Effects of LCZ696 (Sacubitril/Valsartan) on Blood Pressure in Patients with Hypertension: A Meta-Analysis of Randomized Controlled Trials

Qiang Geng Rongqiang Yan Zhengzhong Wang Fangjie Hou

Department of Cardiology, Qingdao Municipal Hospital, Qingdao, China

Keywords

LCZ696 · RAS inhibition · Blood pressure · Hypertension · Meta-analysis

Abstract

Background: LCZ696 (sacubitril/valsartan), a first-in-class angiotensin receptor-neprilysin inhibitor, can significantly reduce blood pressure in patients with heart failure. We performed this meta-analysis to determine the antihypertensive effect of LCZ696 in patients with hypertension. **Methods:** Randomized controlled trials were searched in MEDLINE, the Cochrane Library, and Clinicaltrials.gov. Twelve studies with a total of 6,064 participants were included. **Results:** Compared with angiotensin receptor blockers (ARBs), LCZ696 100 mg caused a significant reduction in systolic blood pressure (SBP) (mean difference [MD] -1.58 mm Hg, 95% confidence interval [CI] -2.09 to -1.07 , $p < 0.05$) and diastolic blood pressure (DBP) (MD -0.66 mm Hg, 95% CI -0.98 to -0.33 , $p < 0.05$). LCZ696 200 mg caused a significant reduction in SBP (MD -4.94 mm Hg, 95% CI -6.54 to -3.35 , $p < 0.05$), DBP (MD -2.24 mm Hg, 95% CI -2.74 to -1.75 , $p < 0.05$), 24-h ambulatory SBP (24 h ASBP; MD -3.69 mm Hg, 95% CI -4.80 to -2.58 , $p < 0.05$), and 24-h ADBP (MD -1.71 mm Hg, 95% CI -2.13 to -1.28 , $p < 0.05$). LCZ696 400 mg

caused a significant reduction in SBP (MD -6.25 mm Hg, 95% CI -7.90 to -4.61 , $p < 0.05$), DBP (MD -2.30 mm Hg, 95% CI -2.80 to -1.80 , $p < 0.05$), 24-h ASBP (MD -4.31 mm Hg, 95% CI -6.56 to -2.07 , $p < 0.05$), and 24 h ADBP (MD -1.69 mm Hg, 95% CI -2.59 to -0.79 , $p < 0.05$). Compared with LCZ696 200 mg, LCZ696 400 mg caused a significant reduction in SBP (MD 1.71 mm Hg, 95% CI 1.15 to 2.27 , $p < 0.05$), DBP (MD 0.90 mm Hg, 95% CI 0.65 to 1.16 , $p < 0.05$), 24-h ASBP (MD 1.50 mm Hg, 95% CI 0.84 to 2.17 , $p < 0.05$), and 24-h ADBP (MD 0.76 mm Hg, 95% CI 0.47 to 1.06 , $p < 0.05$). **Conclusions:** The blood pressure-lowering effect of LCZ696 is dose-related. This meta-analysis confirms the antihypertensive effects of LCZ696.

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Introduction

Neprilysin degrades vasoactive peptides, including natriuretic peptides and bradykinin [1]. Neprilysin inhibitors are expected to increase the levels of these substances and reduce blood pressure. Combined inhibitors of the renin-angiotensin system (RAS) and neprilysin are superior to those of either approach alone in reducing blood pressure [2]. Sacubitril/valsartan (LCZ696), a first-in-

Fig. 1. Flow diagram of the study selection. In total, 1,886 studies were identified. Finally, 12 studies were selected.

class angiotensin receptor-neprilysin inhibitor, can simultaneously block RAS activation and natriuretic peptide degradation, resulting in greater antihypertensive efficacy [2]. LCZ696 has been approved for the treatment of patients with heart failure and was granted a Class IB recommendation in the ACC/AHA and ESC guidelines [3, 4]. Can LCZ696 be used as an antihypertensive agent because of its significant antihypertensive effect? This meta-analysis was performed to evaluate the antihypertensive effect of LCZ696 in patients with hypertension.

Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report this meta-analysis [5]. MEDLINE, the Cochrane Library of Trials, and Clinicaltrials.gov were searched to identify published or unpublished randomized controlled trials (RCTs) from September 1999 to July 2019. The following terms were included: neprilysin inhibitor, LCZ696, sacubitril-valsartan, Entresto.

Inclusion and Exclusion Criteria

All included studies were RCTs of LCZ696 versus angiotensin receptor blockers (ARBs) in patients with hypertension. The studies reported systolic blood pressure (SBP), diastolic blood pressure

(DBP), 24-h ambulatory systolic blood pressure (24 h ASBP), 24-h ambulatory diastolic blood pressure (24 h ADBP), or a change from baseline in blood pressure. Reviews, case reports, and abstracts were excluded.

Quality Assessment and Data Extraction

According to the Cochrane Reviewer's Handbook, 2 reviewers (Q.G. and F.H.) independently extracted data from eligible studies. Discrepancies were resolved by discussion. The risk of bias was estimated by using the parameters: sequence generation, concealment of group allocation, blinding during outcome assessment, selective reporting, and intention-to-treat analysis. A flow diagram is shown in Figure 1.

The following terms were extracted: publication year, study design, blinding method, age, total number, duration of therapy, change from the baseline in SBP and DBP, change from the baseline in 24-h ASBP and 24-h ADBP.

Twelve studies reported SBP and DBP [6–17]. Eight studies reported 24 h ASBP and 24 h ADBP [6–13].

Statistical Analysis

All meta-analyses were performed in Review Manager software (v5.3; Cochrane Collaboration, Oxford, UK). A two-tailed p value <0.05 was considered statistically significant. The heterogeneity of studies was assessed with the I^2 statistic. $I^2 >50\%$ and $p < 0.10$ indicated statistically significant heterogeneity between studies. A funnel plot was used to assess publication bias. The change from baseline in blood pressure was presented as the mean difference (MD) with a 95% confidence interval (CI).

Table 1. Characteristics of the included trials

Study ^a [ref.], year	LCZ696 dosage	ARBs	Mean age, years		Patients, <i>n</i>		Male/female, <i>n</i>		Follow-up, weeks
			LCZ696	ARB	LCZ696	ARB	LCZ696	ARB	
Ruilope [6], 2010 (NCT00549770)	100 mg	valsartan 80 mg	53±10.4	53±9.6	156	163	95/61	95/68	8
	200 mg	valsartan 160 mg	54±9.7	53±9.7	169	166	92/77	98/68	
	400 mg	valsartan 320 mg	52±10.9	53±10.1	172	164	97/75	99/65	
Kario [7], 2014 (NCT01193101)	100 mg	–	52.5±10.03	–	100	–	60/40	–	8
	200 mg		52.1±8.82		101		74/27		
	400 mg		50.9±9.81		96		73/23		
Izzo [8], 2017 (NCT01281306) RATIO ^b	400 mg	valsartan 320 mg	61.2±10.6	62±11.5	142	143	71/71	83/60	8
Supasyndh [9], 2017 (NCT01615198)	100 mg	olmesartan 10 mg	70.5±4.7	70.9±4.7	295	291	142/153	152/139	6
	200 mg	olmesartan 20 mg	70.5±4.7	70.9±4.7	295	291	142/153	152/139	10
Williams [10], 2017 (NCT01692301) PARAMETER ^b	200 mg	olmesartan 20 mg	68.2±5.7	67.2±6.0	226	222	119/107	118/104	12
Schmieder [14], 2017 (NCT01870739)	400 mg	olmesartan 20 mg	60.5±7.8	59.2±13.1	50	50	37/13	40/10	52
Wang [16], 2017 (NCT01681576)	400 mg	valsartan 320 mg	57.3±10.3	57.3±10.3	70	67	23/47	23/44	4
NCT01599104 [11], 2012	200 mg	olmesartan 20 mg	57.9±10.9	59.6±10.5	387	389	264/123	286/103	8
	400 mg		58.7±10.5		385		268/117		
NCT01785472 [12], 2013	200 mg	olmesartan 20 mg	57.5±10.2	57.4±10.1	477	479	252/225	261/218	8
	400 mg		58.1±9.7		469		243/226		
NCT01876368 [13], 2013	200 mg	olmesartan 20 mg	57.1±10.2	58.0±9.1	188	187	97/91	95/92	8
NCT01353508 [15], 2011	400 mg	valsartan 160 mg	58.0±8.0	61.6±8.4	16	16	14/2	9/7	1
NCT01256411 [17], 2010	200 mg	–	52.2±9.7	–	139	–	84/55	–	48
	400 mg		50.3±10.1		89		71/18		

