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Review Article

Neprilysin inhibition with sacubitril/valsartan in the treatment of heart failure: mortality bang for your buck

A. J. Ansara*† PharmD BCPS-AQ Cardiology, D. M. Kolanczyk‡§ PharmD BCPS-AQ Cardiology and J. M. Koehler†¶ PharmD FCCP
**Department of Pharmacy, Indiana University Health Methodist Hospital, Indianapolis, IN, †Department of Pharmacy Practice, Butler University College of Pharmacy and Health Sciences, Indianapolis, IN, ‡Department of Pharmacy, Loyola University Medical Center, Maywood, IL, §Department of Pharmacy Practice, Midwestern University Chicago College of Pharmacy, Downers Grove, IL, and ¶Pulmonary Rehabilitation and Transitional Care, Indiana University Health, Indianapolis, IN, USA*

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SUMMARY

What is known and objective: **Heart failure remains a leading cause of morbidity and mortality worldwide. Advanced therapies have prolonged survival in patients with advanced heart failure, but pharmacotherapeutic optimization remains the mainstay of treatment. It has been over 10 years since the last mortality-reducing medication has been approved by the Food and Drug Administration. This article reviews the background, current knowledge and data supporting the use of sacubitril/valsartan (Entresto®), the newly FDA-approved medication that dually inhibits angiotensin and neprilysin, in the treatment of heart failure.**

Methods: **A literature search was performed (January 1980 to August 2015) using PubMed and the search terms were as follows: neprilysin inhibitor, heart failure, endopeptidase, natriuretic peptides, angiotensin, omapatrilat, LCZ696, valsartan and sacubitril. Peer-reviewed, published clinical trials, review articles, relevant treatment guidelines and prescribing information documents were identified and reviewed for relevance. Additionally, reference citations from publications identified were reviewed.**

Results and discussion: **The inhibition of endopeptidases has been an area of extensive study for the treatment of heart failure. Previously published literature with the endopeptidase inhibitor omapatrilat failed to demonstrate a sufficient balance between clinical efficacy and safety to justify its approval. Omapatrilat blocked three pathways that break down bradykinin, leading to high rates of angioedema. Sacubitril, on the other hand, is metabolized to a form that is highly selective for neprilysin without possessing activity for the other two peptidases, ACE and APP. The combination of sacubitril with valsartan in a single formulation offers the benefit of concurrent blockade of the renin angiotensin aldosterone system and the inhibition of neprilysin while minimizing angioedema risk. When compared to ACE inhibitor therapy in systolic heart failure patients, sacubitril/valsartan demonstrated reductions in all-cause mortality and hospitalization due to heart failure while maintaining a similar safety profile.**

What is new and conclusion: **A formulation that contains both sacubitril and valsartan was manufactured and approved by the FDA in July 2015 for the reduction of mortality and hospitalization in systolic heart failure patients. The new medication offers a potentially superior alternative to ACE inhibitor therapy in the management of systolic heart failure. The effects of treatment with sacubitril/valsartan in the setting of diastolic heart failure are currently under investigation in clinical trials.**

Correspondence: Alexander J. Ansara, Clinical Pharmacist Specialist – Advanced Heart Care, Department of Pharmacy, Indiana University Health Methodist Hospital, Associate Professor of Pharmacy Practice, Department of Pharmacy Practice, Butler University College of Pharmacy and Health Sciences, 1701 N. Senate Blvd, AG 401, Indianapolis, IN 46202, USA. Tel.: 317 962 3701; fax: 317 962 1995; e-mail: aansara@iuhealth.org

WHAT IS KNOWN AND OBJECTIVE

Heart failure (HF) is a complex syndrome that results when diastolic ventricular filling or systolic ejection of blood is impaired. The pathophysiology of HF is most commonly viral, valvular, metabolic or ischaemic in nature.[1] The most common subtype of HF, heart failure with reduced ejection fraction (HFrEF), is defined as a clinical diagnosis of HF in conjunction with an ejection fraction (EF) of ≤40%.[1]

Approximately 5 million Americans aged ≥20 years have HF and the prevalence is expected to increase to 8 million Americans by the year 2030.[2] Despite treatment advancements, 50% of patients die within 5 years of diagnosis.[3,4] While long-term HF survival has improved over time,[4] all-cause 30-day hospital readmission rates in patients admitted for HF remain high at 25%,[5] accounting for over half of the $40 billion annual cost of HF care in the United States.[6] Given the heavy clinical and economic burden of HF care, treatment is focused on the prevention of hospitalization and prolongation of survival.

Advanced therapies including heart transplantation and ventricular assist device placement have proven to prolong survival in end-stage HF patients.[7,8] In patients unsuitable for advanced strategies, treatment focuses on the optimization of pharmacotherapy with medications that include beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone blockers, vasodilators and digoxin.

Randomized clinical trials (RCTs) have extensively been conducted in HFrEF patients, lending to a large body of evidence and a well-defined approach to the management of HF. However,

10 years have passed since the last published evidence of a mortality-reducing medication that provides clinical benefit when combined with conventional therapy. Recent literature supports a new target for HF therapy: neprilysin inhibition. Neurohormonal blockade of detrimental compensatory mechanisms involving norepinephrine, angiotensin II (ATII) and aldosterone prolongs survival in HFrEF patients. But older literature with the vasopeptidase inhibitor omapatrilat failed to show a favourable risk/benefit. However, dual inhibition of ATII and neprilysin, an enzyme responsible for natriuretic and vasoactive peptide breakdown, provides further reductions in hospitalization due to HF and all-cause mortality when compared to standard HF therapy.[9]

This article details the physiology of neprilysin and neutral endopeptidases in HF, the mechanism of neprilysin inhibitor therapy, and provides a review of the literature evaluating the clinical effects of neprilysin inhibitors, including omapatrilat and sacubitril, in HF.

