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Revolutionizing cardiovascular care: the role of natriuretic peptides and neprilysin inhibition

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Abstract
Cardiovascular diseases (CVDs) are the leading cause of death globally, with heart failure (HF) as a significant contributor. Biomarkers, particularly natriuretic peptides like BNP and NT-proBNP, have transformed HF diagnosis and management by offering vital insights into cardiac function and helping to distinguish cardiac from non-cardiac symptoms. Neprilysin inhibitors, such as Sacubitril/Valsartan, enhance the effects of these peptides by preventing their degradation, representing a novel therapeutic approach. This paper examines the impact of natriuretic peptides and neprilysin inhibition on HF management, highlighting their role in improving patient outcomes.

Running title: Natriuretic peptides and neprilysin in heart failure

Keywords: natriuretic peptides, BNP, NT-proBNP, neprilysin inhibitors, renin-angiotensin-aldosterone system

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year. CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. More than four out of five CVD deaths are due to heart attacks and strokes, and one third of these deaths occur prematurely in people under 70 years of age [1]. Advances in biomarker research and developments related to CVD over the past 30 years have led to more sensitive screening methods, a greater emphasis on its early detection and diagnosis, and improved treatments resulting in more favorable clinical outcomes in the community [2]. The National Institute of Health Consortium in 2001 defined a biomarker as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [3]. Useful biomarkers must meet the following criteria: (1) accuracy: that is, the ability to identify individuals at risk; (2) reliability: that is, the stability of results when repeated; and (3) therapeutic impact with early intervention [4]. Clinical management of CVDs could be facilitated by detection of blood-based biomarkers that reliably reflect the current condition of the heart [5].

The aim of this paper is to highlights the importance and therapeutics of cardiovascular disease by focusing with biomarkers such as natriuretic peptides and neprilysin inhibition in treatment of heart failure.

Natriuretic neuropeptides

Natriuretic neuropeptides – Atrial Natriuretic Peptides (ANP), B-type Natriuretic Peptide (BNP), C-type Natriuretic Peptide (CNP) are produced primarily in the cardiac atria under normal conditions. The main stimulus for ANP and BNP peptide synthesis and secretion is cardiac wall stress. Cardiac ventricular myocytes constitute the major source of BNP-related peptides. Ventricular N-terminal pro b-type natriuretic peptide (NT-proBNP) production is upregulated in cardiac failure and locally in the area surrounding a myocardial infarct. NT-proBNP is cleared passively by organs with high rate of blood flow (muscle, liver, kidney). It has a longer half life than BNP and higher plasma concentration. BNP and NTproBNP tend to be higher in women and lower in obese individuals. They are also higher in elderly, in left ventricular tachycardia, right ventricular overload, myocardial ischemia, hypoxaemia, renal dysfunction, liver cirrhosis, sepsis and infection. NT-proBNP is useful both in the diagnosis and prognosis of heart failure and is a gold standard biomarker in heart failure like BNP [6]. BNP is synthesized by human cardiac myocytes as a 108-amino acid prohormone (proBNP), which is cleaved to the 32-residue BNP and the 76-residue N-terminal fragment of proBNP (NT-proBNP) [7]. Stimulation of the natriuretic peptide receptor by BNP triggers natriuresis, diuresis, vasodilation, inhibition of renin and aldosterone and inhibition of fibrosis. BNP is removed from circulation by a receptor-mediated mechanism as well as degradation by neutral endopeptidases such as neprilysin (the same enzyme inhibited by the novel drug, LCZ696 (commercial name **Entresto** which is a combination medication which includes Sacubitril and Valsartan) [8]. Importantly, administration of LCZ696 significantly increases BNP (but not NT-proBNP) values as part of the effect of the drug. Therefore, interpretation of BNP in a patient taking LCZ696 will be challenging, if not impossible. Beyond these modes of clearance, both BNP and NT-proBNP are passively cleared by several organs including kidneys, liver, lungs, skeletal muscle and heart. The half-life of BNP is significantly shorter than that of NT-proBNP (approximately 20 vs. 60-120 minutes) [9]. In acute dyspnea, high BNP and NT-proBNP point to a cardiac rather than a pulmonary origin of the symptoms. BNP and NT-proBNP help in the assessment of the severity of ventricular dysfunction and heart failure and as a prognostic predictor, regardless of the primary cause of the condition [7]. Normally, circulating BNP and NT-proBNP levels are quite low, but in the setting of heart failure (HF) their concentrations rise dramatically. The Breathing Not Properly Multinational Study [9] demonstrated that BNP values >100 pg/mL diagnosed acute HF with high accuracy at 85% and strongly predicted of HF, outperforming clinical criteria. Similar findings were seen for NT-proBNP in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study [10] in which elevated NT-proBNP concentrations were the strongest predictor of HF compared with traditional assessment. A single NT-proBNP cutoff of 900 pg/mL provided similar diagnostic performance as BNP of 100 pg/mL, but age-stratified cutoff points for NT-proBNP (≥450 for ages <50 years, ≥900 for 50-75 years and ≥1800 pg/mL for >75 years) performed the best [11]. The best diagnostic approach for use of either BNP or NT-proBNP is to support clinical judgment, rather than replace it; indeed, both biomarkers are particularly useful when diagnostic indecision is present. Beyond their ability to *diagnose* HF when markedly elevated, both BNP and NT-proBNP are also useful to *exclude* the diagnosis when very low [12].