–, No report; ARB, angiotensin receptor blockers. ^a The ClinicalTrials.gov Identifier is supplied, and, if available, the first author. ^b Name of the trial.

Results

In total, 2,337 studies were identified in MEDLINE, the Cochrane Library of Trials, and Clinicaltrials.gov. Finally, 12 studies with a total of 6,064 participants were selected. Many studies (e.g., PARADIGM-HF, PARAMOUNT, and PIONEER) did not report blood pressure values and were thus not included in our analysis. The baseline characteristics of the included studies appear in Table 1.

Baseline and final SBP levels of LCZ696 and ARBs appear in online supplemental Table 2 (for all online supplemental material, see www.karger.com/doi/10.1159/000507327), and baseline and final DBP levels of LCZ696 and ARBs in

online supplemental Table 3. Risk of bias is summarized in online supplemental Table 1. All studies used a parallel-group design. All studies in our analysis are RCTs.

Two studies [6, 9] reported SBP and DBP in LCZ696 100 mg and ARBs. Compared with ARBs, LCZ696 100 mg caused a significant reduction in SBP (MD –1.58 mm Hg, 95% CI –2.09 to –1.07, $p < 0.05$) and DBP (MD –0.66 mm Hg, 95% CI –0.98 to –0.33, $p < 0.05$) (Fig. 2).

Six studies [6, 9–13] reported SBP, DBP, 24 h ASBP, and 24 h ADBP in LCZ696 200 mg and ARBs. Compared with ARBs, LCZ696 200 mg caused a significant reduction in SBP (MD –4.94 mm Hg, 95% CI –6.54 to –3.35, $p < 0.05$), DBP (MD –2.24 mm Hg, 95% CI –2.74 to –1.75,

$p < 0.05$), 24 h ASBP (MD -3.69 mm Hg, 95% CI -4.80 to -2.58 , $p < 0.05$), and 24 h ADBP (MD -1.71 mm Hg, 95% CI -2.13 to -1.28 , $p < 0.05$) (Fig. 3).

Seven studies [6, 8, 11, 12, 14–16] reported SBP and DBP in LCZ696 400 mg and ARBs. Four studies [6, 8, 11, 12] reported 24 h ASBP and 24 h ADBP in LCZ696 400 mg and ARBs. Compared with ARBs, LCZ696 400 mg caused a significant reduction in SBP (MD -6.25 mm Hg, 95% CI -7.90 to -4.61 , $p < 0.05$), DBP (MD -2.30 mm Hg, 95% CI -2.80 to -1.80 , $p < 0.05$), 24 h ASBP (MD -4.31 mm Hg, 95% CI -6.56 to -2.07 , $p < 0.05$), and 24 h ADBP (MD -1.69 mm Hg, 95% CI -2.59 to -0.79 , $p < 0.05$) (Fig. 4).

Two studies [6, 7] reported SBP, DBP, 24 h ASBP, and 24 h ADBP in LCZ696 100 mg and 200 mg. There were no significant differences in SBP (MD 2.83 mm Hg, 95% CI -1.32 to 6.99 , $p < 0.05$) and DBP (MD 1.20 mm Hg, 95% CI -2.23 to 4.63 , $p < 0.05$). Compared with LCZ696 100 mg, LCZ696 200 mg caused a significant reduction in 24 h ASBP (MD 2.9 mm Hg, 95% CI 1.34 to 4.45 , $p < 0.05$),

but the MD of 24 h ADBP was not statistically significant between LCZ696 100 mg and 200 mg (MD 1.98 mm Hg, 95% CI 0.03 to 3.93 , $p = 0.05$) (Fig. 5).

