Sacubitril/valsartan for chronic heart failure: its future potential

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<table>
<thead>
<tr>
<th>NYHA</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>No symptoms and no limitation in ordinary physical activity, eg shortness of breath when walking, climbing stairs, etc.</td>
</tr>
<tr>
<td>II</td>
<td>Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg walking short distances (20–100m) Comfortable only at rest</td>
</tr>
<tr>
<td>IV</td>
<td>Severe limitations in activity Experiencing symptoms even while at rest Mostly bedbound patients</td>
</tr>
</tbody>
</table>

Table 1. New York Heart Association (NYHA) functional classification of heart failure

Sacubitril/valsartan (Entresto), a combined neprilysin inhibitor/angiotensin II-receptor antagonist for the treatment of chronic heart failure with reduced ejection fraction, was launched in the UK in January. The phase 3 clinical trial PARADIGM-HF established its efficacy in chronic heart failure but what is its future place in therapy, according to the latest guidelines and research?

Few new drugs enjoy the warm reception accorded to sacubitril/valsartan (Entresto) since publication of the international PARADIGM-HF trial (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] vs ACEI [ACE inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) in 2014, and its subsequent launch in the UK in January 2016. Many analyses of PARADIGM-HF have been published since the original trial and new indications are being explored. So what is the potential of this novel combination of a neprilysin inhibitor and an angiotensin II-receptor antagonist?

What makes sacubitril/valsartan special?

In a word, PARADIGM. One of the largest trials of a treatment for heart failure ever conducted, it included 8442 patients with chronic symptomatic heart failure (mostly New York Heart Association (NYHA) class II or III – see Table 1) despite taking an ACE inhibitor and a beta-blocker, and with a reduced ejection fraction averaging about 30 per cent. The double-blind trial randomised patients to treatment with sacubitril/valsartan 97mg/103mg (200mg) twice daily or the ACE inhibitor enalapril 10mg twice daily (see Figure 1). Sacubitril/valsartan significantly reduced the risk of the primary endpoint (a composite of death from cardiovascular causes or first hospitalisation for worsening heart failure) by 20 per cent compared with enalapril after a median 27 months’ follow-up (see Table 2). The trial was terminated early because an interim analysis showed a significant benefit of sacubitril/valsartan over enalapril. Sacubitril/valsartan also significantly decreased all-cause mortality, cardiovascular death and the risk of hospitalisation for heart failure, and improved the symptoms and physical limitations of heart failure compared with enalapril. It did not reduce the decline in renal function or the risk of atrial fibrillation.
What else did PARADIGM-HF show?
The many analyses of the PARADIGM-HF data show that sacubitril/valsartan slows heart failure progression compared with enalapril. Its benefits are consistent despite regional differences in patient populations, there is equal benefit for stable patients and those recently hospitalised, when outpatient dose intensification is assessed and regardless of background therapy. It reduces re-admission for any cause within 30 days. Outcomes were worse after dose reduction during the trial, with worsening ejection fraction at baseline, higher baseline risk score and in patients with diabetes or prediabetes, but efficacy relative to enalapril was unchanged. Sacubitril/valsartan was superior for any cause of death, though differences in clinical outcomes between the treatment arms were not statistically significant in those aged 75 years and older (see Figure 2) and the incidence of symptomatic hypotension in this age group was higher with sacubitril/valsartan (18 vs 12 per cent with enalapril).²

It is estimated that sacubitril/valsartan confers one to two years of increased life expectancy and survival free from heart failure for patients like those in PARADIGM-HF.

Place in therapy
It is clear from the above that there is a lot of evidence for sacubitril/valsartan, all from one phase 3 trial. It is argued that the trial was so large and the results so consistent that the quality of evidence it provides is equivalent to four or five separate trials.³ This was an innovative treatment, and one that made a big difference to patients who were symptomatic despite standard therapy. Consequently, sacubitril/valsartan has already been incorporated into management guidelines – but at different steps.⁴–⁷

The guidance could hardly be more favourable. NICE recommends sacubitril/valsartan as an option for people with chronic heart failure and reduced ejection fraction (≤35 per cent) who have NYHA class II–IV symptoms, despite stable treatment with an ACE inhibitor or an angiotensin II-receptor antagonist.⁷ It does not state that patients must be taking an aldosterone antagonist – formerly the next step – or that they should be intolerant of an ACE inhibitor.

