Medicine®

OPEN

Compound salvia pellet might be more effective and safer for chronic stable angina pectoris compared with nitrates

A systematic review and meta-analysis of randomized controlled trials

Wei Huiping, PhD[a,b,c,d], Wang Yu, MMed[a,c], Jin Pei, MMed[a,b,c], Li Jiao, MMed[b], Zhang Shian, MMed[a], Jiang Hugang, MMed[e], Wang Zheng, MMed[a,b,c], Li Yingdong, MD[b,c,d,*]

Abstract

Background: Chronic stable angina (CSA) resulted in a considerable burden for both individuals and the society. In this study we aimed to critically evaluate the effectiveness and safety of Compound salvia pellet compared with nitrates in the treatment of Chronic Stable Angina (CSA) pectoris, and to provide more credible evidence for clinical practice.

Methods: A comprehensive and exhaustive search strategy was formulated to identify potential RCTs of compound salvia pellet for CSA in international and Chinese databases from their inception to July 4th, 2018. We also searched the bibliographies of relevant studies. Two reviewers independently assessed the quality of included trials by using Cochrane Risk of Bias Tool.

Results: The literature search yielded 1849 citations and 51 RCTs (n = 4732) were included for meta-analysis after titles, abstracts and full text selection according to eligibility criteria. The pooled results suggested that compound salvia pellet was much more effective than nitrates in the improvement of angina symptoms (therapy = 4 weeks, RR = 1.23, 95%CI = [1.17, 1.30], $P < .001$, $I^2 = 0\%$; therapy = 4 weeks, RR = 1.13, 95%CI = [1.08, 1.17], $P < .001$, $I^2 = 45.6\%$), and ECG test (therapy = 4 weeks, RR = 1.24, 95%CI [1.14, 1.35], $P < .001$, $I^2 = 51.5\%$; and therapy > 4 weeks, RR = 1.30, 95%CI[1.20, 1.42], $P < .001$, $I^2 = 36.4\%$) in CSA. Compared with nitrates, the percentage of patients with adverse events significantly decreased when prescribed with compound salvia pellet (3.2% vs 17.0%).

Conclusion: Compound salvia pellet might be more effective on the improvement of angina symptoms, ECG test and with few adverse events compared with nitrates. While there are some limitations in this study, which may weaken the results, we believe the findings could provide useful information for stakeholders concerned with outcomes in patients with CSA. More rigorous RCTs with high quality are needed to confirm these findings.

Abbreviations: CI = confidence intervals, CNKI = China National Knowledge Infrastructure, CONSORT = consolidated standards of reporting trials, CSA = chronic stable angina, ECG = electrocardiogram, GRADE = grades of recommendation, assessment, development and evaluation, PRISMA = preferred reporting items for systematic reviews and meta- analyses, RCTs = randomized controlled trials, SoF = summary of findings, TCM = traditional Chinese medicine, WMD = weighted mean difference.

Keywords: chronic stable angina, compound salvia pellet, meta-analysis, nitrates

[a] Affiliated Hospital of Gansu University of Chinese Medicine, [b] Gansu University of Chinese Medicine, [c] Gansu Institute of Integrated Chinese and Western medicine, [d] Key Laboratory of Traditional Chinese Medicine for Prevention and Treatment of Chronic Diseases, [e] School of Basic Medicine of Lanzhou University, Lanzhou, Gansu, China.

* Correspondence: Li Yingdong, Gansu University of Traditional Chinese Medicine, Lanzhou, Gansu, China (e-mail: lydj412@126.com).

1. Introduction

Chronic stable angina (CSA) is a pain or constricting discomfort that typically occurs in the front of the chest and is brought on by physical exertion or emotional stress,[1] which affects over 9 million adults in the United States, with an estimate of 500,000 new cases annually.[2] CSA resulted in a considerable burden for both individuals and the society. At present, organic nitrates are indicated as the first-line therapy for the long-term management of CSA.[3–6] It has been demonstrated that nitrate treatment provides control of angina symptoms and improves the quality of life.[7] But a major limitation of using nitrates is the development of tolerance, defined as the loss of hemodynamic and antianginal effects during sustained therapy.[8,9]

Traditional Chinese Medicine (TCM), Radix salviae miltiorrhizae (Danshen) and its compound formula as drugs (compound salvia pellet) provides an alternative option for CSA. Experimental studies have shown that compound salvia pellet can dilate coronary arteries, increase coronary blood flow, and scavenge free radicals[10] in ischemic diseases, which could promote blood circulation to activate blood and remove blood stasis. Compound salvia pellet consist of active herbal ingredients extracted from

Danshen (salviae miltiorrhizae), Sanqi (panax notoginseng), and Borneol (Cinnamomum camphora).[11] Compound salvia pellet had been recommended by CSA guidelines in China,[12] and had been selected as an essential drug for CSA by Chinese government since 2009. That is to say, the cost of compound salvia pellet could be covered by medical insurance in China.

Although compound salvia pellet had been widely used in China, no strong evidence was found to support the recommendation and policy decision. Until now, many randomized controlled trials (RCTs) had been published, which indicated that compared with the organic nitrates, the compound salvia pellet might be effective in patients with CSA. Therefore, considering these backgrounds, the aim of this study is to critically evaluate the effectiveness and safety of compound salvia pellet for CSA, hoping to provide more credible evidence for clinical practice.

2. Methods

2.1. Searched databases and search strategies

A comprehensive and exhaustive search strategy was formulated to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Pubmed, Embase, Cochrane Controlled Trials register were searched as international databases and Wanfang Data Knowledge Service Platform, VIP Online Publishing Platform, China National Knowledge Infrastructure (CNKI) and SinoMed were searched as domestic databases to identify RCTs of compound salvia pellet for CSA. The search terms consisted "compound salvia pellet", "Danshen pill", "Danshen droplet pill" and "angina". Database searches were initially conducted at October 31st, 2016, and updated at July 4th, 2018, detailed searching information could be found in Appendix 1, http://links.lww.com/MD/C841. Furthermore, a manual search was performed of the bibliographies of studies and reviews. Some trials reported data that were insufficient for statistical pooling, and then corresponding authors were contacted to provide additional data.

2.2. Including criteria

The articles were reviewed by 2 reviewers and studies were selected systematically according to predefined criteria. Studies were required to meet the following criteria:

1. Type of studies: Randomized controlled trials (RCTs) will be considered for inclusion regardless of publication status and language of publication. Trials with quasi-random designs will not be considered for inclusion.
2. Type of patients: adults with a diagnosis of CSA more than 1 month. Appropriate participants will be included regardless of gender, race, and educational status of CSA.
3. Type of interventions: Trials that compared compound salvia pellet for treatment of patients with CSA compared with
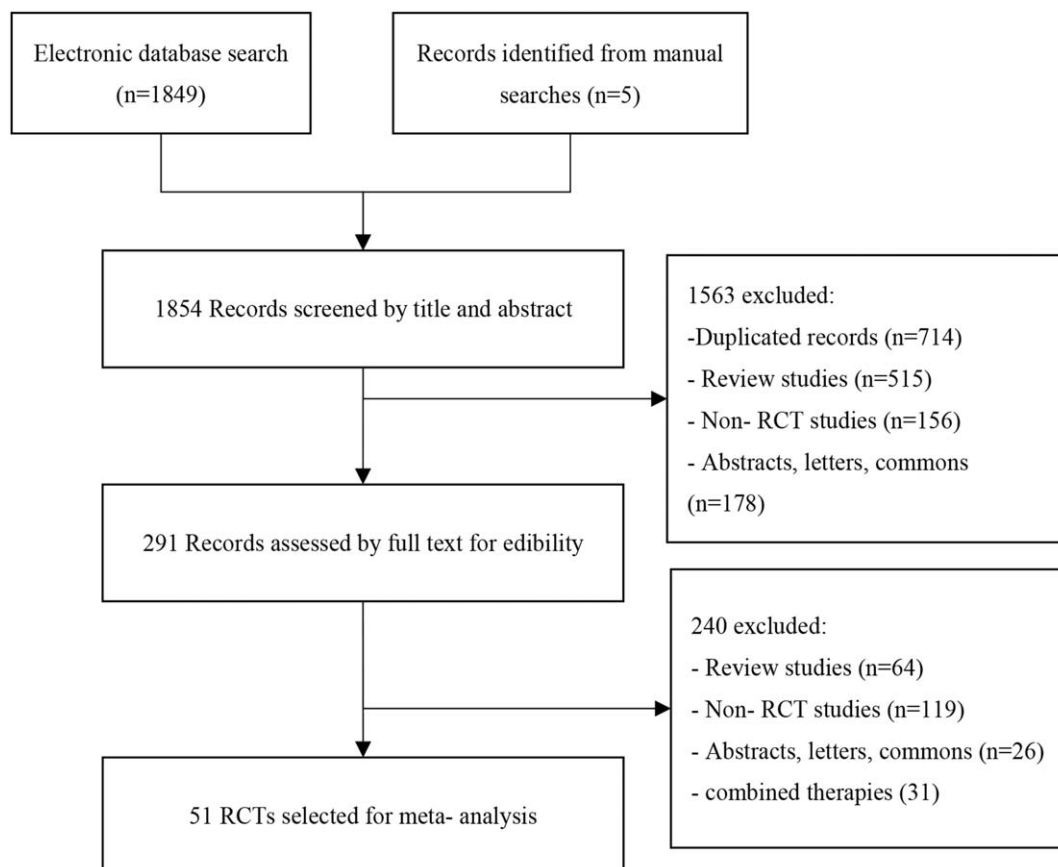

