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Potential Expanded Indications for Neprilysin Inhibitors

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Abstract
Purpose of Review The goal of this article is to review potential expanded indications for neprilysin inhibitors. This article reviews the rationale and design for ongoing and future trials of sacubitril/valsartan in cardiovascular and non-cardiovascular disease.
Recent Findings Randomized trial data are lacking for use of sacubitril/valsartan in acute heart failure and advanced heart failure. Mechanistic data from animal studies suggest a role for neprilysin inhibition in the treatment of post-myocardial infarction systolic dysfunction and heart failure with preserved ejection fraction. Beyond the cardiovascular system, renal and neurological function may be impacted by neprilysin inhibition. Forthcoming randomized trials will address the clinical impact of sacubitril/valsartan on these conditions.
Summary Neprilysin inhibition with sacubitril/valsartan offers a new therapeutic strategy with a broad range of potential therapeutic actions. In PARADIGM-HF, the combination of neprilysin and RAAS inhibition was proven to be superior to enalapril for patients with stable NYHA class II–III heart failure and reduced left ventricular ejection fraction. Preliminary data suggests it may also have a role in other cardiovascular and non-cardiovascular disease. Several ongoing and planned studies will determine the extent of its benefit for these other indications.

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Introduction

Neurohormal Pathways in Heart Failure

The activation of neurohormonal compensatory mechanisms underlies the physiology of heart failure (HF). The contributions of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) to unfavorable changes in renal sodium handling, vascular tone, and cardiomyocyte structure and function were long ago recognized and translated into pharmacotherapies that have been proven in large-scale clinical trials to improve survival and morbidity in patients with HF and reduced left ventricular ejection fraction (HFrEF). These agents formed the backbone of modern HF pharmacotherapy: β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and the mineralocorticoid receptor antagonists (MRA). Modulation of other biologic pathways operant in heart failure has failed to demonstrate clinical benefit—endothelin receptor antagonists failed to improved outcomes and were associated with increased adverse events [1–3] while trials of tumor necrosis factor-alpha inhibition were stopped for futility [4]. Meanwhile, increased inhibition of the RAAS through multiple or higher-dose drugs failed to demonstrate further mortality improvements, suggesting the need to harness another biological pathway to benefit patients with heart failure [5–10].

The natriuretic peptide system (NPS), also activated in HF, has been an alluring target for drug development —not for inhibition but augmentation. This is due to the natriurietic, diuretic, vasodilatory, and lusitropic properties of these

peptides as well as their action to prevent cardiac hypertrophy and fibrosis and to decrease renin release. These peptides include atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Synthetic ANP [11–13] and synthetic BNP [14–16] have been demonstrated to potentiate the above effects, however these molecules are only available in parenteral form and their use has not been demonstrated in large-scale trials to confer a mortality benefit. As an alternative strategy to exogenous administration, targeting the degradation of these molecules presents an opportunity to potentiate their biological effect.

Biological Activity of Neprilysin and Pharmacologic Implications

Neprilysin, a predominantly membrane-bound zinc-dependent metalloproteinase distributed broadly throughout the body, is responsible for the breakdown of multiple endogenous vasoactive peptides including bradykinin, natriuretic peptides, and adrenomedullin [17–19]. Increasing the levels of these peptides through neprilysin inhibition would be expected to counteract the neurohormonal activation and compensatory mechanisms that lead to sodium retention, vasoconstriction, and cardiac remodeling [20, 21]. Inhibitors of neprilysin were developed in the 1980s (thiorphan) [22] and 1990s (sacubitril) [23]. Early animal studies demonstrated that neprilysin blockade effected a rise in natriuretic peptide levels and natriuresis, but had inconsistent effects on blood pressure and systemic vascular resistance [17, 24, 25]. Short-term use in humans conferred beneficial effects on natriuresis, diuresis, and hemodynamics [24, 26, 27]; however, longer-term use resulted in vasoconstriction, and it was subsequently described that neprilysin inhibition also increased the circulating concentration of the vasopressors angiotensin II and endothelin [19, 28]. Dual potentiation of vasodilatory and vasoconstrictor substances results in a neutralized effect of isolated neprilysin inhibition and thwarts its usefulness in treating heart failure.

