Systematic Review and Meta-Analysis

Medicine®

OPEN

Effect and safety of LCZ696 in the treatment of hypertension

A meta-analysis of 9 RCT studies

Qiongqiong Li, MD[a], Lina Li, MD[a], Fanghao Wang, MD[a], Wei Zhang, MD[b], Yipeng Guo, MD[c], Fuzhen Wang, MD[d], Youxia Liu, PhD[a], Junya Jia, PhD[a,*], Shan Lin, MD[a,*]

Abstract

Background: LCZ696 has been introduced in patients with hypertension in several trials. Here, we performed a meta-analysis to evaluate the effect and safety of LCZ696 in hypertensive patients.

Methods: PubMed, Embase, the Cochrane Library and ClinicalTrials.gov databases were searched to identify the available randomized controlled trials (RCTs) investigating the effect and safety of LCZ696 in hypertension patients. The last search date was October 31, 2018.

Results: Nine RCTs with 6765 subjects were finally included, in which 8 trials compared the effect and safety between LCZ696 and angiotensin receptor antagonists (ARBs). Evidences showed LCZ696, compared with ARBs, achieved a better blood pressure control rate (OR 1.24, 95% CI: 1.14–1.35), specifically, LCZ696 were better at reducing systolic blood pressure [WMD −4.11 mmHg, 95% CI: (−5.13, −3.08) mmHg], diastolic blood pressure [WMD −1.79 mmHg, 95% CI: (−2.22, −1.37) mmHg], mean 24-hour ambulatory systolic blood pressure [WMD −3.24 mmHg, 95% CI: (−4.48, −1.99) mmHg] and mean 24-hour ambulatory diastolic blood pressure [WMD −1.25 mmHg, 95% CI: (−1.81, −0.69) mmHg]. There was no difference in the events of adverse events (risk ratio [RR] 1.01, 95% CI: 0.39–1.09), serious adverse events (RR 0.80, 95% CI: 0.52–1.22) and discontinuation of treatment for any adverse events (RR 0.79, 95% CI: 0.56–1.11) between LCZ696 group and ARB/placebo group, except LCZ696 reduced the rate of headaches (RR 0.69, 95% CI: 0.48-0.99) while increased cough (RR 2.12, 95% CI: 1.11–4.04; $P = .02$; $I^2 = 25\%$).

Conclusion: Our finding provides evidence that LCZ 696 was more effective than ARB on blood pressure control and was safe enough in patients with hypertension.

Abbreviations: AEs = adverse events, ARBs = angiotensin receptor antagonists, CI = confidence interval, DBP = diastolic blood pressure, HTN = hypertension, maDBP = mean 24-hour ambulatory DBP, maSBP = mean 24-hour ambulatory SBP, RCTs = randomized controlled trials, RR = risk ratio, SBP = systolic blood pressure.

Keywords: hypertension, LCZ696, meta

1. Introduction

Hypertension (HTN) is a leading risk factor for almost all different cardiovascular diseases (such as coronary disease, left ventricular hypertrophy, atrial fibrillation, stroke, and renal failure, etc). The number of patients with elevated blood pressure is huge, as reported, and its estimated prevalence among adults is 31.1% in 2010.[1,2] Furthermore, the number is predicted to increase with the increasing prevalence of obesity and the aging of the population.[2]

Choosing right drugs is very important for patients with HTN. Currently, thiazide diuretics, calcium channel blockers (CCBs),

Editor: Stefano Omboni.

This work was supported by grants from the National Natural Science Foundation (81600553, 81270791, and 30800529), Tianjin Municipal Science and Technology Commission Foundation (14JCYBJC27900) and Tianjin Public Health Bureau Foundation (2014KR16), The 12th Five-Year Plan National Science and Technology Support Program (No. 2011BAI10B02) and Shanxi Public Health Bureau Foundation (201302051), the General Hospital of Tianjin Medical University Youth Incubation Foundation (ZYYFY2015001). Study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

The authors declare that there is no conflict of interests regarding the publication of this article

Supplemental Digital Content is available for this article.

[a] Department of Nephrology, General Hospital of Tianjin Medical University, [b] Department of Cardiac Surgery, Tianjin Chest Hospital, [c] Department of Epidemiology, Tianjin Public Health Bureau, Tianjin, [d] Department of Statistics, Fenyang Hospital of Shanxi Province, Fenyang, China.

[*] Correspondence: Junya Jia, Nephrology department, Tianjin Medical University General Hospital, NO.154,Anshan road, Heping district, Tianjin, China (e-mail: jiajunya@126.com); Shan Lin, Nephrology department, Tianjin Medical University General Hospital, NO.154,Anshan road, Heping district, Tianjin, China (e-mail: linshan@medmail.com.cn)

Medicine (2019) 98:28(e16093)

Received: 20 December 2018 / Received in final form: 2 May 2019 / Accepted: 25 May 2019

http://dx.doi.org/10.1097/MD.0000000000016093

angiotensin receptor blockers (ARBs), or angiotensin-converting enzyme (ACE) inhibitors have been recommended as the first-line agents for the initiation of pharmacological therapy in HTN patients.[3] However, many treated patients still cannot reach the ideal blood pressure level, and we still need to keep looking for better anti-HTN drugs to achieve BP goals and reduce cardiovascular events and other complications.

LCZ696 (Entresto, sacubitril/valsartan) is the first of a new drug class referred to as angiotensin receptor-neprilysin inhibitor (ARNi). Several large clinical trials have confirmed its role in improving heart failure, and also revealed its potential for blood pressure control.[4,5] Here, we queried literature and performed a meta-analysis on available randomized clinical trials (RCTs) to investigate the effect and safety of LCZ696 in HTN patients.

2. Material and methods

2.1. Ethics statement

As all analyses were based on previously published studies, and no ethical approval or patient consent was required.

