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Review Article

Efficacy of Xuefu Zhuyu decoction compared with nitrates in treating angina pectoris: a meta-analysis of randomized controlled trials

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Abstract: Background: Xuefu Zhuyu decoction (XZD) is a popular Chinese medicinal formula and often compared with nitrates in treating coronary heart disease angina pectoris. This systematic review aims to evaluate the efficacy of XZD in treating angina pectoris according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) systematic review standard. Methods: Randomized controlled trials (RCTs) published from 1983 up to March 2014 on XZD versus nitrates in treating angina pectoris were retrieved from major databases, including Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), WanFang Data (WF), WeiPu Data (VIP), PubMed, Cochrane Library (CL), and Elsevier. No language restrictions were imposed. Meta-analysis was performed on the overall effects on the improvements of symptoms and electrocardiography (ECG). Risks of selection, performance, detection, attrition, reporting, and other bias were assessed by the Cochrane collaboration's tool for assessing risk of bias. Results: Twenty-two RCTs with 1951 participants were included. Summary risk ratios for comparing XZD and nitrates were 1.24 (95% CI 1.16-1.33) by symptoms (n=21) and 1.42 (95% CI 1.22-1.66) by ECG (n=16). Conclusion: Although a consistent result that XZD might be more effective than nitrates in treating angina pectoris is presented in this study, further RCTs of higher quality, larger scale, longer follow-up periods and multi-country are still required to identify the efficacy of XZD.

Keywords: Xuefu Zhuyu decoction, angina pectoris, meta-analysis

Introduction

Xuefu Zhuyu decoction (XZD), consisting of six crude herbs: *Radix PaeoniaeRubra*, *Rhizoma-Chuanxiong*, *Semen Persicae*, *FructusAurantii*, *FlosCarthami* and *Radix Bupleuri*, is first described in *Yilin Gaicuo* (Correction on Errors in Medical Classics) by Qingren Wang in late Qing Dynasty [1]. In a recent report, XZD has been reported with the abilities to induce the differentiation of mesenchymal stem cells into cardiac myoid cells [2]. It also reduces the incidence of pleural effusion in patients with blunt chest injured rib fracture [3], and decreases the serum asymmetric dimethylarginine level in atherosclerosis rabbits [4]. XZD is a famous traditional Chinese medicine prescription to treat coronary heart disease, which is routinely treated by nitrates.

Coronary heart disease, also called coronary artery disease, is a narrowing of the small blood vessels that supply blood and oxygen to the heart caused by the buildup of plaque in the arteries to the heart. Chest pain is the most common symptom of coronary heart disease, named angina pectoris, and even causes sudden death. Angina pectoris is usually clinically diagnosed by examination of symptoms and electrocardiography (ECG) [5].

This systematic review aims to evaluate the efficacy of XZD in treating angina pectoris according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [6] systematic review standard.

Materials and methods

Eligibility criteria

RCTs published from 1983 up to March 2014 on XZD versus nitrates in treating coronary heart disease angina pectoris were screened

and filtered. Inclusion criteria were used to select the RCTs in which (1) XZD was used as the experimental and nitrates were used as the control; (2) participants were suffering from angina pectoris as diagnosed by the criteria consistent with the guideline of World Health Organization [5]; and (3) there was frequency reduction in feeling of chest pain or significant improvement in ST segment in ECG [7]. Exclusion criteria were used to delete RCTs in which (1) XZD was used in combination with other drugs; (2) XZD was used in other dosage forms; (3) nitrates were used in combination with other antianginal drugs; and (4) diagnostic criteria of angina pectoris were not specified.

Information sources

Studies were searched from major databases including Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), WanFang Data (WF), WeiPu Data (VIP), PubMed, Cochrane Library (CL), and Elsevier. Publication dates were from 1983 up to March 2014. The last search was performed on 24 March, 2014.

Search

According to the working language of these databases, we used the following search terms to search PubMed, CL and other English databases in all fields: 1. xue fu zhu yu; 2. xuefu zhuyu; 3. xuefuzhuyu; 4. 1 or 2 or 3; 5. Angina; 6. 4 and 5.

And we used the following search terms to search CBM, CNKI and other Chinese databases: 1. xuefuzhuyu tang [xuefuzhuyu decoction]; 2. xinjiaotong [angina pectoris]; 3. 1 and 2.

Study selection

Clinical studies were screened by titles and abstracts according to the eligibility criteria by two reviewers (Z. Fang and P.P. Guo). Full texts were retrieved and further assessed in the same manner according to the eligibility criteria. Disagreements between reviewers were resolved by discussion.

Data collection process

All included studies were read by independent reviewers (Z. Fang. and P.P. Guo), who extracted data and put into an electronic spreadsheet (Microsoft Excel). Another reviewer (L. Jing) checked the data. The extracted data were then transferred to Review Manager 5.2 and STATA 12.0 for meta-analysis. Disagreements were resolved by discussion.

Data items

The extracted data of the included studies consisted of (1) participants; (2) follow-up periods; (3) outcome measures including symptomatic and ECG improvement.

Symptomatic improvement was defined as (1) improvements achieved at least 25% frequency reduction in feeling of chest pain and (2) improvements achieved approaching normal state. ECG improvement was defined as (1) improvements achieved at least 0.05 mV of horizontal or down sloping ST segment and (2) improvements achieved approaching normal state.

