KCCQ, suggesting the greatest limitation, while dressing yourself and showering had the highest mean scores, suggesting the least limitation.²³ At 8 months, the baseline-adjusted change in scores significantly favoured sacubitril/valsartan over enalapril for all activities except dressing yourself, showering and climbing a flight of stairs.²³ As shown in **Figure 4**, the largest differences in scores with sacubitril/valsartan vs enalapril were seen for sexual relationships and household chores (adjusted change score differences 2.72; 95% CI 0.97-4.46; $p=0.002$ and 2.35; 95% CI 1.19-3.50; $p<0.001$, respectively).²³ When assessed at 36 months, sacubitril/valsartan was associated with significantly greater change in KCCQ score vs enalapril for all activities except dressing yourself, with the greatest improvement seen in sexual relationships.²³

Expert comment

With any chronic disease, the aim is not only to prolong life but to improve quality of life. Our experience of sacubitril/valsartan thus far supports the above evidence, with many patients reporting more energy, less fatigue and as a result able to do more. In addition, as depression commonly coexists with heart failure (like many chronic health conditions) this improvement in quality of life scores should lead to better mood and less clinical depression.

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Real-world studies

To date, published reports on the use of sacubitril/valsartan for patients with heart failure in clinical practice are limited. In a Spanish prospective registry, 427 patients treated with sacubitril/valsartan were followed for a mean of 7 months.²⁴ Both cardiovascular mortality and all-cause mortality were higher in the 12% of patients who discontinued sacubitril/valsartan compared with those who continued (hazard ratios 13.22 [95% CI 6.71-15.73; $p < 0.001$] and 13.51 [95% CI 3.22-56.13; $p < 0.001$], respectively).²⁴ NT-proBNP levels, NYHA functional class and LVEF were significantly improved vs baseline in patients who remained on sacubitril/valsartan (all $p \leq 0.001$).²⁴

In a retrospective analysis of 201 patients in Belgium, 11% had ≥ 1 hospital admission for heart failure after approximately 7 months on sacubitril/valsartan, compared with 25% of patients prior to initiation of this treatment ($p < 0.001$).²⁵ A significant effect was seen in patients with both low and high baseline NYHA class; patients aged > 75 years exhibited a trend towards reduction in heart failure hospitalisation.²⁵ Higher doses of sacubitril/valsartan were associated with a higher reduction in heart failure hospitalisation.²⁵ NYHA functional class was improved in 32% of patients.²⁶

In a US retrospective study of 200 patients, the proportion with ≥ 1 all-cause inpatient stay was significantly decreased after 4 months of sacubitril/valsartan vs baseline (17.0 vs 27.5%; $p = 0.009$).²⁷ Fatigue and shortness of breath were also significantly improved after sacubitril/valsartan treatment vs baseline ($p = 0.027$ and 0.008 , respectively).²⁷

Efficacy data from PIONEER-HF

The PIONEER-HF trial, which involved 881 stabilised patients with acute decompensated heart failure, has extended the evidence base for the use of sacubitril/valsartan in populations for which there is no or little data.²⁸ It is important to note, however, that sacubitril/valsartan is currently not licensed for use in acute heart failure.²

Patients in PIONEER-HF had signs and symptoms of fluid overload, a LVEF $\leq 40\%$, an elevated NT-proBNP concentration and were haemodynamically stable (systolic blood pressure ≥ 100 mm Hg, no increase in the dose of intravenous diuretics and no use of intravenous vasodilators in the preceding 6 hours, no use of intravenous inotropes in the preceding 24 hours).²⁸ Patients were enrolled a median of 68 hours after initial presentation to hospital, and were randomised in a double-blind fashion to treatment with sacubitril/valsartan or enalapril.²⁸ A previous diagnosis of heart failure was noted in only 65% of patients, of whom 60% had been hospitalised at least once in the previous year.²⁸ At the time of hospital admission, 52% of patients were not receiving treatment with an ACE inhibitor or ARB.²⁸ Mean patient age was 61 years, 72% were male and 36% identified as Black.²⁸

There was a 29% reduction in the primary endpoint of time-averaged proportional change in NT-proBNP concentration from baseline at weeks 4 and 8 with sacubitril/valsartan vs enalapril (ratio of change 0.71; 95% CI 0.63-0.81; $p < 0.001$).²⁸ The greater reduction of change in NT-proBNP concentration with sacubitril/valsartan vs enalapril was evident as early as week 1 (ratio of change 0.76; 95% CI 0.69-0.85).²⁸ Furthermore, there was a 46% reduction in the exploratory composite clinical endpoint of death, heart failure rehospitalisation, or the need for a left ventricular device or heart transplant (relative risk with sacubitril/valsartan vs enalapril 0.54; 95% CI 0.37-0.79), which was primarily driven by a reduction in heart failure rehospitalisation (relative risk 0.56; 95% CI 0.37-0.84).²⁸

Expert comment

Although the Pioneer-HF data is encouraging, and supports the larger PARADIGM-HF trial results showing early (30-day) benefit, I believe it is a bit too soon to extrapolate this into widespread current practice. Guidelines and PARADIGM-HF data support sacubitril/valsartan commencement after optimal medical therapy, which includes maximal tolerated doses of β -blockers and an ACE inhibitor or ARB, with or without a mineralocorticoid antagonist.

