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Systematic Review

LCZ696 and preservation of renal function in heart failure: A meta-analysis of 6 randomized trials

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Patients with heart failure (HF) are prone to combine with renal insufficiency. Recently, LCZ696 has been used in the treatment of HF, but whether LCZ696 is better than angiotensin converting enzyme inhibitors/angiotensin receptor antagonists (ACEI/ARB) in renal protection for HF patients has not been investigated. Therefore, we conducted a meta-analysis focusing on LCZ696 and its role in preservation of renal function in HF patients. Embase, PubMed, the Cochrane Library and ClinicalTrials.gov databases were electronically searched for available randomized controlled trials (RCTs). HF patients taking LCZ696 or ACEI/ARB were assessed for renal adverse events. The last search date was Sep 20, 2019. A total of 14959 patients from 6 trials were included in this meta-analysis. As compared to ACEI/ARB, LCZ696 significantly reduced the risk of renal function deterioration (odds ratio 0.77, 95% confidence interval 0.61–0.97, P = 0.02). In summary, LCZ696 may have superior renal protection in HF patients compared with ACEI/ARB.

Keywords

LCZ696; heart failure; ACEI/ARB; worsening renal function

1. Introduction

Therapeutics of chronic heart failure (HF) had undergone great changes since 1980s, from improvement of hemodynamics to biological properties of the heart. Long-term activation of neuroendocrine system has been considered to be the main pathophysiological mechanism of HF, therefore, the focus on HF has changed from traditional "digitalis, diuretics and vasodilator" to "an attempt to inhibit neuroendocrine system", including angiotensin conversion enzyme inhibitors (ACEI)/angiotensin receptor antagonists (ARB), beta blockers and aldosterone receptor antagonists. Following the use of the "Golden Triangle" medications, the prognosis of HF patients has been improved significantly. Recently, a new medication called LCZ696 occurred in clinical practice, the most representative one of angiotensin receptor neprilysin inhibitor (ARNI). The effectiveness of LCZ696 has been proved in PARADIGM-HF trial, where authors showed that treatment with LCZ696 could lead to a significant reduction in the primary endpoints (-20%), including cardiovascular deaths and HF hospitalizations (Berliner and Bauersachs, 2019).

Renal function deterioration is one of the common side effects of ACEI/ARB, which limited their clinical use. However, LCZ696 has been reported to have a protective effect on the renal function and a reduction of risk of renal function deterioration in HF patients. Hence, we reviewed literatures and performed a meta-analysis based on available randomized clinical trials (RCTs) to illustrate the protective effects of LCZ696 on renal function.

2. Material and methods

2.1 Ethics statement

All our processes strictly followed the preferred reporting project of systematic review and meta-analysis (PRISMA). All studies included in the meta-analysis have been previously published, without ethical disputes and informed consent issues.

2.2 Search strategy

We systematically searched the current mainstream medical databases, including PubMed, the Cochrane Library, ClinicalTrials.gov database and Embase, covering a vast majority of medical literatures. Search criteria used were as follows: MeSHterm: "LCZ696", "AHU377", "sacubitril/valsartan", "entresto", "angiotensin receptor neprilysin inhibitor" and "neprilysin inhibitor". Searches were filtered to only output studies published in English, full-text and peer-reviewed (Fig. 1).

2.3 Inclusion and exclusion criteria of enrolled studies

Studies included in the meta-analysis should meet the following criteria:

(I) the type of trial had to be RCT;

(II) the subjects enrolled had to be diagnosed as HF;

(III) ACEI/ARB had to be used as intervention in the control group, LCZ696 as intervention in the experimental group;

(IV) all studies had to have data on renal adverse events (regard of as a secondary endpoint or an adverse reaction).

Studies were excluded if they did not have a measurement of renal function at baseline.

