

Efficacy and safety of LCI699 for hypertension: a meta-analysis of randomized controlled trials and systematic review

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Abstract. – **OBJECTIVE:** This study reviews the available data from randomized controlled trials on efficacy and safety of LCI699, a novel inhibitor of aldosterone synthase, as treatment of hypertension.

MATERIALS AND METHODS: We performed a meta-analysis of phase II randomized, controlled trials comparing the efficacy/safety of LCI699 with placebo in hypertension patients. For this purpose, PubMed, Embase, Cochrane Library database, ISI-Science Citation Index, and the Chinese Biomedicine Literature Database were searched until August 2013. The available data on mean sitting systolic blood pressure (MSSBP), mean sitting diastolic blood pressure (MSDBP), adverse effects, renin-angiotensin-aldosterone system biomarkers (RAASB) and adrenocorticotrophic hormone-stimulated cortisol concentration (AHSC) were collected. All data were analyzed using Review Manager, version 5.2.

RESULTS: The present study finally included three randomized controlled trials, comprising of 623 patients in total. The daily use of ≥ 1 mg LCI699 was associated with a significant reduction of MSSBP (Weighted mean difference/WMD = -8.80 , 95% CI: -11.31 to -5.68 , $p < 0.00001$, $I^2 = 0\%$) and MSDBP (WMD = -4.94 , 95% CI: -7.49 to -2.40 , $p = 0.00001$, $I^2 = 9\%$). Adverse reactions occurred in 73 of the 139 patients (52.51%) treated with LCI699 and in 34 of the 63 patients (53.96%) treated with placebo. Pooled meta-analysis showed that the use of LCI699 was associated with no increased risk of side effects compared with placebo (RR = 0.90 ; 95% CI: 0.68 to 1.18 , $p = 0.43$, $I^2 = 0\%$). Suppression of plasma aldosterone was measured at all doses of LCI699 treatment groups. LCI699 suppressed the ACTH-stimulated cortisol response in a dose- and time-dependent manner.

CONCLUSIONS: Current evidence indicates that the novel aldosterone inhibitor LCI699 is an effective and well-tolerated antihypertensive agent that lowers plasma aldosterone concentration and produces a mild ACTH-stimulated cortisol response suppressive effect.

Key Words:

LCI699, Hypertension, Meta-analysis, Inhibitors, Aldosterone.

Introduction

Hypertension remains as a major risk factor for cardiovascular disease and stroke. The prevalence of hypertension was reported to be 30.5% among men and 28.5% among women¹, and the prevalence was found to be even higher in the hospitalized patients². Aldosterone, the final product of the renin-angiotensin-aldosterone system, acts primarily as a critical regulator of the fluid and electrolyte homeostasis. A higher plasma level of aldosterone may contribute to hypertension onset and hypertension-related alterations of heart, kidneys, and peripheral vasculature³⁻⁷. Animal models corroborate the prognostic significance of aldosterone as a predictor of post-myocardial infarction survival and increased prevalence of atrial fibrillation in patients⁸⁻¹⁴. By preventing the aldosterone binding to its receptor, the efficacies of mineralocorticoid receptor antagonists (MRAs) called spironolactone and eplerenone in lowering blood pressure (BP), particularly in resistant hypertension, and improving outcomes in congestive heart failure have been reported by several studies¹⁵⁻²¹. However, these agents, particularly spironolactone, have limitations due to their reduced selectiveness for the mineralocorticoid receptor (MR) over other steroid receptors. Since these drugs can sometimes interact with progesterone and androgen receptors, progestagenic and anti-androgenic side effects are possible. In addition, hyperkalemia and increases in plasma aldosterone levels are observed among the patients receiving MRAs²². The elevated aldosterone plas-

ma levels could exert action directly or through alternate MR-independent, non-genomic effects on the cardiovascular system^{23,24}. Therefore, reducing circulating aldosterone levels by the inhibition of aldosterone synthesis represents a novel approach and an alternative for treatment with MRAs. Also, this can theoretically lead to the development of new drugs possessing less off-target effects and with an equal antihypertensive outcome.

In recent years, a potent and orally-administrated aldosterone synthase inhibitor (ASI) called LCI699 was demonstrated as an effective and safe reagent for correcting the hypokalemia and decreasing the BP in patients with primary aldosteronism^{23,24}. Several randomized controlled trials have reported the clinical outcomes of LCI699 for management of high BP²⁵⁻²⁷. To our knowledge, no systematic review on the safety and efficacy studies of LCI699 has been so far conducted. Importantly, the data on the efficacy of LCI699 are also inconsistent as is evident from the previous studies²⁵⁻²⁷. Therefore, in order to better assess the clinical benefit and safety of LCI699, we herein present a systematic review of the existing literature and a meta-analysis of Phase II randomized, clinical trials of LCI699 compared with placebo for its efficacy and tolerability in hypertension patients.