Risk of bias in individual studies

Two reviewers (Z. Fang and P.P. Guo) independently assessed the reporting quality of included studies according to CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist [8], then assessed the risks of selection, performance, detection, attrition, reporting, and other bias by the Cochrane collaboration's tool for assessing risk of bias. Disagreements between reviewers were resolved by consensus.

Summary measures

Random-effects model was employed in overall analysis because heterogeneity was expected. Risk ratios (RR) and their 95% confidence intervals (CI) were assessed to compare categorical variables [9].

Planned methods of analysis

The efficacy results of meta-analysis were evaluated by forest plots [9] using Review Manager 5.2. I^2 and χ^2 were determined by Review Manager 5.2 to measure heterogeneity. *P* values lower than 0.05 were considered statistically significant.

Risk of bias across studies

Publication bias was assessed by funnel plots [9], and the statistical significance of the publication bias was tested by Begg's test [10] and Egger's test [11] using STATA 12.0.

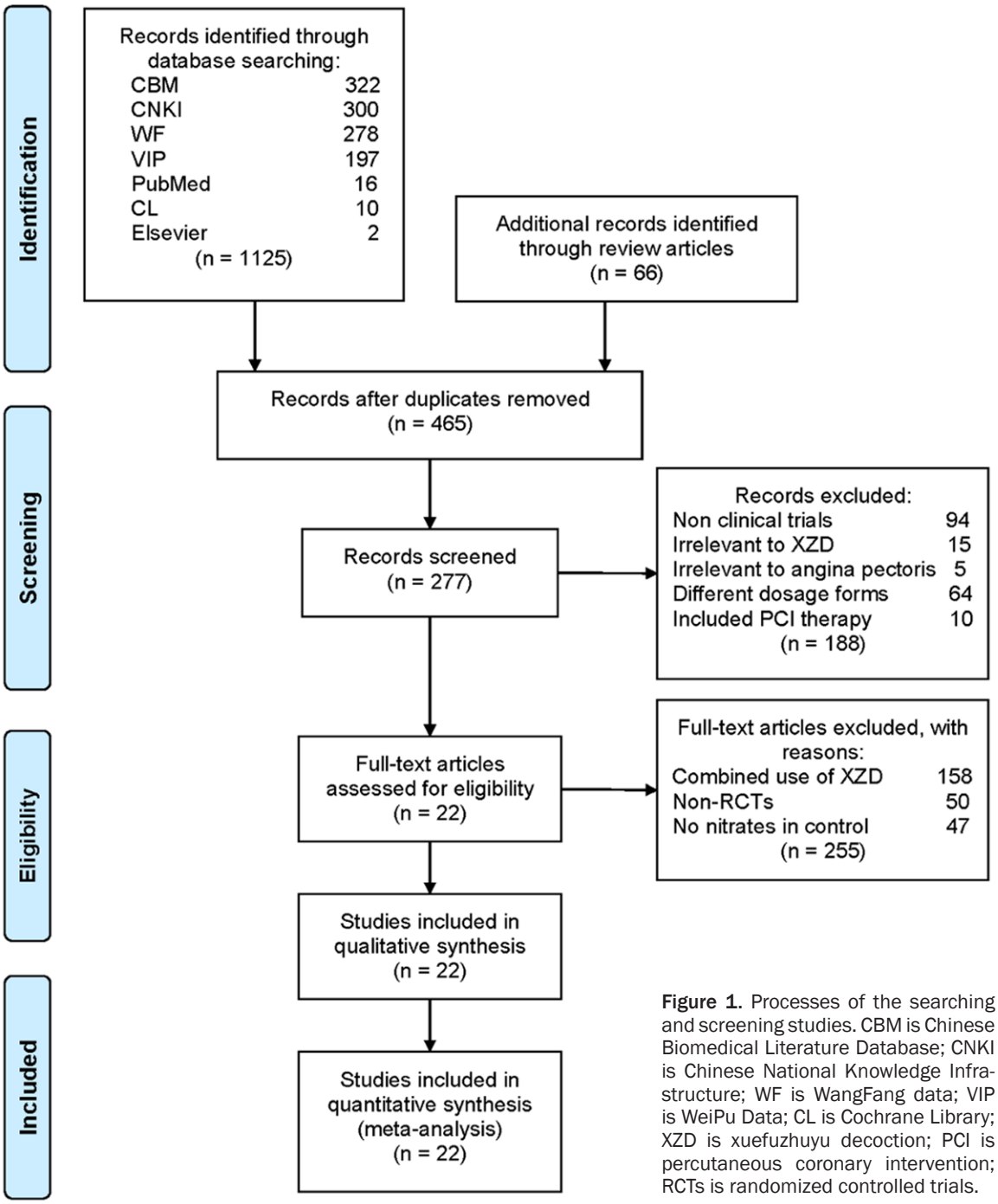

Figure 1. Processes of the searching and screening studies. CBM is Chinese Biomedical Literature Database; CNKI is Chinese National Knowledge Infrastructure; WF is WangFang data; VIP is WeiPu Data; CL is Cochrane Library; XZD is xuefuzhuyu decoction; PCI is percutaneous coronary intervention; RCTs is randomized controlled trials.

Additional analyses

Subgroup analysis was conducted to evaluate the overall effects in subgroups based on sample sizes and follow-up periods.

