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A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension

Zhenfeng Zheng¹, Huilan Shi², Junya Jia¹, Dong Li¹ and Shan Lin¹

Abstract

Background: Candesartan is a relatively novel antihypertensive agent of the angiotensin receptor blocker (ARB). Several clinical trials have compared candesartan with losartan in the management of essential hypertension. However, systematic assessment of efficacy and safety between candesartan and losartan is still lacking.

Methods: We reviewed randomised controlled trials (RCTs) comparing candesartan with losartan for net reduction in blood pressure from baseline, response and control rates, and incidences of common and serious adverse events. Weighted mean differences (WMD), and relative risk (RR) with 95% confidence intervals (CI) were calculated for continuous and dichotomous data, respectively.

Results: A total of 12 RCTs with 3644 patients were included in this meta-analysis. When comparing the efficacy of candesartan and losartan in reducing systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of the follow-up period, results with candesartan were superior to losartan in the reduction SBP and DBP (WMD, -2.97; 95% CI, -4.18 – -1.77; p < 0.001; WMD, -1.76; 95% CI, -2.57 – -0.96; p < 0.001; respectively). Candesartan had better response and control rates than losartan. (RR, 1.12; 95% CI, 1.06–1.18; p < 0.01; RR, 1.26; 95% CI, 1.06–1.50; p = 0.008). Reported common adverse events for the two agents were not significantly different (RR, 0.98; 95% CI, 0.86–1.12; p = 0.78). The incidence of serious adverse events for candesartan was lower than for losartan (RR, 0.48; 95% CI, 0.25–0.92; p = 0.03).

Conclusions: Candesartan is superior to losartan in reducing blood pressure. Candesartan also causes fewer serious adverse events than losartan.

Keywords

Angiotensin receptor blocker, candesartan, hypertension, losartan, meta-analysis

Introduction

The renin–angiotensin–aldosterone system plays an important role in modulating cardiovascular function and in the pathophysiology of hypertension, vascular disease, cardiac hypertrophy and heart failure.¹,² Angiotensin II, a potent vasoconstrictor, is a key effective peptide; its known pressor effects are mediated by the AT1 subtype receptor.³,⁴ The effects of angiotensin II can be directly blocked by selective angiotensin receptor blockers (ARBs) at the AT1 receptor. ARBs exert similar antihypertensive effects as angiotensin-converting enzyme (ACE) inhibitor, and appeared to be better tolerated.⁵,⁶ The effects of angiotensin II are more effectively suppressed by ARBs than by ACE inhibitors, which do not block the transformation of angiotensin I to angiotensin II via enzymes other than ACE, such as chymase.⁷ In contrast to ACE inhibitors, angiotensin II antagonists do not cause accumulation of vasodilatory and pro-inflammatory peptides, such as bradykinin and substance P, and are therefore less likely to cause exaggerated hypotension, dry cough and angioedema.⁸ Various studies and clinical trials have demonstrated their effectiveness in lowering blood pressure, with an excellent tolerability and safety profile. This category of drugs was also proven to be protective of organs, with beneficial effects on morbidity and mortality.⁹

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Losartan was the first non-peptide ARB to be introduced for the treatment of hypertension. It appears to have a flat dose-response curve, and the usual recommended dose is 50 mg once daily. Higher dosage does not generally appear to provide greater effects. Candesartan is a novel AT1 receptor blocker with certain properties that distinguish it from losartan. Candesartan cilexetil is an inactive prodrug that is rapidly and completely hydrolysed to the active compound, candesartan, during absorption via the gastrointestinal mucosa, whereas losartan is an orally active agent that undergoes substantial first-pass metabolism by the cytochrome P450 system to a more potent metabolite. The two angiotensin II type 1 receptor blockers, candesartan and losartan, exhibit different binding characteristics to the AT1 subtype of the angiotensin II receptor. Morsing et al. demonstrated that candesartan acts as an insurmountable antagonist with a marked and long-lasting blockade of the vascular contractile effects of angiotensin II, whereas losartan and its active metabolite, EXP 3174, behave like surmountable or partially surmountable antagonists with a relatively short duration of action. Vanderheyden et al. found that the dissociation half-life from the AT1 receptor was 152 min for candesartan, 5 min for losartan and 31 min for EXP 3174. Candesartan had an affinity for the AT1 receptor 80 times greater than that of losartan and 100 times greater than the active metabolite of losartan. Due to its tight binding to and slow dissociation from the receptors, candesartan provides a dose-related and long-lasting antihypertensive effect. Several clinical trials have indicated that 8 mg or 16 mg once daily is a suitable maintenance dosage of candesartan for management of hypertension. However, the different chemical structures, physical properties, binding affinities, distribution half-lives, and duration of action of compounds relate to their efficacy and safety in clinical treatment. The goal of this study was to systematically assess the antihypertensive effects and tolerability of candesartan and losartan in patients with essential hypertension.

