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Full Length Research Paper

A meta-analysis of the efficacy and safety of candesartan in Chinese patients with mild to moderate essential hypertension

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This study was performed to evaluate the efficacy and safety of Candesartan in treating Chinese patients with mild to moderate essential hypertension. Medical databases and review articles were screened with prespecified criteria for randomized controlled trials that reported the effects of and adverse reactions to Candesartan and other antihypertensive drugs in treating of Chinese patients with mild to moderate essential hypertension. The quality of included studies was critically evaluated. A total of 735 articles were found and 19 articles were finally included. Heterogeneity test: efficacy analysis (Q statistic = 4.60, p = 1.00, I2 = 0%), safety analysis (Q statistic = 12.19, p = 0.84, I2 = 0%). The results of Meta-analysis confessed that there were no significant differences either in efficacy or safety between Candesartan and other active antihypertensive agents. Funnel-plot displayed a symmetrical figure, indicating there was no publication bias. In an analysis excluding the 6 low quality trials, our results were unchanged indicating the sensitivity of the Meta-analysis was fine. The evidence currently available shows that Candesartan has the similar efficacy and safety compared with other active antihypertensive agents with mild to moderate essential hypertension.

Key words: Candesartan, essential hypertension, systemic review, meta-analysis.

INTRODUCTION

Hypertension is one of the most common cardiovascular and cerebrovascular diseases and is associated with human fatal diseases such as coronary artery disease and cerebrovascular diseases. Data from the National Health and Nutritional Examination Survey and from the World Health Organization have clearly demonstrated that, worldwide, less than 30% of hypertensive patients are adequately controlled by our currently accepted blood pressure goals (Papadopoulos et al., 2008). So the important task which medical workers have to face is how to choose a safe and effective antihypertensive drug. Angiotensin receptor blocker (ARB) that works by blocking the rennin angiotensin system (RAS) is a new kind of drugs for hypertension and it was included in the ranks of first-line antihypertensive agents in 2005 by Chinese Guideline for the Prevention and Treatment of Patients with Hypertension (The Committee to Rebise, 1999; Chinese Guideline for the Prevention and Treatment of Patients with Hypertension, 2004). Candesartan is a new member of ARBs used in clinic after Losartan, Valsartan and Irbesartan. Candesartan was first used for patients with hypertension in Sweden in 1997 and the curative effects were affirmative (Belcher et al., 1997). Candesartan has gone on the market in Chinese for several years, however, there have been no evidences about the efficacy and safety of which from evidence-based medicine yet.

Though there are several studies about Candesartan in treatment of hypertension, the conclusions of which are not credible because of small sample size and lacks of systemic evaluation of methodologic quality. This study makes a systemic review about clinical random control trials (RCTs) focused on Candesartan in treatment of mild

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to moderate essential hypertension in Chinese in order to obtain the best evidence about the efficacy and safety of Candesartan in treating Chinese patients with mild to moderate essential hypertension.

METHODS

Search strategy

The search strategy was made according to working handbook 4.2.7 from the Cochrane collaboration (Sackett et al., 2002). We systematically searched Cochrane central register of controlled trials (Issue 3, 2009), MEDLINE (1991 to May 2009), EMbase (1991 to May 2009), CBMdisc (1991 to May 2009), and CNKI (1994 to May 2009) for randomized trials examining the efficacy and safety of Candesartan on mild to moderate essential hypertension among Chinese people. In addition, we conducted a manual search of abstracts from selected conferences and we also searched by hand the bibliographies of all relevant trials. The following search criterion was used: ("hypertension" or "essential hypertension") and ("Candesartan" or "Candesartan Cilexetil") and language is limited to English or Chinese.

Study selection

Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full articles. The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (a) study design—RCTs; (b) population—Chinese patients with mild to moderate essential hypertension (WHO-ISH Hypertension Guidelines Committee, 1999; Committee of guidebook on prevention and treatment of hypertension, 2000); (c) intervention—Candesartan versus other active antihypertensive agents as monotherapy; (d) outcome variable—overall response rate and adverse reaction rate; (e) efficacy criteria—recommendation on evaluation methods of clinical trials about cardiovascular drugs in Guiding principles for clinical research of new drugs made by Chinese Ministry of Health in 1993 (Liu et al., 1998).

Data extraction

From each study, the following information was abstracted: author, year of publication, study design, characteristics of the population, simple size, treatment proposal, time of the therapy, overall response rate and adverse reaction rate.

