Therapeutics and Clinical Risk Management

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REVIEW

Cardiovascular Outcomes with Sacubitril-Valsartan in Heart Failure: Emerging Clinical Data

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

Joseph J Cuthbert[1]
Pierpaolo Pellicori[2]
Andrew L Clark[1]

[1]Department of Academic Cardiology, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Kingston upon Hull HU16 5JQ, UK; [2]Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK

Abstract: One of the defining features of heart failure (HF) is neurohormonal activation. The renin-angiotensin-aldosterone-system (RAAS) and sympathetic nervous system (SNS) cause vasoconstriction and fluid retention and, in response, the secretion of natriuretic peptides (NPs) from volume and pressure-overloaded myocardium promotes vasodilation and diuresis. Inhibition of the RAAS with either angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) has been the cornerstone of medical treatment for HF with a reduced ejection fraction (HFrEF) but, until recently, it was unclear how the beneficial effects of NPs may be augmented in patients with HF. Neprilysin, a metalloproteinase widely distributed throughout the body, plays a role in degrading the gross excess of circulating NPs in patients with HF. Early studies of neprilysin inhibition suggested possible physiological benefits. In 2014, the PARADIGM-HF trial found that sacubitril-valsartan, a combination of the ARB valsartan, and the neprilysin inhibitor sacubitril, was superior to enalapril in patients with HFrEF, reducing the relative risk of cardiovascular (CV) death or first hospitalisation with HF by 20%. Almost half of the patients with HF symptoms have a "preserved" ejection fraction (HFpEF); however, the PARAGON-HF study found that sacubitril-valsartan in patients with LVEF ≥45% had no effect on CV death or first and recurrent hospitalisations with HF compared to valsartan. Guidelines across the world have changed to include sacubitril-valsartan for patients with HFrEF yet, nearly 6 years after PARADIGM-HF, there is still uncertainty as to when and in whom sacubitril-valsartan should be started. Furthermore, there may yet be subsets of patients with HFpEF who might benefit from treatment with sacubitril-valsartan. This review will describe the mechanisms behind the outcome benefit of sacubitril-valsartan in patients with HFrEF and to consider its future role in the management of patients with HF.

Keywords: sacubitril-valsartan, heart failure, PARADIGM-HF, PARAGON-HF, natriuretic peptide, angiotensin receptor neprilysin inhibitor

Plain Language Summary

Heart failure (HF) is characterised by breathlessness that is due, in part, to activation of the renin-angiotensin-aldosterone system (RAAS) which causes widespread vasoconstriction and fluid retention. To counteract these harmful effects the heart secretes hormones called natriuretic peptides (NPs) which increase diuresis. Blockade of the RAAS has been at the centre of medical treatment of HF for the last three decades and the prognosis for patients with HF due to an impaired left ventricle (HFrEF) has vastly improved as a result. Comparatively, treatments to enhance the beneficial effects of NPs have been less successful. However, in 2014, the PARADIGM-HF trial of over 8000 patients with HFrEF found that

Correspondence: Joseph J Cuthbert
Department of Academic Cardiology, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston upon Hull HU16 5JQ, UK
Tel + 44 (0)1482 461776
Fax + 44 (0)1482 461779
Email joe.cuthbert@hey.nhs.uk

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/TCRM.S234772

a new drug, sacubitril-valsartan, was superior to the gold standard treatment, enalapril. Sacubitril-valsartan is a combination drug of two compounds: sacubitril, which acts increase levels of circulating NPs by preventing their enzymatic breakdown and valsartan, which acts to lessen the effects of the RAAS. Despite this success, it is still not clear as to which patients with HF sacubitril-valsartan should be given. Additionally, further trials have found that sacubitril-valsartan may not be effective for all patients with HF. This review will explore how sacubitril-valsartan might benefit some patients with HF (and not others), and how it might fit into medical practice in years to come.

Introduction

Heart failure is characterised by neurohormonal activation. Activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous (SNS) systems is triggered by cardiac dysfunction, whilst the natriuretic peptide (NP) system is activated by fluid retention and consequent myocardial stretch. To some extent the two systems counteract each other with the RAAS and SNS tending to cause vasoconstriction and fluid retention, and the NP system causing vasodilation and diuresis.