Materials and Methods

Data Sources and Searches

The following databases were reviewed to obtain all relevant studies that compared the LCI699 to placebo and reported its efficacy in lowering BP, its effect on plasma aldosterone and cortisol levels and the adverse effects: (1) PubMed (1966-2013); (2) EMBASE (1974-2013), (3) Cochrane Library (2013 issue 7); (4) ISI-Science Citation Index (1955-2013); and (5) the Chinese Biomedicine Literature Database (1978-2013). The following medical-subject heading (MeSH) terms or keywords were used: ('11-beta-Hydroxylase inhibitor' or '18-Hydroxylase inhibitor' or '11-hydroxylase inhibitor' or 'LCI699' or 'LCI-699' or 'LCI 699') and ('high BP' or 'hypertension' or 'high blood pressure'). We also scanned pharmaceutical company websites, ClinicalTrials.gov and the references of retrieved studies to identify the additional potentially relevant data. Our searches were not limited by publication year, language, sex, or age.

Study Selection

All references retrieved via electronic searches were screened independently at the title/abstract level for pertinence by two reviewers (H. Wang and J. Tian), and any disagreements were resolved through discussion or opinion of the third reviewer (K. Yang) as required. In order to reduce bias, both reviewers were blinded to the source of publication and authors' names. A flow diagram of the study selection process is shown (Figure 1). Studies were considered potentially eligible for this systematic review and were retrieved as full reports for further appraisal if they met with the following criteria: (1) Patients with hypertension with mean sitting systolic BP (MSSBP) or mean sitting diastolic BP (MSDBP) >140/90 mmHg²⁸; (2) Men and women aged 18 to 75 years with comparable baseline characteristics; and (3) Phase III randomized clinical trials (RCTs) or phase II RCTs that compared different dosages of LCI699 with placebo group. Studies were excluded if they failed to fulfill one of the above criteria or if they met with any of the following standers: (1) Patients with recent history

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Andersen 2012	?	+	+	?	●	+	+
Calhoun 2012	+	+	+	+	+	+	+
Karns 2013	?	?	?	?	+	+	+

Figure 1. Risk of bias summary: The “?” circle means unclear risk of bias. The “+” circle indicates a low risk of bias, the “-” circle identifies potential risk of bias.

of events, such as myocardial infarction, heart failure, unstable angina, cerebrovascular accident, severe diabetes mellitus, or renal diseases; (2) Reviews, study procedures, letters and animal studies. The final selection yielded three RCTs for current analysis²⁵⁻²⁷.

Data Extraction and Quality Assessment

Two reviewers (H. Wang and J. Tian) independently collected the data on study (country, authors, year of publication, design), base line patient characteristics [number, mean age, sex, body mass index (BMI), MSSBP, MSDBP, glomerular filtration rate (GFR); Tables I and II], and treatment (dose, and duration) according to the Providing Innovative Service Models and Assessment (PRISMA) criteria²⁹. The primary outcomes included MSSBP, MSDBP and adverse effects. The secondary outcomes included renin-angiotensin-aldosterone system biomarkers (RAASB) and adrenocorticotrophic hormone-stimulated cortisol concentration (AHSC). We assessed the quality of RCTs studies included by using Cochrane Collaboration tool³⁰, which included assessment of the sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting of outcomes and other possible sources of bias (Figure 2). Disagreements about data extraction were resolved by consensus or by opinion of a third reviewer (K. Yang).

Data Synthesis and Statistical Analysis

In order to study the efficacy of different doses, we combined subgroups of individual study into 1.0mg once daily above group (including 1.0 mg daily) and 1.0 mg once daily below group. Two reported subgroups of separate doses were

combined into a single group; and if there were more than two groups to combine, we combined group 1 and group 2 to create group '1+2', then combined group '1+2' and group 3 to create group '1+2+3', and so on as recommended³⁰. We have combined the data on dichotomous outcomes using Mantel-Haenszel relative risk method in this systematic review. We also used the inverse variance weighted mean difference (WMD) method and 95% confidence intervals (95% CI) for continuous outcomes. If the study did not report standard deviations (SD), we obtained SD from *p*-values for differences between means in two groups. If the study did not describe the exact *p*-value, then *p*-values were taken at the upper limit e.g. for *p* < 0.01, we considered *p* = 0.01 and for *p* < 0.001, we considered *p* = 0.001 as used before³⁰. Statistical homogeneity and consistency were checked by Chi-Square statistics and *I*². We used a fixed-effect model for calculating summary estimates and their 95% CI if there was no significant heterogeneity. Finally a random-effect statistical model was used to confirm our results. All computations were carried out using RevMan V.5.2.

