

ROLE OF NEPRILYSIN INHIBITORS COMBINATIONS IN CARDIOVASCULAR DISEASE

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ABSTRACT

Neprilysin is a neutral endopeptidase enzyme that contributes to the breakdown of the biologically active natriuretic peptides and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatory, and anti-proliferative effects. Inhibiting neprilysin has been a therapeutic target for several compounds that have been tested in cardiovascular disease, including ecdotril, candoxatril, omapatrilat, and LCZ696 (Valsartan/sacubitril). Although ecdotril, 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 is a first-in-class angiotensin receptor Neprilysin inhibitor that

has been developed for use in heart failure. In concert, these effects are prone to produce a powerful ventricular unloading and antihypertensive response. Some specific advantage of this drug like a) novel mechanism of action, pharmacokinetics, and pharmacodynamics b) In hypertension available data of trials better efficacy, safety, and tolerability of LCZ696 c) evidence from other contemporary trials on combined Neprilysin inhibitors d) In future trials and areas of research, LCZ696 combination is most benefit in hypertensive patient. In future prospect, Neprilysin inhibitors alone and its combination with other antihypertensive agents use in cardiovascular disease.

KEYWORDS: Natriuretic peptide, Neprilysin, LCZ696 (Valsartan + Sacubitril)

INTRODUCTION

More than 20 million people suffering from heart failure worldwide. Incidence of heart failure in developed countries is 2 % and approaches 6-10 % in people aged more than 65

years. The cardiovascular complications of diabetes were previously considered to be caused by structural changes with very slow progression. Historically, with the available methodology, abnormal deposition of extracellular material was studied more extensively than were changes in cellular function. It is now recognized that, on the functional level, cardiovascular dysfunction during deregulated metabolism occurs soon after the onset of metabolic abnormalities, long before the appearance of histopathological changes, and that such dysfunction is regulated by dynamic and complex mechanisms on the cellular and molecular levels.^[1]

Type 2 diabetes mellitus is mainly characterized by the development of increased morbidity and mortality for cardiovascular disease (CVD), so that it has been suggested that diabetes may be considered a cardiovascular disease.^[2] Symptomatic management by diuretics and oral inotropic agent digoxin, the advent of Angiotensive converting enzymes I (ACEI) cause transition in treatment aspect of heart failure. The two distinct advantages of ACEI are good safety margin and ability to reverse the myocardial remodeling is the main reason for selecting them as first line management of heart failure even in asymptomatic high cardiovascular risk patients and some antihypertensive agents also use in cardiovascular complication in diabetes like Valsartan.^[3-4]

WHAT IS NATRIURETIC PEPTIDE AND NEPRILYSIN?

Natriuretic peptides are produced from atrium, brain and named as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) respectively, in addition to c- type natriuretic peptide (CNP). These peptides exert their action by binding natriuretic peptides receptors and activate guanyl cyclase and produces vasodilation. Brain Natriuretic peptide is produced by any factors that stretch atria and its plasma concentration is used as diagnostic tool in assessment of heart failure. Recently, the recombinant form brain natriuretic peptide, Nesiritide is indicated for acute severe heart failure and given as intravenous bolus infusion at the rate of 0.01-0.03microg/kg/minute.

Apart from vasodilation, pleiotropic effects of natriuretic peptide's includes diuresis, decreased sympathetic activation and inhibition rennin angiotensin system, decreases mesangial cell proliferation, attenuation of endothelins, control of and smooth muscle cells and fibroblast proliferation in the vessels.^[5]

Neprilysin, also known as membrane metallo-endopeptidase (MME), neutral endopeptidase, cluster of differentiation 10, and common acute lymphoblastic leukemia antigen is an enzyme that in humans is encoded by the MME gene. Neprilysin is a zinc-dependent metalloprotease that cleaves peptides at the amino side of hydrophobic residues and inactivates several peptide hormones including glucagon, enkephalins, substance P, neurotensin, oxytocin, and bradykinin. It also degrades the amyloid beta peptide whose abnormal misfolding and aggregation in neural tissue has been implicated as a cause of Alzheimer's disease. Synthesized as a membrane-bound protein, the neprilysin ectodomain is released into the extracellular domain after it has been transported from the Golgi apparatus to the cell surface. Neprilysin is expressed in a wide variety of tissues and is particularly abundant in kidney. It is also a common acute lymphocytic leukemia antigen that is an important cell surface marker in the diagnosis of human acute lymphocytic leukemia (ALL). This protein is present on leukemic cells of pre-B phenotype, which represent 85% of cases of ALL.

WHAT IS NEPRILYSIN INHIBITION?

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. Neprilysin has been called many other names, including enkephalinase, neutral endopeptidase (NEP), vasopeptidase, and atriopetidase. Degradation by neprilysin is one of the two major means of elimination of natriuretic peptides, the other being through a clearance receptor (the natriuretic peptide clearance receptor; NPRC or NPR3). Inhibition of neprilysin, therefore, represents one approach to enhancing endogenous natriuretic peptide levels and activity.