Results

Study selection

Figure 1 showed the selection process of relevant studies retrieved from databases. The search of CBM, CNKI, WF, VIP, PubMed, CL, and Elsevier identified respectively 322, 300, 278, 197, 16, 10, and 2 articles. Adding relevant articles cited in review articles [12-14], a total of 1191 articles were manually screened based on titles and abstracts. Seven hundred and twenty-six articles were excluded as redundant records. Ninety-four non-clinical trials were excluded. Twenty studies were excluded for their irrelevance with XZD or angina pectoris. Sixty-four articles were excluded for different

Table 1. The details and results of individual studies

Study ID	Total No. of Patients (Experimental/Control)	Follow-up Periods (Days)	Intervention		Primary Outcomes		Secondary Outcomes	Quality of Reporting	Adverse Events
			Experimental: XZD (Daily Dosage)	Control: Nitrates (Daily Dosage)	Symptoms (RR [95% CI])	ECG (RR [95% CI])			
Deng FR, 2010	107 (57/50)	30	XZD (one dose)	ISMN (40 mg)	2.01 [1.42, 2.83]	2.12 [1.22, 3.69]	None	Medium (CCR =45.95%)	None
Deng HM, 2005	84 (48/36)	28	XZD (one dose)	XXT (30 mg)	1.23 [1.02, 1.48]	1.27 [1.02, 1.58]	None	Poor (CCR =37.84%)	None
Fan K, 2006	100 (50/50)	42	XZD (one dose)	XXT (30 mg)	1.21 [1.02, 1.44]	1.40 [1.01, 1.95]	blood lipid	Medium (CCR =43.24%)	Not mentioned
Fang JJ, 2008	60 (30/30)	28	XZD (one dose =200 ml)	ISDN (30 mg)	1.44 [1.04, 2.00]	1.82 [1.07, 3.10]	other symptoms, blood lipid	Good (CCR =51.35%)	Not mentioned
Geng J, 1999	50 (30/20)	28	XZD (one dose)	XXT (Not mentioned)	0.94 [0.73, 1.22]	1.07 [0.78, 1.45]	other symptoms	Medium (CCR =45.95%)	Not mentioned
Li WB, 2010	200 (100/100)	15	XZD (one dose =200 ml)	XXT (30 mg)	1.29 [1.15, 1.46]	Not mentioned	None	Medium (CCR =40.54%)	None
Li WH, 2006	90 (45/45)	90	XZD (one dose =400 ml)	XXT (30 mg)	0.98 [0.85, 1.12]	0.95 [0.78, 1.15]	blood lipid, blood rheology	Good (CCR =48.65%)	Experimental group: none; Control group: three patients got headache and dizziness
Li XY, 2006	212 (124/88)	30	XZD (one dose =200 ml)	XXT (30 mg)	1.35 [1.16, 1.57]	2.09 [1.58, 2.75]	None	Medium (CCR =40.54%)	Not mentioned
Li YF, 2008	53 (30/23)	21	XZD (one dose)	XXT (30 mg)	1.26 [0.97, 1.64]	1.34 [0.68, 2.64]	None	Medium (CCR =43.24%)	Only 2 patients in XZD group got loose stool, but the symptoms disappeared after adding citrus and salvia to XZD.
Ma GH, 2006	120 (60/60)	30	XZD (one dose)	ISMN (60 mg)	1.58 [1.28, 1.96]	1.56 [1.12, 2.15]	Holter, blood lipid, blood rheology	Good (CCR =51.35%)	None
Ma Z, 2004	38 (26/12)	30	XZD (one dose)	Nitrates (Not mentioned)	1.11 [0.84, 1.46]	Not mentioned	None	Medium (CCR =43.24%)	None
Sun YS, 2013	58 (32/26)	30	XZD (one dose)	XXT (30 mg)	1.10 [0.94, 1.28]	Not mentioned	None	Poor (CCR =37.84%)	Not mentioned
Tang J, 2006	60 (31/29)	30	XZD (one dose =300 ml)	ISMN (40 mg)	Not mentioned	1.80 [1.21, 2.69]	None	Poor (CCR =37.84%)	Not mentioned
Wang BX, 2010	58 (29/29)	30	XZD (one dose =400 ml)	XXT (Not mentioned)	1.35 [1.04, 1.76]	Not mentioned	frequency and duration of angina pectoris, TIB	Medium (CCR =43.24%)	Not mentioned
Wang QJ, 2009	74 (38/36)	30	XZD (one dose)	XXT (Not mentioned)	1.14 [0.96, 1.34]	Not mentioned	None	Medium (CCR =40.54%)	Not mentioned
Wang XP, 2010	154 (104/50)	14	XZD (one dose)	ISMN (40 mg)	1.27 [1.07, 1.51]	1.15 [0.97, 1.37]	None	Medium (CCR =40.54%)	Not mentioned
Wang YD, 2012	80 (40/40)	60	XZD (one dose =400 ml)	ISMN (30mg)	1.23 [1.02, 1.47]	Not mentioned	None	Medium (CCR =40.54%)	Not mentioned
Xiao YF, 1999	70 (40/30)	21	XZD (one dose =400 ml)	XXT (30 mg)	1.46 [0.99, 2.15]	1.11 [0.92, 1.33]	other symptoms, blood rheology	Medium (CCR =43.24%)	Not mentioned
Yang XJ, 2004	83 (42/41)	28	XZD (one dose =300 ml)	Nitroglycerin (10 mg)	1.06 [0.92, 1.22]	1.09 [0.80, 1.48]	ST-segment shift and T wave change	Medium (CCR =45.95%)	Not mentioned
Yi YQ, 2007	60 (30/30)	Not mentioned	XZD (one dose)	XXT (30 mg)	1.32 [1.05, 1.65]	2.22 [1.22, 4.06]	other symptoms	Good (CCR =48.65%)	Not mentioned
Zhou BY, 2010	80 (40/40)	Not mentioned	XZD (one dose =450 ml)	XXT (30 mg)	1.30 [1.08, 1.57]	2.07 [1.30, 3.29]	other symptoms	Good (CCR =51.35%)	Not mentioned
Zhu XH, 2003	60 (30/30)	15	XZD (one dose)	XXT (30 mg)	1.50 [1.09, 2.06]	1.75 [1.06, 2.88]	None	Poor (CCR =37.84%)	Not mentioned

