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

Orly Vardeny, PharmD, MS Ryan Miller, BS Scott D. Solomon, MD

PII: S2213-1779(14)00338-2

DOI: 10.1016/j.jchf.2014.09.001

Reference: JCHF 199

To appear in: *JACC: Heart Failure*

Received Date: 7 August 2014

Revised Date: 10 September 2014

Accepted Date: 10 September 2014

Please cite this article as: Vardeny O, Miller R, Solomon SD, Combined Neprilysin and Renin-Angiotensin System Inhibition for the Treatment of Heart Failure, *JACC: Heart Failure* (2014), doi: 10.1016/j.jchf.2014.09.001.

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

Orly Vardeny, PharmD, MS, Ryan Miller, BS, and Scott D. Solomon, MD

From the University of Wisconsin School of Pharmacy (O.V., R.M.), Madison, WI, USA; Brigham and Women's Hospital, Boston, MA, USA (S.D.S.)

Short title: Neprilysin inhibition in heart failure

Address for Correspondence:
Orly Vardeny, PharmD, MS
University of Wisconsin School of Pharmacy
777 Highland Avenue
Madison, WI 53705-2222
USA
Phone: 608.265.0591
Fax: 608.265.5421
Email: ovardeny@pharmacy.wisc.edu

Word count: 4115 (including references)

Disclosures: Dr. Solomon has received research support in the form of grants to Brigham and Women's Hospital from Novartis. He has consulted for Novartis and Bayer. Dr. Vardeny has no disclosures. Ryan Miller – none.

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, candoxetril, omapatrilat and LCZ696. While ecadotril, candoxetril 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 (ARNI) that has been developed for use in heart failure. This compound is comprised of two molecular moieties in a single crystalline complex – an angiotensin receptor blocker valsartan, and a neprilysin inhibitor pro-drug – and has now been tested in hypertension, in a phase II trial in heart failure with preserved ejection fraction (HFpEF), and has demonstrated greater efficacy than enalapril in a phase III 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.

Keywords: natriuretic peptide, neprilysin, heart failure

Neprilysin, the Natriuretic Peptide System, and other vasoactive peptides

Introduction

Natriuretic peptides are a family of hormones that help maintain sodium and fluid balance. Three natriuretic peptides have been identified: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) (1). ANP is primarily released from cardiac atria in response to increased atrial pressure secondary to intravascular fluid overload. BNP is released primarily from the left ventricle as a result of increased filling pressure. The expression of both ANP and BNP in the both 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 primarily mediated through these peptides binding to the type A (NPR-A) receptors which are coupled to guanylyl cyclase; activation of the receptor increases intracellular cyclic GMP, which mediates the physiologic effects most relevant to the cardiovascular system (2). CNP is mostly found in the central nervous system, kidneys and vascular endothelial cells, and has antithrombotic and anti-fibrotic effects and binds to the type B (NPR-B) receptor. The significance of CNP to the cardiovascular system is less clear (3,4).

By regulating fluid homeostasis, the natriuretic peptides 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 CHF, 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 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 (GFR) 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 natriuretic peptides 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 heart failure (5).

NPs are cleared in several ways; receptor mediated degradation and breakdown by extracellular proteases (6). The NPRC receptor is thought to function primarily as a "clearing" receptor which can bind all three natriuretic peptides resulting in receptor-mediated internalization and degradation. Natriuretic peptides are also broken down by the neutral endopeptidase neprilysin, also known as membrane metallo-endopeptidase. 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, andrenomedullin, glucagon, 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 lack of significant physiologic alterations in mice who lack neprilysin suggest that other degradation pathways may compensate when neprilysin is absent or inhibited (7).

Therapeutic targeting of the NP system in Heart Failure

In heart failure, the natural rise in natriuretic peptides are ineffective at alleviating fluid overload. One treatment strategy that has been employed is exogenous administration of nesiritide, a synthetic BNP drug. In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, nesiritide improved dyspnea at 3 hours compared to placebo, and

reduced pulmonary capillary wedge pressure compared to nitroglycerin, in patients with acute heart failure (8). Nesiritide was associated with significant hypotension, and a subsequent analysis raised concerns about its safety in heart failure (9). Moreover, nesiritide must be delivered intravenously, is costly, and has not proven to reduce morbidity or mortality. In the largest trial to directly test the efficacy of nesiritide in acute heart failure, ASCEND, participants with acute heart failure were randomized to nesiritide or placebo plus usual care.(10) The co-primary endpoints were reductions in death or hospitalization for heart at 30 days or improvement in self-assessed dyspnea at 6 or 24 hours. Nesiritide did not reduce the rate of death or HF hospitalization at 30 days, but was associated with a non-significant improvement in dyspnea to a modest degree.