The neutralized effect of neprilysin inhibition on vascular tone and sodium handling underscores the need to understand the action of neprilysin on a variety of biological pathways. Neprilysin is involved in the metabolism of a broad array of peptides with various and occasionally contradictory biologic actions (Table 1). In addition to its action on the natriuretic peptides, endothelin, and angiotensin II, neprilysin has a role in the degradation of adrenomedullin and bradykinin, compounds which exert vasodilatory effects. In fact, the enzymatic activity of neprilysin against BNP is relatively less compared with its action on other NPS components, suggesting a more complex biological action of neprilysin inhibitors on the circulation than augmentation of BNP alone [29]. The broad enzymatic activity of neprilysin has also led to concerns about implications outside the cardiovascular system. Neprilysin degrades amyloid-β peptide, leading to concerns that its inhibition might contribute to the development of diseases of amyloid-β accumulation such as age-related macular degeneration, cerebral amyloid angiopathy, and Alzheimer disease [30••]. Neprilysin, through its metabolism of mitogenic peptides may also serve as a check against tumor cell proliferation in prostate [31], breast [32•], and other cancers [33–35]. Clinical ramifications of widespread and prolonged use of neprilysin inhibitors on these non-cardiovascular conditions are unclear.

Table 1 Substrates of neprilysin

Vasoactive peptides	Mitogenesis and angiogenesis
Adrenomedullin	Bombesin-like peptides
Angiotensin I	Fibroblast growth
Angiotensin II	
Natriuretic peptides (ANP, BNP, CNP, urodilatin)	Hypothalamic-pituitary axis
Bradykinin	Adrenocorticotrophic hormone
Kallidin	Gonadotropin-releasing hormone
Endothelin	α-melanocyte stimulating hormone
Neurokinin A	Oxytocin
Neuropeptide Y	
Substance P	Digestion and metabolism
	Cholecystokinin
Peptides in neurologic processes	Gastrin-releasing peptide
Amyloid β	Glucagon
Galanin	Glucagon-like peptides
Neurotensin	Insulin-B chain
Peptide YY	
Pain and Inflammation	
Calcitonin gene-related peptide	
Dynrophin	
β endorphin	
Enkephalins	
Neurokinin A	
Vasoactive intestinal peptide	

Adapted from Campbell, *Nature Reviews Cardiology*

Combined Neprilysin and RAAS Inhibition for Heart Failure

Though inhibition of neprilysin alone was not a viable strategy for treating cardiovascular disease, dual inhibition of neprilysin and the RAAS was ultimately explored in large-scale clinical trials. Rodent model data confirmed a greater antihypertensive effect of combined neprilysin inhibition and ACE inhibition [36] and cardiac remodeling data from animal models suggested a rationale for this combined therapy in heart failure [36–38]. The oral agent omipatrilat, a dual inhibitor of neprilysin and ACE was developed for

clinical use and in humans demonstrated antihypertensive and NP-augmenting effects [39]. Large-scale randomized controlled trials of dual neprilysin/ACE inhibition vs. ACE inhibition alone in HF patients followed. In the IMPRESS trial there was a trend towards efficacy of omipatrilat over lisinopril, leading to the OVERTURE trial, in which omapatrilat was superior to enalapril with regard to a secondary outcome of cardiovascular death or hospitalization, but failed to meet the primary endpoint of all-cause mortality or heart failure hospitalization [40, 41]. Concern was also raised over the increased rate of angioedema in the OVERTURE trial. The subsequent large-scale hypertension trial OCTAVE revealed an increased rate and greater severity of angioedema among subjects receiving omipatrilat vs. enalapril, an observation that was more notable among African Americans [42]. The failure of omapatrilat to meet the primary endpoints in OVERTURE coupled with concerns over angioedema resulted in an end to its development as a therapy for heart failure.