METHODS

Peer-reviewed clinical trials, review articles, treatment guidelines, citations from relevant publications and prescribing information documents (January 1980–August 2015) were reviewed. Search terms neprilysin inhibitor, heart failure, endopeptidase, natriuretic peptides, angiotensin, omapatrilat, sacubitril and LCZ696 were utilized.

RESULTS AND DISCUSSION

Physiological role of the natriuretic peptide system and neprilysin in heart failure

Natriuretic peptide system. Three natriuretic peptides (NPs) assist with fluid and sodium homeostasis: atrial NP (ANP), brain (or B type) NP (BNP) and C type NP (CNP).[10] ANP is primarily expressed and stored in the cardiac atria and released in response to atrial stretch resulting from intravascular fluid overload.[10,11] BNP, originally isolated from porcine brain, is released from ventricles in response to increased filling pressures. ANP and BNP protect the cardiovascular system by promoting natriuresis and diuresis, inhibiting the renin–angiotensin–aldosterone (RAA) system, and inducing vasodilation.[12] CNP is found in kidneys, heart and lung, but has higher concentrations in vascular endothelial cells.[13] CNP is released in response to vascular shear stress and may protect against remodelling effects in the post-myocardial infarction setting due to its antifibrotic and antithrombotic effects.[14] CNP, however, has minimal diuretic and natriuretic properties.[13] Table 1 highlights the primary physiological effects of these NPs.

Natriuretic peptides interact with their respective natriuretic peptide receptors (NPR) known as NPR-A, NPR-B and NPR-C.[11] They are also referred to as guanylyl cyclase (GC)-A, GC-B and the clearance receptor, or as NPR1, NPR2 and NPR3, respectively. ANP and BNP bind to NPR-A, whereas CNP binds to NPR-B.[15] NPR-A vastly predominates in blood vessels as compared to NPR-B which is primarily found in the brain.[11,16] Both receptors are located in the adrenal glands and kidneys. When NPs are bound to NPR-A or NPR-B, activation of guanylate cyclase occurs, leading to elevations in intracellular cyclic guanosine monophosphate (cGMP). This pivotal step is responsible for the majority of the NP's physiological actions by controlling blood pressure (BP), volume regulation and energy metabolism. While the NPs (via particulate guanylyl cyclase) increase cGMP, nitric oxide (NO) (via soluble guanylyl cyclase) also stimulates the intracellular second messenger.[17] Increased cGMP from these two pathways is then metabolized via phosphodiesterase-5 (PDE-5) which may limit the respective beneficial actions on the heart, vasculature and kidneys. Sildenafil, a PDE-5 inhibitor, has demonstrated improved exercise tolerance and clinical status in patients with HFrEF.[18–20] Similar effects were not seen in the HFpEF patient population.[21] Soluble guanylyl cyclase (sGC) is another target that can provide therapeutic benefits in cardiopulmonary diseases.[22] Stimulation of sGC to endogenous NO stabilizes NO-sGC binding, which further stimulates the NO-sGC-cGMP pathway. Levels of cGMP are increased, leading to vasodilation. This pathway has demonstrated therapeutic benefits in pulmonary hypertension with riociguat, a sGC stimulator.[23,24]

NPR-C mediates the clearance of all three NPs from the circulation through receptor-mediated internalization and degradation. In addition, neutral endopeptidase, also known as neprilysin, clears NPs through enzymatic degradation. Increasing active NPs in HF has been studied with exogenous administration

Table 1. Overview of the natriuretic peptide system[11,13,16]

Natriuretic peptide	ANP	BNP	CNP
Location	Atria	Ventricles	Vascular endothelial cells
Releasing trigger(s)	Atrial distension	Increased ventricular volume	Increased sheer stress
Receptor	NPR-A	NPR-A	NPR-B
Physiologic actions	Natriuresis and diuresis	Natriuresis and diuresis	Vasodilation
	Vasodilation	Vasodilation	Antihypertrophic
	RAAS and SNS suppression	RAAS and SNS suppression	Antifibrotic
	Increased renal blood flow and GFR	Increased renal blood flow and GFR	Anti-inflammatory
	Increased myocardial relaxation	Increased myocardial relaxation	Antithrombotic
	Lipid mobilization, metabolic effects	Lipid mobilization, metabolic effects	Bone growth regulation
	Antihypertrophic	Antifibrotic	
	Antifibrotic		
	Increased endothelial permeability		
	Anti-inflammatory		
Clearance of NP/enzymatic degradation	Clearance via NPR-C	Clearance via NPR-C	Clearance via NPR-C
	NEP degradation	NEP degradation	NEP degradation

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C type natriuretic peptide; GFR, glomerular filtration rate; NEP, neprilysin; NP, natriuretic peptide; NPR, neprilysin peptide receptor; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

of NPs. A synthetic BNP, nesiritide, showed improvement in dyspnoea in acute decompensated heart failure (ADHF), while maintaining favourable effects on hemodynamics and the kidneys.[25] However, limitations surround its use. It has failed to show reductions in morbidity and mortality; in addition, there are no clear long-term benefits surrounding its use.[26] It is only available for intravenous administration, limiting its role to hospitalized ADHF patients. The rest of this review will focus on amplifying endogenous NPs through inhibition of their degradation.

