This review discusses the evidence in support of the use of sacubitril/valsartan (Entresto®) for the treatment of patients with heart failure and reduced ejection fraction. Sacubitril/valsartan is the first in a new class of agents, the angiotensin receptor neprilysin inhibitors (ARNIs), which have been designed to block the renin-angiotensin-aldosterone system (RAAS) and enhance natriuretic peptides, thereby improving neurohormonal balance in patients with heart failure. In 2015, sacubitril/valsartan was granted approval in the US and the EU, based on data from the PARADIGM-HF trial, which demonstrated the superiority of sacubitril/valsartan over enalapril in reducing the risks of death and hospitalisation for heart failure. 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. European and American heart failure treatment guidelines were updated in May 2016 to include recommendations for the use of sacubitril/valsartan. ARNIs have the potential to change the treatment landscape for heart failure, with a shift towards targeted neurohormonal rebalancing.

### Pharmacodynamics of sacubitril/valsartan

ARNIs have recently been developed to enhance natriuretic peptides while achieving RAAS blockade via activation of guanylate cyclase and the production of cyclic guanylate monophosphate (cGMP). Clearance occurs via binding to natriuretic peptide receptor C and enzymatic degradation with neprilysin. The natriuretic peptide system is a potentially beneficial counter-regulatory system in heart failure, promoting vasodilatation and natriuresis, inhibiting abnormal growth, suppressing the RAAS and sympathetic nervous system, inhibiting the release of and actions of vasopressin and augmenting the parasympathetic nervous system. Atrial natriuretic peptide (ANP) is mainly synthesised and secreted in the atria in response to distension. B-type natriuretic peptide (BNP) is predominantly synthesised and secreted by ventricular myocytes in response to volume overload leading to ventricular stretch. The physiological effects of natriuretic peptides are exerted via activation of guanylate cyclase and the production of cyclic guanylate monophosphate (cGMP). Clearance occurs via binding to natriuretic peptide receptor C and enzymatic degradation with neprilysin.

### Role of the natriuretic peptide system in heart failure pathophysiology

The natriuretic peptide system is a potentially beneficial counter-regulatory system in heart failure, promoting vasodilatation and natriuresis, inhibiting abnormal growth, suppressing the RAAS and sympathetic nervous system, inhibiting the release of and actions of vasopressin and augmenting the parasympathetic nervous system. ANP is mainly synthesised and secreted in the atria in response to distension. BNP is predominantly synthesised and secreted by ventricular myocytes in response to volume overload leading to ventricular stretch. The physiological effects of natriuretic peptides are exerted via activation of guanylate cyclase and the production of cyclic guanylate monophosphate (cGMP). Clearance occurs via binding to natriuretic peptide receptor C and enzymatic degradation with neprilysin.

### The natriuretic peptide system as a therapeutic target

Enhancement of the natriuretic peptide system has been investigated as a treatment strategy in heart failure for more than 20 years. However, oral delivery of exogenous natriuretic peptides or analogues is ineffective and long-term parenteral delivery is problematic. An alternative approach has centred around blockade of natriuretic peptide breakdown via neprilysin inhibition. Clinical studies of neprilysin inhibition alone in patients with heart failure have not produced favourable results, most likely due to effects on other systems such as RAAS and the kinin system. Dual-acting neprilysin and ACE inhibitor molecules were then developed, of which omapatrilat was the most extensively studied. Development of omapatrilat was discontinued because of nonsuperiority compared with ACE inhibition alone and an unacceptable rate of angioedema, which was thought to occur as a result of the combined effects of neprilysin and ACE inhibition on bradykinin. ARNIs have recently been developed to enhance natriuretic peptides while achieving RAAS blockade via antagonism of the angiotensin II type 1 receptor, thus minimising the risk of serious angioedema. The first ARNI to be investigated in clinical trials is sacubitril/valsartan.

### Pharmacodynamics of sacubitril/valsartan

Sacubitril/valsartan is a sodium salt complex comprising the anionic forms of sacubitril and valsartan in a 1:1 molar ratio. Studies in healthy volunteers and patients with heart failure have shown simultaneous neprilysin inhibition and RAAS blockade after administration of sacubitril/valsartan.

In a small, open-label study of sacubitril/valsartan in patients with heart failure and reduced ejection fraction, urine ANP, urine cGMP and plasma cGMP levels were significantly increased after treatment for 21 days compared with baseline. Plasma renin markers were also increased following treatment with sacubitril/valsartan. Plasma NT-proBNP, aldosterone and endothelin-1 levels were significantly decreased compared with baseline.