Patients with HF are classified into different phenotypes based on their left ventricular ejection fraction (LVEF) on imaging: LVEF <40% - HF with reduced ejection fraction (HFrEF); LVEF 40–49% - HF with mid-range ejection fraction (HFmrEF) and LVEF ≥50% - HF with preserved ejection fraction (HFpEF), which has therapeutic implications.[1] However, activation of the SNS and RAAS and high levels of NPs occur in each phenotype.[2]

Treatment of patients with HFrEF with medications that inhibit the RAAS and SNS is one of the great success stories of modern medicine;[3] the PARADIGM-HF trial of sacubitril-valsartan is one of the more recent chapters.[4]

Sacubitril-valsartan is a "first-in-class" angiotensin receptor neprilysin inhibitor (ARNI) combining a neprilysin inhibitor, sacubitril, with the angiotensin receptor blocker (ARB) valsartan.[5] The purpose of this review is to describe and understand the mechanisms behind the outcome benefit of sacubitril-valsartan in patients with HFrEF, and to consider its future role in the management of patients with HF.

Natriuretic Peptides and Neprilysin in Heart Failure

NPs – predominantly atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) – are hormones that are synthesised as pro-peptides and stored in granules within myocytes.[6] In response to myocardial stretch due to increased intracardiac pressure or volume (or both), the pro-peptides are cleaved by enzymes – corin and furin for ANP and BNP, respectively – and are secreted; the biological effects are then mediated via transmembrane receptors (NPRs).[7] Binding to NPR-A causes increased intracellular cyclic guanosine monophosphate (cGMP) second messenger activity which, via intracellular signalling cascades, causes increased renal sodium and water excretion, increased glomerular filtration, vasodilation, and reduced renin and aldosterone secretion (Figure 1).[8]

NPs are degraded via two pathways. The predominant pathway in normal physiology is via binding to a "clearance receptor", NPR-C (the most abundant NPR), thus removing NPs from the circulation.[7,8] Only once NPR-C receptors become saturated does the second pathway, hydrolysis by neprilysin, begin to play a significant role in NP clearance.[9] Neprilysin is a zinc-dependant metalloproteinase distributed throughout the body and has many substrates aside from NPs including angiotensin II (ATII), bradykinin, substance P, adrenomedullin, and oxytocin among others.[10] In patients with symptomatic HF who have very high levels of NPs,[11] NPR-C is saturated (and may also be down-regulated due to chronic exposure to NPs),[12] and thus degradation by neprilysin becomes the main pathway for NP clearance (Figure 1).[13,14]

From OVERTURE to PARADIGM-HF

Attempts to harness the beneficial effects of NPs in patients with cardiovascular disease has been a focus of research for over 20 years with varying degrees of success (Table 1). Despite promising Phase I and II results,[15,16] trials of exogenous NPs failed to demonstrate morbidity or mortality benefit in patients admitted with HF.[17,18] Trials of oral or intravenous neprilysin inhibitors were tried with the notion that blocking breakdown of NPs would result in higher circulating levels and hence a diuresis. However, because neprilysin also degrades ATII,[19] neprilysin inhibitors are unlikely to benefit patients with heart failure without concurrent RAAS inhibition. Used as single agents, they yielded disappointing results during pre-clinical and early clinical stages.[20–24]

The IMPRESS[26] and OVERTURE[27] trials of omapatrilat (an oral inhibitor of both angiotensin converting enzyme (ACE) and neprilysin)[25] found possible outcome benefit over ACEI in patients with HFrEF. However, development of the drug was stopped following a high incidence of angio-oedema in the omapatrilat arm of the above trials and the OCTAVE trial of omapatrilat in patients with hypertension (N~25,000).[28]