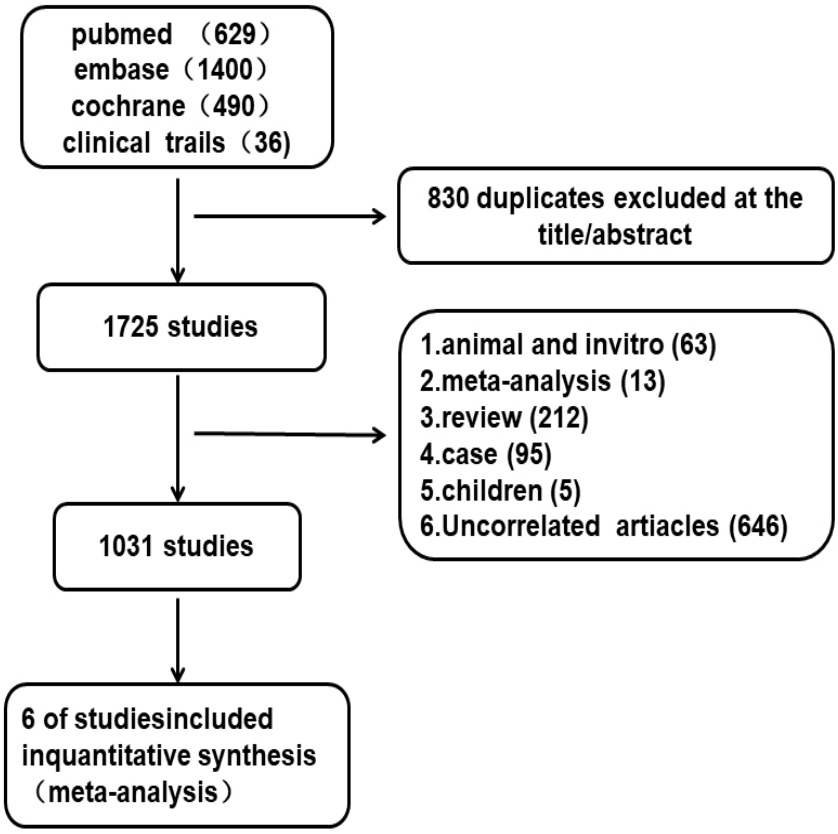

Figure 1. Literature screening flow chart

2.4 Data extraction

Two researchers with knowledge of systematic evaluation independently carried out literature screening and quality evaluation to ensure the objectivity of the process and results. At times of disagreement, a third party was enrolled for final judgment. Studies were excluded if full text could not be obtained. The studies were read in great detail to follow the inclusion and exclusion criteria. The specific screening process used is shown in Fig. 1. Following information was extracted from each study (Table 1):

(I) trial's name;

(II) year of publication;

(III) numbers of subjects enrolled;

(V) general characteristics of participants, including base estimated Glomerular Filtration Rate (eGFR) or Creatine, Ejection Fraction (EF), New York Heart Association functional class (NYHA), age and so on;

(VI) names of intervention drugs and control drugs and durations of visit;

(VII) renal function scoring and renal adverse events (Worsening renal function).

2.5 Quality assessment andStatistical analysis

We used common literature quality evaluation method called the Jadad Score Scale to evaluate literatures from four aspects: the method of randomization, allocation concealment, double-blind design, and the reasons and analysis of withdrawals and dropouts. According to the data type, we selected the outcomes which could reasonably reflect the data as a whole. Outcomes were measured and displayed as Dichotomous variables and the odds ratio (OR) with 95% confidence interval (CI). We tested the heterogeneity of meta-analysis through I2 and forest maps, and if I2 is less than 20%, it was considered to have good homogeneity. P-value of $<$ 0.05 (both side) was considered statistically significant.

3. Results

A total of 6 clinical RCT trials comparing LCZ696 vs. ACEI/ARB included in the meta-analysis (Desai et al., 2019; Kang et al., 2019; McMurray et al., 2014; Solomon et al., 2012, 2019; Velazquez et al., 2019). The detailed characteristics of these 6 studies are listed in Table 1. The total number of participants was 14,959, and the number of participants in individual trial ranged from 118 to 8422. The follow up time ranged from 8 weeks to 27 months. All trials were randomized and double-blinded, with parallel-group, placebo and/or active-control group. Only PIONEER-HF trial assessed the study population with acute decompensated HF for hemodynamics stabilization, others assessed patients with chronic stable HF. Studies were quantitatively classified according to the Jadad scale. Multicenter studies were considered to be high-quality studies and assigned a Jadad score $\geq$ 3.