Methods

Fields inclusion and exclusion criteria

We developed inclusion criteria for this review which included the following absolute requirement items: adult population, a clear diagnosis of primary hypertension, randomised controlled trials (RCTs), follow-up of at least 4 weeks, objectives of the study precisely defined, clear description of inclusion and exclusion criteria, treatment and control group comparable at entry, clear description of withdrawals and dropouts, raw data available, statistical method described, and written in English. The exclusion criteria included hypertension with coronary disease, stroke, congestive heart failure, secondary hypertension, poorly controlled diabetes mellitus, chronic kidney failure, administration of any ACE inhibitors or ARB or other antihypertensive agents within 2 weeks, missing data in articles.

Search techniques

We developed a protocol for the review and followed standard QUOROM reporting guidelines. We performed electronic searches of the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 1, 2009), MEDLINE and PREMEDLINE (1966–May 2009), EMBASE (1980–May 2009), review articles, prospective trial registers, relevant trials and abstracts from hypertension meetings, and RCTs and quasi-RCTs comparing any benefits of candesartan and losartan for the treatment essential hypertension. The following medical subject heading terms and text words were used: candesartan, losartan, randomised controlled trials, essential hypertension, blood pressure, angiotensin receptor blockers.

Data collection

Included trials were evaluated independently by two of the reviewers. For studies that could possibly have been RCTs, or in the case of disagreement between the two reviewers, the full articles were obtained. In turn, the same reviewers, who were not blinded to authorship or journal, compiled an ad hoc questionnaire and independently reviewed these articles. The questionnaires then were cross-checked, and disagreement was resolved by consensus or by a third reviewer. Agreement between reviewers on inclusion was evaluated using a kappa statistic. Strength of agreement as evaluated by the kappa statistic was defined as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) or almost perfect (0.81–1.00). The following general descriptive data were extracted from each trial: number, age, gender and race of participants, hypertension duration, baseline trough seated systolic and diastolic blood pressure (SBP and DBP), number of participants randomised assigned to each intervention, duration of follow-up, number of dropouts or withdrawals because of adverse events and discontinuation, change from baseline of seated SBP and DBP, response rate and control rate based on achievement of target blood pressure, and the incidence of adverse events.

Quality assessment

Trials were inspected for three principle aspects of the randomisation process: (1) generation of allocation sequence; (2) allocation concealment; and (3) blinding. In generation of allocation sequence, the approaches were considered as computer, random number table, shuffled cards or tossed coins. Allocation concealment strategies were considered as central randomisation, numbered or coded containers, and sequentially numbered, opaque, sealed envelopes. Also assessed was whether the analysis was by intention-to-treat or not, and the completeness of follow-up. The following Cochrane quality checklist was compiled: (1) allocation concealment: adequate/unclear/
inadequate; (2) blinding: blinding of investigators (yes/no/not stated), blinding of participants (yes/no/not stated), blinding of outcome assessors (yes/no/not stated), blinding of data analysis (yes/no/not stated); (3) intention-to-treat: (A) yes; specifically reported by investigators that intention-to-treat analysis was undertaken and this was confirmed on study assessment; (B) yes; not stated, but confirmed on study assessment; (C) no; not reported and lack of intention-to-treat analysis confirmed on study assessment; (D) no; stated, but not confirmed on study assessment; and (E) not stated; unable to be determined on study assessment. Study quality was assessed using the Jadad scale.20 The Jadad scale was designed to examine elements of clinical studies that may affect bias. A 5-point scoring system is described and summarised as follows: was the study described as randomised? (1 = yes; 0 = no); was the study described as double-blind? (1 = yes; 0 = no); was there a description of withdrawals and dropouts? (1 = yes; 0 = no); was the method of randomisation well described and appropriate? (1 = yes; 0 = no); was the method of double-blinding well described and appropriate? (1 = yes; 0 = no). A score of 0–2 reflects low quality, a score of 3–4 indicates moderate quality and a score of 5 represents a high-quality study.