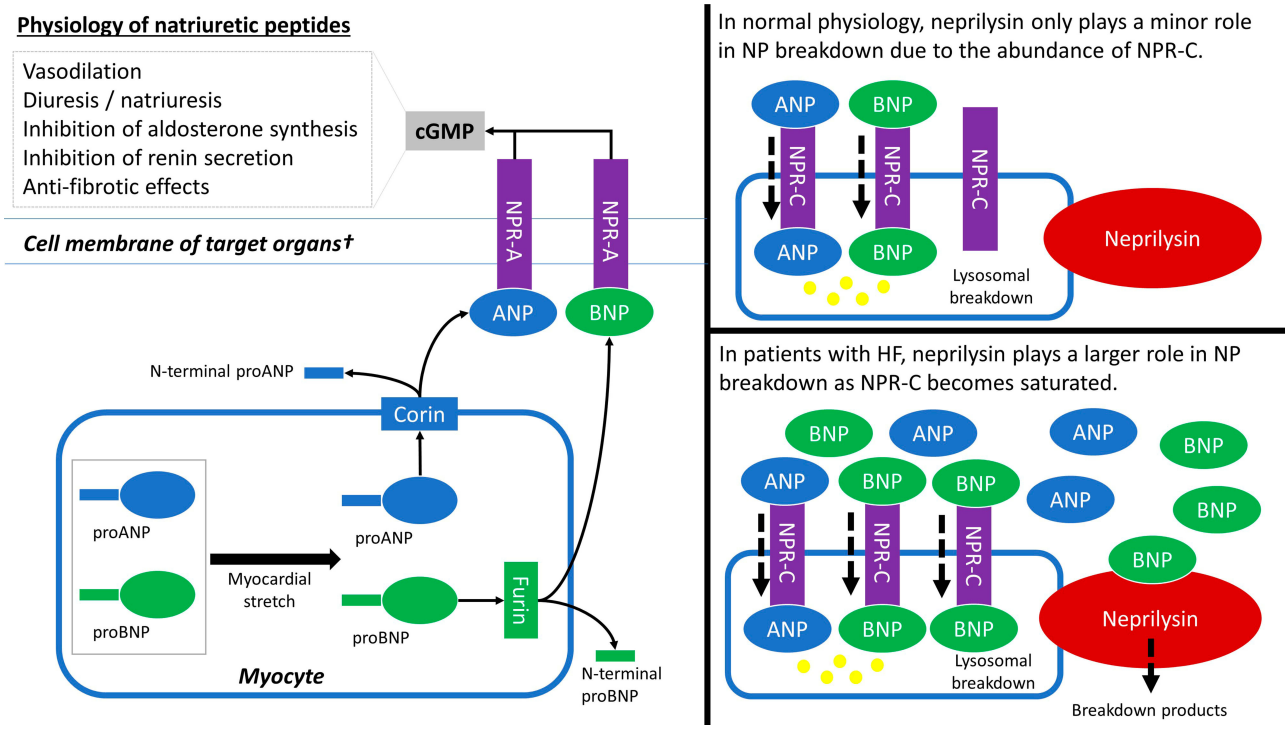

Figure 1 Physiology of natriuretic peptides. Synthesis, secretion, physiological action and breakdown of natriuretic peptides. ANP and BNP bind to NRP-A, C-natriuretic peptide binds to NPR-B but has less well understood cardiovascular effects. NPR-C is the NP clearance receptor which is widely distributed throughout the body. † Renal tubular cells, adrenal cortical cells, cardiac myocytes and fibroblasts and vascular endothelium.

Abbreviations: ANP, atrial natriuretic peptide; BNP, b-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; NPR-A, natriuretic peptide receptor A; NPR-C, natriuretic peptide receptor C.

Sacubitril-Valsartan

Heart Failure with a Reduced Ejection Fraction

The PARADIGM-HF investigators enrolled 8442 ambulatory patients with symptomatic HFrEF (mean age 63 years, LVEF 29%, median N terminal pro-BNP (NTproBNP) 1631 pg/mL in the treatment arm). Following a run-in period during which all patients were separately titrated to target doses of enalapril and then sacubitril-valsartan, those without adverse effects to either were randomised to either sacubitril-valsartan 97/103mg twice daily (BD) or enalapril 10mg BD (Figure 2).[4]

Treatment with sacubitril-valsartan was associated with a 20% relative risk reduction (RRR) in the primary endpoint, a composite of cardiovascular death or first hospitalisation with heart failure compared to enalapril (Table 2).[4,29] The outcome benefit was the same regardless of heart failure aetiology[30] or age,[31] and sacubitril-valsartan reduced the risk of recurrent admissions not just for heart failure,[32] but for any cause.[33]

A putative placebo analysis of the PARADIGM-HF data (using outcome data from the placebo arms of the SOLVD and CHARM-alternative studies as the control group)[34] suggested that the number needed to treat to reduce all-cause mortality at 5 years with sacubitril-valsartan was 11, an effect size second only to beta-blockers amongst other treatments for HFrEF.[35]

Although there was no difference in the pre-specified outcome of new-onset diabetes mellitus (DM) between the treatment groups in PARADIGM-HF (2.9% vs 3.2%),[4] sacubitril-valsartan was associated with better glycaemic control in patients with DM than enalapril.[36] Similarly, while there was no difference in the pre-specified outcome of time to worsening renal function (end-stage renal failure, from >60 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 or a decrease in the estimated glomerular filtration rate (eGFR) of ≥50%, or by >30 mL/min/1.73 m^2 from baseline), the rate of decline of eGFR was slower in patients taking sacubitril-valsartan compared to enalapril (−1.6 mL/min/1.73m^2/year vs −2.0 mL/min/1.73m^2/year; P<0.001), regardless of the presence of renal impairment at baseline.[37]

There was a greater fall in KCCQ score in the enalapril group (indicating poorer quality of life) than in the sacubitril-valsartan group,[4] equivalent to the difference of 9 years of ageing.[38] While this last detail is eye-catching, the difference between the groups was small (1.64 at 8 months; P=0.001) with only a weak inverse relationship between

