

COMMENTARY

Benefits and pitfalls of sacubitril/valsartan treatment in patients with hypertension

Steven G. Chrysant MD, PhD 

University of Oklahoma College of Medicine, Oklahoma City, OK, USA

Correspondence

Steven G. Chrysant, MD, PhD, 5700 Mistletoe Court, Oklahoma City, OK 73142, USA.

Email: schrysant@yahoo.com

LCZ696 (sacubitril/valsartan) is a first-in-class dual action molecule of the neprilysin inhibitor sacubitril and the angiotensin II type 1 receptor blocker valsartan. This drug has been approved by the Food and Drug Administration for the treatment of heart failure (HF) and awaits Food and Drug Administration approval for the treatment of hypertension. Several recent studies have shown it to be more effective than monotherapy in lowering blood pressure (BP) and improving HF and is fairly safe and well tolerated by patients.^{1,2} Its antihypertensive and beneficial HF effects are mediated through the inhibition by neprilysin of the catabolism of the natriuretic peptides (NPs) and the blockade by the angiotensin II type 1 receptor valsartan. These actions by sacubitril/valsartan result in systemic vasodilation and increased diuresis and natriuresis, leading to reduction of peripheral vascular resistance and volume contraction, all important actions for lowering BP and improving HF symptoms.^{3,4} NP, atrial NP, and B-type NP exert their diuretic and natriuretic effects through the generation of cyclic guanosine monophosphate.^{5,6} However, their half-life is short, being rapidly metabolized by different enzymes including neprilysin; thus, the benefit of sacubitril/valsartan is the inhibition of their catabolism and the prolongation of their half-life.⁷ In addition to NPs, neprilysin catabolizes many other peptide hormones including adrenomedullin, angiotensin, bradykinin, endothelin-1, neurotensin, oxytocin, substance P, and especially amyloid β (A β). Therefore, sacubitril could result in actions that are either beneficial or detrimental to patient health. For a better understanding of the actions of sacubitril/valsartan, a focused MEDLINE search of the English language literature was performed between 2011 and 2017 and the data from this search is discussed in this commentary.

1 | BENEFICIAL EFFECTS OF SACUBITRIL/VALSATAN IN PATIENTS WITH HYPERTENSION

Several clinical trials have shown that sacubitril/valsartan either alone or in combination with other antihypertensive drugs results in a significant reduction of BP and its effects have been shown

to be significantly higher compared with monotherapy.¹ The results from these clinical trials are summarized in Table 1. In an active comparator trial, Ruilope and colleagues¹ studied the antihypertensive effectiveness of different doses of LCZ696 (100, 200, 400 mg/d), valsartan (80, 160, 320 mg/d), and placebo monotherapies in 1215 patients with uncomplicated hypertension for 8 weeks. BP was measured by clinical and ambulatory BP monitoring. LCZ696 monotherapy was dose-dependently superior to valsartan monotherapy by clinical and ambulatory BP measurements for all doses tested. Similar results were recently reported by Kario and colleagues⁸ in a randomized double-blind study of 389 Asian patients with uncomplicated hypertension. LCZ696 resulted in significant BP reductions in all doses tested compared with placebo. Also, a 52-week extension study showed that LCZ696 400 mg either alone or in combination with amlodipine 5 to 10 mg $\pm$ hydrochlorothiazide 6.25 to 25 mg/d resulted in significant reduction of BP.⁹ In another study by Kario and coworkers,¹⁰ 35 patients with severe hypertension (baseline BP 173.4/112.4 mm Hg) treated with LCZ696 400 mg/d either alone or in combination with other drugs except angiotensin-converting enzyme inhibitors and angiotensin receptor blockers resulted in significant reduction of BP. In another study, Ito and colleagues¹¹ tested the antihypertensive effectiveness and safety of LCZ696 in daily doses of 100, 200, and 400 mg in 32 patients with hypertension and renal failure (estimated glomerular filtration rate $\geq$ 30 to $<$ 60 mL/min per 1.73 m²). LCZ696 400 mg/d resulted in significant reduction of BP without changes in serum creatinine, serum urea nitrogen, potassium, or estimated glomerular filtration rate. In a recent study, Wang and colleagues¹² tested the natriuretic, diuretic, and BP-lowering effects of LCZ696 400 mg/d compared with valsartan 320 mg/d for 4 weeks in 72 Asian patients with salt-sensitive hypertension. LCZ696 400 mg/d produced greater BP reductions by clinic and ambulatory BP measurements than valsartan 320 mg/d and greater natriuresis at 1 week but not by week 28. In addition, it decreased N-terminal pro-brain NP (NT-proBNP) more than valsartan, which was independent of BP reduction. Another recent study by Wang and associates¹³ compared the BP-lowering effects of the combination of

