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Original Article

The effects of azelnidipine and amlodipine in treatment of mild to moderate hypertension: a systematic review

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Abstract: Hypertension is an important risk factor for patients with cardiovascular disease. Long-acting calcium channel blockers are frequently used to treat patients with mild to moderate hypertension, among which azelnidipine and amlodipine are two dihydropyridine (DHP) type calcium channel blockers that are widely used in Japan and China. We offer a current evaluation and comparison of the efficacy and safety of azelnidipine with amlodipine. To confirm location of all relevant trials databases including Cochrane Handbook 5.1, CBM (1966 to December 2014), CNKI (1911 to December 2014), EMBASE (1966 to December 2014), and Medline (1950 to December 2014), were searched to identify randomized controlled trials (RCT) assessing the effects and safety of azelnidipine. Studies included were assessed using the RevMan 5.1. STATA 10.0 for meta-analysis. Based on study quality and other selection criteria, 19 of 405 studies were selected for the meta-analysis (subjects=1,482). Data show that lowered systolic pressure of azelnidipine were similar to those of amlodipine and there were no significant differences between azelnidipine and amlodipine for mild to moderate hypertension (relative risk=1.00, 95% confidence interval 0.92-1.10). Neither drug was different with respect to adverse events, either. Still, the limited number of RCTs suggests caution when interpreting data due to bias risk.

Keywords: Hypertension, calcium channel, azelnidipine, amlodipine

Introduction

Hypertension is a global disease and important risk factor for many cardiovascular diseases. Antihypertensive medications that effectively control blood pressure can reduce the incidence of cardiovascular disease and associated complications. Calcium channel blockers are often used to treat hypertension because they are reliable, effective antihypertensives with few adverse reactions and they are especially effective for prevention of stroke [1-3]. Long-acting formulations are generally recommended because short-acting calcium channel blockers are associated with ischemic events [4-6].

Amlodipine can slowly and continuously reduce blood pressure over time [7] and azelnidipine is a lipophilic DHP calcium channel blocker that can be taken up into blood vessel walls to reduce blood pressure after plasma clearance [8]. Both of these drugs can be used to treat mild to moderate hypertension, and studies suggest that the antihypertensive effects of the two drugs are similar [9-11]. However, the number of cases included in published studies was relatively small and whether the effect of azelnidipine is the same as that of amlodipine in large populations is uncertain. The last review on this topic was 11 years ago and was a summary of the efficacy and tolerability of azelnidipine as of June 2003 [12]. Thus, updated data are needed. Here, we systematically searched the literature for randomized controlled trials (RCT) comparing the effects of azelnidipine and amlodipine for mild to moderate hypertension. Then, a meta-analysis was performed to compare blood pressure changes before and after azelnidipine and amlodipine treatment. We sought to objectively assess efficacy and safety of both drugs for treating mild to moderate hypertension.

Investigations and results

Study selection

All relevant literature obtained from computer searches and reference tracking were entered into Endnote X6 software management. After a