Figure 1. The flow chart of systematic studies search and selection procedure.

nitrates were considered for inclusion, regardless of therapy time and follow up duration.

4. Type of outcome measures: the improvement of angina symptoms (angina times after intervention in 1 week happens half or less than treatment before) and reduced angina attack were defined as primary outcome.

The improvement of electrocardiogram (ECG) (ST segment of ECG recovery to be normal), and adverse events during the treatment were defined as secondary outcome.

2.3. Data extraction and quality assessment of trials

Data were extracted independently by 2 authors using a standard form. Data extracted include:

1. general information (e.g., title, authors, reference, language, year of publication, and setting);
2. trial characteristics related to methodological quality (e.g., design, duration of follow up, sequence generation, allocation sequence concealment, and blinding);
3. intervention and comparison (dose, route, and timing);
4. patients information (e.g., baseline characteristics and diagnostic criteria);
5. outcomes data (e.g., events, estimates, standard error, and P value).

Discrepancies were resolved by discussion. Data on the number of patients with each outcome event by allocated treatment group, irrespective of compliance or follow-up, were sought to allow an intention-to-treat analysis. If the above data were not

Table 1

Characteristics of included studies.

Study ID	Intervention group	Controlled group	Sample size Intervention group	Sample size Controlled group	Mean age (year) Intervention group	Mean age (year) Controlled group	Male (%) Intervention group	Male (%) Controlled group	Course of disease (years)	Therapy (weeks)	Outcomes
Zhang D 2018[17]	CSP,270 mg, tid	Isosorbid dinitrate,20 mg,tid	50	50	44–76	42–78	44%	48%	NR	8	①④
Liu YF 2018[18]	CSP,250 mg, tid	Isosorbid dinitrate,20 mg,tid	50	50	51.63±4.67	51.08±5.27	54%	48%	3.65±1.05	4	①③④
LU NM 2017[19]	CSP,270 mg, tid	Isosorbid dinitrate,10 mg,tid	43	43	64.53±6.47	63.94±6.72	48.8%	58.1%	8.63±2.32	12	①②
Hu KX 2017[20]	CSP,270 mg, tid	Isosorbid dinitrate,10 mg,tid	43	43	52.4±3.1	51.2±3.2	58.1%	46.5%	2.7±1.3	4	①
Liu YS 2017[21]	CSP,200 mg, tid	Isosorbid dinitrate,10 mg,tid	53	53	56.96±4.93	57.53±4.37	60.3%	62.6%	3.14±1.61	4	①
Zhang C 2017[22]	CSP,270 mg, tid	Isosorbid dinitrate,5 mg,tid	44	44	61. 84±2.45	62. 04±2.15	59.1%	63,6%	3.12±1.64	4	①②
Bao JT 2016[23]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	70	70	41.5±20.9	42.1±21.3	32.80%	58.60%	NR	8	②④
Zeng QH 2011[24]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	86	86	61–87 (66.8)		59.30%		NR	8	②
Chen CW 2011[25]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	40	30	46–65 (54.6)		70%		NR	8	②④
Chen GQ 2005[26]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	30	30	64.3±9.8	60. 4±8. 4	60%	56.70%	NR	4	①②④
Deng GH 2002[27]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	56	30	52–70		62%		1–3	8	①②④
Ding XM 1999[28]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	52	50	46–74		72.50%		1–3.5	8	①②④
Guo LX 2001[29]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	25	25	56±7	55±8	60%	56%	5.6±0.9	8	②
He YQ 2012[30]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	84	84	48.9±10.1		55.30%		3.06±2.15	4	①②④
He YZ 2004[31]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	40	20	40–70		67%		NR	8	①②④
Hou JF 2016[32]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	47	47	58.11±4.21	57.85±4.19	53.20%	55.30%	4.59±1.71	6	①
Huang CX 2016[33]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	40	38	62±7.5	63±5.5	62.50%	57.90%	NR	8	①②④
Huang SW 2004[34]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	43	43	51.6±7.8	52.7±8.9	55.30%	60.70%	3.02±2.12	4	②
Ji Y 2007[35]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	80	80	56–80	57–78	65%	63.70%	NR	8	②
Jiang GR 2010[36]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	60	60	52–78		62.50%		NR	8	①②
Kang JH 2011[37]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	52	49	59±9	61±10	86.50%	87.70%	11.3±5.1	4	①②③
Li HB 2008[38]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	30	30	39–76		66.70%		NR	8	①②④
Li YP 2006[39]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	56	50	45–73	50–72	62.50%	64%	3-12	6	①②④
Lin DL 2013[40]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	33	33	39–76		62.10%		1–5	10	②④
Liu H 2008[41]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	80	40	69.5±7.8		70%		NR	4	①④
Liu JB 2016[42]	CSP,125 mg, tid	Isosorbid dinitrate,10 mg,tid	30	30	59.45±2.24	59.49±3.32	60%	56.70%	NR	4	②
Liu YH 2013[43]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	100	60	51±6		50%		3.1±1.1	12	①④
Pan C 2008[44]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	50	30	51–70		61.20%		2–5.	6	①②④
Peng XY 2010[45]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	60	60	52.6±7.8	53.7±8.9	58.30%	61.70%	NR	4	①②③
Rong JH 2004[46]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	40	35	60–88		68%		NR	4	①②④
Shao ZH 2013[47]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	66	60	45–73		71.40%		1–8.	4	①②④
Shi YH 1997[48]	CSP,250–300 mg, tid	Isosorbid dinitrate,10–15 mg,tid	34	30	40–64	41–68	67.60%	67.70%	1–2.5	8	②③④
Song J 2011[49]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	42	40	62.5±9.9	59.5±8.5	59.50%	55%	1.5-16	4	①②④
Song LF 2016[50]	CSP,250 mg, tid	Isosorbid dinitrate,8 mg,tid	50	50	43–79		55%		NR	4	②④
Tu EX 2011[51]	CSP,250 mg, tid	Isosorbid dinitrate,10–20 mg,tid	50	50	46–79	45–80	60%	66%	NR	4	①②③④
Wang J 2014[52]	CSP,250 mg, tid	Isosorbid dinitrate,40 mg, once/day	34	34	41–82		63.20%		NR	8	①②③
Wang J 2009[53]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	28	29	57.8±6.76	55.68±7.45	36.60%	28.60%	2.75±2.22	8	②③④
Wang B 2014[54]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	50	50	NR	NR	NR	NR	NR	8	②③
Wei ZH 2009[55]	CSP,250 mg, tid	Isosorbid dinitrate,20 mg,tid	42	38	60.2±9.8	61.3±8.9	66.70%	63.20%	NR	8	②③④
Wu WB 2005[56]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	52	50	NR	NR	NR	NR	NR	8	①②④
Wu S 2000[57]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	69	66	46–80	45–79	60.90%	57.60%	8.3±3.2	12	①②
Xia H 2011[58]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	22	22	37–78		59.10%		1–4.	8	②④
Xu HB 2009[59]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	68	57	45–72	50–73.8	61.80%	64.90%	3-12.	6	①②④
Yao P 2005[60]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	38	35	41–84		68.50%		NR	4	①②
Zhang SL 2009[61]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	30	30	69–74	68–74	73.30%	80%	NR	8	①②④
Zhang XH 2014[62]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	30	30	58±5.2	58±5.1	50%	53.30%	1-12.	4	②③④
Zhao DL 2015[63]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	40	40	49.6±10.2	49.6±10.5	45%	50%	4.2±1.6	4	③
Zhao FC 2007[64]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	30	15	40–75		70%		NR	8	①②④
Zhao N 2001[65]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	32	28	44–74	45–76	62.50%	59.70%	5.8	8	①②④
Zhou YM 1998[66]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	120	60	46–62	48–60	51.60%	50.70%	3.2±1.1	8	①②④
Zuang DR 2007[67]	CSP,250 mg, tid	Isosorbid dinitrate,10 mg,tid	60	57	61.4±12.3	63.3±11.2	68.30%	68.40%	4.4±3.1	8	①②