Neprilysin as a target in heart failure. Neprilysin is a zinc-dependent enzyme expressed on the plasma membrane and is found in several tissues, with highest concentrations in renal proximal tubules.[11] Neprilysin is responsible for degrading all three NPs, with higher affinity for ANP and CNP. Additionally, it degrades vasoactive peptides including vasodilators such as bradykinin, adrenomedullin and urodilatin while aiding in clearance of substance P and vasoconstrictors such as endothelin-1 and ATII. Due to its ability to degrade multiple substrates, neprilysin inhibition is an attractive therapeutic modality in HF.

Interactions of the NP and RAA systems. The NP and RAA systems play roles in electrolytes, blood volume and arterial pressure homeostasis (Fig. 1). However, these systems contrast in their physiologic effects. The NP system is primarily activated by volume expansion, whereas the RAA system is activated by decreased renal perfusion and volume contraction.[13] By activating the NP system, BP decreases via vasodilation, diuresis and natriuresis, promoting fluid shifts from intravascular to extravascular spaces. In contrast, activation of the RAA system results in increased BP through vasoconstriction mediated by ATII and water and sodium retention via aldosterone release. Studies show that NPs inhibit renin and aldosterone release which antagonizes the effects of ATII.[27,28] This leads to decreased sodium and water retention and stimulates vasodilation.

The RAA system and renal-body fluid feedback mechanisms play major roles in controlling long-term fluid and electrolyte homeostasis.[29] To achieve this, kidneys respond to alterations in arterial pressure by altering sodium and water secretion. Only small changes in atrial pressure occur, leaving the NP system minimally activated.

However, in a condition known for large and persistent atrial pressure elevation such as chronic HF, the renal-body fluid feedback mechanism is impaired.[29] Large increases in atrial pressure are clinically relevant and long-term activation of the NP system occurs. This results in sustained natriuresis and suppression of pressor hormones. Failure of NP system activation would ultimately result in decreased arterial pressure in compensated HF patients and lead to salt and water retention and worsening fluid status. While playing a minor role in normal conditions, the activated NP system is critical in long-term fluid and electrolyte balance in chronic HF.

NEPRILYSIN INHIBITION IN HEART FAILURE

The first oral neprilysin inhibitor (NEPi), candoxatril, was studied in a double-blind, placebo-controlled, parallel-group study in patients with essential hypertension.[30] Participants received

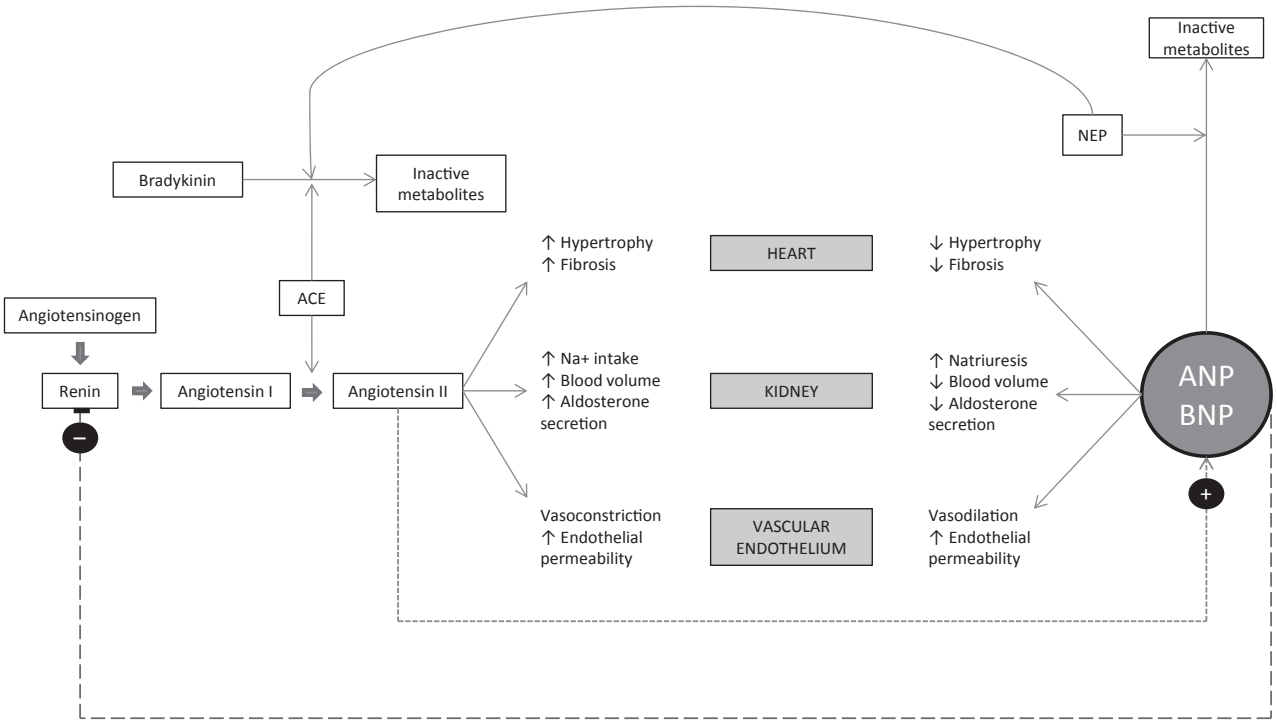

Fig. 1. The above diagram illustrates how the NP and RAA systems work together to achieve cardio-renal homeostasis. It also reflects counter-regulatory effects of the two systems on key organs.[13,27,28] ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; Na, sodium; NEP, neprilysin.

