Research Review™
CLINICAL REVIEW
Sacubitril/Valsartan (Entresto®)

Making Education Easy 2018

This review is intended as a practical guide for the use of sacubitril/valsartan (Entresto®) in patients with heart failure. It includes extensive commentary from Professor Andrew Sindone on use of sacubitril/valsartan in the clinical setting. It also summarises recently published literature highlighting the key clinical outcomes of cardiovascular death, 30-day hospital readmission and quality of life in patients treated with sacubitril/valsartan. Sacubitril/valsartan was registered by the Australian Therapeutic Goods Administration in January 2016 for the treatment of adult patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction, and was listed on the Australian Pharmaceutical Benefits Schedule in June 2017.

Independent expert commentary provided by Professor Andrew Sindone

Professor Andrew Sindone is the director of the Heart Failure Unit and Department of Cardiac Rehabilitation at Concord Hospital in Sydney. He has been involved in cardiac research, teaching and improving the lives of those living with cardiovascular disease for over twenty years. He set up the Heart Failure Unit at Concord Hospital with the Heart Failure Clinic, research, rehabilitation and outreach programs. He is involved in teaching medical students, junior doctors, General Practitioners and specialists, and ran a program to update specialists in the management of heart failure over a ten year period.

Professor Sindone has been Principal Investigator in over 30 international multicentre clinical trials, has presented over 80 research papers and continues to publish in cardiovascular disease. He is a Chairman of the NSW Cardiovascular Expert Reference Group, member of the Heart Foundation of Australia and co-author of the Australian Guidelines for the Management of Heart Failure. He is patron of multiple charities and assists the Italian Community in education and support of those with heart disease.

Introduction

Heart failure is a clinical syndrome characterised by typical symptoms (eg. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (eg. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1]

The prevalence of heart failure is approximately 1-2% of the population in developed countries, including Australia, rising to ≥10% amongst those aged >70 years.[2-6] Approximately 1 in 6 individuals aged >65 years presenting to primary care with breathlessness on exertion have unrecognised heart failure.[7-8] At age 55 years, the lifetime risk of heart failure is 33% for men and 28% for women.[4]

Although there is a clear relationship between symptom severity and survival, even patients with mild symptoms have an increased risk of hospitalisation and death.[9-11] Thus symptoms and signs are important in monitoring a patient's response to treatment and stability over time.[1] Persistence of symptoms despite treatment usually indicates the need for additional therapy, and worsening of symptoms is a serious development meriting prompt medical attention.[1]

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. Corresponding 12-month hospitalisation rates were 44% and 32%, respectively.[12] Most deaths in patients with heart failure are due to cardiovascular causes, mainly sudden death and worsening heart failure.[12,13] Trials conducted in patients with mild-to-moderate symptoms of heart failure have shown these patients are more likely to experience sudden death than death due to worsening heart failure.[14-17]

Sacubitril/valsartan: a new treatment option 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.[18] 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.[19] In May 2016, European and American heart failure treatment guidelines were updated to include recommendations for the use of sacubitril/valsartan.[1,20] American guidelines recommend that patients with chronic symptomatic heart failure (NYHA class II or III) and reduced ejection fraction who tolerate an ACE inhibitor or ARB are switched to sacubitril/valsartan.[20] European guidelines recommend sacubitril/valsartan as a replacement for an ACE inhibitor in patients with heart failure (NYHA class II-IV) and reduced ejection fraction who remain symptomatic despite optimal treatment with an ACE inhibitor, ß-blocker and an MRA.[1]

In January 2016, sacubitril/valsartan was registered by the Australian Therapeutic Goods Administration for the treatment of adult patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction.[21] In June 2017, following a Product Familiarisation Program, sacubitril/valsartan was approved for listing on the Australian Pharmaceutical Benefits Schedule, with the following criteria:[22]

- Patients must be symptomatic with NYHA class II, III or IV
- Patients must have documented LVEF ≤40%
- Patients must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a β-blocker, unless contraindicated or not tolerated
- Patients must have been stabilised on an ACE inhibitor OR an ARB at the time of initiation of sacubitril/valsartan, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated
- Sacubitril/valsartan must not be co-administered with an ACE inhibitor or ARB.