XXT is xiaoxintong, a kind of antianginal drugs which is made of isosorbidedinitrate. ISMN is isosorbidemononitrate tablets. ISDN is isosorbidedinitrate tablets. Other symptoms include chest distress, palpitation, asthma, etc. CCR is CONSORT compliance rate, which is checklist score of each study/total number of items. TIB is total ischemia burden.

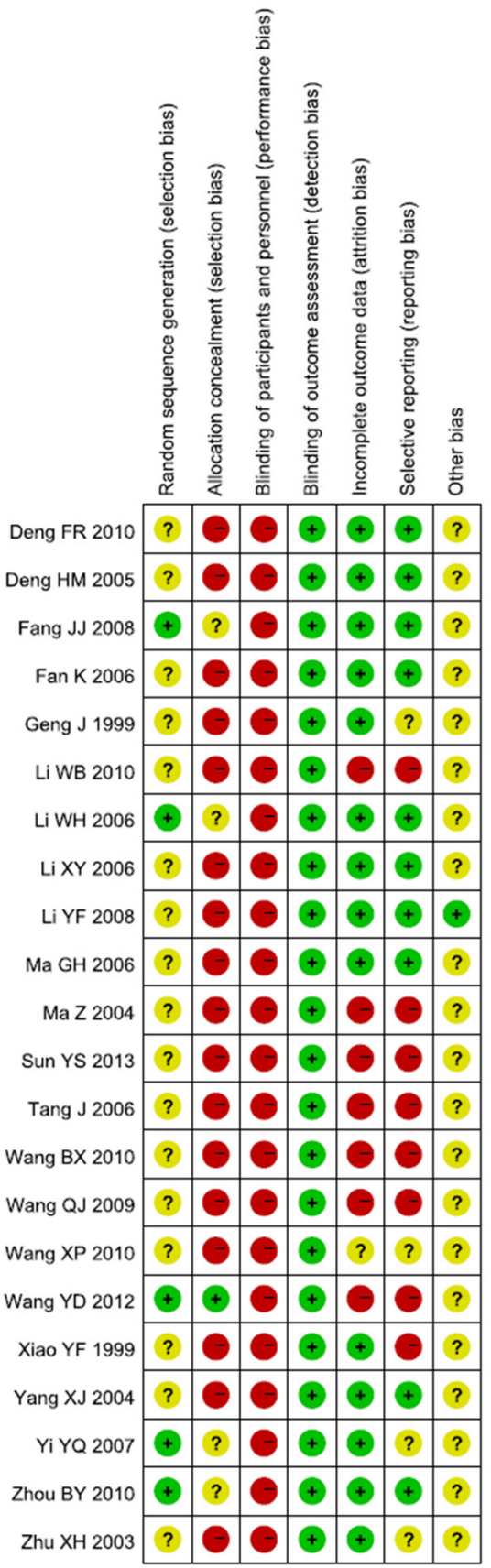

Figure 2. The Cochrane collaboration's tool for assessing risk of bias I. It is a summary of risk of bias, which reviews authors' judgments about risk of bias on each item for each included study.

dosage forms. Ten studies included insignificant data, because the patients were treated with percutaneous coronary intervention (PCI) therapy. Full texts of 277 studies were carefully examined for further eligibility evaluation. Based on the eligibility criteria described in Methods section, 22 studies [15-36] were finally included for quality assessment and meta-analysis.

Study characteristics

The 22 included studies involving 1951 participants suffering from angina pectoris were RCTs published in Chinese between 1999 and 2013. The mean sample size was 88.68, and the follow-up periods were mainly 28 and 30 days.

The dosage of XZD was all one dose, two times daily. Fourteen out of 22 studies used a kind of antianginal drugs named xiaoxintong (XXT) in control group, which is made of isosorbidedinitrate. The dosage of XXT was 30 mg daily in eleven studies, and another three studies did not report the dosage. Isosorbidemononitrate tablets were used in five studies. Three out of the studies adopted a daily dose of 40 mg, and others respectively adopted 60 mg and 30 mg daily. One out of 22 studies used isosorbidedinitrate tablets adopting a daily dose of 30 mg, and another one used nitroglycerin adopting a daily dose of 10 mg. Another one study did not provide enough information about nitrates in control group.

Twenty-one of the included studies employed symptoms changes and sixteen employed ECG changes as primary outcomes. Secondary outcomes, such as blood lipid, blood rheology and other symptoms, were available in 10 out of 22 (45.45%) studies. Other symptoms include chest distress, palpitation, asthma, etc.

The details of included trials were presented in **Table 1**.