### Statistical analysis

This meta-analysis combined data at study level and not at individual patient level. Outcome data were synthesised using weighted mean differences (WMD) for continuous data and relative risk (RR) for dichotomous data. We tested for heterogeneity using the Cochran Q test and quantified the degree of heterogeneity with the I² statistic. The I² statistic ranges from 0–100% and measures the degree of inconsistency across studies in a meta-analysis as low, moderate, and high to very high inconsistencies.21 As the Q test is a low-power test, the α level was set at 0.10. A random-effect model or fixed-effect model was chosen according to the Q test. It was still possible that important trials had not been published and thus would not be included in this meta-analysis. We used funnel plots to detect and visualise publication bias. The publication bias test was performed using the Egger’s test.22 Meta-regression analysis was used to assess whether baseline blood pressure, length of treatment and age of patients were associated with the effect of therapy with these agents. This meta-analysis was performed with STATA 10.0 (StataCorp, College Station, TX, USA).

### Results

#### Description of studies

From MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials 239 citations were retrieved. Subsequently, 215 articles were excluded. The majority of these citations were excluded at the level of title or abstract. Specifically, the excluded articles included 45 narrative and systematic reviews, 23 comments, 66 unrelated blood pressure studies, 52 un referenced candesartan versus losartan trials, seven duplications, three letters and 18 other unreferenced articles. Some 24 studies were evaluated in a closer inspection and 12 studies were discarded. Twelve trials were considered eligible to be included in the meta-analysis.23-34 Each included study is summarised in table 1. All 12 included studies were published as full articles. The total number of patients randomised in the included trials was 3644. Four studies compared candesartan 8 mg with losartan 50 mg in fixed-dose monotherapy.23,25,27,34 Five studies compared candesartan 8 mg with losartan 50 mg and titrated to 16 mg and 100 mg.25,27,32,33 Three trials compared candesartan 16 mg with losartan 50 mg.23,26,28 Three trials compared candesartan with losartan on double or titration to double dose.24,30,31 Ten trials compared with ARB combination therapy23-25,27,29-34 and two trials compared ARBs/HCTZ combination therapy.26,30 Two trials followed-up for 6 weeks,30,34 seven trials followed-up for 8 weeks23-25,30,33 and three trials followed-up for 12 weeks.27-29 Eight trials reported adverse events during follow-up.23-26,28,31 and six trials reported serious adverse events.23,24,26,29,31 The progress through the different stages of systematic review is documented in figure 1. The detailed information of the included studies is listed in table 1.