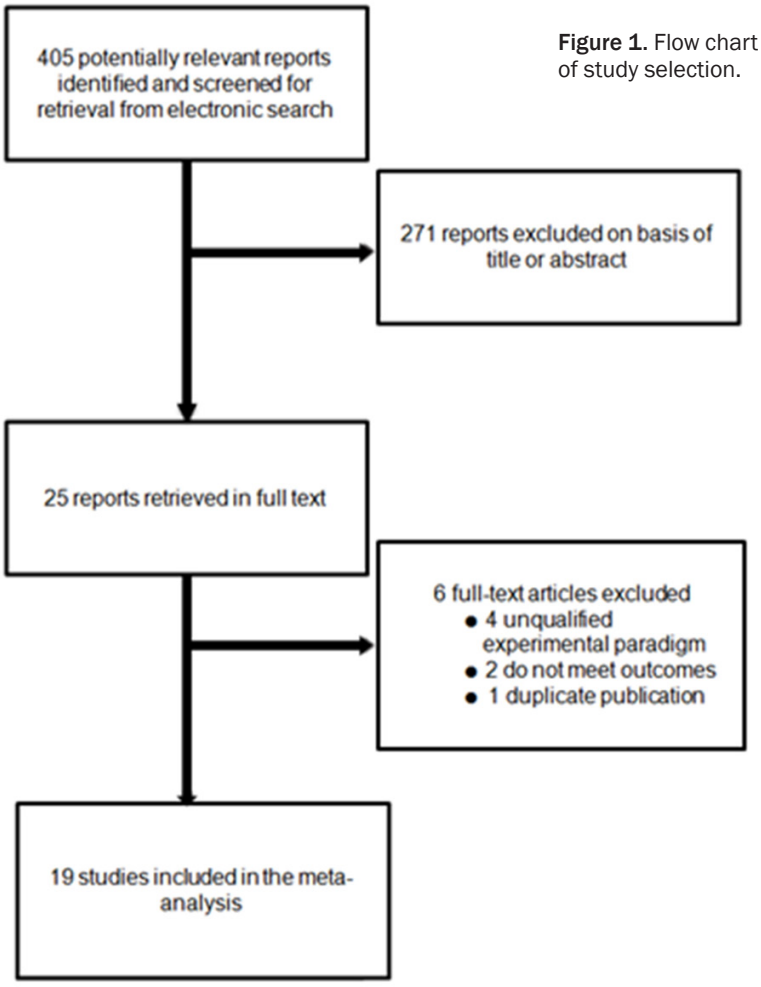

Figure 1. Flow chart of study selection.

thorough review of the initial search products, 405 relevant papers were obtained and titles and abstract scanning allowed the removal of 271 papers. After full text studies, another four papers were excluded due to an unqualified experimental paradigm; one paper was excluded because it was a repeated publication; and one paper was excluded due to unqualified outcome indicators. Thus, 19 papers were included in the final analysis: 8 Chinese papers [13-20] and 11 English papers [10, 21-29] (see **Figure 1**).

Criteria for inclusion and exclusion

For inclusion in the meta-analysis, a study had to fulfill the following criteria: (1) all cases were diagnosed through pathology tests or more than two image logical examinations combined with clinical data comparing the initial therapeutic effects of; calcium channel; azelnidipine or amlodipine for the treatment of hypertension, despite the etiology; (2) no patients received any treatment before; (3) clearly documented indications for hypertension; (4) if two or more studies were reported by the same authors in the same institution, either the study of higher quality or the most recent publication was included in the analysis; (5) Child-Pugh class A or B; (6) follow-up time >3 years.

The exclusion criteria for this meta-analysis were as follows: (1) only one treatment method was used and no contrastive study was performed; (2) previously treated patients; (3) follow-up time <3 years or a small sample size (<100).

Study characteristics

In nine of the 19 papers included in this study the population under research was Chinese; and the other ten papers studied Japanese populations. Sample sizes ranged from 30 to 231 subjects (total subjects 1,482). In three of the 19 studies, patients also had concomitant chronic kidney disease [23, 24, 27]; in one study a patient had concomitant cardiovascular disease [22]; in one study the patients had concomitant type 2 diabetes [21], and in one study, patients had hypertension complicated with left ventricular hypertrophy [29]. Study durations were typically 8 weeks, and the longest was 2 years [26]. **Table 1** shows the body mass index (BMI), ages, and other baseline characteristics of the included patients.