Pharmacological properties

Sacubitril/valsartan is a sodium salt complex comprising the anionic forms of sacubitril and valsartan in a 1:1 molar ratio.² Studies in healthy volunteers and patients with heart failure have shown simultaneous neprilysin inhibition and RAAS blockade after administration of sacubitril/valsartan.^{17,24,26} In the PARADIGM-HF trial, plasma BNP and urine cGMP levels (biomarkers of neprilysin inhibition) were significantly increased at 4 weeks and 8 months in patients treated with sacubitril/valsartan compared with enalapril, while plasma NT-proBNP (a biomarker for cardiac wall stress) and troponin T (a biomarker for cardiac injury) levels were significantly decreased.¹⁷

The valsartan contained within sacubitril/valsartan is more bioavailable than valsartan in other marketed tablet formulations.² Thus a 97mg/103mg dose of sacubitril/valsartan gives equivalent exposure to valsartan as a 160mg valsartan tablet.² Steady-state concentrations of sacubitril, valsartan and the sacubitril metabolite LBQ657 are reached 3 days after twice daily administration.² Administration with food has no significant effect on the systemic exposure of sacubitril/valsartan.²

Prescribing considerations

Dose titration

Sacubitril/valsartan is available in three dose strengths:

- 24 mg/26 mg
- 49 mg/51 mg
- 97 mg/103 mg.²

The recommended starting dosage of sacubitril/valsartan for most patients is 49mg/51mg twice daily.² This should be increased to the target maintenance dosage of 97mg/103mg twice daily after 2-4 weeks, depending on patient tolerability.² For patients developing systolic blood pressure ≤ 95 mm Hg, symptomatic hypotension, hyperkalaemia or renal dysfunction while on sacubitril/valsartan, consideration should be given to adjustment of concomitant medications, or to temporary down-titration or discontinuation of sacubitril/valsartan.²

A lower starting dosage of 24mg/26mg twice daily is recommended for patients not currently receiving an ACE inhibitor or ARB, and for patients receiving those agents at a low dosage.² The lower starting dosage should also be used in patients at risk of hypotension, including those aged ≥ 75 years and those with a systolic BP ≥ 100 -110 mm Hg, and in patients with moderate hepatic impairment or severe renal impairment.² Sacubitril/valsartan dosage should then be doubled every 2-4 weeks until the target maintenance dosage is reached, depending on patient tolerability.²

In the TITRATION study, which investigated the tolerability of up-titrating sacubitril/valsartan in patients with NYHA class II-IV chronic heart failure and LVEF $\leq 35\%$, 76% of patients achieved and maintained the target dose of 97 mg/103 mg twice daily, without any dose interruption or down-titration over the 12-week period.²⁷

Drug interactions

Sacubitril/valsartan is contraindicated in patients receiving an ACE inhibitor because of the risk of angioedema.² A 36-hour washout period must be applied when switching between these treatments.² Caution is required when sacubitril/valsartan is given in combination with direct renin inhibitors such as aliskiren.² Concomitant use of these agents is contraindicated in patients with type 2 diabetes mellitus, and should be avoided in patients with renal impairment.² Sacubitril/valsartan should not be co-administered with an ARB.²



Other interactions to be considered include the following:

- Statins or PDE-5 inhibitors such as sildenafil – the effects of these drugs may be potentiated with concomitant administration of sacubitril/valsartan – caution should be exercised
- Potassium-sparing diuretics, mineralocorticoid antagonists, potassium supplements or salt substitutes containing potassium – monitoring of serum potassium is recommended
- NSAIDs – monitoring of renal function is recommended when initiating or modifying sacubitril/valsartan treatment
- Lithium – monitoring of serum lithium levels is recommended
- Furosemide – coadministration with sacubitril/valsartan may reduce urinary excretion of sodium
- Inhibitors of OATP1B1, OATP1B3, OAT3 or MRP2, including rifampicin, cyclosporin and ritonavir – care should be exercised when initiating or ending coadministration of sacubitril/valsartan
- Metformin – the clinical status of patients should be evaluated upon initiation of sacubitril/valsartan.²