Assessment of study quality

Jadad score was used to assess the methodologic quality of the trials by two reviewers (Jadad et al., 1996). Articles gained 1 to 2 points were regarded as low quality and the ones gained 3 to 5 points were regards as high quality (Moher et al., 1998).

Statistical methods

For dichotomous outcomes, we calculated a pooled odds ratio (OR) and 95% confidence interval (CI). The OR was defined as the odds of an outcome in those who received Candesartan compared with the odds in those who received other active hypertensive agents. The ORs of different RCTs were combined by using the random-effects model of Der Simonian and Laird (Der Simonian et al., 1986), if true between-study heterogeneity exists or else using Mantel and Haenszel fixed-effects model instead (Mantel et al., 1959). Intertrial statistical heterogeneity was explored using the Cochran Q test with calculated I^2, indicating the percentage of the total variability in effect estimates among trials that is, due to heterogeneity rather than to chance (Higgins et al., 2003). I^2 values of 50% or more indicate a substantial level of heterogeneity. We evaluated the presence of publication bias by means of visual inspection of the funnel plot (whether it was symmetrical or not). To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by excluding those studies with low quality and then rerunning the analysis to assess the change in Ors. All p values were two-sided with statistical significance set at an α level of 0.05. We followed the "quality of reporting meta-analysis guidelines" for reporting and discussing these Meta-analytical results (Moher et al., 1999).

All the statistical analysis was carried out by the Cochrane collaboration's RevMan 4.2 software.

RESULTS

Characteristics of trials

There were 735 articles relevant to the search term and 19 articles (Chen, 2007; Gao and Jiang, 2008; Liu, 2008; Lv, 2008; Xu, 2008; Zhang et al., 2006, 2007; Huang, 2007; Wang et al., 2007; Fu et al., 2006; Geng et al., 2006; Hu et al., 2006; He and Yi, 2006; Chen et al., 2005; Qian et al., 2005; Xu et al., 2005; Chang et al., 2004; Huang et al., 2004; Sun et al., 2003) involving 1587 Chinese patients with mild to moderate essential hypertension (group Candesartan: 794 patients, group control: 793 patients) were included in this Meta-analysis finally. Ages, sex ratio and initial blood pressure were similar in each group, respectively. The flow chart for the selection of RCTs to be included in our analysis is shown in Figure 1. The characteristics of these trials were showed in Table 1.

Methodologic quality assessment

All the trials included in this Meta-analysis mentioned the term 'random', but the detail method was illuminated in 1 article only. There were 13 trials mentioned the term 'double blind', but only 9 articles explained the detail method. All the 19 trials described the data of the patients who withdrew during the treatment. According to the Jadad score, 13 articles and 6 articles were regarded as high quality literature and low quality literature, respectively (Table 1).

Heterogeneity test

We choose fixed-effect model to make Meta-analysis because there were no significant heterogeneities between studies in both efficacy analysis (Q statistic = 4.60, p = 1.00, I^2 = 0%) and safety analysis (Q statistic =