Five studies [6, 7, 11, 12, 17] reported SBP and DBP in LCZ696 200 mg and 400 mg. Four studies [6, 7, 11, 12] reported 24 h ASBP and 24 h ADBP in LCZ696 200 mg and 400 mg. Compared with LCZ696 200 mg, LCZ696 400 mg caused a significant reduction in SBP (MD 1.71 mm Hg, 95% CI 1.15 to 2.27 , $p < 0.05$), DBP (MD 0.90 mm Hg, 95% CI 0.65 to 1.16 , $p < 0.05$), 24 h ASBP (MD 1.50 mm Hg, 95% CI 0.84 to 2.17 , $p < 0.05$), and 24 h ADBP (MD 0.76 mm Hg, 95% CI 0.47 to 1.06 , $p < 0.05$) (Fig. 6).

Discussion

Currently, the available evidence shows that LCZ696 can provide greater benefits for heart failure patients [18–20]. There has been little research into LCZ696 as an an-

Fig. 2. Forest plots of SBP and DBP in LCZ696 100 mg versus ARBs. LCZ696 100 mg showed a significant reduction in SBP (MD -1.58 mm Hg, 95% CI -2.09 to -1.07 , $p < 0.05$) and DBP (MD -0.66 mm Hg, 95% CI -0.98 to -0.33 , $p < 0.05$) when compared with ARBs.

Fig. 3. Forest plots of SBP, DBP, 24 h ASBP, and 24 h ADBP in LCZ696 200 mg versus ARBs. LCZ696 200 mg showed a significant reduction in SBP (MD -4.94 mm Hg, 95% CI -6.54 to -3.35 , $p < 0.05$), DBP (MD -2.24 mm Hg, 95% CI -2.74 to -1.75 , $p < 0.05$), 24 h ASBP (MD -3.69 mm Hg, 95% CI -4.80 to -2.58 , $p < 0.05$), and 24 h ADBP (MD -1.71 mm Hg, 95% CI -2.13 to -1.28 , $p < 0.05$) when compared with ARBs.

(For figure see next page.)

SBP **DBP** **24 h ASBP** **24 h ADBP**

Fig. 5. Forest plots of SBP, DBP, 24 h ASBP, and 24h ADBP in LCZ696 100 versus 200 mg. The MD of SBP (MD 2.83 mm Hg, 95% CI -1.32 to 6.99, $p < 0.05$), DBP (MD 1.20 mm Hg, 95% CI -2.23 to 4.63, $p < 0.05$), and 24 h ADBP (MD 1.98 mm Hg, 95% CI 0.03 to 3.93, $p = 0.05$) was not statistically significant between 100 and 200 mg LCZ696. LCZ696 200 mg showed a significant reduction in 24 h ASBP (MD 2.9 mm Hg, 95% CI 1.34 to 4.45, $p < 0.05$).

Fig. 4. Forest plots of SBP, DBP, 24 h ASBP, and 24 h ADBP in LCZ696 400 mg versus ARBs. LCZ696 400 mg showed a significant reduction in SBP (MD -6.25 mm Hg, 95% CI -7.90 to -4.61, $p < 0.05$), DBP (MD -2.30 mm Hg, 95% CI -2.80 to -1.80, $p < 0.05$), 24 h ASBP (MD -4.31 mm Hg, 95% CI -6.56 to -2.07, $p < 0.05$), and 24 h ADBP (MD -1.69 mm Hg, 95% CI -2.59 to -0.79, $p < 0.05$) when compared with ARBs.