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. Another Neprilysin inhibitor, ecdotril, was tested in a dose-ranging study in 279 patients with HF with reduced ejection fraction (HFrEF) in which safety and efficacy were assessed. Patients were randomized to 1 of 5 doses of ecdotril 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. 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. 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 the inhibition of 3 proteases - ACE, aminopeptidase, and neprilysin - which all contribute to its degradation, with resulting increased vasodilation and vascular permeability.

WHAT IS THE ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITORS LCZ696?

LCZ696 (Sacubitril/Valsartan) is a first-in-class angiotensin receptor neprilysin inhibitor. LCZ696 is a novel, dual-acting crystalline complex composed of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan in their anionic forms, sodium cations, and water molecules (Figure 1). Soon after oral ingestion, LCZ696 dissociates into sacubitril (a neprilysin inhibitor prodrug, AHU-377, which is enzymatically cleaved to the active form, LBQ657) and valsartan. LCZ696 was designed to have a reduced risk for angioedema because it inhibits only one of the enzymes responsible for bradykinin breakdown.

In a single-dose pharmacokinetic study, Valsartan and AHU377 were rapidly absorbed after LCZ696 administration, with maximal concentrations achieved at between 1.7 to 2.2 h and 0.5 to 1.1 h after dosing, respectively. Conversion of the prodrug sacubitril to LBQ657, the active compound, occurs within 3.5 h of ingestion. The LBQ657 component exhibits dose-related increases in maximal concentration and area under the concentration-versus-time curve. The half-lives of LBQ657 and valsartan are similar at 12 and 14 h, respectively, allowing twice daily administration. In a multidose study, similar to the single-dose study, peak plasma concentrations were rapidly reached for LCZ696, sacubitril, and LBQ657, which indicates rapid breakdown and absorption. A comparison of maximal concentration and areas

under the curve between days 1 and 14 of the trial revealed no significant accumulation for valsartan or sacubitril and only a minor amount of accumulation of LBQ657. The dose-normalized bioavailability of the valsartan component of LCZ696 is 40% to 60% higher than would be delivered by the equimolar amount of Valsartan as an individual drug. This increased bioavailability may be due in part to the fact that valsartan in LCZ is present in its anionic form, whereas is normally in the form of a free acid.^[6]

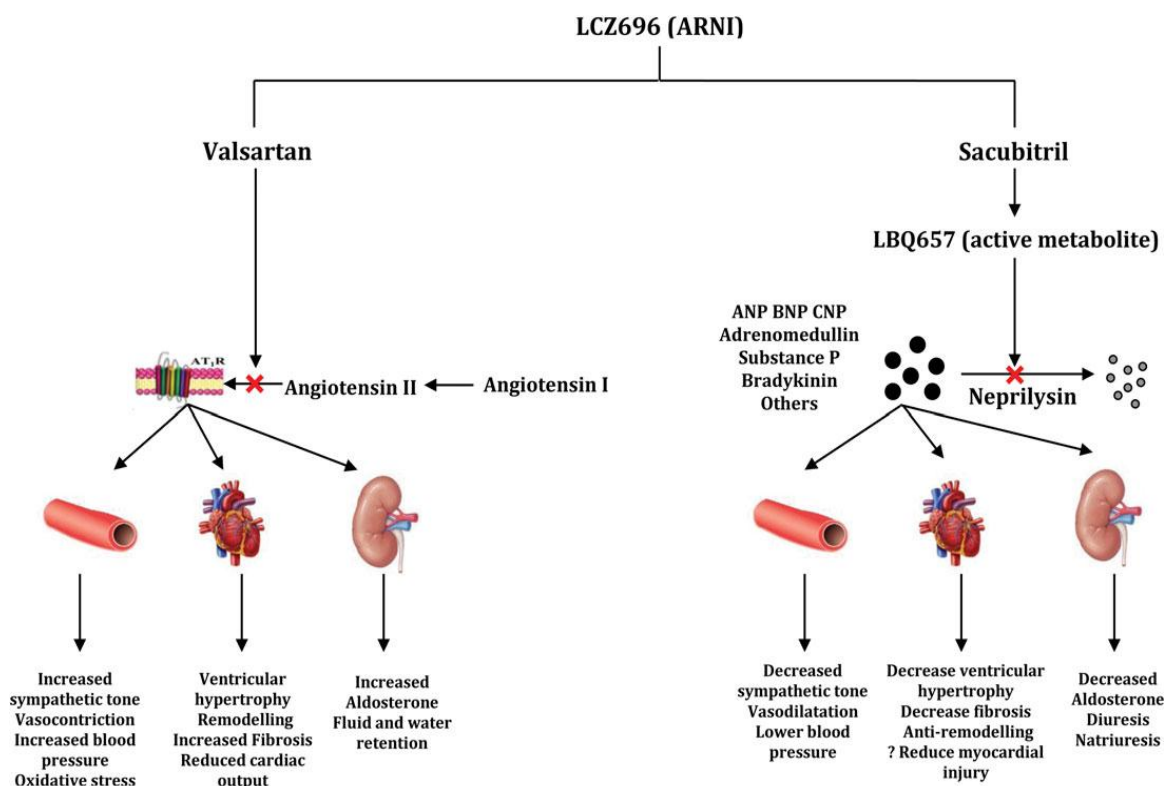


Figure 1: Mechanism of Action of LCZ696^[7]