Results

Study Identification and Selection

The study identification and selection progression are summarized in Figure 1. We identified 67 potentially eligible studies i.e. 22 from MEDLINE, 1 from Cochrane Library, 36 from ISI-Science Citation Index (1955-2013), 8 from EMBASE and 0 from the Chinese Biomedicine Literature Database. No articles were retrieved from the pharmaceutical company websites, Clinical-

Table I. Characteristics of studies.

Study	Design	Setting	Duration	Outcome measurement
Andersen et al 2012	Perspective RCT Phase-II Double-blind	Multicenter	6-week	① ② ③ ④ ⑤
Karns et al 2013	Perspective RCT Phase-II Double-blind	Multicenter	8-week treatment and 2-week safety assessment	① ② ③ ④
Calhoun et al 2012	RCT Phase-II	8-week treatment and 1-week withdrawal		
Double-blind	Multicenter			① ② ③ ④ ⑤

① MSSBP ② MSDBP ③ Adverse effects ④ RAAS Biomarkers ⑤ Adrenocorticotrophic Hormone-Stimulated Cortisol Concentration.

Table II. Baseline characteristics of patients.

Study	Intervention (n)	Age mean (SD), years	Sex male/female (%)	BMI mean (SD), kg/m ²	MSSBP mean (SD), mm Hg	SDBP mean (SD), mm Hg	GFR mean (SD), mL/min
Andersen et al 2012	Placebo (n=13)	56.8 (10.08)	69.2/30.8	34.45 (6.196)	140.2 (10.57)	86.8 (8.17)	85.8 (28.15)
	LCI699 0.5 mg QD (n=12)	56.1 (6.37)	66.7/33.3	31.19 (6.563)	151.1 (12.23)	87.8 (12.68)	89.5 (18.90)
	LCI699 1.0 mg QD (n=12)	54.2 (16.01)	58.3/41.7	33.63 (4.853)	149.4 (13.22)	90.4 (10.60)	89.1 (18.46)
	LCI699 1.0 mg BID (n=13)	57.9 (9.09)	76.9/23.1	32.73 (5.399)	145.2 (12.15)	88.9 (8.75)	81.8 (17.08)
Karns et al 2013	LCI699 2.0 mg QD (n=13)	56.2 (10.37)	61.5/38.5	30.70 (4.158)	146.2 (11.02)	85.6 (10.56)	78.4 (18.03)
	Placebo (n=33)	59.8 (9.33)	62.6/37.4	31.92 (7.785)	153.4 (9.61)	90.1 (11.65)	76.9 (16.65)
	LCI699 0.25 mg BID (n=32)	53.6 (10.36)	62.5/37.5	33.95 (5.918)	152.4 (11.21)	91.8 (11.68)	83.5 (16.64)
	LCI699 1 mg QD (n=26)	55.4 (9.58)	69.2/30.8	32.18 (5.286)	152.5 (9.79)	89.2 (9.56)	83.6 (20.77)
Calhoun et al 2012	LCI699 0.5/1 mg* BID (n=31)	57.2 (10.77)	58.1/41.9	33.49 (8.128)	152.2 (7.58)	88.9 (11.89)	79.7 (14.80)
	Placebo (n=77)	53.9 (8.7)	59.7/40.3	—	156.7 (10.1)	100.5 (3.8)	85.4 (15.2)
	LCI699 0.25 mg QD (n=92)	53.9 (10.5)	68.5/31.5	—	157.7 (12.2)	100.4 (3.9)	86.3 (15.6)
	LCI699 0.5 mg QD (n=87)	54.8 (7.8)	66.7/33.3	—	157.0 (11.6)	99.9 (3.3)	84.5 (15.1)
	LCI699 1 mg QD (n=86)	54.5 (9.7)	64/36	—	159.2 (10.4)	100.0 (3.6)	82.1 (14.4)
	LCI699 0.5 mg BID (n=96)	54.4 (10.78)	65.6/34.4	—	158.5 (11.0)	100.2 (3.4)	86.5 (17.0)

BID: twice daily; BMI: body mass index; GFR: glomerular filtration rate; SD: standard deviation; QD: once daily; *0.5 mg BID titrated to 1 mg BID after 4 weeks.

Trials.gov and reference lists of the studies included. No duplicate studies were found, and we excluded 62 studies after screening titles and abstracts using our inclusion and exclusion criteria. The remaining 5 studies were subjected to full-text detailed evaluation. Finally, three RCTs²⁵⁻²⁷ were selected for this systematic review after exclusion of 2 non-randomized studies.

Study Characteristics and Study Quality

A total of 623 patients were involved in the selected three trials, and the studies were phase II parallel-group double-blind RCTs. All studies were published in English. The duration of these three studies ranged from 6 weeks to 8 weeks. All three studies included the above 1.0mg once daily treatment group and the below 1.0mg once daily treatment group. Only two studies evaluated the AHSC^{25,27}. The characteristics and quality of the studies included herein are shown in Table I and Figure 2; baseline characteristics of patients of these studies are summarized in Table II.