Despite the failure of omapatrilat to result in an approved pharmacotherapy for heart failure, development of combined neprilysin and RAAS inhibition continued. The action of omapatrilat on both the inhibition of neprilysin-based degradation of bradykinin as well as its inhibition of substance P, which itself breaks down bradykinin, likely accounts for the prohibitive rate of angioedema observed in clinical trials [18]. LCZ696, a compound of the neprilysin inhibitor pro-drug sacubitril and the ARB valsartan, emerged as the next, ultimately successful, strategy. This compound demonstrated a favorable hemodynamic profile without cough and angioedema concerns in early-phase trials [43] and in a phase II study of HF subjects with preserved LVEF it demonstrated more favorable cardiac remodeling and improvements in heart failure status than comparators receiving valsartan [44••]. Ultimately, it was LCZ696 (sacubitril/valsartan), the first in class angiotensin receptor neprilysin inhibitor (ARNI), that would deliver a trail with a favorable mortality endpoint, leading to FDA approval for use in systolic heart failure.

Current Evidence and Indications for Combined Neprilysin Inhibition and Aldosterone Receptor Blockade

The 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure includes recommendations for use of sacubitril/valsartan in heart failure patients with reduced ejection fraction (LVEF <40%) [45••]. Sacubitril/valsartan is recommended in patients with chronic symptomatic HFrEF and NYHA class II or III symptoms (who previously tolerated an ACEI or ARB) to further reduce morbidity and mortality (Class I, Level of Evidence B). Specifically, replacement of ACEI or ARB with ARNI is recommended. Current labeling of the drug by the FDA is slightly broader than these guidelines, indicating ARNI for NYHA Class II–IV heart failure. The rationale for these indications is derived from the PARADIGM-HF trial.

The PARADIGM-HF trial compared LCZ696 (sacubitril/valsartan) to enalapril in a prospective, randomized, double-blind, international trial of 9419 patients with NYHA class II–IV heart failure and reduced left ventricular ejection fraction (≤35%) [46••]. Patients were required to be on 4 weeks of stable medical therapy and have elevated NP levels. Key exclusion criteria included symptomatic hypotension, SBP < 100 mmHg, serum potassium >5.2 mmol/L, eGFR < 30 ml/min, or a history of angioedema. Prior to randomization, a single-blind run-in period was required in which patients received enalapril for at least 2 weeks followed by sacubitril/valsartan for a period of 4 to 6 weeks. A total of 9419 subjects entered the run-in and 8442 subjects were randomized. Study drugs were titrated to a goal dose of sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily. Most patients enrolled in the study had NYHA class II (70%) or III (24%) heart failure, with <1% having Class IV HF. The mean LVEF of the study population was 29% and concomitant treatment with guideline-directed heart failure therapies was typical for a heart failure trial population. The trial was concluded early after meeting a pre-specified stopping point for compelling clinical benefit. After a median follow-up of 27 months, subjects taking sacubitril/valsartan had a 20% reduction in the combined endpoint of cardiovascular death or HF hospitalization. All-cause mortality was also significantly less among the valsartan/sacubitril group (17 vs. 19.8%).

The impressive results of PARADIGM and the approval of sacubitril/valsartan for clinical use have provided the opportunity to explore the role of neprilysin inhibition, NP potentiation, and the action of ARNI in a variety of cardiovascular and non-cardiovascular disease states (Table 2). Here, we detail the biologic rationale and context for these forthcoming trials.

Potential Expanded/Future Indications of ARNI Use in HFrEF

Acute or Recently Decompensated Heart Failure

In terms of acute heart failure (AHF), patients treated with sacubitril/valsartan in the PARADIGM trial, experienced reduced readmission, both at 30 and 60 days, for all-cause and HF readmission [47]. Further, the benefit of sacubitril/valsartan over enalparil was not attenuated or accentuated by proximity of trial enrollment to most recent prior hospitalization for HF. [48] Unfortunately, whether these inferences can be extended to patients with currently or recently decompensated HF is not knowable from the PARADIGM trial, which