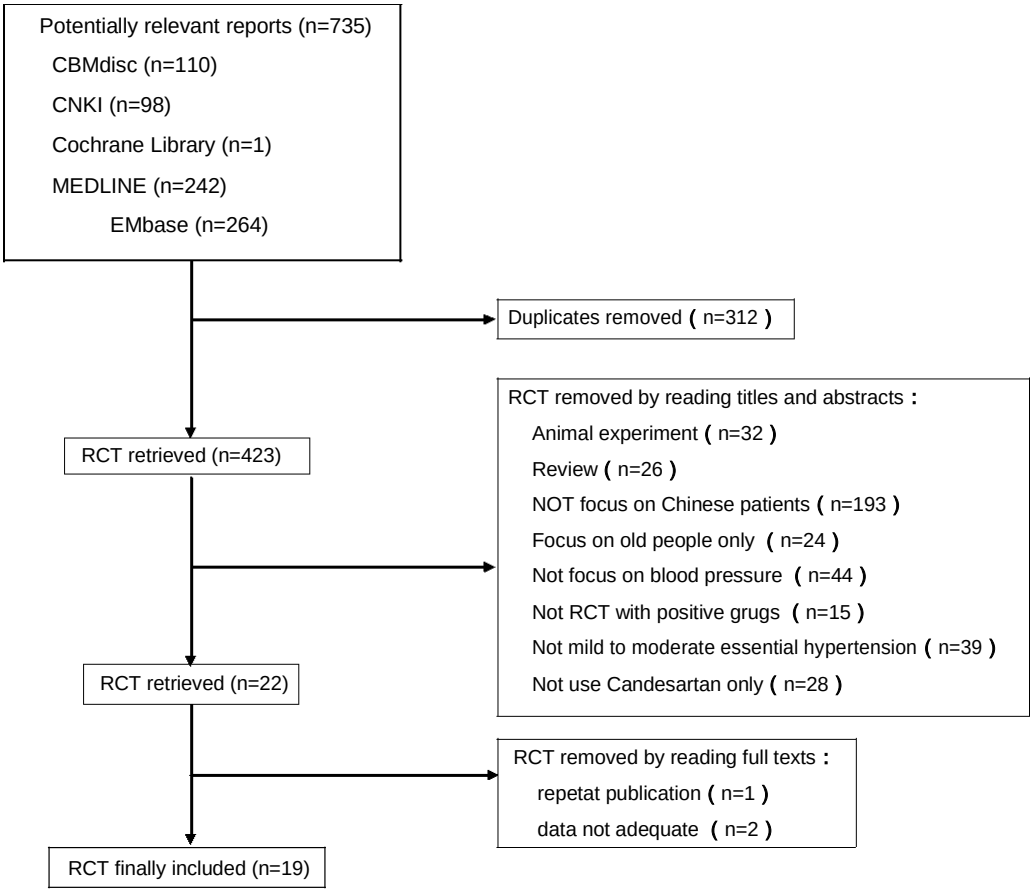

Figure 1. Flow chart of article selection.

Table 1. Characteristics of important studies admitted.

Studies	Groups	Treatment proposal (mg/d)	Time of therapy (weeks)	Sample size	Overall response rate (%)	Adverse reaction rate (%)	Jadad score
Chen (2008)	Candesartan	4	8	38	94.3	10.8	2
	Perindopril	4	8	42	89.7	22.5	
Gao (2008)	Candesartan	8	4	50	76.0	2.0	2
	Amlodipine	5	4	50	74.0	0	
Liu (2008)	Candesartan	4	8	45	84.4	8.9	2
	Valstartan	80	8	45	82.2	11.1	
Lv (2008)	Candesartan	4	8	33	87.9	10.0	2
	Enalapril	10	8	32	75.0	12.5	
Xu (2008)	Candesartan	8	8	28	89.3	0	2
	Enalapril	10	8	28	85.7	14.3	
	Candesartan	4	8	36	75.0	8.3	
	Losartan	50	8	36	71.4	11.1	

Table 1. Contd.

Huang (2007)	Candesartan Eanlapril	4 5	8 8	23 24	82.6 87.5	8.7 29.2	2
Wang et al. (2007)	Candesartan Valsartan	4 80	8 8	40 40	85.0 87.2	5.0 5.0	4
Fu (2006)	Candesartan Irbesartan	8 150	8 8	30 30	80.0 76.7	13.3 16.7	4
Geng (2006)	Candesartan Losartan	8 50	8 8	24 24	81.8 81.0	11.7 0	3
Hu (2006)	Candesartan Irbesartan	8 150	4 4	29 29	89.7 79.3	6.9 0	4
He (2006)	Candesartan Fosinopril	4 10	20 20	66 64	74.2 73.4	7.6 9.4	3
Zhang et al. (2006)	Candesartan Valsartan	4 80	8 8	32 30	87.5 86.7	9.4 6.7	4
Chen et al. (2005)	Candesartan Losartan	8 50	8 8	24 24	91.7 91.7	8.3 8.3	4
Qian et al. (2005)	Candesartan Losartan	8 50	8 8	127 127	82.2 84.2	3.9 1.6	4
Xu et al. (2005)	Candesartan Enalapril	8 10	8 8	110 108	81.9 77.8	12.7 16.5	4
Chang et al. (2004)	Candesartan Losartan	8 50	8 8	20 20	75.0 70.0	5.0 10.0	4
Huang et al. (2004)	Candesartan Losartan	8 50	8 8	30 31	82.1 76.7	3.1 6.5	4
Sun (2003)	Candesartan Losartan	8 50	8 8	18 18	77.8 72.2	5.6 11.1	3

12.19, p = 0.84, I^2 = 0%) in our primary analysis.