Prescribing is allowed by medical practitioners and nurse practitioners,[22] however the Product Information leaflet states that sacubitril/valsartan should be initiated and up-titrated by a physician experienced with the treatment of heart failure.[23]

Pharmacological properties of sacubitril/valsartan

Sacubitril/valsartan is a sodium salt complex comprising the anionic forms of sacubitril and valsartan in a 1:1 molar ratio.[23] Studies in healthy volunteers and patients with heart failure have shown simultaneous neprilysin inhibition and RAAS blockade after administration of sacubitril/valsartan.[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 valsartan, while plasma NT-proBNP (a biomarker for cardiac wall stress) and troponin T (a biomarker for cardiac injury) levels were significantly decreased.[25]

The valsartan contained within sacubitril/valsartan is more bioavailable than valsartan in other marketed tablet formulations.[23] Thus a 97mg/103mg dose of sacubitril/ valsartan gives equivalent exposure to valsartan as a 160mg valsartan tablet.[23] Steady state concentrations of sacubitril, valsartan and the sacubitril metabolite LBQ657 are reached 3 days after twice daily administration. Administration with food has no significant effect on the systemic exposure of sacubitril/valsartan.[23]

Recommendations for sacubitril/valsartan dose titration

Sacubitril/valsartan is available in three dose strengths:

- 24 mg/26 mg
- 49 mg/51 mg
- 97 mg/103 mg.[23]

The recommended starting dosage of sacubitril/valsartan for most patients is 49 mg/51 mg twice daily.[23] This should be increased to the target maintenance dosage of 97 mg/103 mg twice daily after 2-4 weeks, depending on patient tolerability. For patients developing systolic blood pressure ≤95mm 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.[23]

A lower starting dosage of 24 mg/26 mg twice daily is recommended for patients not currently receiving an ACE inhibitor or ARB, and for patients receiving those agents at a low dosage.[23] 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 ≥100-110mm Hg, and in patients with moderate hepatic impairment or severe renal impairment. Sacubitril/valsartan dosage should then be doubled every 2-4 weeks until the target maintenance dosage is reached, depending on patient tolerability.[23]

The TITRATION study investigated the tolerability of up-titrating sacubitril/valsartan over 3 or 6 weeks in patients who were naïve to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry.[27] The randomised, double-blind study included 538 patients with chronic heart failure (NYHA class II-IV) and LVEF ≤35%. All patients were started on sacubitril/valsartan 24 mg/26 mg twice daily, were up-titrated to 49 mg/51 mg twice daily, and then to 97 mg/103 mg twice daily.

Overall, 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. More patients who were naïve to previous ACE inhibitor or ARB therapy or were on low dose therapy (equivalent to enalapril <10 mg/day) were able to achieve and maintain the target dose when up-titrated over 6 rather than 3 weeks.[27]

Managing drug interactions with sacubitril/valsartan

Sacubitril/valsartan is contraindicated in patients receiving an ACE inhibitor because of the risk of angioedema.[23] A 36-hour washout period must be applied when switching between these treatments. Caution is required when sacubitril/valsartan is given in combination with direct renin inhibitors such as aliskiren. Concomitant use of these agents is contraindicated in patients with type 2 diabetes mellitus, and should be avoided in patients with renal impairment. Sacubitril/valsartan should not be co-administered with an ARB.[23]

Other interactions to be considered include the following:[23]

- 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, MRAs, 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.

Managing adverse events with sacubitril/valsartan

In the PARADIGM-HF trial, hyperkalaemia, hypotension and renal impairment were the events most commonly associated with interruption or dosage adjustment of sacubitril/valsartan.[19]

Hyperkalaemia

During the double-blind treatment period of the PARADIGM-HF trial, rates of hyperkalaemia (serum potassium >5.5 mmol/L) were comparable in sacubitril/valsartan recipients (16.1%) and enalapril recipients (17.3%).[19] However, the rate of severe hyperkalaemia (serum potassium >6 mmol/L) was significantly lower in sacubitril/valsartan vs enalapril recipients (4.3% vs 5.6%, respectively; $p<0.01$).[19] In a sub-analysis of PARADIGM-HF trial participants who were receiving an MRA at baseline, rates of hyperkalaemia were comparable in sacubitril/valsartan and enalapril recipients (17.0% and 18.7%, respectively). Again, the rate of severe hyperkalaemia was higher amongst enalapril vs sacubitril/valsartan recipients (6.1% vs 4.5%; $p<0.05$).[28] The rate of severe hyperkalaemia was also higher in enalapril vs sacubitril/valsartan recipients who had newly started on MRAs during the PARADIGM-HF trial.

