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HEART FAILURE (F PEACOCK AND L ZHANG, SECTION EDITORS)

Monitoring Biomarkers in Patients Receiving Neprilysin Inhibitors

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Abstract

Purpose of Review To understand the role of neprilysin inhibition in the management of chronic heart failure with reduced ejection fraction (HFrEF) and review effects of neprilysin inhibition on concentrations of natriuretic peptides and other biomarkers.

Recent Findings Neprilysin inhibition improves cardiovascular outcomes in patients with chronic HFrEF. As bioactive natriuretic peptides are degraded by neprilysin, treatment with sacubitril/valsartan results in an increase in concentrations of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). In contrast, neprilysin inhibition led to reduction in concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Reduction in NT-proBNP to ≤ 1000 pg/mL with neprilysin inhibition improved cardiovascular outcomes in a recent analysis. Other biomarkers may be affected by neprilysin inhibition.

Summary Neprilysin inhibition results in an increase in ANP, BNP, and CNP with corresponding reduction in NT-proBNP concentrations. Other biomarkers may be similarly affected. Given widespread clinical measurement, more data are needed to better understand potential impact on neprilysin inhibition on ability to interpret BNP.

Keywords Biomarker · Natriuretic peptide · Neprilysin inhibition · Heart failure

Introduction

The role of neprilysin and its substrates in vascular homeostasis has been the subject of study for years. Inhibition of neprilysin (raising concentrations of several favorable vasoactive substances degraded by the enzyme) had been explored in earlier pre-clinical and clinical studies; due to challenges with safety in use of neprilysin inhibition, the approach was not fully realized until the recent groundbreaking Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF) trial [1•]. Following this landmark study of neprilysin inhibition in the care of patients with heart failure and reduced ejection fraction (HFrEF), the angiotensin-receptor neprilysin-inhibitor (ARNI) combination of sacubitril/valsartan was included in the most recent update of the American College of Cardiology Foundation/American Heart Association/Heart Failure Society of American guidelines as a class I indication for the management of such patients [2•]. Other studies are now ongoing to evaluate efficacy and/or safety of neprilysin inhibition to care for patients with acute HF, as well as those with HF and preserved ejection fraction (HFpEF).

With anticipated increase in the utilization of ARNI in the treatment of patients, it is imperative to not only understand the role of neprilysin and its inhibition in the pathophysiology of HF, but to also understand impact of such therapy on the traditional aspects of HF management. Natriuretic peptides—specifically B-type natriuretic peptide (BNP) and its precursor N-terminal pro-B-type natriuretic peptide (NT-proBNP)—are currently have a class I guideline recommendation to support a clinical diagnosis of HF, to assess disease severity, or to establish prognosis [3]; accordingly, both peptides are globally measured for these indications. Furthermore, on-treatment monitoring of BNP and NT-proBNP concentrations is also widely employed, either as a prognostic tool or as a target for therapy, with lower concentrations of each peptide a goal of standard HF care [4, 5]. Generally, favorable therapies for HF lead to reduction of BNP or NT-proBNP in parallel with

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their benefit. An exception to this interaction is the response to therapy from neprilysin inhibition with sacubitril/valsartan: when neprilysin inhibition is used, concentrations of BNP tend to rise and conversely, NT-proBNP concentrations tend to decrease [6].

This review will focus on the role played by neprilysin in the cardiovascular system, including discussion regarding physiology of neprilysin inhibition and its effects on concentrations of BNP and NT-proBNP. This discussion is essential to understand as the use of sacubitril/valsartan in the treatment of patients with HFrEF continues to increase [2•].

Neprilysin

Neprilysin is a membrane-bound endopeptidase found in many tissues including the brain, lung, heart, and vasculature; the highest concentrations of neprilysin are found in the lung as well as the renal brush border epithelia [7–9]. It is an 86-kDa zinc-dependent metalloprotease that is known by many names including enkephalinase, neutral endopeptidase 24.11, membrane metalloproteinase, common acute lymphoblastic leukemia antigen, vasopeptidase, and atriopeptidase [7].

Neprilysin Substrates

Neprilysin cleaves and inactivates several vasoactive peptides that have important roles in the pathogenesis and progression of HF [10], including natriuretic peptides, adrenomedullin, bradykinin, endothelin, substance P, and angiotensin II; all of these are relevant to the cardiovascular and renal systems [9], and in turn the pathophysiological pathways of relevant to the progression of HF (Table 1). Given the important cardiovascular role played by numerous neprilysin substrates, interest developed regarding neprilysin inhibition as a therapy for heart disease. It is important to first understand these neprilysin targets and their biological effects.