US guidance specifies a lower symptom severity but is more explicit, stating: “In patients with chronic symptomatic HFrEF [heart failure with reduced ejection fraction] NYHA class II or III who tolerate an ACE inhibitor or ARB [angiotensin II-receptor antagonist], replacement by an ARNI [angiotensin receptor–neprilysin inhibitor] is recommended to further reduce morbidity and mortality.”⁶

By contrast, the Scottish Intercollegiate Guidelines Network (SIGN) positions sacubitril/valsartan after the addition of an aldosterone antagonist and for patients with ejection fraction ≤40 per cent.⁴ An aldosterone antagonist is considered as effective as sacubitril/valsartan, though it is an addition to an ACE inhibitor rather than a substitute. A meta-analysis of eight trials involving almost 4000 patients showed that adding an aldosterone antagonist in this way reduces all-cause mortality (relative risk [RR] 0.79) and admission due to cardiac causes (RR 0.62).⁹ In PARADIGM-HF, about half of participants were taking an aldosterone antagonist but it made no difference to the efficacy of sacubitril/valsartan.

Adoption despite qualms
NICE accommodated several reservations about the evidence when it recommended sacubitril/valsartan. It noted that in participants from western Europe, who were most representative of patients in the UK, the difference between the treatment arms in the primary endpoint was not statistically significant (hazard ratio [HR] 0.89; CI 95% 0.74–1.07). However, NICE decided this “would not factor in its decision-making”.

Compared with UK practice, participants in PARADIGM-HF were younger (mean age 64 years), there were only 60 patients (0.7 per cent) with NYHA class IV symptoms, and fewer were women (22 per cent), had co-morbidities or used a cardiac device. Black people were under-represented (5 per cent), which is important because they are at higher risk of angioedema.¹⁰ The dose of valsartan used was higher than some patients tolerate and the ACE inhibitor comparator was enalapril, whereas
UK clinicians prefer ramipril (though everyone accepted a class effect was likely). Finally, the trial’s run-in phase included a period when all participants received sacubitril/valsartan, during which 6.4 per cent withdrew from the study due to adverse effects or abnormal lab results. Selecting patients for tolerability in this way may have reduced the incidence of angioedema in the trial. Whether these patient differences mean that outcomes in clinical practice differ from those in PARADIGM-HF remains to be seen.

**Uptake so far**

Statistics on NHS prescribing are not yet available (and will have been influenced by the wait for NICE guidance) but NICE estimates that the number of people taking sacubitril/valsartan will grow to about 64,500 by 2020/21. There are about 411,000 people with heart failure in England, of whom 107,000 meet the NICE eligibility criteria for treatment with the new combination. Within five years it is expected that 60 per cent of eligible patients will be taking sacubitril/valsartan (see Figure 3), 34 per cent will have an ACE inhibitor and the remainder will take an angiotensin II-receptor antagonist.

Prescribing costs will increase: a year’s treatment with an ACE inhibitor costs only £32 compared with £1194 for sacubitril/valsartan and the estimated cost per quality-adjusted life year (QALY) saved was “at the upper end of the range that would normally be considered a cost-effective use of NHS resources”. This will be offset by savings totalling £5.4 million per year through fewer hospital admissions, leaving a net impact of about £70 million annually by 2020/21.

Uptake in Europe is reportedly higher than in the USA, where sales have been slower than forecast due to administrative obstacles imposed by medical insurance companies and concerns about cost and long-term safety. Nepriylis is one of many pathways for clearing amyloid beta and its inhibition raises the spectre of Alzheimer’s disease. There’s no evidence of an increased risk of Alzheimer’s disease so far, but a three-year trial will begin shortly to compare measures of cognitive function in patients treated with sacubitril/valsartan or valsartan monotherapy.

**Other heart failure trials**

In a move widely interpreted as an attempt to bolster confidence in sacubitril/valsartan in the USA, Novartis has announced a new programme of clinical trials, some of which are already under way. FortiHyF will include 40 trials, generating data on “symptom reduction, efficacy, safety, quality of life benefits and real world evidence” in heart failure.

Most of the success to date has been in patients with reduced ejection fraction but heart failure with preserved ejection fraction accounts for around half of cases and its prevalence appears to be growing. Treatment is less successful than when ejection fraction is reduced. Drug treatment focuses on symptom relief and has not been shown to reduce mortality, morbidity or improve exercise intolerance. PARAGON-HF is a trial comparing the effects of sacubitril/valsartan and valsartan monotherapy on

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Sacubitril/valsartan (% patients)</th>
<th>Enalapril (% patients)</th>
<th>Hazard ratio (CI 95%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes or first hospitalisation for heart failure</td>
<td>21.8</td>
<td>26.5</td>
<td>0.80 (0.73–0.87)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>17.0</td>
<td>19.8</td>
<td>0.84 (0.76–0.93)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>13.3</td>
<td>16.5</td>
<td>0.80 (0.71–0.89)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>First hospitalisation for heart failure</td>
<td>12.8</td>
<td>15.6</td>
<td>0.79 (0.71–0.89)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.0</td>
<td>19.8</td>
<td>0.84 (0.76–0.93)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in clinical summary score from baseline to 8 months*</td>
<td>-2.99 ±0.36</td>
<td>-4.63 ±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>3.1</td>
<td>3.1</td>
<td>0.97 (0.72–1.31)</td>
<td>p=0.83</td>
</tr>
<tr>
<td>Decline in renal function**</td>
<td>2.2</td>
<td>2.6</td>
<td>0.86 (0.65–1.13)</td>
<td>p=0.28</td>
</tr>
</tbody>
</table>

