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Tolerability and Effectiveness of (*S*)-Amlodipine Compared With Racemic Amlodipine in Hypertension: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Amlodipine is a calcium channel blocker prescribed for the management of angina and hypertension. As a racemic mixture, amlodipine contains (*R*)- and (*S*)-amlodipine isomers, but only (*S*)-amlodipine as the active moiety possesses therapeutic activity. Based on pharmacologic research, it remains uncertain if (*S*)-amlodipine alone has similar efficacy and fewer associated adverse events (AEs) compared with the racemic mixtures.

Objective: The aim of this systematic review and meta-analysis was to determine the effectiveness and tolerability of (*S*)-amlodipine compared with that of racemic amlodipine.

Methods: A systematic literature search was performed using MEDLINE (1966–2009), EMBASE (1966–2009), the Cochrane Central Register of Controlled Trials (issue 3, 2009), the Chinese Biomedical Database (1978–2009), and the China National Knowledge Internet (1980–2009). All randomized controlled trials (RCTs) comparing (*S*)-amlodipine 2.5 mg and racemic amlodipine 5.0 mg in the treatment of hypertension were included in the review. The outcome measures to be collected were cardiovascular events, systolic blood pressure (SBP), diastolic BP (DBP), and AEs. Quality assessments of clinical trials were conducted using a modified Jadad Scale, with trials being rated as low quality (score 0–3) or high quality (score 4–7). Meta-analysis of the included studies was performed using RevMan software.

Results: Of the 229 references identified, 214 were excluded after screening the titles, abstracts, or full texts. Fifteen RCTs were included, of which 13 were in Chinese and 2 in English. Based on the Jadad Scale score, 3 of the RCTs were classified as high quality (score 5 or 6) and the remaining 12 as low quality (score 1–3). None of the trials evaluated cardiovascular events beyond 40 weeks. Meta-analysis of the 15 trials indicated that (*S*)-amlodipine was not significantly different from racemic amlodipine in the effect on BP. When only high-quality studies were included, after 4 weeks' treatment, the weighted mean difference (WMD) of SBP and DBP decrease (1 study) was –2.84 (95% CI, –6.42 to 0.74) with (*S*)-amlodipine and –1.71 (95% CI, –3.48 to 0.06) with racemic amlodipine. After 8 weeks' treatment, the WMD of SBP and DBP decrease (2 studies) was –1.13 (95% CI, –5.29 to 3.03)

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and –1.34 (95% CI, –2.67 to –0.01), respectively. The risk difference (RD) for the number of patients who experienced AEs with (*S*)-amlodipine and racemic amlodipine was found to be –0.04 (95% CI, –0.06 to –0.02). When all the trials were included, (*S*)-amlodipine treatment was associated with significantly less edema than racemic amlodipine (RD, –0.02; 95% CI, –0.03 to 0.00); however, when only high-quality studies (2 studies) were included, no difference was found between the 2 groups (RD, 0.01; 95% CI, –0.02 to 0.03). One high-quality study found significant differences in increases in aspartate and alanine aminotransferase activities in the 2 groups (RD, 0.08; 95% CI, 0.01 to 0.05). No significant differences between the 2 groups were found in the incidence of headache (RD, 0.00; 95% CI, –0.02 to 0.01) or flushing (RD, –0.01; 95% CI, –0.02 to 0.00).

CONCLUSIONS: The majority of the clinical trials comparing (*S*)-amlodipine and racemic amlodipine treatment were low quality (12/15 [80%]). According to the limited evidence, there were no significant differences between (*S*)-amlodipine 2.5 mg and racemic amlodipine 5.0 mg in controlling BP. When all the trials were considered, (*S*)-amlodipine treatment was associated with significantly less edema than racemic amlodipine; however, when only high-quality trials were included, no significant difference was found. More long-term, high-quality RCTs with cardiovascular events as the primary outcome are needed to compare the safety and efficacy of (*S*)-amlodipine and racemic amlodipine. (*Curr Ther Res Clin Exp.* 2010;71:1–29)

KEY WORDS: (*S*)-amlodipine, hypertension, systematic review.

INTRODUCTION

Amlodipine, a third-generation dihydropyridine calcium channel blocker, is prescribed for the management of angina and hypertension. In addition to the high degree of specificity for vascular smooth muscle that racemic amlodipine shares with the other dihydropyridine drugs, racemic amlodipine also has unique pharmacokinetic characteristics (eg, slow time-to-effect and a long $t_{1/2}$). As a result, racemic amlodipine has become one of the most commonly used antihypertensive agents in China and other countries.[1]

Adverse events (AEs) commonly associated with racemic amlodipine include edema, flushing, dizziness, and headache, which are usually not serious but can affect the patient's daily life and performance at work, leading to noncompliance with the treatment regimen.[2] As a racemic mixture, racemic amlodipine contains (*R*)- and (*S*)-amlodipine isomers in a 1:1 ratio, but only (*S*)-amlodipine as the active moiety possesses therapeutic activity.[3] Therefore, a racemic amlodipine formulation composed of only (*S*)-amlodipine was developed. The standard dose of (*S*)-amlodipine is half that of racemic amlodipine.

Although (*S*)-amlodipine has been marketed in some countries and clinical trials have been conducted comparing the 2 drugs, a systematic review of the trials has not been done. Therefore, we conducted this systematic review and meta-analysis to determine the effectiveness and tolerability of (*S*)-amlodipine compared with racemic amlodipine.

METHODS

Search Strategy

A computer-aided systematic search of MEDLINE (1966–2009), EMBASE (1966–2009), the Cochrane Central Register of Controlled Trials (issue 3, 2009), the Chinese Biomedical Database (1978–2009), and the China National Knowledge Internet (1980–2009) was conducted in August 2009 using combinations of the following search terms: *(*S*)-amlodipine*, *levoamlodipine*, *amlodipine isomer*, *amlodipine enantiomer*, and *chiral switch of amlodipine*. The bibliographies of the extracted articles were reviewed to find other related randomized controlled trials (RCTs). Google academic searching was used to find meeting abstracts. The Web site www.clinicaltrials.gov was searched, and we requested that Pfizer Pharmaceuticals Ltd. and Jilin Tianfeng Pharmaceutical Co., Ltd., provide data from unpublished trials.

Inclusion and Exclusion Criteria

All RCTs of (*S*)-amlodipine compared with racemic amlodipine for the treatment of hypertension were included. In the trials, the standard doses were (*S*)-amlodipine 2.5 mg and racemic amlodipine 5.0 mg. Male and female patients aged 18 to 75 years diagnosed as having mild to moderate primary hypertension were included. The primary outcome measures to be collected included mortality, stroke, coronary heart disease, and cardiovascular events. The secondary outcome measures included blood pressure (BP), heart rate, and AEs occurring during treatment.

Publications meeting any of the following criteria were excluded: reviews, case reports, and experimental studies; studies using drugs other than racemic amlodipine as control; studies having factors other than (*S*)-amlodipine and racemic amlodipine that might affect findings in the treatment groups; repeated publication of the results of the same study; and having a nonrandomized controlled trial design.

Quality Assessment and Data Collection

Each potentially eligible study was independently assessed by 2 qualified reviewers (F.L. and M.Q.) to determine whether it met the inclusion criteria and to assess its methodologic quality. A modified Jadad Scale[4] that added allocation concealment as a criterion was used to assess methodologic quality. The Jadad Scale criteria were as follows: sequence generation—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; allocation concealment—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; blinding method—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; withdrawal and exit—described = 1 point and not described = 0 points. A total score was computed by summing the scores given for all the criteria (range, 0–7 points). Low quality was defined as a score of 0 to 3 points and high quality as 4 to 7 points.