Table 1 Table of Studies Which Led to the Development of Combined Angiotensin Receptor Blocker and Neprilysin Inhibitor

Study and Year	Population	Study Drug	Comparator	Primary Outcome(s)	Results
Exogenous Natriuretic Peptides					
VMAC Investigators (2002)[15]	AHF (N=489)	Nesiritide	Nitroglycerin or placebo	1. Change in PCWP in those undergoing RHC (N=246) 2. Change in patient-assessed symptoms after 3 hours	Change in PCWP nesiritide vs nitroglycerin (−8.2 vs −6.3 mmHg; P=0.03). Improved symptoms vs placebo (P=0.03) but not vs nitroglycerin
ASCEND-HF (2011)[17]	AHF (N=7141)	Nesiritide	Placebo	1. Change in breathlessness at 6 and 24 hours 1. Rehospitalisation with HF or death at 30 days	More patients reported an improvement in breathlessness in the nesiritide group but there was no difference in the primary endpoints.
TRUE-AHF (2017)[18]	AHF (N=2157)	Ularitide	Placebo	1. Cardiovascular death during follow up (15 months) 2. Clinical endpoint in first 48 hours of treatment classifying patients as "worse", "unchanged" or "improved"	Greater reductions in SBP and NTproBNP with ularitide but no effect on primary endpoints.
Neprilysin Inhibitors					
Northridge et al (1989)[20]	Healthy controls (N=16) CHF (N=6)	UK69,578	Placebo	Physiological effects	Increase in plasma ANP levels and urinary sodium levels and decrease in plasma renin levels vs placebo (P<0.01, P<0.01 and P<0.05 respectively)
Gros et al (1989)[21]	Healthy controls (N=8)	Acetorphan	Placebo	Physiological effects	Increase in plasma ANP levels and urine volume and sodium concentration.
Kahn et al (1990)[22]	CHF (N=12)	Sinorphan	Pre-treatment	Physiological effects	Increase in ANP levels (P<0.01) and decrease in renin levels and PCWP (P<0.04) compared to pre-treatment.
Good et al (1995)[23]	CHF (N=12)	Candoxatrilat	Placebo	Physiological effects	Increase in ANP levels and urine volume and sodium concentration vs placebo
Cleland et al (1998)[24]	CHF (N=279)	Ecadotril	Placebo	Safety and tolerability of varying doses	Dose-dependent increases in cGMP but no effect on renin, ang II, NTproANP, or symptoms. Possibility of drug-induced pancytopenia causing death in 2 patients in ecadotril arm.
Dual ACE and Neprilysin Inhibition					
Liao et al (2003)[25]	Healthy controls (N=47)	Omapatrilat	Placebo	Pharmacokinetics	Dose-dependent increases in urinary ANP and cGMP levels and decrease in SBP.
IMPRESS (2000)[26]	CHF (N=573)	Omapatrilat	Placebo	1. Improvement in ETT at 12 weeks. 2. Composite of death or comorbid events due to HF (secondary endpoint)	No effect on ETT. 48% RRR of death, HF hospitalisation or worsening HF (P=0.035) – study not powered to detect secondary endpoint

(*Continued*)

Table 1 (Continued).

Study and Year	Population	Study Drug	Comparator	Primary Outcome(s)	Results
OVERTURE (2002)[27]	CHF (N=5770)	Omapatrilat	Enalapril	Composite of death or hospitalisation with HF requiring IV treatment	Primary endpoint occurred in 32% vs 34% in the omapatrilat and enalapril groups (P=0.187): omapatrilat was noninferior (but not superior) to enalapril
OCTAVE (2004)[28]	Hypertension (N=25,302)	Omapatrilat	Enalapril	1. Reduction in SBP at 8 weeks 2. Need for new antihypertensive treatment at 24 weeks	Between group difference of 3.6 mmHg in favour of omapatrilat at week 8 with fewer new antihypertensives started by week 24 (P<0.001). Angio-oedema occurred in 2.17% the omapatrilat group (vs 0.68%; P<0.001) two of whom had airway compromise.

Abbreviations: AHF, acute heart failure; CHF, chronic heart failure; ACE, angiotensin-converting enzyme; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterisation; HF, heart failure; SBP, systolic blood pressure; NTproBNP, N-terminal pro-B-type Natriuretic Peptide; ANP, atrial natriuretic peptide; NTproANP, N-terminal pro-ANP; ang II, angiotensin II; cGMP, cyclic guanosine monophosphate; ETT, exercise treadmill test; RRR, relative risk reduction.

NTproBNP levels and KCCQ score.[4] Whether such a small change in KCCQ score equates to any noticeable change for the patient is unknown.