Evaluation of azelnidipine and amlodipine efficacy

SBP reducing effects: Eight studies [10-11, 14-17, 19] reported reductions in SBP after 8 weeks of treatment; and significant heterogeneity existed among these 8 studies (P=0.008, I^2=63.6%). A meta-analysis using a random effects model revealed that both drug groups did not differ significantly regarding SBP-

Table 1. Baseline characteristics of included studies

Author	Year	Country	BMI[a] (kg/m^2)	Age (years old)	Sample size	Regimen/dose	Follow-up (W or M)	Concomitant diseases
Yunyi	2013	China		50.00±7.51 vs 49.26±6.15	31 vs 31	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day) after breakfast. At 4 W if SeDBP[b] ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Hong	2011	China	26.90±2.02 vs 26.70±2.32	51.4±8.3 vs 53.1±8.8	27 vs 28	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day) after breakfast. At 4 W if SeDBP ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Rongjie	2012	China		18-70	35 vs 36	azelnidipine (8 mg/day) or 5 mg amlodipine besylate once per day after breakfast. At 4 W if SeDBP ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	12 W	Unclear
Haixu	2012	China		56.23±9.58 vs 54.23±8.63	24 vs 24	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day) after breakfast. At 4 W if SeDBP ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Dandan	2013	China	26.06±2.33 (M) 25.35±2.57 (F) vs 25.51±2.33 (M) 25.89±2.45 (F)	52.17±8.49 vs 52.81±8.3	116 vs 115	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day) after breakfast. At 4 W if SeDBP ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Yuping	2011	China	24.63±2.60 vs 25.01±3.12	50.18±8.96 vs 48.92±9.10	40 vs 21	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day) after breakfast. At 4 W if SeDBP ≥90 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Xishan	2013	China		52±8	47 vs 45	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day). If at 3 W the blood pressure still did not reach the standard the dose was increased; otherwise the dose was not changed.	5 M	
Jianliang	2011	China		68±11 vs 67±12	28 vs 26	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day)	12 W	
Abe	2011	Japan	23.9±0.6 vs 23.8±0.6	65.8±1.7 vs 66.0±1.4	34 vs 33	azelnidipine (8 mg/day) per day increased to 16 mg per day, or 2.or amlodipine besylate (5 mg/day) increased to 5 mg per day	24 W	Type 2 diabetes
Kojima	2011	Japan	25.0±2.8 vs 24.6±3.6	67.2±9.2 vs 66.2±8.5	61 vs 54	16 mg azelnidipine or amlodipine besylate (5 mg/day)	48 W	Cardiovascular disease
Zhao	2010	China	25.97±2.26 vs 25.96±2.33	52.87±9.37 vs 52.63±9.00	110 vs 110	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day). At 4 W if SeDBP ≥90 mmHg, dose was doubled.	8 W	
Kizuku KURAMOTO	2002	Japan		54±7.2 vs 54±6.5	22 vs 23	azelnidipine (16 mg/day) or amlodipine besylate (5 mg/day)	6 W	
Takeshi Takami	2013	Japan	25.7±1.1 vs 25.8±1.3	66.2±4.4 vs 67.5±4.5	26 vs 26	azelnidipine (16 mg/day) or amlodipine besylate (5 mg/day)	2 Y	
Tsukasa Nakamura	2007	Japan		48±16 vs 46±14	15 vs 15	azelnidipine (16 mg/day) or amlodipine besylate (5 mg/day)	6 M	CKD[d]
Tsukasa Nakamura	2011	Japan	22.6±2.0 vs 22.8±2.2	45.3±9.6 vs 45.5±8.8	15 vs 15	azelnidipine (16 mg/day) or amlodipine besylate (5 mg/day)	6 M	CKD
Takeshi Takami	2011	Japan	25.8±1.0 vs 25.8±1.3	65.8±4.1 vs 67.5±4.6	25 vs 25	azelnidipine (8 mg/day) or amlodipine besylate (5 mg/day)	24 W	
Toshio Yamagishi	2006	Japan	23.8±3.6 vs 24.1±3.5	58.0±12.261.7±12.1	54 vs 54	azelnidipine (8 mg/day) 2.or amlodipine besylate (5 mg/day) after breakfast. At 4W if SBP[c] >135 mmHg, dose was doubled; otherwise the dose was not changed.	8 W	
Tsuneo Takenaka	2012	Japan		66±2 vs 67±2	29 vs 30	azelnidipine (16 mg/day) or amlodipine besylate (5 mg/day)	12 M	CKD

[a]body mass index (BMI); [b]SeDBP, seated diastolic blood pressure; [c]SBP, systolic blood pressure; [d]CKD.