In a bioavailability study, the mean plasma concentration-time curves of valsartan 320 mg and LCZ696 400 mg were very similar, meeting criteria for drug bioequivalence for systemic exposure of valsartan. There are limited data regarding metabolic pathways for sacubitril and LBQ657 and their alteration of metabolism of drugs that are substrates for the CYP450 system.^[6]

MEDICAL USE OF LCZ696 (VALSARTAN + SACUBITRIL)

Valsartan/sacubitril is used to treat heart failure in people with reduced left ventricular ejection fraction (LVEF).^[8] It is not known whether valsartan/sacubitril is useful for the treatment of heart failure people with normal LVEF.^[9]

The Paradigm-HF trial compared treatment with valsartan/sacubitril to treatment with enalapril. People with heart failure and reduced LVEF were sequentially treated on a short term basis with enalapril and then with valsartan/sacubitril. Those that were able to tolerate both regimens (8442, 80%) were randomly assigned to long-term treatment with either enalapril or valsartan/sacubitril. Participants were mainly white (66%), male (78%), middle aged (median 63.8 +/- 11 years) with NYHA stage II (71.6%) or stage III (23.1%) heart failure.^[9]

Some specific advantage of this drug like a) novel mechanism of action, pharmacokinetics, and pharmacodynamics b) In hypertension available data of trials better efficacy, safety, and tolerability of LCZ696 c) evidence from other contemporary trials on combined Neprilysin inhibitors d) In future trials and areas of research, LCZ696 combination is most benefit in hypertensive patient.

The trial was stopped early after a prespecified interim analysis revealed a reduction in the primary endpoint of cardiovascular death or heart failure in the valsartan/sacubitril group relative to those treated with enalapril. Taken individually, the reductions in cardiovascular death and heart failure hospitalizations retained statistical significance.^[10] Relative to enalapril, valsartan-sacubitril provided reductions^[9] in

- ✚ The composite endpoint of cardiovascular death or hospitalization for heart failure (incidence 21.8% vs 26.5%)
- ✚ Cardiovascular death (incidence 13.3% vs 16.5%)
- ✚ First hospitalization for worsening heart failure (incidence 12.8% vs 15.6%), and
- ✚ All cause mortality (incidence 17.0% vs 19.8%)

The favorable effect of valsartan/sacubitril was seen in all subgroups examined, including those based on age, sex, weight, race, NYHA class, presence or absence of reduced kidney function, diabetes mellitus, atrial fibrillation, hypertension, and prior hospitalization. Limitations of the trial include limited representation of important subgroups, such as blacks and those with implantable pacemakers, and lack of data regarding those with NYHA heart failure stages other than II or III.^[9]

DISADVANTAGE OF NEPRILYSIN INHIBITION

In addition to angioedema, concern has been raised that Neprilysin inhibition might lead to accumulation of amyloid-beta peptides in the brain as this enzyme is one of the clearance

mechanisms for these neurotoxins which are implicated in the development of Alzheimer's disease. LBQ657 does cross the blood-brain barrier and in short-term studies increases cerebrospinal fluid (CSF) amyloid-beta peptides in cynomolgus monkeys and amyloid beta-38 in human CSF but does not increase amyloid-beta peptide levels in the brain tissue of monkeys. As multiple other enzymatic pathways (possibly as many as 20) and transport proteins are involved in the clearance of amyloid-beta peptides in the brain, it is not known whether long-term neprilysin inhibition might have a significant effect on accumulation of these peptides.

Common adverse effects the main study were cough, hyperkalemia (high potassium levels in the blood, which can be caused by valsartan), kidney dysfunction, and hypotension (low blood pressure, a common side effect of vasodilators and ECF volume reducers). 12% of the patients withdrew from the study during the run-in phase because of such events. Valsartan/sacubitril is contraindicated in pregnancy because it contains valsartan, a known risk for birth defects.

CONCLUSION

Most of alone and combination antihypertensive drugs therapy, allows lowering of BP with comfort and convenience. Many drugs have an adverse effect only one day treatment and some resistant hypertension can most often be managed with combination therapy without causing inconvenient adverse effects. Some drug side effect is initial BP decreases to about the same extent whether therapy is initiated with a diuretic, a calcium-channel blocker, a beta-blocker, or renin angiotensive blocker. This would indicate that the risk/benefit ratio of many antihypertensive drugs is exceedingly low. Dual inhibition of the renin-angiotensin-aldosterone system and neprilysin inhibition represent a novel approach to treating patients with HF and hypertension. Clearly, this represents a challenging milieu for introducing a new drug class. The outcomes data so far accumulated in heart failure or other cardiovascular disease seem to indicate that this may be indeed the case with Neprilysin inhibitors and its combination therapy. In future this group of drugs may be more beneficial for cardiovascular disease management.

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