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COMMENTARY

Dual inhibitory action on aldosterone by combined angiotensin receptor antagonism and neprilysin inhibition

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Noncommunicable diseases (NCDs), such as cardiovascular disease, cancer and diabetes, are the most common causes of premature death and morbidity. Hypertension and heart failure are major NCDs that, despite advances in medical therapy, continue to be associated with high morbidity and mortality. The accumulated results of clinical studies have shown that strict blood pressure (BP) control is important for efficient suppression of target organ damage and cardiovascular complications in hypertensive patients. In Japan, the major antihypertensive drugs are calcium channel blockers, angiotensin II (Ang II) type 1 receptor (AT1R) blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, diuretics, and β-blockers (including α-/β-blockers), as recommended by the international hypertension guidelines.[1–5]

The final common pathway in cardiovascular disease is heart failure, which is often mediated by progressive uncontrolled hypertension. Although several compensatory mechanisms occur in heart failure patients, including left ventricular remodeling and neurohormonal activation, these compensatory mechanisms gradually become maladaptive and lead to exacerbation of heart failure. Angiotensin-converting enzyme inhibitors, ARBs, β-blockers and aldosterone antagonists are designed to inhibit these maladaptive compensatory changes and have beneficial effects in heart failure patients with reduced ejection fraction.[6] However, despite treatment with these recommended drugs, mortality from heart failure remains high.[7] Therefore, there is an urgent need for the development of innovative therapeutic agents that better control BP and have therapeutic potential in the context of heart failure.

The natriuretic peptide system consists primarily of three well-characterized and structurally similar peptides, each of which is a distinct gene product: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), produced mainly by cardiomyocytes, and C-type natriuretic peptide (CNP), produced mostly by endothelial and renal cells. These natriuretic peptides (ANP, BNP and CNP) interact with their respective receptors, guanylyl cyclase-A (GC-A) and guanylyl cyclase-B (GC-B). ANP and BNP bind to GC-A, and CNP binds to GC-B to generate the second messenger cyclic guanosine 3′–5′ monophosphate (cGMP). The cGMP produced by these interactions mediates potent natriuretic and vasodilatory properties, inhibiting the activity of the renin–angiotensin system (RAS), lowering sympathetic drive, and producing antiproliferative and antihypertrophic effects. This nucleotide therefore exerts cardioprotective and renal-protective effects.[8] These natriuretic peptides (ANP, BNP and CNP) are cleared by a clearance receptor, natriuretic peptide receptor-C (NPR-C), which is not linked to a GC.

In addition, these natriuretic peptides (ANP, BNP and CNP) are cleared from the circulation via enzymatic degradation by neutral endopeptidase-24.11 (neprilysin). Neprilysin is a zinc-dependent, membrane-bound endopeptidase that hydrolyzes peptides on the amino side of hydrophobic residues, and is critical for the processing and catabolism of vasoactive peptides, and peptides involved in diuresis and natriuresis, for example, the natriuretic peptides, angiotensin I, bradykinin (BK) and endothelin-1 (ET-1).[8] In mammals, neprilysin is widely expressed, for example, in kidney, lung and endothelial cells; vascular smooth muscle cells; cardiac myocytes, fibroblasts, neutrophils and adipocytes; the testes; and the brain. The highest concentrations are found in the renal proximal tubule.

Studies have shown dysregulation of the natriuretic peptide system in cardiovascular and renal diseases, including hypertension and heart failure. Therefore, pharmacological strategies for enhancing the actions of these natriuretic peptides (ANP, BNP and CNP) have included exogenous administration of endogenous peptides or degradation-resistant peptides as well as the use of neprilysin inhibitors. However, neprilysin also contributes to the breakdown of other vasoactive peptides with opposing physiological actions. Therefore, although neprilysin inhibitors would cause increases in the circulating levels of the natriuretic peptides and BK, they would also increase the vasoconstrictors Ang II and ET-1. Indeed, the results of clinical studies of neprilysin inhibition in the treatment of heart failure and hypertension have failed to show clear therapeutic benefits, thereby supporting the notion that clinically therapeutic benefits of neprilysin inhibition may not be realized unless there is simultaneous suppression of the RAS and/or ET-1.

LCZ696 is the first of a new class of drugs to employ this potential therapeutic strategy in cardiovascular and renal diseases. It

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combines the ARB, valsartan, and the neprilysin inhibitor prodrug sacubitril (AHU377) in a 1:1 ratio in a sodium supramolecular complex.[9,10] Sacubitril is then rapidly metabolized by nonspecific esterases to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, the enzyme responsible for the degradation of the natriuretic peptides and other vasoactive peptides, as described above. Therefore, the combined ARB/neprilysin inhibitor, LCZ696, is able to address two pathophysiological mechanisms underlying certain cardiovascular and renal diseases, including hypertension and heart failure: activation of the RAS and decreased sensitivity to natriuretic peptides caused by the dysregulation of the natriuretic peptide system that occurs in these pathological situations.