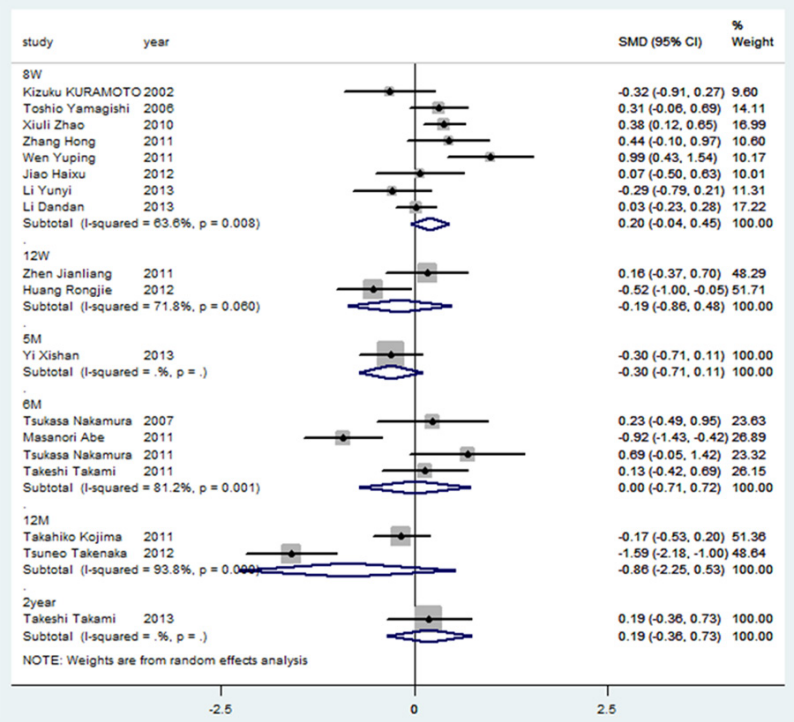

Figure 2. SBP-reducing effect of both drugs.

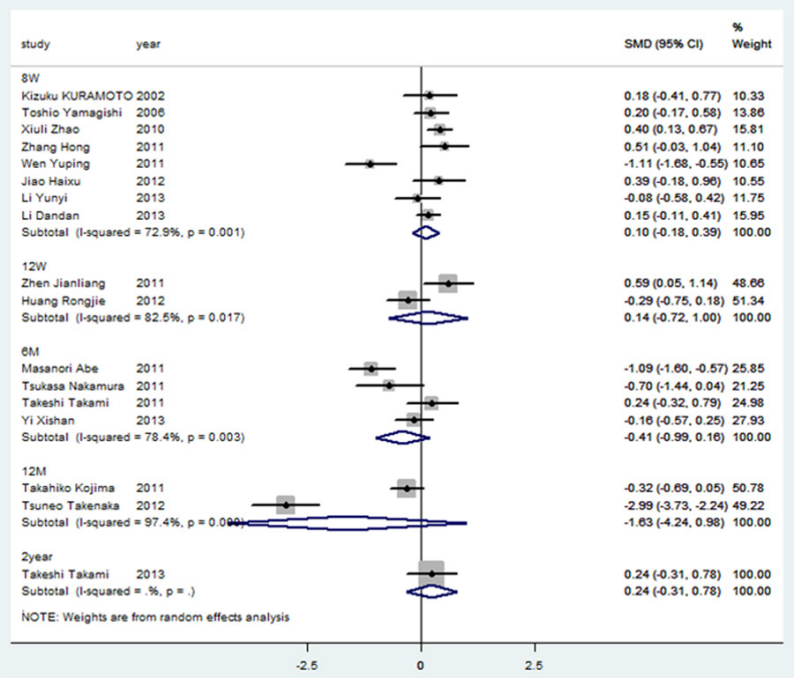

Figure 3. DBP-reducing effect of both drugs.