Risk of bias within studies

The average CONSORT 2010 checklist score of the 22 included studies was 16.14, thus the

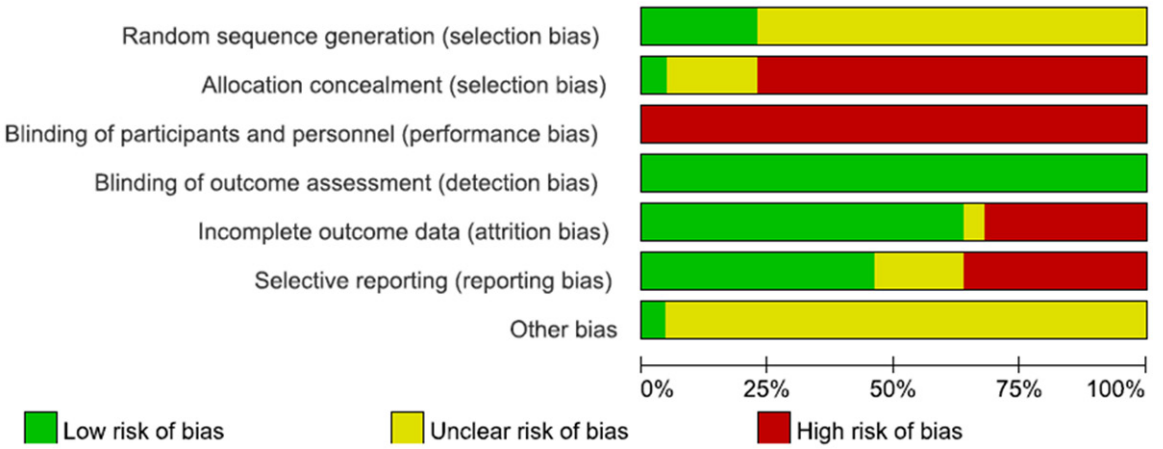

Figure 3. The Cochrane collaboration's tool for assessing risk of bias II. It is a risk of bias graph, which reviews authors' judgments about risk of bias of each item, presented as percentages across all included studies.

overall CONSORT compliance rate (i.e. average checklist score/total number of items) was (16.14/37) 43.62%, indicating 43.62% of all items on average were satisfactorily reported. The score of each item in CONSORT 2010 checklist showed the included studies mainly lacked of information about (1) allocation concealment mechanism, implementation, and blinding in randomization section (No. 9-11 items); (2) limitations and generalizability in discussion section (No. 20-21 items); and (3) other information section (No. 23-25 items).

The Cochrane collaboration's tool for assessing risk of bias was used to measure the quality of the 22 included studies (**Figures 2** and **3**). Green, red, and yellow icon respectively represented low risk of bias, high risk of bias, and unclear. Obviously, the risk of performance bias was high in all the included studies, and the majority of the studies got high selection bias. Most studies had low risks of detection bias, attrition bias and reporting bias. In addition, the risks of selection bias and other bias were unclear in most of the included studies.

Results of individual studies

Table 1 presented the results of individual studies included primary outcomes, secondary outcomes, quality of reporting based on CONSORT compliance rate (CCR, i.e. checklist score of each study/total number of items), and adverse events.

Risk ratios were more than 1.0 in 19 out of 21 studies employing symptoms changes as primary outcomes, indicating 19 out of 21 (90.48%) studies reported that XZD was more effective than nitrates in treating angina pectoris based on symptomatic improvement. Risk ratios were more than 1.0 in 15 out of 16 studies employing ECG changes as primary outcomes, indicating 15 out of 16 (93.75%) studies reported that XZD was more effective than nitrates in treating angina pectoris based on ECG improvement. XZD also benefited blood lipid, blood rheology and other symptoms such as chest distress, palpitation and asthma according to 10 out of 22 studies providing secondary outcomes.

Seeing that the overall CONSORT compliance rate of the included studies was 43.62%, we assessed the quality of reporting as (1) medium if CCR was 43.62±5%; (2) good if CCR was higher than 48.62%; and (3) poor if CCR was lower than 38.62%. In the 22 included studies, five studies were assessed as good, thirteen studies were assessed as medium, and four studies were assessed as poor.

Only 7 out of 22 included studies reported adverse effects. Five studies indicated that no adverse effects were observed. One study reported three patients in nitrates group got headache and dizziness, and another one reported two patients in XZD group got loose stool but the symptoms disappeared after adding citrus and salvia to XZD. According to the reported adverse effects, the adverse effects of XZD appeared to be milder than nitrates as the patients much easier recovered. To ensure the safety of XZD, further RCTs reporting adverse effects needed to be provided.