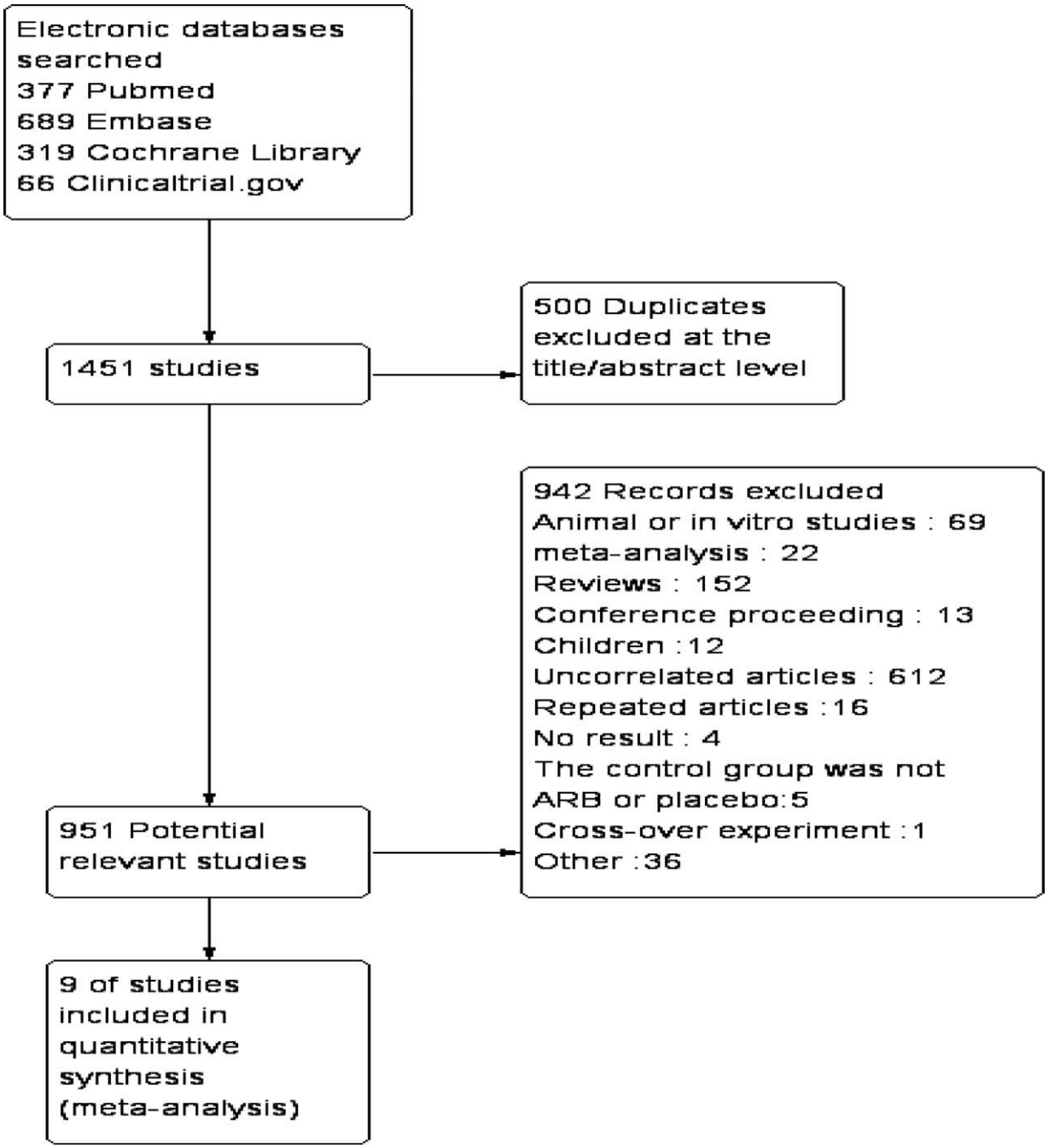

Figure 1. Flow diagram of the study selection process.

2.2. Search strategy

Our authors searched the following several databases for primary studies: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com), the Cochrane Library (http://www.cochrane.org), and ClinicalTrials.gov databases (http://www.clinicaltrials.gov/) (all up to October 14, 2018). Medical Subject Headings (MeSH) and corresponding keywords including as shown below: "sacubitril/valsartan", "LCZ696", "neprilysin inhibitor", "AHU377", "entresto", and "angiotensin receptor neprilysin inhibitor". Relevant articles' reference lists were also used to supplement the search entry. No language restrictions were set.

2.3. Study selection

Suitable studies were elected if they met the following inclusion criteria:

(I) the trial was a RCT;
(II) the experimental group used LCZ696;
(III) the control group used ARBs or placebo (any dose, type);
(IV) investigating the impact of LCZ696 on blood pressure control;
(V) providing data about adverse events.

We excluded some unqualified articles. Two cross-over trials, which has less patients and shorter observation time, were excluded. Conference articles were excluded for avoiding to incorporate repeated publication. Specific details of the study selection for this meta-analysis are shown in Figure 1.

2.4. Data extraction

A rigorous data collection table was used for data extracting important information. Two investigators (Q.L. and L. L.) independently finished the task of finding reference lists of the eligible articles. Controversial articles were adjudicated by a third author. Among the eligible articles, data extracted including the following information:

(I) first author's name;
(II) publication year;
(III) types of trials design;
(IV) numbers of subjects enrolled;
(V) general characteristics of participants, including age, sex, BP, and so on;
(VI) names and doses of intervention drugs, and durations of treatment;
(VII) change of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean 24-hour ambulatory SBP (maSBP), and mean 24-hour ambulatory DBP (maDBP);
(VIII) numbers of patients who achieved BP control;
(IX) incidence of adverse events (AEs).

2.5. Quality assessment

The Jadad scale was used for the quality assessment, which is an established procedure. The scores of the Jadad scale range from 0 to 7 points, and mainly in 4 aspects:

(1) the appropriateness of the randomization methods (1–2 points);
(2) allocation concealment (1–2 points);
(3) double-blind design (1–2 points);
(4) the analysis and reasons for withdrawals and dropouts (0–1 point).

Two reviewers independently assessed the quality of included studies. Fortunately, they had no disagreements. The scores of Jadad scale range from 0 to 7, Studies with the score ≥4 should be

Table 1

Baseline Characteristics of Trials included in the Meta-Analysis.