reducing effects (SMD=0.20, 95% CI-0.04~0.45) (see **Figure 2**). Two studies [12, 20] reported reductions in SBP after 12 weeks of treatment; and there was significant heterogeneity between the two studies (P=0.060, I^2=71.8%). A similar meta-analysis (random effects model) confirmed again no differences between either drugs. (SMD=-0.19, 95% CI -0.86~0.48) (**Figure 2**). One study [18] reported lowered SBP after 5 months of treatment, and both groups were found not different (SMD=-0.30, 95% CI-0.71~0.11). Four studies [21, 23, 24, 26] reported the SBP reducing effect of the drugs after 6 months of treatment; there was significant heterogeneity between these four studies (P=0.001, I^2=81.2%), and meta-analysis using the random effects model showed that the two groups did not differ significantly regarding their SBP reducing effect (SMD=0.00, 95% CI-0.71~0.72) (see **Figure 2**). Three studies [22, 27, 29] reported the SBP reducing effect of the drugs after 12 months of treatment; there was significant heterogeneity between the two studies (P<0.001, I^2 =87.8%), and meta-analysis using the random effects model showed that the two drug groups did not differ significantly regarding their SBP reducing effect (SMD=-0.69, 95% CI-1.59~0.20) (see **Figure 2**). One study [25] examined the SBP reducing effect of the drugs after 2 years of treatment, and the two groups were found not to differ significantly in their SBP reducing effect (SMD =0.19, 95% CI-0.36~0.73).

DBP-reducing effects: Eight studies [10-11, 14-17, 19] reported reductions in DBP for both drugs after 8 weeks of treatment and there was significant heterogeneity among these eight studies (P=0.001, I^2=72.9%). A meta-analysis