The 2 reviewers independently extracted data from each included study using a standardized form and assessed the quality of the studies. Conflict between the reviewers was resolved through discussion, and if consensus could not be reached, the third reviewer (S.-D.Z.) determined the outcome. The characteristics of each study were identified and extracted, including methodology, number of cases, participant characteristics (eg,

age, sex, and ethnicity), detailed experimental and control interventions, and primary and secondary outcomes. The original investigators were contacted to obtain missing information, and the unclear data were not used until the investigators replied.

Statistical Analysis

RevMan version 5.0 (Cochrane Collaboration, Copenhagen, Denmark) was used to combine results from ≥2 separate trials. Before the results of the studies were combined, statistical heterogeneity was identified and measured using the χ^2 test (P = 0.05). When heterogeneity was identified in a group of trials ($P < 0.05$), random-effects models were applied. Otherwise, fixed-effects models were used and CIs of pooled effects were calculated. Odds ratio and risk difference (RD) were calculated for dichotomous outcomes, while the weighted mean difference (WMD) was used for continuous outcomes measured using the same methodology. The range of the RD or WMD was expressed as 95% CI. $P < 0.05$ was considered statistically significant. Subgroup analysis was performed to answer specific questions about particular patient groups or types of interventions.

Using the RevMan software, a funnel plot was made to identify potential publication bias.

RESULTS

No unpublished studies were provided by the manufacturers. No meeting abstracts in English or other languages were found in a Google academic search. An RCT titled *Efficacy and Safety Study of* S-*Amlodipine Gentisate Compared to Amlodipine Besylate to Treat Mild-to-Moderate Hypertension* was found at www.clinicaltrials.gov, but the results were not provided; therefore, the trial was not included here. A total of 229 references were identified, and 15 RCTs were included (**Figure 1**). All 15 studies used a dose of 2.5 mg of (*S*)-amlodipine and 5.0 mg of racemic amlodipine. The characteristics of the included trials are listed in **Table I**.[5–19]

Quality Assessments

Twelve studies, in which the description of the randomization process was not given, allocation concealment was not done, blinding was not used, or follow-up was not conducted, were classified as low quality (modified Jadad score 1–3).[5–7,9–12,14–17,19] Three trials were classified as high quality (modified Jadad score 5 or 6) (**Table II**).[8,13,18] One trial[11] did not demonstrate comparability between groups, while all other trials conducted a statistical test for comparability between groups. Ten trials had a 2-week washout period before administering the study drugs.[5–10,12,13,15,18]

Antihypertensive Effects

Although the search strategy was designed to identify all related RCTs, the RCTs that assessed primary outcomes, including mortality, stroke, coronary heart disease, and cardiovascular events, were not identified in the searches.

When including both low- and high-quality studies, after 4, 6, 8, 32, and 40 weeks' treatment, decreases in systolic BP (SBP) and diastolic BP (DBP) were not

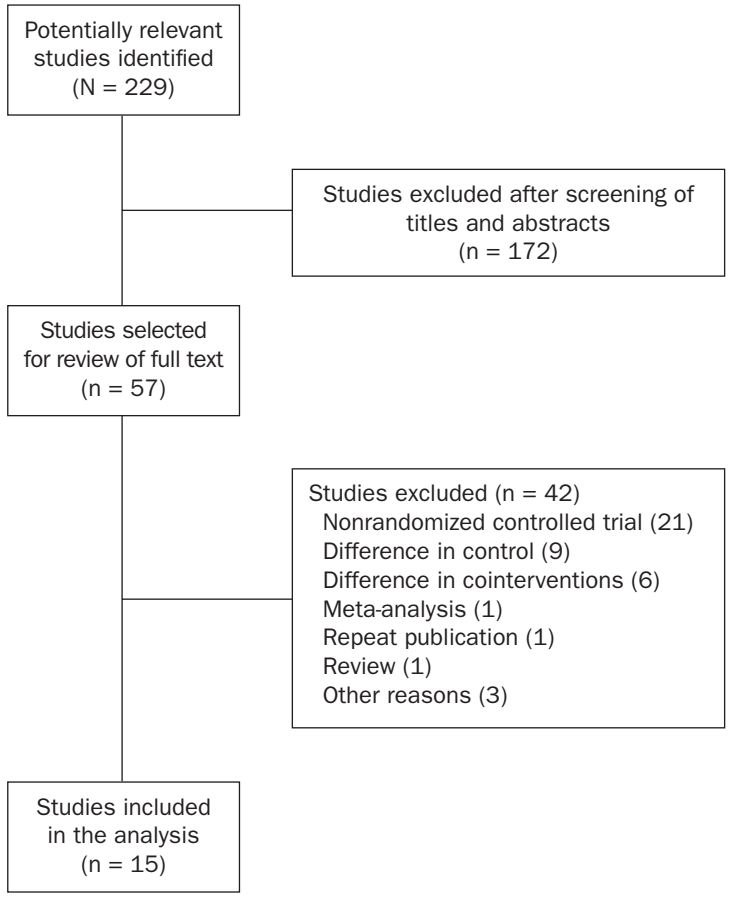

Figure 1. Identification of eligible randomized controlled trials.

significantly different in patients receiving (*S*)-amlodipine 2.5 mg compared with racemic amlodipine 5.0 mg (**Figures 2–11**). When only the high-quality studies were included, after 4 weeks' treatment, the WMD of the SBP and DBP decrease was –2.84 (95% CI, –6.42 to 0.74) and –1.71 (95% CI, –3.48 to 0.06), respectively,[8] indicating the BP decrease was not significantly different in the 2 groups. Again, when only the high-quality studies were considered, after 8 weeks' treatment, the WMD of the SBP and DBP decrease, respectively, was not significantly different in the 2 groups (–1.38 [95% CI, –3.62 to 0.86] and –1.33 [95% CI, –2.66 to 0.00])[8,18] (**Figures 12** and **13**).

To assess the effects of publication bias on the results of the meta-analysis, funnel plots of BP at 4 and 8 weeks were made. Asymmetrical plots were obtained, indicating the presence of reporting bias (**Figures 14–17**).

Table I. Randomized controlled trials of (*S*)-amlodipine and racemic amlodipine in the treatment of adults with mild to moderate hypertension included in the systematic review and meta-analysis.

Trial	No. of Patients, (S)-Amlodipine/ Racemic Amlodipine	Washout Period	Inclusion Criteria	Exclusion Criteria	Duration	Outcomes
Liu et al[5]	30/30	4 Weeks (placebo for the last 2 wk)	Primary hypertension	Allergy to racemic amlodipine, suffered cardiac, brain, and kidney complications	4 Weeks	Blood pressure, heart rate, AEs
Cheng et al[6]	60/60	2 Weeks	Mild to moderate primary hypertension	Severe liver or renal dysfunction, pregnancy, other conditions associated with poor compliance	5 Weeks	Blood pressure, AEs
Fang[7]	140/140	2 Weeks	Mild to moderate primary hypertension	Secondary hypertension, other organic heart disease, liver or renal dysfunction	40 Weeks	Blood pressure, ultrasound
Hu et al[8]	110/107	2 Weeks	Mild to moderate primary hypertension	Secondary hypertension, serious cardiac, brain, or renal disease	8 Weeks	Blood pressure, heart rate, AEs

(continued)

Table I (continued).

