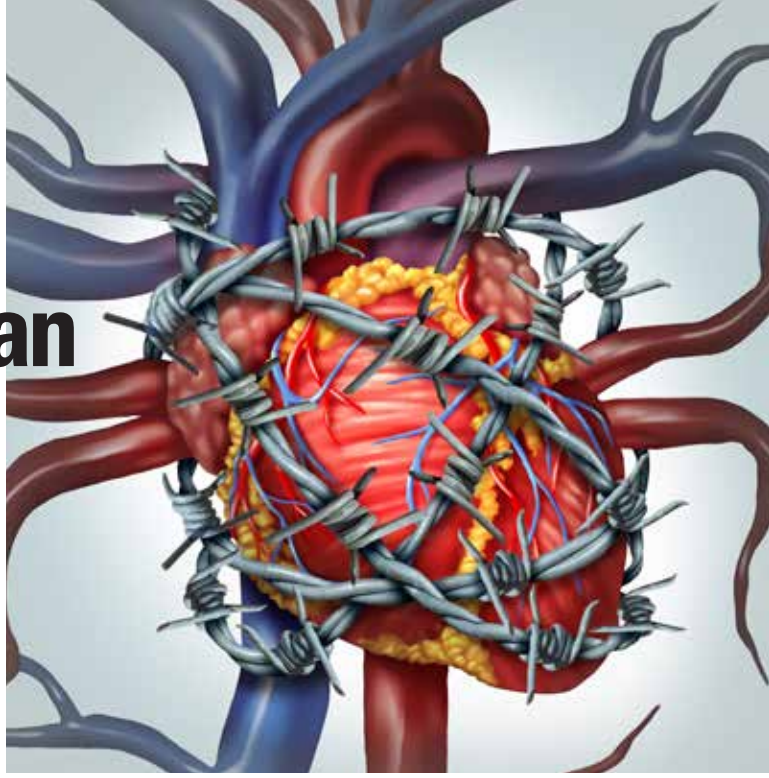

Sacubitril–valsartan

Changing the paradigm for heart failure with reduced ejection fraction

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Sacubitril–valsartan represents a new drug class, the angiotensin receptor–neprilysin inhibitors, that shows potential to replace ACE inhibitors in the treatment of selected patients with heart failure with reduced ejection fraction.

Following the recent PARADIGM-HF trial involving sacubitril–valsartan, recommendations on the optimal medical therapy for a significant proportion of patients with heart failure may be on the cusp of change.[1,2] The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan has potential to replace ACE inhibitors in the treatment of selected patients with heart failure with reduced ejection fraction.

Evolution of heart failure treatment

Since the 1980s, when ACE inhibitors were introduced after showing mortality benefit in patients with symptomatic or asymptomatic heart failure (Studies of Left Ventricular Dysfunction [SOLVD] trials), advances in heart failure treatment have involved adding successful new pharmacological agents to older agents. The combination of ACE inhibitors, β-blockers and aldosterone antagonists is the bedrock of therapy for patients with heart failure (Figure).

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Numerous other therapies have been studied with the hope of further reducing the burden of heart failure symptoms and improving survival. Agents such as the angiotensin receptor blocker (ARB) candesartan have been shown to be helpful, particularly when ACE inhibitors are contraindicated or not tolerated and possibly when β-blockers are not being taken.[3-5] Therapies that were apparently tried and true, such as digoxin, have been more closely examined and shown not to have any mortality benefit, although digoxin is helpful for the management of symptomatic heart failure in some patients.[6] The most recent addition to the armamentarium for selected patients with heart failure, the selective sinus node inhibitor ivabradine, has been shown to reduce the primary endpoint of cardiovascular death or hospitalisation for worsening heart failure.[7]

The availability of various successful therapies means that, with the addition of the requisite diuretics, anginal and antihypertensive therapies, statins and antiplatelet or antithrombotic therapies, patients receiving 'optimal treatment' for heart failure may take five to six different classes of medication daily, just for their heart.

It is against this substantial pharmacological armamentarium that new therapies for heart failure are tested. Vasopressin antagonists, adenosine A1 receptor antagonists, endopeptidase inhibitors and metalloproteinase inhibitors have failed to show incremental benefit in large-scale clinical trials and have been abandoned. However, nonpharmacological therapies such as implantable defibrillators and biventricular pacemakers decrease sudden cardiac death and pump failure, further raising the bar for medical therapy.

What is sacubitril–valsartan?