Table 2 Ongoing and forthcoming trials of sacubitril/valsartan

Trial name	NCT/ISDN	Population	Primary endpoint	Subjects	Duration
PIONEER-HF	NCT02554890	Recent AHF (HFrEF)	Δ NT-proBNP	736	8 weeks
TRANSITION	NCT02661217	Inpatient AHF (HFrEF)	% taking max dose sac/val at 10 weeks	1000	26 weeks
HFN-LIFE	NCT02816736	NYHA Class IV HFrEF	Δ NT-proBNP	400	24 weeks
PROVE-HF	NCT02887183	NYHA Class II–IV HFrEF	Remodeling parameters	830	52 weeks
EVALUATE-HF	NCT02874794	NYHA Class I–III with hypertension	Δ aortic impedance	432	12 weeks
PARENT	NCT02788656	NYHA Class II–III HFrEF	Δ mean PA pressure	20	32 weeks
PARADISE-MI	NCT02924727	Post-MI LVEF ≤ 40% with risk factors	Time to CV death, HF hospitalization, or outpatient HF	4650	156 weeks
PARAGON-HF	NCT01920711	HFpEF with elevated NTproBNP, structural heart disease	Rate of CV death and total HF hospitalizations	4600	57 months
UK HARP-III	ISRCTN 11958993	CKD with an eGFR between 20 and 60 mL/min/1.73 m2	Δ GFR	400	12 months
PERSPECTIVE	NCT02884206	HFpEF with elevated NTproBNP, structural heart disease	Δ global cognitive composite score	520	36 months
AWAKE-HF	NCT02970669	NYHA Class II–IV HFrEF	Δ daily actigraphy	136	16 weeks
ENTRESTO-SAS	NCT02916160	LVEF ≤45%	Δ apnea–hypopnea index	100	3 months
Peripheral Arterial Disease Trial	NCT02636283	No HF. Claudication with ankle-brachial index ≤0.90	Treadmill walk until pain initiated	40	8 weeks
PARASAIL (Post-approval study)	NCT02690974	NYHA II–III, HFrEF	% tolerating max dose	300	12 months
Pediatric trial	NCT02678312	Age <18. NHYHA II–IV, HFrEF	Combined clinical outcome	360	52 weeks
Japanese trial	NCT02468232	Same as PARADIGM	Time to CV death or HF hospitalization	220	40 months
PARABLE	NCT02682719	LVEF >50%, elevated BNP, LAVI >28 mL/m2	Δ left atrial volume index	250	18 months
PRIME	NCT02687932	LVEF 25–50% with secondary MR (EROA >0.1 cm2)	Δ EROA	118	12 months

excluded patients with a current episode of decompensation and patients not taking at least 4 weeks of stable medical therapy with at least 10 mg/day of enalapril or equivalent.

The impact of initiating or up-titrating of any neurohormonal antagonist during an episode of acute heart failure is not well-described. Initiation of beta-blocker prior to discharge during an AHF hospitalization resulted in superior rates of beta-blocker use at 60 days but resulted in no difference in subsequent death or re-hospitalization [49]. While analogous prospective data are lacking for ACEI/ARB use at discharge, it is evident from Medicare data that patients discharged on ACEI or ARB are substantially more likely to be maintained on long-term therapy [50]. Aggregated data from clinical trials also suggest that ACEI/ARB non-use at discharge is associated with greater risk for post-discharge adverse events [51•]. Thus, there is interest in the role of early ARNI initiation relative to HF hospitalization.

Two forthcoming trials will address the role of inpatient initiation of ARNI in acute heart failure. PIONEER-HF trial will be an 8-week randomized, double-blind, multicenter study to compare safety and tolerability of initiation of sacubitril/valsartan vs. enalapril initiation prior to hospital discharge in patients with HFrEF who have been stabilized following admission for AHF with a primary efficacy endpoint of time-averaged percentage change of NT-proBNP (NCT02554890). Patients will be randomized between 1 and 10 days after hospital presentation provided they meet a definition of stability including SBP ≥100 mmHg for 6 h prior to randomization with no symptomatic hypotension, no increase in IV diuretic dose or administration of IV vasodilators within 6 h prior to randomization, and no administration of inotropes for 24 h prior to randomization. Meanwhile, the TRANSITION trial will be a 1000 subject international trial similar to IMPACT-HF, randomizing subjects to a strategy of either inpatient initiation of sacubitril/valsartan or outpatient initiation of sacubitril/valsartan from day 1 to 14 post-discharge (NCT02661217). The primary endpoint will be the percentage of subjects receiving maximum dose sacubitril/valsartan at 10 weeks post-randomization.