① improvement of angina symptoms; fx6 improvement of ECG test; ③ times of angina symptoms decreased; ④ adverse events.
NR = not reported.

available in the trial reports, further information was sought by correspondence with the principal investigator.

The methodological quality of included randomized trials was assessed and reported according to Cochrane Collaboration's handbook to assess the risk of bias.[13] The methodological quality assessed included:

1. sequence generation,
2. allocation sequence concealment,
3. blinding of participants and personnel,
4. blinding of outcome assessment,
5. incomplete outcome data,
6. selective reporting and
7. other potential sources of bias.

The evaluation of methodological quality was performed independently by the 2 reviewers, and discrepancies were solved through discussion.

2.4. Sensitivity analysis

Sensitivity analyses were performed to check the influence of the removed data set to the overall estimates effects through deleting one single study from the overall pooled analysis each time.

2.5. Assessment of publication bias

We used Egg test[14] to assess publication bias and other small-study effects in a qualitative manner for comparisons and outcomes in which more than 7 trials were included.

2.6. Summary of findings

We used the principles of GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system[15] in our review to assess the quality of the body of evidence associated with specific outcomes and constructed a 'Summary of findings' (SoF) table. The GRADE approach is used to assess the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers study methodological quality, directness of the evidence, heterogeneity of the data, precision of the effect estimates and risk of publication bias.

2.7. Data analysis

We pooled data using Stata statistical software version 12.0 (Stata Corp, College Station, TX) and implemented the meta-analysis with the random effect model for the potential heterogeneity between the trials. Relative Risk (RR) was used to construct forest plots of binary variable data, standard mean difference (SMD) with 95% confidence intervals (CI) was used to construct forest plots of continuous data. $P < .05$ was considered statistically significant. The presence of heterogeneity across the studies was evaluated using the Q statistic quantified with the I^2 statistic. The heterogeneity was considered as significant when P value was not bigger than .10. Heterogeneity could be quantified by I^2 statistic with 75%, 50%, and 25% that, respectively, corresponds to high, moderate, and low heterogeneity.[16]

3. Results

3.1. Search results and study characteristics

The literature search yielded 1849 citations from electronic database concerning compound salvia pellet for CSA (Fig. 1). After the 2 reviewers screened the titles, abstracts and full text according to inclusion criteria, 1563 articles were excluded as duplicates, non-clinical studies, obvious error, or study objectives different from the aim of this review. Finally, 51 RCTs[17–67] with 4732 patients (2511 received compound salvia pellet and 2221 received nitrates) were identified, none of them was multi-center study. Forty-six studies were given the dose of compound salvia pellet of 250 mg, tid, 4 were 250 mg, tid and the last 2 were 200 mg, tid and 1 was 125 mg, tid respectively (Table 1). Patients in control group received isosorbid dinitrate ranged from 8 to 20 mg, tid. The course of disease in most included studies over 1 year and the therapy period in 18 studies was 4 weeks, 6 weeks in
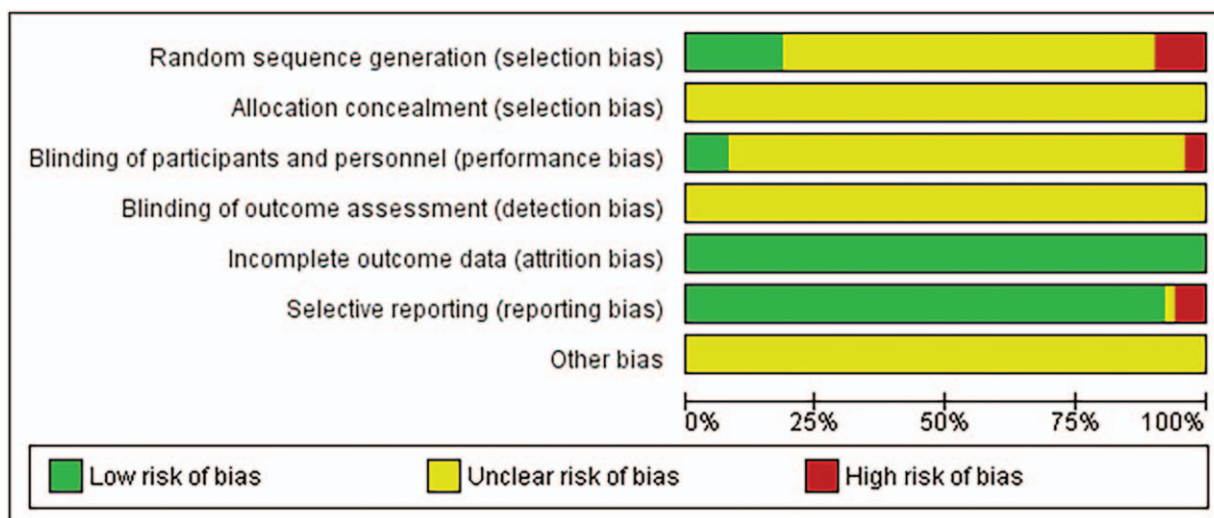

Figure 2. Risk of bias graph about each risk of bias item presented as percentages across all included studies.

4 studies, 8 weeks in 24 studies, 10 weeks in 1 studies and 12 weeks in 3 studies. More characteristics information about included RCTs could be seen in Table 1.

3.2. Methodological quality of the included studies

Nine studies[17,18,21,28–30,33,52,56] with low risk in random sequence generation, 4 studies[28,29,42,56] with low risk in blinding of participants and personnel, all studies with low risk in incomplete outcome data, and 47 studies with low risk in selective reporting, and none studies with low risk in allocation concealment and blinding of outcome assessment. (Figs. 2 and 3). No trials described a beforehand sample size calculation. The average sample size of the included trials was 95 patients, varying from 44 to 180, and there were more than 100 subjects in 23 trials (45.1%). The homogeneity test for the difference between the treatment group and the control group with a P value was used in 16 trials, the other trials only described the baseline levels without statistical analysis, and therefore it was difficult to make sure whether the 2 groups were comparable in all aspects.

3.3. Compound salvia pellet versus nitrates

Forty-four studies (n = 4149) reported improvement of angina symptoms. Pooled results showed compound salvia pellet had significant effect on the improvement of angina symptoms compared with nitrates (RR = 1.16, 95%CI = [1.12, 1.20], $P < .001$), with moderate heterogeneity found in the pooled estimates ($I^2 = 46.3\%$). Stratified analysis was conducted in terms of treatment durations. Pooling data showed a significant difference was found in the improvement of angina symptoms of compound salvia pellet group with a 4-week treatment duration (RR = 1.23, 95%CI = [1.17, 1.30], $P < .001$, $I^2 = 0\%$) and over 4-week treatment duration (RR = 1.13, 95%CI = [1.08, 1.17], $P < .001$, $I^2 = 45.6\%$) (Fig. 4).