Trial	No. of Patients, (S)-Amlodipine/ Racemic Amlodipine	Washout Period	Inclusion Criteria	Exclusion Criteria	Duration	Outcomes
Zeng et al[9]	262/262	2 Weeks	Mild to moderate primary hypertension	Secondary hypertension, valvular disease, acute cardiac infarction, heart dysfunction, diabetes, hyperthyroidism, cerebral infarction in the preceding 2 mo, serious liver or renal dysfunction	8 Weeks	Blood pressure, heart rate, AEs
Zhang et al[10]	30/30	2 Weeks	Mild to moderate primary hypertension	Chronic cardiac, liver, or renal dysfunction	6 Weeks	Endothelial function, serum cholesterin, AEs
Fang and Feng[11]	53/53	Discontinue anti-ischemic drugs, such as nitrates, for 1 wk	CHD or angina	Pregnant or breastfeeding, moderate to severe anemia, hypertension emergency, hypersensitivity, severe heart block, acute cardiac infarction	8 Weeks	Blood pressure, heart rate, ST elevation, angina, AEs

(continued)

Table I (continued).

Trial	No. of Patients, (S)-Amlodipine/ Racemic Amlodipine	Washout Period	Inclusion Criteria	Exclusion Criteria	Duration	Outcomes
Yang[12]	31/26	2 Weeks	Hypertension, stage 1 or 2	Secondary hypertension	8 Weeks	Blood pressure, AEs
Pathak et al[13]	97/91	2 Weeks	Hypertension, stage 1 or 2	Secondary hypertension	6 Weeks	Blood pressure, blood lipids, aminotransferases
Li[14]	40/40	Not mentioned	Mild to moderate primary hypertension	Severe liver or renal dysfunction, secondary hypertension, pregnancy, poor compliance	5 Weeks	Ratio of patients with normalized blood pressure, AEs
Yang et al[15]	30/30	2 Weeks	Mild to moderate primary hypertension	Severe liver and renal dysfunction, acute myocardial infarction, cardiac insufficiency, diabetes, hyperthyroidism, secondary hypertension	8 Weeks	Blood pressure
Zhang[16]	36/36	Medication for the first time or using antihypertensives other than CCBs	Mild to moderate primary hypertension	Severe cardiac, brain, or renal complications	8 Weeks	Blood pressure, heart rate, AEs

(continued)

Table I (continued).

Trial	No. of Patients, (S)-Amlodipine/ Racemic Amlodipine	Washout Period	Inclusion Criteria	Exclusion Criteria	Duration	Outcomes
Gao and Zhou[17]	47/47	Not using a CCB for ≥8 wk or medication for the first time	Primary hypertension	Secondary hypertension, diabetes, cardiac insufficiency, and renal or liver dysfunction	32 Weeks	Blood pressure, left ventricular wall thickness, carotid artery wall thickness
Kim et al[18]	63/61	2 Weeks	Primary hypertension	Secondary hypertension; angina pectoris, myocardial infarction, cerebrovascular disease, or clinically significant arrhythmia	8 Weeks	Blood pressure, heart rate, AEs
Zhu et al[19]	22/22	1 Week	Primary hypertension	Serious cardiac, cerebral, kidney, digestive, respiratory, or blood disease; malignant tumor; history of drug allergy; pregnancy or breast feeding; surgery within 2 wk	8 Weeks	Blood pressure, AEs

AEs = adverse events; CHD = coronary heart disease; CCB = calcium channel blocker.

Table II. Quality of studies included in the systematic review and meta-analysis based on the modified Jadad Scale* scores.[4]

Study	Randomization	Allocation Concealment	Blinding Method	Withdrawals	Total Score
Liu et al[5]	1	0	1	0	2
Cheng et al[6]	1	0	0	0	1
Fang[7]	1	0	1	1	3
Hu et al[8]	1	1	2	1	5
Zeng et al[9]	1	0	0	0	1
Zhang et al[10]	2	0	0	1	3
Fang and Feng[11]	1	0	0	0	1
Yang[12]	1	0	0	0	1
Pathak et al[13]	1	1	2	1	5
Li[14]	1	0	0	1	2
Yang et al[15]	1	0	0	0	1
Zhang[16]	1	1	0	1	3
Gao and Zhou[17]	1	1	0	0	2
Kim et al[18]	2	1	2	1	6
Zhu et al[19]	1	1	0	1	3

*Jadad scale: *sequence generation*—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; *allocation concealment*—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; *blinding method*—appropriate = 2 points, unclear = 1 point, and inappropriate = 0 points; *withdrawal and exit*—described = 1 point and not described = 0 points.

CHANGES IN HEART RATE

When low- and high-quality trials were considered, meta-analysis of 4 trials[5,8,9,16] showed that, after 4 weeks' treatment, (*S*)-amlodipine was associated with a significantly smaller change in heart rate than with racemic amlodipine (WMD, –0.99; 95% CI, –1.70 to –0.28). Meta-analysis of 4 trials[8,11,16,18] found that after 8 weeks' treatment, changes in heart rate were not significantly different in the 2 treatment groups (WMD, –0.10; 95% CI, –1.36 to 1.17) (**Figures 18** and **19**). When only the high-quality study was included, after 4 and 8 weeks' treatment, the WMD of heart rate change was –0.82 (95% CI, –2.94 to 1.30)[8] and –0.87 (95% CI, –2.53 to 0.79),[8,18] respectively, indicating the heart rate changes were not significantly different in the 2 groups.

ADVERSE-EVENT RATES

AEs were reported in 13 studies (both low and high quality).[5–12,14–16,18,19] The RD of the number of patients who experienced AEs with (*S*)-amlodipine and racemic amlodipine was –0.04 (95% CI, –0.06 to –0.02) (**Figure 20**). When only high-quality studies[8,18] were included, no difference was found between the 2 formulations in the number of patients who experienced AEs (RD, –0.04; 95% CI, –0.10 to 0.02).

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Liu et al[5]	–20.20	14.21	30	–20.10	14.38	30	5.3%	–0.10 (–7.33 to 7.13)	2001
Hu et al[8]	–15.90	14.45	110	–13.06	12.42	107	21.6%	–2.84 (–6.42 to 0.74)	2002
Zeng et al[9]	–15.60	16.35	262	–14.40	19.02	262	30.0%	–1.20 (–4.24 to 1.84)	2002
Yang et al[15]	–20.10	5.61	30	–16.20	7.34	30	25.3%	–3.90 (–7.21 to –0.59)	2006
Zhang[16]	–26.64	11.86	36	–25.10	10.93	36	10.0%	–1.54 (–6.81 to 3.73)	2006
Zhu et al[19]	–22.66	10.10	22	–23.96	10.06	22	7.8%	1.30 (–4.66 to 7.26)	2008
Total (95% CI)			490			487		–2.02 (–3.68 to –0.35)	

Heterogeneity: $\chi^2 = 3.22$, $df = 5$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $z = 2.38$ ($P = 0.02$)