NYHA Class IV Heart Failure

The effectiveness of sacubtril/valsartan in the patients with the most advanced HF is not clear. When PARADIGM subjects were characterized by use of the MAGGIC risk model, an externally validated predictor of adverse events in HF, a consistent degree of benefit was noted across all quintiles [52•]. However, while a number of high-risk patients were certainly represented in the trial, PARADIGM included only 60 NYHA Class IV patients, comprising <1% of the total enrollment. The clinical features that were associated with an inability to complete the run-in period of the PARADIGM trial—an eGFR <60 ml/m2, lower SBP, and highter NTproBNP—are particularly prevalent in Class IV patients [53]. Ultimately, the absolute benefit of ARNI in patients with Class IV heart failure and the relative benefit of ARNI over standard ACEI/ARB use are difficult to ascertain from available data. To this end, the HFN-LIFE trial will prospectively address the comparative effectiveness of sacubitril/valsartan vs. valsartan alone in a randomized, double-blind trial of approximately 400 subjects with NYHA Class IV heart failure (NCT02816736). Subjects will be followed for 24 weeks and the primary study outcome will be an AUC difference in NT-proBNP as assessed at 4, 8, 12, and 24 weeks. Secondary outcomes will include clinical worsening of heart failure and tolerability will provide valuable insight into the practical use of this agent in patients with advanced heart failure.

Structural, Hemodynamic, and Biochemical Evidence of Cardiac Remodeling

Despite demonstrating improvement in survival and hospitalization, the PARADIGM trial did not include serial echocardiography, thus the degree of ventricular remodeling experienced with ARNI use in the trial is not known. Previous trials of ACEI, ARB, and β-blockers demonstrating mortality improvement have also demonstrated improvement in left ventricular volumes compared to placebo. For ACE inhibitors this favorable remodeling effect extends to patients with asymptomatic LV systolic dysfunction [54]. Whether cardiac remodeling undergirds the benefit of ARNI will be assessed in forthcoming trials assessing biomarker changes and ventricular remodeling among patients with NYHA Class II–IV heart failure with reduced LVEF ≤40% (PROVE-HF, NCT02887183), changes in aortic impedance among patients with NYHA Class I–III HF and hypertension (EVALUATE-HF, NCT02874794), changes in functional mitral regurgitation (PRIME, NCT02687932) in patients with LVEF between 25 and 50%, and changes in mean pulmonary artery pressure in patients with LVEF <35% (PARENT, NCT02788656). Finally, the potential for sacubitril/valsartan to attenuate atrial remodeling in patients with risk for future heart failure will be addressed by the PARABLE study. These trials should provide useful insights into the role of ARNI at several stages in the progression of HF.

Potential Therapeutic Strategies Beyond Systolic Heart Failure

Post-Acute Myocardial Infarction

Use of an ACEI or ARB is indicated for all patients with LVEF ≤40% following either ST segment elevation or non-ST segment elevation myocardial infarction (Class 1, Level of Evidence A) [55, 56]. Large-scale clinical trials demonstrate the mortality benefit of ACEI in this setting [57, 58]. ARBs are similarly effective, but produce undesired adverse effects when added to ACEI [59, 60]. Additionally, beta blockers and mineralocorticoid receptor antagonists improve mortality in post-MI patients with reduced LVEF and carry a Class 1, Level of Evidence A recommendation.

Natriuretic peptide levels rise in the setting of myocardial infarction and are associated with reduced survival [61]. The stimulus for NP release appears to be both wall stress and ischemia [62]. NPs have potentially favorable effects on the infarcted myocardium, reducing ischemia reperfusion injury, inhibiting neutrophil degranulation, and blunting sympathetic nerve activity [63]. In humans with anterior myocardial infarction, infusion of ANP results in a reduction of cardiac sympathetic nerve activity and less LV remodeling [64] and infusion of BNP results in improved LVEF and less ventricular dilatation [65]. ARNI are a logical consideration for therapy post-MI and indeed animal data show that sacubitril/valsartan attenuates LV dilatation, preserves LV systolic function and mechanics, and reduces myocardial hypertrophy and fibrosis [66••]. The PARADISE-MI study will test the hypothesis that sacubitril/valsartan is superior to ACEI with regard to the cumulative hazard of CV death, HF hospitalization, or outpatient HF in an international trial of 4650 subjects with new LV systolic dysfunction (LVEF ≤40% and no prior history of chronic heart failure) following acute myocardial infarction (NCT02924727). In addition to providing data on long-term post-infarct ventricular remodeling with ARNI, the dual effects of potentiating NPs and inhibiting neprilysin should provide insights into post-infarction neutrophil function and the associated consequences on post-infarction myocardial inflammation.

