

# Were Traditional Chinese Medicine Injections Efficacious for Angina Pectoris? A Frequentist Network Meta-Analysis of Randomized Controlled Trials

**Guoying Gao**

University of Macau

**Siu-wai Leung**

University of Macau

**Yongliang Jia** (✉ [gentrany@gmail.com](mailto:gentrany@gmail.com))

University of Macau <https://orcid.org/0000-0002-4981-9282>

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## Original investigation

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# Abstract

**Background:** The efficacy of traditional Chinese medicine injections (TCMIs) for angina pectoris has never been well investigated for lacking quality assessment of evidence. This study aimed to conduct a comprehensive and rigorous network meta-analysis and assess the quality of evidence according to the Grading of Recommendations and Assessment, Development, and Evaluation (GRADE) approach to compare the efficacy of all TCMIs in treating angina pectoris.

**Methods:** Following the protocol (reference: CRD42018117720), randomized controlled trials (RCTs) which compared one TCMI with another TCMI or conventional treatments on anginal outcome measures (i.e. symptomatic improvement, electrocardiography improvement, symptomatic recovery, and electrocardiography recovery) were included. The risk of bias among included RCTs was assessed with the revised Cochrane's risk of bias tool 2. Frequentist statistical analyses including subgroup analysis, sensitivity analysis, meta-regression and publication bias analysis were performed. The certainty of evidence was assessed with the GRADE approach.

**Results:** Totally, 475 RCTs including all 24 TCMIs were identified, while the quality of all but two included RCTs was poor. According to the network meta-analysis, Honghua (Safflower) injection were preferable both in improving symptoms and electrocardiography. However, significant inconsistency showed the intransitivity among indirect comparisons, results in network meta-analysis seemed thus not trustworthy. The quality of evidence was assessed as low or very low.

**Conclusions:** The low-quality evidence reduced the confidence in the efficacious results. Current evidence hardly supports the beneficial effects of TCMIs in treating angina pectoris.

## 1. Introduction

Angina pectoris represents the clinical manifestation of temporary myocardial ischemia resulting from the insufficient coronary blood supply [1]. Patients suffer from episodes of pain or discomfort in the chest which could spread to the back, shoulder, the lower jaw or fingers lasting for several minutes [2]. It was estimated that angina pectoris affected 3.6% of population in China [3]. Guidelines recommended first-line agents including beta-blockers (e.g., metoprolol), calcium channel blockers (e.g., verapamil), and nitrates (e.g., nitroglycerin) as conventional treatments for ischemia relief [4, 5]. In China, traditional Chinese medicines (TCM) are commonly used as complementary or alternative therapy in treating angina pectoris [6, 7].

Traditional Chinese medicine injections (TCMIs) are prepared by extracting active substances from the single herb or the herbal medicine compounds [8]. With a rapid onset and high bioavailability, TCMIs have an advantage for the management of circulatory diseases [9]. The sales of TCMIs for cardio-cerebrovascular diseases have reached over 10 billion dollars in 2016, accounting for two thirds whole market of TCMIs in hospital [10]. China's National Medical Products Administration (NMPA) has approved twenty-four TCMIs for angina pectoris (Supplement 2), including seven of the top 10 sales of TCMIs [10, 11].

Network meta-analysis evaluates comparative efficacy by synthesizing direct and indirect evidence of multiple treatments [12]. Without the restriction for head-to-head comparisons, network meta-analysis has become increasingly employed to recommend the optimal treatments in healthcare decision-making. Nevertheless, clinicians not only balanced the benefits and risks of the intervention, but also considered the certainty of efficacy estimates [13]. Quality of evidence indicates the confidence of estimates of treatment effects [14]. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach [15] was developed to rate the quality of evidence and extended to the network meta-analysis [16, 17].

NMPA urged to re-evaluate the overall performance of TCMIs in 2018 [18], thus, it is more pressing to evaluate the efficacy. Currently, two network meta-analyses have respectively compared the efficacy of four *Salvia miltiorrhiza* injectable preparations for unstable angina[19], and the efficacy of eight TCMIs for angina pectoris[20], while the lack of quality assessment of evidence in both network meta-analyses [19, 20] not only was non-compliant with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement[21, 22] but also weakened the strength of informing the healthcare recommendations. As the evidence from the previous network meta-analyses[19, 20] was limited by lacking quality assessment of the evidence and selectively including TCMIs, we conducted a comprehensive and rigorous meta-analysis in accordance with the PRISMA statements[21–23] to evaluate the efficacy of all TCMIs in treating angina pectoris.