Sacubitril–valsartan is a fixed-dose combination product containing the angiotensin II receptor blocker valsartan and the novel neprilysin inhibitor sacubitril. It was approved by the TGA

in January 2016 for treatment of chronic heart failure (NYHA Class II to IV) with reduced ejection fraction in adults. It was recommended by the PBAC in August 2016 for PBS listing but at the time of writing had not been listed.

Sacubitril–valsartan should be initiated and uptitrated by a physician experienced with the treatment of patients with heart failure. It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. Other medications, such as diuretics, may also need to be adjusted with the commencement of sacubutril–valsartan.

What is the mechanism of action?

Currently successful therapies for heart failure target the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, both of which are deleteriously upregulated in patients with heart failure. Use of sacubitril–valsartan on a background of β-blockade therapy further inhibits the RAAS and the downstream sympathetic overactivity that contribute to vasoconstriction, cellular fibrosis and sodium and water retention in patients with heart failure.

Sacubitril has a novel mechanism of action, targeting the natriuretic peptide system through neprilysin inhibition. Neprilysin (also known as neutral endopeptidase) is an enzyme involved in the degradation of a number of peptides within the natriuretic peptide system, including atrial, B-type and C-type natriuretic peptides and bradykinin. By inhibiting neprilysin, sacubitril increases the concentration of these peptides and their activity. Augmentation of the inherent natriuretic peptide pathway enhances vasodilation and reduces the cellular changes of fibrosis and hypertrophy that occur in heart failure. Sacubitril has a further added benefit, with a direct renal response involving natriuresis and diuresis. Surprisingly, synthetic and recombinant B-type natriuretic peptides such as nesiritide have not shown the benefits seen with sacubitril–valsartan in the PARADIGM-HF trial (see below).

Given the wide variety of neprilysin substrates, it is not surprising that sacubitril inhibits the degradation of some peptides that are not among the intended targets. These include angiotensin I and angiotensin II as well as adrenomedullin, endothelin and amyloid β-protein. The increase in angiotensin II that occurs with isolated neprilysin inhibition results in lack of vasodilation, explaining the need to combine sacubitril with an angiotensin II receptor blocker.

What is the evidence?

The pivotal trial that raised the possibility that angiotensin receptor–neprilysin inhibition might redefine optimal heart failure management is PARADIGM-HF (Prospective Comparison of ARNI with ACE Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure).[1] This was a large (8442 patients), prospective, randomised, multinational controlled trial of maximally tolerated sacubutril–valsartan compared with enalapril in patients with symptomatic (NYHA class II to III) heart failure with reduced ejection fraction who were receiving otherwise optimal medical therapies. After enrolment, patients were given target-dose therapy in a run-in phase, to ensure that they would be able to tolerate therapy for the duration of the four years of follow up.

The convincingly positive outcome of the PARADIGM-HF trial was a 20% relative risk reduction in the primary endpoint of cardiovascular death or hospitalisation (4.7% absolute reduction) and a 16% relative reduction in the secondary endpoint of all-cause mortality (2.8% absolute reduction) with sacubutril–valsartan compared with enalapril. There was a similar (20%) reduction in either pump failure or sudden death as the cause of death. In addition, quality of life was significantly improved, and there was marked (34%) reduction in emergency department presentations with heart failure. Subgroup analyses have shown the consistency of results across patient groups, apart from a suggested lack of significant benefit in patients with the most severe heart failure (NYHA class IV