Natriuretic Peptides

The natriuretic peptides exist in multiple forms but the ones with the most relevance to the cardiovascular system are atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP) [11, 12]. During the synthesis of both ANP and BNP, a pro-peptide precursor is cleaved by the proteolytic convertase enzymes corin and furin to generate pro-ANP and NT-proBNP from mature ANP and BNP, respectively. A significant percentage of circulating natriuretic peptides in HF consists of the un-cleaved precursor peptide known as pro-$BNP_{1–108}$ [13]. Assays for BNP and NT-proBNP cannot differentiate between the free peptides and $proBNP_{1–108}$ due to the fact that the peptides contain both regions recognized by the assays [14]. Three NP receptors (NPRs) have been identified; each plays a role in clearance of ANP, BNP, and CNP and to an extent $proBNP_{1–108}$. On the other hand, NT-proBNP and pro-ANP are not thought to bind to the NPRs.

Following their binding to NPR-A and B, NPs stimulate generation of cyclic guanosine monophosphate (cGMP), a second messenger leading to regulation of blood pressure and plasma volume by enhancing natriuresis and diuresis, reduction of peripheral vascular resistance, smooth muscle relaxation, lowering of blood pressure, and inhibition of both the sympathetic nervous system and the renin-angiotensin-aldosterone system [14]. The NPR-C receptor clears its ligands through internalization and hydrolysis and generates no cGMP response.

Neprilysin plays an important role in clearance of ANP, BNP, and CNP. Among the NPs degraded by neprilysin, BNP is relatively resistant to degradation, while CNP is modestly susceptible, and ANP is most susceptible. In contrast, NT-proBNP has no cleavage sites for action of neprilysin. It remains uncertain if $proBNP_{1–108}$ concentrations are affected by inhibition of neprilysin as its clearance is not yet well understood. Curiously, though a pro-peptide, pro-ANP appears to be able to significantly stimulate cGMP production (presumably due to peripheral conversion to mature ANP) and may thus be vulnerable to neprilysin degradation [15].

Bradykinin

Bradykinin is a 9-amino acid peptide that increases vascular permeability and is a potent vasodilator that acts through endothelial B_2 receptors [16]. Bradykinin is broken down by angiotensin-converting enzyme (ACE); ACE inhibitors (ACEi) stimulate endothelial release of nitric oxide and prostacyclin by a bradykinin-mediated mechanism [17]. Importantly, bradykinin may play a role in the risk of angioedema, through its effects to increase vascular permeability of post-capillary venules leading to plasma extravasation into submucosal tissue [16, 18].

Substance P

Substance P is an 11-amino acid peptide member of the tachykinin family that behaves as a neurotransmitter and a neuromodulator [16]. In the periphery, substance P induces vasodilation and increased vascular permeability by an endothelium-dependent mechanism. Substance P is hypothesized to counteract blood pressure increases seen in animal models of salt-dependent hypertension. Finally, decreased degradation of substance P has been implicated in the pathogenesis of ACEi-associated angioedema [19].

Table 1 Known targets of neprilysin substrates and their biological effects [9, 16]

Substrate	Vascular effects	Biological effect
Adrenomedullin	Vasodilator	Vasodilation, natriuresis, cellular growth, and differentiation
Amyloid-β	None	Substrate of amyloid-β polymer; amyloid-β degradation reduces risk of Alzheimer's
Angiotensin II	Vasoconstrictor	Vasoconstriction, fluid and sodium retention, myocyte hypertrophy and growth, gastric, endocrine, immunological, and antimicrobial effect
ANP	Vasodilator	Natriuresis, vasodilation, blood pressure regulation, cardiac remodeling, anti-RAAS
BNP	Vasodilator	Natriuresis, vasodilation, blood pressure regulation, cardiac remodeling, anti-RAAS
		More resistant to neprilysin degradation compared to ANP or CNP
Bombesin-like peptides	None	Stimulate the growth of small-cell carcinoma of the lung
Bradykinin	Vasodilator	Vasodilatation of epicardial coronary arteries via endothelial B_2 receptors
CNP	Vasodilator	Vasodilation, cardiac remodeling
Endothelin-1	Vasoconstrictor	Vasoconstriction, vascular smooth muscle proliferation, cardiac hypertrophy
Enkephalin	None	Opioid receptor agonist that induces analgesia
Insulin B chain	None	Part of insulin chains; controls blood glucose
Substance P	Vasodilator	Vasodilation, inflammation, plasma extravasation, platelet and leukocyte aggregation
Urodilatin	Vasodilation	Induces enhanced renal effects with vasodilation, antifibrosis, and anti-RAAS.
		Less susceptible to neprilysin degradation compared to ANP or CNP