SBP

Study or subgroup	LCZ696 200 mg			LCZ696 400 mg			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Ruilope LM	-18.7	1.1	168	-20.17	1.1	170	24.2%	1.47 [1.25, 1.70]
NCT01785472	-20.48	0.61	477	-21.67	0.62	469	25.1%	1.19 [1.11, 1.27]
NCT01599104	-18.21	0.7	387	-20.18	0.7	385	25.0%	1.97 [1.87, 2.07]
NCT01256411	-24.11	12.16	139	-21.3	11.46	89	2.8%	-2.81 [-5.93, 0.31]
Kario K	-17.54	1.27	98	-20.35	1.28	96	22.9%	2.81 [2.45, 3.17]

Total (95% CI) 1,269 1,209 100% 1.71 [1.15, 2.27]

Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 205.01$, $df = 4$ ($p < 0.00001$); $I^2 = 98\%$

Test of overall effect: $Z = 6.01$ ($p < 0.00001$)

DBP

Study or subgroup	LCZ696 200 mg			LCZ696 400 mg			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Ruilope LM	-12.92	0.7	168	-13.63	0.7	170	24.4%	0.7 [0.56, 0.86]
NCT01785472	-8.1	0.37	477	-8.8	0.38	469	26.1%	0.7 [0.65, 0.75]
NCT01599104	-7.76	0.4	387	-8.79	0.41	385	26.3%	1.03 [0.97, 1.09]
NCT01256411	-16.6	7.63	139	-14.2	7.05	89	1.6%	-2.40 [-4.34, -0.46]
Kario K	-10.98	0.89	98	-12.45	0.9	96	21.2%	1.47 [1.22, 1.72]

Total (95% CI) 1,269 1,209 100% 0.90 [0.65, 1.16]

Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 113.10$, $df = 4$ ($p < 0.00001$); $I^2 = 96\%$

Test of overall effect: $Z = 6.93$ ($p < 0.00001$)

24 h ASBP

Study or subgroup	LCZ696 200 mg			LCZ696 400 mg			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Ruilope LM	-11.5	0.93	61	-14.56	1.03	53	23.8%	3.06 [2.70, 3.42]
NCT01785472	-12.07	0.49	188	-12.76	0.49	184	25.5%	0.69 [0.59, 0.79]
NCT01599104	-13.44	0.45	216	-14.99	0.45	216	25.6%	1.55 [1.47, 1.63]
Kario K	-15.18	0.64	84	-15.98	0.65	82	25.1%	0.80 [0.60, 1.00]

Total (95% CI) 549 535 100% 1.50 [0.84, 2.17]

Heterogeneity: $\tau^2 = 0.45$; $\chi^2 = 283.18$, $df = 3$ ($p < 0.00001$); $I^2 = 99\%$

Test of overall effect: $Z = 4.43$ ($p < 0.00001$)

24 h ADBP

Study or subgroup	LCZ696 200 mg			LCZ696 400 mg			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Ruilope LM	-6.78	0.64	61	-8.32	0.71	53	22.4%	1.54 [1.29, 1.79]
NCT01785472	-6.36	0.31	188	-6.82	0.32	184	26.3%	0.46 [0.40, 0.52]
NCT01599104	-7.65	0.3	216	-8.44	0.3	216	26.4%	0.79 [0.73, 0.85]
Kario K	-9.33	0.49	84	-9.69	0.5	82	24.9%	0.36 [0.21, 0.51]

Total (95% CI) 549 535 100% 0.76 [0.47, 1.06]

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 120.38$, $df = 3$ ($p < 0.00001$); $I^2 = 98\%$

Test of overall effect: $Z = 5.07$ ($p < 0.00001$)

Fig. 6. Forest plots of SBP, DBP, 24 h ASBP, and 24 h ADBP in LCZ696 200 versus 400 mg. LCZ696 400 mg showed a significant reduction in SBP (MD 1.71 mm Hg, 95% CI 1.15 to 2.27, $p < 0.05$), DBP (MD 0.90 mm Hg, 95% CI 0.65 to 1.16, $p < 0.05$), 24 h ASBP (MD 1.50 mm Hg, 95% CI 0.84 to 2.17, $p < 0.05$), and 24 h ADBP (MD 0.76 mm Hg, 95% CI 0.47 to 1.06, $p < 0.05$) when compared with LCZ696 200 mg.