28 days of candoxatril 200 mg twice daily or placebo. Although ANP levels were significantly increased, the effect on BP was not clinically relevant. Candoxatril also increased ATII levels.[31] When studied in HF patients, it performed as expected by increasing ANP and BNP levels, producing diuresis and natriuresis.[32] However, systemic and pulmonary vascular resistances were not affected. This led to the conclusion that selective neprilysin inhibition via candoxatril was not beneficial and further development was halted. Another compound, ecadotril, was dismissed after a dose-ranging study was performed in patients with HFrEF and showed higher rates of mortality when compared to placebo.[33]

Increased levels of ATII is a possible reason why sole neprilysin inhibition failed. Given the above findings, the focus of drug development with a NEPi in HF has concentrated on dual inhibition of NP degradation and activation of the RAA system.

INHIBITION OF METALLO PROTEASE BY BMS-186716 IN A RANDOMIZED EXERCISE AND SYMPTOMS STUDY IN SUBJECTS WITH HEART FAILURE

It had been established that BBs, ACEIs and ARBs diminish the effects of maladaptive mechanisms in HF and effectively reduce morbidity and mortality,[34] but long-term survival in HF remained low.

In 573 patients with 'stable' symptomatic HF (New York Heart Association [NYHA] functional class II, III or IV), the Inhibition of Metallo Protease by BMS-186716 in a Randomized Exercise and Symptoms Study in Subjects with Heart Failure (IMPRESS) trial evaluated the impact of omapatrilat on change in exercise duration over 12 weeks compared to lisinopril.[35] Secondary endpoints included death, worsening HF and the combination of death and comorbidity for worsening HF, defined as hospital admission, study drug discontinuation or emergency department visit for diuresis. After a baseline exercise tolerance test, patients were randomized to receive omapatrilat 10 mg daily, titrated over 3 weeks to 40 mg daily, or lisinopril 5 mg, titrated over 3 weeks to 20 mg daily. Concomitant BB use was permitted if patients had been on prior BB for ≥6 months. Calcium channel blockers (CCB) were permitted for purposes of rate control in patients with atrial fibrillation (AF). Patients with uncontrolled hypertension or systolic blood pressure (SBP) ≤ 90 mmHg were excluded.

The two treatment groups were similar with respect to mean age (64·3 ± 10·7 years in the omapatrilat group vs. 63·6 ± 10·0 years in the lisinopril group). Gender was also similar between the two groups (78·5% male vs. 78·9% male in the omapatrilat and lisinopril groups, respectively). Target doses were reached in 88% (254 of 289) of omapatrilat patients and 94% (267 of 284) of lisinopril patients. BB use in both groups was similar (30% of patients), although doses were not reported. CCB use (presumably non-dihydropyridine) was higher in the lisinopril group compared to the omapatrilat group (4% vs. 2%, respectively). There was no difference in the primary endpoint of exercise duration between study groups (exercise tolerance test: 24 s with omapatrilat vs. 31 s with lisinopril, $P = 0{\cdot}45$). Among secondary endpoints, the incidence of death, hospital admission for HF or discontinuation of study treatment for worsening HF was lower with omapatrilat ($P = 0{\cdot}035$; hazard ratio 0·52 [95% CI 0·28–0·96]). Differences in the number of deaths and number of hospitalizations for heart failure were not found to be statistically significant between the two groups. At week 24, either more improvement or less worsening in NYHA class was noted overall in the omapatrilat group ($P = 0{\cdot}059$), but this finding was only significant when patients with NYHA functional class II were excluded from the analysis. Among the 116 patients in the neurohormone substudy, radionuclide ventriculography revealed similarities in ventricular volumes, EFs and mean change in left ventricular end-diastolic volumes between the two groups, whereas plasma neurohormone levels differed only slightly. Dizziness occurred more frequently with omapatrilat (33% vs. 18%, $P = 0{\cdot}001$), and patients with baseline SBP of <120 mmHg more frequently experienced hypotension with omapatrilat.

When compared to lisinopril, the results of the IMPRESS trial did not demonstrate that omapatrilat improved exercise tolerance. Authors point out, however, that pharmacologic agents, such as digoxin, that yield improvements in exercise tolerance are not necessarily linked to improvements in mortality,[36] and drugs, such as BBs and ACEIs, which have been shown to improve survival, do not significantly improve exercise tolerance. Despite the lack of difference observed in the primary outcome, significant differences in secondary outcomes suggest that omapatrilat could have some advantages over lisinopril in the treatment of HF. Based on findings within the neurohormone substudy, the authors acknowledge that differences in outcomes between the two treatments are unlikely to be explained by changes in ventricular function or differences in plasma neurohormone concentrations, noting that the levels of ATII were slightly higher in the omapatrilat group. Limitations of the IMPRESS trial include its small number of patients and short duration. The authors indicated that the target dose of omapatrilat (40 mg daily) was chosen based on a prior study that demonstrated a decrease in pulmonary capillary wedge pressure.[37] The dose of lisinopril (20 mg daily) is one commonly targeted in HF. However, some experts believe a higher dose of lisinopril (at least 35 mg daily) should be targeted for adequate morbidity and mortality reduction based on the ATLAS trial.[38] Although BB use at baseline was comparable between groups, it is unclear which BBs were used and at what doses. An inverse relationship between BB dose and the combined endpoint of all-cause mortality or hospitalization in HF patients has been demonstrated,[39] and higher target doses of BBs are typically recommended. Additionally, twice as many patients in the lisinopril group received CCBs (4% vs. 2%). While this represents a small proportion of patients in each group, CCBs with negative inotropic effect are thought to have the potential to worsen HF when EF is reduced.[40] The findings of IMPRESS suggested a potential benefit with omapatrilat in patients with HF phase 3 follow-up trials to evaluate the impact of omapatrilat on HF outcomes were needed.