ANP atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *CNP* C-type natriuretic peptide, *RAAS* renin angiotensin aldosterone system

Adrenomedullin

Adrenomedullin is a 52-amino acid protein expressed in multiple tissues including vascular endothelial cells, smooth muscle cells, and adventitial fibroblasts [20]. Adrenomedullin is among the most potent vasodilators in the body and also possesses natriuretic effects that are mediated by the cyclic adenosine monophosphate, nitric oxide, and renal prostaglandin systems [16]. In vitro experiments have also demonstrated that adrenomedullin exerts multiple protective or inhibitory actions against vascular damage and progression of arteriosclerosis [20].

Angiotensin II

Notably, not all substances degraded by neprilysin are vasodilatory. Angiotensin II is an octapeptide that is a potent vasoconstrictor formed by enzymatic cleavage from its precursor angiotensinogen. It is found in the pulmonary circulation and vascular endothelium of multiple tissues [16]. Angiotensin II has been shown to play important roles in mediating hypertension, HF, cardiac remodeling, diabetes, and the proliferative and inflammatory responses to arterial injury [21]. Circulating angiotensin II stimulates sodium and water reabsorption, causes systemic arteriolar vasoconstriction, and potentiates vascular resistance and cardiac afterload [16]. Angiotensin II's effects stimulate a cascade of events such as systemic and renal vasoconstriction, cardiomyocyte remodeling, and stimulation of aldosterone secretion [22]; all play a role in the pathogenesis and progression of HF. Several trials have shown use of renin-angiotensin-aldosterone system (RAAS) inhibitors produces a survival benefit in patients with HFrEF, which has set the stage for evaluating combined neprilysin-RAAS inhibition, as discussed below.

Endothelin-1

In a similar fashion to angiotensin II, endothelin-1 is a vasoconstrictive substance also degraded by activity of neprilysin. An endothelial product released in response to inflammation, neurohormonal activation, and vascular shear stress [23],

endothelin-1 causes profound vasoconstriction, pro-inflammatory actions, proliferative effects, and stimulation of free radical formation [24]. Endothelin-1 increases mean arterial blood pressure and causes potent and long-lasting vasoconstriction in the pulmonary, renal, splanchnic, myocardial, and skeletal muscle vasculature [24]. Endothelin-1 also induces vascular smooth muscle proliferation and cardiac hypertrophy.

Amyloid-β

Among the "non-cardiovascular" targets of neprilysin is amyloid-β, a mixture of peptides involved in Alzheimer's disease; following secretion, amyloid-β assembles into oligomers, which may deposit in the brain. Amyloid-β is cleared by a number of pathways, including through degradation by neprilysin; in this regard, it has been demonstrated that inhibition of neprilysin in mice has resulted in increased concentrations of the amyloid-β peptide and plaque-like deposits in the brain, which may lead to cognitive impairment [16]. The factors leading to excessive production of amyloid-β in those developing dementia, how amyloid-β is deposited in the brains of those affected, or how clearance mechanisms prevent or mitigate such deposition remains entirely unknown. In point of fact, biology leading to Alzheimer's disease is considerably more complex than simple accumulation of amyloid protein; indeed, data suggest systemic concentrations of amyloid-β [1•, 2•, 3–36, 37••, 38–40] in those with HF do not associate with cognitive function [25]. As well, whether neprilysin inhibition in humans has impact on cerebral deposition of amyloid-β is uncertain; more fundamentally, it is not even certain if neprilysin inhibitors in clinical use even penetrate the cerebrospinal fluid to sufficient levels to affect amyloid-β degradation: a small study by Langenickel and colleagues demonstrated that sacubitril/valsartan did not change cerebrospinal fluid concentrations of amyloid-β peptides compared to placebo [26]. Larger studies are ongoing.