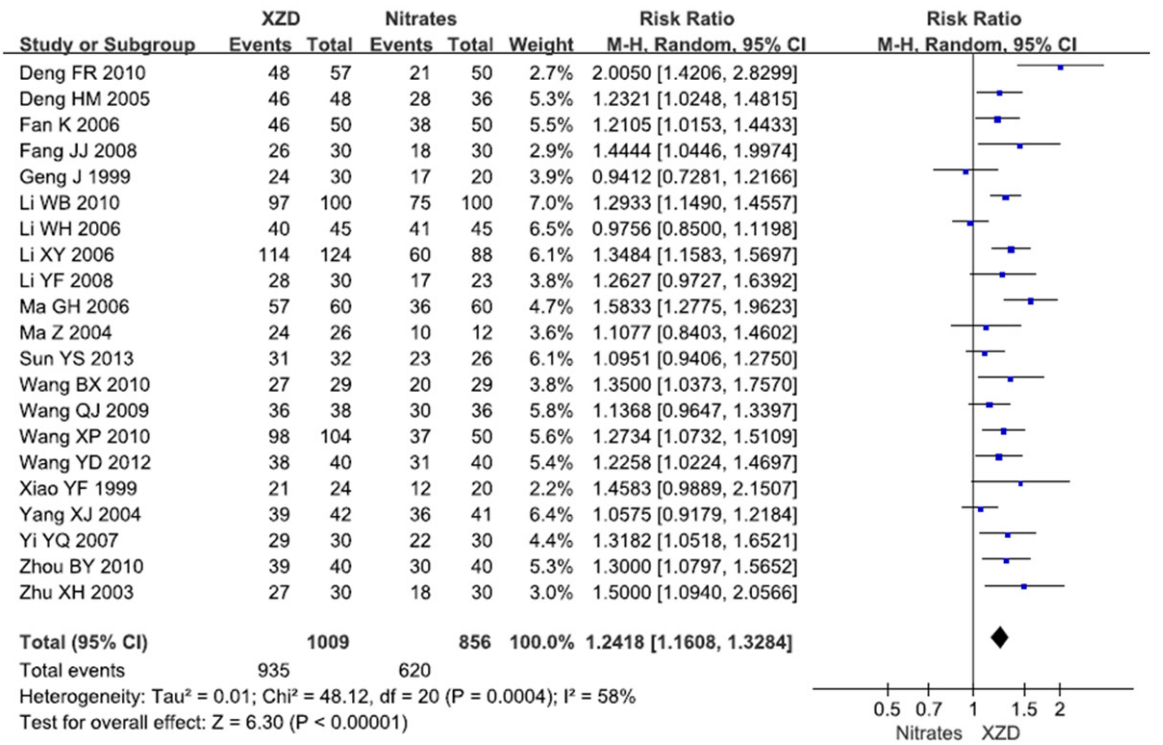

Figure 4. The forest plot of outcome measure symptoms.

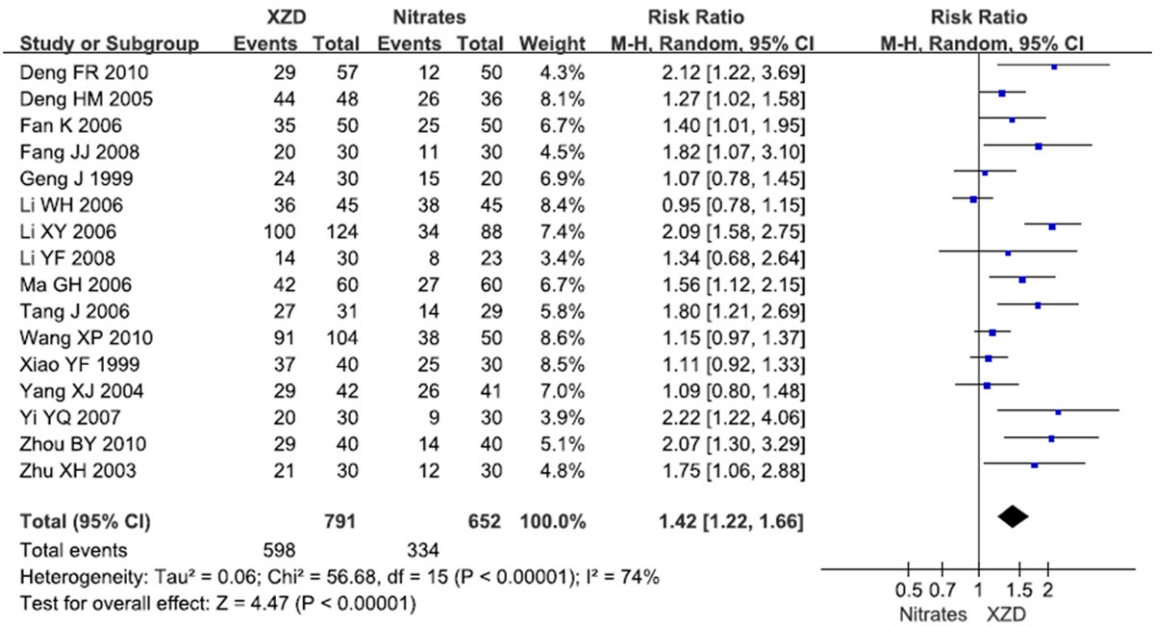

Figure 5. The forest plot of outcome measure ECG.

Syntheses of results

Figure 4 showed an overall risk ratio of 1.24 (95% CI 1.16-1.33, Z=6.30, P<0.00001) with a significant heterogeneity (I^2=58%, Tau^2=0.01, Chi^2=48.12, df=20, P=0.0004) among the 21 studies with symptoms as outcome. **Figure 5** showed an overall risk ratio of 1.42 (95% CI 1.22-1.66, Z=4.47, P<0.00001) with a significant heterogeneity (I^2=74%, Tau^2=0.06, Chi^2=