OMAPATRILAT VERSUS ENALAPRIL RANDOMIZED TRIAL OF UTILITY IN REDUCING EVENTS

As a follow-up to IMPRESS, the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial compared omapatrilat to enalapril in 5770 patients with a history of NYHA functional class II, III or IV HF secondary to either ischaemic or non-ischaemic cardiomyopathy for at least 2 months, or a reduced EF of 30% or less and hospitalization for HF within the previous 12 months.[41] The primary endpoint was a combined risk of all-cause mortality for HF. Secondary endpoints included all-cause mortality, risk of cardiovascular death or cardiovascular hospitalization, and combined risk of cardiovascular death, myocardial infarction, stroke or myocardial revascularization.

Upon study entry, all ACEIs or ARBs were discontinued. Patients were randomized to omapatrilat ($n = 2886$) 10 mg daily,

titrated at 3- to 14-day intervals to 20 mg, then 40 mg once daily; or to enalapril (n = 2884) 2·5 mg twice daily, titrated at 3- to 14-day intervals to 5 mg twice daily, then 10 mg twice daily. Target doses were chosen based on the IMPRESS and SOLVD trials.[35,42] While patients were excluded from the study if they had received intravenous inotropic therapy within 2 weeks of randomization, diuretics and other treatments for HF were continued, and adjustments could be made in any open-label HF treatments if clinically indicated throughout the study (excluding ACEIs or ARBs).

A prospective analysis of the impact of omapatrilat vs. enalapril on the primary endpoint was assessed in predetermined subgroups, which included age, sex, race, EF, cause of HF, NYHA functional class, diabetes mellitus, and concomitant use of aspirin, BBs and spironolactone. The two treatment groups were similarly matched in age (mean of 63·5 ± 11·9 years in the enalapril group vs. 63·4 ± 11·6 years omapatrilat group). Patients were predominantly male in both treatment groups, with 78% of the patients being male in the enalapril group vs. 80% in the omapatrilat group. Target doses were reached in 82·5% of omapatrilat patients (2380) and 86·4% of enalapril patients (2492). The mean follow-up was 14·5 months. There were a total of 914 omapatrilat patients and 973 enalapril patients (HR 0·94 [95% CI, 0·86–1·03], P = 0·187) who died or were hospitalized for HF. The difference in the primary endpoint fulfilled pre-specified criteria for non-inferiority, but not superiority. However, a post hoc analysis of non-inferiority for all hospitalizations for HF suggested a significantly lower risk of death or hospitalization for HF with omapatrilat (HR 0·89 [95% CI, 0·82–0·98], nominal P = 0·012).

A significant difference (P = 0·024) between groups in favour of omapatrilat was noted with respect to the risk for death or hospitalization for cardiovascular reasons. A post hoc analysis further suggested that the greatest difference in combined risk was noted in patients with a baseline SBP of >140 mmHg. Hypotension and dizziness were more common with omapatrilat (19·5% and 19·4% of omapatrilat patients vs. 11·5% and 13·9% of enalapril patients, respectively). Additionally, angioedema was more common with omapatrilat than enalapril (0·8%, n = 24 patients vs. 0·5%, n = 14).

The OVERTURE trial did not demonstrate that omapatrilat was more effective than enalapril in reducing the risk of death or hospitalization for HF. The authors reported a significant 9% decrease in the risk of cardiovascular death or hospitalization (a secondary outcome) with omapatrilat, which they suggested may be due to its BP-lowering effect. To that end, the authors suggested shorter dosing intervals could be explored with omapatrilat to allow for more consistent BP lowering (potentially reducing cardiovascular outcomes) and to minimize side effects. While split dosing of ACEIs is employed in clinical settings to minimize the hypotension and dizziness that occur as a peak effect with high doses, it is usually carried out with ACEIs whose trough-to-peak ratios do not significantly exceed 50%. Trough-to-peak ratios with omapatrilat appear to range from 61% to 71%, which indicates that omapatrilat is capable of producing persistent 24-h BP reduction without need for dosing more than once daily.[13]

With respect to concomitant medication use, it may be important to note that at baseline, more patients in the enalapril group received digoxin (66% vs. 59%). While the use of digoxin has not been associated with mortality reduction, it has been demonstrated to reduce hospitalizations for HF.[36] The impact of baseline digoxin use was not assessed, or if it was, it was not reported. Open-label medication use and intensification of HF treatment were permitted when clinically indicated, but details of such prescribing were not reported. While OVERTURE's strengths included its size and length of follow-up, the lack of effect on the primary outcome in comparison with ACEI treatment led investigators to concur that further study was warranted.

OMAPATRILAT CARDIOVASCULAR TREATMENT ASSESSMENT VERSUS ENALAPRIL

As a follow-up to IMPRESS and OVERTURE, the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) trial was designed to evaluate the efficacy and safety of omapatrilat in comparison with enalapril.[43] Early phase III trials conducted with omapatrilat suggest a greater BP-lowering capability than ACEIs,[44] but concerns remained regarding omapatrilat's angioedema risk. Because 20 mg of omapatrilat was used as a starting dose in many of the early trials with strict protocols and more highly selective study populations, OCTAVE was designed to evaluate the impact and safety of a 10 mg starting dose of omapatrilat in a broader population and under conditions more closely resembling clinical practice.