TABLE 1 Clinical trials in patients with hypertension demonstrating a blood pressure–lowering effects of LCZ696 vs a comparator

Author	Patients, No.	Age, y	Follow-up, wk	SBP, mm Hg	Δ , mm Hg	DBP, mm Hg	Δ , mm Hg
Drug dose, mg							
Ruilopec ¹							
LCZ696 100	156	53	8	155	−3.2	100	−4.7
LCZ696 200	169	54	8	157	−11.0	100	−6.1
LCZ696 400	172	53	8	155	−12.5	100	−6.9
Valsartan 80	163	53	8	155	−4.7	100	−2.4
Valsartan 160	166	53	8	155	−5.7	100	−3.2
Valsartan 320	164	53	8	156	−12.5	100	−4.2
Kario ⁸							
LCZ696 100	100	3	8	156	−11.5	100	−4.7
LCZ696 200	101	52	8	156	−11.0	100	−6.5
LCZ696 400	96	51	8	154	−12.5	100	−7.8
Kario ¹⁰							
LCZ696 200	35	51	4	173	−23.1	112	−14
LCZ696 400	32	51	8	173	−35.3	112	−22.1
Ito ¹¹							
LCZ696 100	32	66	4	152	−13.4	87	−5.2
LCZ696 200	26	66	6	152	−19.4	87	−7.8
LCZ696 400	18	66	8	152	−20.7	87	−8.4
Wang ¹²							
LCZ696 200 + amlodipine 5	123	55	8	138	−13.9	86	−0.8
Amlodipine 5	128	55	8	140	−8.0	86	−0.3
Wang ¹³							
LCZ696 400	36	56	8	147	−13.3	90	−6.2
Valsartan 320	36	59	8	148	−5.8	90	−4.2
Williams ¹⁴							
LCZ696 400	207	68	12	158	−13.7	87	−5.9
Olmesartan 40	206	67	12	159	−9.9	90	−4.9
LCZ696 400	209	68	52	158	−17.7	87	−8.7
Olmesartan 40	208	67	52	159	−16.1	90	−8.1

Abbreviations: Δ , change from baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure.

LCZ696 200 mg + amlodipine 5 mg/d compared with monotherapy with amlodipine 5 mg/d + placebo. LCZ696 + amlodipine resulted in greater 24-hour ambulatory BP measurement and nighttime reduction of BP than amlodipine + placebo. Of interest are the results of the recently published PARAMETER (Prospective Comparison of an Angiotensin-Receptor Neprilysin Inhibitor With an Angiotensin-Receptor Blocker Measuring Arterial Stiffness in the Elderly) study by Williams and colleagues¹⁴ of 454 patients with hypertension with a mean age of 67.7 years initially randomized to LCZ696 200 mg/d or olmesartan 20 mg/d, uptitrated to 400 and 40 mg/d, respectively, as required and followed for 52 weeks. Depending on BP response, amlodipine 2.5 to 5.0 mg/d + hydrochlorothiazide 6.25 to 25.0 mg/d were added to both treatment groups. At the end of the 52-week extension, the brachial BP was similarly decreased by both drug regimens. Similar results were observed in central BP

and pulse pressure. Regarding the safety of LCZ696, the drug was well tolerated in all studies listed and no instances of angioedema were reported.