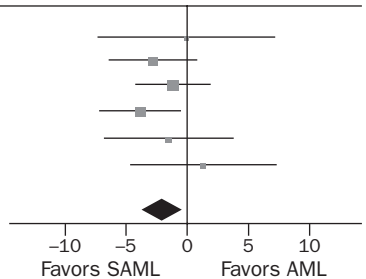

Figure 2. Forest plot illustrating systolic blood pressure after 4 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Random, 95% CI	Year
Liu et al[5]	–11.70	11.42	30	–11.60	11.31	30	11.6%	–0.10 (–5.85 to 5.65)	2001
Hu et al[8]	–13.14	7.26	110	–11.43	5.97	107	18.7%	–1.71 (–3.48 to 0.06)	2002
Zeng et al[9]	–14.60	9.03	262	–7.40	9.40	262	18.9%	–7.20 (–8.78 to –5.62)	2002
Yang et al[15]	–4.40	5.35	30	–4.40	5.35	30	17.2%	0.00 (–2.71 to 2.71)	2006
Zhang[16]	–12.60	6.14	36	–12.80	5.10	36	17.4%	0.20 (–2.41 to 2.81)	2006
Zhu et al[19]	–12.04	5.46	22	–11.97	5.39	22	16.3%	–0.07 (–3.28 to 3.14)	2008
Total (95% CI)			490			487		–1.67 (–4.68 to 1.34)	

Heterogeneity: $\tau^2 = 11.85$, $\chi^2 = 43.94$, $df = 5$ ($P < 0.001$); $I^2 = 89\%$
Test for overall effect: $z = 1.09$ ($P = 0.28$)

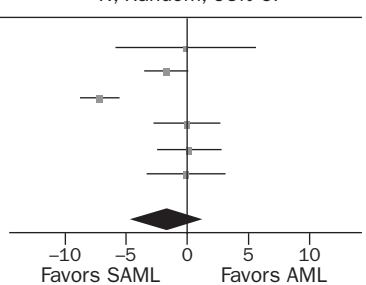

Figure 3. Forest plot illustrating diastolic blood pressure after 4 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Pathak et al[13]	–19.88	9.60	97	–19.24	9.20	91	83.4%	–0.64 (–3.33 to 2.05)	2004
Zhu et al[19]	–23.83	9.96	22	–25.31	10.43	22	16.6%	1.48 (–4.55 to 7.51)	2008
Total (95% CI)			119			113		–0.29 (–2.74 to 2.17)	

Heterogeneity: $\chi^2 = 0.40$, $df = 1$ ($P = 0.53$); $I^2 = 0\%$
Test for overall effect: $z = 0.23$ ($P = 0.82$)

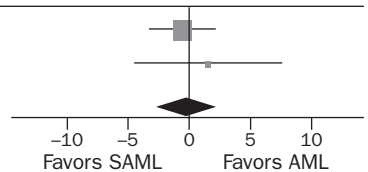

Figure 4. Forest plot illustrating systolic blood pressure after 6 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Pathak et al[13]	–14.32	6.2	97	–13.05	6.20	91	77.6%	–1.27 (–3.04 to 0.50)	2004
Zhu et al[19]	–14.94	5.6	22	–15.13	5.57	22	22.4%	0.19 (–3.11 to 3.49)	2008
Total (95% CI)			119			113		–0.94 (–2.51 to 0.62)	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.58$, $df = 1$ ($P = 0.45$); $I^2 = 0\%$
Test for overall effect: $z = 1.18$ ($P = 0.24$)

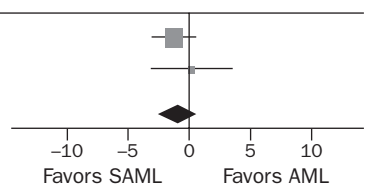

Figure 5. Forest plot illustrating diastolic blood pressure after 6 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Random, 95% CI	Year
Hu et al[8]	–20.76	13.07	110	–17.61	8.53	107	14.6%	–3.15 (–6.08 to –0.22)	2002
Zeng et al[9]	–17.10	16.72	262	–16.80	19.34	262	14.2%	–0.30 (–3.40 to 2.80)	2002
Fang and Feng[11]	–31.00	7.65	53	–28.00	8.51	53	14.2%	–3.00 (–6.08 to 0.08)	2004
Yang[12]	–24.06	12.42	31	–25.21	12.38	26	6.9%	1.15 (–5.31 to 7.61)	2004
Yang et al[15]	–21.60	6.08	30	–13.70	7.42	30	13.2%	–7.90 (–11.33 to –4.47)	2006
Zhang[16]	–32.60	5.51	36	–30.30	6.42	36	15.1%	–2.30 (–5.06 to 0.46)	2006
Kim et al[18]	–16.70	10.30	63	–17.80	9.40	61	13.1%	1.10 (–2.37 to 4.57)	2008
Zhu et al[19]	–24.76	9.29	22	–26.49	9.05	22	8.6%	1.73 (–3.69 to 7.15)	2008
Total (95% CI)			607			597		–1.95 (–4.03 to 0.13)	

Heterogeneity: $\tau^2 = 5.47$; $\chi^2 = 19.24$, $df = 7$ ($P = 0.007$); $I^2 = 64\%$
Test for overall effect: $z = 1.84$ ($P = 0.07$)

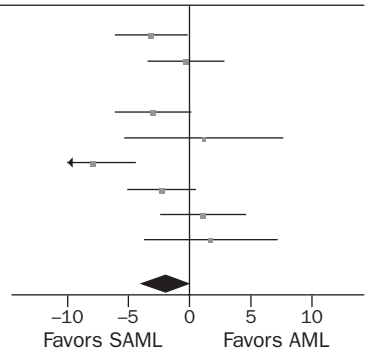

Figure 6. Forest plot illustrating systolic blood pressure after 8 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Hu et al[8]	–15.97	6.90	110	–13.68	6.00	107	19.8%	–2.29 (–4.01 to –0.57)	2002
Zeng et al[9]	–15.10	9.03	262	–13.40	8.40	262	26.2%	–1.70 (–3.19 to –0.21)	2002
Fang and Feng[11]	–23.00	9.62	53	–24.00	7.70	53	5.3%	1.00 (–2.32 to 4.32)	2004
Yang[12]	–13.60	6.80	31	–13.30	6.60	26	4.8%	–0.30 (–3.79 to 3.19)	2004
Yang et al[15]	–13.70	4.72	30	–13.30	6.59	30	6.9%	–0.40 (–3.30 to 2.50)	2006
Zhang[16]	–16.33	3.98	36	–12.69	3.80	36	18.1%	–3.64 (–5.44 to –1.84)	2006
Kim et al[18]	–12.00	5.70	63	–12.10	6.20	61	13.3%	0.10 (–2.00 to 2.20)	2008
Zhu et al[19]	–15.20	5.36	22	–15.99	5.50	22	5.7%	0.79 (–2.42 to 4.00)	2008
Total (95% CI)			607			597		–1.49 (–2.25 to –0.72)	

Heterogeneity: $\chi^2 = 13.70$, $df = 7$ ($P = 0.06$); $I^2 = 49\%$
Test for overall effect: $z = 3.81$ ($P = 0.001$)

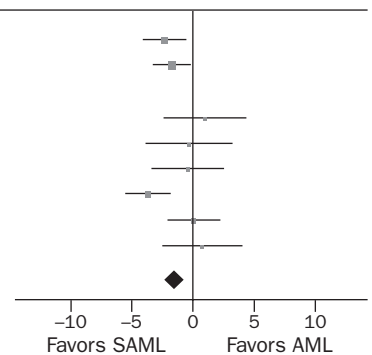

Figure 7. Forest plot illustrating diastolic blood pressure after 8 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Gao and Zhou[17]	–39.00	8.34	47	–40.00	8.63	47	100.0%	1.00 (–2.43 to 4.43)	2007
Total (95% CI)			47			47		1.00 (–2.43 to 4.43)	
Heterogeneity: Not applicable									
Test for overall effect: $z = 0.57$ ($P = 0.57$)									