Expert comment:

Hyperkalaemia may occur with agents which inhibit the renin-angiotensin system such as ARBs (a component of sacubitril/valsartan) or ACE inhibitors, particularly when combined with MRAs such as spironolactone or eplerenone. Potassium levels should be monitored approximately two weeks after commencing sacubitril/valsartan and if hyperkalaemia occurs, then the MRA should be reduced.

The potassium level should be maintained below 5.5 mmol/l. If the potassium level is above this level then the following steps can be undertaken sequentially, depending on the potassium level and response:

1. Reduce the frequency of the MRA from daily to alternate daily if the potassium is only mildly elevated (eg 5.5 to 6.0 mmol/l).
2. Cease the MRA if the potassium level is >6.0 mmol/l.
3. If the potassium level falls below 5.5 mmol/l after repeating the potassium level in one week, then the sacubitril/valsartan can be continued at the current dose.
4. If the potassium level remains >5.5 mmol/l, and the patient is fluid overloaded, increase dose of frusemide.
5. If the patient is not fluid overloaded add hydrochlorothiazide 25 mg daily.
6. Repeat the potassium level once weekly.
7. If the potassium level remains >5.5 mmol/l, consider reducing the dosage of sacubitril/valsartan.
8. If the potassium level remains >5.5 mmol/l, despite reducing the dosage of sacubitril/valsartan, consider reducing the dosage of beta-blocker (beta-blockers may increase potassium levels due to reductions in renin secretion).
9. Consider consultation from a renal physician to exclude other causes of hyperkalaemia and suitability for resonium or dialysis if appropriate.
10. Consider referral to a dietician for low potassium diet.
11. In the future, newer agents such as patiromer will be available to lower potassium levels.

Hypotension

Hypotension was more frequent in patients treated with sacubitril/valsartan compared with enalapril during the double-blind treatment period of the PARADIGM-HF trial.[19] Respective rates of symptomatic hypotension were 14.0% vs 9.2% (p<0.001), and symptomatic hypotension with systolic BP <90mm Hg 2.7% vs 1.4% (p<0.001). Symptomatic hypotension occurred in 11.5% of patients aged <55 years treated with sacubitril/valsartan and 17.7% of those aged ≥75 years. Corresponding rates in the enalapril group were 7.6% and 11.9%.[29]

Expert comment:

The most common adverse event when initiating or uptitrating sacubitril/valsartan is hypotension. The management of this includes:

1. Ensure that the patient is not dehydrated/intravascularly volume depleted, and if so, reduce diuretics and delay introduction of sacubitril/valsartan until the patient is euvolaemic.
2. Commence sacubitril/valsartan at the lowest dose (24 mg/26 mg twice daily).
3. Give the first dose at night to avoid day-time light headedness with the first dose.
4. Before initiating sacubitril/valsartan, as well as ceasing the ACE inhibitor/ARB, if the baseline systolic blood pressure is <100mm Hg, consider reducing or ceasing the other vasodilatory agents such as nitrates, hydralazine, thiazide diuretics, alpha-blockers or calcium channel blockers.
5. Monitor the blood pressure regularly to evaluate the response to sacubitril/valsartan, particularly when uptitrating the dose.

Renal impairment

Renal impairment occurred in 10.1% of patients treated with sacubitril/valsartan in the double-blind phase of the PARADIGM-HF trial, and 11.5% of patients treated with enalapril. The rate of treatment discontinuation because of renal impairment was lower in sacubitril/valsartan recipients compared with enalapril recipients (0.7% vs 1.4%, respectively; p<0.01).[19]

Expert comment:

Renal impairment can occur with initiation of sacubitril/valsartan. This may be managed by:

1. Ensure that the patient is not dehydrated/intravascularly volume depleted, and if so, reduce diuretics and delay introduction of sacubitril/valsartan until the patient is euvolaemic.
2. Reduce the dose of diuretics slightly when initiating sacubitril/valsartan if the patient is euvolaemic and has mild or more renal impairment.
3. Consider reducing the frequency of the MRA to alternate daily if the patient has mild or more renal impairment before commencing sacubitril/valsartan.
4. Avoid any potentially nephrotoxic agents such as non-steroidal anti-inflammatory agents, etc.
5. Exclude other causes of renal impairment such as renal artery stenosis, nephrolithiasis/obstruction, urinary tract infection, etc.
6. Consider consultation from a renal physician.