First author Year	Sample size	Study design	Gender (F/M)	Mean age (yr)	Control group	Duration	Baseline BP (mm Hg)
Cheung[7] 2018	376	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	183/192	57.6 (9.65)	Olmesartan20 mg/day	8 wk	mild to moderate hypertension
Izzo[8] 2017	910	Randomized, double-blind, parallel-group, placebo and active-controlled, multicenter Study	412/495	61.5 (11.13)	Valsartan320 mg/day	8 wk	SBP≥150-<180 mm Hg, DBP≥70mmHg
Schmieder[9] 2017	115	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	37/77	59.8 (10.7)	Olmesartan 40 mg/day	52 wk	SBP≥140 mmHg and <180 mmHg
Supasyndh[10] 2017	588	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	294/294	70.7 (4.67)	Olmesartan 20 mg/day	14 wk	SBP≥150 mmHg and <180 mmHg
Williams[11] 2017	454	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	217/237	67.7 (5.87)	Olmesartan 20mg/day	52w	SBP≥150 mmHg and <180 mmHg
Nct[12] 2013	1438	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	679/756	57.7 (10.01)	Olmesartan 20 mg/day	8 wk	SBP≥150 mmHg and <180 mmHg
Nct[14] 2012	1161	Randomized, double-blind, parallel-group, active-controlled, multicenter Study	343/818	58.7 (10.64)	Olmesartan 20 mg/day	8 wk	SBP≥ 150 mmHg and < 180 mmHg
Ruilope[13] 2010	1334	Randomized, double-blind, parallel-group, placebo and active-controlled, multicenter Study	568/760	53 (10.2)	Valsartan 80 mg/day; Valsartan160 mg/day; Valsartan320 mg/day; placebo	8 wk	mild-to-moderate hypertension
Kario[15] 2014	389	Randomized, double-blind, parallel-group, placebo and active-controlled, multicenter Study	114/275	51.6 (9.82)	placebo	8 wk	SBP≥140 mmHg and < 180 mmHg, DBP ≥ 95 mmHg and < 110 mmHg

F = female, M = male, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table 2

Quality evaluation of clinical trials inclued using the Jadad scale.

First author	Year	Random sequence generation	Allocation concealment	Double blinding	Description of withdrawals and drop-out	Score
Cheung[7]	2018	1	1	2	1	5
Izzo [8]	2017	1	1	2	1	5
Schmieder[9]	2017	2	1	2	1	5
Supasyndh[10]	2017	1	1	2	1	5
Williams[11]	2017	1	1	1	1	4
Nct[12]	2013	1	1	1	1	4
Nct[14]	2012	1	1	1	1	4
Ruilope[13]	2010	2	2	2	1	7
Kario[15]	2014	1	1	1	1	4

considered as having a good quality, while ≤ 3 as having a poor quality.

2.6. Outcome measures

The end points were compared between the LCZ696 group and ARB or placebo group:

(1) changes from the baseline in SBP, DBP, maSBP, and maDBP;
(2) numbers of participants who achieved BP control, defined as SBP/DBP $<140/90$ mm Hg;
(3) AEs, mentioned by the researchers.

2.7. Statistical analysis

This meta-analysis was conducted using statistical software STATA version 12.0. For continuous variable, data were represented as the weighted mean difference (WMD) with a 95% confidence interval (CI) between the intervention and control groups. We performed subgroup analysis to assess the effect on BP control based on the dose of LCZ696. For dichotomous outcome data, the risk ratio (RR) with 95% CI was calculated. The Heterogeneity between studies was assessed using the chi-squared test (presented as I^2), the random effects model

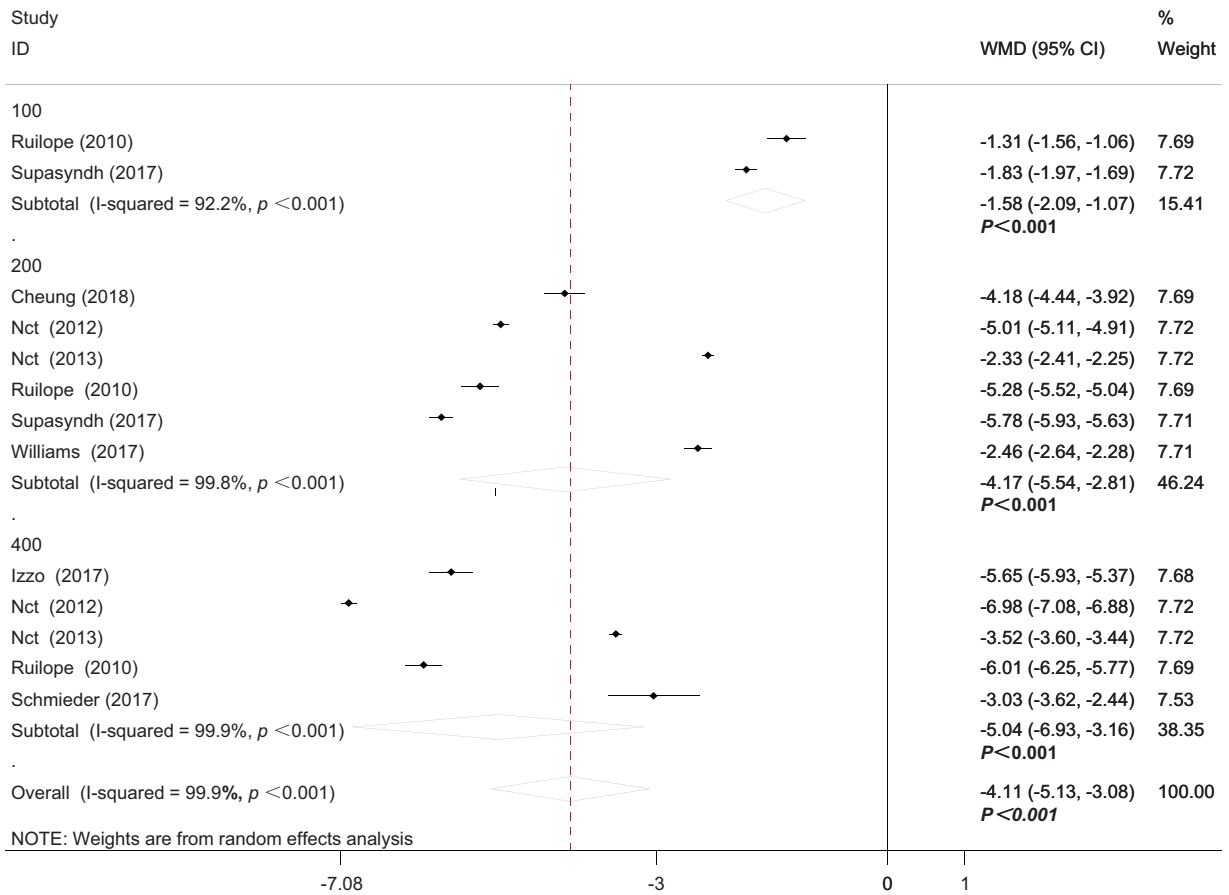

Figure 2. Comparison of LCZ696 with ARB groups on the outcome of systolic blood pressure. ARB = angiotensin receptor antagonist.