Efficacy of LCI699 on MSSBP

Data from two available studies^{25,27} of 208 patients reported the efficacy of LCI699 above 1.0mg once daily vs. placebo. We performed a meta-analysis using a fixed-effect model and the pooling showed that LCI699 was associated with a significant reduction of the MSSBP (WMD = -8.80, 95% CI: -11.31 to -5.68, $p < 0.00001$, $I^2 = 0\%$; Figure 3). Re-analysis with a random effects (RE) model did not change these results. Due to the lacking data of below 1.0 mg once daily groups, we were unable to perform the meta-analysis. Even though a lower dose generally showed smaller BP reductions from baseline (2.6-11.2 mmHg), these reductions were not statistically significant^{25,26}; however, Calhoun et al²⁷ reported that all LCI699 doses of below 1.0 mg once daily group were significantly more effective in reducing the MSSBP than placebo.

Efficacy of LCI699 on MSDBP

Data from two available studies^{25,27} of 111 patients reported the efficacy of LCI699 above 1.0mg once daily vs. placebo. The meta-analysis we performed used a fixed-effect model and the pooling showed that LCI699 was associated with a significant reduction of the MSDBP (WMD = -4.94, 95% CI: -7.49 to -2.40, $p = 0.00001$, $I^2 = 9\%$; Figure 4). Again, re-analysis with an RE model did not change these results. We could not perform meta-analysis due to the lacking data of

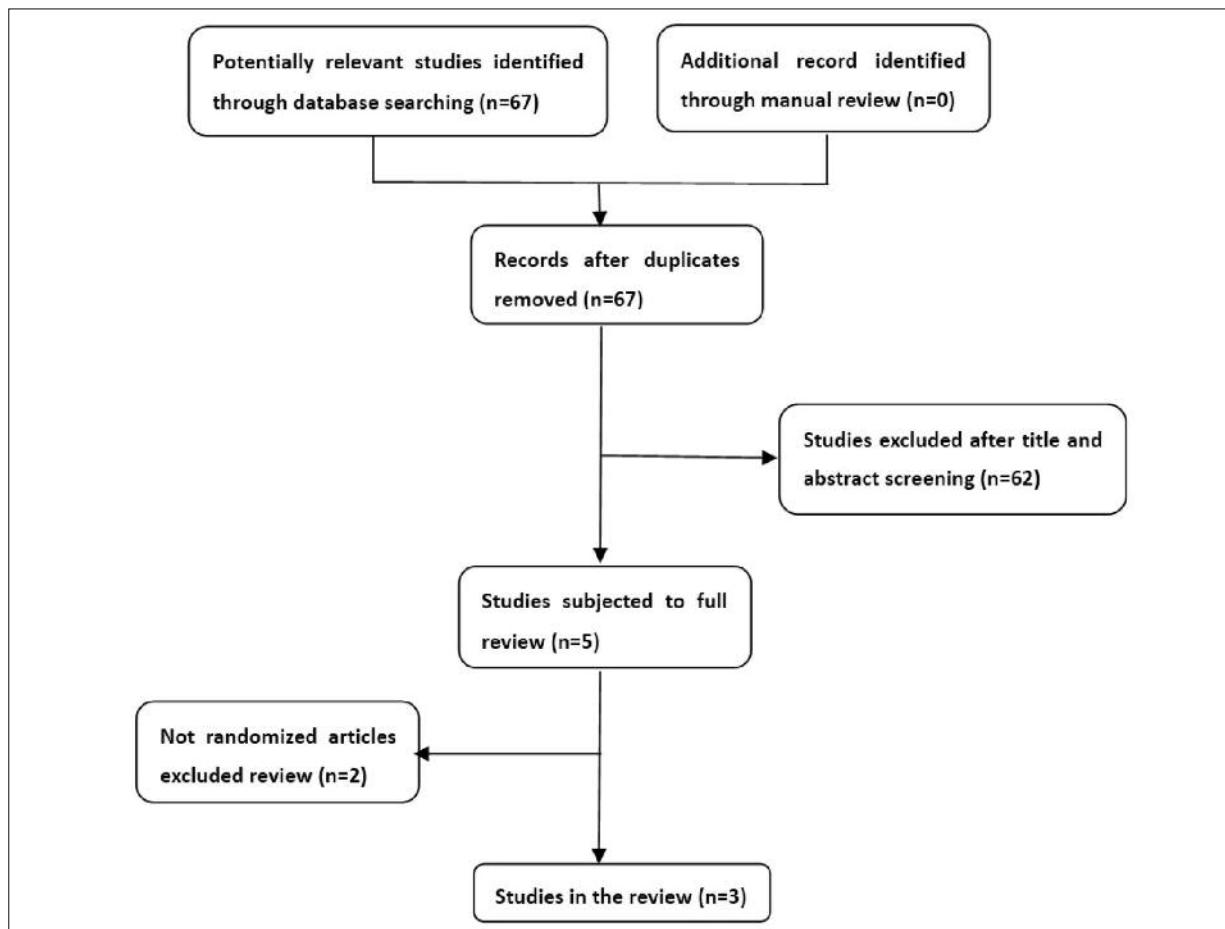


Figure 2. The study identification and selection progression.

below 1.0 mg once daily groups. In addition, the reductions (1.2–5.2 mmHg) from baseline showed by lower doses were statistically non-significant^{25–27}.