The ECG test was used in 35 trials (n = 3419). The meta-analysis of the ECG test suggested that treatment with compound salvia pellet had a significant improvement effect of ECG compared with nitrates (RR = 1.28, 95%CI = [1.20, 1.36], $P < .001$), low heterogeneity was found in the pooled estimates ($I^2 = 45.4\%$). Furthermore, compound salvia pellet showed greater increased effect on the improvement of ECG with both 4 weeks and over 4 weeks of treatment durations (RR = 1.24, 95%CI [1.14, 1.35], $P < .001$, $I^2 = 51.5\%$; RR = 1.30, 95%CI [1.20, 1.42], $P < .001$, $I^2 = 36.4\%$, respectively) (Fig. 5).

Times of angina symptoms decreased was reported in 11 studies (n = 930). The pooled results indicated that compound salvia pellet group had less times of angina attack decreased within a week and a day (SMD = 1.39, 95%CI = [1.21, 1.57], $I^2 = 87.4\%$; SMD = 1.06, 95%CI = [0.82, 1.30], $I^2 = 93.9\%$, respectively) (Fig. 6).

Adverse events were reported in 55 of 1723 (3.2%) patients treated with compound salvia pellet, among which, abdominal complaints, nausea, and dyspepsia were mostly reported, and no dropouts or withdrawals for adverse events was founded in compound salvia pellet group. In patients treated with nitrates, adverse events were reported in 248 of 1461 subjects (17.0%), and there were 21 withdrawals for some serious complaints such as flush, dizziness, headache, and syncope. The pooled results indicated the rate of adverse events in compound salvia pellet group was significant lower than nitrates group (RR = 0.22, 95% CI = [0.17, 0.30], $P < .001$), no heterogeneity was found in the pooled estimates ($I^2 = 0\%$) (Fig. 7).

Figure 3. Risk of bias summary about each risk of bias item for each included study.
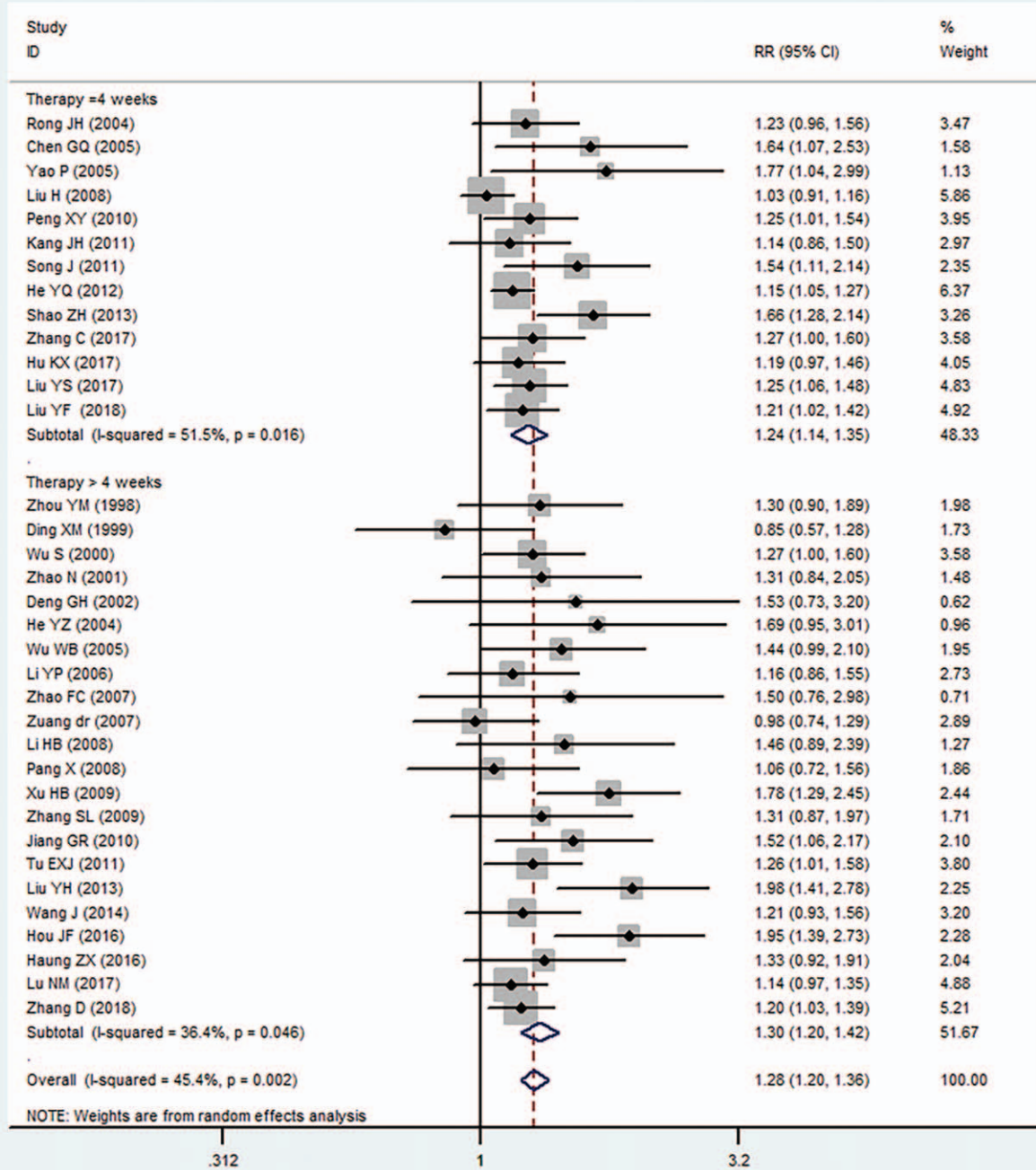
Figure 4. A meta-analysis of improvement of angina symptoms for compound salvia pellet versus nitrates.

3.4. Sensitivity analysis

We deleted 1 single study from the overall pooled analysis each time to check the influence of removed data set to the overall RRs. Finally, the sensitivity analysis showed that the pooled results were stable, which improved our confidence to compound salvia pellet for CSA.

3.5. Publication bias

Publication bias assessment of each outcomes by Egg test were presented in Table 2. Weighted linear regression of effect estimates on their standard error revealed evidence of publication bias or other small-study effects in outcomes of improvement of angina symptoms (therapy > 4weeks and therapy = 4 weeks) and improvement of ECG (therapy = 4 weeks).

4. Discussion

This meta-analysis of randomized trials suggested that compound salvia pellet was more effective than nitrates in the improvement of angina symptom, ECG test and times of
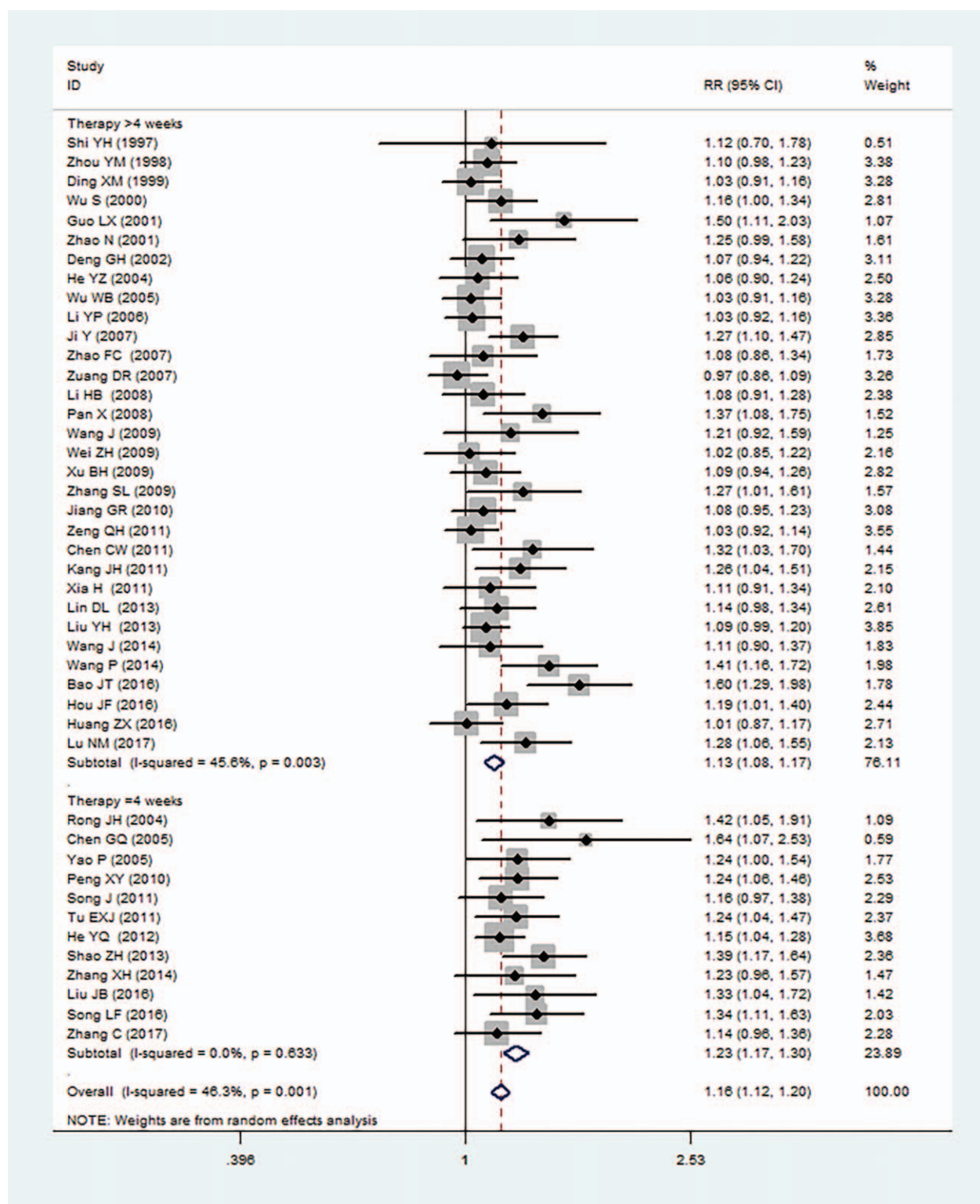
Figure 5. A meta-analysis of improvement effect of ECG for compound salvia pellet versus nitrates. ECG = electrocardiogram.