Neprilysin Inhibition as a Therapeutic Strategy in HF

The pathophysiology of HF is marked by up-regulation of the sympathetic nervous system and RAAS. Accordingly, therapeutic strategies for HF have primarily relied on inhibition of these two deleterious pathways. On the other hand, enhancement of favorable pathways in the cardiovascular system (such as cGMP stimulation through the NP system) as a therapeutic strategy for chronic HF had until recently not been successfully achieved. Early reports demonstrated that inhibition of neprilysin increased ANP concentrations and urinary sodium excretion [7]. In 1989, Northridge and colleagues demonstrated that a neprilysin inhibitor (UK 69 578) given to patients with mild HF decreased renin concentrations, right atrial pressure, and pulmonary artery wedge pressure [27].

Subsequent studies found both oral (racecadotril) and intravenous (candoxatrilat) neprilysin inhibitors promoted natriuresis and increased cGMP. However, early on, it was clear that neprilysin inhibition did not lead to sustained effects to lower blood pressure. Recalling neprilysin degrades vasoconstrictors (notably including angiotensin II), it became clear inhibiting neprilysin alone would not be sufficient to be of benefit. This led to exploration of dual therapy with agents inhibiting not only neprilysin but also the RAAS.

The earliest and most extensively investigated dual inhibitor was BMS-186716, also known as omapatrilat, an ACE-neprilysin inhibitor. In the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial of 5770 ambulatory patients with New York Heart Association (NYHA) class II–IV HF, omapatrilat reduced the risk of death and hospitalization, but it was not more effective than ACE inhibition alone [28]. More worrisome, in the subsequent Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial in 25,302 ambulatory patients with untreated or uncontrolled hypertension, angioedema was reported in 2.2% of patients receiving omapatrilat and in 0.7% of patients receiving enalapril [29]. Non-superiority together with the higher rate of angioedema resulted in halting the development of omapatrilat [6].

Following suspension of the omapatrilat development program, a reconsideration of dual inhibition of neprilysin and RAAS focused on mechanisms of angioedema; with less risk for this dreaded side effect, intensity of neprilysin inhibition could theoretically be intensified. Angioedema is thought to be mediated by increased concentrations of potent vasoactive peptides that cause vasodilation and increased vascular permeability: bradykinin, des-Arg9-bradykin, and substance P [6]. Bradykinin and substance P are both degraded in part by ACE and neprilysin; inhibition of both (as in the case of omapatrilat) results in increased concentrations of bradykinin and substance P, which explains the increased incidence of angioedema in patients taking omapatrilat in the OCTAVE trial.

The incidence of angioedema with use of angiotensin type 1 receptor blockers (ARB) is considerably lower than that with ACEi [6, 30]. As such, it made increasing sense to attempt neprilysin inhibition in the context of ARB therapy; this led to development of the ARNI LCZ696, now known as sacubitril/valsartan [6].

Sacubitril/Valsartan

Sacubitril/valsartan contains the neprilysin inhibitor prodrug sacubitril (AHU377) and the ARB valsartan in equimolar concentrations. After oral administration, sacubitril/valsartan

dissociates into valsartan and AHU377; this pro-drug is metabolized to LBQ657. As expected, effects of LBQ657 include significant natriuresis, increased urine cGMP, and reduction in NT-proBNP.

The PARADIGM-HF trial [1•] was a large Phase 3 randomized controlled study comparing therapy with well-dosed enalapril versus sacubitril/valsartan in patients with chronic HFrEF. The trial was stopped prematurely by the Data Safety Monitoring Board after data analyses revealed 20% reduction in the primary outcome of cardiovascular death or HF hospitalization (hazard ratio [HR] = 0.80, 95% confidence interval [CI] 0.73–0.87, $P = 0.0000004$); the number needed to treat in order to see one reduction in the primary endpoint was 21. In PARADIGM-HF, mortality was reduced significantly, and an actuarial analysis done by Claggett [31] and colleagues suggested an increment of about 1–2 years in life expectancy in patients using sacubitril/valsartan over enalapril. Following these results, the United States Food and Drug Administration approved sacubitril/valsartan for the care of patients with chronic HFrEF; soon after, clinical practice guidelines embedded sacubitril/valsartan as a front-line therapy for care of such patients.