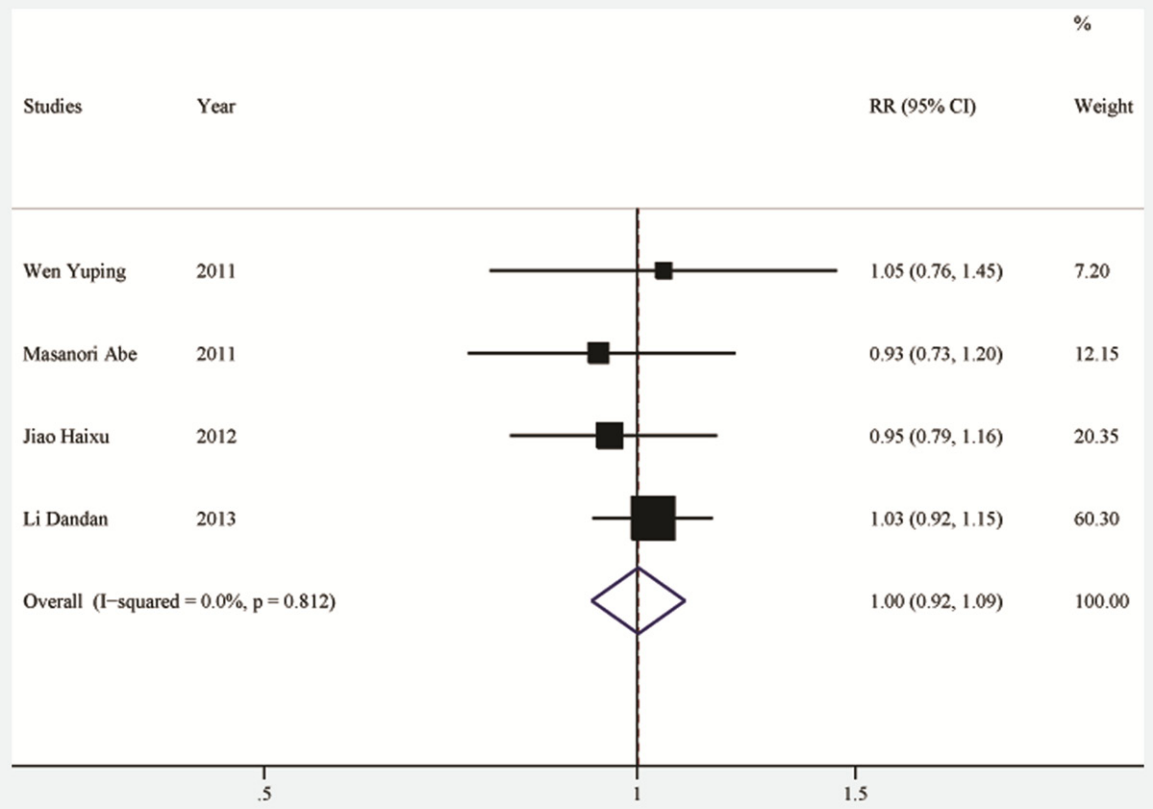

Figure 4. Overall antihypertensive efficacies of both drugs.

using a random effects model indicated no significant differences in these effects (SMD=0.10, 95% CI-0.18~0.39) (see **Figure 3**). Two studies [12, 20] reported reductions in DBP of both drugs after 12 weeks of treatment and these studies were significant heterogeneous (P=0.017, I^2=82.5%), but they were not significantly different (random effects model; SMD=0.14, 95% CI-0.72~1.00) (see **Figure 3**). Four studies [21, 23, 24, 26] reported reduced DBP for both drugs after 6 months of treatment and these studies were significantly heterogeneous (P=0.003, I^2=78.4%), but not significantly different (random effects model; SMD=-0.41, 95% CI-0.99~0.16) (see **Figure 3**). Three studies [22, 27, 29] reported reductions in DBP for both drugs after 12 months of treatment and again, these were significant heterogeneous (P<0.001, I^2=94.9%), but not significantly different (random effects model; SMD=-1.30, 95% CI-2.83~0.24) (see **Figure 3**). One study [18] examined reductions in DBP for both drugs after 2 years of treatment, and again these two groups were different significantly (SMD=0.24, 95% CI-0.31~0.78).

Overall antihypertensive efficacies of both drugs: Four studies [14, 15, 17, 21] reported overall antihypertensive efficacies of the two drugs as being not significantly heterogeneous (P=0.847, I^2=0.0%), as well as not significantly different with respect to overall antihypertensive efficacy (RR=1.00, 95% CI0.92~1.10) (**Figure 4**).

Assessment of publication bias: An analysis of publication bias regarding DBP values reported in the 19 included papers was performed. A funnel plot, where the abscissa is SMD and the ordinate is the standard error of SMD, was almost symmetrical (see **Figure 5**), and Egger's test yielded P=0.417, suggesting a relatively small likelihood of publication bias. SBP values were similarly analyzed and again the funnel plot was almost symmetrical (see **Figure 6**), and Egger's test yielded P=0.037, suggesting again, a relatively small likelihood of publication bias.

Adverse effects due to azelnidipine: In the study by Jiao's group [14], two cases of dizzi-