Table 1. Baseline Characteristics of Trials included in the Meta-Analysis.

Trial Name	Number of Participants	Follow-up	Definition of decline in renal function	Inclusion criteria	Age(years)	Gender (male)	Control group	Baseline Serum Cr (mg/dl)	Baseline eGFR (ml/min per 1.73 m^2)
PARAMOUNT-HF (2012)	301	3 months	Scr $\geq$ 0.5 mg/dL $\uparrow$ and/or $>$ 25% $\uparrow$	NYHA II–III HFpEF, EF $\geq$ 45%	70.9 $\pm$ 9.4	152 (57%)	Valsartan		66.5 $\pm$ 19.4 VS. 64.3 $\pm$ 21.3
PARADIGM-HF (2014)	8442	27months	end-stage renal disease, 50% $\downarrow$GFR, 30$\downarrow$GFR to $<$ 60ml/min.per 1.73 m^2	NYHA II–IV, EF $\leq$ 40%	63.8 $\pm$ 11.5 VS. 63.8 $\pm$ 11.3	6567 (78%)	Enalapril	1.13 $\pm$ 0.3 VS. 1.27 $\pm$ 0.03	
PIONEER-HF (2019)	881	8 weeks	Scr $\geq$ 0.5 $\uparrow$mg/dL ($\geq$ 44 μmol/L) , 25%$\downarrow$GFR.	Hemody-namic stabi-lization after ADHF EF $\leq$ 40%	61 (51-71) VS. 63(54-72)	635 (72.1%)	Enalapril	1.28 (1.07-1.51) VS. 1.27 (1.05-1.50)	58.4 (47.5-71.5) VS. 58.9 (47.4-70.9)
EVALUATE-H (2019)	464	12 weeks.	35%$\downarrow$GFR, Scr $\geq$ 0.5 $\uparrow$mg/dL AND 25%$\downarrow$GFR	Hypertension; EF $\leq$ 40% NYHA I-III	67.8 (9.8) VS. 66.7 (8.5)	355 (76.5%)	Enalapril		70 (22) VS. 69 (20)
PRIME (2019)	118	12months	SCr $\geq$ 2.5mg/dL	(NYHA) II or III EF of 25% to $<$ 50% and significant functional MR	(64.7 $\pm$ 10.2) VS. (60.5 $\pm$ 11.8)	672 (61%)	Valsartan	(1.00 $\pm$ 0.32) VS 0.98 $\pm$ 0.28	
PARAGONHF (2019)	4822	26 months	death from renal failure, end□stage renal disease, or 50% $\downarrow$GFR	NYHA class II toIV EF $\geq$ 45%	72.7 $\pm$ 8.3 VS. 72.8 $\pm$ 8.5	2317 (48.3%)	Valsartan	1.1 $\pm$ 0.3 VS 1.1 $\pm$ 0.3)	63 $\pm$ 19 VS 62 $\pm$ 19

Abbreviation: GFR, Glomerular filtration rate; SCr, Serum creatinine; NYHA, New York Heart Association functional class; EF, Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; ADHF, Acute Decompensated Heart Failure; MR, Mitral Regurgitation;$\uparrow$,increase ;$\downarrow$ decrease.