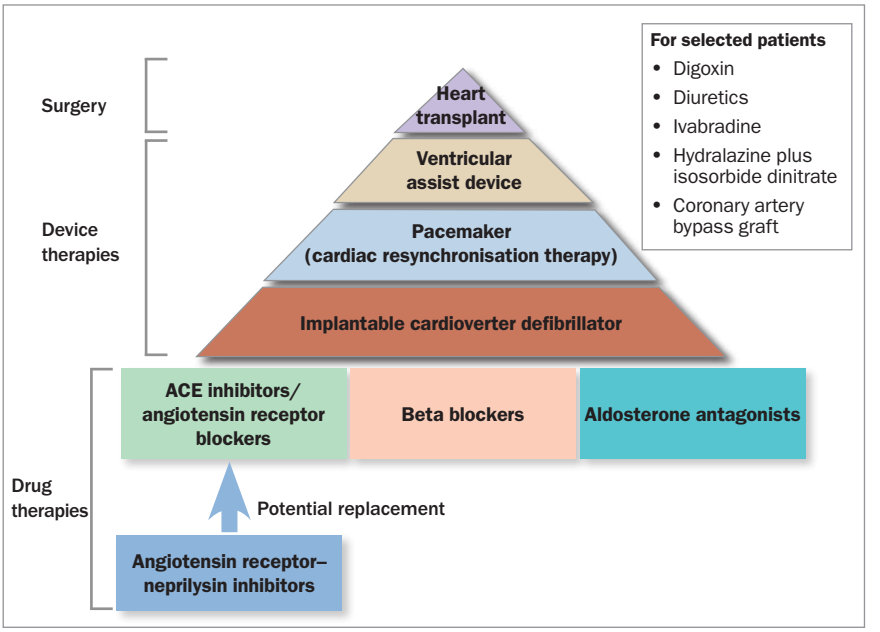

Figure. Optimal therapy for patients with heart failure with reduced ejection fraction showing the potential role of angiotensin receptor–neprilysin inhibitors such as sacubitril–valsartan.
Adapted from McMurray. Eur J Heart Fail 2015; 17: 242-247.[2]

symptoms) and hypotension at enrolment. Patients with decompensated heart failure were excluded.

Tolerability and side effects

In the PARADIGM-HF trial, patients were excluded if they had a history of angioedema (related to accumulation of bradykinin, levels of which would be expected to increase with sacubitril–valsartan), significant renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2), hyperkalaemia (potassium level above 5.2 mmol/L at screening or above 5.4 mmol/L at the end of run-in) or symptomatic hypotension (systolic blood pressure less than 100 mmHg at screening or less than 95 mmHg at the end of run-in).

The PARADIGM-HF trial involved a run-in phase, during which around 10% of participants discontinued because of an adverse event. A similar proportion of those taking sacubitril–valsartan discontinued during the trial. The most common adverse events were hypotension, hyperkalaemia, renal impairment and cough. Angioedema was a rare but serious side effect.

Importantly, there were significantly more adverse events in the enalapril arm of the trial (12.3% with enalapril *vs* 10.7% with sacubitril–valsartan). The frequency of hypotension and hyperkalaemia were similar with enalapril and sacubitril–valsartan in the run-in phase, but during the trial there was more hypotension in the sacubitril–valsartan arm compared with the enalapril arm. Cough was more frequent with enalapril. Angioedema was infrequent in both patient groups.

Sacubitril–valsartan interacts with many other drugs. These include ACE inhibitors, other ARBs, potassium-sparing diuretics, NSAIDs, aldosterone antagonists, furosemide (frusemide), metformin and statins.

How might sacubitril–valsartan change practice?

The mortality, morbidity and hospitalisation data from the PARADIGM-HF trial are difficult to ignore, and sacubitril–valsartan is expected to be recommended when heart failure management guidelines are updated. The potential role of sacubitril–valsartan in replacing ACE inhibitors or ARBs in patients with heart failure with reduced ejection fraction is shown in the Figure.

At present, sacubitril–valsartan has not been assessed in a 'de novo' cohort of patients who are ACE inhibitor-naïve. New patients with heart failure should be commenced on optimal medical therapy (including ACE inhibition) in the first instance, with consideration of transitioning to sacubutril–valsartan when they are stabilised.

In patients with NYHA class II to III heart failure with reduced ejection fraction who are stable on an ACE inhibitor, there is a good case to trial replacing the ACE inhibitor with sacubitril–valsartan (with a 36-hour washout period), in view of the clear mortality and hospitalisation benefit. It might also be reasonable for patients who have been intolerant of ACE inhibitors previously and have been managed with an ARB to change to sacubitril–valsartan, although this was not tested in the PARADIGM-HF trial. Unfortunately, patients taking sacubitril–valsartan instead of an ACE inhibitor or ARB would still be taking the same number of medications, as this would be a simple substitution.

Patients with low blood pressure or symptomatic hypotension may be more sensitive to sacubitril–valsartan, and it would be important to closely monitor these patients when changing therapy. Patients with decompensated heart failure, class IV symptoms or very poor ejection fraction may not be expected to tolerate sacubitril–valsartan to the same extent and are a high-risk group. Renal function should be checked within the first month of therapy, and sacubitril–valsartan should be stopped if significant hyperkalaemia occurs.

Conclusion

Sacubutril–valsartan is a novel therapy for patients with heart failure that increases the level of natriuretic peptides within the circulation and is significantly superior to enalapril in its effects on overall mortality and morbidity, with an acceptable safety profile. At present, sacubutril–valsartan has not been included in guidelines for management of heart failure, although this is likely to change as these guidelines are updated. Over the coming years, sacubutril–valsartan may replace ACE inhibitors as a cornerstone of optimal medical therapy in selected patients with heart failure with reduced ejection fraction. MT

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