## 2. Methods

This study was registered in PROSPERO with the registered number CRD42018117720[24]. We conducted this network meta-analysis according to the protocol [24, 25] and the PRISMA statements [21–23].

### 2.1 Literature search and study selection

We searched studies using TCMI for angina pectoris to end of November 2019 in PubMed, the Cochrane Library, Embase, Web of Science, ScienceDirect, China National Knowledge Infrastructure Library (CNKI), Wanfang Data, ClinTrials.gov. Chinese databases (i.e. CNKI and Wanfang data) were searched with the combination of the TCMI and angina pectoris in title or abstract. The full-text search with the TCMI's synonyms was performed in English databases. We included RCTs in adults which were head-to-head comparisons of selected TCMI, or comparing with conventional treatments, and included RCTs were required to report symptomatic improvement (SYM-I), symptomatic recovery (SYM-R) or electrocardiography improvement (ECG-I), electrocardiography recovery (ECG-R). Definitions of outcome measures were in accordance with guidelines for clinical research of TCMs or cardiovascular drugs [26, 27].

## 2.2 Data extraction and quality assessment

Two authors (G Gao and Y Jia) independently extracted data and compared results. Data items were extracted as follows: (a) the first author, (b) number of authors, (c) years of publication, (d) type of angina, (e) drugs and their dosages, (f) outcome data, (g) sample sizes, (h) follow-up periods, (i) gender proportions, (j) average ages, (k) methods of random sequence generation, (l) allocation concealment, (m) blinding methods.

Two authors (G Gao and Y Jia) independently assessed the quality of eligible RCTs according to the revised Cochrane's risk of bias tool for randomized trials (RoB 2) [28] with discrepancies resolved by consulting the third author (SW Leung). The RoB 2 was the structural approach to set a series of signalling questions for five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, the selection of the reported result). Following the algorithm based on answers to signalling questions, we judged each domain as low risk, some concerns or high risk. The overall risk of bias was determined by the lowest judgment in any of the domains [28].

## 2.3 Data analysis

We selected a random-effects model [29] to perform the pairwise meta-analysis and network meta-analysis with the R software (version 3.3.3) [30]. For each outcome measure, the treatment effect was presented as odds ratios (ORs) and 95% confidence intervals (CIs). Frequentist pairwise meta-analysis was conducted with the R package "metafor" [31]. Study heterogeneity was assessed by the statistic of I-square ( $I^2$ ) [32]. For groups including at least 5 RCTs, we performed subgroup analysis, sensitivity analysis and meta-regression based on study characteristics and RCT quality. Publication bias was investigated with the funnel plot [33], Begg's rank correlation test [34], Egger's regression test [35], the trim-fill methods [36] and the Copas methods [37]. A  $p$ -value < 0.05 was considered statistically significant.

Frequentist network meta-analysis on each outcome measure was conducted using the R package "netmeta" [38]. The ranking of treatments was determined by the P-score, and P-score from 1 to 0 indicated the treatment effects decreased [39]. Inconsistency in network meta-analysis was assessed by total Q statistics which was composed of heterogeneity Q of within designs and inconsistency Q of between designs. Local inconsistency was explored by the node-splitting approach [40], and highlighted in the heat graph [41]. Besides, subgroup and sensitivity analyses based on study characteristics and RCT quality were performed to determine the preferable treatments on each outcome measure (Supplement 10).

## 2.4 Evaluation of evidence quality

According to the GRADE approach [15–17], the quality of evidence on each outcome measure was assessed as high, moderate, low, or very low. The initial evidence from RCTs was "high", then would rate down in five reasons (high risk of bias, imprecision, inconsistency, indirectness, or publication bias) [15]. We downgraded the quality of evidence by high risk of bias (i.e. low quality of RCTs), imprecision (i.e. the 95% CI covering the threshold 1, the number of included studies less 5), inconsistency (i.e.  $I^2 > 30\%$ , significant difference in subgroup analysis), or publication bias (i.e. statistically significant results of Begg's or Egger's test). The initial quality of indirect evidence was determined by the lower quality between pieces of direct evidence having the common comparator, then we downgraded the indirect evidence by imprecision whose 95% CI covered the threshold 1. The certainty of evidence from network meta-analysis depended on the higher quality between the direct and indirect efficacy evidence [16, 17].