2 | BENEFICIAL EFFECTS OF SACUBITRIL/ VALSARTAN IN PATIENTS WITH HF

Sacubitril/valsartan was approved by the Food and Drug Administration on July 15, 2015, on a priority basis for the treatment of HF because of its proven effectiveness in two trials (the PARADIGM-HF [Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure] and PARAMOUNT [Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection

TABLE 2 Main actions of peptide hormones catabolized by neprilysin

Name	Action
Adrenomedullin	Circulatory peptide hormone causing systemic vasodilation and new angiogenesis
Angiotensin II	Circulatory peptide hormone causing systemic vasoconstriction and cardiovascular remodeling
Bradykinin	Circulatory peptide hormone causing systemic vasodilation and cough stimulation
Endothelin-1	Circulatory peptide hormone causing systemic vasoconstriction
Glucagon	Peptide hormone released from the α -cells of the pancreas catalyzing glycogen and increasing blood glucose levels
Natriuretic peptides	Circulatory peptide hormones causing systemic vasodilation and increasing diuresis and natriuresis
Neurotensin	Circulatory neuropeptide hormone regulating the release of luteinizing and prolactin hormone release and causing systemic vasodilation through its interaction with the dopaminergic system
Oxytocin	Circulatory peptide hormone released from the paraventricular nucleus of the brain and facilitating child birth
Substance P	Circulatory neuropeptide hormone acting as a neurotransmitter and neuromodulator and stimulating cough production
Amyloid β	Increased brain deposition of amyloid β has been implicated as a cause of Alzheimer disease

Fraction] trials). In the PARADIGM-HF trial, 8442 patients with a mean age of 63 ± 11.5 years with reduced ejection fraction $\leq 40\%$ were treated with either LCZ696 200 mg twice daily or enalapril 10 mg twice daily and followed for a median of 27 months (premature termination). At study end, the primary outcome (a composite of death from cardiovascular causes or hospitalization from HF) occurred in 21.8% in patients treated with LCZ696 versus 26.5% in those treated with enalapril (hazard ratio, 0.80; 95% confidence interval, 0.73–0.87 [$P < .001$]). A total of 13.3% and 16.5% of patients treated with either LCZ696 or enalapril died from cardiovascular causes (hazard ratio, 0.80; 95% confidence interval, 0.71–0.89 [$P < .001$]). Instances of hypotension and increases in serum creatinine and potassium were small and similar between the two drug regimens. Cough or angioedema occurred in 0.2% in patients treated with LCZ696 and 0.1% in those treated with enalapril ($P = .19$). The PARAMOUNT trial¹⁶ was a phase 2, randomized, parallel-group, double-blind multicenter study of 301 patients with a mean age of 71 years, New York Heart Association class II or III, ejection fraction $\geq 45\%$, and NT-proBNP > 400 pg/dL. Patients were treated with LCZ696 400 mg or valsartan 160 mg twice daily in addition to background therapy, except angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and followed for 12 weeks with an extension to 36 weeks. The analysis of data at week 12 showed that LCZ696 decreased NT-proBNP more than valsartan ($P = .005$), but not at week 36 ($P = .20$). In addition, there were small, not significant, decreases in left atrial diameter, atrial volume, left ventricular end-diastolic and end-systolic volume, and left ventricular wall thickness by both drug regimens. The drugs were well tolerated and there were no significant clinical or metabolic side effects noted.

3 | PITFALLS OF TREATMENT WITH SACUBITRIL/VALSARTAN

Sacubitril/valsartan (LCZ696) is a dual action molecule consisting of the neutral endopeptidase (NEP) neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan combined in a molar ratio of 1:1.¹⁷ The NEP neprilysin is known to catabolize several peptide hormones such as glucagon, bradykinin, angiotensin, endothelin-1, substance P, oxytocin, neurotensin, adrenomedullin, the NPs, and A β (Table 2). Some of these peptides have hemodynamic effects (adrenomedullin, NPs, bradykinin, angiotensin, endothelin-1), whereas others do not (glucagon, neurotensin, oxytocin, substance P, amyloid β). Therefore, the effect of NEP (neprilysin) inhibition is different and depends on the relative dominance of the various substrates.¹⁸ Consequently, NEP inhibition could either decrease BP by inhibiting the degradation of adrenomedullin, NPs, and bradykinin through vasodilation and natriuresis or increase it by blocking the degradation of angiotensin and endothelin-1, as has been demonstrated in healthy men given an NEP inhibitor.¹⁹ However, in the case of sacubitril/valsartan, the vasoconstrictive action of angiotensin II is antagonized by valsartan through its blockade of angiotensin II type 1 receptors.⁴ The decreased catabolism of bradykinin and substance P elevates blood levels and increases the risk of cough and angioedema, although these effects are not as prominent with sacubitril/valsartan as with the combination of NEP/angiotensin-converting enzyme inhibitor omapatrilat in the OCTAVE (Omapatrilat cardiovascular Treatment vs Enalapril).²⁰ The most troublesome effect of long-term NEP inhibition is the decreased catabolism of A β peptide and the possible increased