Meta-analysis of efficacy

Overall response rates of both group: Candesartan and group control were recorded in all the 19 trials finally included. Active antihypertensive agents involved in this analysis were Losartan, valsartan, Irbesartan, Enalapril, Fosinopril, Perindopril and Amlodipine. The results of Meta-analysis confessed that there were no significant differences in efficacy between Candesartan and control group in treating Chinese patients with mild to moderate essential hypertension (Figure 2).

Meta-analysis of safety

Adverse reaction rates of both Candesartan and control group were recorded in all the 19 trials finally included. Main adverse reactions of Candesartan group were headache and dizziness. Otherwise, chief adverse re-actions of control group were cough, headache, dizziness and gastrointestinal symptoms. The results of Meta-analysis

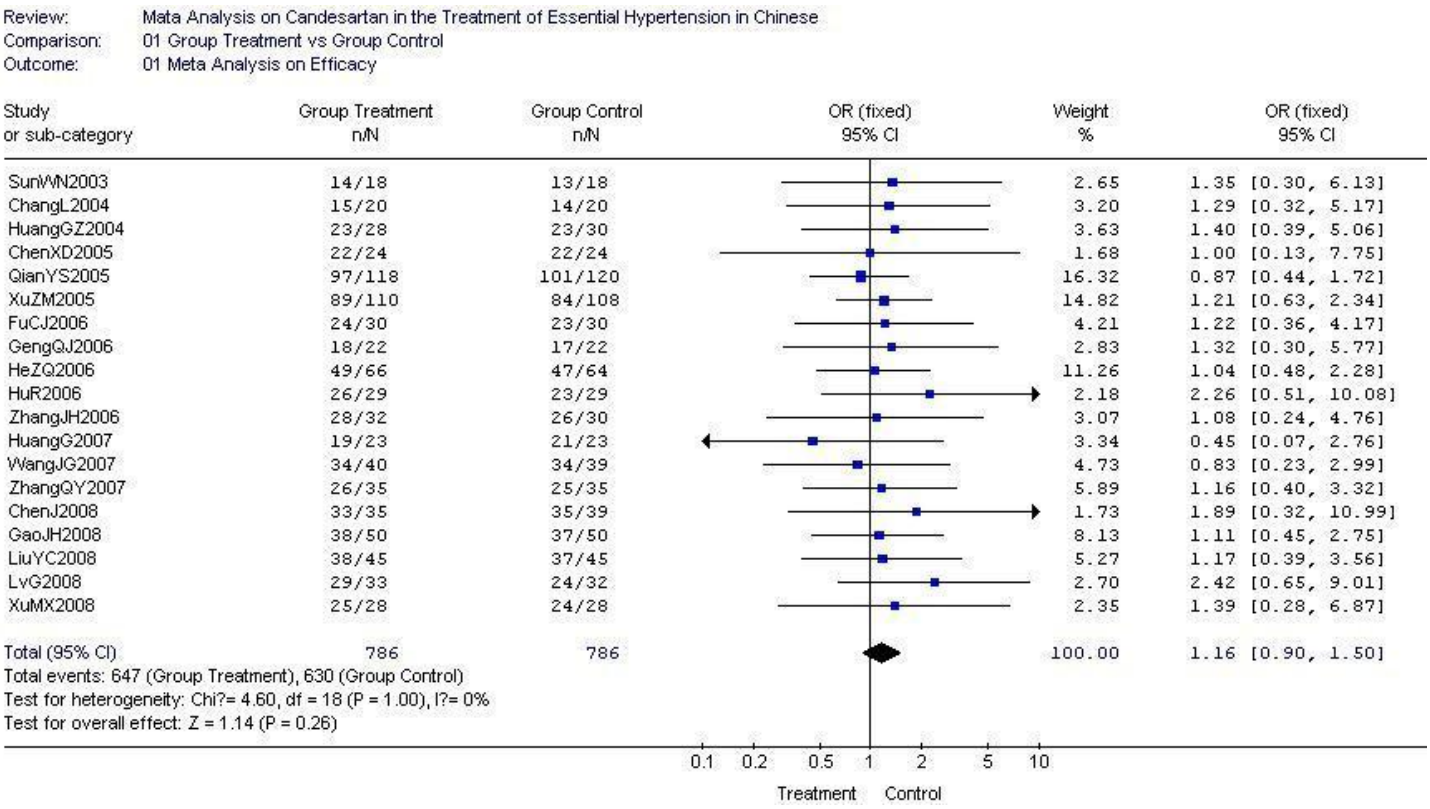

Figure 2. OR estimates with the corresponding 95% CI for the efficacy. The OR estimate of each study is marked with a ■.The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond, this line might be contained within the diamond if the confidence interval is narrow.

analysis confessed that there were no significant differences in safety between Candesartan and control group in treating Chinese patients with mild to moderate essential hypertension (Figure 3).