Heart Failure with Preserved LVEF

Patients with heart failure with preserved LV ejection fraction (HFpEF) have a similar, but less severe profile of derangements in neurohormonal activity, exercise capacity, and quality of life compared to patients with heart failure and reduced LV ejection fraction (HFrEF) [67]. Despite these similarities,

clinical trials of RAAS inhibitors and beta blockers have failed to demonstrate statistically significant improvements in survival, while MRAs have shown promise, albeit controversial [68•].

Modulation of the NPS in patients with HFpEF is appealing, as NP activity appears to adhere to a similar paradigm in HFpEF as in HFrEF. Elevated BNP levels predict adverse clinical outcomes in patients with HFpEF as they do in patients with HFrEF. [69] Though BNP levels tend to be lower in patients with HFpEF than in patients with HFrEF, a given BNP level is similarly prognostic [70]. In addition to the previously described actions of the NPs in heart failure, the action of the NPS on cardiomyocyte protein-kinase G (PKG) may suggest a particular pathway of benefit. LV biopsy specimens in HFpEF reveal low activity of PKG, a powerful regulator of titin stiffness, and this is associated with an elevation in cardiomyocyte resting passive tension [71]. PKG activity is regulated by the availability of cyclic GMP, which is elaborated by guanylate cyclase (GC), occuring in both soluble (sGC) or receptor-bound (rGC) forms. There appear to be separate pools of PKG activity, with nitric oxide synthetase and donors of nitric oxide stimulating sGC and NPs signaling via rGC with separate regulation by phosphodiesterase 9 [72•]. Even as enthusiasm builds for agents that more effectively deliver nitric oxide to hypoxic tissues (eg: inorganic nitrate and inorganic nitrite) or directly stimulate soluble guanylate cyclase (e.g., riociguat), the signaling of NPs through the rGC-cGMP-PKA pathway may represent a unique pathway to modulate cardiomyocyte function [73••].

Phase 2 clinical trial data exist for the use of ARNI in patients with HFpEF. The PARAMOUNT study randomized 308 patients with HFpEF (LVEF ≥45%), hypertension, and elevated NTproBNP >400 pg/mL to therapy with sacubitril/valsartan or valsartan. Use of sacubitril/valsartan was associated with greater decline in NTproBNP at 12 weeks, greater improvement in left atrial volumes at 36 weeks, no increase in clinical adverse events, and lower levels of high sensitivity troponin [74, 75]. Moreover, the favorable changes in NYHA class, renal function, left atrial volumes, and NT-proBNP were not correlated with changes in blood pressure, suggesting a more complex mechanism of benefit [44••]. PARAGON-HF is the subsequent ongoing phase 3 trial of sacubitril/valsartan use in HFpEF (NCT01920711). As the largest HFpEF trial ever conducted, it will enroll 4600 subjects with NYHA Class II–IV HF with an LVEF ≥ 45% and compare the rate of CV death and HF hospitalization among subjects treated with sacubitril/valsartan vs. valsartan.

Hypertension

The biologic rationale for blockade of the RAAS and potentiation of the NPS with regard to blood pressure lowering is described in previous sections of this review. At present, three randomized controlled trials of sacubitril/valsartan therapy for hypertension have been reported. A comparison of sacubitril/valsartan vs. valsartan vs. placebo in 1328 patients with mild-moderate hypertension demonstrated greater lowering of blood pressure in sacubitril/valsartan treated subjects compared to subjects treated with the comparable bioactive dose of valsartan [43]. Importantly, no cases of angioedema were reported. Subsequently, Kario et al. demonstrated the effectiveness of sacubitril/valsartan compared to placebo in 389 hypertensive Asian subjects in lowering daytime and nighttime blood pressures with no cases of angioedema [76]. Finally, the recently reported PARAMETER study demonstrated that in a group of 454 elderly hypertensive patients with elevated pulse pressure ≥60 mmHg, sacubitril/valsartan was more effective than olmesartan at lowering central aortic blood pressure and 24-h ambulatory blood pressure at 12 weeks and required fewer add-on antihypertensive therapies over the course of 52 weeks [77]. While these data are promising, to date no phase 3 clinical trial of sacubitril/valsartan for the treatment of hypertension is planned.