PIONEER-HF and TRANSITION

PARADIGM-HF established the safety and efficacy of sacubitril-valsartan in patients with chronic heart failure, the PIONEER-HF and TRANSITION studies sought to do the same in patients who had recently been admitted with heart failure.[39,40]

PIONEER-HF was a head-to-head comparison of enalapril and sacubitril-valsartan initiated in hospital. Sacubitril-valsartan was associated with a greater reduction in NTproBNP between weeks 4 and 8 than enalapril (primary end-point); a significant difference was detected after 1 week of treatment.[41]

TRANSITION was a comparison of pre- versus post-discharge initiation of sacubitril-valsartan. There was no significant difference in the primary endpoint of the proportion of patients who reached target dose

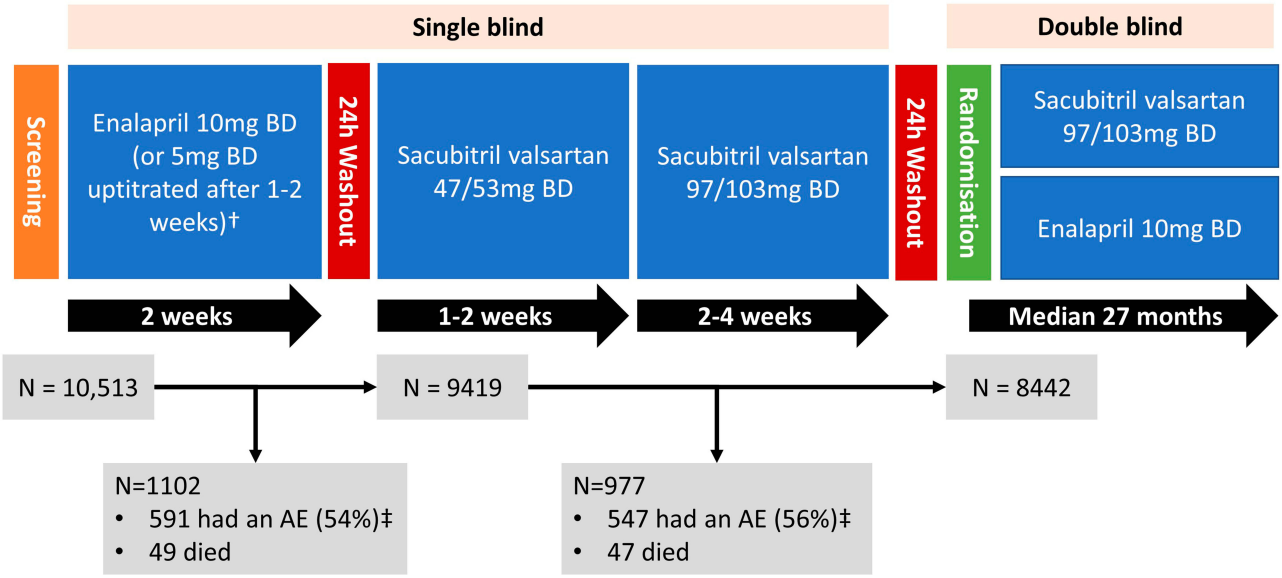

Figure 2 Run-in phases of PARADIGM-HF. †Patients who were on an ARB, low-dose ACEI or those in who the investigator did not think 10mg enalapril twice daily would be immediately tolerated. ‡The most common AEs during the run in phase were hypotension, cough, hyperkalemia, and renal dysfunction.
Abbreviations: BD, bis in die (twice daily); hr, hours; N, number; AE, adverse event; ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor.

Table 2 Outcomes in the PARADIGM-HF and PARAGON-HF

Endpoint	PARADIGM-HF (N=8442)				PARAGON-HF (N=4822)			
	Sacubitril-Valsartan	Enalapril	Hazard Ratio (95% CI)	P	Sacubitril-Valsartan	Valsartan	Hazard or Risk Ratio (95% CI)	P
Primary endpoint	21.8%	26.5%	0.80 (0.73–0.87)	<0.001	37.1%[a]	42.2%[a]	0.87 (0.75–1.01)	0.06
Hospitalisation with HF	12.8%	15.6%	0.79 (0.71–0.89)	<0.001	28.7%[a]	33.4%[a]	0.85 (0.72–1.00)	NS
CV mortality	13.3%	16.5%	0.80 (0.71–0.89)	<0.001	8.5%	8.9%	0.95 (0.79–1.16)	NS
Non-CV Mortality	2.8%	2.5%	1.09 (0.84–1.41)	0.56	5.7%	5.7%	NR	NS
All-cause mortality	17%	20%	0.84 (0.76–0.93)	<0.001	14.2%	14.6%	0.97 (0.84–1.13)	NS