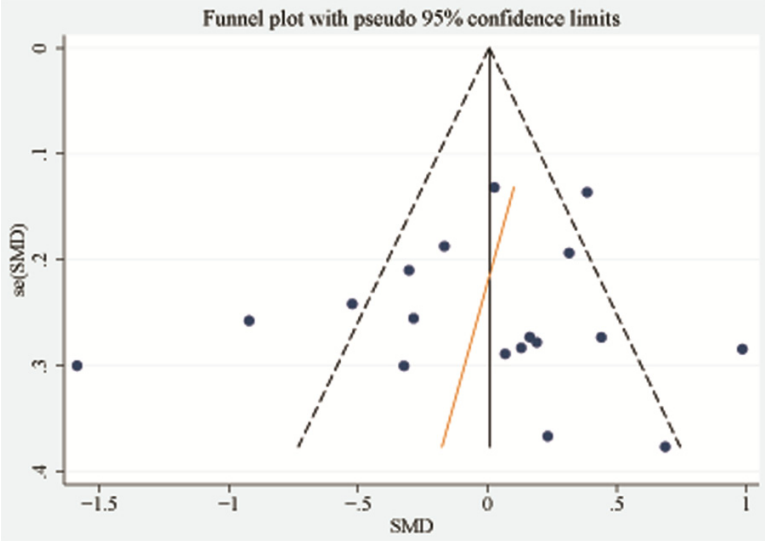

Figure 5. Funnel plot of DBP.

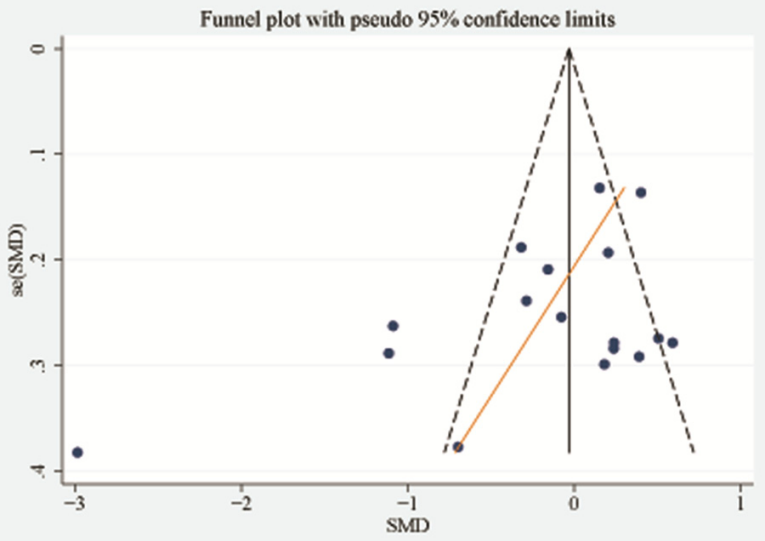

Figure 6. Funnel plot of SBP.

ness, one case of headache, one case of toothache, one case of constipation, and one case of chest distress were reported in the azelnidipine group. Li and colleagues [15], reported one case of edema of the bilateral lower extremities and two cases of facial flushing with azelnidipine group. Wen [17] confirmed one case of headache in the azelnidipine group. In the study by Kuramoto's group [11], one case of loose stools was reported with azelnidipine group. Statistically, the incidence of adverse effects for azelnidipine group was not significantly different from amlodipine.

Discussion

Last review on this topic comparing the efficacy and safety of azelnidipine with amlodipine to treat patients with low to moderate hypertension was published eleven years ago and was based on published studies as of June 2003. Thus, a comprehensive systematic review of all relevant studies since is needed. Therefore, we performed a meta-analysis of all relevant RCTs on the comparison of azelnidipine and amlodipine. Our study offers sufficient rigor to be of interest to physicians in Japan and China where azelnidipine is approved, as well as offer data for clinical trials ongoing worldwide.

Our data show that antihypertensive effects of azelnidipine and amlodipine do not differ significantly in any patient group studied whether for short-or long-term treatment. Azelnidipine can satisfactorily control low to moderate hypertension without increasing the incidence of adverse effects.

Systematic retrospective examinations of clinical trials comparing azelnidipine and amlodipine reveal that, although the antihypertensive effects of both drugs are not significantly different, patients with concomitant chronic kidney diseases may benefit more from azelnidipine because e azelnidipine can alleviate proteinuria [23, 24, 27]. Azelnidipine also reduces the albumin-to-creatinine ratio in hypertensive patients with concomitant type 2 diabetic nephropathy better than amlodipine (260±54 $mg.g^{-1}$ Cr vs. 352±68 $mg.g^{-1}$ Cr, $P<0.05$) [21].