Conducted as a randomized, double-blind, multicentre, controlled trial, OCTAVE was a 24-week study in which 25 302 patients were divided into three subgroups at randomization based on trough BP readings: Group 1: previously untreated hypertensive patients [SBP ≥ 140 or diastolic blood pressure (DBP) ≥ 90 mmHg]; Group 2: previously treated hypertensive patients, Stage 1 according to JNC VI [SBP 140–159 or DBP 90–99 mmHg]; and Group 3: previously treated hypertensive patients, Stage 2 according to JNC VI [SBP ≥ 160 but <180, or DBP ≥ 100, but <110 mmHg]. Group 1 patients were started on either omapatrilat or enalapril. Group 2 patients were switched to omapatrilat or enalapril. Group 3 patients had either omapatrilat or enalapril added to their existing antihypertensive therapy. Patients were excluded if they had a contraindication to ACEIs or ARBs, prior history of angioedema, anaphylaxis, urticarial or multiple drug sensitivities, or if they fell in Group 3 based on trough BP measurement and were already receiving treatment ACEI therapy. During weeks 1 through 8, blinded study medications were titrated to reach target BP. During weeks 9 through 24 of the study, blinded study medications were maintained at the current dose, but additional open-label antihypertensive therapy was allowed to reach target BP.

Primary endpoints were a decrease in SBP at the end of the titration phase (week 8) and need for additional BP-lowering medication by the end of the maintenance phase (week 24). Secondary endpoints included decrease in DBP at week 8, decrease in SBP and DBP at week 24, BP control (defined as SBP <140 mmHg and DBP <90 mmHg) at weeks 8 and 24 and BP control by subgroup.

A total of 12 668 and 12 634 patients were randomized to receive omapatrilat and enalapril, respectively. Gender was evenly matched between the two groups at 52% male. Age was also similar between the two groups with a mean of 56·9 years (range of 18–95 years in the omapatrilat group vs. 18–93 years in the enalapril group).

From an efficacy perspective, a significant reduction in BP (3·6 mmHg systolic and 2·0 mmHg diastolic) was observed in patients randomized to receive omapatrilat (P < 0·001). From a safety perspective, omapatrilat was associated with a 3·2 times higher incidence of angioedema (2·17% vs. 0·68%) and severe angioedema (P < 0·05) than that observed with enalapril. (The risk

of angioedema requiring hospitalization was 9·5 times higher.) In the subset of black patients, the risk of angioedema increased 3-fold in both groups (5·54% with omapatrilat and 1·62% with enalapril.) Angioedema risk was 2·58 in current smokers within the omapatrilat group.

Omapatrilat appeared to be superior to enalapril with respect to BP lowering, and given the large number of subjects and clinical sites of investigation, the results are applicable to broad variety of patients. Given the combined mechanism of action offered by omapatrilat and its demonstrated superior antihypertensive effect when compared to drugs that solely inhibit ACE, the use of omapatrilat as an antihypertensive agent may allow for a monotherapeutic approach in the achievement of BP control, an observation which differs from that suggested by the results of the Hypertension Optimal Treatment (HOT) trial,[45] where the majority of patients required more than one antihypertensive drug to achieve BP control. However, despite the observation that BP control rates were better with omapatrilat, it should be noted that BP control in OCTAVE was defined as a SBP of <140 mmHg and a DBP of <90 mmHg for all patients, a target determined at the time on JNC VI recommendations. Current guidelines support different BP targets in some patients, based on age and the presence of comorbidities (factors which, if OCTAVE were conducted in the present day, would alter the definition of BP 'control').[46,47]

It's important to note that up-titration of medications did not occur at every visit when patients were eligible. Some argue that the design of OCTAVE, in contrast to studies like ALLHAT,[48] did not allow or encourage aggressive addition of other antihypertensives to achieve target BP.

Omapatrilat cardiovascular treatment assessment vs. enalapril did not alleviate concerns regarding increased risk for angioedema, especially in smokers and black patients, despite lower initial doses. As vasopeptidase inhibitors increase bradykinin levels more than ACEIs, the occurrence of angioedema is not surprising. The results also support the argument that vasopeptidase inhibitor-induced angioedema is a non-dose-related class effect (88 of the 91 cases were reported on the first day of study drug exposure).

SACUBITRIL/VALSARTAN CLINICAL TRIAL EVIDENCE

Sacubitril/valsartan in HFrEF: the PARADIGM-HF trial

The Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was an intention-to-treat study evaluating the clinical benefit of sacubitril/valsartan and was conducted in 1043 clinical institutions worldwide from December 2009 to November 2012.[9] Patients (n = 8442; 78% male) aged ≥18 years (mean 63·8 years) with NYHA class II-IV symptoms and an EF < 40% (protocol subsequently amended to an EF < 35%) were included. Patients were required to have BNP levels of ≥150 pg/mL or ≥100 pg/mL with hospitalization secondary to HF in the preceding 12 months, in addition to taking stable BB and ACEI/ARB doses that were equivalent to enalapril 10 mg daily in the 4 weeks prior to screening.[9]

Patients were excluded from study consideration for the following criteria: symptomatic hypotension, SBP < 100 mmHg at screening or <95 mmHg at randomization, estimated glomerular filtration rate (GFR) < 30 mL/min/1·73 m^2 of body surface area, a decline in GFR ≥ 25% between the times of screening and randomization, history of angioedema or intolerable side effects with ACEI or ARB therapy, or serum potassium ≥5·2 mmol/L at screening or ≥5·4 mmol/L at the time of randomization.