tihypertensive drug. In addition to the cardiovascular benefits of RAS blockade, LCZ696 is capable of neprilysin inhibition, which enhances the reduction of blood pressure. Ruilope et al. [6] were the first to demonstrate the antihypertensive efficacy of LCZ696. Ye et al. [21] showed that LCZ696 is more effective in reducing blood pressure than placebo. Ito et al. [22] suggested that LCZ696 administration may be a promising therapeutic approach for Japanese patients with hypertension and renal dysfunction. In our meta-analysis, we found that LCZ696 (100, 200, and 400 mg) produced significantly greater reductions in SBP, DBP, 24 h ASBP, and 24 h ADBP than ARBs alone in hypertensive patients. These results are consistent with the meta-analyses of Ye et al. [21] and Zhao et al. [23]. Compared with ARBs alone, LCZ696 causes a greater reduction in blood pressure, mainly attributed to RAS inhibition occurring simultaneously with neprilysin inhibition.

Ours is the first meta-analysis to evaluate the efficacy of different LCZ696 dosages on blood pressure. We demonstrated the efficacy of LCZ696 100 mg versus 200 mg and LCZ696 200 mg versus 400 mg. We found no significant differences in the reduction in SBP and DBP between 100 and 200 mg of LCZ696. However, LCZ696 200 mg caused a significantly greater 24 h ASBP reduction than LCZ696 100 mg. 24 h ADBP did not differ significantly between 100 and 200 mg LCZ696 ($p = 0.05$). However, as shown in Figure 5, there was a tendency towards a reduction in 24 h ADBP associated with 200 mg LCZ696. This result should be interpreted with caution. Large-scale RCTs need to confirm the antihypertensive effects of 100 and 200 mg LCZ696.

Compared with SBP and DBP, 24 h ASBP and 24 h ADBP are better able to reflect the antihypertensive effect of drugs. For patients with hypertension, we should pay more attention to 24-h ambulatory blood pressure, as this is a better predictor of cardiovascular mortality and stroke than office blood pressure [24, 25]. Mean plasma concentration time profiles for valsartan were found to be similar after the administration of LCZ696 400 mg or valsartan 320 mg [26]. Mean terminal half-life (median 18 h) was similar between LCZ696 400 mg and valsartan 320 mg treatments. We found that 400 mg LCZ696 caused significant reductions in SBP, DBP, 24 h ASBP, and 24 h ADBP compared with 200 mg LCZ696. The guidelines recommended ARBs as the first-line therapy. LCZ696 is also effective in lowering blood pressure.

Several limitations of this meta-analysis should be noted. First, 5 of the included studies (NCT01353508, NCT01256411, NCT01599104, NCT01785472, and

NCT01876368) were not published in scientific articles and were derived from the Novartis Pharma database. This could affect the observed results. Second, most of the trials included had a short follow-up period. The reductions in blood pressure only reflected the short-term effects of LCZ696. Third, the types and dosages of ARBs were different; the olmesartan dosage was 20 or 40 mg and the valsartan dosage was 80–320 mg. Fourth, the sample sizes in the LCZ696 100 mg and 200 mg groups were very small. Additional large-scale studies are needed to confirm the effects of 100 and 200 mg of LCZ696 on SBP, DBP, 24 h ASBP, and 24 h ADBP.

To summarize, LCZ696 was found to be safe and well tolerated [27]. This study provides new evidence for the reduction in blood pressure achieved with LCZ696 and adds new indications for LCZ696 in the instructions. The antihypertensive effect of LCZ696 is dose-related. LCZ696 can provide a reduction in blood pressure in addition to beneficial cardiovascular effects. For patients with heart failure and hypertension, treatment with LCZ696 should be given preference. Our results confirm the antihypertensive effects of LCZ696, a novel, dual-acting angiotensin receptor-neprilysin inhibitor.

Highlights

LCZ696 was found to be more effective in reducing blood pressure than ARBs. The antihypertensive effect of LCZ696 is dose-related. For heart failure complicated with hypertension, treatment with LCZ696 should be given preference.

Author Contributions

All authors had access to the data and participated in writing this manuscript.

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