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 (p<0.001 for all differences between treatment groups).

### Introduction

Heart failure is a significant disease burden in developed countries. Despite a reduction in the prevalence of hospital mortality, quality of life and prognostic outlook for patients with heart failure who survive an acute hospitalisation remain poor. It is estimated that 50-75% of patients with heart failure die within 5 years of diagnosis.

A recent review has shown the prevalence of heart failure in Australia to be 1-2%, similar to data obtained in Europe and North America, where prevalence rates of 1.3-2.2% have been reported. The Australian review found heart failure prevalence to be at least three times higher in the elderly compared with the general population. A statistical report from the American Heart Association notes that heart failure prevalence is expected to rise markedly in coming years due to population aging.

The pathophysiology of heart failure involves activation of neurohormonal pathways, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and the natriuretic peptide system. Standard therapeutic approaches have focused on down-modulation of RAAS (with ACE inhibitors, ARBs and mineralocorticoid antagonists) and the sympathetic nervous system (with β-blockers).

Angiotensin receptor neprilysin inhibitors (ARNIs) are a new drug class designed to block the RAAS and enhance natriuretic peptides, thereby improving neurohormonal balance in patients with heart failure.

The natriuretic peptide system is a potentially beneficial counter-regulatory system in heart failure, promoting vasodilatation and natriuresis, inhibiting abnormal growth, suppressing the RAAS and sympathetic nervous system, inhibiting the release of and actions of vasopressin and augmenting the parasympathetic nervous system. Atrial natriuretic peptide (ANP) is mainly synthesised and secreted in the atria in response to distension. B-type natriuretic peptide (BNP) is predominantly synthesised and secreted by ventricular myocytes in response to volume overload leading to ventricular stretch. The physiological effects of natriuretic peptides are exerted via activation of guanylate cyclase and the production of cyclic guanylate monophosphate (cGMP). Clearance occurs via binding to natriuretic peptide receptor C and enzymatic degradation with neprilysin.

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Sacubitril/valsartan is superior to enalapril in reducing the risks of cardiovascular death and hospitalisation for heart failure. At baseline, most patients were receiving standard heart failure therapies, consisting of beta-blockers (93%), diuretics (80%), mineralocorticoid antagonists (56%), digitals (30%), implantable cardioverter-defibrillator (15%) and cardiac resynchronisation therapy (7%). These treatments were continued throughout the study period. NYHA class was I in 5% of patients, II in 70% of patients, III in 24% of patients and IV in 1% of patients. Mean age of study participants was 64 years and 78% were male.

Pharmacokinetics of sacubitril/valsartan

The valsartan contained within sacubitril/valsartan is more bioavailable than valsartan in other marketed tablet formulations.1 Thus a 97mg/103mg dose of sacubitril/valsartan gives equivalent exposure to valsartan as a 160mg valsartan tablet.19 Absolute oral bioavailabilities of sacubitril and valsartan are estimated to be ≥60% and 23%, respectively.20 Sacubitril/valsartan dissociates into its separate components following oral administration, with sacubitril being further metabolised to LBQ657. Peak plasma concentrations of sacubitril, LBQ657 and valsartan are seen at 0.5-1.25, 2-3 and 1.5-2.5 hours, respectively.19,21

Study design and baseline characteristics

PARADIGM-HF was a randomised, double-blind trial of patients with NYHA class II-IV heart failure and left ventricular ejection fraction <40% (later amended to ≤35%). The trial was conducted across 1043 institutions and 47 countries.1

Patients were aged ≥18 years and had a plasma BNP level of ≥150 pg/ml or NT-proBNP level >600 pg/ml, or if they had been hospitalised for heart failure within the previous 12 months, a BNP >100 pg/ml or NT-proBNP >400 pg/ml, respectively. Patients had been receiving an ACE inhibitor or ARB at a dosage equivalent to enalapril 10 mg/day for ≥4 weeks prior to screening, as well as a β-blocker at stable dosage (unless contraindicated or not tolerated). Patients with symptomatic hypotension or systolic BP <100mmHg, severe renal impairment, hyperkalaemia, a history of angioedema or intolerance to ACE inhibitors or ARBs were not eligible for study entry.1