#### Efficacy of candesartan versus losartan in blood pressure reduction

We analysed a total of 12 RCTs with 3644 patients for the SBP and DBP reduction efficacy of candesartan and losartan at trough after 24 h at the end of the follow-up. Candesartan showed more effective SBP and DBP reduction (WMD, -2.97; 95% CI, -4.18–-1.77; p < 0.001; WMD, -1.76; 95% CI, -2.57–-0.96; p < 0.001; respectively, figure 2). We also performed subgroup analysis of the included 12 trials. First, we found that 8 mg of candesartan was superior to 50 mg of losartan in SBP and DBP reduction (WMD, -2.45; 95% CI, -4.33–-0.56; p = 0.01; WMD, -1.48; 95% CI, -2.53–-0.42; p = 0.006, respectively). When each dosage titration was doubled, candesartan was still superior to losartan in SBP and DBP reduction (WMD, -1.09; 95% CI, -2.17–-0.01; p = 0.046; WMD, -0.83; 95% CI, -1.60–-0.07; p = 0.032, respectively). Second, we compared 16 mg of candesartan with 50 mg of losartan. The results showed that candesartan brought more net SBP and DBP reduction than losartan (WMD, -5.35; 95% CI, -9.23–-1.46; p = 0.007; WMD, -3.28; 95% CI, -6.19–-0.36; p = 0.028, respectively). A similar result was found when the dosage was titrated to 32 mg and 100 mg in candesartan and losartan, respectively (WMD, -3.12; 95% CI, -4.50–-1.73; p < 0.001; WMD, -1.85; 95% CI, -2.67–-1.03; p = 0.005, respectively).
Three trials reported consistent blood pressure reduction at 6h post dose. Candesartan projected a higher level of effectiveness in SBP and DBP reduction at trough at 6h post dose (WMD, -2.76; 95% CI, -3.93–-1.59; \( p < 0.01 \); WMD, -2.18; 95% CI, -2.99–-1.38; \( p < 0.01 \), respectively). Eight and four trials generated therapy response and control rates, respectively, at the end of the follow-up. Candesartan had better response and control rates than losartan. (RR, 1.12; 95% CI, 1.06–1.18; \( p < 0.01 \); RR, 1.26; 95% CI, 1.06–1.50; \( p = 0.008 \), respectively).

**Safety of candesartan versus losartan in blood pressure control**

We also compared the common adverse events related to candesartan and losartan treatment. Unfortunately, not all trials included in the systematic review provided specific descriptions of adverse events. Eight trials reported adverse events related to treatment with the two agents. The incidence rates of these adverse events in candesartan and losartan were similar; no obvious difference was found in the results for the two agents (RR, 0.98; 95% CI, 0.86–1.12; \( p = 0.78 \); figure 3). The most common adverse events related to treatment were headache, dizziness, respiratory infections and fatigue. The incidence of these adverse events was comparable between candesartan and losartan, so no differences were found in headache (RR, 1.04; 95% CI, 0.75–1.44; \( p = 0.83 \)), respiratory infections (RR, 0.82; 95% CI, 0.60–1.12; \( p = 0.21 \)), dizziness (RR, 1.09; 95% CI, 0.61–1.94; \( p = 0.77 \)), fatigue (RR, 1.03; 95% CI, 0.42–2.52; \( p = 0.94 \)) and gastroenteritis (RR, 0.55; 95% CI, 0.21–1.45; \( p = 0.23 \)), see table 2. Six trials reported serious adverse events during follow-up in detail. Candesartan generated a lower incidence than losartan of reported serious adverse events. (RR, 0.48; 95% CI, 0.25–0.92; \( p = 0.03 \); figure 3).

**Publication bias analysis and meta-regression analysis**

We performed a publication bias analysis with Egger’s test. No evidence for publication bias was found in reduction of SBP (\( p = 0.633 \)) and DBP (\( p = 0.572 \)). The funnel plots of the included RCTs were symmetrical. This may reflect that no publication bias was found in our meta-analysis; see figure 4. We also performed a meta-regression analysis of the study baseline characteristics in both candesartan and losartan. In candesartan, the net reduction of DBP showed negative correlation with baseline DBP (regression coefficient -1.81, \( p = 0.03 \)). In losartan, the net reduction of DBP was in correlation with participants and baseline DBP (regression coefficient 0.02 and -1.56, \( p = 0.03 \) and = 0.02, respectively), see table 3.