Potential Non-cardiac Indications

Renal Disease

In the normal kidney, autoregulation permits the maintenance of GFR across a range of blood pressures; however, heart failure, particularly in the setting of therapies that reduce the action of angiotensin II at the glomerulus, is characterized by altered renal function and heightened sensitivity of GFR to reductions in blood pressure and renal perfusion [78]. Thus, use of RAAS inhibiting drugs in heart failure may lower GFR. Even as GFR may fall with RAAS blockade in HF, it is evident that compared with placebo, ACEI/ARB use provides a clinical benefit for patients with stage III and possibly stage IV CKD [79•], and that continued ACEI/ARB use even in the face of worsening renal function is beneficial over discontinuation [80•]. Meanwhile, the NPS, particularly ANP, has been demonstrated to effect an increase in GFR through glomerular afferent arteriolar dilatation and efferent arteriolar constriction in both dog [81] and rat models [82]. Further, in healthy humans ANP infusion [83] and BNP infusion [84] have been demonstrated to improve GFR. Through direct effects on the renal vasculature and indirect effects on the RAAS, the NPS appears to be a pathway for treating renal dysfunction and it is tempting to think that dual RAAS inhibition and neprilysin inhibition might permit both improved heart failure outcomes and preserve renal function. What is the evidence for this?

The dual ACEI and neprilysin inhibitor omapatrilat attenuated the progression of renal failure more-so than ACEI in animal models [85] and in the IMPRESS study was shown to result in fewer episodes of elevated serum creatinine than

ACEI [41]. While advancement of this agent was thwarted by angioedema concerns, there is reason to believe the successor ARNI may confer similar favorable effects. In the PARAMOUNT phase 2 trial of subjects with HFpEF and hypertension, treatment with sacubitril/valsartan as compared to valsartan resulted in significantly less decline in eGFR and lower levels of serum creatinine, albeit with no significant difference in cystatin C and a slightly higher urine albumin/creatinine ratio (UACR) [86•]. The observed elevation in UACR was not seen in a study of hypertensive subjects without HFpEF [43] and might relate to direct inhibitory effects of natriuretic peptides on glomerular mesangial cell proliferation and contraction [87, 88]. Finally, in the PARADIGM trial, despite being associated with more symptomatic hypotension, sacubitril/valsartan was associated with fewer episodes of elevated creatinine or serum potassium [46••]. In aggregate, these data suggest ARNI use should be no less indicated in patients with HF and CKD than ACEI/ARB and may possibly be preferable to these agents in patients with CKD.

Whether the action of ARNI on renal function in non-HF patients is favorable remains to be determined. Considerable data suggest a benefit of ACEI/ARB use on slowing the progression of renal failure among patients with proteinuria and chronic kidney disease, both among diabetics [89] and non-diabetics [90]. These benefits appear minimal or absent among patients with proteinuria <500 mg/day [91]. Even so, international treatment guidelines recommend the use of ACEI or ARB for the treatment of hypertension in all non-dialysis dependent chronic kidney disease even in settings where there is minimal or no proteinuria [92]. It remains an open question whether combined neprilysin and RAAS inhibition may have additive effects, and this will first be studied among patients with CKD and proteinuria. The UK Heart and Renal Protection (HARP)-III is a randomized, controlled trial to be conducted in the UK that will compare the effectiveness of sacubitril/valsartan vs. irbesartan in preserving GFR over 12 months among 360 diabetic and nondiabetic patients with an initial GFR between 20 and 60 ml/m2/1.73 m2 and a UACR ≥20 mg/mmol (ISRCTN 11958993).