Patients (n = 10,521) entered a sequential, single-blind run-in period prior to treatment randomisation, to maximise attainment of target doses and to provide short-term tolerability data. Most patients received enalapril 10mg twice daily for 2 weeks, although they could be started on 5mg twice daily and then up-titrated if they had been receiving an ARB or low dose of ACE inhibitor prior to study entry. All patients then received sacubitril/valsartan 100mg (sacubitril 49mg/valsartan 51mg) twice daily for 1-2 weeks, followed by 200mg (sacubitril 97mg/valsartan 103mg) twice daily for a further 2-4 weeks.1

Patients who tolerated enalapril and sacubitril/valsartan during the run-in period (n = 8442) were randomised to double-blind treatment with sacubitril/valsartan 200mg twice daily or enalapril 10mg twice daily, although 43 were excluded before treatment was assigned. Therefore 4187 sacubitril/valsartan recipients and 4212 enalapril recipients were included in the intention-to-treat analysis.1

The primary endpoint was a composite of cardiovascular death or first hospitalisation for heart failure, although the trial was designed to detect a difference in the rates of death from cardiovascular causes. Secondary endpoints were time to death from any cause, change in clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to new onset of atrial fibrillation, and time to first occurrence of a decline in renal function.1

Analyses were also conducted to determine the effects of treatment on mode of death22 and on clinical progression in surviving patients.23 A retrospective analysis of trial data was conducted to assess outcomes according to age.24

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Clinical trial evidence for sacubitril/valsartan: PARADIGM-HF

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Effects on cardiovascular death and hospitalisations for heart failure

Summary: Sacubitril/valsartan is superior to enalapril in reducing the risks of cardiovascular death and hospitalisation for heart failure.

Results: PARADIGM-HF was terminated early, after a median follow-up of 27 months, when the prespecified stopping boundary for an overwhelming benefit with sacubitril/valsartan was crossed. At the last assessment, the mean daily doses of sacubitril/valsartan and enalapril were 375mg and 18.9mg, respectively.

Sacubitril/valsartan reduced the risk of cardiovascular death or heart failure hospitalisation by 20% compared with enalapril (see Table 1). This benefit was observed early in the trial and at each interim analysis. Risk of death from any cause was reduced by 16% with sacubitril/valsartan compared with enalapril, and risk of cardiovascular death by 20%. Risk of hospitalisation for worsening heart failure was reduced by 21%.

<table>
<thead>
<tr>
<th>Primary composite endpoint</th>
<th>Sacubitril/valsartan (n = 4187)</th>
<th>Enalapril (n = 4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or first hospitalisation for worsening heart failure</td>
<td>914 (21.8%)</td>
<td>1171 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>558 (13.3%)</td>
<td>693 (15.6%)</td>
<td>0.80 (0.71-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalisation for worsening heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoint</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>711 (17.0%)</td>
<td>835 (19.8%)</td>
</tr>
</tbody>
</table>

Table 1. Cardiovascular death, hospitalisation for worsening heart failure and death from any cause in PARADIGM-HF.

Sacubitril/valsartan was associated with significantly less worsening of heart failure symptoms and physical limitations compared with enalapril, as assessed by mean change in KCCQ score from baseline at 8 months (-2.99 vs -4.63, respectively; p=0.001).

The rate of new-onset atrial fibrillation was 3.1% in both treatment groups, while a decline in renal function occurred in 2.2% of sacubitril/valsartan recipients and 2.6% of enalapril recipients.

The benefit with sacubitril/valsartan was seen in all prespecified patient subgroups. A nominally significant interaction between NYHA class at randomisation and the effect of treatment on the primary endpoint was observed (p<0.05). However, this interaction was not apparent for cardiovascular death.
Sacubitril/Valsartan (Entresto®)

**Expert commentary**

The PARADIGM study was a large, well designed, randomised, double-blind, placebo controlled study. The primary endpoint of cardiovascular mortality or heart failure hospitalisation is the standard endpoint in heart failure trials and has been used in many landmark trials such as the CHARM® and SHIFT® studies. It is important to assess the driving factor in improved primary endpoint, and in the PARADIGM study it appeared to be related to both the reduction in cardiovascular mortality and heart failure hospitalisation. These are, in part, competing endpoints, because if a patient has died, they can no longer be at risk of hospitalisation and those who survive are at risk of hospitalisation.

By assessing the time to first heart failure hospitalisation, some of the biases against those patients who continue to survive are removed. The fact that the secondary analyses showed an improvement in cardiovascular mortality and that the reduction in overall mortality was identical to the reduction in cardiovascular mortality shows that the improvements were not related to non-cardiovascular effects and that there was no increase in non-cardiovascular mortality.