Adverse Effects of LCI699

Adverse effects occurred in 73 of the 139 patients (52.51%) treated with LCI699 and in 34 of the 63 patients (53.96%) treated with placebo^{25,27}. The results obtained by pooled meta-analysis

showed that use of LCI699 was associated with no increased risk of side effects as compared with placebo (RR = 0.90; 95% CI: 0.68 to 1.18, $p = 0.43$, $I^2 = 0\%$; Figure 5). Re-analysis using RE model did not change these results. There were no deaths and only one serious adverse effect (retinal vein occlusion) was reported to occur during the study. The most commonly reported side effects were headache and dizziness. No significant increases in creatinine with any of

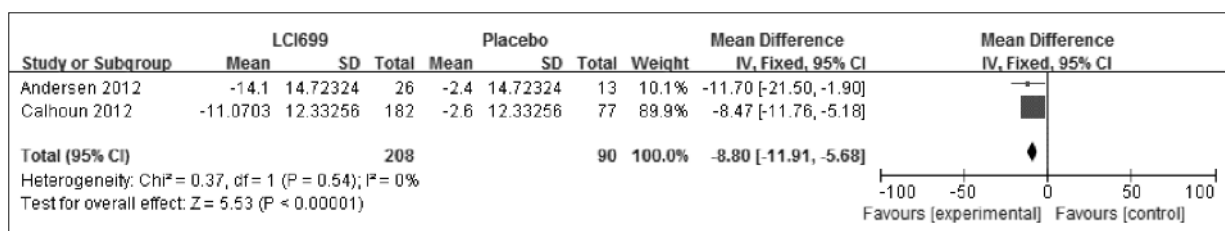


Figure 3. Forest plots of efficacy of LCI699 on Mean Sitting Systolic BP (MSSBP) with 95% CI.

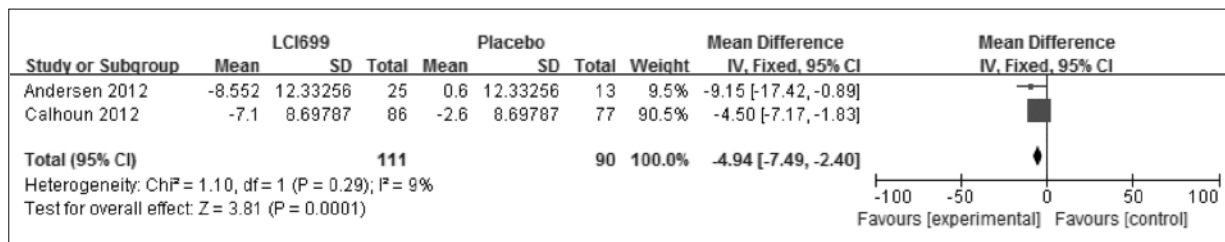


Figure 4. Forest plots of efficacy of LCI699 on Mean Diastolic Blood Pressure (MSDBP) with 95% CI.

LCI699 doses were reported. We found a dose-dependent relationship between the LCI699 and the mean potassium concentration, but the occurrence of hyperkalemia remained low (3.4%-4.8%)²⁷. Small but statistically significant decreases in serum sodium from baseline were also observed.

Effect of LCI699 on Renin-Angiotensin-Aldosterone System Biomarkers (RAASB)

Suppression of the plasma aldosterone was measured at all LCI699 dose groups. The reductions ranged from 11.6 to 55.8 pmol/L, and the dose-dependent effect of LCI699 on aldosterone concentration was observed. Increased plasma renin activity (PRA), ranging from 0.4 to 1.2 µg/L*h, was also observed in a dose-dependent manner²⁷. Similar results of aldosterone reduction (18.2% to 80%) and PRA elevation (44.7% to 112.2%) were reported in other two trials^{25,26}.

Effect of LCI699 on Adrenocorticotrophic Hormone-Stimulated Cortisol (AHSC) concentration

LCI699 suppressed the ACTH-stimulated cortisol response in a dose- and time-dependent manner. A reduction in cortisol level ranging from 81 to 199 nmol/L was reported²⁷.