Cognition, Behavior, and Neurologic Disease

As previously described, owing to the broad expression and action of neprilysin, non-cardiovascular concerns have been raised for the use of sacubitril/valsartan. Of particular concern is the possible interaction of neprilysin inhibition and Alzheimer disease. Neprilysin degrades Aβ peptides and oligomers, and in animal models, there is an inverse relationship between peripheral expression of neprilysin and brain amyloid burden [93, 94]. Further, animal models have suggested the possibility of a therapeutic benefit of neprilysin potentiation [95]. In humans, there are less certain and occasionally conflicting data on this paradigm of neprilysin activity inverse to Alzheimer disease progression [30••]. However, as neprilysin plays a salutary role in animal models of several amyloid deposition diseases such as age-related macular degeneration, cerebral amyloid angiopathy, and sensorimotor axonal polyneuropathy, concerns remain that ARNI may have long-term unfavorable effects on neurologic function.

In healthy subjects sacubitril/valsartan does not increase CSF levels of the aggregable Aβ isoforms (1–42 and 1–40), but does significantly increase the concentration soluble CSF Aβ 1–38 [96•]. Whether there are clinical consequences to neprilysin inhibition and the described changes in CSF Aβ through ARNI is unclear. A retrospective analysis of PARADIGM revealed no greater rate of dementia-related adverse events in the sacubitril/valsartan arm than the enalapril arm and instead showed that dementia-related AEs were linked to a higher burden of cardiovascular disease and associated risk factors as represented by coronary disease, stroke, atrial fibrillation, higher NT-proBNP levels, and lower eGFR [97•]. Given the potential for competing effects of Aβ-related disease and modification of the impact of cardiovascular comorbidity on cognition in patients treated with ARNI, ongoing trials will seek to better characterize the effects of these agents on cognition and brain structure and function. The ongoing PARAGON trial includes a Mini Mental State exam and the forthcoming PERSPECTIVE trial will employ a more powerful battery of cognitive tests as well as brain positron emission tomography imaging to the brain using florbetapir-18F to assess changes in amyloid plaque deposition over time (NCT02884206).

Finally, the role of neprilysin and ARNI in disorders of sleep in heart failure is an emerging area of interest. Sleep disordered breathing is common in heart failure, with approximately half of patients affected, the majority of whom have central sleep apnea (CSA) [98]. Greater elevations in left heart filling pressures are correlated with CSA [99] and CSA is associated with reduced survival in heart failure [100]. Unfortunately, treatment of HF patients with CSA using adaptive servo-ventilation was shown to increase mortality, limiting enthusiasm for nocturnal respiratory support in these patients [101•]. Cardiovascular pharmacotherapies have to date not been show to improve sleep disordered breathing [102]. Elevated levels of NPs are associated with CSA in HF, but there are no data to demonstrate that potentiation of NPs has salutary effects on sleep [103, 104]. That said, in a rat model of sleep deprivation, there is evidence of neprilysin activation in the pituitary gland, potentially implicating neprilysin in sleep regulation [105]. Neprilysin or neprilysin-like endopeptidases may also play a role in the regulation of circadian rhythm in *Drosphophila* models [106]. Whether these limited and early observations translate to a role for neprilysin inhibition in the sleep-wake cycle or nocturnal breathing in heart failure is not clear. Currently trials are planned for measuring the impact of sacubitril/valsartan on apnea-hypopnea in patients with sleep

apnea (ENTRESTO-SAS, NCT02916160) and daytime activity and nighttime actigraphy in patients with HFrEF treated with sacubitril/valsartan (AWAKE-HF, NCT02970669), potentially illuminating the action of neprilysin inhibition on sleep.

Conclusion

Neprilysin inhibition represents a powerful therapeutic tool in treating chronic heart failure with reduced LVEF and preliminary data suggest a potential role for the use of ARNI in a broader spectrum of cardiovascular and non-cardiovascular disease. Insights from a vast array of clinical trials over the course of the next several years will demonstrate whether the promise of combined neprilysin and RAAS inhibition in these disease states will translate to clinical effectiveness.

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Compliance with Ethical Standards

Conflict of Interest Elizabeth Riddell and Justin M. Vader declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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