**Discussion**

ARBs, which do not produce a dry cough, unlike ACE inhibitors, are increasingly being used to treat hypertension. Losartan was the first of the ARBs, and now several others such as valsartan, eprosartan, irbesartan, olmesartan, tasosartan, telmisartan and candesartan have been developed. In this systematic review and meta-analysis, we reviewed 12 studies that compared the effects and safety of candesartan versus losartan. Comparing the common therapeutic dose of the two agents, candesartan showed a superior lowering of SBP and DBP compared with losartan at trough after a 24h dose. When comparing double dosage or titration to double dosage of the two agents, similar results were found at trough and peak after administration. Nevertheless, the response and blood pressure-controlling efficacy of candesartan in follow-up was superior to that of...
losartan. We suggest that the efficacy of blood pressure reduction might be related to ARB dosage and duration of therapy. In a fixed-dosage RCT, the reduction of SBP was 11.6 mmHg and 13.4 mmHg for administration of candesartan 8 mg and 16 mg, losartan 50 mg and placebo, respectively. A similar reduction in blood pressure was observed in losartan group. Candesartan is able to provide a greater effect perhaps due to its stronger binding affinity to the AT1 receptor. Pharmacokinetic and pharmacodynamic experiments have proved that candesartan is an insurmountable AT1 receptor blocker, characterised by 80- and 100-fold greater in vitro binding affinity to the AT1 receptor than losartan and its active metabolite EXP 3174, respectively. The prolonged antihypertensive effect of candesartan is most probably related to the slow dissociation of candesartan from its binding site at the AT1 receptor. Candesartan also has a longer plasma elimination half-life in humans (7–12.9 h) than losartan and EXP 3174. We also found that the pooled results of trials in blood pressure reduction indicated that candesartan lowered SBP and DBP to a greater extent, which would lead to a larger reduction of the pulse pressure; candesartan has also been demonstrated to be an independent predictor of cardiovascular and, in particular, coronary mortality. In an analysis involving one million adults in 61 prospective studies, the relationship between the reduction in blood pressure and cardiovascular morbidity and mortality events supported that a 2 mmHg reduction in systolic blood pressure would provide a lower stroke mortality of around 10%, and a 7% lower mortality from ischaemic heart disease or other vascular death without a blood pressure threshold down to the 115/75 mmHg level. In another study, it was suggested that a 1 mmHg diastolic blood pressure reduction

### Table 1. Characteristics of included studies

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<th>First author</th>
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<th>Follow-up</th>
<th>Drop out</th>
<th>ITT analysis</th>
<th>Jadad score</th>
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<td>3</td>
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<td>23</td>
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ITT: intention-to-treat 5 = yes; specifically reported by investigators that intention-to-treat analysis was undertaken and this was confirmed on study assessment; 4 = yes; not stated, but confirmed on study assessment; 3 = no; not reported and lack of intention-to-treat analysis confirmed on study assessment; 2 = no; stated, but not confirmed on study assessment; 1=not stated; unable to be determined on study assessment. HCTZ: hydrochlorothiazide.
may be associated with a 5% reduction in risk of coronary heart disease and an 8% reduction in risk of stroke. These findings provide a useful strategy in clinical hypertension management.

Another index for evaluating antihypertensive therapy is the trough-to-peak ratio. Calculation of the trough-to-peak ratio has been a popular approach for assessing the homogeneity of antihypertensive treatment and for justifying administration of drugs in a once-daily regimen. It is generally believed that a low trough-to-peak ratio has three disadvantages. First, it may lead to an excessive decrease in blood pressure at peak response, resulting in lower

Figure 2. Forest plot of net blood pressure reduction from baseline of candesartan and losartan. (a) Comparison of net systolic blood pressure (SBP). (b) Comparison of net diastolic blood pressure (DBP).
perfusion of vital organs. Second, it may result in inability to control blood pressure during the latter part of the dosing interval. Third, it may cause a general increase in blood pressure variability, due to the effect of the pharmacological variability of the normal spontaneous variability seen in hypertensive individuals. The homogeneity of antihypertensive treatment during the entire dosing interval is another important consideration, because the degree of blood pressure variability is significantly and independently associated with increased risk for end-organ damage seen in hypertension.40 In our systematic review, only three trials

<table>
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<th>losartan event</th>
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Heterogeneity $\chi^2 = 5.20$ df $= 7$ $p = 0.64$ $I^2 = 0$

Test of overall effect $z = 0.28$ $p = 0.78$ 

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</tbody>
</table>

Heterogeneity $\chi^2 = 5.04$ df $= 5$ $p = 0.41$ $I^2 = 11$

Test of overall effect $z = 2.20$ $p = 0.03$

Favours candesartan  Favoris losartan

Table 2. Comparison common adverse events of candesartan and losartan

<table>
<thead>
<tr>
<th>AE</th>
<th>RR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1.04</td>
<td>0.75–1.44</td>
<td>0.83</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>0.82</td>
<td>0.60–1.12</td>
<td>0.21</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.09</td>
<td>0.61–1.94</td>
<td>0.77</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.03</td>
<td>0.42–2.52</td>
<td>0.94</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.55</td>
<td>0.21–1.45</td>
<td>0.23</td>
</tr>
</tbody>
</table>

