

Entresto (sacubitril/valsartan)

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Introduction

Heart failure has a high prevalence and poor prognosis, with ~900 000 patients in the UK and 30–40% of patients likely to die within one year of diagnosis.¹ It is caused by any structural or functional abnormality that impairs the ability of the heart to pump effectively, most commonly due to ischaemic heart disease, but can also be as a result of valvular, pericardial, endocardial or conduction problems. One-third of patients with heart failure have diabetes, where a combination of abnormal systolic function and diastolic filling abnormalities contribute to the disorder. Entresto (a combination of sacubitril/valsartan) has demonstrated efficacy in reducing morbidity and mortality in patients with heart failure.

Pathophysiology

Elevated cardiac filling pressures, decreased cardiac output and reduced oxygen delivery cause an activation of the renin angiotensin aldosterone system (RAAS) and sympathetic nervous systems leading over time to complications such as myocardial remodelling, increased systemic

vascular resistance and increased sodium and water retention. The RAAS as a target for treatment in heart failure is well established with good evidence for therapeutic benefit from ACE inhibitors (ACEIs) and angiotensin II receptor blockers (A2RBs). Raised cardiac filling pressures also cause increased mechanical stretch activating the secretion of precursor natriuretic peptides, which in their active form cause vasodilatation, natriuresis and inhibit the RAAS. The natriuretic peptides that are significant in heart failure are atrial natriuretic peptide (ANP), B natriuretic peptide (BNP) and C natriuretic peptide (CNP). In chronic heart failure (CHF), levels of natriuretic peptide are reduced in part due to the increased activity of neprilysin which enhances the rate of their degradation.

Previous attempts at increasing active BNP using the synthetic BNP nesiritide were unsuccessful due to associated significant hypotension, high cost, need for intravenous administration route and studies not showing a reduction in death or hospitalisation

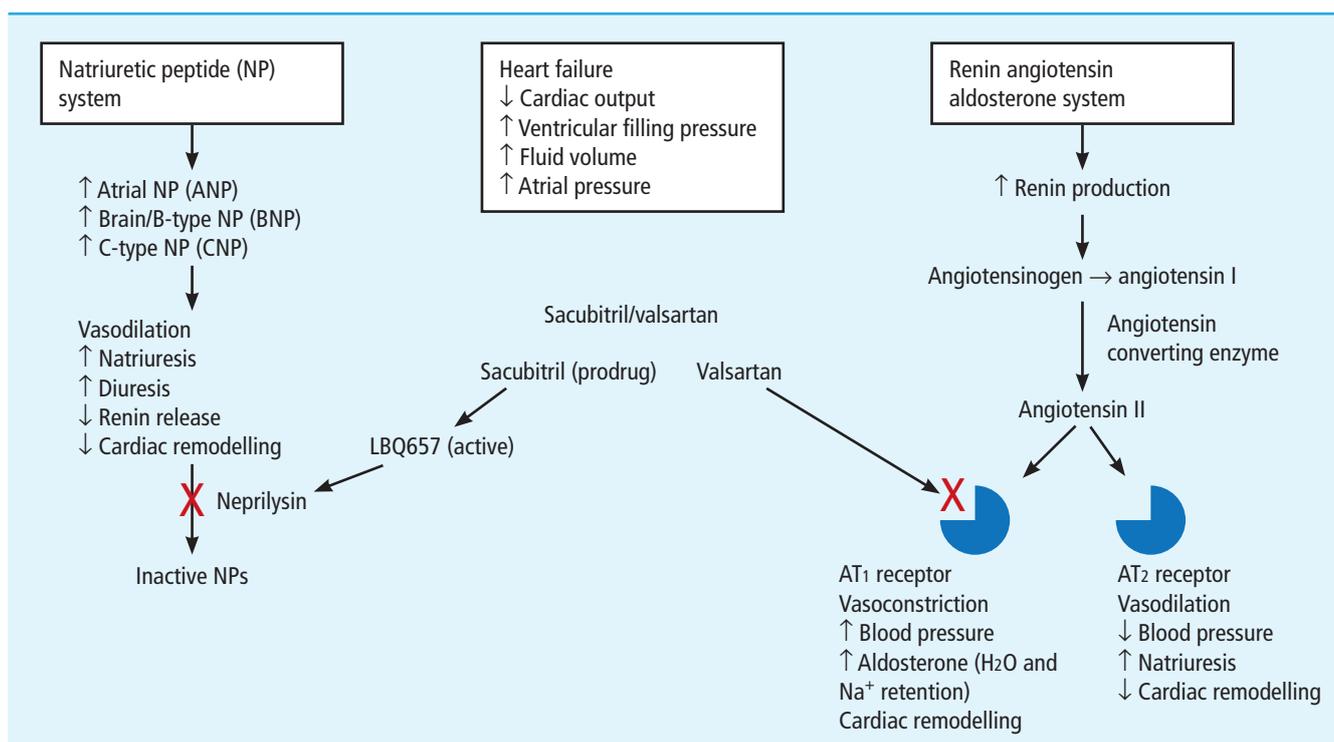


Figure 1. Entresto works by a dual effect on the natriuretic system and the renin angiotensin aldosterone system

rates.² Trials of neprilysin inhibitors showed increases in ANP levels and natriuresis but also had associated increased levels of angiotensin II as neprilysin also has a role in angiotensin II degradation. The first neprilysin-ACEI combination, omapatrilat, failed to demonstrate superiority over enalapril and was withdrawn due to the high occurrence and severity of angioedema thought to be due to increased levels of bradykinin and substance P caused by the inhibition of neprilysin, ACE and aminopeptidase.³ Entresto (sacubitril/valsartan) is a first-in-class drug combining a neprilysin inhibitor and A2RB.