Natriuretic Peptide Concentrations During Neprilysin Inhibition

Though impact of neprilysin inhibition on natriuretic peptide concentrations is expected, surprisingly little is known about this phenomenon. In the Phase 2 Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection fraction (PARAMOUNT) trial, 301 patients with chronic HFpEF, NYHA class II–III symptoms, and elevated NP concentrations were treated with sacubitril/valsartan versus valsartan alone. By 12 weeks, ARNI therapy resulted in more significant reduction in NT-proBNP, and greater increases in urinary cGMP and plasma BNP compared to valsartan alone [32]; however, the rise in BNP concentrations appeared to wane somewhat by 36 weeks.

More data regarding impact of ARNI therapy on circulating BNP or NT-proBNP emerged from the PARADIGM-HF Study. In this trial, measurements of BNP and NT-proBNP concentrations were made at baseline, 4 weeks, and 8 months. Consistent with effects of neprilysin inhibition, a significant increase in measured BNP concentrations was seen by 4 weeks after randomization to sacubitril/valsartan; by 8 months, patients treated with neprilysin inhibition still had higher concentrations of BNP when compared to those treated with enalapril. In contrast, in keeping with the fact NT-proBNP is not metabolized by neprilysin, those treated with sacubitril/valsartan had early and sustained reduction in NT-proBNP across the duration of the study.

Monitoring Natriuretic Peptides in Neprilysin Inhibition

Guideline-directed medical therapy (GDMT), such as beta blockers, agents blocking the RAAS, and diuretics, lead to a reduction in BNP and NT-proBNP concentrations in parallel with the benefits of these therapies. Those whose natriuretic peptide concentrations do not fall with GDMT have a worse prognosis in both acute and chronic HF [33] [34–36]. In a post hoc analysis of 2080 patients in the PARADIGM-HF study, Zile and colleagues demonstrated that higher post-treatment NT-proBNP concentrations strongly predicted outcomes such as cardiovascular death or HF hospitalization. Those HFrEF patients with significant post-treatment NT-proBNP reductions had lower subsequent rates of such adverse outcomes, independent of whether the patients were treated with angiotensin-converting enzyme inhibition (i.e., enalapril) or with neprilysin inhibition (i.e., sacubitril/valsartan) [37••]; the risk of cardiovascular death or HF hospitalization was 59% lower in patients with a decrease in NT-proBNP to ≤ 1000 pg/mL. Notably, those treated with sacubitril/valsartan were more likely to achieve an NT-proBNP ≤ 1000 pg/mL than those treated with enalapril (31 vs. 17%).

In contrast to the robust data available to support monitoring of NT-proBNP in the context of ARNI therapy, there are remarkably few data available regarding measurement of BNP for the diagnosis, prognosis, or therapy monitoring of patients receiving sacubitril/valsartan. This may suggest NT-proBNP is preferred as the biomarker of choice when measuring natriuretic peptides in those taking sacubitril/valsartan.

Open Questions

The absence of robust data to inform proper use of BNP testing in those taking sacubitril/valsartan has left several open questions.

How Much Increase in BNP or Decrease in NT-proBNP Is Expected When Initiating ARNI Therapy?

Although the average BNP increase in PARADIGM-HF was modest (< 50 pg/mL), the range of increase was broad, with some patients demonstrating more significant increases than others, while some patients showed little, if any increase. In a similar fashion, no "expected" or "reassuring" reduction in NT-proBNP after ARNI initiation has been defined; work by Zile and colleagues would suggest achievement of an NT-proBNP ≤ 1000 pg/mL among those treated with sacubitril/valsartan is desirable [37••]. Unfortunately, given design of PARADIGM-HF (where patients unable to tolerate higher doses of sacubitril/valsartan were removed from the trial), it remains uncertain if the change in NP concentration is

maximal with higher doses of sacubitril/valsartan or if most rise in BNP/reduction in NT-proBNP is seen at lower doses.

How Does ARNI Therapy Affect NP Concentrations in Those With Acute HF?