(which using the D-L method) was applied when I^2 ≥50%, otherwise the fixed effects model (which using the Mantel-Haenszel method) was used for data analysis.[6] And z test used for overall effect. Statistical significance was set at 0.05.

2.8. Publication bias

Funnel plots and Begg test were used to probe for publication bias. Two-sided *P* value <.05 was regarded as statistically significant for all included studies. All statistical analysis was performed using STATA version12.0 and Review Manager 5.3 statistical software for the meta-analysis.

3. Results

3.1. Characteristics of enrolled studies

A total of 1451 relevant studies had been found from the above-mentioned databases, of which 9 studies (Cheung's study,[7] Izzo's study[8], Schmieder's study[9], Supasyndh's study[10], Williams's study[11], Nct's study[12], Ruilope's study[13], Nct 's study[14], Kario's study [15]) with 6765 individuals were finally assessed for eligibility based on the inclusion and exclusion criteria.

A summary of the primary details of these included studies are showed in Figure 1 below. Here, 8 trials touch on a comparison between LCZ696 and ARB groups. All selected studies are clinical RCTs. The mean age ranged from 51.6 to 70.7 years old, and more male than female. The duration over which outcomes were measured ranged from 8 weeks to 52 weeks. The detailed characteristics of these studies are listed in Table 1.

3.2. Quality assessment

Studies were quantitatively classified according to the Jadad scale respectively. All trials included are judged as high-quality articles (Jadad score ≥3), and they are randomized, double-blind, parallel-group, placebo and/or active-controlled, multicenter studies. The details of the risk-of-bias analysis are shown in Table 2.

3.3. Assessment of blood pressure control

As outlined in the following figures (), we identified 8 RCTs (Cheung's study[7], Izzo's study[8], Schmieder's study[9], Supasyndh's study[10], Williams's study[11], Nct's study[12], Ruilope's study[13], Nct 's study[14]) which enrolled in 5401 patients for the effect of LCZ696 on BP reduction compared with ARB groups.

LCZ696 significantly lowered SBP (WMD −4.11 mmHg;95% CI, −5.13 to −3.08; *P* <.001; I^2 = 99.9%), DBP (WMD, −1.79mmHg; 95% CI, −2.22 to −1.37; *P* <.001; I^2 = 99.7%), maSBP (WMD, −3.24mmHg; 95% CI, −4.48 to −1.99; *P* <.001; I^2 = 99.9%), maDBP (WMD, −1.25mmHg; 95% CI, −1.81

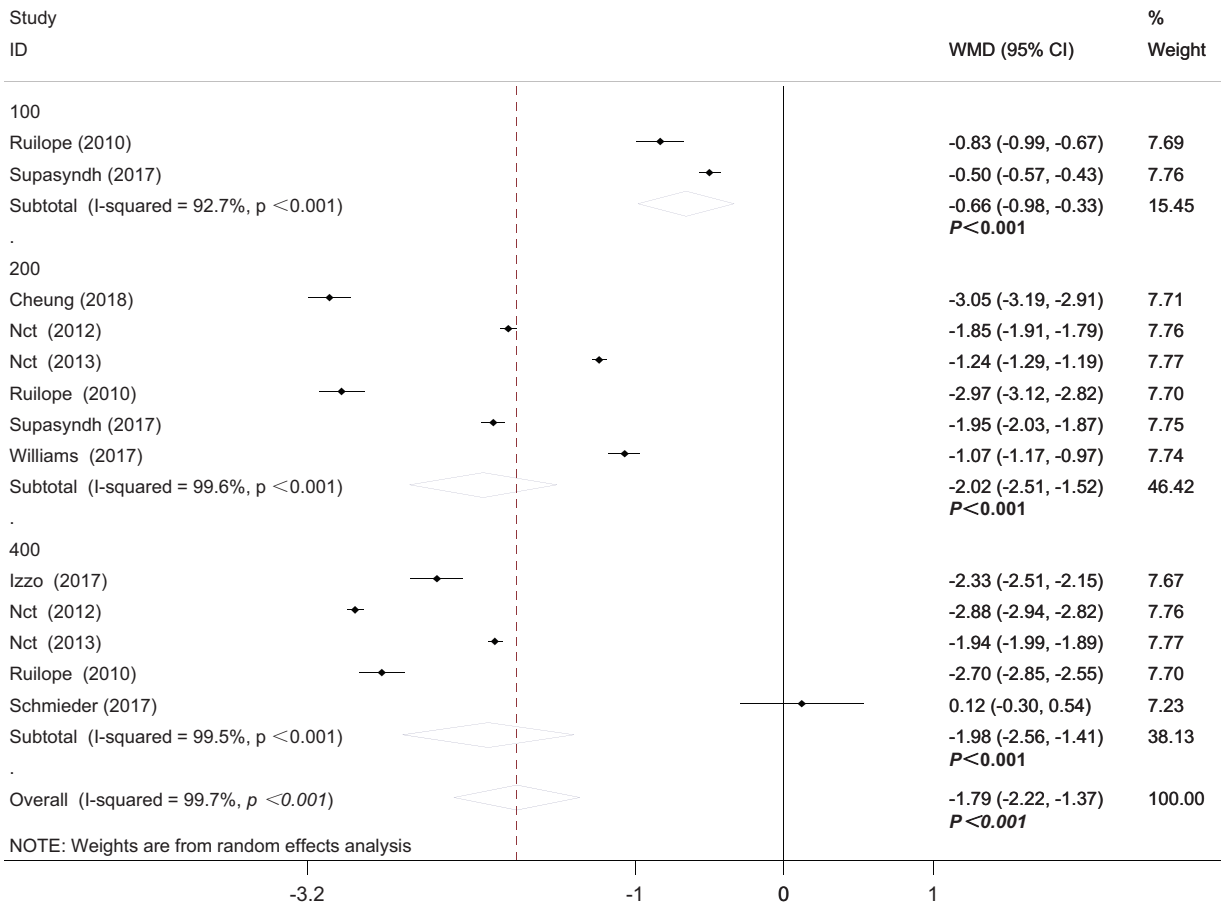

Figure 3. Comparison of LCZ696 with ARB groups on the outcome of diastolic blood pressure. ARB = angiotensin receptor antagonist.

to −0.69; $P < .001$; $I^2 = 99.8\%$) in comparing with ARB. People with LCZ696 treatment more easily achieved a successful BP control (OR = 1.24; 95% CI, 1.14 to 1.35; $P < .001$; $I^2 = 35.7\%$) than ARB treatment.