**Effects on mode of death in patients with heart failure**

**Summary:** Sacubitril/valsartan is superior to enalapril in reducing the risks of sudden cardiac death and death from worsening heart failure.

**Results:** The majority of cardiovascular deaths in PARADIGM-HF were classified as sudden (44.8%) or heart failure related (26.5%). Sacubitril/valsartan reduced the risk of sudden death by 20% compared with enalapril, and death due to worsening heart failure by 21% (see Table 2).

**Table 2.** Sudden death and death due to worsening heart failure in PARADIGM-HF.

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan (n = 4187)</th>
<th>Enalapril (n = 4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>250 (6.0%)</td>
<td>311 (7.4%)</td>
<td>0.80 (0.68-0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Last contact &lt;1h</td>
<td>167 (4.0%)</td>
<td>213 (5.1%)</td>
<td>0.78 (0.64-0.95)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Last contact 1-24h</td>
<td>83 (2.0%)</td>
<td>98 (2.3%)</td>
<td>0.84 (0.63-1.13)</td>
<td>NS</td>
</tr>
<tr>
<td>Death due to worsening heart failure</td>
<td>147 (3.5%)</td>
<td>184 (4.4%)</td>
<td>0.79 (0.64-0.98)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Deaths from other cardiovascular causes were infrequent - fatal MI and stroke both occurred in <1% of patients. Rates of death from cardiovascular causes were similar between treatment groups. Malignancy and infection accounted for more than 50% of non-cardiovascular deaths, and there were no differences between treatment groups in rates of non-cardiovascular death.

**Effects on clinical progression of surviving patients with heart failure**

**Summary:** Sacubitril/valsartan is superior to enalapril in preventing clinical progression in patients with heart failure.

**Results:** In PARADIGM-HF, the risk of requiring intensified outpatient therapy for heart failure was reduced by 16% in sacubitril/valsartan-treated patients compared with enalapril-treated patients (see Table 3). The risk of an ED visit for worsening heart failure was reduced by 34%, and the risk of hospital admission for heart failure was reduced by 21%, in patients treated with sacubitril/valsartan compared with enalapril. The incremental benefit of sacubitril/valsartan on heart failure hospital admission rate was statistically significant after 30 days of treatment (p<0.05). When compared with the enalapril group, the sacubitril/valsartan group had 15.6% fewer hospitalisations for any reason, 16.0% fewer hospitalisations for a cardiovascular reason and 23.0% fewer admissions for heart failure.

Furthermore, sacubitril/valsartan-treated patients had 18% fewer stays in intensive care compared with enalapril-treated patients, and were 31% less likely to require intravenous positive inotropic agents.

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**Table 3.** Measures of nonfatal worsening heart failure in PARADIGM-HF.

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan (n = 4187)</th>
<th>Enalapril (n = 4212)</th>
<th>Hazard/Rate Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients requiring intensified outpatient therapy for heart failure</td>
<td>520 (12.4%)</td>
<td>604 (14.3%)</td>
<td>0.84 (0.74-0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients requiring an ED visit for heart failure</td>
<td>102 (2.4%)</td>
<td>150 (3.6%)</td>
<td>0.66 (0.52-0.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total number of ED visits for heart failure</td>
<td>151</td>
<td>208</td>
<td>0.70 (0.52-0.89)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients hospitalised for heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of hospitalisations for heart failure for cardiovascular reason</td>
<td>2216</td>
<td>2537</td>
<td>0.84 (0.76-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of hospitalisations for any reason</td>
<td>3564</td>
<td>4053</td>
<td>0.84 (0.78-0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of stays in intensive care</td>
<td>768</td>
<td>879</td>
<td>0.82 (0.72-0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients requiring IV positive inotropic drugs</td>
<td>161 (3.9%)</td>
<td>229 (5.4%)</td>
<td>0.69 (0.57-0.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Expert commentary**

Treatment with sacubitril/valsartan appears to work early, as demonstrated by the statistically significant reduction in heart failure hospital admission rate after only 30 days of treatment vs enalapril. This appears to be because sacubitril/valsartan changes the course of progression of the patients’ heart failure journey. There is a natriuresis facilitated by the increase in circulating natriuretic peptides, but also vasodilatation which contributes to the reduction in blood pressure and these two effects reduce cardiac preload and afterload. The combination of these haemodynamic and neurohormonal effects when sacubitril/valsartan is added to standard heart failure therapy appears to improve survival and reduce time to first heart failure hospitalisation as well as overall hospitalisation. This will improve resource utilisation and result in a favourable cost-benefit ratio for therapy with sacubitril/valsartan.