Patient outcomes with sacubitril/valsartan

The goals of treatment for heart failure are to improve clinical status, functional capacity and quality of life, prevent hospital admissions and reduce mortality.[1] In the PARADIGM-HF trial, sacubitril/valsartan reduced the risk of cardiovascular death or heart failure hospitalisation by 20% compared with enalapril (HR 0.80; 95% CI 0.73-0.87; p<0.001).[19] Data from the trial showing the effect of sacubitril/valsartan on the key outcome measures of cardiovascular death, 30-day hospital readmission and health-related quality of life are discussed in detail below.

Effects on cardiovascular death

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,[30-33] 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 hospitalisation vs enalapril).[19]

The benefit of sacubitril/valsartan on cardiovascular death was seen in all prespecified patient subgroups, including groupings by age, sex, race, geographic region, NYHA class, renal function, systolic BP, LVEF, presence of diabetes, atrial fibrillation or hypertension, NT-proBNP level, prior use of ACE inhibitors or aldosterone antagonists, prior hospitalisation for heart failure and time since diagnosis of heart failure.[19] Similar benefits across patient subgroups were seen for the primary endpoint of cardiovascular death or first hospitalisation for worsening heart failure, except for a nominally significant interaction between NYHA class at randomisation and treatment effect, with sacubitril/valsartan more effective vs enalapril in patients with NYHA class I or II vs III or IV heart failure (p<0.05).[19]

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).[14]

Expert comment:

Patients who are most suitable for sacubitril/valsartan are:

1. Those who have LVEF <40%.
2. NYHA class II-IV.
3. Systolic blood pressure >100mm Hg.
4. Stable on ACE inhibitor or ARB for minimum of 3 months.
5. Any degree of renal dysfunction except those requiring dialysis.
6. Baseline potassium <5.5 mmol/l unless MRA is being reduced/ceased.
7. No evidence of bilateral renal artery stenosis.
8. Not taking potentially nephrotoxic medications.

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 Readmissions Reduction Program.[34] A further analysis of the PARADIGM-HF trial examined the effect of sacubitril/valsartan on 30-day readmission rates after hospitalisation for heart failure.[35]

At 30 days, the rate of hospital readmission for any cause was 26% lower in patients who received sacubitril/valsartan compared with enalapril, and the rate of readmission for heart failure was 38% lower (see **Table 1**).[35] The benefit of sacubitril/valsartan persisted at 60 days, with a 23% lower rate of hospital readmission for any cause and a 32% lower rate of readmission for heart failure.

Table 1. **Readmission after heart failure hospitalisation in the PARADIGM-HF trial.**[35]

	Sacubitril/valsartan	Enalapril	Odds Ratio (95% CI)	P value
30 days				
All-cause readmission	192/1076 (17.8%)	275/1307 (21.0%)	0.74 (0.56-0.97)	0.031
Heart failure readmission	104/1074 (9.7%)	175/1302 (13.4%)	0.62 (0.45-0.87)	0.006
60 days				
All-cause readmission	294/1059 (27.8%)	391/1283 (30.5%)	0.77 (0.60-0.99)	0.045
Heart failure readmission	180/1055 (17.1%)	259/1275 (20.3%)	0.68 (0.50-0.92)	0.013

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.

Expert comment:

The rehospitalisation data regarding sacubitril/valsartan is very important because, as well as having a high mortality and poor quality of life, patients with heart failure have a high rate of hospitalisation. This is despite the fact that more patients in the sacubitril/valsartan group were alive and therefore 'at risk' of hospitalisation.

The fact that sacubitril/valsartan reduced hospitalisations is most likely related to the improved quality of life/reduction in heart failure symptoms, eventual improvements in haemodynamics and cardiac function and reduction in adverse neurohormonal effects.