Clinical studies of LCZ696 in the treatment of hypertension and heart failure have shown promising therapeutic benefits. Previous studies have demonstrated that patients with mild-to-moderate hypertension treated with LCZ696 had significantly lower office and ambulatory BP than those treated with valsartan or placebo.[11–13] Furthermore, in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, LCZ696 significantly reduced mortality and hospitalization for heart failure in addition to lowering BP. Its performance was superior to that of enalapril in heart failure patients with reduced ejection fraction,[14] and the US Food and Drug Administration approved LCZ696 for the treatment of heart failure.

Activation of the circulating and tissue RAS also stimulates the aldosterone-mineralocorticoid receptor pathway and promotes the cardiovascular remodeling that accompanies hypertension and chronic kidney disease.[15,16] It is well-known that ARBs decrease aldosterone production and increase natriuresis by blocking adrenal AT1R. ARBs also decrease cardiac, vascular and renal injuries by decreasing AT1R-, mineralocorticoid receptor- and aldosterone-mediated hypertrophy; inflammation; and fibrosis. However, long-term administration of ARBs, like long-term administration of ACE inhibitors, causes circulating aldosterone concentrations to 'escape' back to baseline levels, providing the rationale for the concurrent use of antagonists of the aldosterone-mineralocorticoid receptor pathway. Although it is thought that neprilysin enhances the natriuretic peptide-evoked signals that can block Ang II/AT1R-induced aldosterone production, the exact relevant mechanisms of the beneficial inhibitory effects of LCZ696 on the aldosterone-mineralocorticoid receptor pathway remain to be elucidated. Indeed, in one study, LCZ696 treatment significantly increased the circulating ANP and cGMP concentrations, but did not affect plasma aldosterone concentration compared with placebo in hypertensive patients.[11]

Interestingly, Miura *et al.*,[17] as reported in this issue, examined the effects of valsartan, ARB and LBQ657—the active moiety of LCZ696—on aldosterone synthesis in a human adrenocortical cell line (NCI-H295R cells) to investigate the possible mechanisms of the beneficial effects of LCZ696.[17] Although there was no difference in the dissociation from AT1R between valsartan +LBQ657 and valsartan alone, the binding affinity of valsartan+LBQ657 to AT1R was greater than that of valsartan alone in an AT1R-expressing human embryonic kidney cell-based living assay.[17] The authors also showed that the natriuretic peptide-mediated suppression of aldosterone synthesis was further augmented by co-administration of LBQ657.[17] Collectively, the authors demonstrated that the combined AT1R antagonism by valsartan and LBQ657 neprilysin inhibition significantly enhanced the natriuretic peptide-mediated signaling effects to suppress Ang II-AT1R-induced aldosterone production in adrenocortical cells, without affecting the expression of aldosterone synthase genes[17] (Figure 1). The results revealed a dual inhibitory action of LCZ696 on the aldosterone cascade as an important drug property and revealed a new aspect of the mechanism of LCZ696-mediated beneficial effects in cardiovascular and renal physiology, thereby contributing an interesting finding to the field of hypertension research.

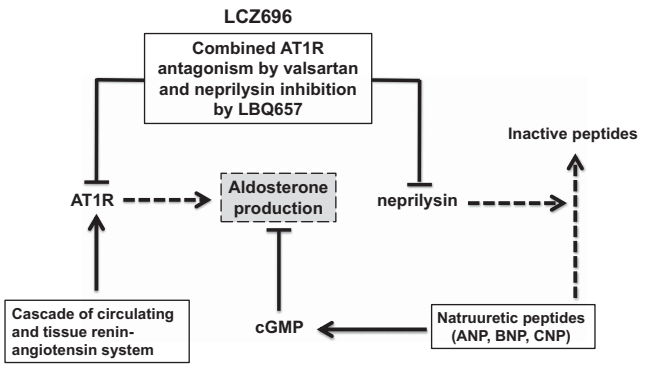

Figure 1 Schema of the dual inhibitory action on aldosterone production by combined angiotensin receptor antagonism and neprilysin inhibition. The dotted arrows indicate inhibited action or cascade by LCZ696. ANP, atrial natriuretic peptide; AT1R, angiotensin II type 1 receptor; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine 3′–5′ monophosphate; CNP, C-type natriuretic peptide; LBQ657, active moiety of LCZ696; LCZ696, valsartan/sacubitril.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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