incidence of Alzheimer disease, since neprilysin has been touted as a drug to prevent or treat Alzheimer disease.²¹ Experimental studies have shown that intracerebral infusion of the NEP inhibitor thiorphan induced hippocampal accumulation and deposition of A β ₁₋₄₂ in rats.²² Aggregation of A β ₁₋₄₂ is believed to play a critical role in the development of Alzheimer disease.²³ However, in a study of 17 healthy volunteers administered LCZ696 400 mg/d for 2 weeks, there was no difference in the cerebrospinal fluid concentration of A β ₁₋₄₂ between controls and LCZ696-treated patients.²⁴ However, the results of this study do not dispel all concerns regarding brain accumulation of A β ₁₋₄₂, which could go undetected by cerebrospinal fluid measurements, since the brain traffics most of the A β into the peripheral circulation.²⁵

4 | DISCUSSION

From the available clinical data, it appears that sacubitril/valsartan possesses significant beneficial antihypertensive and HF effects and is fairly safe and well tolerated short term. Its effects in lowering the central aortic and nocturnal BP are more important than its peripheral BP effects for the prevention of cardiovascular events.²⁶ In addition, the lowering of blood levels of NT-proBNP is also significant since high levels of NT-proBNP predict the onset of cardiovascular events.²⁷ In other studies, sacubitril/valsartan has been shown to improve insulin sensitivity in obese persons and could prevent the onset of diabetes mellitus in this population.²⁸ The prevention of degradation of NPs is beneficial in patients with hypertension and HF, since both conditions benefit from the diuretic, natriuretic, and vasodilating effects of NPs. The prevention of degradation of bradykinin has ambivalent effects since its increased blood levels could contribute to vasodilation and reduction of BP on the one hand and the induction of cough and angioedema on the other, although the incidence of cough and angioedema is low with the use of sacubitril/valsartan in both hypertension and HF, as has been previously reported in hypertension and HF studies. The only worrisome adverse effect of sacubitril/valsartan is the prevention of degradation of A β peptide, which could result, long term, in an increased incidence of Alzheimer disease.²²⁻²⁵ This is not a problem in patients with HF treated with sacubitril/valsartan since their survival is short, but it is not the same with patients with hypertension, who live for a long time. In addition, hypertension is known to contribute to blood-brain barrier dysfunction, rendering these patients more vulnerable to NEP inhibition.²² Also, a postmortem study in patients with hypertension and Alzheimer disease showed increased deposition of A β in the frontal cortex, indicating a possible decreased degradation of A β peptide in patients with hypertension.²¹ Another problem is the monitoring of accumulation of A β in the brain since its measurement in cerebrospinal fluid is not representative of its levels in the brain,²⁵ and there is compelling genetic evidence that A β deposition plays a critical role in Alzheimer disease.²⁵ Should sacubitril/valsartan be approved for the treatment of hypertension, prolonged monitoring of brain function will be necessary to determine an increased deterioration of mental function.

CONFLICTS OF INTEREST

The author declares no conflicts of interest and that no funds were received for the preparation of this article.