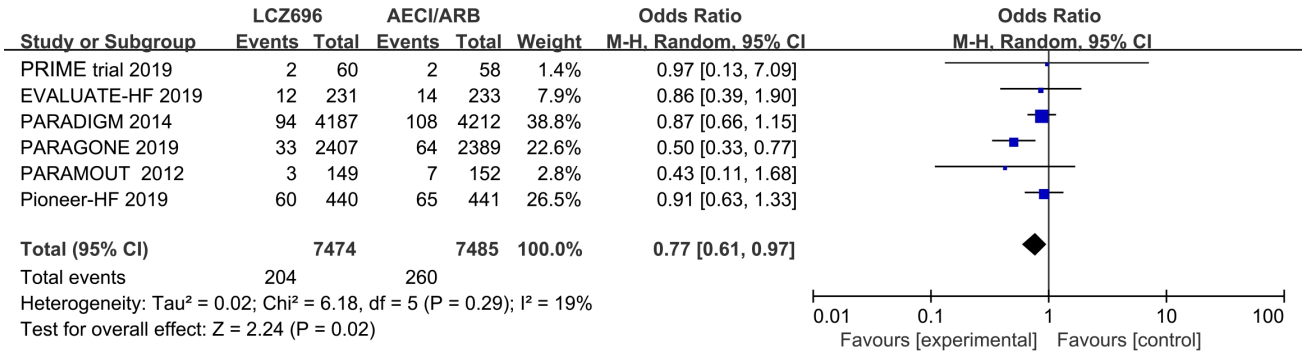

Figure 2. Forest plot of worsening renal function comparison: LCZ696 group vs ACEI/ARB group

Decline in renal function was the only outcome that could be extracted. The definition of renal deterioration was slightly different in each clinical trial. Compared to ACEI or ARB alone, LCZ696 resulted in significantly reduced risk of renal function deterioration (odds ratio 0.77, 95% confidence interval 0.61--0.97, P = 0.02) (Fig. 2). Both I2 (< 20%) and Forest maps showed only a mild degree of homogeneity between studies (Fig. 3). Acute HF is thought to be a condition characterized by cardio-renal syndrome and pathophysiologically different from chronic HF, therefore we also performed a meta-analysis after excluding the PIONEER-HF trial, and we had the same conclusion that LCZ696 significantly reduced the risk of renal function deterioration (odds ratio 0.71, 95% CI 0.52--0.96, P = 0.03) (Fig. 4).

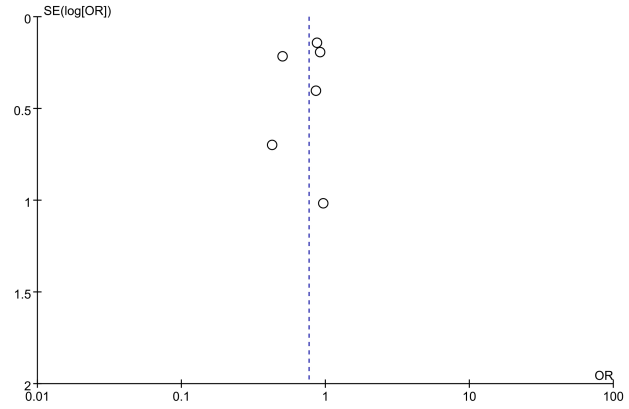

Figure 3. Forest map of 6 RCTs

4. Discussion

There are a number of important interactions between heart and kidney disease. The interaction is bidirectional and can induce acute or chronic dysfunction in the other organ. Customarily, this condition is described as "cardio-renal syndrome". Worsening renal function (WRF) is strongly associated with the mortality in all HF patients (Löfman et al., 2019). WRF is particularly relevant to the use of renin--angiotensin--aldosterone system (RAAS) inhibitors as these agents may reduce the glomerular filtration rate (GFR) and worse the renal function. LCZ696, as anangiotensin receptor neprilysin inhibitor, seems to have the same problem. However, this meta-analysis showed that LCZ696 had a lower incidence of renal function deterioration compared to ACEI/ARB, indicating that LCZ696 may protect renal function. LCZ696 decomposes into valsartan and neprilysin inhibitor (NEPi) after entering the human body. At present, the mechanism of renal protection by these two compounds has been explained by some animal experiments. Valsartan has been shown to have convincing mechanisms of renal protection through alleviating the sympathetic tone and improving hemodynamic state by inhibiting the activity of RAAS system. NEPi has been reported to have a beneficial effect on the treatment of chronic kidney disease in many experiments, as NEPi may have the ability to cut down the disintegration of natriuretic peptides and increase their bioavailability. Natriuretic peptide, especially atrial natriuretic peptide (ANP) and ventricular natriuretic peptide, can induce vasodilation in the bulbar artery and relative vasoconstriction of the posterior globular artery. By giving valsartan and brain natriuretic enzyme inhibitors to reduce systemic blood pressure and renal perfusion pressure, glomerular arterial-output increased the arterial pressure difference, maintained renal filtration fraction and GFR in high level. More specifically, ANP could inhibit the activation of nuclear factor NF-κB and inducible nitric oxide synthase (iNOS) (Kiemer et al., 2000). which is responsible for the production of reactive oxygen species, peroxides, cytokines and chemokines. In addition, ANP can inhibit the production of inflammatory mediators in macrophages, endothelial cells and cardiomyocytes (Della Penna et al., 2015; Rosón et al., 2006). Hence, ANP could promote the anti-inflammatory, antioxidative and anti-fibrosis effects in kidney therapy (Judge et al., 2015).