## 3. Results

### 3.1 475 RCTs for inclusion

A total of 12654 records were identified through database searching. After removing duplicates and ineligible records, 475 RCTs ( $n = 48511$ ) with all 24 TCMI were finally included in this study (Supplement 3), of which 102 RCTs were head-to-head comparisons of TCMI, 373 RCTs compared the TCMI with convention treatments. All included studies were published in Chinese between 2000 and 2019. The sample size ranged from 30 to 789, the average sample size was 102.13, and the median sample size was 86. The follow-up periods ranged from 7 days to 60 days with a median of 14 days (Supplement 4).

### 3.2 High risk of bias among included RCTs

As Fig. 1 showed, the overall risk of bias across included RCTs was high. Two RCTs [42, 43] were judged to be at low risk of bias. Three RCTs [44–46] had some concerns about the overall risk of bias considering the potential bias in selection of the reported result. Other 470 RCTs failed to describe detailed randomization, blinding methods, the change of the number of participants from initial to completing trials, the pre-specific trial protocol or statistical analysis plan, leading to the overall high risk of bias (Supplement 5). The proportion of the high risk of bias in five domains was 99.5% (randomization process), 87.79% (deviations from intended interventions), 87.79% (missing outcome data), 98.95% (measurement of the outcome), and 53.68% (the selection of the reported result).

## **3.3 Results of pairwise meta-analysis**

### **3.3.1 Efficacious overall effect sizes**

Twenty-seven pairwise meta-analyses including 19 TCMIIs compared with conventional treatments and 8 TCMIIs of head-to-head comparisons were conducted on symptomatic outcome data (Table 1). Twenty-eight pairwise meta-analyses including 17 comparisons of conventional treatments and 11 head-to-head comparisons were conducted on electrocardiography outcome data (Table 2). Results showed the interventions of treatment groups always more efficacious than comparators.

Table 1  
Results of pairwise meta-analysis on symptomatic outcomes

Intervention - comparator	No. of studies	Participants(n)	SYM-I				SYM-R			
			I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)	I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)
DSDf-CT	17	1528	0	0.9999	<b>4.37 (3.17, 6.02)</b>	< 0.0001	0	0.9967	<b>2.35 (1.89, 2.92)</b>	< 0.0001
DSDf-DH	2	161	22.08	0.2573	2.62 (0.82, 8.45)	0.1058	15.97	0.2753	1.61 (0.80, 3.23)	0.1842
DSDf-DS	7	1192	0	0.9939	<b>3.68 (2.75, 4.92)</b>	< 0.0001	0	0.7447	<b>1.80 (1.42, 2.30)</b>	< 0.0001
CWJ-DS	2	118	0	0.5462	<b>4.76 (1.79, 12.66)</b>	0.0018	0	0.8002	2.33 (0.76, 7.12)	0.1371
DS-CT	9	1046	0	0.7607	<b>3.60 (2.42, 5.33)</b>	< 0.0001	5.58	0.6335	<b>1.82 (1.38, 2.38)</b>	< 0.0001
HHH-CT	13	1370	0	0.9154	<b>4.14 (2.98, 5.76)</b>	< 0.0001	0	0.9418	<b>1.95 (1.56, 2.43)</b>	< 0.0001
HHH-DS	3	388	0	0.9743	<b>4.65 (2.45, 8.82)</b>	< 0.0001	0	0.9145	<b>2.58 (1.71, 3.91)</b>	< 0.0001
DZH-CT	7	651	0	0.9022	<b>3.41 (2.11, 5.51)</b>	< 0.0001	0	0.8003	<b>2.19 (1.59, 3.02)</b>	< 0.0001
HJT-CT	5	614	0	0.9457	<b>4.37 (2.80, 6.81)</b>	< 0.0001	0	0.8514	<b>1.88 (1.31, 2.69)</b>	0.0006
GLP-CT	2	220	0	0.4956	<b>2.60 (1.36, 4.95)</b>	0.0038	27.03	0.2417	1.69 (0.87, 3.30)	0.1241
GXN-CT	12	1267	0	0.9594	<b>4.39 (3.06, 6.30)</b>	< 0.0001	0	0.8294	<b>1.59 (1.26, 2.00)</b>	< 0.0001
DZXX-CT	16	1480	0	0.7467	<b>3.22 (2.36, 4.40)</b>	< 0.0001	41.25	0.0594	<b>1.88 (1.40, 2.53)</b>	< 0.0001
DZXX-DS	5	443	0	0.7830	<b>2.67 (1.63, 4.38)</b>	0.0001	0	0.7610	<b>1.79 (1.20, 2.66)</b>	0.0041
SM-CT	10	770	0	0.9496	<b>3.61 (2.47, 5.28)</b>	< 0.0001	0	0.9168	<b>2.22 (1.62, 3.03)</b>	< 0.0001
SM-DS	3	220	18.29	0.1910	<b>6.98 (2.83, 17.25)</b>	< 0.0001	32.61	0.2996	<b>4.11 (1.77, 9.54)</b>	0.0010
SXN-CT	12	1446	10.22	0.5973	<b>5.69 (3.98, 8.13)</b>	< 0.0001	48.05	0.0291	<b>2.62 (1.89, 3.63)</b>	< 0.0001

