Review Article

Angiotensin Receptor Neprilysin Inhibition in Heart Failure: Mechanistic Action and Clinical Impact

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ABSTRACT

Heart failure (HF) is an increasingly common syndrome associated with high mortality and economic burden, and there has been a paucity over the past decade of new pharmacotherapies that improve outcomes. However, recent data from a large randomized controlled trial compared the novel agent LCZ696, a dual-acting angiotensin receptor blocker and neprilysin inhibitor (ARNi), with the well established angiotensin-converting enzyme (ACE) inhibitor enalapril and found significant reduction in mortality among the chronic reduced ejection fraction HF population. Preclinical and clinical data suggest that neprilysin inhibition provides beneficial outcomes in HF patients by preventing the degradation of natriuretic peptides and thereby promoting natriuresis and vasodilatation and counteracting the negative cardiorenal effects of the up-regulated renin-angiotensin-aldosterone system. Agents such as omapatrilat combined neprilysin and ACE inhibition but had increased rates of angioedema. Goals of an improved safety profile provided the rationale for the development of the ARNi LCZ696. Along with significant reductions in mortality and hospitalizations, clinical trials suggest that LCZ696 may improve surrogate markers of HF severity. In this paper, we review the preclinical and clinical data that led to the development of LCZ696, the understanding of the underlying mechanistic action, and the robust clinical impact that LCZ696 may have in the near future. (*J Cardiac Fail 2015;21:741−750*)

Key Words: Angiotensin receptor neprilysin inhibition, LCZ696, heart failure.

Heart failure (HF) is a common disease that currently affects 5.7 million Americans and will affect an estimated >8 million adults, with a projected total cost of almost $70 billion, by 2030.[1] Over the past 30 years, there has been significant improvement in survival rates after the diagnosis of HF,[2] but the 5-year mortality rate remains high at ~50%[1] and the syndrome is associated with significant morbidity. The reduction in HF mortality in recent decades can be largely attributed to the discovery and implementation of optimal medical therapy including inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors[3] or angiotensin II receptor blockers (ARBs),[4] beta-blockers,[5,6] and aldosterone receptor blockers.[7] However, the past decade had been essentially void of any new pharmacotherapy offering an additional mortality benefit in HF patients until the recently published Prospective Comparison of ARNi (Angiotensin Receptor−Neprilysin Inhibitor) With ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[8] The trial demonstrated a reduction in mortality when comparing the long-term effects of LCZ696, a 1st-in-class agent that delivers simultaneous angiotensin receptor blockade (valsartan) and neprilysin inhibition (sacubitril), versus enalapril in addition to current standard of care therapy.[8] Neprilysin is a neutral endopeptidase (NEP) that is responsible for degradation of several vasoactive peptides, including natriuretic peptides (NPs),[9] and has been the therapeutic target of numerous agents over the last several decades. In this paper, we review the preclinical and clinical data related to the mechanistic action of neprilysin

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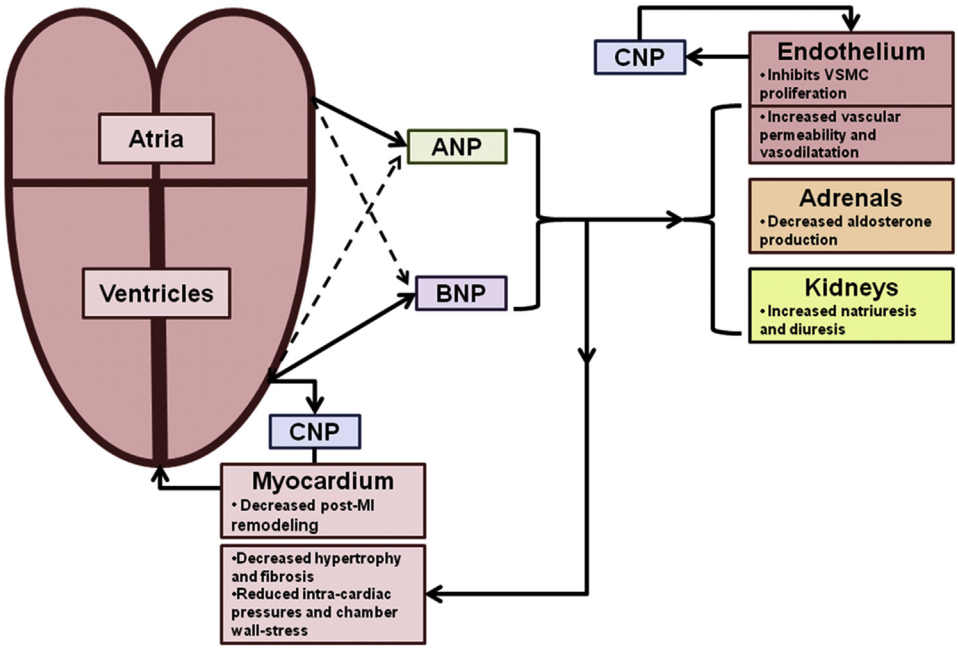