angina symptoms decreased. After stratified analysis was conducted in terms of treatment durations, pooled results showed significant differences in the improvement of angina symptoms (Fig. 4) and ECG test (Fig. 5) in compound salvia pellet group with both 4-week treatment duration and over 4-week treatment duration. The advantage of compound salvia pellet was still obvious when subgroup analysis was conducted according to the times of angina symptoms decreased counted in a day or a week (Fig. 6). In addition, compound salvia pellet seemed to be safer than nitrates, as compound salvia pellet had lower adverse events rate compared with nitrates (3.2% vs 17.0%).
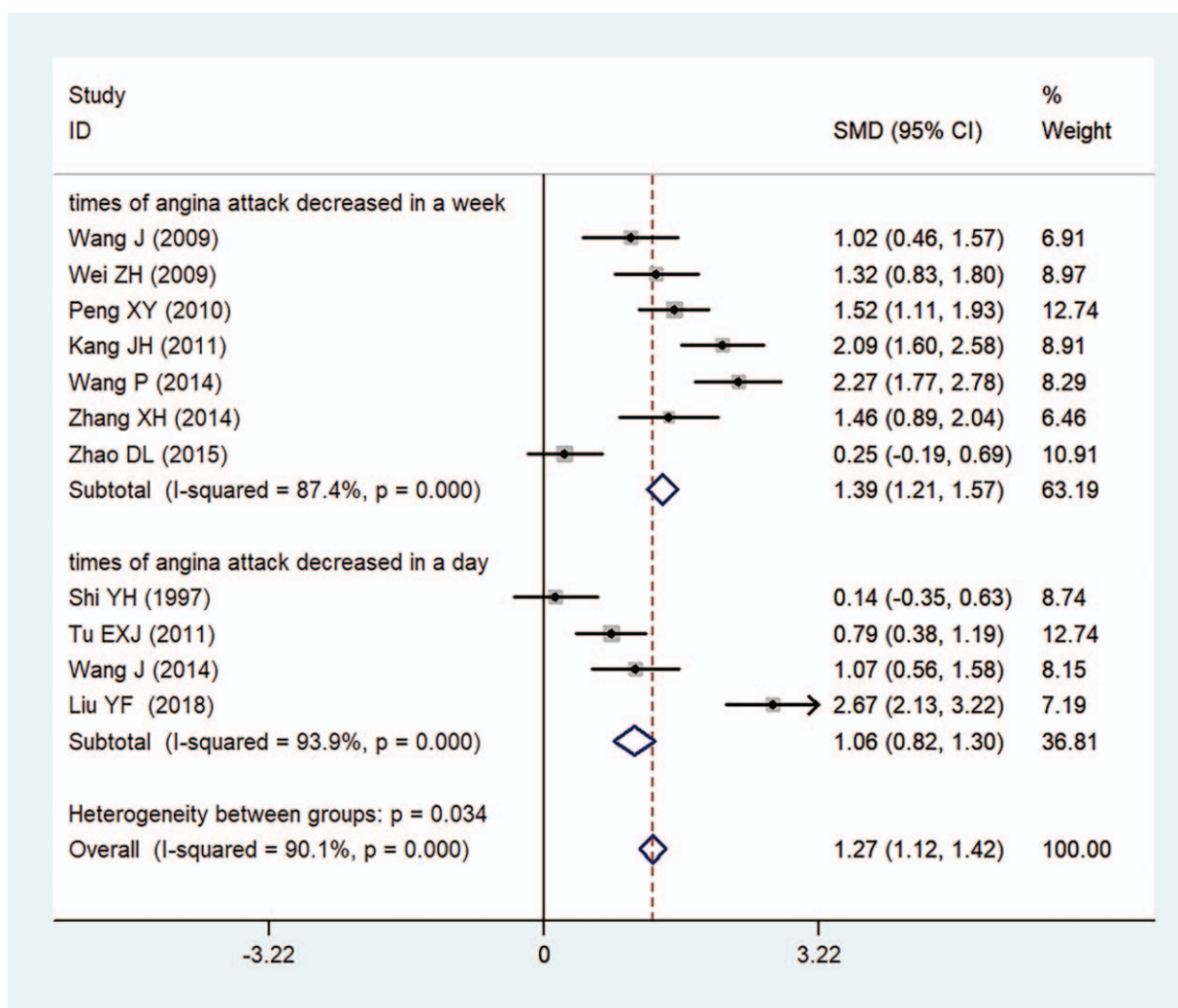
Figure 6. A meta-analysis of times of angina symptoms decreased for compound salvia pellet versus nitrates.

These main findings of the review are presented in summary of findings for the main comparison (Table 3). However, none of the included trials, reported endpoint events with long-term follow-up duration, such as mortality, and quality of life, which actually are more useful for evaluating the effectiveness of the 2 arms.

Patients with angina are at substantially higher risk of cardiac death or myocardial infarction than general population. Therapies for patients with chronic stable angina aims at reducing symptoms, so as to reduce the risk of death and myocardial infarction. Symptomatic therapy is targeted at either reducing oxygen demand by decreasing the work of the heart or increasing oxygen supply by dilating coronary arteries.

The reason why compound salvia pellet showed a superior effect than nitrates perhaps due to their different active ingredients and pharmacological mechanism. Compound salvia pellet protects cardiomyocytes against myocardial ischemia and inhibits apoptosis via the Akt-eNOS signaling pathway.[68] Moreover, it may have extensive effects on four metabolites (hypoxanthine, xanthine, inosine, and allantoin) in the pathway of purine metabolism which contribute to a decrease of oxygen-free radical.[69] While nitrates dilate veins, arteries, and coronary arteries by relaxing vascular smooth muscle. They produce these effects by entering vascular smooth muscle cells where they are metabolized to 1, 2-glyceryl dinitrate and nitrite, via mitochondrial aldehyde dehydrogenase-2 (ALDH2 or mtALDH), and then nitric oxide and S-nitrosothiols.[70] Sulfhydryl groups on ALDH2 are required for activity.