In the included RCTs, neither the methods used to generate the random sequences nor the spe-

cific implementation of hiding treatment regimens nor blinding was described in detail. Although baseline conditions were relatively balanced among all studies and comparability was relatively good, risk of bias in the included studies could not be determined with the available data. When merging data for SBP and DBP reducing effects, significant heterogeneity was observed for antihypertensive effects among the studies, which may have been caused by differences in treatment cycles, initial doses, concomitant diseases, and baseline blood pressures. To validate the beneficial effects of azelnidipine for patients with hypertension, large-scale trials are still needed to determine if long-term use of azelnidipine may reduce cardiovascular and cerebrovascular risks, protect renal function, and therefore be preferred among other antihypertensive medications in clinical practice.

Experimental

Eligibility criteria

A thorough research strategy was implemented to locate all related RCTs comparing azelnidipine and amlodipine for treating patients with mild to moderate hypertension. In the included studies, the patients fit the diagnostic criteria for low to moderate hypertension, and there were no restrictions on the age, sex, or concomitant diseases. Interventions involved included: (1) a comparison between azelnidipine and amlodipine; and (2) a comparison between azelnidipine and amlodipine, each combined with a third treatment (the third treatment had to be the same for azelnidipine and amlodipine to ensure comparability between the two groups). The outcome indicators examined in this study included: (1) efficacy indicators, i.e., changes in diastolic (DBP) and systolic blood pressure (SBP) after treatment in the two groups, total efficacy of the two groups, and differences in total effective rates between the two groups; and (2) safety indicators, i.e., adverse effects of azelnidipine reported in the studies.

Search strategy

The Chinese or English term for "azelnidipine" was used as the keyword to search databases in the Chinese and English languages for literature with publication dates spanning the period between the dates the respective databases were established and December 2014. The databases included Chinese databases: Chinese Biomedical Literature Database (CBM, 1966-December 2014), Chinese Journal Fulltext Database (CJFD, 1911-December 2014), and the Digital Journal of Wanfang Database (1985-2014); and English databases: Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. Reference sections of papers were also analyzed to avoid missing relevant literature.

Data extraction

The literature screening was performed under the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two authors (Yu Xiao and Gang Hu) extracted data independently and reached consensus on all items. Disagreement about specific studies between the two reviewers was resolved through discussion.

The literature screening process was completed in three steps. First, a preliminary screening was conducted which was based on citation information, titles, and abstracts. Clearly unqualified papers were removed, and full texts of papers that were clearly or probably qualified were retrieved for further screening. Second, retrieved full texts of all probably qualified papers were read and analyzed individually to determine whether they should be included in the final analysis. Finally, the authors were contacted if the information provided was incomplete or unclear.

Statistical analysis

Using a descriptive method, clinical study characteristics, including subjects, interventions, and research outcomes, were listed in a table to facilitate comparisons. STATA 10.0 software (StataCorp, College Station, TX) was used for statistical analysis. For studies lacking data for differences in SBP and DBP between, before, and after treatment, the mean and the standard deviations of differences were calculated according to the method provided by RevMan-5.1 handbook ($SD=\sqrt{(SD_1^2+SD_2^2-2_*R_*SD_{1*}SD_2)}$, R=0.8). For binomial variables, relative risk (RR) was used as the effect size for analysis; for numerical variables, standardized mean differ-

ences (SMD) were used, and a 95% confidence interval (95% CI) was calculated. χ^2 tests were performed to assess heterogeneity among different experiments, and α was set at 0.1. A *P* value >0.1 indicated non-significant differences in heterogeneity between different experiments, and a fixed effects model was used for meta-analysis. A *P* value <0.1 indicated statistically significant differences in heterogeneity. In the latter case, possible causes of heterogeneity were first analyzed; and, if necessary, a random effects model was used for meta-analysis. A Funnel plot and Egger's test were applied to measure publication bias.

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Disclosure of conflict of interest

None.

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