Among those in the PARADIGM-HF biomarker sub-study, median baseline BNP concentration in PARADIGM-HF was approximately 200 pg/mL, increasing by ~25% after initiation of therapy. It is reassuring to note the range of BNP post-treatment concentrations among those randomized to sacubitril/valsartan in PARADIGM-HF was thus lower than those seen in patients suffering from acute HF (typically in excess of 500 pg/mL); this implies patients generally resembling those randomized in PARADIGM-HF who receive sacubitril/valsartan while stable but then develop very high BNP concentrations can safely be diagnosed with acute HF in the appropriate context. However, more complex patients with higher baseline BNP values were not well-represented in PARADIGM-HF; whether similar proportional rise of BNP in such patients is expected remains unclear. More challenging will be those ARNI-treated patients presenting with ambiguous symptoms and "gray zone" BNP values (e.g., between 100 and 500 pg/mL); such patients may be incrementally more challenging to accurately triage. Regarding NT-proBNP, it is unknown if therapy with neprilysin inhibition will result in lower than expected NT-proBNP concentrations in acute HF patients, but this is important to consider when evaluating such patients. Ultimately, when interpreting either BNP or NT-proBNP in an ARNI-treated patient with acute HF, importance of good clinical history and physical examination, along with use of complementary objective tools for evaluating such patients (e.g., lung ultrasound), is emphasized.

How Durable Is the Effect of Neprilysin Inhibition on BNP Increase or NT-proBNP Decrease?

Some have suggested BNP elevation in those treated with sacubitril/valsartan in PARADIGM-HF was resolving toward baseline concentrations by 8 months, implying potential for "escape" from neprilysin inhibition. More likely to explain, this observation was the parallel reduction of BNP seen in the enalapril arm (seen in NT-proBNP values as well), implying gradual reduction of initial release of peptide over time in both arms of the trial.

Are All BNP and NT-proBNP Assays Affected the Same by Neprilysin Inhibition?

Figure 1 details the structure of BNP, the zones bound by typical immunoassays used clinically for BNP measurement, and the areas where neprilysin cleaves the BNP ring.

	Antibody	
Assay group	Capture	Detection
Group A: Alere/Beckman	Ring	N-terminus
Group B: Siemens/Bayer	Ring	C-terminus
Group C: Abbott	N-terminus	C-terminus

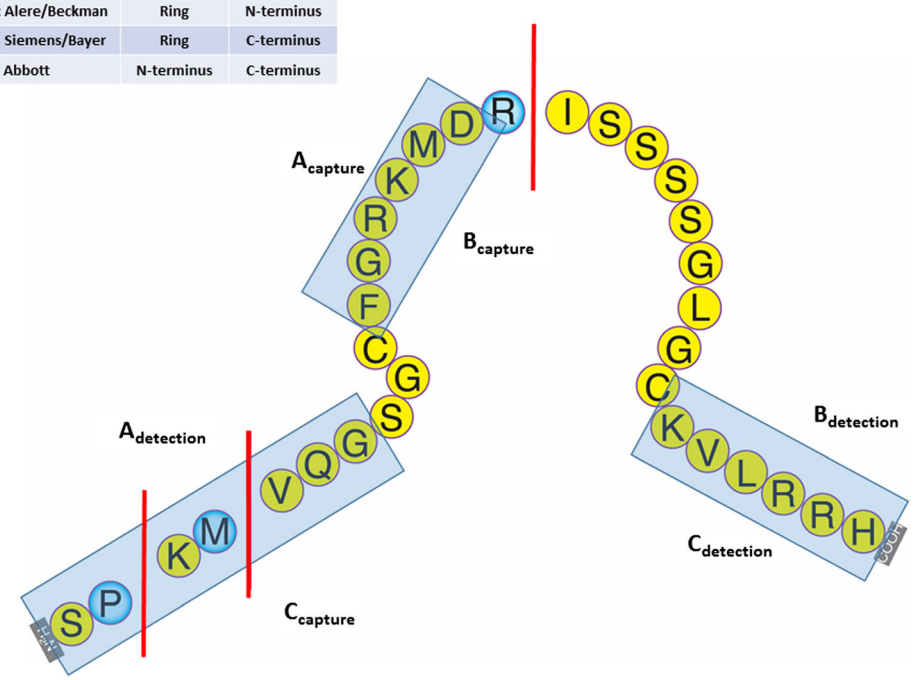

Fig. 1 The structure of BNP, the zones bound by typical immunoassays used clinically for BNP and NT-proBNP measurement, and the areas where neprilysin cleaves the BNP ring. Boxes indicate sites of binding of either the capture or detection antibodies for the tests used for BNP measurement, while the cleavage sites identified by the blue amino acid target for neprilysin along with where the peptide is divided