This review examined data from 51 studies with 4732 participants diagnosed with CSA, which formed the basis of this review certainly provided a considerable body of evidence. The overall methodological quality of the included studies was low, with most studies assessed as having one or more domains of unclear or high risk of bias. In light of the subjective nature of most of the outcomes of this review, the greatest concern was lack of adequate blinding which might result in big bias in outcomes measured. The quality of evidence of outcomes in this review were presented in Table 3, the quality of evidence of improvement of ECG (therapy > 4 weeks) and adverse events were rated to be "moderate" level, which indicated that the true effect was likely to be close to the estimate of the effect. While the quality of evidence of the other outcomes were rated to be "low" or "very low", which suggested that our confidence in the effect estimate is limited.
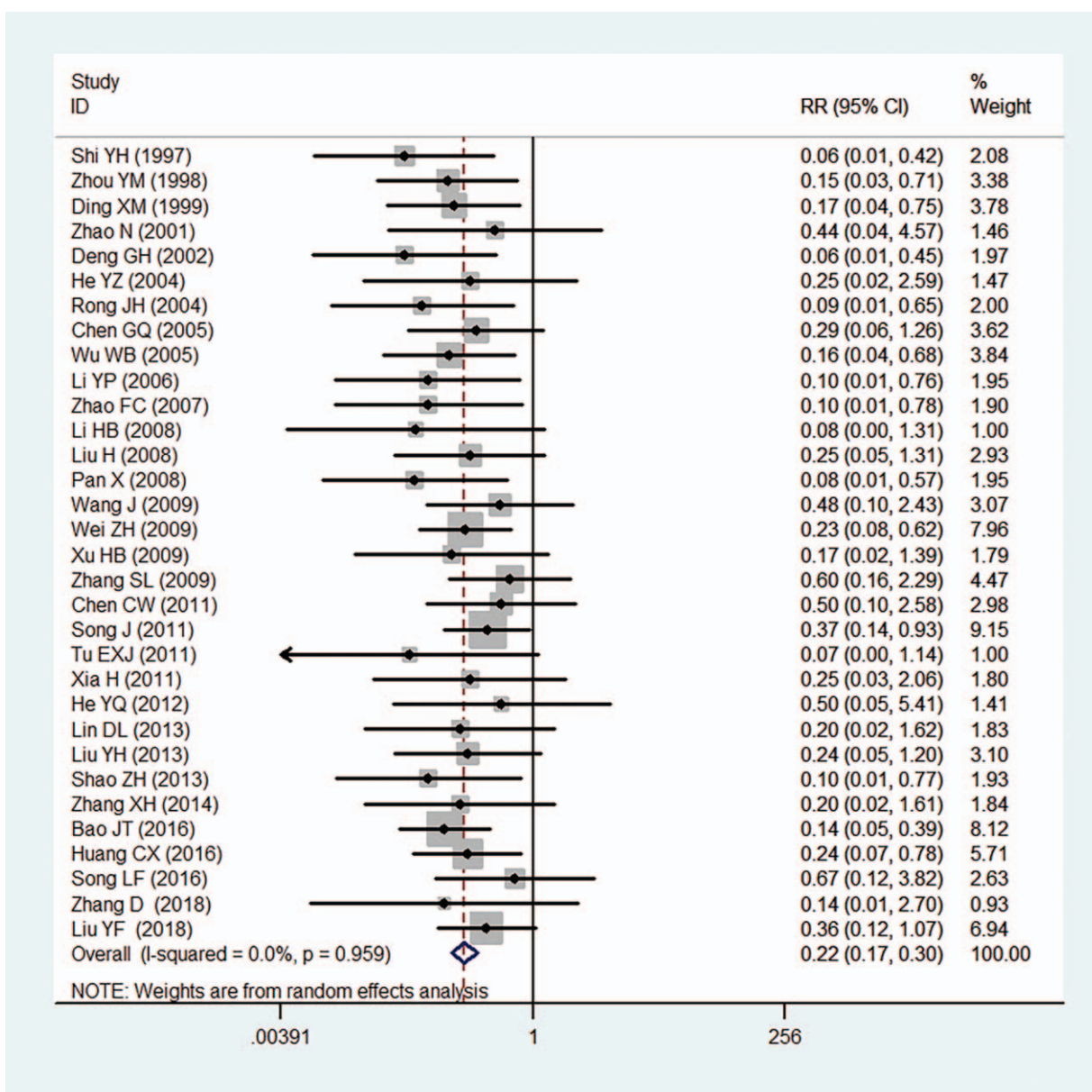
Figure 7. A meta-analysis of adverse events for compound salvia pellet versus nitrates.

Heterogeneity was moderate in the assessment of improvement in both symptoms and ECG test. Possible reasons for the heterogeneity are:

1. misuse of randomization,
2. different criteria for assessing the therapeutic efficacy, and
3. the kinds of nitrates with different quality criteria from different pharmaceutical companies. And heterogeneity was statistically significant in the outcome of times of angina symptoms decreased.

One of the main reasons might be, for several studies, the central tendency of the data was reported as a median rather than as a mean, and the spread was reported as a range or interquartile range. These data were approximated to mean and standard deviation by using the techniques described in Hozo study.[71] However, it is important to note that these approximations may differ from the reported mean and standard deviation statistics.

Table 2

Publication bias assessment by Egg test.

Outcomes	t value	Standard error	P value
Improvement of angina symptoms (therapy > 4 weeks)	4.04	0.752	< .001
Improvement of angina symptoms (therapy = 4 weeks)	3.22	0.733	.009
Improvement of ECG (therapy > 4 weeks)	1.87	0.897	.076
Improvement of ECG (therapy = 4 weeks)	3.84	0.772	.0003
Times of angina symptoms decreased in a week	0.47	10.298	.658
Adverse events	−1.24	0.109	.226

Table 3

Summary of findings for the main outcomes.

CSP compared with nitrates for chronic stable angina pectoris.
Patient or population: patients diagnosed with chronic stable angina pectoris.
Settings: secondary and tertiary care.
Intervention: Compound salvia pellet.
Comparison: Nitrates.

| | Illustrative comparative risks* (95% CI) | | | | |
| | Assumed risk | Corresponding risk | | | |
Outcomes	Nitrates	CSP	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Improvement of angina symptoms (therapy > 4 weeks)	800 per 1000	1000 per 1000 (1000 to 1000)	RR 1.13 (1.08 to 1.17)	3036 (32 studies)	⊕⊕◯◯ low[†,‡]
Improvement of angina symptoms (therapy = 4 weeks)	727 per 1000	1000 per 1000 (1000 to 1000)	RR 1.23 (1.17 to 1.30)	1113 (12 studies)	⊕⊕◯◯ low[†,‡]
Improvement of ECG (therapy > 4 weeks)	498 per 1000	866 per 1000 (791 to 946)	RR 1.30 (1.20 to 1.42)	2122 (20 studies)	⊕⊕⊕◯ moderate[†]
Improvement of ECG (therapy = 4 weeks)	651 per 1000	892 per 1000 (814 to 970)	RR 1.24 (1.14 to 1.35)	1297 (13 studies)	⊕⊕◯◯ low[†,‡]
Times of angina symptoms decreased in a week	The mean times of angina symptoms decreased in a week in the control groups was 3.9 times	The mean times of angina symptoms decreased in a week in the intervention groups was lower than control groups SMD = 1.39 times (1.21 to 1.57)		598 (7 studies)	⊕⊕◯◯ low[†,‡]
Times of angina symptoms decreased in a day	The mean times of angina symptoms decreased in a day in the control groups was 1.1 times	The mean times of angina symptoms decreased in a day in the intervention groups was lower than control groups 1.06 times lower (0.82 lower to 1.30 lower)		332 (4 studies)	⊕◯◯◯ very low[†,§,¶]
Adverse events	179 per 1000	39 per 1000 (29 to 52)	RR 0.22 (0.17 to 0.30)	3184 (34 studies)	⊕⊕⊕◯ moderate[†]

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
CI = Confidence interval, RR = Relative ratio.
* The basis for the *assumed risk* is the mean control group risk across studies. The *corresponding risk* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI).
[†] Risk of bias was unclear or high in the studies.
[‡] Potential publication bias was suspected.
[§] The heterogeneity was high.
[¶] The sample size was insufficient.