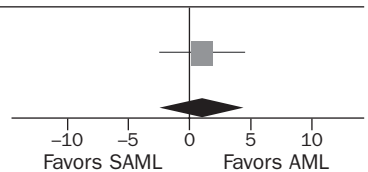

Figure 8. Forest plot illustrating systolic blood pressure after 32 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Gao and Zhou[17]	–15.00	6.25	47	–16.00	5.56	47	100.0%	1.00 (–1.39 to 3.39)	2007
Total (95% CI)			47			47		1.00 (–1.39 to 3.39)	
Heterogeneity: Not applicable									
Test for overall effect: $z = 0.82$ ($P = 0.41$)									

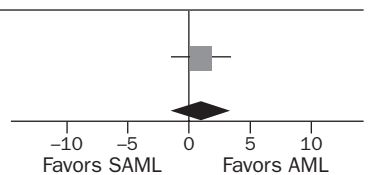

Figure 9. Forest plot illustrating diastolic blood pressure after 32 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML Mean	SAML SD	SAML Total	AML Mean	AML SD	AML Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Fang[7]	–29.30	14.10	140	–24.10	10.90	140	100.0%	–5.20 (–8.15 to –2.25)	2002
Total (95% CI)			140			140		–5.20 (–8.15 to –2.25)	
Heterogeneity: Not applicable									
Test for overall effect: $z = 3.45$ ($P < 0.001$)									

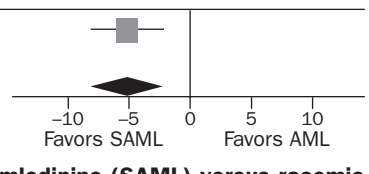

Figure 10. Forest plot illustrating systolic blood pressure after 40 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

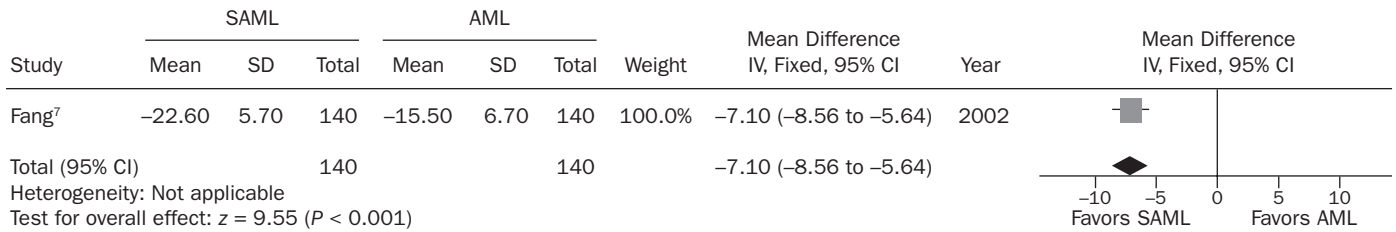

Figure 11. Forest plot illustrating diastolic blood pressure after 40 weeks' treatment with (S)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

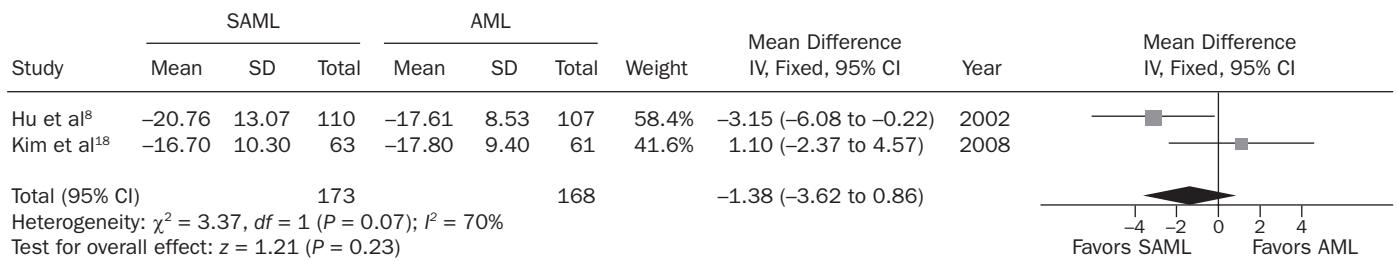

Figure 12. Forest plot illustrating systolic blood pressure in the high-quality studies after 8 weeks' treatment with (S)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

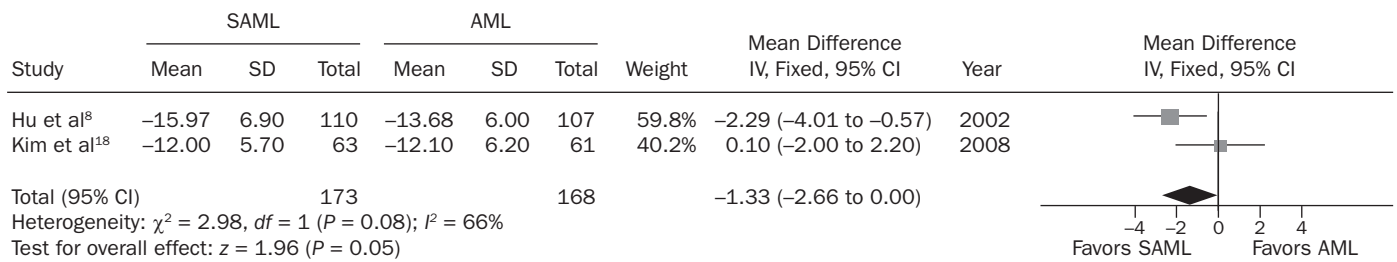

Figure 13. Forest plot illustrating diastolic blood pressure in the high-quality studies after 8 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Figure 14. Funnel plot of the meta-analysis of systolic blood pressure after 4 weeks' treatment with (*S*)-amlodipine versus racemic amlodipine.

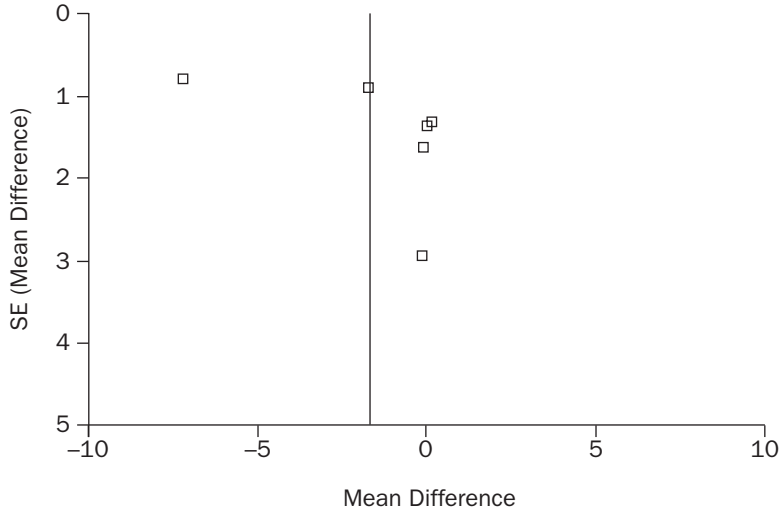

Figure 15. Funnel plot of the meta-analysis of diastolic blood pressure after 4 weeks' treatment with (*S*)-amlodipine versus racemic amlodipine.