*Kansas City Cardiomyopathy Questionnaire (KCCQ) score (on a scale of 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure); data are least-squares mean ± standard error of the between group difference **Defined as end-stage renal disease or as a decrease in the estimated glomerular filtration rate (eGFR) of ≥50 per cent or a decrease of >30ml/min/1.73m² from randomisation to <60ml/min/1.73m²

Table 2. Primary and secondary outcomes in the PARADIGM-HF trial, comparing sacubitril/valsartan and enalapril in patients with symptoms of heart failure
Sacubitril/valsartan l THERAPY REVIEW

Cardiovascular death and hospitalisation for heart failure when added to standard care (excluding ACE inhibitors and angiotensin II-receptor antagonists) in patients with preserved ejection fraction. Patients are ≥55 years of age with left ventricular ejection fraction ≥45 per cent who need treatment with a diuretic to relieve NYHA class II–IV symptoms. Follow-up will be four to five years and results are expected in 2019.

A 12-week phase 2 trial in patients with preserved ejection fraction (PARAMOUNT, n=266) showed that, compared with valsartan monotherapy, sacubitril/valsartan reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP; the primary endpoint, a marker of left ventricular wall stress) and this was independent of the greater reduction in systolic blood pressure.

PARADISE-MI is testing the hypothesis that sacubitril/valsartan can reduce cardiovascular death, hospitalisation for heart failure and new-onset heart failure in patients at high risk of heart failure after a myocardial infarction. Ramipril is the comparator; completion is expected in 2020. A trial in Ireland is also looking at prevention by comparing the effects of sacubitril/valsartan with valsartan alone on left ventricular diastolic function in people with hypertension, diabetes or other risk factors for heart failure.

Other trials in people with heart failure include TRANSITION, which is comparing initiation of sacubitril/valsartan before or after discharge in patients admitted with acute decompensation; and PIONEER-HF, a comparison with enalapril of the effects of sacubitril/valsartan treatment on NT-proBNP in stable patients admitted for acute decompensated heart failure and reduced ejection fraction. Results for both are expected in 2018.

**Figure 2.** Clinical outcomes with sacubitril/valsartan vs enalapril in PARADIGM-HF according to age (rate per 100 patient-years of treatment; error bars are 95% confidence intervals). Reproduced from Jhund et al. 2015.
Use in hypertension
In PARADIGM-HF, sacubitril/valsartan was associated with a greater reduction in systolic blood pressure than enalapril (3.2mmHg) and symptomatic hypotension was significantly more common (14.0 vs 9.2 per cent respectively). Its therapeutic potential in hypertension has since been evaluated in many trials (see Clinicaltrials.gov for a full list), suggesting a greater blood pressure-lowering effect than valsartan alone or olmesartan and efficacy as add-on therapy when amlodipine has failed.

A recent review assessing the efficacy and safety of sacubitril/valsartan in hypertension suggests that the effect on blood pressure is greater in Asian patients than Caucasian patients and treatment is well tolerated, though the risk of orthostatic hypotension requires further study. The authors of this review speculate that sacubitril/valsartan may offer greater efficacy and a similar safety profile compared with established anti-hypertensive drugs.

The results of the PARAMETER trial in elderly people with systolic hypertension were reported recently. Compared with the angiotensin II-receptor antagonist olmesartan, once-daily sacubitril/valsartan significantly reduced measures of aortic stiffness (including aortic systolic pressure and pulse pressure) at 12 weeks but not after 52 weeks. It is rumoured that Novartis will not pursue marketing authorisation for hypertension.

Other nepriylisin inhibitors in development
Several nepriylisin inhibitors have been in development over the past 30 years but only sacubitril (in combination with valsartan) has successfully reached the market. Interest in this class of agents appears to have stalled in the early to mid-2000s and there is surprisingly little information in the public domain about forthcoming nepriylisin inhibitors.

Therevance Biopharma has TD-0714 and TD-1439 in phase 1 development for heart failure and CKD, but otherwise Novartis appears to have the market to itself for the near future. Solvay Pharmaceuticals was developing daglutril, a dual inhibitor of nepriylisin and endothelin-converting enzyme that has been shown to lower blood pressure in people with type 2 diabetes, nephropathy and hypertension, but no studies have been published more recently.