Text in bold indicated significant statistical results.

CI, confidence interval; CT, conventional treatments; CWJ, Ciwujia injection; DH, Danchong injection; DS, Danshen (Salvia miltiorrhiza) injection; DSDf, Danshenduofofen (Salvianolate) injection; DZH, Dengzhanhuasu (Breviscapine) injection; DZXX, Dengzhanxixin (Erigeron breviscapus) injection; GLP, Gualoupi (Pericarpium Trichosanthis) injection; GXN, Guanxinning injection; HH, Honghua (Safflower) injection; HHH, Honghua huangsesu (Safflower yellow) injection; HJT, Hongjingtian (Rhodiola) injection; HQ, Huangqi (Astragalus) injection; KDZ, Kudiezi injection; OR, odds ratio; SF, Shenfu injection; SM, Shenmai injection; SGM, Shengmai injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; SYM-I, symptomatic improvement; SYM-R, symptomatic recovery; XD, Xiangdan injection; XML, Xinmailong injection; XST, Xuesaitong injection.

Intervention - comparator	No. of studies	Participants(n)	SYM-I				SYM-R			
			I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)	I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)
SXT-DS	23	1784	37.29	0.0581	<b>3.15 (2.21, 4.48)</b>	< 0.0001	17.06	0.2141	<b>1.66 (1.33, 2.07)</b>	< 0.0001
SGM-CT	4	244	0	0.9405	<b>3.45 (1.66, 7.17)</b>	0.0009	0	0.6357	<b>2.73 (1.59, 4.67)</b>	0.0003
HQ-CT	2	153	0	0.6492	<b>3.93 (1.74, 8.87)</b>	0.0010	60.29	0.1126	2.98 (0.88, 10.09)	0.0791
KDZ-CT	8	736	0	0.8688	<b>4.79 (3.07, 7.43)</b>	< 0.0001	0	0.5737	<b>2.03 (1.48, 2.78)</b>	< 0.0001
DH-CT	101	9725	5.6	0.9203	<b>4.05 (3.55, 4.62)</b>	< 0.0001	0	0.8894	<b>1.98 (1.81, 2.15)</b>	< 0.0001
DH-DS	2	290	0	0.4721	<b>4.52 (2.23, 9.13)</b>	< 0.0001	62.01	0.1047	<b>2.63 (1.10, 6.29)</b>	0.0293
HH-CT	3	214	0	0.9194	<b>4.86 (2.09, 11.29)</b>	0.0002	0	0.9184	<b>2.56 (1.46, 4.47)</b>	0.0010
HH-DS	2	186	50.92	0.1535	3.36 (0.35, 32.46)	0.2956	0	0.5866	<b>4.75 (2.32, 9.72)</b>	< 0.0001
SXT-CT	14	1491	0	0.9179	<b>4.18 (3.00, 5.84)</b>	< 0.0001	28.76	0.1694	<b>2.25 (1.72, 2.93)</b>	< 0.0001
XML-CT	2	122	0	0.8514	<b>8.21 (1.41, 47.66)</b>	0.0190	0	0.4414	<b>2.86 (1.34, 6.11)</b>	0.0068
SF-CT	3	193	0	0.9884	<b>3.00 (1.41, 6.37)</b>	0.0042	0	0.9947	1.80 (0.93, 3.47)	0.0794
Text in bold indicated significant statistical results.										