Publication bias

An analysis of publication bias was conducted. No evidence of publication bias was found since the funnel plots was symmetrical based on a visual analysis (Figure 4).

Sensitivity analyses

In an analysis excluding the 6 low quality trials, our results were consistent with those found in our main analysis described earlier: in the efficacy analysis, there was no difference in overall response rates between Candesartan and control group [Z = 0.79 (p = 0.43), OR = 1.13, 95% CL (0.84 ~ 1.51)], furthermore, no difference was found in adverse reaction rates between Candesartan and control group in the safety analysis [Z = 0.05 (p = 0.96), OR = 0.99, 95% CL (0.65 ~ 1.51)].

DISCUSSION

Summary of the literature quality

A total of 19 literatures were finally included in this systemic review. All these articles, including a sample size of 1587 totally were RCTs. Jadad score in 13 out of the 19 articles were more than two points and the results were not changed significantly after removing the other 6 articles with Jadad score less than three points. Moreover, no evidence of publication bias was found and there were no significant heterogeneities between studies in both efficacy analysis and safety analysis, too. It was suggested that the overall quality of this systemic review was high.

However, there was still methodological insufficiency:

(a) Randomization method may not be rigorous because the specific program of randomization was inferred in only one literature.

(b) Selection bias may exist for allocation concealment was not described in all of these articles included.

(c) Selection bias, measuring bias and implementation bias may exist because 7 studies did not describe whether blind method was used or not.

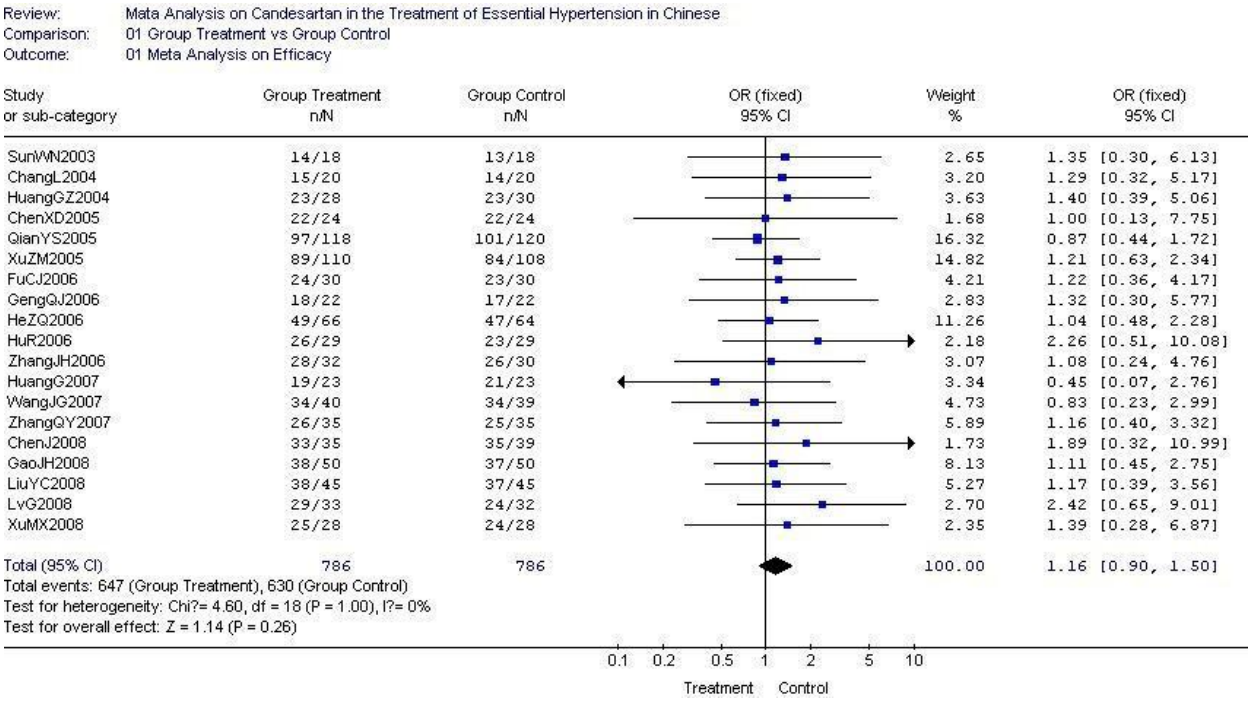

Figure 3. OR estimates with the corresponding 95% CI for the safety. The OR estimate of each study is marked with a ■.The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond, this line might be contained within the diamond if the confidence interval is narrow.