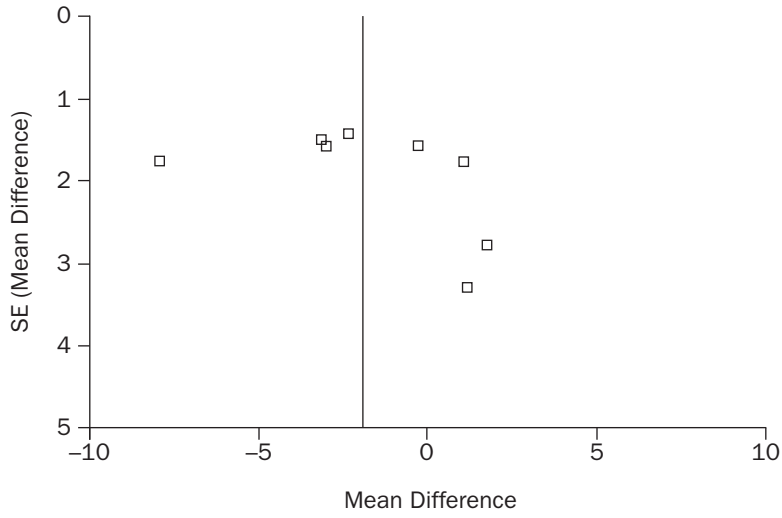

Figure 16. Funnel plot of the meta-analysis of systolic blood pressure after 8 weeks' treatment with (*S*)-amlodipine versus racemic amlodipine.

Figure 17. Funnel plot of the meta-analysis of diastolic blood pressure after 8 weeks' treatment with (*S*)-amlodipine versus racemic amlodipine.

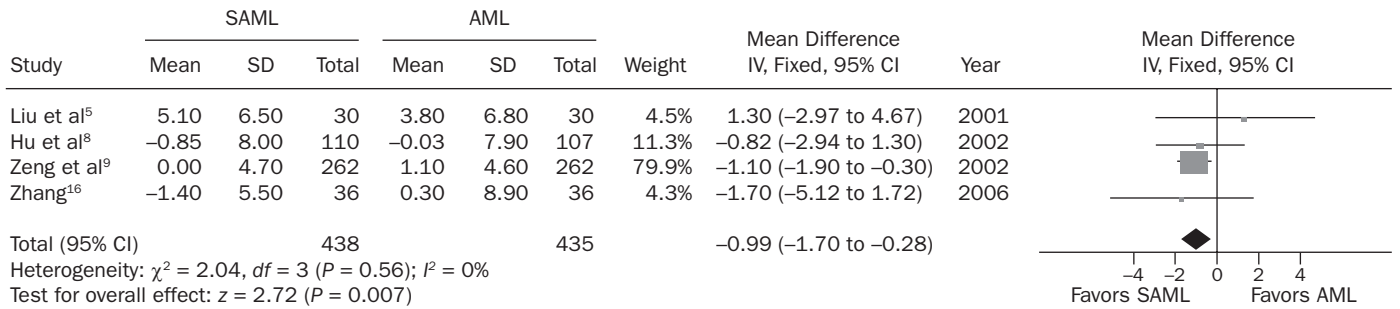

Figure 18. Forest plot illustrating heart rate after 4 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

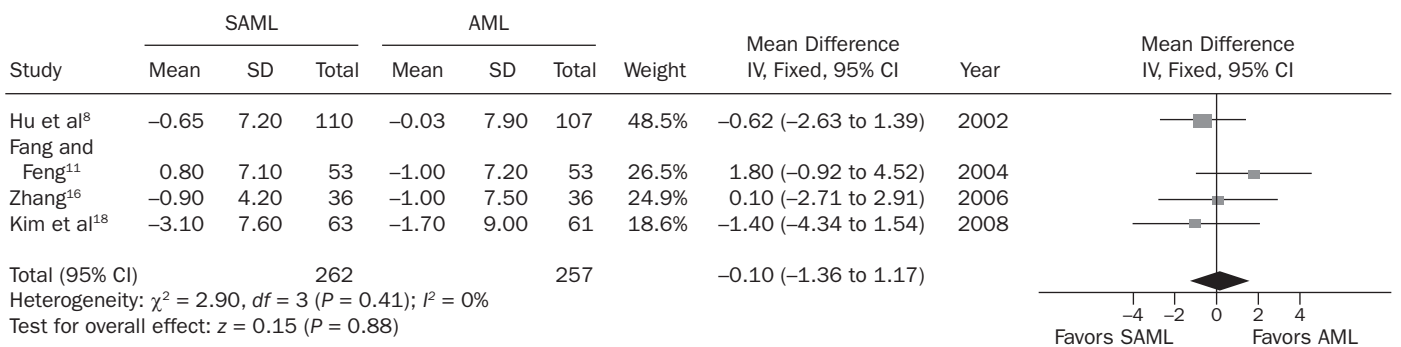

Figure 19. Forest plot illustrating heart rate after 8 weeks' treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). IV = inverse variance.

Study	SAML No. of AEs	SAML Total	AML No. of AEs	AML Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Liu et al[5]	2	30	2	30	3.3%	0.00 (–0.13 to 0.13)	2001
Cheng et al[6]	4	60	10	60	6.7%	–0.10 (–0.21 to 0.01)	2002
Fang[7]	5	140	8	140	15.5%	–0.02 (–0.07 to 0.03)	2002
Hu et al[8]	5	110	11	107	12.0%	–0.06 (–0.13 to 0.01)	2002
Zeng et al[9]	6	262	8	262	29.1%	–0.01 (–0.04 to 0.02)	2002
Zhang et al[10]	5	30	5	30	3.3%	0.00 (–0.19 to 0.19)	2003
Fang and Feng[11]	0	53	1	53	5.9%	–0.02 (–0.07 to 0.03)	2004
Yang[12]	1	31	3	26	3.1%	–0.08 (–0.22 to 0.05)	2004
Li[14]	2	40	6	40	4.4%	–0.10 (–0.23 to 0.03)	2006
Yang et al[15]	2	30	5	30	3.3%	–0.10 (–0.26 to 0.06)	2006
Zhang[16]	1	36	6	36	4.0%	–0.14 (–0.27 to –0.01)	2006
Kim et al[18]	6	63	7	61	6.9%	–0.02 (–0.13 to 0.09)	2008
Zhu et al[19]	1	22	1	22	2.4%	0.00 (–0.12 to 0.12)	2008
Total (95% CI)		907		897		–0.04 (–0.06 to –0.02)	
Total no. of AEs	40		73				

Heterogeneity: $\chi^2 = 11.97$, $df = 12$ ($P = 0.45$); $I^2 = 0\%$
Test for overall effect: $z = 3.32$ ($P < 0.001$)

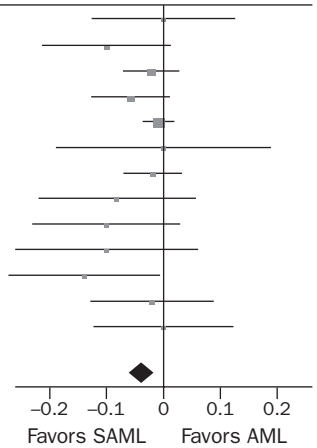

Figure 20. Forest plot illustrating the incidence of reports of adverse events (AEs) during treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). M-H = Mantel-Haenszel.

To assess the contribution of different kinds of AEs, the AEs were divided into different categories and were compared between (*S*)-amlodipine and racemic amlodipine. Fifteen categories of AEs were identified, among which edema, flushing, and headache were the most commonly observed.