CI, confidence interval; CT, conventional treatments; CWJ, Ciwujia injection; DH, Danhong injection; DS, Danshen (Salvia miltiorrhiza) injection; DSDF, Danshenduofen (Salvianolate) injection; DZH, Dengzhanhuasu (Breviscapine) injection; DZXX, Dengzhanxixin (Erigeron breviscapus) injection; GLP, Gualoupi (Pericarpium Trichosanthis) injection; GXN, Guanxinning injection; HH, Honghua (Safflower) injection; HHH, Honghua huangsesu (Safflower yellow) injection; HJT, Hongjingtian (Rhodiola) injection; HQ, Huangqi (Astragalus) injection; KDZ, Kudiezi injection; OR, odds ratio; SF, Shenfu injection; SM, Shenmai injection; SGM, Shengmai injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; SYM-I, symptomatic improvement; SYM-R, symptomatic recovery; XD, Xiangdan injection; XML, Xinmailong injection; XST, Xuesaitong injection.										

Table 2  
Results of pairwise meta-analysis on electrocardiographic outcomes

Intervention-comparator	No. of studies	Participants(n)	ECG-I				ECG-R			
			I <sup>2</sup> (%)	p (I <sup>2</sup> )	OR (95% CI)	p (OR)	I <sup>2</sup> (%)	p (I <sup>2</sup> )	OR (95% CI)	p (OR)
DSDf-CT	10	813	0	0.9403	<b>3.23 (2.26, 4.62)</b>	< 0.0001	0	0.9724	<b>1.62 (1.20, 2.18)</b>	0.0016
DSDf-DS	4	402	60.31	0.0273	<b>3.51 (1.69, 7.27)</b>	0.0007	0	0.5317	<b>1.98 (1.20, 3.28)</b>	0.008
DS-CT	3	525	0	0.7626	<b>3.46 (2.28, 5.24)</b>	< 0.0001	42.06	0.1873	<b>1.85 (1.09, 3.15)</b>	0.0257
HHH-CT	9	987	54.79	0.0100	<b>3.13 (1.86, 5.29)</b>	< 0.0001	38.31	0.1457	<b>2.00 (1.41, 2.83)</b>	0.0001
HHH-DS	6	1395	0	0.9333	<b>2.92 (2.29, 3.72)</b>	< 0.0001	35.59	0.2076	<b>2.11 (1.49, 3.00)</b>	< 0.0001
HHH-XD	4	718	0	0.7620	<b>1.47 (1.05, 2.05)</b>	0.0252	0	0.7328	<b>1.86 (1.10, 3.14)</b>	0.0201
DZH-CT	8	650	0	0.8571	<b>2.55 (1.72, 3.76)</b>	< 0.0001	0	0.9787	<b>2.41 (1.70, 3.42)</b>	< 0.0001
HJT-CT	10	1087	0	0.5879	<b>3.14 (2.29, 4.30)</b>	< 0.0001	0	0.7318	<b>1.78 (1.38, 2.29)</b>	< 0.0001
HJT-XD	3	732	0	0.4841	<b>1.64 (1.19, 2.26)</b>	0.0025	0	0.9506	1.21 (0.82, 1.80)	0.3402
GXN-CT	8	780	28.14	0.2063	<b>3.00 (1.97, 4.58)</b>	< 0.0001	0	0.5713	<b>1.92 (1.37, 2.69)</b>	0.0001
DZXX-CT	16	1452	0	0.5523	<b>2.30 (1.82, 2.91)</b>	< 0.0001	1.33	0.4972	<b>1.74 (1.37, 2.20)</b>	< 0.0001
DZXX-DS	6	560	0	0.8964	<b>3.17 (2.16, 4.66)</b>	< 0.0001	0	0.8574	<b>1.92 (1.33, 2.77)</b>	0.0005
DZXX-XD	2	142	0	0.9754	<b>2.07 (1.04, 4.13)</b>	0.0393	0	0.3531	<b>2.64 (1.24, 5.64)</b>	0.0121
SM-CT	6	568	0	0.8554	<b>2.84 (1.93, 4.19)</b>	< 0.0001	0	0.9628	<b>2.16 (1.45, 3.21)</b>	0.0002
SM-DS	2	262	49.99	0.1583	<b>3.28 (1.52, 7.08)</b>	0.0026	0	0.8515	<b>3.35 (1.86, 6.03)</b>	< 0.0001
SXN-CT	27	2806	0	0.9603	<b>3.36 (2.81, 4.01)</b>	< 0.0001	0	0.9195	<b>2.35 (1.97, 2.80)</b>	< 0.0001