The fact that there was also an improvement in quality of life in patients with heart failure treated with sacubitril/valsartan compared to enalapril is very important. Patients with heart failure have worse quality of life than those with most other chronic illnesses and improving their quality of life is an important goal. Part of the improvement in quality of life is due to keeping the patients out of hospital, but reducing symptoms, improving dyspnoea, fatigue and overall well-being are important parameters which should also be measured in heart failure trials. There is no point in making a patient live longer if they feel miserable. Increasing patient independence and self-efficacy is a goal that should be sought in improving outcomes in a condition which leads to such a poor quality of life.
Efficacy according to age of patients with heart failure

Summary: The superiority of sacubitril/valsartan compared with enalapril for the treatment of heart failure is evident across all patient age groups.

Results: In PARADIGM-HF, 1624 patients (19.3%) were aged <55 years, 2655 (31.6%) were aged 55-64 years, 2557 (30.4%) were aged 65-74 years and 1563 (18.6%) were aged ≥75 years. Of those aged ≥75 years, 587 (7.0%) were ≥80 years and 121 (1.4%) were ≥85 years.

Older patients were more likely to be female, White and enrolled in Western Europe and North America compared with younger patients. They also had higher systolic BP, creatinine, and natriuretic peptide levels, and a higher average ejection fraction. Older patients were more likely to be in NYHA functional class III/IV compared with II, and to have comorbidity. Median KCCQ score was significantly lower in patients aged ≥75 years compared with younger patients, but was similar across other age categories.

The superiority of sacubitril/valsartan compared with enalapril in reducing the primary composite outcome of cardiovascular death or hospitalisation for heart failure was consistent across the age categories studied. 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. The incremental benefit of sacubitril/valsartan compared with enalapril on hospitalisation for heart failure, all-cause mortality and worsening KCCQ score was consistent across all age categories.

Adverse events

The safety profile of sacubitril/valsartan in patients with chronic heart failure has been evaluated in the PARADIGM-HF trial. Patients in this trial received sacubitril/valsartan 200mg (sacubitril 97mg/valsartan 103mg) twice daily or enalapril 10mg twice daily for a median of 27 months.

The rate of withdrawal because of adverse events during the run-in period of PARADIGM-HF was 5.8% with sacubitril/valsartan and 5.6% with enalapril. The most common adverse events requiring withdrawal of both treatments were renal dysfunction, hypotension and hyperkalaemia. The rate of withdrawal was higher in the enalapril group than the sacubitril/valsartan group after adjustment for length of run-in treatment.

During the double-blind treatment period, the rate of discontinuation because of adverse events was lower in the sacubitril/valsartan group (10.7%) compared with the enalapril group (12.2%; p<0.05). Hypotension, hyperkalaemia and renal impairment were the events most commonly associated with interruption or dosage adjustment of both treatments. The overall incidence of adverse events with sacubitril/valsartan was comparable to that seen with enalapril. Incidence in both groups may be lower than observed in clinical practice, as a result of withdrawals during the run-in phase and the fact that patients had been receiving an ACE inhibitor or ARB prior to study entry.

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.

Adverse events of specific interest discussed below are those which arose during the double-blind phase of PARADIGM-HF.

Hypotension

Hypotension was more frequent in patients treated with sacubitril/valsartan compared with enalapril. 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 11.5% respectively.

Mean systolic BP at 8 months was 3.2mm Hg lower in the sacubitril/valsartan group than in the enalapril group (12.2%; p<0.05). Hypotension, hyperkalaemia and renal impairment were the events most commonly associated with interruption or dosage adjustment of both treatments. The overall incidence of adverse events with sacubitril/valsartan was comparable to that seen with enalapril. Incidence in both groups may be lower than observed in clinical practice, as a result of withdrawals during the run-in phase and the fact that patients had been receiving an ACE inhibitor or ARB prior to study entry.

Renal impairment occurred in 10.1% of patients treated with sacubitril/valsartan 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).

Elevated serum creatinine

Fewer patients treated with sacubitril/valsartan had serum creatinine ≥2.5 mg/dl compared with enalapril-treated patients (3.3% vs 4.5%, respectively; p<0.01). The percentage of patients with serum creatinine ≥3.0 mg/dl were comparable between treatment groups at 1.5% and 2.0%, respectively.