LCZ696 treatment with 100 mg daily showed a more obvious reduction in SBP (WMD, −1.58 mmHg; 95% CI, −2.09 to −1.07; $P < .001$; $I^2 = 92.2\%$), DBP (WMD, −0.66mmHg; 95% CI, −0.98 to −0.33; $P < .001$; $I^2 = 92.7\%$), maSBP (WMD, −0.51mmHg; 95% CI, −0.9 to −0.12; $P = .01$; $I^2 < 0.001\%$), maDBP (WMD, 0.76mmHg; 95% CI, 0.49 to 1.03; $P < .001$; $I^2 < 0.001\%$) in comparing with ARB groups. And LCZ696 treatment showed an advantage in successfully achieving BP control (OR, 1.15; 95% CI, 0.96–1.38; $P = .131$; $I^2 = 0\%$).

LCZ696 at 200 mg/d displayed a further reduction in SBP (WMD, −4.17 mmHg; 95% CI, −5.54 to −2.81; $P < .001$; $I^2 = 99.8\%$), DBP (WMD, −2.02 mmHg; 95% CI, −2.51 to −1.52; $P < .001$; $I^2 = 99.6\%$), maSBP (WMD, −2.97 mmHg; 95% CI, −4.64 to −1.31; $P < .001$; $I^2 = 99.9\%$), maDBP (WMD, -1.37 mmHg; 95% CI, -2.09 to −0.64; $P < .0001$; $I^2 = 99.8\%$) in comparing with ARB. The data proved that advantage of LCZ696 treatment in achieving BP control successfully (OR, 1.25; 95% CI, 1.05 to 1.48; $P = .011$; $I^2 = 60.6\%$) than ARB treatment.

LCZ696 at 400 mg/d also displayed a more obvious reduction in SBP (WMD, −5.04 mmHg;95% CI, −6.93 to −3.16; $P < .001$; $I^2 = 99.9\%$), DBP (WMD, −1.98 mmHg; 95% CI, −2.56 to −1.41; $P < .001$; $I^2 = 99.5\%$), maSBP (WMD, −4.31 mmHg; 95% CI, −6.55 to −2.06; $P < .001$; $I^2 = 99.9\%$), maDBP (WMD, −1.56 mmHg; 95% CI, −2.65 to −0.48; $P = .005$; $I^2 = 99.8\%$). Besides, LCZ696 treatment more easily achieved a better BP control (OR, 1.28; 95% CI, 1.13–1.46; $P < .001$; $I^2 = 38.5\%$) than ARB treatment.

3.4. Adverse events

Systematic evaluations of AEs data analysis were shown in the Table 3. In 9 trials enrolled, the result showed no statistical difference found between LCZ696 and ARB/placebo group in any adverse events (RR= 1.01; 95% CI: 0.39–1.09; $P = .83$; $I^2 = 38\%$), serious adverse events (RR= 0.80; 95% CI: 0.52–1.22; $P = .30$; $I^2 = 45\%$) and discontinued because of adverse events (RR= 0.79; 95% CI: 0.56–1.11; $P = .18$;$I^2 = 20\%$).And the results also demonstrated that adverse events such as dizziness, diarrhea, upper respiratory tract infection, nasopharyngitis, back pain, arthralgia, atrial fibrillation, edema had the same incidence in LCZ696 group and ARB/placebo groups. It is worth noting that LCZ696 treatment could decreased the incidence rate of headache (RR= 0.69; 95% CI: 0.48–0.99; $P = .004$; $I^2 = 0\%$) while increase cough (RR= 2.12; 95% CI: 1.11–4.04; $P = .02$; $I^2 = 25\%$).