Neprilysin inhibition represents a potential alternative strategy to exogenous BNP administration by preventing the breakdown of endogenous natriuretic peptides. 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 hypertensive individuals, failed to show reduction in systemic vascular or pulmonary resistance in heart failure patients, and its development was discontinued (12). Another neprilysin inhibitor, ecadotril, was tested in a dose-ranging study in 279 heart failure with reduced ejection fraction patients in which safety and efficacy were assessed (13). Patients were randomized to one of five doses of ecadotril or placebo. Plasma and urinary cGMP were increased in a dose-dependent manner, but there were no changes in plasma renin activity, angiotensin II levels, endothelin I, norepinephrine or NT-proBNP. There were numerically more deaths in the patients receiving ecadotril and no evidence of efficacy, so development of the compound was discontinued.

Omapatrilat was the first representative drug acting through a dual neprilysin—renin-angiotensin system (RAS) 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 and improving hemodynamics in patients with heart failure (14,15). While these initial results with omapatrilat in both hypertension and heart failure were promising, an outcomes trial in heart failure 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 FDA approval. The increased risk of angioedema was thought to be due to an increased circulating concentration of bradykinin resulting from inhibition of three proteases – ACE, aminopeptidase and neprilysin – which all contribute to its degradation, with resulting increased vasodilation and vascular permeability.

The Angiotensin receptor neprilysin inhibitor LCZ696

LCZ696 (sacubitril-valsartan) is a first in class angiotensin receptor neprilysin inhibitor (ARNI). LCZ696 is a novel, dual-acting crystalline complex comprised of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan in their anionic forms, sodium cations and water molecules. Soon after oral ingestion, LCZ696 dissociates into sacubitril (a neprilysin inhibitor pro-drug AHU-377, which is enzymatically cleaved to the active form LBQ657) and valsartan (17). LCZ696 was designed to have a reduced risk of angioedema owing to the fact that it only inhibits one of the enzymes responsible for bradykinin breakdown.

In a single dose pharmacokinetic study, valsartan and AHU377 were rapidly absorbed following LCZ696 administration with a maximum concentration achieved between 1.7-2.2 and 0.5-1.1 hours after dosing, respectively.(18) Conversion of the pro-drug sacubitril to LBQ657,

the active compound, occurs within 3.5 hours of ingestion. The LBQ657 component exhibits dose related increases in maximal concentration and AUC (concentration versus time curve). Half-lives of LBQ657 and valsartan are similar at 12 hours and 14 hours, respectively, allowing for twice daily administration.

In a multi-dose 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 AUC values 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%-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. In a bioavailability study, the mean plasma concentration time curves of valsartan 320mg 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 which are substrates for the CYP450 system.

CLINICAL TRIALS OF LCZ696

There have been relatively few clinical trials of LCZ696, although these include trials in hypertension, heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

Hypertension

Similarly to omapatrilat, LCZ696 is a potent blood pressure reducing agent. In a randomized, double-blind, placebo-controlled, active comparator study, the antihypertensive effects of LCZ696 were compared with those of the angiotensin-receptor blocker valsartan (19). The study enrolled 1328 patients aged 18-75 with mild-to-moderate hypertension. Patients were randomly assigned to one of 8 treatment arms for a duration of 8 weeks: LCZ696 at doses of 100 mg, 200 mg or 400 mg were compared to valsartan at doses of 80 mg, 160 mg, or 320 mg, or AHU377 (the neprilysin inhibitor alone) at a dose of 200 mg; or placebo. All patients underwent a 2 week wash out period and a 2 week placebo period prior to randomization to control for previous treatment with other anti-hypertensives. The primary endpoint of this trial was the mean blood pressure difference across three single-dose pairwise comparisons between LCZ696 and valsartan (100 mg vs 80 mg, 200 mg vs 160 mg, and 400 mg vs 320 mg). In the 1215 patients who completed 8 weeks of therapy, both systolic and diastolic blood pressure was significantly reduced in participants receiving LCZ 200mg compared with valsartan 160mg, and in those receiving LCZ 400mg compared with valsartan 320mg. Ambulatory blood pressure was also significantly reduced at these doses. The study reported similar overall numbers of adverse events and no occurrences of angioedema.