This data appears to fulfil the three pillars of heart failure management:

1. Reduction in mortality.
2. Reduction in symptoms.
3. Reduction in hospitalisations.

Effects on QOL

Health-related quality of life is predictive of future risk for morbidity and mortality in patients with heart failure.[36,37] Further, improving health-related quality of life, rather than simply prolonging life, is an important outcome for many patients with heart failure.[38] Health-related quality of life was a prespecified secondary outcome measure of the PARADIGM-HF trial, and a comprehensive analysis of this measure has recently been published.[39]

At 8 months, KCCQ clinical summary score and KCCQ overall summary score was significantly improved with sacubitril/valsartan compared with enalapril (see **Table 2**).[39] Furthermore, significantly fewer patients had a ≥5 point decrease on both KCCQ scores with sacubitril/valsartan vs enalapril (27% vs 31%; p=0.01).

Table 1. **Change in KCCQ domains and summary scores at 8 months in the PARADIGM-HF trial.**[39]

	Sacubitril/valsartan	Enalapril	LSM Difference (95% CI)	P value
KCCQ domain				
Physical limitation	0.83	-0.00	0.83 (0.00-1.66)	0.05
Symptom stability	-2.90	-4.31	1.40 (0.42-2.39)	0.005
Symptom frequency	0.75	-0.70	1.44 (0.63-2.26)	0.001
Symptom burden	0.36	-0.56	0.93 (0.14-1.17)	0.02
Total symptom score	0.53	-0.61	1.14 (0.39-1.89)	0.003
Quality of life	2.25	0.71	1.54 (0.68-2.14)	<0.001
Self efficacy	2.37	1.58	0.78 (0.00-1.56)	0.05
Social limitation	1.35	-0.56	1.91 (0.91-2.90)	<0.001
KCCQ-CS score	0.64	-0.29	0.92 (0.24-1.61)	0.008
KCCQ-OS score	1.13	-0.14	1.27 (0.58-1.96)	<0.001

Consistent improvements in KCCQ-CS and KCCQ-OS scores with sacubitril/valsartan vs enalapril were observed through to 36 months.

Expert comment:

Patients with chronic heart failure have a worse quality of life than most chronic diseases. The fact that sacubitril/valsartan actually improved quality of life is an 'added bonus'. It could have been possible that there was no improvement in quality of life in the PARADIGM study because the most symptomatic patients in the ACE inhibitor group died and therefore the less symptomatic patients survived.

The improvement in quality of life in the patients receiving sacubitril/valsartan compared to the previous standard of care, an ACE inhibitor, is therefore quite impressive. The measures used to evaluate quality of life are quite robust and the improvements appear to be across the spectrum of heart failure symptoms.

Patients not only want to live longer – they also want to feel better and this seems to have been achieved with sacubitril/valsartan in the PARADIGM study.

Using sacubitril/valsartan in the general practice setting

Expert comment:

Heart failure is a clinical syndrome causing dyspnoea, ankle oedema and fatigue due to the heart being unable to meet the metabolic demands of the body.

Echocardiography can be used to assess left ventricular function in patients with clinical symptoms of heart failure, particularly to determine if the patient has heart failure with reduced (HeFrEF: LVEF <40%), preserved (HeFpEF: LVEF >40%) or mid-range ejection fraction (HeFmrEF: LVEF 40–50%).

Echocardiograms can also evaluate cardiac valvular function, exclude pericardial disease and measure pulmonary pressures. Echocardiograms can also be used to monitor progress in patients with HeFrEF and assess response to therapy.

Sacubitril/valsartan can be initiated by doctors who are comfortable in managing patients with heart failure and where the ACE inhibitor/ARB is stopped 36 hours before initiation of sacubitril/valsartan, the blood pressure is regularly monitored, the renal function is measured after 2-4 weeks and adverse effects are excluded.

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Expert conclusions

Sacubitril/valsartan is a significant advance in the management of patients with heart failure and reduced ejection fraction. It is suitable for patients with LVEF <40%, all classes of severity who are stable on an ACE inhibitor or ARB without hypotension, renal dysfunction or hyperkalaemia.

In these appropriate patients, sacubitril/valsartan can lead to a 20% reduction in cardiovascular mortality, 21% reduction in heart failure hospitalisation, 16% reduction in total mortality and significant improvements in quality of life.

This is an agent which can be commenced by doctors who are comfortable in monitoring the patients' blood pressure, renal function and electrolytes and following them up carefully to evaluate for adverse events. This does not necessarily require a specialist, but rather a doctor who wants to improve the outcomes for their patients with heart failure and reduced ejection fraction.

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