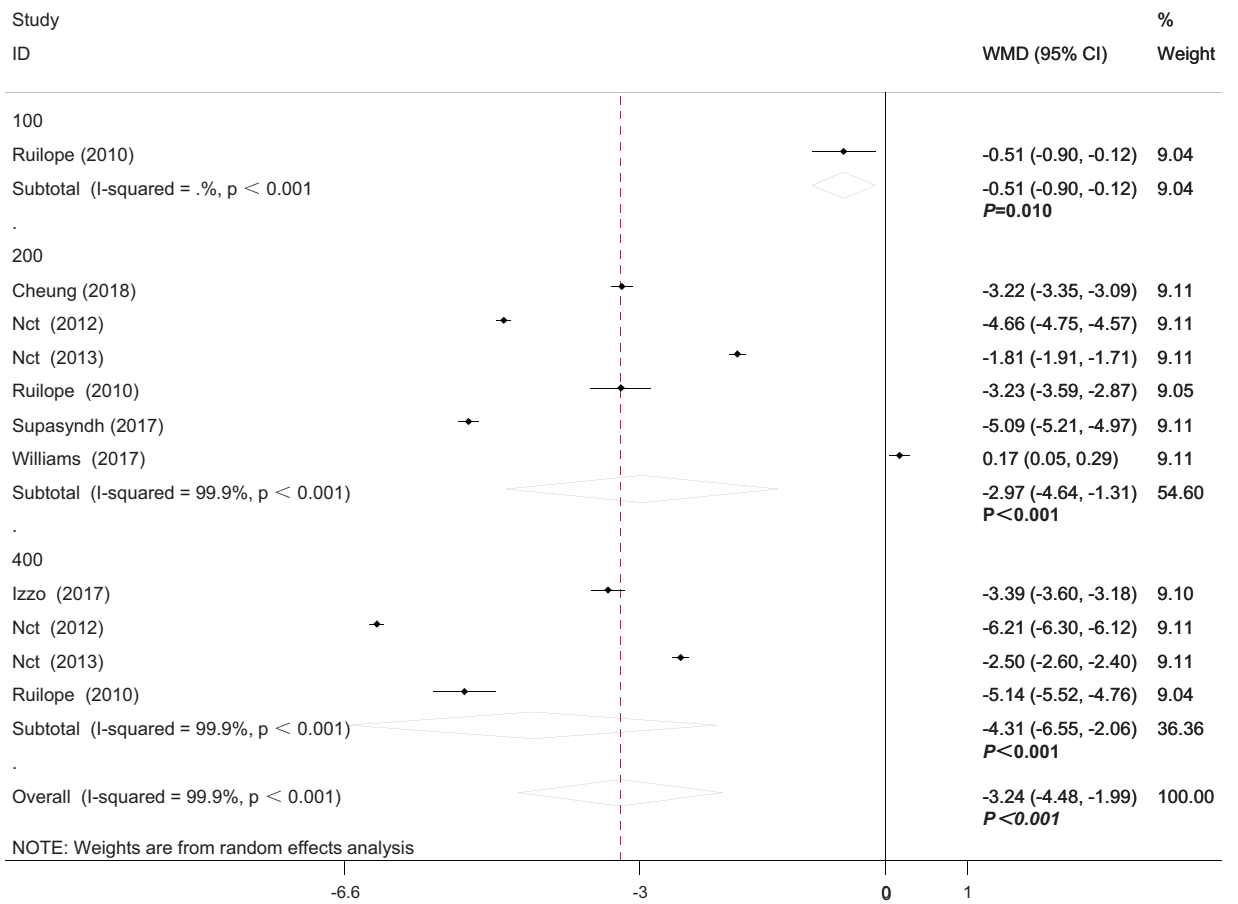

Figure 4. Comparison of LCZ696 with ARB groups on the outcome of mean 24-hour ambulatory SBP. ARB = angiotensin receptor antagonist, SBP = systolic blood pressure.

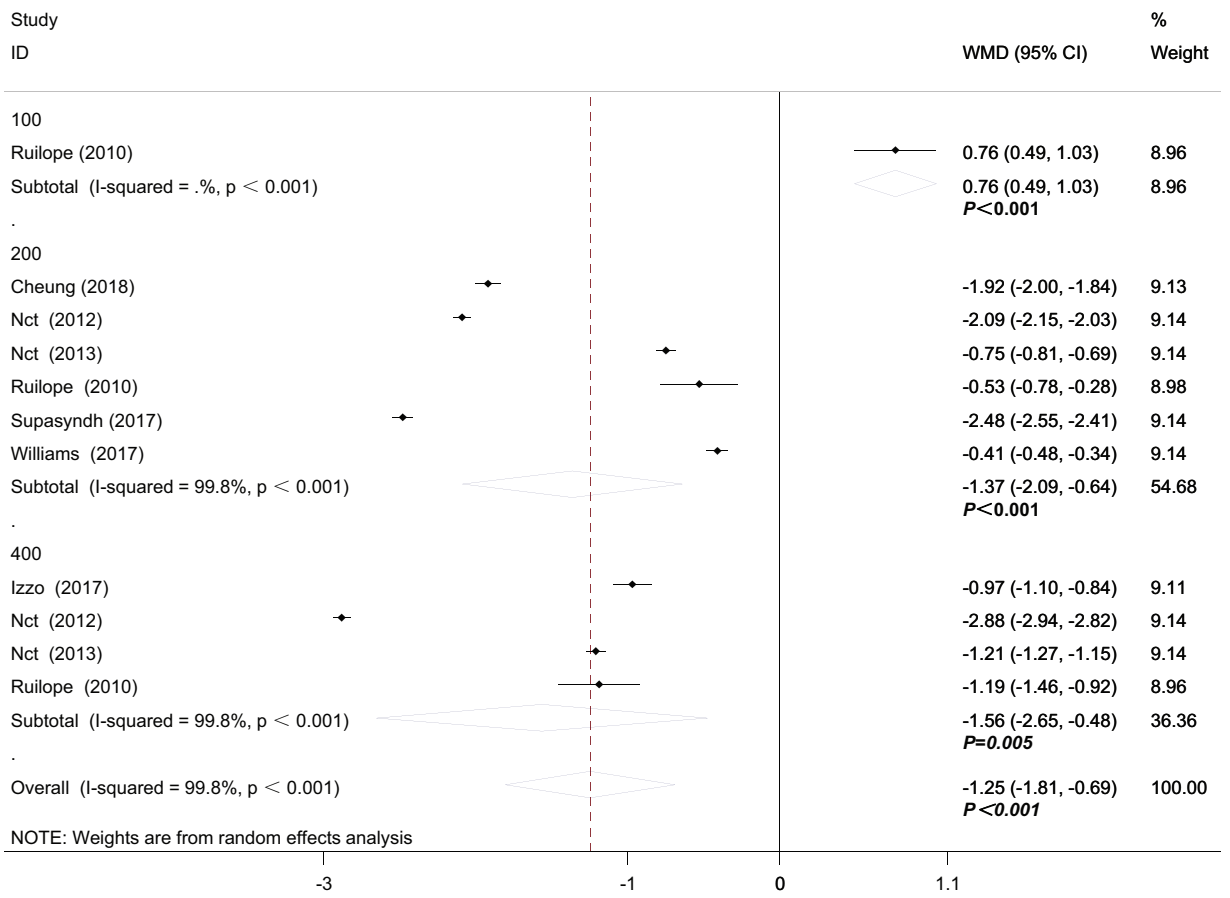

Figure 5. Comparison of LCZ696 with ARB groups on the outcome of mean 24-hour ambulatory DBP. ARB = angiotensin receptor antagonist, DBP = diastolic blood pressure.

3.5. Assessment of publication bias

Sensitivity analysis was conducted to evaluate the effect of studies with a high risk of bias on overall effect size. Among these RCTs, no evidence of publication bias was detected (see S1and S2, Supplemental Content, http://links.lww.com/MD/D87, which demonstrates the result of publication bias).

4. Discussion

4.1. Main findings

In the present study, we systematically analyse the current available studies that investigate the effects and safety of LCZ696 on blood pressure control. These findings from the current study demonstrated that LCZ696, comparing with ARBs, can lower effectively BP (including SBP, DBP, maSBP, maDBP), and elevate the numbers of participants who achieved BP control. And the subgroup analysis clearly showed that LCZ696's intensity of BP-lowering is in relation to the dose of drug. In addition, LCZ696 group had no more adverse events occurrence comparing with ARB/ placebo groups among the eligible trials. LCZ696 treatment effectively reduced the rate of headache comparing with ARB/ placebo groups however increased cough. In brief, as a drug combining of with ARB and neprilysin inhibitor, LCZ696 exhibited its superiority.