Text in bold indicated significant statistical results.

CI, confidence interval; CT, conventional treatments; CWJ, Ciwujia injection; DH, Danchong injection; DS, Danshen (Salvia miltiorrhiza) injection; DSDf, Danshenduofen (Salvianolate) injection; DZH, Dengzhanhuasu (Breviscapine) injection; DZXX, Dengzhanxixin (Erigeron Breviscapus) injection; ECG-I, electrocardiographic improvement; ECG-R, electrocardiographic recovery; GLP, Gualoupi (Pericarpium Trichosanthis) injection; GXN, Guanxinning injection; HH, Honghua (Safflower) injection; HHH, Honghua Huangsesu (Safflower Yellow) injection; HJT, Hongjingtian (Rhodiola) injection; HQ, Huangqi (Astragalus) injection; KDZ, Kudiezi injection; OR, odds ratio; SF, Shenfu injection; SM, Shenmai injection; SGM, Shengmai injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; XD, Xiangdan injection; XST, Xuesaitong injection.

Intervention-comparator	No. of studies	Participants(n)	ECG-I				ECG-R			
			I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)	I <sup>2</sup> (%)	p(I <sup>2</sup> )	OR (95% CI)	p(OR)
SXN- DS	2	108	0	0.8994	<b>2.50 (1.15, 5.45)</b>	0.0213	0	0.9860	2.30 (0.97, 5.45)	0.0584
XST- CT	20	1472	17.48	0.4429	<b>2.63 (1.98, 3.50)</b>	< 0.0001	0	0.8501	<b>1.89 (1.51, 2.38)</b>	< 0.0001
SGM -CT	3	225	0	0.7065	<b>3.12 (1.72, 5.65)</b>	0.0002	0	0.6742	<b>1.93 (1.02, 3.66)</b>	0.0437
HQ-CT	8	685	46.27	0.0732	<b>2.89 (1.72, 4.85)</b>	< 0.0001	0	0.7316	<b>1.95 (1.38, 2.76)</b>	0.0001
HQ-DS	3	302	0	0.6108	<b>2.30 (1.43, 3.69)</b>	0.0006	0	0.6244	<b>1.86 (1.12, 3.10)</b>	0.0168
KDZ- CT	10	829	0	0.9599	<b>2.49 (1.82, 3.41)</b>	< 0.0001	0	0.9830	<b>1.57 (1.16, 2.13)</b>	0.0035
DH- SXT	2	172	0	0.7836	1.47 (0.62, 3.51)	0.3857	0	0.6843	1.35 (0.72, 2.52)	0.3431
DH-CT	41	4059	0	1.0000	<b>2.80 (2.39, 3.28)</b>	< 0.0001	0	0.9164	<b>1.86 (1.63, 2.13)</b>	< 0.0001
HH-CT	2	242	71.29	0.0620	<b>4.30 (1.04, 17.85)</b>	0.0446	87.84	0.0041	2.99 (0.64, 16.66)	0.2122
HH- DS	3	535	0	0.9708	<b>2.23 (1.54, 3.22)</b>	< 0.0001	0	0.8053	<b>1.73 (1.16, 2.59)</b>	0.0070
SXT-CT	4	255	0	0.9760	<b>2.61 (1.31, 5.19)</b>	0.0063	0	0.8703	<b>1.77 (1.07, 2.93)</b>	0.0273
SF - CT	2	120	2.64	0.3108	<b>2.52 (1.00, 6.35)</b>	0.0508	0	0.7946	<b>2.91 (1.12, 7.55)</b>	0.0283

Text in bold indicated significant statistical results.