Another possible reason that contributed to the high heterogeneity might be misuse of randomization.[72–74]

It was significant that most important information in the included trials did not report adequately, which led to unclear risk of bias in most domains. Investigators and editors have developed the CONSORT (Consolidated Standards of Reporting Trials) statement to help authors improve reporting quality of RTCs by referring to the checklist and flow diagram.[75]

Although several previous meta-analyses had been published,[76–79] the results from this systematic review are more reliable because

1. their studies mixed stable and unstable angina pectoris together, which could confuse potential readers,
2. their studies provided no subgroup analysis according to therapy duration or some other factors, which is a significant bias to heterogeneity,
3. their conduct did not follow PRISMA requirements, and

4. their results had been outdated because of new trials published in recent years.

By contrast, this systematic review includes only the RCTs comparing compound salvia pellet and nitrates. The interpretation of the pooled results is used by GRADE approach, and subgroup and sensitivity analyses were conducted to avoid possible biases of specific groups of studies.

This review also has some limitations:

1. most of the included trials were of low metrological quality, with high or unclear risk of bias random sequence generation, allocation concealment and blinding;
2. the course of disease ranged from 1 to 16 years, and the diagnostic criteria to CSA varied because the studies published from 1997 to 2018 which might result in heterogeneity;
3. no trials described the beforehand sample size calculation and the allocation concealment.

5. Conclusions

This meta-analysis suggests that compound salvia pellet might be more effective on the improvement of angina symptoms, ECG test and with few adverse events compared with nitrates. Therefore, compound salvia pellet might be used as an alternative option for nitrates in the treatment of CSA. While there are some limitations in this study, which may weaken the results, we believe the findings could provide useful information for stakeholders concerned with outcomes in patients with CSA. More rigorous RCTs with high quality are needed to confirm these findings.

Author contributions

W.H.P, W.X.Q, W.Y, and Y.L had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. W.H.P and W.X.Q contributed to drafting and critical revision of the article; W.H.P, J.P, and W. Z contributed to the data extraction, and data analysis; Y.K.H and L.Y.D. contributed to the study design and critical review. All authors contributed to the interpretation of study data and critically reviewed and approved the article before submission.

Conceptualization: Wei Huiping, Wang Yu, Li yingdong.

Data curation: Wei Huiping, Wang Yu, Li yingdong.

Formal analysis: Wei Huiping, Wang Yu, Li Jiao, Jiang Hugang, Li yingdong.

Funding acquisition: Wei Huiping, Wang Yu.

Investigation: Wei Huiping, Wang Yu.

Methodology: Wei Huiping, Jin Pei, Jiang Hugang, Wang Zheng, Li yingdong.

Project administration: Wang Zheng.

Resources: Wei Huiping, Jin Pei, Li Jiao, Zhang Shian, Wang Zheng.

Software: Wei Huiping, Jin Pei, Wang Zheng.

Supervision: Wei Huiping, Jin Pei, Wang Zheng, Li yingdong.

Validation: Wei Huiping, Jin Pei, Zhang Shian, Wang Zheng.

Visualization: Wei Huiping, Wang Zheng.

Writing – original draft: Wei Huiping.

Writing – review & editing: Wei Huiping, Li yingdong.

References

[1] Henderson RA, O'Flynn N. Management of stable angina: summary of NICE guidance. Heart 2012;6:500–7.

[2] Mickie P, Ronit Peled , Matityhau L, et al. Reasons for overprescription of mononitrates: the paradigm of stable angina pectoris treatment. Curr Ther Res 2003;64:662–75.

[3] Glasser SP. Clinical mechanisms of nitrate action. Am J Cardiol 1998;81:49A–53A.

[4] Fihn SD, Williams SV, Daley J, et al. American College of Cardiology, American Heart Association, American College of Physicians American Society of Internal Medicine Guidelines for the management of patients with chronic stable angina: treatment. Ann Intern Med 2001;135:616–32.

[5] Martin E, Nick F, James M, et al. North of England evidence based guidelines development project: summary version of evidence based guideline for the primary care management of angina. BMJ 1996;312:827–32.

[6] Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina-summary article: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (committee on the management of patients with chronic stable angina). Circulation 2003;107:149–58.

[7] Niemeyer MG, Kleinjans HAJ, de Ree R, et al. Comparison of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: effects on quality-of life indices. Angiology 1997;48:855–62.

[8] Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. N Engl J Med 1998;338:520–31.

[9] Thadani U. Nitrate tolerance, rebound, and their clinical relevance in stable angina pectoris, unstable angina, and heart failure. Cardiovasc Drugs Ther 1997;10:735–42.

[10] Wang AM, Sha SH, Lesniak W, et al. Tanshinone (Salviae miltiorrhizae extract) preparations attenuate aminoglycoside-induced free radical formation: in Vitro and ototoxicity in Vivo. Antimicrob Agents Chemother 2003;47:1836–41.

[11] Guo ZX, Jia W, Gao WY, et al. Clinical investigation of composite Danshen pill for the treatment of angina pectoris. Chin J Nat Med 2003;1:124–8.

[12] China Association of Traditional Chinese Medicine. Guidelines for Chinese internal disease: chronic stable angina pectoris. Chin Med Mod Distance Edu 2011;9:142–3.

[13] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated 2011 Mar]. Birmingham, UK: The Cochrane Collaboration; 2011.

[14] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clin Res Ed) 1997;7109: 629–34.

[15] Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians. BMJ 2008;336:995–8.

[16] Unverzagt S, Peinemann F, Oemler M, et al. Meta-regression analyses to explain statistical heterogeneity in a systematic review of strategies for guideline implementation in primary health care. PLoS One 2014;10: e110619.

[17] Zhang D. The clinical effect of compound salvia pellet and isosorbide mononitrate tablets for stable angina pectoris. World Latest Med Inf (Electron Vers) 2018;18:74–5.

[18] Liu YF. Clinical observation on compound Danshen dripping pills on angina pectoris of coronary heart disease. CJGMCM 2018;33:757–8.

[19] Lu NM. A comparative study of compound salvia pellet and isosorbid dinitrate for stable angina pectoris. Cardiovasc Dis J Integr Med 2017;5:55–6.

[20] Hu KX, Zhang JH. Effect analysis of coronary heart disease angina pectoris patients treated with Fufang Danshen Diwan. Liaoning J Tradit Chin Med 2017;44:1427–9.

[21] Liu YS. Wang N. the effect and safety of compound salvia pellet for stable angina pectoris. Cardiovasc Dis J Integr Tradit ChinWest Med 2017;5:56–7.

[22] Zhang C. The effect of compound salvia pellet for 44 patients of stable angina pectoris. Inner Mong J Tradit Chin Med 2017;8:43–4.

[23] Bao JT, Hu YX. The effect and safety analysis of the treatment of compound Danshen dropping pills on angina pectoris. Chin J Evid-Based Med 2016;3:90–1.

[24] Zeng QH. Clinical observation on the treatment of 86 cases of angina pectoris of coronary heart diseases with Fufangdanshen drop Pill. Chin Mail Rehab Med 2011;24:141.

[25] Chen CW, Zhou Y. The curative effect of compound Danshen dripping pills in treatment of angina pectoris of coronary heart disease. Contemp Med 2011;17:142–3.

[26] Chen GQ. Clinical observation on the treatment of 60 cases of angina pectoris of coronary heart diseases with Fufang Danshen drop pill. Guid J TCM 2005;11:12–3.

[27] Deng GH, He JT, Li BL. Treating stable angina pectoris with compound Danshen dropping pill. Chin J Evid-Based Med 2002;14:48.

[28] Ding XM, Jia LZ, Wang CH, et al. The effects of compound Danshen dropping pill treating stable angina. Acta Academiae Medcinae Suzhou 1999;19:512–3.

[29] Guo LX, Li SX, Zhang WH. Clinical observation on compound Danshen dropping pill treating angina. J Linyi Med Coll 2001;23:113–5.

[30] He YQ, Cao ZY, Li AP, et al. Clinical observation on compound salvia pellet in the treatment of angina pectoris: a report of 84 cases. Chin J Integr Med Cardio-Cerebrovasc Dis 2012;10:746.

[31] He YZ. Clinical observation on compound salvia pellet in the treatment of angina pectoris: a report of 40 cases. Health Vocat Edu 2004;22: 107–8.