A study in reducing blood pressure revealed that in patients with uncontrolled hypertension, fixed-dose combinations may help to improve adherence and persistence, which were crucial for the success of medical treatment.[16] Besides, the combination therapy is superior to a doubling of monotherapy by 4 to 5 times.[17]

LCZ696 is an angiotensin receptor-neprilysin inhibitor, literally, LCZ696 consists of valsartan and sacubitril in a salt delivering a 1:1 molar ratio of its constituents after oral administration.[18] Valsartan, one of Angiotensin II receptor blockers, selectively blocks AT 1 and inhibits angiotensin-II-dependent aldosterone release. By inhibiting renin-angiotensin-aldosterone system which plays a big role in the pathogenesis of HTN, ARBs are regarded as potent, effective and largely safe drugs for the management of hypertension. Sacubitril is a prodrug that can be hydrolyzed to form LBQ657, which also potently inhibit neprilysin (NEP).[18]The NEP is known as a key enzyme in the degradation of natriuretic peptides, and direct consequence of NEP inhibition is circulating natriuretic peptides (NPs) and other vasoactive peptides increase. The synergistic effect of sacubitril and valsartan is systemic vasodilation, meanwhile diuresis and natriuresis increase, which decreases in peripheral vascular resistance and plasma volume contraction, all important actions for the lowering of BP.[19]

4.2. Findings in relation to other studies

Searched in databases mentioned, we found several meta-analyses concerning the LCZ696. Our results are consistent

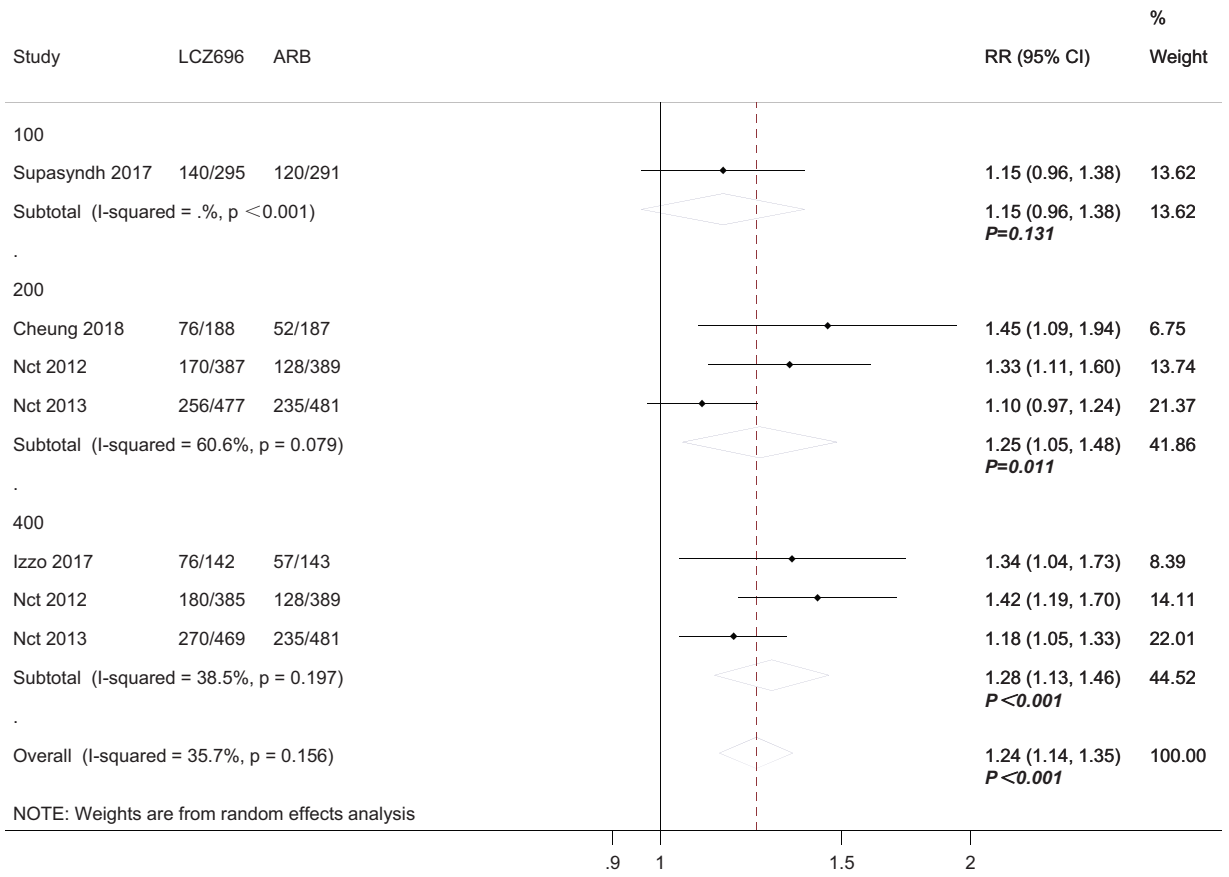

Figure 6. Comparison of LCZ696 with ARB on the blood pressure control rate. ARB = angiotensin receptor antagonist.

with Zhao' conclusion[20] that LCZ696 effectively reduce BP and patients with LCZ696 treatment could more easily achieve the BP goals, although inclusion and exclusion criteria differ: we excluded conference articles and cross-over trials as mentioned before. Li et al[21] conducted a meta-analysis about the safety of LCZ 696, and they got a conclusion that LCZ696 significantly increased the risk of angioedema and dizziness. After expanding the sample size, we got different conclusions that LCZ696 significantly reduced incidence of headache, while not affect edema.

4.3. Implications for clinical practice and further research

Studies confirmed the efficacy of sacubitril/valsartan on improving heart failure. McMurray et al performed a big study named PARADIGM-HF study, which enrolled 8442 patients with

Table 3

Adverse events reported in the included studies.