Angioedema

Angioedema occurred in a small number of patients treated with sacubitril/valsartan (0.5%) and enalapril (0.2%). None of these patients had compromised airways or required mechanical airway protection. Black patients had a higher rate of angioedema, at 2.4% for sacubitril/valsartan recipients and 0.5% for enalapril recipients.

Expert commentary

Sacubitril/valsartan has been demonstrated to be a major advance in the management of patients with chronic heart failure and reduced left ventricular ejection fraction. When compared to an ACE inhibitor, which is the accepted first-line therapy, sacubitril/valsartan was very well tolerated. The rates of renal dysfunction, hypokalaemia and treatment cessation for biochemical abnormalities in patients treated with sacubitril/valsartan were similar to rates in patients treated with enalapril, in spite of their lower blood pressure and natriuresis. This may be because of some degree of nephroprotection from the enhanced levels of BNP, bradykinin and other vasodilatory peptides or perhaps that patients on sacubitril/valsartan may have required lower doses of diuretics. Diuretics reduce renal blood flow, whilst intravenous BNP is at least neutral as far as renal dysfunction is concerned despite causing natriuresis.

Other adverse events were similar between patients treated with sacubitril/valsartan and those treated with enalapril, even though there were improved clinical outcomes in the former group. Sacubitril/valsartan appears to be a treatment which leads to net clinical benefit without additional risk. Replacing an ACE inhibitor with sacubitril/valsartan can therefore be done safely and with a degree of confidence that patients are likely to benefit with little additional risk. Patients being switched to sacubitril/valsartan from an ACE inhibitor or an ARB should be monitored carefully for hypotension or angioedema, as well as renal dysfunction, but apart from slightly lower blood pressure, these parameters did not differ significantly from the enalapril-treated group in the PARADIGM study.
Dosage and administration
Sacubitril/valsartan is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or ARB.

The recommended starting dosage of sacubitril/valsartan for most patients is 49mg/51mg twice daily. This should be increased to the target maintenance dosage of 97mg/103mg twice daily after 2-4 weeks, depending on patient tolerability.

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. 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.

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

Use of sacubitril/valsartan is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy, and in patients with hereditary or idiopathic angioedema. Caution is recommended in patients with moderate hepatic impairment due to limited clinical data. Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Sacubitril/valsartan is contraindicated for use during pregnancy (category D).

Sacubitril/valsartan is contraindicated in patients with end-stage renal disease who have not been studied and sacubitril/valsartan is therefore not recommended for this population.

Renal function should be monitored prior to and during treatment with sacubitril/valsartan. Caution should be exercised in patients with severe renal impairment as there are no adequate data supporting use in this group. Patients with end-stage renal disease have not been studied and sacubitril/valsartan is therefore not recommended in these patients.

Serum potassium levels should be monitored periodically during treatment with sacubitril/valsartan. Patients with levels >5.4 mmol/L at baseline should not be started on this treatment.

Expert concluding remarks and take-home message
The PARADIGM study is a landmark trial. It has compared an ACE inhibitor, which until this trial was the standard, first-line therapy in heart failure, to sacubitril/valsartan and shown that sacubitril/valsartan is superior in cardiovascular mortality, heart failure hospitalisation and their combination, as well as overall mortality, quality of life and health care utilisation.

This is a practice-changing study. The design of the trial, the inclusion of stable heart failure patients on optimised, best-practice therapy and the dramatic reduction in events challenges heart failure treatment protocols. Therefore, European and American heart failure treatment guidelines were updated in May 2016 to include recommendations for the use of sacubitril/valsartan.

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. 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, 8-blocker and a mineralocorticoid antagonist.

Both sets of guidelines acknowledge that further long-term safety data on sacubitril/valsartan are needed. Patients who have been previously treated with an ACE inhibitor or ARB and are relatively stable should derive a significant benefit from changing to sacubitril/valsartan. It was envisaged that they should achieve similar results to the PARADIGM study of a 20% reduction in cardiovascular mortality and heart failure hospitalisation.

Rather than being an additional treatment, sacubitril/valsartan should soon replace ACE inhibitors and ARBs and be suitable for a very large proportion of patients with heart failure. Once generally available, the patients most likely to receive sacubitril/valsartan, at least initially, would be patients who are stable on an ACE inhibitor or ARB, who are not hypotensive, who are not hyperkalaemic, who do not have moderate or severe renal dysfunction and who are willing to change to a treatment which should make a positive impact on their survival, risk of hospitalisation and quality of life.