Notes: [a]Number of events as a percentage of the number of patients in each group. Unlike PARADIGM-HF which recorded only the first hospitalisation, PARAGON-HF included all hospitalisations with heart failure in the primary endpoint.
Abbreviations: HF, heart failure; CV, cardiovascular; NR, not reported; NS, not significant.

sacubitril-valsartan (97/103mg BD) by 10 weeks (45.4% vs 50.7%).[42]

Approximately half of the patients in PIONEER-HF and TRANSITION were ACEI or ARB naïve prior to randomisation, but this had no impact on tolerability nor the chance of achieving target dose.[40,41] Neither study was powered to detect outcome benefit but sacubitril-valsartan was associated with a 42% RRR in cardiovascular death or readmission with heart failure in PIONEER-HF (P=0.007).[43]

Safety and Tolerability of Sacubitril-Valsartan in Patients with HFrEF

The most common adverse event with sacubitril-valsartan is symptomatic hypotension but consequent discontinuation in PARADIGM-HF was uncommon (Table 3).[4,40,41,44] However, it is important to note that the run in phase of the study design means that patients eventually randomised in the trial proper were pre-selected to be tolerant of both drugs (Figure 2).[4] In PARADIGM-HF, the rate of discontinuation was higher in the enalapril group than the sacubitril-valsartan group (12.3% vs 10.7%; P=0.03)[4] and was lower than was seen in most other landmark studies (Table 4).[4,45-49]

Target dose sacubitril-valsartan was not particularly well tolerated: almost half (42%) of patients randomised to sacubitril-valsartan in PARADIGM-HF, all of whom started at the target dose of 97/103 mg BD, required dose reduction within the first year, and only a minority returned to target dose.[50] The proportion of patients who achieved target dose by the end of the study in PIONEER-HF (55.2%) and TRANSITION (47.6%) was similarly modest.[40,41] Slower up-titration from a lower starting dose of 50mg BD may enable more patients to reach target dose.[51]

Another substrate of neprilysin is beta amyloid protein accumulation of which is related to Alzheimer's dementia.[52] There is thus a theoretical concern that neprilysin inhibition may increase the risk of dementia.[53,54,

Table 3 Adverse Event Rates in PARADIGM-HF, PIONEER-HF and TRANSITION

Adverse Event	PARADIGM-HF			PIONEER-HF			TRANSITION
	Sacubitril-Valsartan	Enalapril	P	Sacubitril-Valsartan	Enalapril	P	Sacubitril-Valsartan
Symptomatic hypotension	14.0%	9.2%	<0.001	15.0%	12.7%	NS	11.1%
Discontinuation due to symptomatic hypotension	0.9%	0.7%	0.38	2.5%	2.5%	NS	1.4%
Worsening renal function[a]	3.3%	4.5%	0.007	13.6%	14.7%	NS	4.1%
Hyperkalaemia[b]	4.3%	5.6%	0.007	11.6%	9.3%	NS	11.3%
Cough	11.3%	14.3%	<0.001	0.7%	0.2%	NR	2.2%
Angio-oedema	0.4%	0.2%	NS	0.2%	1.4%	NS	0.3%

Notes: [a]Serum creatinine ≥221 μmmol/L in PARADIGM-HF and serum creatine rise of >44 μmol/L and a decrease in estimated glomerular filtration rate of >25% in PIONEER-HF; [b]Serum potassium >6.0 mmol/L; NR – not reported; NS – not significant.

Table 4 Rate of Discontinuation Due to an Adverse Event in Landmark Studies of Medical Therapies for Heart Failure Due to a Reduced Ejection Fraction

Study	Drug	Follow up	Discontinuation During Follow-Up	
			Control	Study drug
CONSENSUS[44]	Enalapril	12 months	14%	17%
SOLVD[45]	Enalapril	40 months	8.6%	15.2%
COPERNICUS[46]	Carvedilol	12 months	18.5%	14.8%
RALES[47]	Spironolactone	24 months	5%	8%
EMPHASIS[48]	Eplerenone	42 months	16.3%	16.6%
PARADIGM-HF[4]	Sacubitril-Valsartan	27 months	12.3%	10.7%

PARADIGM-HF showed no evidence of increased risk, but was, perhaps, too short to identify a trend. The PERSPECTIVE study is designed to investigate a possible link. The primary endpoint is the change in cognition from baseline to 3 years in a population of patients with HF and normal ejection fraction.[55]

Mechanisms of Benefit

One curiosity of the PARADIGM-HF results is the robust benefit offered by a drug that combines an ARB (a drug class with no consistent mortality benefit in HFrEF)[56,57] with a medication that increases already very high levels of NPs. The mechanism of benefit is likely to be multifactorial and is not fully understood.