Subjects were randomized in a double-blinded manner to receive sacubitril/valsartan 200 mg twice daily (n = 4187) or enalapril 10 mg twice daily (n = 4212) in combination with conventional systolic HF therapy including BB (93% of patients), diuretic (80%), aldosterone antagonist therapy (56%) and digitalis (30%) therapy, in addition to any required devices for implantable cardioverter defibrillators (ICD) (15%), or chronic resynchronization therapy (CRT) (7%).[9]

The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for HF. Secondary endpoints included time to all-cause death, change from baseline at 8 months on the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to new onset of AF, and the first occurrence of a decline in renal function. Three interim efficacy analyses were conducted to assess whether data met prespecified criteria for overwhelming benefit and study termination.

Baseline characteristics of the two groups were comparable as 60% of patients in each group exhibited ischaemic cardiomyopathy, about 70% of patients were in NYHA functional class II, and mean left ventricular ejection fraction (LVEF) was 29·6%. Median BNP levels were 255 pg/mL and 251 pg/mL at baseline in the sacubitril/valsartan and enalapril arms, respectively.[9]

The trial was terminated early on 31 March 2014 after results of the third interim efficacy analysis demonstrated overwhelming reductions in death from cardiovascular causes and the primary endpoint (CV death or hospitalization secondary to HF). After a mean treatment duration of 27 months, treatment with sacubitril/valsartan was associated with significant reductions in the primary endpoint, as there were 914 events in the sacubitril/valsartan group and 1117 in the enalapril group (21·8% vs. 26·5%, respectively, RRR 20%; $P < 0·001$).[9] The incidence of both components of the composite endpoint was significantly reduced with sacubitril/valsartan as CV death occurred in 13·3% vs. 16·5% of enalapril patients (RRR 20%, $P < 0·001$), and first hospitalization from worsened HF occurring in 12·8% and 15·6% of patients, respectively (RRR 21%, $P < 0·001$). All-cause mortality rates were significantly reduced (17·0% vs. 19·8%, RRR 16%, $P < 0·001$), and the average reduction in the KCCQ clinical score at 8 months ($-2·99 \pm 0·36$ vs. $-4·63 \pm 0·36$, least-squares mean (±SE) of the between-group difference) reflects significantly fewer symptoms or physical limitations secondary to HF in the sacubitril/valsartan group.[9] There was no difference in the incidence of new-onset AF or worsened renal function.

Despite a higher incidence of hypotension in the sacubitril/valsartan arm, discontinuation of therapy was significantly less common overall in the sacubitril/valsartan group (17·8% vs. 19·8%, $P = 0·02$). Additionally, fewer patients taking sacubitril/valsartan required a discontinuation of therapy due to renal failure (0·7% vs. 1·4%, $P = 0·002$) or adverse events (10·7% vs. 12·3%, $P = 0·03$).[9] Angioedema occurred in 19 patients receiving sacubitril/valsartan and 10 patients on enalapril, but this finding was not significant statistically. BPs were significantly lower by $3·2 \pm 0·4$ mmHg at 8 months in the sacubitril/valsartan group ($P < 0·001$) but were not determined to have impacted the outcomes. At the final study assessment among patients still receiving treatment, the mean doses of study drugs were 375 mg and 18·9 mg for sacubitril/valsartan and enalapril, respectively.

Strengths of PARADIGM-HF include its randomized, prospective, active treatment-controlled design and clinically relevant

endpoints. The trial was adequately powered to detect differences in hospitalization and mortality, two endpoints that practitioners focus therapy on preventing in HF patients. Potential limitations of the trial include the underrepresentation of advanced HF patients as 70% of participants had Class II NYHA HF. However, the fact that sacubitril/valsartan was able to show mortality reduction in these more functional HF patients, where it would be expected to be more difficult to show a mortality reduction given the lower risk, suggests that this is not a limitation of the trial. The small numbers of patients requiring ICD/CRT may not be representative of the general HF population, and the low numbers of African American patients receiving sacubitril/valsartan (n = 213) may make it difficult to quantify the benefits of sacubitril/valsartan and risk of angioedema in this population.

The authors of PARADIGM-HF conclude that sacubitril/valsartan was superior to enalapril at reducing the risk of mortality and hospitalization due to HF. The absolute reductions in the primary endpoint, CV death and all-cause mortality (4·7%, 3·2%, and 2·8%) translate to numbers needed-to-treat of 21, 32 and 36 patients over a 27-month period, respectively. The significant prolongation of survival with sacubitril/valsartan compared to doses of enalapril that had demonstrated mortality reductions in prior trials was seen early and was consistent among subgroups. A subsequent analysis of PARADIGM-HF focusing on non-fatal markers of clinical deterioration demonstrated that fewer patients receiving sacubitril/valsartan required intensification of their pharmacological heart failure regimen (520 pts vs. 604 pts, HR 0·84, P = 0·003) than those receiving enalapril.[49] Also, 23% fewer patients were admitted for worsening HF (851 pts vs. 1079, P < 0·001), 18% fewer patients were admitted to an intensive care unit (768 vs. 879 pts, P = 0·005), 31% fewer required inotropic therapy (P < 0·001) and 22% fewer required advanced therapies of LVAD or heart transplantation. Additionally, an early and consistent reduction in N-terminal pro-BNP serum levels was demonstrated in patients receiving sacubitril/valsartan compared to those receiving enalapril,[49] an objective finding that supports the dual mechanistic theory and clinical benefits of combination therapy with sacubitril/valsartan.