[32] Hou JF. Observation on compound Danshen dropping pill in the treatment of coronary heart disease and angina pectoris. Prim Health Care 2016;20:1335–6.

[33] Huang CX. Clinical observation on compound salvia pellet in the treatment of angina pectoris: a report of 80 cases. East Health Care 2016;109:101.

[34] Huang SW, Zou XQ, Li P. Clinical observation on compound Danshen dropping pill and isosorbid dinitrate treating stable angina. Mod Diagn Treat 2004;15:349–50.

[35] Ji Y, Wang AN. Clinical effectiveness of compound Danshen dropping pill in the treatment of coronary heart disease and angina pectoris. Med Qingdao 2007;39:437–8.

[36] Jiang GR, Chen WM. Clinical investigation on compound Danshen dropping pill in treatment of coronary heart disease and angina pectoris. J Contemp Med 2010;17:53.

[37] Ang JH, Guo LN, Li LM. The effectiveness of compound Danshen dripping pills in treatment of angina pectoris of coronary heart disease. Mod J Integr Tradit Chin West Med 2011;20:4367–8.

[38] Li HB, Gao D. Observation on curative effect of compound Danshen dripping pills in treatment of angina pectoris of coronary heart disease. J Health Dig 2008;5:28–9.

[39] Li YP, Xi YX, Zhou CL, et al. Observation on efficacy of compound Danshen dropping pills in treatment of stable angina pectoris. Clin J Med Off 2006;34:673–4.

[40] Lin DL, Lin XF, Yuan XL. Clinical analysis on compound salvia pellet in the treatment of coronary heart disease. J Math Med 2013;26:82–3.

[41] Ju H. Clinical observation on compound Danshen dropping pill in the treatment of coronary heart disease and angina pectoris. Tradit Med Mong 2008;27:15–6.

[42] Liu JB. Clinical research of 60 cases of angina pectoris treated with compound Danshen dropping pill. Chin Health Care Nutr 2016;26:249–50.

[43] Liu YH. The curative effect contrast of compound salvia miltiorrhiza particles and isosorbid dinitrate treatment of stable angina pectoris. Tradit Med Mong 2013;32:2–3.

[44] Pan C. The effectiveness of compound Danshen dripping pills in treatment of stable angina pectoris. J Tianjin Pharm 2008;20:56–7.

[45] Peng XY. Observation on efficacy of compound Danshen dropping pills in treatment of angina pectoris. Clin Med Eng 2010;17:100.

[46] Rong JH, Gu JG, Qian XF. The effect of compound salvia pellet on angina symptoms and hemorheology in senile patients with coronary heart disease. J Nantong MedColl 2004;24:44.

[47] Shao ZH, Ji LL, Jin HY. Curative effect of compound Danshen dripping pills in treatment of stable angina pectoris. People's Mil Surg 2013;56:423–4.

[48] Shi YH. Comparative study of compound Danshen droplet pills and Sordi in treatment of patients with chronic stable angina. J Integr Tradit Chin West Med 1997;17:23–5.

[49] Song J, Gao SX. Curative effect of compound Danshen dripping pills for stable angina pectoris: a report of 42 cases. Chin J Clin Ration Drug Use 2011;4:41–2.

[50] Song LF, Gong W. Compound Danshen dropping pill for 50 cases of coronary heart disease angina pectoris. J He Ze Med Coll 2016;28:38–9.

[51] Tu EXJ. Observation on curative effect of compound Danshen dripping pills in treatment of coronary heart disease and angina pectoris. Seek Med Ask Med 2011;9:105–6.

[52] Wang J, Chen JF. The effectiveness of compound Danshen dripping pills for angina pectoris. Contemp Med 2014;20:148–9.

[53] Wang J. Observation on curative effect of compound Danshen dripping pills in treatment of stable angina pectoris: a report of 29 cases. Chin J Evid-Based Med 2009;10:32–3.

[54] Wang P. Using compound Danshen pill to treat 50 cases of coronary heart disease angina pectoris. Med Mod Distance Edu China 2014;12:130–1.

[55] Wei ZH, Han X. Clinical observation on compound Danshen dropping pill in the treatment of stable angina pectoris. Chin J Misdiagn 2009;9:1563–4.

[56] Wu WB, Guo XL. The effective comparison between compound Danshen dropping pill and isosorbid dinitrate treating stable angina pectoris. Chin J Misdiagn 2005;145–6.

[57] Wu S, Liu HF. The analysis of long-term effects of compound Danshen dropping pill treating 135 cases of angina. Ningxia Med J 2000;22:407–8.

[58] Xia H. Clinical analysis of treating coronary heart disease by CSDP. Clin J Chin Med 2011;3:38–9.

[59] Xu BH. Effects of the treatment of compound Danshen dropping pills on angina pectoris. Mod Med 2009;25:527–8.

[60] Yao P, Zhu JH, Lei YR. Compound Danshen dropping pill to treat 38 cases of coronary heart disease angina pectoris. Chin Med 2005;14:81–2.

[61] Zhang SL. Observation on curative effect of compound Danshen dropping pills in treatment of stable angina pectoris. J Chang Univ Tradit Chin Med 2009;25:89.

[62] Zhang XH. The effect of compound Danshen dripping pills for angina pectoris of coronary heart disease. Chin J Clin Ration Drug Use 2014;7:46.

[63] Zhao DL, Wang DM, Pan X. Observation on curative effect of compound Danshen dripping pills for angina pectoris of coronary heart disease. China Contin Med Edu 2015;7:244–5.

[64] Zhao FC. The effectiveness of compound Danshen dripping pills for angina pectoris of coronary heart disease: a report of 30 cases. Hei Long Jing Med J 2007;31:934.

[65] Zhao N. Clinical observation of 32 cases of stable angina pectoris treated with compound Danshen dropping pill. J Zhe Jing Coll TCM 2001;25:22–3.

[66] Zhou YM. Treating 120 cases of stable angina pectoris with compound Danshen dropping pill. Chin J New Drugs Clin Rem 1998;17:375–6.

[67] Zhuang DR. Observation on curative effect of compound Danshen dropping pills on stable angina pectoris. Mod J Integr Tradit Chin West Med 2007;16:4127–8.

[68] Ren-an Q, Juan L, Chuyuan L, et al. Study of the protective mechanisms of compound Danshen tablet (Fufang Danshen Pian) against myocardial ischemia/reperfusion injury via the Akt-eNOS signaling pathway in rats. J Ethnopharmacol 2014;23:190–8.

[69] Lv Y, Liu X, Yan S, et al. Metabolomic study of myocardial ischemia and intervention effects of compound Danshen tablets in rats using ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry. J Pharm Biomed Anal 2010;52:129–35.

[70] Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. Proc Natl Acad Sci U S A 2002;99:8306–11.

[71] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.

[72] Zhang D, Yin P, Freemantle N, et al. An assessment of the quality of randomised controlled trials conducted in China. Trials 2008;9:22.

[73] He J, Du L, Liu G, et al. Quality assessment of reporting of randomization, allocation concealment, and blinding in traditional Chinese medicine RCTs: a review of 3159 RCTs identified from 260 systematic reviews. Trials 2011;12:122.

[74] Downs M, Tucker K, Christ-Schmidt H, et al. Some practical problems in implementing randomization. Clin Trials 2010;7:235–45.

[75] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Lancet 2001;357:1191–4.

[76] Wang G, Wang L, Xiong ZY, et al. Compound salvia pellet, a traditional Chinese medicine, for the treatment of chronic stable angina pectoris compared with nitrates: a meta-analysis. Med Sci Monit 2006;12:SR1–7.

[77] Jia Y, Huang F, Zhang S, et al. Is Danshen (Salvia miltiorrhiza) dripping pill more effective than isosorbide dinitrate in treating angina pectoris? A systematic review of randomized controlled trials. Int J Cardiol 2012;157:330–40.

[78] Yao Y, Feng Y, Lin W. Systematic review and meta-analysis of randomized controlled trials comparing compound Danshen dripping pills and isosorbide dinitrate in treating angina pectoris. Int J Cardiol 2015;182:46–7.

[79] Li YF, Wang TL, Wei KN, et al. Compound Danshen dripping pills for stable angina: meta-analysis of randomized controlled trials. J Med Plant Res 2011;5:2245–51.