Meta-analysis of the low- and high-quality studies that reported AEs[5–12,14–16,18,19] indicated that the incidence of edema was significantly lower in the (*S*)-amlodipine group than the racemic amlodipine group (RD, –0.02; 95% CI, –0.03 to 0.00) (**Figure 21**). To assess the effects of publication bias on the results of the meta-analysis, a funnel plot of edema was made. An asymmetrical plot was obtained, indicating the presence of reporting bias (**Figure 22**). Moreover, when only high-quality studies[8,18] were included, no difference was found between the 2 formulations in the incidence of edema (RD, 0.01; 95% CI, –0.02 to 0.03).

Significant differences in increases in aspartate and alanine aminotransferase activities were found between the (*S*)-amlodipine and racemic amlodipine treatment groups (RD, 0.08; 95% CI, 0.01 to 0.05) (**Table III**), but this was reported by only 1 trial, which was high-quality.[18] No differences between the 2 groups were found in the other 13 categories of AEs, including headache (RD, 0.00; 95% CI, –0.02 to 0.01) (**Figure 23**) and flushing (RD, 0.01; 95% CI, –0.02 to 0.00) (**Figure 24**).

Quantified analysis of the seriousness of the AEs was not carried out in any of the studies.

DISCUSSION

This review compared the effectiveness and tolerability of (*S*)-amlodipine 2.5 mg and racemic amlodipine 5.0 mg. However, because the majority of the studies included in this meta-analysis were of poor quality, the results must be interpreted cautiously.

Although clinical trials that compared (*S*)-amlodipine and racemic amlodipine were collected systematically in this systematic review and meta-analysis, no trials that reported cardiovascular outcomes (eg, the incidence of stroke and myocardial infarction) were identified. For the secondary outcome measurements (eg, decrease in BP), the combined results suggested that (*S*)-amlodipine 2.5 mg was not significantly different from racemic amlodipine 5.0 mg. However, including the findings of the low-quality studies reduced the reliability of the results. A conclusion could be drawn when only high-quality studies were included in the meta-analysis, but the small sample size limited their credibility. As shown by pharmacologic studies, racemic amlodipine decreases BP by blocking the L-type calcium tunnel in cell membranes. In fact, (*S*)-amlodipine has this activity but (*R*)-amlodipine does not. This suggests that to achieve the same degree of BP decrease, the dosage of (*S*)-amlodipine would need to be only half that of racemic amlodipine.[20]

Edema, which was reported in 2% to 11% of patients administered racemic amlodipine,[21] is a common AE associated with dihydropyridine calcium channel blockers. When the findings of the low-quality studies were included, (*S*)-amlodipine 2.5 mg was associated with significantly less edema than racemic amlodipine 5.0 mg. However, these findings were not considered reliable because of publication bias. When only the high-quality studies were considered, no difference in edema was

Study	SAML No. of AEs	SAML Total	AML No. of AEs	AML Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Liu et al[5]	0	30	1	30	3.3%	–0.03 (–0.12 to 0.05)	2001
Cheng et al[6]	2	60	6	60	6.7%	–0.07 (–0.16 to 0.02)	2002
Fang[7]	1	140	3	140	15.5%	–0.01 (–0.04 to 0.01)	2002
Hu et al[8]	0	110	1	107	12.0%	–0.01 (–0.03 to 0.02)	2002
Zeng et al[9]	3	262	5	262	29.1%	–0.01 (–0.03 to 0.01)	2002
Zhang et al[10]	4	30	4	30	3.3%	0.00 (–0.17 to 0.17)	2003
Fang and Feng[11]	0	53	0	53	5.9%	0.00 (–0.04 to 0.04)	2004
Yang[12]	0	31	1	26	3.1%	–0.04 (–0.13 to 0.06)	2004
Li[14]	1	40	2	40	4.4%	–0.03 (–0.11 to 0.06)	2006
Yang et al[15]	1	30	3	30	3.3%	–0.07 (–0.19 to 0.06)	2006
Zhang[16]	0	36	2	36	4.0%	–0.06 (–0.14 to 0.03)	2006
Kim et al[18]	2	63	0	61	6.9%	0.03 (–0.02 to 0.08)	2008
Zhu et al[19]	0	22	1	22	2.4%	–0.05 (–0.16 to 0.07)	2008
Total (95% CI)		907		897		–0.02 (–0.03 to 0.00)	
Total no. of AEs	14		29				

Heterogeneity: $\chi^2 = 8.41$, $df = 12$ ($P = 0.75$); $I^2 = 0\%$
Test for overall effect: $z = 2.20$ ($P = 0.03$)

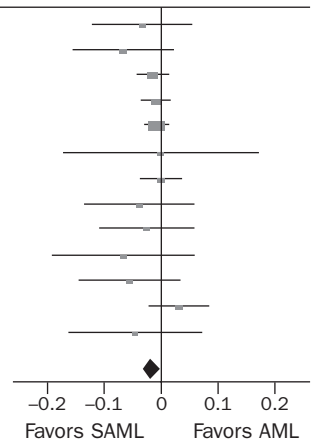

Figure 21. Forest plot illustrating the incidence of reports of edema during treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). AEs = adverse events; M-H = Mantel-Haenszel.

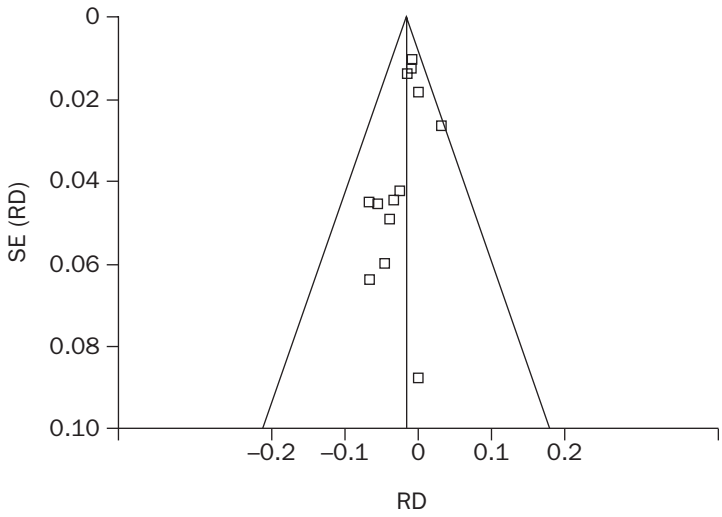

Figure 22. Funnel plot of the meta-analysis of the incidence of edema in patients treated with (*S*)-amlodipine versus racemic amlodipine. RD = risk difference.

found between the 2 groups. The small number of cases was also an obstacle to reaching definite conclusions.

Because drug therapy for hypertension needs to be long term, patient compliance is an important factor for the successful control of the disease. As reported, patients with a high degree of compliance (between 80% and 100%) have a 19% risk of hospitalization compared with 28% in patients with a compliance between 1% and 19%.[22] AEs can considerably influence drug use behavior, as shown by 1 study which reported that 7% of the poor compliance was due to AEs.[23] Therefore, more studies are needed to assess the influence of edema on compliance with (*S*)-amlodipine and racemic amlodipine therapy.

Though studies focused on outcomes are lacking, outcomes are essential in comparing the efficacy of (*S*)-amlodipine and racemic amlodipine. A major goal of the treatment of hypertension is to reduce cardiovascular events; thus, so cardiovascular outcomes are key criteria in assessing the effectiveness of antihypertensive drugs. In addition, although (*R*)-amlodipine has not been found to have a protective effect on the cardiovascular system and to be associated with AEs, it was found to promote the production of nitric oxide (NO) from vessel endothelium.[24,25] Because NO has a complicated influence on the cardiovascular system, the role of (*R*)-amlodipine in hypertension needs further research.