BNP and NT-proBNP are strong predictors of clinical outcomes in all stages of HF. In the Acute Decompensated Heart Failure National Registry (ADHERE) registry, [13] admission BNP values for acute HF decompensation in the highest quartile (BNP ≥1730 pg/mL) was associated with 2.23-fold increase in in-hospital mortality compared with

BNP in the lowest quartile (<430 pg/mL), even after adjustment for potential confounders and regardless of Ejection Fraction (EF). Likewise, NT-proBNP concentrations are strongly predictive of short and long-term clinical outcomes; admission NT-proBNP >986 pg/mL was associated with almost three-fold increase in one-year mortality (adjusted hazard ratio [HR] 2.88) [11,14]. Importantly, both absolute natriuretic peptide concentrations at discharge as well as percent change from admission to discharge provide substantially greater information regarding risk for subsequent mortality and/or rehospitalization than admission values. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) trial [15], the discharge (rather than admission) log-transformed BNP was the most important predictor of one-year mortality (HR of 1.34) and one-year death or rehospitalization (HR 1.15). This suggests a strategy of admission/discharge sampling is justifiable.

Serial measurement in chronic HF patients also strongly predict prognosis. In the Valsartan Heart Failure Trial (Val-HeFT) study [16], a four-month log-transformed continuous NT-proBNP value added incremental prognostic value to a baseline measurement in a multivariable model to predict mortality (HR = 1.99). A direction of change in NT-proBNP values over time closely reflected changes in prognosis. Patients with baseline NT-proBNP increase over four months from below the cutoff value of 1,078 pg/mL to above the cutoff value was associated with a 1.7-fold increase in risk of mortality (HR = 1.70), compared with NT-proBNP below the cutoff value throughout, and similar in risk to those whose NT-proBNP values remained high throughout (HR 1.88).

HF therapies that improve mortality and morbidity in HF reduce these natriuretic peptide values [17]. This observation has led to the concept of biomarker-guided HF management using BNP or NT-proBNP to supplement clinical judgment. Meta-analyses suggest a 20-30% mortality reduction with biomarker-guided HF care over standard HF care and prospective studies have demonstrated that serial outpatient assessment of natriuretic peptides leads to more uptitration of HF medications and decrease in natriuretic peptides [18].

ANP, BNP, CNP and urodilatin are cleaved and inactivated by a membrane bound endopeptidase, neprilysin (as well as insulin degrading enzyme). Neprilysin is found in several tissues but in especially high concentrations in the kidney. Natriuretic peptides are also cleared via the natriuretic peptide clearance receptor. Neprilysin has over 40 substrates in human biology, which act within the cardiovascular, renal, central nervous, gastrointestinal and respiratory systems. Many have vasoactive actions and others mediate metabolic and inflammatory pathways. Dissecting the main drivers of benefit (or harm) from NEPi is therefore complex. [19]. The solution to the problem of lone neprilysin inhibition appeared to be dual blockade of Renin-Angiotensin-Aldosterone System (RAAS) and the natriuretic peptide system. [20]. Neprilysin also breaks down angiotensin II. Therefore, inhibiting neprilysin alone, while raising natriuretic peptides levels, also increases angiotensin II levels (and other substrates for neprilysin such as endothelin, vasopressin, bradykinin, etc) potentially counteracting the actions of the former peptides. [21].