A second hypertension trial evaluating the safety and efficacy of LCZ696 in 389 Asian individuals using 24-hour BP monitoring showed similar efficacy with LCZ696.(20) Patients were randomized to LCZ696 100mg, 200mg, 400mg or placebo for 8 weeks. In 362 completers, all doses of LCZ696 were associated with significant reduction in systolic and diastolic pressures, pulse pressure, as well as significant reductions in 24 hour, daytime and nighttime ambulatory systolic, diastolic and pulse pressures for all doses. Moreover, in this study LCZ696 was well tolerated.

LCZ in Heart Failure with Preserved Ejection Fraction (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) accounts for up to 50% of patients with HFpEF (21). Despite the fact that patients hospitalized with HFpEF have similar overall mortality as patients with HFrEF, no specific therapies have proven benefit in HFpEF. The ability of the angiotensin receptor neprilysin inhibitor to simultaneously inhibit the renin-angiotensin aldosterone axis and augment endogenous natriuretic peptides provided the rationale for testing this therapy in heart failure across the spectrum of ejection fraction. The PARAMOUNT trial assessed the efficacy LCZ696 in patients with heart failure preserved ejection fraction (22). Inclusion in this trial required patients to have an ejection fraction equal to or greater than 45%, signs and symptoms of heart failure, and elevation of NT-proBNP. Patients were randomized to LCZ696 200 mg b.i.d. or valsartan 160 mg b.i.d., which is the bioequivalent amount of valsartan in that dose of LCZ696. The primary endpoint of the trial was change in NT-proBNP level from baseline to 12 weeks. NT-proBNP is not a substrate for neprilysin and thus remains an accurate measure of the severity of heart failure even in the setting of neprilysin inhibition. Patients were followed through 36 weeks for additional endpoints.

By 4 weeks, NT-proBNP level was reduced in the LCZ 696 arm, and was significantly reduced by 26% compared with valsartan at 12 weeks, meeting the primary endpoint. In addition, at 36 weeks, patients in the LCZ arm had greater improvement in left atrial size and greater improvement in NYHA class. These findings were similar in all pre-specified subgroups. NT-proBNP reduction was sustained in the LCZ arm through 36 weeks, though by 36 weeks, NT-proBNP had declined in the valsartan arm so that levels were no longer significantly different. Blood pressure was lowered to a greater extent in the LCZ696 arm. Nevertheless, subsequent analyses have shown that the effect on reduction in NT-proBNP, improvement in LA

size and NYHA class were independent of the blood pressure lowering effect (23). Moreover, despite the substantial reduction in blood pressure in the LCZ696 arm, eGFR was not reduced in patients receiving LCZ696 and was significantly higher than in those receiving valsartan. LCZ696 was well tolerated in these patients, with no significant differences in adverse events between groups.

These hypothesis generating findings have provided the rationale for a large outcomes trial in HFpEF. PARAGON-HF (NCT 01920711) will utilize a similar overall study design to PARAMOUNT to determine whether LCZ can reduce cardiovascular death or total heart failure hospitalizations in patients with HFpEF. PARAGON-HF will enroll 4300 patients with HFpEF, LVEF >= 45%, history of heart failure hospitalization within 9 months or elevated natriuretic peptides, and evidence of structural heart disease, evidenced by left ventricular hypertrophy or left atrial enlargement. The primary endpoint for the trial will be a composite of cardiovascular death or total heart failure hospitalizations utilizing recurrent event methods.

Heart Failure with Reduced Ejection Fraction

The PARADIGM trial was designed to test the hypothesis that LCZ696 could result in reduced morbidity and mortality in patients with heart failure and reduced ejection fraction (LVEF <= 40%). Inclusion criteria included NYHA functional class II–IV, LVEF ≤40%, plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL), or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) if the patient was previously hospitalized for heart failure within the last 12 months. Patients were required to be taking a stable dose of an ACE inhibitor or ARB equivalent to enalapril ≥10mg daily for at least 4 weeks prior to screening. Other inclusion criteria included eGFR ≥30 mL/min/1.73 m2, systolic BP ≥95 mmHg, and potassium ≤5.4 mmol/L. The primary endpoint was the composite of cardiovascular mortality or hospitalization for heart failure.

Secondary endpoints included time to worsening of renal function and all-cause mortality. PARADIGM employed a unique study design, with a single-blind active run-in period designed to ensure that patients tolerated both study drugs. Patients who completed run-in were randomly assigned to LCZ696 200mg bid or enalapril 10mg bid in a double-blind fashion (24). The run-in period afforded the data safety monitoring board early information regarding measures of safety, including hypotension, renal function and hyperkalemia since prior experience with this drug in heart failure had been extremely limited. Enalapril 10mg bid was utilized as the active compared as this has been considered both standard of care and the regulatory gold standard in heart failure. A sample size of approximately 8000 patients was required to have 80% power to reduce cardiovascular death by 15%. This number of patients provided > 97% power to reduce the primary composite endpoint by 15%. By powering the study for cardiovascular death, it was overpowered for the primary endpoint.