ORCID

Steven G. Chrysant  <http://orcid.org/0000-0001-9972-7151>

REFERENCES

1. Ruilope LM, Dukat A, Bohm M, et al. Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomized, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-1266.
2. Solomon SD, Claggett B, McMurray JJ, et al. Combined, neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail*. 2016;18:1238-1243.
3. Chrysant SG. LCZ696, angiotensin AT1 receptor blocker/neprilysin inhibitor for the treatment of heart failure and hypertension. *Drugs of the Future*. 2011;36:183-190.
4. Chrysant SG, Chrysant GS. Clinical experience with angiotensin receptor blockers with particular reference to valsartan. *J Clin Hypertens (Greenwich)*. 2004;6:445-451.
5. Lee CY, Burnett JC Jr. Natriuretic peptides and therapeutic implications. *Heart Fail Rev*. 2007;12:131-142.
6. Rubattu S, Sciarretta S, Valenti V, et al. Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implications in cardiovascular diseases. *Am J Hypertens*. 2008;21:733-741.
7. Mangiafico S, Costello-Boerrigter LC, Anderson IA, et al. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J*. 2013;34:886-893.
8. Kario K, Sun N, Chiang FT, 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;63:698-705.
9. Supasyndh O, Sun N, Kario K, et al. Long-term (52-week) safety and efficacy of sacubitril/valsartan in Asian patients with hypertension. *Hypertens Res*. 2016;40:472-476.
10. Kario K, Tamaki Y, Okino N, et al. LCZ696, a first-in-class angiotensin receptor-neprilysin inhibitor: the first clinical experience in patients with severe hypertension. *J Clin Hypertens (Greenwich)*. 2016;18:308-314.
11. Ito S, Satoh M, Tamaki Y, et al. Safety and efficacy of LCZ696, first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. *Hypertens Res*. 2015;38:269-275.
12. Wang TD, Tan RS, Lee HY, et al. Effects of sacubitril/valsartan (LCZ696) on natriuresis, diuresis, blood pressure, and NT-ProBNP in salt-sensitive hypertension. *Hypertension*. 2017;69:411-420.
13. Wang JG, Yukisada K, Sibuto A, et al. Efficacy and safety of a sacubitril/valsartan (LCZ696) add-on to amlodipine in Asian patients with systolic hypertension uncontrolled with amlodipine monotherapy. *J Hypertens*. 2017;35:877-885.
14. Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension. The PARAMETER study. *Hypertension*. 2017;69:411-420.
15. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
16. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection

- fraction: a phase 2 double-blind randomized controlled trial. *Lancet*. 2012;380:1387-1395.
17. Gu J, Noe A, Chandra P, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNI). *J Clin Pharmacol*. 2010;50:401-414.
 18. Uji E, Roksnoer CW, Hoorn EJ, Jan Danser AH. From ARB to ARNI in cardiovascular control. *Curr Hypertens Rep*. 2016;18:86.
 19. Ando S, Rahman MA, Butler GC, et al. Comparison of candoxatril and atrial natriuretic factor in healthy men. Effects on hemodynamics, sympathetic activity, heart rate variability, and endothelin. *Hypertension*. 1995;26:1160-1166.
 20. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111.
 21. Ashby EL, Miners JS, Kehoe PG, et al. Effects of hypertension and anti-hypertensive treatment on amyloid β (A β) plaque load and A β -degrading enzymes in frontal cortex. *J Alzheimers Dis*. 2016;50:1191-1203.
 22. Iwata N, Tsubuki S, Takaki Y, et al. Identification of the major Abeta-42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. *Nat Med*. 2000;6:143-150.
 23. Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov*. 2011;10:698-712.
 24. Langenickel TH, Tsubouchi C, Ayalasomayajula S, et al. The effect of LCZ696 (sacubitril/valsartan) on amyloid-beta concentrations in cerebrospinal fluid in healthy subjects. *Br J Clin Pharmacol*. 2016;81:878-890.
 25. Qosa H, Abuasal BS, Romero IA, et al. Differences in amyloid-beta clearance across mouse and human blood-brain barrier models: kinetic analysis and mechanistic modeling. *Neuropharmacology*. 2014;79:668-678.
 26. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomono Study. *J Am Coll Cardiol*. 2008;51:2432-2439.
 27. Chrysant SG. The clinical significance of N-terminal Pro-brain natriuretic peptide in detecting the residual cardiovascular risk in hypertension and other clinical conditions and in predicting future cardiovascular events. *J Clin Hypertens (Greenwich)*. 2017;19:340-343.
 28. Jordan J, Stinkens R, Jax T, et al. Improved insulin sensitivity with angiotensin receptor neprilysin inhibition in individuals with obesity hypertension. *Clin Pharmacol Ther*. 2017;101:254-263.

How to cite this article: Chrysant SG. Benefits and pitfalls of sacubitril/valsartan treatment in patients with hypertension. *J Clin Hypertens*. 2018;20:351-355. <https://doi.org/10.1111/jch.13169>