Discussion

LCI699 is an ASI that belongs to a novel antihypertensive class of drugs and it provides an additional option for physicians for treatment of hypertension cases. To our knowledge, meta-analysis data on phase II, randomized, double-blind, placebo-controlled studies comparing the LCI699 with placebo are still lacking. This systematic review and a meta-analysis of phase II randomized, double-blind, placebo-controlled clinical trials of LCI699 in hypertension patients show that statistically significant numerical placebo-adjusted reduction of MSDBP and MSSDP from the baseline were observed among the above 1.0 mg once daily groups. The similar findings were reported previously for patients with primary aldosteronism²³. However, when compared with MRAs, these reductions were smaller than those observed with eplerenone 50 mg BID^{26,27}. In addition, LCI699 seems to be less effective in patients with resistant hypertension than in the patients with primary hypertension²⁶. These observations suggest that further evaluations using higher doses of LCI699 need to be carried out. Besides, the trials comparing eplerenone 50 mg and higher doses of LCI699 are also required. Of note, such trials might become limited by high-dose-

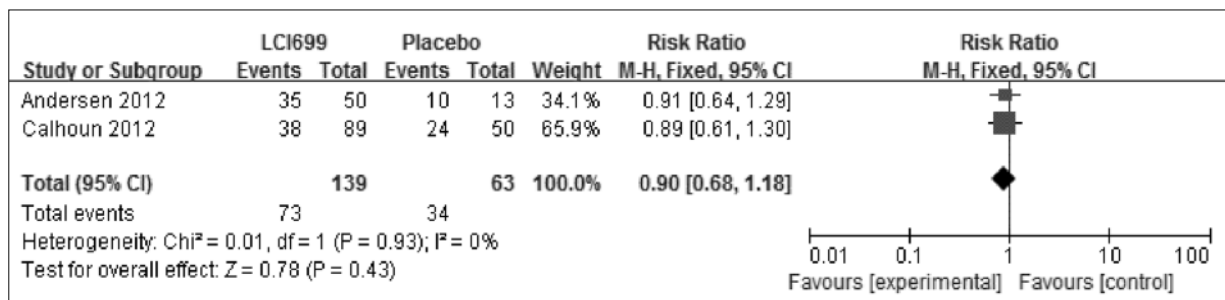


Figure 5. Forest plots of RR and overall RR with 95% CI for adverse effect of LCI699.

associated off target effects of LCI699 on the electrolyte homeostasis and glucocorticoid axis as were previously reported for 11 β -hydroxylase (*CYP11B1*) in addition to its target enzyme *CYP11B2*^{23,25-27}. Therefore, cautious assessment and surveillance would have to be put in place before and during the use of LCI699.

In a community-based study, increased aldosterone levels within the physiologic range were used as predictor of hypertension development¹⁷. Similar outcome that the hypertension-related alterations were correlated with aldosterone was reported by Kotchen et al⁷ in a study involving African Americans, as well as by other studies^{31,32}. In addition, given the important role of aldosterone in the prognosis of cardiovascular and renal disease^{4,6}, and in the maintenance of electrolyte homeostasis, circulating aldosterone levels may have a causal relationship with cardiovascular disease and hypertension; therefore, lowering the circulating aldosterone levels to achieve beneficial effects would be both relevant and feasible. In the three trials included in this review, a dose-dependent effect of plasma LCI699 was observed which is consistent with its aldosterone synthase inhibition through the *CYP11B2*. Similar results of up to 70-80% reduction in plasma and urinary aldosterone concentrations were observed in patients with primary aldosteronism²⁴. On the other hand, reactive increases in the plasma aldosterone levels were associated with the use of MRAs^{25,27}, and higher doses of the blocker were also required. Therefore, an advantage of LCI699 over MRAs is obvious.

The first-approved MRAs spironolactone has been in clinical use for more than 20 years, and recent studies showed that spironolactone and the second generation drug, eplerenone, could significantly benefit treating in hypertension and resistant hypertension, as well as reduce the risk of morbidity and mortality in heart failure patients¹⁵⁻²¹. However, affinity of MRAs, especially of spironolactone, to steroid receptors could result in side effects such as sexual dysfunction and menstrual irregularity, deeply affecting the life quality of patients. On the other hand, LCI699 administration was overall clinically and biologically well tolerated. No increased risk of side effects compared with placebo was observed in the pooled meta-analysis, which is consistent with the results from previous studies^{23,24}. Besides, the majority cases of adverse effects such as headache and dizzi-