Summary
Sacubitril/valsartan is an innovative treatment for heart failure that improves symptoms and reduces the risk of death and hospital admission compared with ACE inhibitor therapy – the standard for many years. It has generated huge enthusiasm among specialists and has already found a place in management guidelines. There are differences between UK patients with heart failure and the participants in the clinical trial on which its reputation is built but it is not yet known if they are important. More clinical trials will refine its role, especially in patients with heart failure and preserved ejection fraction and in CKD, but a licence for hypertension looks unlikely in the near future.

People with heart failure in England, proportion eligible for treatment and predicted proportion treated with sacubitril/valsartan in five years’ time

<table>
<thead>
<tr>
<th>Description</th>
<th>Eligible for Treatment</th>
<th>Predicted Treated</th>
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<tbody>
<tr>
<td>Reduced ejection fraction</td>
<td>295,764</td>
<td></td>
</tr>
<tr>
<td>Reduced ejection fraction and NYHA class II–IV symptoms</td>
<td>210,288</td>
<td></td>
</tr>
<tr>
<td>Reduced ejection fraction ≤35 per cent and NYHA class II–IV symptoms</td>
<td>125,121</td>
<td></td>
</tr>
<tr>
<td>Reduced ejection fraction ≤35 per cent and NYHA class II–IV symptoms and</td>
<td>107,541</td>
<td></td>
</tr>
<tr>
<td>taking an ACE inhibitor/angiotensin II-receptor antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People taking sacubitril/valsartan from year five onwards</td>
<td>64,525</td>
<td></td>
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</tbody>
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Figure 3. Number of people with heart failure in England, proportion eligible for treatment and predicted proportion treated with sacubitril/valsartan in five years’ time. This Oxford-based trial is comparing sacubitril/valsartan with the angiotensin II-receptor antagonist irbesartan as monotherapy in patients with proteinuric CKD. The primary endpoint is the change in glomerular filtration rate after 12 months. Recruitment is now complete (n=414).
In patients with type 2 diabetes and cardiovascular disease, empagliflozin reduces cardiovascular and all-cause mortality

Clinical question: In patients with type 2 diabetes and cardiovascular disease, does the addition of empagliflozin improve outcomes?

Bottom line: In patients with established cardiovascular disease and type 2 diabetes, the addition of empagliflozin to standard therapy reduces all-cause mortality and cardiovascular mortality. This is notable because empagliflozin is the only drug other than metformin to demonstrate a mortality benefit, albeit for a fairly narrow group of patients. A dose of 10mg appears to provide a similar benefit to the 25mg dose, but with half the risk of genital infections. It is not appropriate to extend these conclusions to all patients with type 2 diabetes, as they are at lower risk of bad outcomes and are unlikely to benefit to the same degree. (LOE = 1b)

Synopsis: Empagliflozin decreases reabsorption of glucose in the kidneys, leading to greater urinary excretion. In this industry-sponsored trial, adults with type 2 diabetes and known cardiovascular disease were randomised to receive either empagliflozin 10mg, empagliflozin 25mg, or placebo. The 7028 patients were recruited from 590 sites in 42 countries. The mean age of participants was 63 years, 71 percent were male, and 5 percent were African-American. This was a very high-risk group: 75 percent had coronary artery disease, 23 percent had a previous stroke, 20 percent had peripheral arterial disease and 25 percent had a coronary artery bypass graft. The other diabetes medications used by patients included metformin (75 percent), insulin (53 percent), or a sulfonylurea (43 percent). Analysis was by modified intention to treat for all patients who received at least one dose of the study drug. The primary outcome was a composite of myocardial infarction (MI), stroke, or cardiovascular death. Patients were followed up for a median of 3.1 years. Results for the two empagliflozin doses were pooled and compared with placebo.

The patients in the intervention groups had lower all-cause mortality (5.7 vs 8.3 percent; p<0.001; number needed to treat [NNT] = 38 over 3.3 years), cardiovascular mortality (3.7 vs 5.9 percent; p<0.001; NNT=45 over 3.3 years), and hospitalisation for heart failure (2.7 vs 4.1 percent; p=0.002, NNT=71). There were no differences in other outcomes, including MI, stroke, coronary revascularisations or transient ischaemic attacks. The pooled dropout rate due to adverse events was 11.5 percent for the study drug and 13.0 percent for placebo. There were more episodes of urosepsis or pyelonephritis in the empagliflozin groups (0.8 vs 0.5 percent), and far more genital infections (5.0 vs 1.5 percent in men; 10.0 vs 2.6 percent in women).

15. Efficacy and Safety of LCZ696 Compared to Valsartan on Cognitive Function in Patients With Heart Failure and Preserved Ejection Fraction (PERSPECTIVE). ClinicalTrials.gov; identifier: NCT02884206.
18. Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF). ClinicalTrials.gov; identifier: NCT01920711.
21. Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE-MI). ClinicalTrials.gov; identifier: NCT02924727.

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.