AE: adverse event; RR: relative risk; 95%CI: 95% confidence interval

Figure 3. Forest plot of adverse events of candesartan and losartan. (a) Comparison of common adverse events (AE). (b) Comparison of serious adverse events (SAE).
reported blood pressure level at trough and peak time; the trough-to-peak ratio of candesartan and losartan was about 1 and 0.7, respectively. We favour recommending candesartan in clinical antihypertensive therapy because of a higher trough-to-peak ratio.

Recently, further evidence has suggested that a smoothness index is a better indicator than the trough-to-peak ratio in assessing antihypertensive treatment. The smoothness index is calculated from the standard deviation of all hourly blood pressure measurements during a 24-h period, and normalised for the mean blood pressure decrease during this period. Compared with the trough-to-peak ratio, the smoothness index, which is calculated from ambulatory SBP and DBP, provides a greater reproducibility and better correlation to some prognostic indicators. The advantage of using the smoothness index instead of the trough-to-peak ratio for assessing antihypertensive treatment is illustrated by results from the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE).41,42 Unfortunately, none of the included trials in our meta-analysis calculated and compared the smoothness index of candesartan and losartan.

Our systematic review assessed eight prospective studies which evaluated, in detail, adverse events of these two agents. The proportion of participants who reported adverse events which were considered relevant to treatment in the whole study process was approximately 20–30%. It should be noted that these reported adverse events were generally mild or moderate, and were tolerated by the majority of participants. The most common adverse events were headache, dizziness, fatigue, infections and gastroenteritis. Other infrequent adverse events included dry mouth, taste disturbance, oesophagitis, sweating, paresthesia, sleep disturbance, sinusitis, pharyngitis, back pain, rhinitis, etc. The reported adverse events in the two groups were comparable. It was interesting that the incidence of serious adverse events in candesartan was lower than that of losartan. Candesartan showed a safety advantage over losartan, although there was no clear evidence that these reported serious adverse events were related to treatment with these agents.

Although there were unpublished studies evaluating candesartan versus losartan in hypertension management, no publication bias was found in the clinical trials which were included in our meta-analysis. The results of Egger’s test indicate the high quality of the included studies. There were several limitations to this meta-analysis such as high heterogeneity, different patient populations, and lack of

| Table 3. Meta-regression analysis of baseline characteristics on average net reduction blood pressure |
| Characteristic | Candesartan group | Losartan group |
| Age | 0.60 | 1.02 |
| Follow-up | –1.16 | –1.07 |
| Sample size | 0.02 | 0.02 |
| Baseline SBP | 0.12 | 0.04 |
| Baseline DBP | –2.04 | –1.81** |

BP: blood pressure; SBP: systolic blood pressure; DBP diastolic blood pressure;*: p = 0.03;**: p = 0.02

Figure 4. Funnel plot of included studies. (a) Publication bias analysis of comparison net systolic blood pressure on double dose. (b) Publication bias analysis of comparison net diastolic blood pressure on double dose.
detailed data, all of which limit the conclusions that can be drawn from this analysis. Different patient populations and various methods of blood pressure measurement may be sources of heterogeneity. A randomised effect model was selected for the analysis of the pooled studies, and more conservative evaluations were made. Meta-regression analysis showed that the net reduction of DBP was in negative correlation with baseline DBP for both candesartan and losartan. A conceivable explanation was that reduction of DBP could be correlated with hypovolaema rather than vasodilatation. We did not find that other indexes, such as age, gender, race, weight, participant number, and duration of follow-up, correlated with the net blood pressure reduction.

In conclusion, the results of this meta-analysis indicate that candesartan is more effective than losartan in reducing blood pressure. There was no evident difference in their common adverse events profiles. Candesartan seems to cause fewer serious adverse events than losartan.

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**Conflict of interest**

The authors have no conflicts of interest to declare.

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