ness were mild and thought to have no relation with the study drug. Mild and reversible hyponatremia and hyperkalemia were also observed in a dose-dependent manner, requiring monitoring for the plasma potassium and sodium levels, which is similar as suggested earlier for spironolactone and eplerenone. Only one serious adverse effect i.e. retinal vein occlusion was observed in LCI699 group, but there were no data to prove that this episode was related to the use of LCI699. Also, the ACTH-stimulated cortisol response suppression in a dose-dependent manner was observed, whereas plasma cortisol concentrations remained stable and no patients exhibited the signs of adrenal insufficiency. This finding compares to the data reported by a previous study²⁴. New generations of aldosterone synthase inhibitor should focus on lowering these off target effects. However, given the relatively short duration of these studies, long-term effects of LCI699 are still unknown and need to be addressed in the future investigation. Other reports also suggested that LCI699 could effectively and safely inhibit aldosterone synthase, correct hypokalemia and decrease BP in patients with primary aldosteronism^{23,24,33,34} and, thus, it might represent an alternative treatment other than the MRAs or adrenal surgery.

Last but not least, some limitations of this systematic review need to be considered as well. First, LCI699 belongs to the 1st-generation of aldosterone synthase inhibitor and relevant research studies are still limited, therefore, further work should focus more on the comparison of LCI699 with other types of commonly-used antihypertensive drugs as well as interactions between LCI699 and other drugs. Second, the optimal dose of LCI699 is still controversial, even though the maximally tolerated dose of 1.30 mg once daily (0.88-1.81 mg once daily, 90% prediction interval), based on ACTH-stimulated cortisol response, was reported in Anderson et al study²⁵; the placebo-adjusted reduction of MSDBP and MSSDP in above 1.0 mg daily group is still inferior to that of MRAs. Third, some of the data remain incomplete as not all outcomes were reported in certain trails which may introduce a bias. Due to the incomplete data and limited number of available studies on this relatively new drug at present, there is still a need of more large-cohort, multi-center, long-term RCTs; including in-depth studies of the mechanism(s) of action of LCI699.

Conclusions

This meta-analysis suggested that LCI699 effectively lowered the MSDBP and MSSDP and was generally well-tolerated. At the same time, the effect of LCI699 in decreasing circulating aldosterone level was also obvious. As though the first-generation LCI699 is not very selective, the ACTH-stimulated cortisol response suppression is not uncommon; thus LCI699 still holds the possibility to become a novel antihypertensive class of drugs. This systematic review provides a reference/guidance for the future research addressing clinical benefits of LCI699 in hypertensive patients.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- GUO F, HE D, ZHANG W, WALTON RG. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. *J Am Coll Cardiol* 2012; 60: 599-606.
- AXON RN, COUSINEAU L, EGAN BM. Prevalence and management of hypertension in the inpatient setting: a systematic review. *J Hosp Med* 2011; 6: 417-422.
- XANTHAKIS V, VASAN RS. Aldosterone and the risk of hypertension. *Curr Hypertens Rep* 2013; 15: 102-107.
- MATSUMURA K, FUJII K, ONIKI H, OKA M, IIDA M. Role of aldosterone in left ventricular hypertrophy in hypertension. *Am J Hypertens* 2006; 19: 13-18.
- KIDAMBI S, KOTCHEN JM, KRISHNASWAMI S, GRIM CE, KOTCHEN TA. Aldosterone contributes to blood pressure variance and to likelihood of hypertension in normal-weight and overweight African Americans. *Am J Hypertens* 2009; 22: 1303-1308.
- FUNDER JW. The nongenomic actions of aldosterone. *Endocr Rev* 2005; 26: 313-321.
- KOTCHEN TA, KOTCHEN JM, GRIM CE, KRISHNASWAMI S, KIDAMBI S. Aldosterone and alterations of hypertension-related vascular function in African Americans. *Am J Hypertens* 2009; 22: 319-324.
- PALMER BR, PILBROW AP, FRAMPTON CM, YANDLE TG, SKELTON L, NICHOLLS MG, RICHARDS AM. Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction. *Eur Heart J* 2008; 29: 2489-2496.
- YUYUN MF, JUTLA SK, QUINN PA, NG LL. Aldosterone predicts major adverse cardiovascular events in patients with acute myocardial infarction. *Heart Asia* 2012; 4: 102-107.
- EDELMANN F, TOMASCHITZ A, WACHTER R, GELBRICH G, KNOKE M, DÜNGEN HD, PILZ S, BINDER L, STAHLRENBURG R, SCHMIDT A, MÄRZ W, PIESKE B. Serum aldosterone and its relationship to left ventricular structure and geometry in patients with preserved left ventricular ejection fraction. *Eur Heart J* 2012; 33: 203-312.
- REIL JC, HOHL M, SELEJAN S, LIPP P, DRAUTZ F, KAZAKOW A, MÜNZ BM, MÜLLER P, STEENDUK P, REIL GH, ALLESSIE MA, BÖHM M, NEUBERGER HR. Aldosterone promotes atrial fibrillation. *Eur Heart J* 2012; 33: 2098-2108.
- KLONER RA, CANNOM DS. Uncertainty on the use of aldosterone antagonists for primary therapy for sudden cardiac death in the setting of implanted devices. *Circulation* 2007; 115: 2983-2989;
- TOMASCHITZ A, PILZ S, RITZ E, MEINITZER A, BOEHM BO, MÄRZ W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Eur Heart J* 2010; 31: 1237-1247.
- BEYGUI F, COLLET JP, BENOLIEL JJ, VIGNOLLES N, DUMAINE R, BARTHÉLÉMY O, MONTALESCOT G. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. *Circulation* 2006; 114: 2604-2610.
- ZANNAD F, McMURRAY JJ, KRUM H, VAN VELDHIJSEN DJ, SWEDBERG K, SHI H, PITT B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11-21.
- PITT B, ZANNAD F, REMME WJ, CODY R, CASTAIGNE A, PEREZ A, PALENSKY J, WITTES J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709-717.
- VASAN RS, EVANS JC, LARSON MG, WILSON PW, MEIGS JB, RIFAI N, BENJAMIN EJ, LEVY D. Serum aldosterone and the incidence of hypertension in non-hypertensive persons. *N Engl J Med* 2004; 351: 33-41.
- PHELAN D, THAVENDIRANATHAN P, COLLIER P, MARWICK TH. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. *Heart* 2012; 98: 1693-1700.
- VÁCLAVÍK J, SEDLÁK R, PLACHY M, NAVRÁTIL K, PLÁSEK J, JARKOVSKÝ J, VÁCLAVÍK T, HUSÁR R, KOCIÁNOVÁ E, TÁBORSKY M. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. *Hypertension* 2011; 57: 1069-1075.