Reduced Cardiac Fibrosis and Reverse Remodelling

Myocardial fibrosis is central to the development of heart failure. It is driven by various peptides and hormones secreted in response to overlapping haemodynamic, neurohormonal and pro-fibrotic triggers.[58] Sacubitril-valsartan reduces levels of pro-fibrotic biomarkers (aldosterone, soluble ST2, tissue inhibitor of matrix metalloproteinase, galectin-3, and N-terminal propeptide of collagen I and collagen III) to a greater extent than enalapril,[59–61] and may inhibit cardiac fibroblast activity.[62] Sacubitril-valsartan increases LVEF, and reduces left ventricular and atrial volumes more than either ACEI or ARB,[63,64] even in patients with a normal LVEF.[65]

It may be that the anti-fibrotic and reverse remodelling effects are, in part, responsible for the lower risk of ventricular arrhythmia (VA) and sudden death – the most common mode of death in PARADIGM-HF – seen in patients randomised to sacubitril-valsartan. In a small study in patients with HFrEF and an implantable cardioverter-defibrillator, treatment with sacubitril-valsartan was associated with a lower burden of VA.[66]

Effects on Mitral Regurgitation

Functional mitral regurgitation (MR) is common amongst patients with HFrEF,[67] and is associated with adverse outcome despite optimal treatment.[68] The PRIME study found a greater reduction in the area and volume of the MR jet with sacubitril-valsartan compared to valsartan in 117 patients with significant functional MR (LVEF 25–49%);[69] it is likely the reduction in MR severity resulted from a decrease in LV volume.[70]

Other Effects of Neprilysin Inhibition

Neprilysin has a greater affinity for bradykinin, adrenomedullin and substance P than it does for NPs,[14,71] all of which have potentially beneficial physiological effects for patients with HF:

- Bradykinin activates B2 kinin receptors triggering release of nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarising factor which cause vasodilation.[72,73]
- Adrenomedullin causes vasodilation, natriuresis and diuresis and decreases pulmonary capillary wedge pressure in patients with HF.[74]
- Substance P binds to neurokinin-1 receptors causing NO-mediated vasodilation.[75] It increases myocardial perfusion and reduces hypoxic cellular damage in rat models of ischaemia-reperfusion.[76]

Uric acid (UA) is a product of purine metabolism by xanthine oxidase (XO) which also produces harmful reactive oxygen species; high UA levels may reflect increased oxidative stress.[77] Sacubitril-valsartan was associated with reduced UA levels in PARADIGM-HF,[78] which might reflect reduced action of XO. The mechanism is unknown.

Pre-Empting Worsening Heart Failure

During a decompensation episode, NPR-C receptors become saturated and neprilysin becomes the main pathway for NP degradation (Figure 1). A possible mechanism for benefit might thus be that, compared to a patient taking enalapril, a patient taking sacubitril-valsartan has higher levels of NPs levels at the onset of an episode of decompensation, perhaps lessening the severity of the episode.[14,79] In PARADIGM-HF, patients taking

sacubitril-valsartan were less likely to have worsening symptoms; to require inotropic support during admission; to be readmitted for heart failure; or to have their diuretic treatment increased as an outpatient compared to patients taking enalapril.[33,80,81]

Heart Failure with a Preserved Ejection Fraction

Some reports suggest that up to half of patients with HF have a normal ejection fraction on echocardiography – HFpEF,[82,83] – a condition for which no treatments are known to improve outcome (other than in the specific case of underlying amyloidosis).[84] The PARAMOUNT study showed that sacubitril-valsartan reduced NTproBNP and left atrial diameter and volume more than valsartan alone after 12 weeks in patients with HFpEF, although there was no significant difference between the groups after 36 weeks.[64]

The PARAGON-HF investigators randomised 4822 patients (mean age 72, LVEF ≥45%, median NTproBNP 904 ng/L, NYHA class II–IV, with either left ventricular hypertrophy or a dilated left atrium as evidence of cardiac dysfunction) to either sacubitril/valsartan 97/103mg BD or valsartan 160mg BD.[85]

The primary endpoint was a composite of first *and* recurrent hospitalisations for heart failure or cardiovascular death. All-cause mortality rate, change in QoL from baseline to 8 months assessed by the KCCQ, and an improvement in NYHA class from baseline to 8 months were among secondary endpoints.[85]

Sacubitril-valsartan had no effect on the rate of the primary composite outcome or its components (Table 2).[85] Patients taking sacubitril-valsartan were more likely to have a reduction in their NYHA class (odds ratio 1.45 (95% confidence interval (CI) 1.13–1.86)), but other secondary endpoints were unaffected.[85] Pre-specified sub-group analysis found possible outcome benefit for patients with LVEF 45–57% (RRR for the primary endpoint 22%), and for women (RRR 27%).[85]

Heart Failure with a Mid-Range Ejection Fraction

Data from PARAGON-HF suggest sacubitril-valsartan may confer benefit to patients with LVEF between 45% and 57%. The PARALLAX study of sacubitril-valsartan vs "standard therapy" for comorbidities in patients with HFpEF, and the PERSPECTIVE study described above, will include patients with an LVEF >40%. However, neither include morbidity and mortality endpoints and more work will be required.