Adverse events	Studies reporting, n	LCZ696 group, n/n	Control group, n/n	RR (95%CI)	*P value*
Any adverse events	9	1032/3628	787/2674	1.01 (0.93, 1.09)	*P = .83*
serious adverse events	9	39/3428	37/2450	0.80 (0.52, 1.22)	*P = .30*
Discontinued because of adverse events	9	62/3430	63/2598	0.79 (0.56, 1.11)	*P = .18*
Headache	7	45/2030	55/1542	0.69 (0.48,0.99)	*P = .004**
Dizziness	8	56/2656	35/2205	1.26 (0.83, 1.91)	*P = .29*
Diarrhea	4	17/1165	20/1184	0.90 (0.48, 1.71)	*P = .76*
Nasopharyngitis	8	172/2478	98/2110	1.14 (0.90, 1.44)	*P = .28*
Edema	4	9/616	3/612	2.31 (0.77, 6.95)	*P = .14*
Upper respiratory tract infection	6	46/2411	34/1960	1.09 (0.70, 1.71)	*P = .70*
Cough	5	35/2006	13/1532	2.12 (1.11, 4.06)	*P = .02**
Atrial fibrillation	3	3/1475	2/1001	1.09 (0.27, 4.40)	*P = .90*
Arthralgia	4	11/770	7/762	1.48 (0.61, 3.59)	*P = .38*
Influenza	3	15/783	12/390	0.59 (0.30, 1.18)	*P = .14*
Back pain	3	10/783	20/775	0.49 (0.23, 1.05)	*P = .07*

RR = risk ratio.
* *P* <.05.

reduced ejection fraction (EF ≤40%) to compare the effects of LCZ696 monotherapy with enalapril, they terminated the experiment in advance with finding that LCZ696 was superior to enalapril in significantly improving heart function, and could reduce death from cardiovascular causes or hospitalization for HF.[22] Besides treatment with LCZ696 don't influence renal function, even can do better for it.[23] Currently, LCZ696 combination has been approved in multiple countries.

Given its ideal validity and reliable safety, LCZ696 may be another first-line medication for patients with hypertension. But still, need enough experimental research to prove its feasibility. Subsequent trials should investigate issues such as characteristics of applicable people, fluctuation of blood pressure, cardiovascular events, and observation of long-term adverse reactions.

4.4. Strengths and limitations

The strength of our work lies in the comprehensive literature search, rigorous inclusion and exclusion criteria, careful screening process and enlarged sample size. In our study, we affirmed the advantage of LCZ696 on BP control. However, several possible limitations should be noted. First, 8 trials included had an unclear risk of bias with lacking adequate methodological information such as sequence generation and allocation concealment. Second, except for Schmieder's study[9] (52 weeks), Williams's study[11] (52 weeks), the other trials had short period of experimental observation, so the results on the adverse effects only reflected the short-term effects of LCZ696 treatment. As for long-term adverse reactions, more efforts should be made.

5. Conclusion

Overall, the meta-analyses illustrated that LCZ696 was more effective than ARB on blood control and as safe as ARB/placebo in patients with hypertension.

Author contributions

Data curation: Qiongqiong Li, Lina Li.
Formal analysis: Fuzhen Wang, Youxia Liu.
Methodology: Wei Zhang, Youxia Liu.
Software: Fanghao Wang, Yipeng Guo.
Supervision: Junya Jia, Shan Lin.
Writing – original draft: Qiongqiong Li, Lina Li.
Writing – review & editing: Junya Jia, Shan Lin.

References

[1] Kjeldsen SE. Hypertension and cardiovascular risk: general aspects. Pharmacol Res 2018;129:95–9.
[2] Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation 2016;134:441–50.
[3] Ali A, Abu Zar M, Kamal A, et al. American heart association high blood pressure protocol 2017: a literature review. Cureus 2018;10:e3230.
[4] Vardeny O, Claggett B, Kachadourian J, et al. Incidence, predictors, and outcomes associated with hypotensive episodes among heart failure patients receiving sacubitril/valsartan or enalapril: the PARADIGM-HF trial (prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin-converting enzyme inhibitor to determine impact on global mortality and morbidity in heart failure). Circ Heart Fail 2018;11: e004745.
[5] De Vecchis R, Ariano C, Di Biase G, et al. Sacubitril/valsartan for heart failure with reduced left ventricular ejection fraction: a retrospective cohort study. Herz 2018.
[6] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[7] Cheung DG, Aizenberg D, Gorbunov V, et al. Efficacy and safety of sacubitril/valsartan in patients with essential hypertension uncontrolled by olmesartan: a randomized, double-blind, 8-week study. J Clin Hypertens 2018;20:150–8.
[8] Izzo JL, Zappe DH, Jia Y, et al. Efficacy and safety of crystalline valsartan/sacubitril (LCZ696) compared to placebo and combinations of free valsartan and sacubitril in patients with systolic hypertension: the RATIO study. J Cardiovasc Pharmacol 2017.
[9] Schmieder RE, Wagner F, Mayr M, et al. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. Eur Heart J 2017;38:3308–17.
[10] Supasyndh O, Wang J, Hafeez K, et al. Efficacy and safety of sacubitril/valsartan (LCZ696) compared with olmesartan in elderly asian patients (>=65 years) with systolic hypertension. Am J Hypertens 2017;30:1163–9.
[11] Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension. Hypertension 2017;69:411–20.
[12] Nct. A Multi-center, Randomized, Double-blind, Active-controlled, 8-week Study to Evaluate the Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Patients With Essential Hypertension. Clinicaltrialsgov [http://clinicaltrialsgov]. 2013.
[13] Ruilope L, Schaefer A. The fixed-dose combination of olmesartan/amlodipine was superior in central aortic blood pressure reduction compared with perindopril/amlodipine: a randomized, double-blind trial in patients with hypertension. Adv Ther 2013;30:1086–99.
[14] Nct. A Multi-center, Randomized, Double-blind, Active-controlled, 8-week Study to Evaluate the Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension. Clinicaltrialsgov. Available at: http://clinicaltrialsgov. 2012.
[15] 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.
[16] Berra E, Azizi M, Capron A, et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension 2016;68:297–306.
[17] Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290–300.
[18] Howell EH, Cameron SJ. Neprilysin inhibition: a brief review of past pharmacological strategies for heart failure treatment and future directions. Cardiol J 2016;23:591–8.
[19] Mangiafico S, Costello-Boerrigter LC, Andersen IA, et al. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J 2013;34:886–93c.
[20] Zhao Y, Yu H, Zhao X, et al. The effects of LCZ696 in patients with hypertension compared with angiotensin receptor blockers: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol Ther 2017;22:447–57.
[21] Li B, Zhao Y, Yin B, et al. Safety of the neprilysin/renin-angiotensin system inhibitor LCZ696. Oncotarget 2017;8:83323–33.
[22] McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
[23] Ito S, Satoh M, Tamaki Y, et al. Safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. Hypertens Res 2015;38:269–75.