- 20) WEINBERGER MH, RONIKE B, KRAUSE SL, WEISS RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens* 2002; 15: 709-716.
- 21) BURGESS ED, LACOURCIÈRE Y, RUILOPE-URIOSTE LM, OPARIL S, KLEIMAN JH, KRAUSE S, RONIKE B, MAURATH C. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with essential hypertension. *Clin Ther* 2003; 25: 2388-2404.
- 22) JUURLINK DN, MAMDANI MM, LEE DS, KOPP A, AUSTIN PC, LAUPACIS A, REDELMEIER DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351: 543-551.
- 23) AZIZI M, AMAR L, MENARD J, PEYRARD S, WATSON C, PLOUIN PF. Blood pressure and potassium effects of the new direct aldosterone synthase inhibitor, Lci699, in patients with primary aldosteronism. *J Hypertens* 2010; 28: e441-442.
- 24) AMAR L, AZIZI M, MENARD J, PEYRARD S, WATSON C, PLOUIN PF. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. *Hypertension* 2010; 56: 831-838.
- 25) ANDERSEN K, HARTMAN D, PEPPARD T, HERMANN D, VAN ESS P, LEFKOWITZ M, TRAPANI A. The effects of aldosterone synthase inhibition on aldosterone and cortisol in patients with hypertension: a phase II, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Hypertens (Greenwich)* 2012; 14: 580-587.
- 26) KARNS AD, BRAL JM, HARTMAN D, PEPPARD T, SCHUMACHER C. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. *J Clin Hypertens (Greenwich)* 2013; 15: 186-192.
- 27) CALHOUN DA, WHITE WB, KRUM H, GUO W, BERMAN G, TRAPANI A, LEFKOWITZ MP, MÉNARD J. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. *Circulation* 2011; 124: 1945-1955.
- 28) CHOBANIAN AV, BAKRIS GL, BLACK HR, CUSHMAN WC, GREEN LA, IZZO JL JR, ROCCELLA EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2004; 42: 1206-1252.
- 29) KNOBLOCH K, YOON U, VOGT PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. *J Craniomaxillofac Surg* 2011; 39: 91-92.
- 30) HIGGINS JPT, GREEN S (EDITORS). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration*, 2011.
- 31) VINSON GP, COGHILAN JP. Expanding view of aldosterone action, with an emphasis on rapid action. *Clin Exp Pharmacol Physiol* 2010; 37: 410-416.
- 32) FUNDER JW. Minireview: aldosterone and the cardiovascular system: genomic and non-genomic effects. *Endocrinology* 2006; 147: 5564-5567.
- 33) AMAR L, AZIZI M, MENARD J, PEYRARD S, WATSON C, PLOUIN PF. Hormonal effects of the new direct aldosterone synthase inhibitor, Lci699, in patients with primary aldosteronism. *J Hypertens* 2010; 28: e226-227.
- 34) AMAR L, AZIZI M, MENARD J, PEYRARD S, PLOUIN PF. Sequential comparison of aldosterone synthase inhibition and mineralocorticoid blockade in patients with primary aldosteronism. *J Hypertens* 2013; 31: 624-629.