These are muddy waters. Dividing patients into three diagnostic categories based on a poorly reproducible technique – namely, LVEF on echocardiography[86] – is arbitrary at best. The same patient with the same symptoms might be described as having HFrEF on one day with one operator or HFpEF on a different day with a different operator: discrete boundaries between categories based on LVEF do not represent a biological reality.

What can be said is that there is a consistent general trend that the worse the left ventricular systolic function, the greater the likelihood of benefit from standard heart failure treatment: this is true for ACE inhibitors, beta-blockers and mineralocorticoid receptors, and now seems to be true for ARNIs as well.

Real-World Data and Future Perspectives

One of the frequent criticisms of heart failure trials is that the sample populations rarely reflect "real-world" patients. For example: the average age of a patient with heart failure in the UK is 77 years at diagnosis,[87] whereas the average age of a patient in PARADIGM-HF was over 10 years younger.[4] However, data from real-world populations suggest that treatment with sacubitril-valsartan is associated with significant reductions in NTproBNP,[88] increases in LVEF,[88] and reductions in the rate of heart failure hospitalisation compared to pre-initiation.[89,90] The ARIADNE registry, which aims to describe current prescribing trends with regards to sacubitril-valsartan, is recruiting and will highlight any discrepancies.[91]

The role of sacubitril-valsartan is yet to be properly defined: the European Society of Cardiology (ESC) guidelines state that sacubitril-valsartan can replace "optimal" dose ACEI if patients remain symptomatic with raised NP levels,[1] and the National Institute of Health and Clinical Excellence (NICE) in the UK state that sacubitril-valsartan is recommended for patients with ongoing symptoms despite "stable" dose ACEI or ARB.[92] "Optimal" and "stable" are entirely different concepts and practice varies greatly as a result: estimates of the proportion of patients eligible for sacubitril-valsartan vary from 75% to 21%.[93–95]

In a patient not taking a RAAS inhibitor at diagnosis, it is not clear what clinical benefit titrating medications to the maximum tolerated dose then switching to sacubitril-valsartan might have over starting sacubitril-valsartan from scratch. One limiting factor might be cost: in the

UK, fifty-six 10 mg enalapril tablets costs £3.98 compared to £91.56 for the same number of 97/103mg sacubitril-valsartan tablets.[96,97]

A significant proportion of patients in PARADIGM-HF were unable to tolerate target doses during the course of the trial despite tolerating target doses of both medications during the short run-in phase (Figure 2). Whether low-dose sacubitril-valsartan is superior to low-dose enalapril in patients who have *never* been able to tolerate target doses of RAAS inhibitors is unanswered by PARADIGM-HF. Approximately 4 in 5 patients with HFrEF in Europe are on sub-target doses of RAAS inhibitor.[98] The proportion of patients who cannot tolerate target doses seems to be high.

Matters have been further complicated by the success of the DAPA-HF study (N=4744, average age 66, 98% NYHA II–III, median NTproBNP 1428 ng/L) which found a reduced risk of worsening heart failure or cardiovascular death with dapagliflozin, a sodium-glucose transport protein-2 inhibitor (SGLT2-I), compared to placebo (16% vs 21%; P<0.001).[99] Only 10% of patients in the dapagliflozin arm were taking sacubitril/valsartan and quite how SGLT2-Is will fit into future heart failure guidelines is unclear: is the benefit conferred by dapagliflozin greater than, less than or incremental to that of sacubitril/valsartan in patients otherwise taking a beta-blocker, MRA and ACEI or ARB?

Conclusion

Sacubitril-valsartan improves symptoms and outcome for patients with HFrEF compared with standard therapy with ACEI. The mechanism of benefit is complex and multifactorial. Different regulatory bodies have different criteria for considering sacubitril-valsartan, and there is still uncertainty as to when and in whom sacubitril-valsartan should be started. There may yet be subsets of patients with HF and LVEF >40% who might benefit from sacubitril-valsartan.

Disclosure

Professor Andrew L Clark and Joseph J Cuthbert report personal fees from Novartis, outside the submitted work. The authors report no other conflicts of interest in this work.

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