Early work by Norman and colleagues in 1991 using mass spectrometry demonstrated that neprilysin cleaves BNP at three distinct regions [38]. Cleavage at each site of the BNP is not simultaneous, resulting in mixtures of BNP fragments of different lengths. Given overlap of each neprilysin cleavage site with commercially available BNP assays, it is reasonable to expect all such assays to reflect a rise in BNP concentration when patients are treated with ARNI therapy; depending on the balance of degradation fragments generated, however, the degree of elevation of each BNP method may vary [39]. This may lead to clinical confusion. In the PARADIGM-HF trial, BNP concentrations were measured using only one BNP method, so assumptions about how this biomarker behaves following initiation and long-term treatment with sacubitril/valsartan apply only to this version of the BNP assay [40]. Though NT-proBNP assays are not expected to be directly influenced by neprilysin inhibition, the effects of ARNI therapy on post-translational glycosylation of NT-proBNP itself may affect results from the test [41]; data are lacking with regard to this hypothesis, however.

What About Other Biomarkers?

In the course of the PARADIGM-HF study, significant impact of sacubitril/valsartan was noted on several prognostically meaningful biomarkers. ST2 has been studied in patients with both acute and chronic HF and given a class II recommendation in current practice guidelines for risk assessment in HF [3]. ST2 is a member of the interleukin-1 receptor family and is released under conditions of mechanical myocardial strain. The role of ST2 lies in its ability to prognosticate adverse events in both acute HFrEF and HFpEF. In acute and chronic HF, concentrations of ST2 predict worsening HF, rehospitalization, heart transplantation, ventricular remodeling, and death [42]. In a post hoc analysis from PARADIGM-HF [43], O'Meara and colleagues demonstrated that the primary outcome of cardiovascular mortality or HF hospitalization occurred more frequently in those with a high ST2 at baseline versus those with a low ST2 (27.6 vs. 18.3% with primary outcome, $P < 0.0001$). Additionally, at 1 month, the geometric mean change in sST2 was − 6.5% in the sacubitril/valsartan group versus − 1.2% in the enalapril group ($P < 0.0001$), with similar results at 8 months [43].

High-sensitivity troponin (hsTn) assays detect more myocardial necrosis as compared to conventional assays, and concentrations of troponin are very frequently detectable or frankly elevated when hsTn assays are run in patients with both acute and chronic HF [44]. Concentrations of hsTn are prognostic for adverse outcomes, predict LV remodeling, and are additive to natriuretic peptides for prognostication [44]. Recent data suggest that neprilysin inhibition may similarly attenuate hsTnT in chronic HF [45]. In another post hoc analysis from PARADIGM-HF, Pandey and colleagues demonstrated that compared with enalapril, sacubitril/valsartan was associated with reduced hsTn at 1 and 8 months (both $P < 0.001$).

To further understand effects of neprilysin inhibition on BNP and NT-proBNP, the Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure (PROVE-HF) Study (NCT02887183) is currently enrolling patients. In this study, approximately 830 patients with chronic HFrEF will be initiated on sacubitril/valsartan with intensive blood sampling across a 1-year period. Among the objectives of the PROVE-HF study will be to compare effects of sacubitril/valsartan on several different BNP assays, the magnitude of BNP increase or NT-proBNP decrease after initiation, the effect of different sacubitril/valsartan doses on such changes, and the durability of effects on natriuretic peptides across the period of follow-up. Changes in BNP and NT-proBNP over a year's time will be correlated to changes in cardiac structure and function by echocardiography, and compared to symptom changes and outcomes. Results from PROVE-HF are expected in 2019.

Conclusion

With anticipated increase in the use of sacubitril/valsartan following its incorporation into clinical treatment guidelines, it is essential for the clinician to understand the effects of neprilysin inhibition on natriuretic peptide concentrations. Unlike the response to traditional GDMT, neprilysin inhibition increases BNP concentrations and reduces NT-proBNP concentrations in parallel with clinical benefit. Importantly, recent studies have demonstrated that a reduction in NT-proBNP to ≤ 1000 pg/mL with neprilysin inhibition was associated with improved cardiovascular outcomes. The PROVE-HF study will clarify many open questions about effects of ARNI therapy on numerous biomarkers, including multiple BNP assays.

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Compliance with Ethical Standards

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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 importance
- •• Of major importance

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