Ultimately, 8442 patients were randomized from 947 sites in 47 countries (of these, 43 were removed from final analysis due to mis-randomization or major good clinical practice violations at the sites).(25) Baseline characteristics represented a typical HFrEF population, with a mean LVEF = 29 ± 6%, and optimized background therapy including beta blockers (93%) and mineralocorticoid receptor antagonists (60%). The study population was predominantly NYHA class II (70%) and class III (24%). Natriuretic peptides were elevated (NT-proBNP mean 1600 pg/ml; BNP mean 250 pg/ml).

In late March, 2014, the PARADIGM data monitoring committee (DMC) reviewed the interim safety and efficacy data and recommended early termination of the trial for efficacy, indicating a significant reduction in both the primary endpoint (cardiovascular death or heart failure hospitalization) and in cardiovascular death. The final results confirmed the benefit

observed by the DMC. After a median duration of follow-up of 27 months, 17.8% of patients in the LCZ696 group and 19.8% of patients in the enalapril group had been discontinued from study drug. The mean doses of LCZ696 and enalapril received were 375mg and 18.9 mg respectively.

LCZ696 reduced the primary composite endpoint of cardiovascular death or heart failure hospitalization by 20% (HR 0.80, 95% CI 0.73-0.87, p = 0.0000004).(26) Similar reduction was observed for cardiovascular death (0.80, 95% CI 0.71, 0.89, p = 0.00008) and hospitalization for heart failure (HR 0.79, 95% CI 0.71, 0.89, p = 0.00008). All-cause mortality was reduced by 16% (HR 0.84, 95% CI 0.76, 0.93, p < 0.0002). These findings were consistent across all pre-specified subgroups. Hypotension was more common in patients receiving LCZ696 (p < 0.001) although discontinuation due to hypotension was similar in both arms. Elevations in serum creatinine or potassium, and cough were less frequent in those assigned to LCZ696. Serious angioedema was rare and similar between groups, although numerically greater in the LCZ arm (19 vs. 10) and in no circumstance resulted in airway compromise.

The results of PARADIGM need to be viewed in the context of the trials that established ACE inhibitors as the gold-standard in heart failure. LCZ696 resulted in similar incremental reduction in mortality as the SOLVD-Treatment trial which established ACE inhibitors as first-line therapy, with the dose of the active comparator, enalapril, higher than that achieved in SOLVD-T. While LCZ696 still needs to undergo regulatory approval, the results of PARADIGM-HF provide support for the use of LCZ696 instead of ACE inhibitors as first-line therapy in chronic HF.

Conclusions

Dual inhibition of the renin-angiotensin-aldosterone system and neprilysin inhibition represents a novel approach to treating patients with heart failure. The results of PARADIGM showing significant reduction in the primary composite endpoint, cardiovascular death, and all-cause mortality in patients receiving LCZ696 in comparison to those receiving enalapril suggesting that this drug could replace ACE inhibitors and ARBs as first-line therapy in the treatment of patients with heart failure with reduced ejection fraction following regulatory approval. Further studies will determine whether this agent has a role in heart failure with preserved ejection fraction and for other indications.

References

1. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol. 2007 Dec 18;50(25):2357-68.

2. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Endocr Rev. 2006 Feb;27(1):47-72.

3. Scotland RS, Cohen M, Foster P, Lovell M, Mathur A, Ahluwalia A, et al. C-type natriuretic peptide inhibits leukocyte recruitment and platelet-leukocyte interactions via suppression of P-selectin expression. Proceedings of the National Academy of Sciences of the United States of America. 2005 Oct 4;102(40):14452-7.

4. Soeki T, Kishimoto I, Okumura H, Tokudome T, Horio T, Mori K, et al. C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. J Am Coll Cardiol. 2005 Feb 15;45(4):608-16.

5. Maisel AS, Daniels LB. Breathing not properly 10 years later: what we have learned and what we still need to learn. J Am Coll Cardiol. 2012 Jul 24;60(4):277-82.

6. Potter LR. Natriuretic peptide metabolism, clearance and degradation. FEBS J. 2011 Jun;278(11):1808-17.

7. Lu B, Gerard NP, Kolakowski LF, Jr., Bozza M, Zurakowski D, Finco O, et al. Neutral endopeptidase modulation of septic shock. The Journal of experimental medicine. 1995 Jun 1;181(6):2271-5.

8. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002 Mar 27;287(12):1531-40.

9. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005 Apr 20;293(15):1900-5.

10. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. The New England journal of medicine. 2011 Jul 7;365(1):32-43.

11. Ando S, Rahman MA, Butler GC, Senn BL, Floras JS. Comparison of candoxatril and atrial natriuretic factor in healthy men. Effects on hemodynamics, sympathetic activity, heart rate variability, and endothelin. Hypertension. 1995 Dec;26(6 Pt 2):1160-6.

12. McDowell G, Nicholls DP. The endopeptidase inhibitor, candoxatril, and its therapeutic potential in the treatment of chronic cardiac failure in man. Expert Opin Investig Drugs. 1999 Jan;8(1):79-84.

13. Cleland JG, Swedberg K. Lack of efficacy of neutral endopeptidase inhibitor ecadotril in heart failure. The International Ecadotril Multi-centre Dose-ranging Study Investigators. Lancet. 1998 May 30;351(9116):1657-8.

14. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens. 2004 Feb;17(2):103-11.

15. Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet. 2000 Aug 19;356(9230):615-20.

16. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat

Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002 Aug 20;106(8):920-6.

17. Feng l, Karpinski ph, Sutton p, Liu y, Hook df, Hu b, et al. LCZ696: a dual-acting sodium supramolecular complex. Tetrahedron Letters 2012;53(3):275-6.

18. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). Journal of clinical pharmacology. 2010 Apr;50(4):401-14.

19. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010 Apr 10;375(9722):1255-66.

20. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, et al. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study. Hypertension. 2014 Apr;63(4):698-705.

21. Komajda M, Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. Eur Heart J. 2014 Apr;35(16):1022-32.

22. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012 Oct 20;380(9851):1387-95.

23. Jhund PS, Claggett B, Packer M, Zile MR, Voors AA, Pieske B, et al. Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor,

LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. Eur J Heart Fail. 2014 Jun;16(6):671-7.

24. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2013 Sep;15(9):1062-73.

25. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2014 Jul;16(7):817-25.

26. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. The New England journal of medicine. 2014 Aug 30.

Figure Legend

Figure 1. **Schematic showing the mechanism of action of LCZ696**. Heart failure stimulates both the renin-angiotensin system and the natriuretic peptide system. LCZ696 is composed of two molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril (AHU377). Valsartan blocks the angiotensin type I receptor. Sabubitril is converted enzymatically to the active neprilysin inhibitor LBQ657 which inhibits neprilysin, an enzyme that breaks down the breakdown of ANP, BNP and CNP as well as other vasoactive substances. NT-proBNP is not a substrate for neprilysin.

Table 1. Clinical trials of LCZ696

Study	Sample size and patient population	Study Medications	Study Design	Main Findings
Ruilope et al.(19)	N=1328 with hypertension	LCZ696 100mg, 200mg and 400mg vs. valsartan 80mg, 160mg, 320mg, vs. AHU377 200mg	Randomized controlled dose ranging study. Primary endpoint was reduction in BP between groups at 8 weeks	Significant reduction in systolic and diastolic blood pressure with LCZ696 200mg vs. valsartan 160mg, and LCZ696 400mg vs. valsartan 320mg; significant reduction in ambulatory blood pressure with LCZ versus valsartan.
Kario et al.(20)	N=309 Asians with hypertension	LCZ696 100mg, 200mg or 400mg vs. placebo	Randomized controlled dose ranging study	Significant reduction in systolic, diastolic, pulse pressure and ambulatory pressure with LCZ696
Solomon et al. (PARAMOUNT)(22)	N=301 with heart failure	LCZ696 200mg bid vs. Valsartan 160mg	Randomized controlled trial,	Significant reduction in NT-proBNP at 12 weeks with LCZ696, as well as left atrial

	with preserved ejection fraction	bid	primary endpoint reduction in NT-ProBNP at 12 weeks	volume at 36 weeks, improvement in NYHA class in patients receiving LCZ696 compared with placebo
McMurray et al. (PARADIGM)(26)	N=8442 with heart failure with reduced ejection fraction	LCZ696 200mg bid vs. enalapril 10mg bid	Randomized controlled trial. Primary outcome cardiovascular death or heart failure hospitalization	Significant reductions in the primary outcome (20%), cardiovascular death (20%) and all-cause mortality (16%) with LCZ696 compared with enalapril