Pharmacology

Figure 1 outlines the pharmacological actions of Entresto. It is administered orally as a complex of sacubitril and valsartan. Once ingested the complex dissociates. Sacubitril, a prodrug, is metabolised by esterases to the active metabolite LBQ657. This inhibits neprilysin which is responsible for the breakdown of natriuretic peptides. This results in increasing levels of endogenous natriuretic peptide and therefore increased benefit of natriuresis, diuresis, vasodilatation and inhibition of RAAS. As neprilysin is also responsible for the breakdown of angiotensin II, an ACEI or A2RB is necessary to counteract this. Valsartan acts by selective blockade of the angiotensin II AT₁ receptor thereby restricting the stimulation of aldosterone secretion and vasoconstriction while allowing the stimulation of the angiotensin II AT₂ receptor. This has the effect of decreased cell proliferation, apoptosis and bradykinin and nitric oxide induced vasodilation. The mean elimination half-life of sacubitril, LBQ657 and valsartan ranges from 0.9–3.3, 12.3–14.7 and 15–22.6 hours. The prodrug sacubitril is hydrolysed by esterases but LBQ657 and valsartan do not undergo significant hepatic metabolism.

Trials of safety and efficacy

The PARADIGM-HF study was a phase 3, randomised, double-blind trial in 1043 centres across 47 countries conducted with the aim of showing superiority over enalapril on morbidity and mortality in patients with CHF.⁴

A total of 10 521 were recruited with an NYHA class of II, III or IV, an ejection fraction of $\leq 40\%$ (later amended to $\leq 35\%$), plasma BNP level of $>150\text{pg/ml}$ (or if hospitalised in the last 12 months with heart failure $>100\text{pg/ml}$). Eligible patients were switched from their usual ACEI or A2RB to single-blind treatment with enalapril 10mg bd for two weeks. If tolerated, the regimen was switched to Entresto for 4–6 weeks titrated up from 100mg bd to 200mg bd. Patients were then randomly assigned to double-blind treatment with either enalapril 10mg bd or Entresto 200mg bd. Enalapril was withheld a day before initiation of treatment with Entresto and Entresto was withheld a day before randomisation to minimise the risk of angioedema. The primary outcome was death from cardiovascular causes and first hospitalisation for heart failure. There were significantly fewer deaths due to cardiovascular causes for those on Entresto (558 [13.3%]) compared with those on enalapril (693 [16.5%]); (hazard ratio 0.80, 95% CI 0.71–0.89; $p < 0.001$). The Entresto-treated patients also demonstrated lower rates of hospitalisation for heart failure (537 [12.8%] compared with 658 [15.6%]) in those receiving enalapril (hazard ratio 0.79, 95% CI 0.71–0.89; $p < 0.001$). Death from any cause was also lower in those treated with Entresto compared with enalapril (711 [17.0%] vs 835 [19.8%]; hazard ratio 0.84, 95% CI 0.76–0.93; $p < 0.001$). Symptoms were also assessed via the Kansas City Cardiomyopathy Questionnaire. In the first eight months, the Entresto-treated patients performed better with a reduction of 2.99 points versus a reduction of 4.63 points in the enalapril-treated patients (between-group difference 1.64 points; 95% CI 0.63 or 2.65; $p = 0.001$). At the third interim analysis the trial was halted as the prespecified stopping boundary for an overwhelming benefit had been crossed.

Evidence specific to diabetes

While there was no specific subgroup analysis for those with diabetes in PARADIGM-HF, they contributed to 34.7% of the Entresto group and 34.6% of the enalapril group making a significant proportion of both study groups.

Key points

- Heart failure has a high prevalence with a poor prognosis
- There are a number of medications available for use that have been shown to improve prognosis in heart failure including ACE inhibitors, A2RBs, beta blockers and mineralocorticoid inhibitors
- The combination of sacubitril/valsartan (Entresto) has been shown to improve morbidity and mortality in patients with heart failure, even in patients who would have previously been considered to be on optimal treatment

Discussion

The superiority of Entresto over enalapril in reducing both morbidity and mortality in chronic heart disease in the PARADIGM-HF trial demonstrates an exciting development in the treatment of CHF. This, coupled with a lower incidence of adverse reaction in the Entresto group during the study, raises the possibility that patients who have had an ACEI withdrawn due to hyperkalaemia, cough or renal dysfunction may have another treatment option available to them. Current NICE guidance suggests Entresto is an option for treating symptomatic CHF with reduced ejection fraction, but only in patients with NYHA class II–IV symptoms and a left ventricular ejection fraction of $\leq 35\%$ and who are already taking a stable dose of ACEI or A2RB. Treatment with sacubitril/valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Similar advice is given by the Scottish Medicines Consortium who approved its use.

Declaration of interests

Professor Fisher has received honoraria for advisory boards and lectures from Novartis.

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