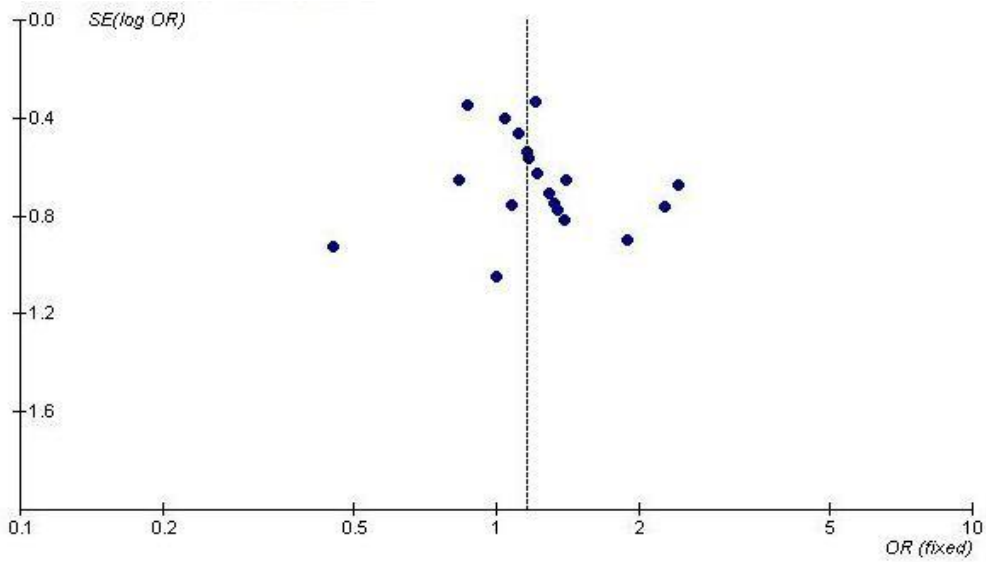

Figure 4. Funnel plot.

Analysis of efficacy and safety

Candesartan, a new non-peptide ARBs, takes antihypertensive role by selectively combining the AT_1 receptor, subtype of angiotensin Ⅱ receptor, inhibiting RAS system and then blocking vascular smooth muscle contraction mediated, sympathetic nerves excitation and aldosterone release (Perrone-Filardi et al., 2009). Since AT_1 receptor

subtype is combined with Candesartan, angiotensin Ⅱ has to combine and stimulate with AT_2 receptor subtype which may induce a further step of antihypertension. Compared with other ARBs, Candesartan has the characteristics of stronger affinity to AT_1 receptor subtype and slower dissociation rate (Unger, 2000), so it has the smallest application dose in the current listing of ARBs. The results of this systemic review showed that there were no significant differences in efficacy in treating Chinese patients with mild to moderate essential hypertension between Candesartan and control group. Thus we can conclude that Candesarntan has the same antihypertensive effect compared with other first-line antihypertensive drugs. Because of the specificity of reacting in RAS system, Candesartan may void the complication of cough and angioneurotic edema (Kim-Mitsuvama, 2009) while using ACEI in the treatment of hypertension. The adverse effects, including dizziness and headache mainly, of Candesartan in treating essential hypertension referred in this study were less likely to happen and tolerated, moreover, it was not necessary to stop administrating. The results of this systemic review showed that there were no significant differences in safety in treating Chinese patients with mild to moderate essential hypertension between Candesartan and control group.

It suggests that Candesartan has the similar safety compared with other positive antihypertensive agents.

CONCLUSION

In summary, the evidence currently available shows that Candesartan has the similar efficacy and safety compared with other active antihypertensive agents in treatment of Chinese patients with mild to moderate essential hypertension. However, as the methodological insufficiency more literatures with high quality are needed to obtain more rigorous and objective clinical evidence.

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