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STATE-OF-THE-ART PAPER

Combined Neprilysin and Renin-Angiotensin System Inhibition for the Treatment of Heart Failure

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ABSTRACT

Neprilysin is an enzyme that contributes to the breakdown of the biologically active natriuretic peptides and several other vasoactive compounds. Inhibiting neprilysin has been a therapeutic target for several compounds that have been tested in cardiovascular disease, including ecadotril, candoxatril, omapatrilat, and LCZ696. Although ecadotril, candoxatril, and omapatrilat were initially tested in hypertension and/or heart failure, lack of efficacy and side effects led to discontinuation of their development. LCZ696 (sacubitril valsartan) is a first-in-class angiotensin receptor neprilysin inhibitor that has been developed for use in heart failure. This compound is composed of 2 molecular moieties in a single crystalline complex—the angiotensin receptor blocker valsartan and a neprilysin inhibitor prodrug—and has now been tested in hypertension, in a phase 2 trial in heart failure with preserved ejection fraction, and has demonstrated greater efficacy than enalapril in a phase 3 trial in heart failure with reduced ejection fraction. Its ability to inhibit the renin-angiotensin-aldosterone axis and augment the endogenous natriuretic peptide system provides a distinctive mechanism of action in cardiovascular disease. (J Am Coll Cardiol HF 2014;■:■–■) © 2014 by the American College of Cardiology Foundation.

Natriuretic peptides (NPs) are a family of hormones that help maintain sodium and fluid balance. Three NPs have been identified: atrial NP (ANP), brain (or B-type) NP (BNP), and C-type NP (CNP) (1). ANP is primarily released from the cardiac atria in response to increased atrial pressure secondary to intravascular fluid overload. BNP is released mainly from the left ventricle as a result of increased filling pressure. The expression of ANP and BNP in the both the atria and ventricles is increased in the setting of cardiac hypertrophy and other conditions that increase cardiac chamber wall stress. Both ANP and BNP have multiple mechanisms of actions, including vasodilation, natriuresis, and diuresis. These mechanisms are mediated primarily through these peptides' binding to the type A receptors, which are coupled to guanylyl cyclase; activation of the receptor increases intracellular cyclic guanosine monophosphate, which mediates the physiologic effects most relevant to the cardiovascular system (2). CNP is found mostly in the central nervous system, kidneys, and vascular endothelial cells and has antithrombotic and antifibrotic effects and binds to the type B receptor. The significance of CNP to the cardiovascular system is less clear (3,4).

By regulating fluid homeostasis, ANP and BNP help protect the cardiovascular system from negative effects of fluid overload (2). NPs are secreted in response to excess plasma volume and left ventricular filling pressures, commonly found in patients with heart failure (HF), and are thus elevated in these patients (1). NPs contribute to the regulation of sodium and water balance, blood volume, arterial pressure, and sympathetic inhibition through their effects on

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ANP = atrial natriuretic peptide

BNP = brain (or B-type) natriuretic peptide

CI = confidence interval

CNP = C-type natriuretic peptide

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LVEF = left ventricular ejection fraction

NP = natriuretic peptide

NT-proBNP = N-terminal pro-brain (or B-type) natriuretic peptide

NYHA = New York Heart Association

the venous system, kidneys, and brain. NPs cause direct vasodilation, which results in decreased ventricular preload, systemic vascular resistance, and arterial pressure. Additionally, NPs increase glomerular filtration rate, resulting in natriuresis and diuresis, thus decreasing total body sodium and fluid. Finally, the NPs also reduce renin release from renal juxtaglomerular cells, thereby reducing plasma angiotensin II (and subsequent secretion of aldosterone), resulting in vasodilation. Because NPs are released in the setting of fluid overload, measurement of NPs is a reliable diagnostic marker of dyspnea due to cardiac causes and of the severity of HF (5).

NPs are cleared in several ways: receptor-mediated degradation and breakdown by extracellular proteases (6). The NP type C receptor is thought to function primarily as a "clearing" receptor that can bind all 3 NPs, resulting in receptor-mediated internalization and degradation. NPs are also broken down by the neutral endopeptidase neprilysin, also known as membrane metalloendopeptidase. Neprilysin is expressed in several tissues but most commonly in the kidney. It catalyzes the degradation of numerous endogenous peptides, such as ANP, BNP, CNP, bradykinin, substance P, adrenomedullin, glucagon, and vasoactive intestinal peptide, and also contributes to the breakdown of angiotensin II (1). Other proteases, such as insulin-degrading enzyme, may play a role in NP degradation as well, and the absence of significant physiologic alterations in mice that lack neprilysin suggest that other degradation pathways may compensate when neprilysin is absent or inhibited (7).

THERAPEUTIC TARGETING OF THE NP SYSTEM IN HF

In HF, the natural increases in NPs are ineffective at alleviating fluid overload. One treatment strategy that has been used is exogenous administration of nesiritide, a synthetic BNP drug. In the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure trial), nesiritide alleviated dyspnea at 3 h compared with placebo, and reduced pulmonary capillary wedge pressure compared with nitroglycerin, in patients with acute HF (8). Nesiritide was associated with significant hypotension, and a subsequent analysis raised concerns about its safety in HF (9). Moreover, nesiritide must be delivered intravenously, it is costly, and it has not been proven to reduce morbidity or mortality. In the largest trial to directly test the efficacy of nesiritide in acute HF, ASCEND (the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial), participants with acute HF were randomized to nesiritide or placebo plus usual care (10). The coprimary end points were reductions in death or hospitalization for HF at 30 days or reduction in self-assessed dyspnea at 6 or 24 h. Nesiritide did not reduce the rate of death or HF hospitalization at 30 days but was associated with a nonsignificant reduction in dyspnea to a modest degree.

Neprilysin inhibition represents a potential alternative strategy to exogenous BNP administration by preventing the breakdown of endogenous NPs. Candoxatril, the first neprilysin inhibitor available orally, was associated with a dose-dependent increase in ANP and natriuresis but also increased concentrations of angiotensin II because of the effect of neprilysin on the breakdown of angiotensin II (11). Candoxatril was not shown to reduce BP in patients with hypertension, it failed to show reduction in systemic vascular or pulmonary resistance in patients with HF, and its development was discontinued (12). Another neprilysin inhibitor, ecadotril, was tested in a dose-ranging study in 279 patients with HF with reduced ejection fraction (HFrEF) in which safety and efficacy were assessed (13). Patients were randomized to 1 of 5 doses of ecadotril or placebo. Plasma and urinary cyclic guanosine monophosphate were increased in a dose-dependent manner, but there were no changes in plasma renin activity, angiotensin II levels, endothelin I, norepinephrine, and N-terminal pro-BNP (NT-proBNP). There were numerically more deaths in the patients receiving ecadotril and no evidence of efficacy, so development of the compound was stopped.

Omapatrilat was the first representative drug acting through a dual neprilysin and renin-angiotensin system inhibition mechanism. As an inhibitor of both neprilysin and the angiotensin-converting enzyme (ACE), this drug proved more potent than candoxatril in lowering blood pressure (BP) and improving hemodynamics in patients with HF (14,15). Although these initial results with omapatrilat in both hypertension and HF were promising, an outcomes trial in patients with HF failed to show substantial benefit in comparison with the ACE inhibitor enalapril (16). Moreover, the high occurrence and greater severity of angioedema observed in several hypertension clinical studies resulted in withdrawal of the drug from its route to United States Food and Drug Administration approval. The increased risk for angioedema was thought to be due to an increased circulating concentration of bradykinin resulting from