The evidence from PARADIGM-HF supports neprilysin inhibition as an effective strategy for further optimization of outcomes in patients with HFrEF, but its role in the management of HF with preserved ejection fraction (HFpEF) required further investigation.

Sacubitril/valsartan in HFpEF: the PARAMOUNT trial

Approximately 50% of HF patients have HFpEF.[1] Therapies for HFpEF are directed towards symptom management and cardiovascular risk factors due to the lack of clinical trials that demonstrate therapeutic benefits with agents commonly utilized in HFrEF. The safety and efficacy of sacubitril/valsartan among HFpEF patients showed promising results in a phase 2 trial.[50] The Prospective Comparison of ARNI with ARB on Management of Heart Failure Preserved Ejection Fraction (PARAMOUNT) trial was a randomized, double-blind, parallel-group, active controlled trial. Patients were eligible if they were aged ≥40 years with an LVEF of at least 45% and a documented history of HF with associated signs or symptoms (dyspnoea on exertion, orthopnea, paroxysmal dyspnoea and peripheral oedema). Additional requirements included a NT-proBNP level >400 pg/mL, concurrent diuretic therapy, and SBP of <140 mmHg, or 160 mmHg or less if on ≥3 antihypertensive agents, an estimated GFR of at least 30 mL/min/1·73 m^2, and a potassium concentration ≤5·2 mmol/L. Patients were excluded if they had a previously documented LVEF < 45%, right HF due to pulmonary disease, dyspnoea due to non-cardiac related causes, primary valvular or myocardial diseases, coronary artery or cerebrovascular disease within 3 months of screening, or likely need for revascularization during the trial.

Patients were randomized to sacubitril/valsartan 50 mg twice daily or valsartan 40 mg twice daily. Both arms were titrated to their final doses of 200 mg twice daily or 160 mg twice daily, respectively, over 2–4 weeks. The primary endpoint was a change from baseline in NT-proBNP at 12 weeks. Secondary endpoints included changes in echocardiographic measures, BP, NYHA class, clinical composite assessment and quality of life using the KCCQ. NT-proBNP was measured at screening, randomization, week 4, week 12 and week 36.

Baseline characteristics were similar between groups. The mean LVEF was 58% (SD 7·7), and LVEF was 50% or greater in 79% of patients. Most patients were elderly, female and overweight and classified as NYHA class II.

The change in NT-proBNP was seen at week 4 in the sacubitril/valsartan group compared to the valsartan group, although the result was not significant (P = 0·063). However, the change from baseline to 12 weeks was significantly reduced in the sacubitril/valsartan group compared to valsartan (95% CI 0·64–0·92, P = 0·005). The difference at 36 weeks between the groups remained reduced from baseline, but was no longer significant (P = 0·20).

Blood pressure was also reduced at 12 weeks and showed greater reductions for the sacubitril/valsartan treatment group compared to valsartan, 9·3 (SD 14)/4·9 (10) mmHg for SBP and 2·9 (17)/2·1 (11) mmHg for SBP, respectively (P = 0·001 for SBP and P = 0·09 for DBP). There were no significant changes in echocardiographic measures, clinical composite assessment or KCCQ score at weeks 12 and 36. However, improvement was noted in NYHA class at 36 weeks in the sacubitril/valsartan group compared to the valsartan group (P = 0·05). There were no significant differences in adverse effects.

The findings from PARAMOUNT suggest that sacubitril/valsartan may have favourable effects in patients with HFpEF, but further investigation is needed to determine whether sacubitril/valsartan significantly reduces morbidity and mortality. The Prospective Comparison in ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF), a phase 3 clinical trial, is currently recruiting to determine whether sacubitril/valsartan reduces cardiovascular death or HF hospitalizations in patients with HFpEF.[51] Eligible patients must have a LVEF at least 45%, structural heart disease, symptoms of HF requiring diuretic therapy for 30 or more days prior to study entry, and either a prior hospitalization due to HF within 9 months of study entry or an elevated NT-proBNP. The study is estimated to be complete in May 2019.

WHAT IS NEW AND CONCLUSION

While clinical trial data in patients with HFpEF are ongoing, the FDA granted approval status for sacubitril–valsartan (Entresto®) in July 2015 with the indication to reduce the risk of death and hospitalization in patients with NYHA Class II-IV HFrEF. The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice daily with doses doubled after 2–4 weeks to a target maintenance dose of 97/103 mg twice daily, as tolerated. A lower starting dose of 24/26 mg twice daily is recommended for patients

with severe renal impairment (GFR < 30 mL/min/1·73 m^2). While treatment regimens must be individualized for all HF patients, sacubitril/valsartan now warrants consideration in all suitable patients given its impact on improved survival and reduced hospitalization.

Current US guidelines do not address the role of sacubitril/valsartan in patients with HFrEF, but in 2015, the Canadian Cardiovascular Society published a focused update on the management of anaemia, biomarkers and recent therapeutic trials in HF. A conditional recommendation of 'high-quality evidence' was given to sacubitril/valsartan, stating that patients with mild-to-moderate HF with an EF of <40%, elevated BNP or hospitalizations for HF in the past 12 months on appropriate doses of guideline-directed medical therapy should receive the combination over an ACEI or ARB.[52] Additional recommendations include close monitoring of serum potassium and creatinine. In determining the appropriate place of therapy, patient candidacy and cost of sacubitril/valsartan, pharmacists will continue to have an important role in the optimization of management and reduction of HF outcomes.

CONFLICT OF INTEREST STATEMENT

We, the authors, have none of the following conflict of interests to report: consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or other financial or material gain that may involve the subject matter of this manuscript.

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