Discussion

The management of cardiovascular diseases, particularly heart failure (HF), has evolved significantly with the advent of biomarkers and targeted therapies. Natriuretic peptides, such as BNP and NT-proBNP, have become indispensable in HF diagnosis, prognosis, and therapeutic guidance. These biomarkers, released in response to cardiac stress, provide direct insights into cardiac function, facilitating differentiation between cardiac and non-cardiac causes of symptoms, especially in acute settings like dyspnea. As shown in studies like the Breathing Not Properly Multinational Study and the PRIDE Study, these biomarkers offer robust predictive capabilities for HF diagnosis, often outperforming traditional clinical assessments.

The therapeutic landscape for HF has also been transformed with the introduction of neprilysin inhibitors, particularly Sacubitril/Valsartan. This novel class of drugs works by preventing the degradation of beneficial peptides, including natriuretic peptides, bradykinin, and adrenomedullin, thus enhancing their cardioprotective effects. By concurrently inhibiting neprilysin and blocking the renin-angiotensin-aldosterone system (RAAS), Sacubitril/Valsartan provides a dual mechanism that addresses key pathophysiological pathways in HF: enhancing vasodilation and natriuresis while inhibiting harmful vasoconstrictive and fluid-retentive effects of angiotensin II.

Implications of natriuretic peptides in clinical practice

Natriuretic peptides, particularly BNP and NT-proBNP, not only aid in HF diagnosis but also play a crucial role in risk stratification and management decisions. Elevated levels are strongly associated with worse clinical outcomes, as evidenced by studies such as the ADHERE registry and the Val-HeFT study, where higher natriuretic peptide levels correlated with increased mortality and morbidity in HF patients . Moreover, the dynamic assessment of these biomarkers, such as measuring changes from admission to discharge or during follow-up, provides valuable prognostic information that can guide therapy adjustments. For instance, reductions in natriuretic peptide levels have been linked to improved outcomes, supporting their use in biomarker-guided therapy.

Challenges and considerations with neprilysin inhibitors

The integration of neprilysin inhibitors into clinical practice, while revolutionary, introduces challenges, particularly in the interpretation of BNP levels. Sacubitril/Valsartan increases BNP levels due to neprilysin inhibition but does not affect NT-proBNP, which remains a reliable marker of HF severity and prognosis under this treatment. This distinction necessitates careful clinical interpretation and reliance on NT-proBNP for monitoring HF in patients receiving neprilysin inhibitors, to avoid misinterpretation of BNP elevations as worsening HF.

Furthermore, neprilysin's broad substrate specificity complicates the clinical picture, as it degrades over 40 peptides involved in various physiological processes, including those related to cardiovascular, renal, and neurohormonal functions. This complexity underscores the importance of comprehensive clinical judgment when employing neprilysin inhibitors, as the modulation of these pathways can have both beneficial and potentially adverse effects.

Comparative effectiveness and future directions

Comparatively, neprilysin inhibitors have demonstrated superior efficacy over traditional RAAS inhibitors alone, as seen in clinical trials like the Prospective Comparison of ARNI (Angiotensin Receptor-Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study, where Sacubitril/Valsartan was associated with a significant reduction in HF hospitalizations and mortality compared to enalapril. These findings highlight the therapeutic potential of dual neprilysin and RAAS inhibition in optimizing HF management.

However, there remain unanswered questions regarding the long-term effects of neprilysin inhibition on non-cardiovascular pathways and the potential development of resistance or compensatory mechanisms. Future research should focus on elucidating these broader impacts and refining patient selection criteria to maximize benefits while minimizing risks. Additionally, the exploration of novel biomarkers that can complement natriuretic peptides and neprilysin inhibitors, providing more nuanced insights into HF pathophysiology and treatment response, will be crucial.

Conclusions

The integration of natriuretic peptides and neprilysin inhibition represents a paradigm shift in the management of HF, offering enhanced diagnostic accuracy and therapeutic efficacy. While challenges in biomarker interpretation and the complexity of neprilysin's actions exist, the overall impact on patient outcomes has been profoundly positive. Continued advancements in biomarker research and therapeutic innovations hold the potential to further improve the care of patients with cardiovascular diseases, ultimately aiming to reduce the global burden of HF.

Ethical Approval

The study was a descriptive one. No human or animals were a subject of examination.

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Conflict of interest

The authors declare no conflict of interest.

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