Adverse events

In the PARADIGM-HF trial of patients with chronic heart failure and reduced ejection fraction, hyperkalaemia, hypotension and renal impairment were the events most commonly associated with interruption or dosage adjustment for both sacubitril/valsartan and enalapril (see **Table 1**).¹⁰ Symptomatic hypotension was the only adverse event that was significantly more frequent in sacubitril/valsartan-treated patients than enalapril-treated patients (14.0% vs 9.2% overall; $p < 0.001$),¹⁰ and was comparable to the rate of 16.6% seen in the Spanish prospective registry of sacubitril/valsartan.²⁴

In general, adverse events were more common with increasing age in both sacubitril/valsartan- and enalapril-treated patients, but the distribution of events according to treatment remained consistent across age categories.¹⁸ Symptomatic hypotension occurred in 11.5% of patients aged <55 years treated with sacubitril/valsartan and 17.7% of those aged ≥75 years.¹⁸ Corresponding rates in the enalapril group were 7.6% and 11.9%.¹⁸ Mean systolic BP at 8 months was 3.2mm Hg lower in the sacubitril/valsartan group compared with the enalapril group ($p < 0.001$).¹⁰

None of patients who developed angioedema had compromised airways or required mechanical airway ventilation.¹⁰ Black patients had a higher rate of

angioedema, at 2.4% for sacubitril/valsartan recipients and 0.5% for enalapril recipients.¹⁰

In the PIONEER-HF trial of patients with acute decompensated heart failure, rates of worsening renal function, hyperkalaemia and symptomatic hypotension did not differ significantly between the sacubitril/valsartan and enalapril groups.²⁸ The rate of angioedema was 0.2% in the sacubitril/valsartan group (occurring in 1 White patient) and 1.4% in the enalapril group (occurring in 6 Black patients).²⁸

Table 1. Key adverse events with sacubitril/valsartan in the PARADIGM-HF trial.¹⁰

	Sacubitril/ valsartan (n=4187)	Enalapril (n=4212)
Hypotension		
Symptomatic	14.0%*	9.2%
Symptomatic with systolic BP <90 mm Hg	2.7%*	1.4%
Hyperkalaemia		
>5.5 mmol/L	16.1%	17.3%
>6.0 mmol/L	4.3%#	5.6%
Renal impairment	10.1%	11.5%
Elevated serum creatinine		
≥2.5 mg/dl	3.3%#	4.5%
≥3.0 mg/dl	1.5%	2.0%
Angioedema	0.5%	0.2%

* $p < 0.001$ vs enalapril; # $p < 0.01$ vs enalapril.

Expert comment

As with the introduction and up-titration of ACE inhibitors/ARBs and β -blockers in heart failure patients, careful monitoring of blood pressure along with fluid status, renal function and potassium is required. Symptomatic hypotension can be avoided or managed by a reduction in sacubitril/valsartan dose (often temporarily) and a reduction of other hypotensive medications; a reduction in diuretic doses can also be helpful. A clinical and biochemical review should be undertaken within 2 weeks of starting or up-titrating sacubitril/valsartan.

TAKE-HOME MESSAGES

In patients with chronic heart failure and reduced ejection fraction:

- Sacubitril/valsartan significantly reduces the risks of cardiovascular death and hospitalisation for heart failure compared with enalapril¹⁰
- Sacubitril/valsartan significantly improves clinical progression of heart failure compared with enalapril¹⁷

- Sacubitril/valsartan significantly improves health-related quality of life compared with enalapril,²² in particular physical and social activity items.²³
- Hyperkalaemia, hypotension and renal impairment are the adverse events most commonly requiring dosage adjustment of sacubitril/valsartan; although only hypotension is significantly more frequent with sacubitril/valsartan than enalapril.¹⁰

EXPERT CONCLUSIONS

The introduction of sacubitril/valsartan to the New Zealand armamentarium of heart failure therapies is exciting for heart failure practitioners, patients and their families. It has provided a renewed focus on guideline-based therapies that have been often poorly adhered to, along with the opportunity to further improve morbidity, mortality and well-being of a large group of our patient population.

It is well-tolerated and effective, but should be used in the appropriate patient group (those with chronic heart failure and LVEF ≤35%, NYHA class II-IV, already on optimal therapy). Commencing therapy is usually straightforward with early monitoring of renal function, potassium and blood pressure, as well as remembering the requirement for a 36-hour wash-out period when transitioning from an ACE inhibitor.



APPLICATION FOR SUBSIDY BY SPECIAL AUTHORITY

Form SA1751

Sacubitril with valsartan

INITIAL APPLICATION

Applications from any relevant practitioner. Approvals valid for 12 months.

Prerequisites (tick boxes where appropriate)

Patient has heart failure

and

<input type="checkbox"/> Patient is in NYHA/WHO functional class II or <input type="checkbox"/> Patient is in NYHA/WHO functional class III or <input type="checkbox"/> Patient is in NYHA/WHO functional class IV
--

and

Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%

and

Patient is receiving concomitant optimal standard chronic heart failure treatments

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