In addition to a lack of outcome assessment, a limitation of the present systematic review was the small number of high-quality trials. There were few studies in languages other than Chinese. Some non-Chinese studies of healthy volunteers were excluded because they did not comply with the inclusion criteria. However, the studies carried out in healthy volunteers found that (*S*)-amlodipine had comparable pharma-

Table III. Adverse events (AEs) besides edema, headache, and flushing.

AE	Included Trials	No. of Patients, (S)-Amlodipine/Racemic Amlodipine	No. of Patients with AEs, (S)-Amlodipine/Racemic Amlodipine	RD	95% CI	*P*
AST or ALT elevation	1[18]	63/61	5/0	0.08	0.01 to 0.05	0.03
Chest pain	1[18]	63/61	1/1	0.00	–0.04 to 0.04	0.98
Diarrhea	1[18]	63/61	0/1	0.02	–0.06 to 0.03	0.46
Dizziness	3[5,8,14]	180/177	4/4	0.00	–0.03 to 0.03	0.98
Fatigue	1[6]	60/60	1/2	–0.02	–0.07 to 0.04	0.56
Gastrointestinal	2[7,8]	250/247	1/2	0.00	–0.02 to 0.01	0.65
Insomnia	1[8]	110/107	0/1	–0.01	–0.03 to 0.02	0.47
Lymphocytic panniculitis	1[18]	63/61	1/0	0.02	–0.03 to 0.06	0.47
Myalgia	1[18]	63/61	0/1	0.02	–0.06 to 0.03	0.46
Numbness	2[8,16]	142/138	0/2	–0.01	–0.04 to 0.01	0.31
Palpitations	2[5,8]	140/137	2/1	0.01	–0.02 to 0.03	0.62
Rash	1[18]	63/61	0/1	0.02	–0.06 to 0.03	0.46

RD = risk difference; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Study	SAML No. of AEs	SAML Total	AML No. of AEs	AML Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Liu et al[5]	1	30	1	30	3.3%	0.00 (–0.09 to 0.09)	2001
Cheng et al[6]	1	60	2	60	6.7%	–0.02 (–0.07 to 0.04)	2002
Fang[7]	2	140	3	140	15.5%	–0.01 (–0.04 to 0.02)	2002
Hu et al[8]	4	110	5	107	12.0%	–0.01 (–0.06 to 0.04)	2002
Zeng et al[9]	3	262	3	262	29.1%	0.00 (–0.02 to 0.02)	2002
Zhang et al[10]	1	30	1	30	3.3%	0.00 (–0.09 to 0.09)	2003
Fang and Feng[11]	0	53	1	53	5.9%	–0.02 (–0.07 to 0.03)	2004
Yang[12]	1	31	2	26	3.1%	–0.04 (–0.16 to 0.08)	2004
Li[14]	1	40	1	40	4.4%	0.00 (–0.07 to 0.07)	2006
Yang et al[15]	1	30	1	30	3.3%	0.00 (–0.09 to 0.09)	2006
Zhang[16]	0	36	1	36	4.0%	–0.03 (–0.10 to 0.05)	2006
Kim et al[18]	2	63	0	63	6.9%	0.03 (–0.02 to 0.08)	2008
Zhu et al[19]	1	22	1	22	2.4%	0.00 (–0.12 to 0.12)	2008
Total (95% CI)		907		897		0.00 (–0.02 to 0.01)	
Total no. of AEs	18		22				

Heterogeneity: $\chi^2 = 3.53$, $df = 12$ ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: $z = 0.68$ ($P = 0.49$)

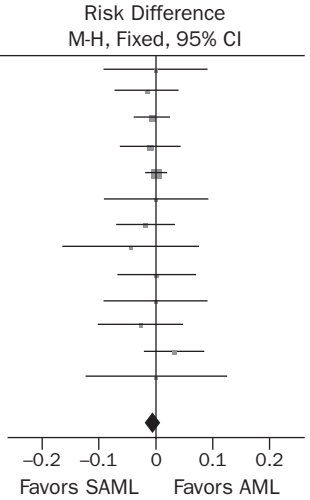

Figure 23. Forest plot illustrating the incidence of reports of headache during treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). AEs = adverse events; M-H = Mantel-Haenszel.

Study	SAML No. of AEs	SAML Total	AML No. of AEs	AML Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Liu et al[5]	0	30	0	30	3.4%	0.00 (–0.06 to 0.06)	2001
Cheng et al[6]	0	60	2	60	6.8%	–0.03 (–0.09 to 0.02)	2002
Fang[7]	1	140	2	140	15.9%	–0.01 (–0.03 to 0.02)	2002
Hu et al[8]	0	110	0	107	12.3%	0.00 (–0.02 to 0.02)	2002
Zeng et al[9]	0	262	0	262	29.8%	0.00 (–0.01 to 0.01)	2002
Zhang et al[10]	0	30	0	30	3.4%	0.00 (–0.06 to 0.06)	2003
Fang and Feng[11]	0	53	0	53	6.0%	0.00 (–0.04 to 0.04)	2004
Yang[12]	0	31	0	26	3.2%	0.00 (–0.07 to 0.07)	2004
Li[14]	0	40	2	40	4.5%	–0.05 (–0.13 to 0.03)	2006
Yang et al[15]	0	30	1	30	3.4%	–0.03 (–0.12 to 0.05)	2006
Zhang[16]	1	36	2	36	4.1%	–0.03 (–0.12 to 0.06)	2006
Kim et al[18]	1	63	2	61	7.0%	–0.02 (–0.07 to 0.04)	2008
Total (95% CI)		885		875		0.01 (–0.02 to 0.00)	
Total no. of AEs	3		11				

Heterogeneity: $\chi^2 = 9.58$, $df = 11$ ($P = 0.57$); $I^2 = 0\%$
Test for overall effect: $z = 1.70$ ($P = 0.09$)

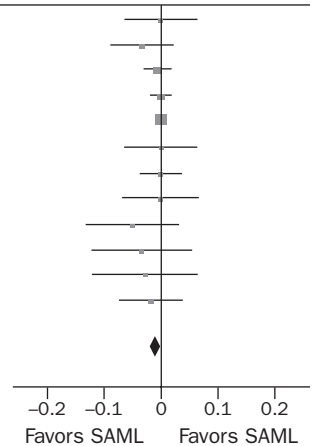

Figure 24. Forest plot illustrating the incidence of reports of flushing during treatment with (*S*)-amlodipine (SAML) versus racemic amlodipine (AML). AEs = adverse events; M-H = Mantel-Haenszel.

cokinetics to racemic amlodipine, and the formulations were not associated with significant differences in decreasing BP or safety profiles.[26,27] Their conclusions were consistent with the findings of our systematic review.

There is a lack of evidence comparing cardiovascular morbidity and mortality associated with (*S*)-amlodipine and racemic amlodipine therapy. More long-term, high-quality RCTs with cardiovascular events as the primary outcome are needed to compare the safety and effectiveness of (*S*)-amlodipine and racemic amlodipine.

CONCLUSIONS

The majority of the clinical trials comparing (*S*)-amlodipine and racemic amlodipine therapy were low-quality (12/15 [80%]). According to the limited evidence, there were no significant differences between (*S*)-amlodipine 2.5 mg and racemic amlodipine 5.0 mg in controlling BP. When all the trials were considered, (*S*)-amlodipine treatment was associated with significantly less edema than racemic amlodipine; however, when only high-quality studies were included, no significant difference was found between the 2 treatments.

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