However we recognize 2 major limitations in our meta-analysis. Firstly, only 6 randomized controlled trials of LCZ696 met the inclusion criteria were entered for final analysis. The definition of renal deterioration used by each trial was different and in some RCTs renal deterioration was monitored as secondary endpoint or adverse event. PARADIGM-HF and PARAGONE-HF weighed heavily in this meta-analysis. TRANSITION as well as TITRATION answered the question of when and how to start and titrate LCZ696, showing that LCZ696 should be started as early as possible for hemodynamic stability after acute decompensation of HF, which can be tolerated in terms of renal function. However we can't incorporated the two trials into this meta-analysis for the absense of ACEI/ARB as control group (Senni et al., 2016; Wachter et al., 2019).Secondly, the study population in the 6 trials showed a

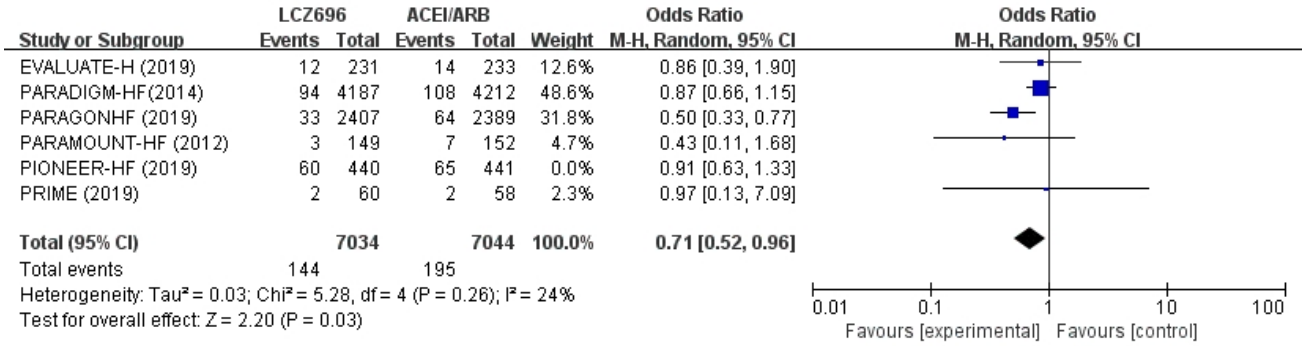

Figure 4. Forest plot of worsening renal function comparison: LCZ696 group vs ACEI/ARB group after excluding the PIONEER-HF

certain extent of inconsistency. Due to the limited number of qualified trials, we included all the HF patients with different types of HF (preserved ejection fraction or reduced ejection fraction), as well as combined with high blood pressure, or functional mitral regurgitation. It's still interest to know the role of LCZ696 in renal protection in different types of HF, with or without complications.

Regardless of these limitations, this meta-analysis did show that LCZ696 may preserve renal function in HF patients compared with ACEI/ARB alone. While a larger multicenter randomized controlled trial still needs to be further investigated. The primary endpoint should include annually eGFR change and deterioration of renal function, as LCZ696 was reported to have a slower rate of decrease in the eGFR ($P < 0.001$) when compared to ACEI/ARB in PARAMOUT study (Solomon et al., 2012) and PARADIGM-HF study (McMurray et al., 2014). The declining incidence of adverse events can better explain the function of renal protection (Damman et al., 2018). Hence, it is possible to improve the overall prognosis of patients with HF if renal function can be preserved when using LCZ696.

Abbreviations

ACEI: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor antagonists; CI: confidence interval; EF: ejection Fraction; GFR: glomerular filtration rate; HF: heart failure; NYHA: New York Heart Association functional class; OR: odds ratio; RCTs: randomized controlled trials; WRF: worsening renal function

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Conflict of interest

The authors reported no relationships that could be construed as a conflict of interest.

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