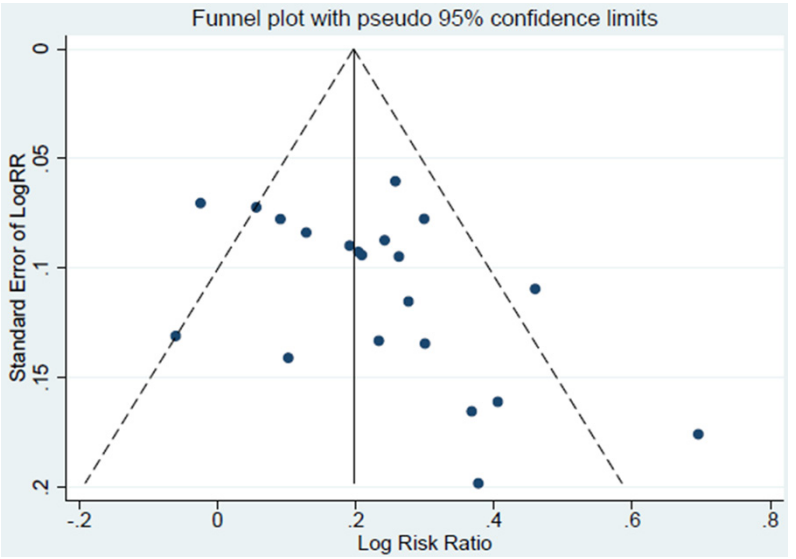

Figure 6. The funnel plots of the included studies with symptomatic data.

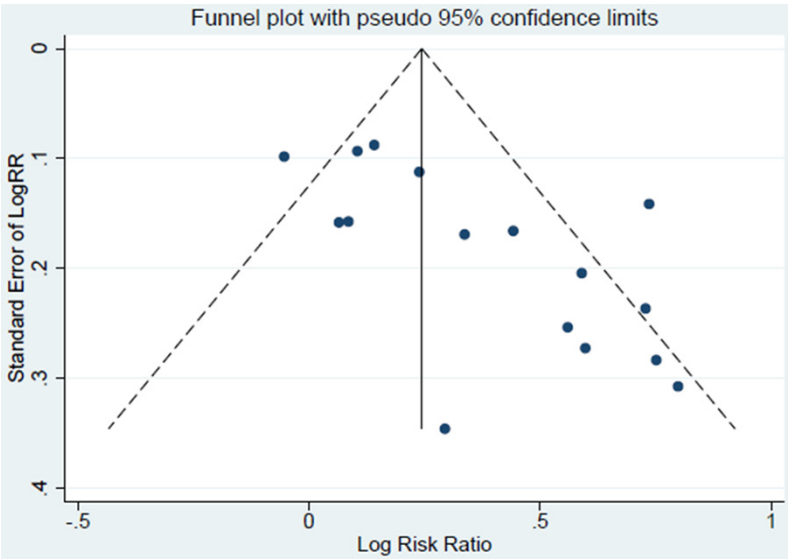

Figure 7. The funnel plots of the included studies with ECG data.

56.68, df=15, *P*<0.00001) among the 16 studies with ECG as outcome. The results of meta-analysis in the included studies indicated that XZD was more effective than nitrates in treating angina pectoris.

Risk of bias across studies

Publication biases of major outcomes of symptoms and ECG were assessed by funnel plots (**Figures 6** and **7**) showing little asymmetries in the plots. For symptoms, there was no significant publication bias assessed by Begg's test (*Z*=0.60, *P*=0.546) and Egger's test (*t*=-0.86, *P*=0.399). For ECG, there was also no significant publication bias assessed by Begg's test (*Z*=1.40, *P*=0.162) and Egger's test (*t*=1.02, *P*=0.326). *P* values higher than 0.05 were considered no significant publication bias.

The analysis of publication bias indicated that the evidence for the overall efficacy of XZD over nitrates was conclusive.

Additional analyses

Subgroup analysis was performed on sample sizes and follow-up periods of symptoms (**Table 2**) and ECG (**Table 3**) to investigate specific factors affecting the overall effect.

The mean sample size of the 22 included studies is 88.68, lower than 134 which is the adequate sample size calculated by an alpha of 0.05, a power of 0.8, proportions of 0.756 for experimental group and 0.512 for control group using PASS (Power Analysis and Sample Size) software version 13. The studies were divided into two subgroups by samples sizes to obtain (1) approximately equal numbers of studies (n<80 and n≥80 of symptoms, n≤80 and n>80 of ECG), (2) approximately equal number of participants (n<100 and n≥100), and (3) adequate sample sizes (n≥134) in one subgroup and inadequate sample sizes (n<134) in the other subgroup. Only 3 out of 22 (13.64%) studies satisfied the sample size requirement. The largest difference between risk ratios among the subgroups with different sample sizes was found in subgroups of approximately equal number of par-

Table 2. Subgroup analysis based on symptoms

Group		No. of studies	No. of participants	RR	95% CI	Overall effect		Heterogeneity				
						Z	P	Tau^2	Chi^2	df	P	I^2
Sample Size	<80	10	555	1.21	1.10,1.32	4.09	<0.0001	0.01	12.52	9	0.19	28%
	≥80	11	1310	1.26	1.15,1.39	4.74	<0.00001	0.02	35.10	10	0.0001	72%
	<100	15	972	1.18	1.10,1.26	4.54	<0.00001	0.01	23.68	14	0.05	41%
	≥100	6	893	1.37	1.23,1.52	5.81	<0.00001	0.01	10.42	5	0.06	52%
	<134	18	1299	1.23	1.14,1.34	5.01	<0.00001	0.02	45.47	17	0.00002	63%
	≥134	3	566	1.30	1.20,1.42	6.36	<0.00001	0.00	0.28	2	0.87	0%
Follow-up	<28	5	511	1.31	1.20,1.42	6.14	<0.00001	0.00	1.26	4	0.87	0%
Periods (day)	[28, 30]	11	944	1.25	1.11,1.40	3.77	0.0002	0.02	34.00	10	0.0002	71%
	>30	3	270	1.12	0.96,1.32	1.40	0.16	0.01	5.67	2	0.06	65%
	<30	9	788	1.23	1.12,1.34	4.46	<0.00001	0.01	13.30	8	0.1	40%
	≥30	10	937	1.25	1.11,1.41	3.63	0.0003	0.03	35.43	9	<0.0001	75%

The overall efficacy was meta-analyzed for different sample sizes and different follow-up periods. *Z* and *P* (overall effect) evaluated the statistics of overall effect; Tau^2, Chi^2, df, *P* (heterogeneity), and I^2 were computed to assess heterogeneity. Sample size of 134 was set to achieve a power of 0.8. RR is risk ratio; CI is confidence interval.