Fig. 1. Origins and sites of action of natriuretic peptides in heart failure. A-Type natriuretic peptide (ANP) is predominantly released from the atria, B-type natriuretic peptide (BNP) is predominantly released from the ventricles, and C-type natriuretic peptide (CNP) is predominantly found locally in myocardium and endothelium with minimal systemic release. In states of cardiac stress and volume overload (eg, heart failure), both ANP and BNP may be released from either cardiac chambers (dashed lines). ANP and BNP act on the endothelium to increase vascular permeability and vasodilatation, on the adrenals to inhibit aldosterone production, on the kidneys to promote natriuresis and diuresis, and at the level of myocardium to inhibit fibrosis and cellular hypertrophy leading to decreased intra-cardiac pressure and chamber wall-stress. CNP also acts on the myocardium to inhibit fibrosis and cellular hypertrophy and may decrease post−myocardial infarction (MI) remodeling. CNP acts locally on the endothelium to inhibit vascular smooth muscle cell (VSMC) proliferation as well as promote vascular permeability and vasodilatation.

inhibition combined with angiotensin receptor blockade and the clinical impact of this novel therapy in HF patients.

Natriuretic Peptides

Because one of the actions of ARNIs is to modulate NP levels, mechanistic data need to be placed in the context of the contemporary understanding of the role of NPs in HF. NPs in HF have been reviewed previously.[10] Although other NPs, such as renally produced urodilatin, may play an important role in HF[11] there are 3 main NPs that originate from cardiac tissue, A-type (or atrial) natriuretic peptide (ANP), B-type (or brain) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP; Fig. 1). In healthy subjects, ANP is mainly secreted from the atria and BNP from the ventricles, however, in patients with left ventricular (LV) dysfunction both peptides are secreted from the LV in response to wall tension to promote natriuresis, diuresis, vasodilatation, and RAAS blockade via aldosterone and renin inhibition.[10,12] These peptides therefore block the negative cardiac effects of angiotensin II (Ang II) and aldosterone in HF patients, including sodium retention, vasoconstriction, and endothelial dysfunction.[13,14] Whereas ANP and BNP predominantly serve as circulating hormones, CNP is derived from endothelial cells and synthesized in cardiac fibroblasts and may have important antiremodeling effects in the myocardium by means of local regulation of collagen synthesis and cellular hypertrophy inhibition.[15,16] These actions are all mediated by means of NP receptors via the cyclic guanosine monophosphate (cGMP) second messenger system.[17] However, as HF advances, there is inadequate activation of or a diminished response to NPs coupled with further activation of the RAAS, which ultimately overcomes the beneficial effects of the NPs and leads to neurohormonal imbalance.[18,19]

Because serum levels of NPs become elevated in HF patients, assays were developed to assess these biomarkers to diagnose and offer prognostic information related to acute decompensated heart failure (ADHF).[20] Despite high levels of circulating NPs, ADHF patients are thought to be in a state of relative BNP insufficiency[10] owing to relatively higher levels of the high-molecular-weight proBNP, which has less biologic activity than the low-molecular-weight BNP,[21] as well as increased cellular phosphodiesterase, which inhibits the downstream affects of BNP on target cells.[22]

In canine models of HF, the acute administration of subcutaneous BNP significantly improved several hemodynamic measurements, natriuresis, and diuresis.[23] These observations and additional preclinical work led to the development of nesiritide, a recombinant human BNP. A study of 489 patients with ADHF compared intravenous