Table 3. Subgroup analysis based on ECG

Group		No. of studies	No. of participants	RR	95% CI	Overall effect		Heterogeneity				
						Z	P	Tau^2	Chi^2	df	P	I^2
Sample Size	≤80	8	493	1.53	1.19,1.99	3.26	0.001	0.09	22.26	7	0.002	69%
	>80	8	950	1.35	1.10,1.66	2.84	0.005	0.07	34.23	7	<0.0001	80%
	<100	11	750	1.34	1.12,1.61	3.24	0.001	0.05	31.17	10	0.0006	68%
	≥100	5	693	1.57	1.18,2.10	3.07	0.002	0.08	18.49	4	0.001	78%
	<134	14	1077	1.40	1.19,1.64	4.10	<0.0001	0.05	39.33	13	0.0002	67%
	≥134	2	366	1.54	0.80,2.97	1.28	0.2	0.21	16.24	1	<0.0001	94%
Follow-up	<28	4	337	1.18	1.02,1.37	2.22	0.03	0.00	3.73	3	0.29	20%
Periods (day)	[28, 30]	8	776	1.50	1.22,1.85	3.81	0.0001	0.06	21.41	7	0.003	67%
	>30	2	190	1.13	0.74,1.71	0.57	0.57	0.07	4.77	1	0.03	79%
	<30	8	614	1.19	1.08,1.31	3.41	0.0006	0.00	7.44	7	0.38	6%
	≥30	6	689	1.56	1.12,2.18	2.61	0.009	0.14	33.35	5	<0.00001	85%

The overall efficacy was meta-analyzed for different sample sizes and different follow-up periods. *Z* and *P* (overall effect) evaluated the statistics of overall effect; Tau^2, Chi^2, df, *P* (heterogeneity), and I^2 were computed to assess heterogeneity. Sample size of 134 was set to achieve a power of 0.8. RR is risk ratio; CI is confidence interval.

ticipants (n<100 and n≥100) both of symptoms and ECG.

As the follow-up periods were mainly 28 and 30 days, the studies were divided into subgroups by different follow-up periods. It is visible that differences between risk ratios among the subgroups with different follow-up periods of symptoms were much smaller than those of ECG. Compared with subgroups with different sample sizes both of symptoms and ECG, there were also more differences between risk ratios among the subgroups with different follow-up periods of ECG.

The subgroup analysis showed that the overall efficacy of XZD over nitrates was still significantly positive even with different sample sizes and different follow-up periods.

Discussion

The meta-analysis of the 22 included RCTs suggests a result that XZD might be more effective

than nitrates in treating angina pectoris with statistical significance. Publication biases were not significant. Subgroup analysis on sample sizes and follow-up periods also shows the consistent result.

This article is the most reliable systematic review because (1) our conduct follows PRISMA requirements; (2) all included studies are RCTs; (3) our study selection does not allow combined use of drugs in experimental groups and nitrates are not used in combination with other antianginal drugs in control groups; (4) each included studies' quality of reporting is evaluated according to CONSORT 2010 checklist in detail; (5) all kinds of risks of bias are assessed by the Cochrane collaboration's tool for assessing risk of bias in each study, while previous reviews used Jadad scale instead, which was not recommended to use considering its deficiencies listed in *Cochrane handbook for systematic reviews of interventions version 5.1.0.*; and (6) subgroup analysis is conducted to avoid possible biases of specific groups of studies.

Although this article is reliable, it is not without limitations. The quality of the RCTs is the main limitation. The study found most of the RCTs were of low or medium quality. The overall rate of compliance with the CONSORT 2010 checklist was 43.62%. According to the Cochrane collaboration's tool for assessing risk of bias, some risks of bias including performance bias and selection bias were high. Briefly, higher quality RCTs are required to further support the efficacy of XZD.

The heterogeneity of the included studies is another limitation. The heterogeneities of overall effects on symptoms and ECG were moderately high. Most of the heterogeneities remained high even subgroups of different sample sizes and different follow-up periods were assessed.

There are some other limitations of this article. The mean sample size of 100.91 did not satisfy the sample size requirement of 134. More than half of the studies did not report the adverse effects in detail, and adequate information on the safety of XZD was not provided. Furthermore, the included studies were all reported in Chinese with Chinese patients.

To sum up, further RCTs of higher quality, larger scale, longer follow-up periods and multi-country are still required to verify the efficacy of XZD compared with the most common therapy in treating angina pectoris.

Conclusions

Although a consistent result that XZD might be more effective than nitrates in treating angina pectoris is presented in this study, further RCTs of higher quality, larger scale, longer follow-up periods and multi-country are still required to identify the efficacy of XZD.

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Disclosure of conflict of interest

None.

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