CI, confidence interval; CT, conventional treatments; CWJ, Ciwujia injection; DH, Danhong injection; DS, Danshen (Salvia miltiorrhiza) injection; DSDL, Danshenduofen (Salvianolate) injection; DZH, Dengzhanhuasu (Breviscapine) injection; DZXX, Dengzhanxixin (Erigeron Breviscapus) injection; ECG-I, electrocardiographic improvement; ECG-R, electrocardiographic recovery; GLP, Gualoupi (Pericarpium Trichosanthis) injection; GXN, Guanxinning injection; HH, Honghua (Safflower) injection; HHH, Honghua Huangsesu (Safflower Yellow) injection; HJT, Hongjingtian (Rhodiola) injection; HQ, Huangqi (Astragalus) injection; KDZ, Kudiezi injection; OR, odds ratio; SF, Shenfu injection; SM, Shenmai injection; SGM, Shengmai injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; XD, Xiangdan injection; XST, Xuesaitong injection.

### 3.3.2 Significant difference of subgroup analysis showed heterogeneity

We conducted subgroup analysis for each outcome measure based on conventional treatments (monotherapy or combinational therapy), types of angina pectoris (unstable, stable or angina pectoris), the mean sample size (> 102.13 or ≤ 102.13), the median sample size (> 86 or ≤ 86), quality of RCTs (the number of domains with high risk of bias > 3 or ≤ 3). Results with significant difference in subgroup analysis were summarized in Table 3. We performed sensitivity analysis by respectively removing RCTs with high risk of bias or some concerns in each domain of RoB 2 [28]. Sensitivity analysis adjusting for included studies did not find significant difference compared with the overall results.

Table 3  
Summary of subgroup with a statistical difference

Intervention-comparator	characteristics	subgroups	No. of studies	outcomes	OR (95% CI)	<i>p</i>	Wilcoxon test
SXN-CT	types of angina	AP	7	SYM-I	4.32 (2.90, 4.95)	< 0.0001	W = 4
		SAP	0		NA	NA	<i>p</i> = 0.0344
		UAP	5		10.53 (5.78, 19.25)	< 0.0001	
SM-CT	mean follow-up period	> 14.83	3	SYM-R	3.13 (1.87, 5.25)	< 0.0001	W = 20
		≤ 14.83	7		1.82 (1.23, 2.69)	< 0.0001	<i>p</i> = 0.0333
DSDF-DS	types of angina	AP	4	SYM-R	1.60 (1.21, 2.13)	0.0011	W = 1
		SAP	3		2.49 (1.56, 3.96)	0.0001	<i>p</i> = 0.0317
		UAP	0		NA	NA	
DZXX-CT	treatments	combination	10	SYM-R	2.18 (1.64, 2.88)	< 0.0001	W = 50
		monotherapy	6		1.40 (0.77, 2.54)	0.2703	<i>p</i> = 0.0343
KDZ-CT	median sample size	≥ 86	4	ECG-R	1.35 (0.88, 2.07)	0.1731	W = 0.5
		< 86	6		1.84 (1.20, 2.83)	0.0056	<i>p</i> = 0.0187
DH-CT	treatments	combination	34	ECG-R	2.66 (1.86, 3.81)	< 0.0001	W = 42
		monotherapy	7		1.76 (1.86, 3.81)	< 0.0001	<i>p</i> = 0.0059

AP, angina pectoris; CI, confidence interval; CT, conventional treatments; DH, Danhong injection; DS, Danshen (*Salvia miltiorrhiza*) injection; DSDF, Danshenduofen (*Salvianolate*) injection; DZXX, Dengzhanxixin (*Erigeron breviscapus*) injection; ECG-R, electrocardiography recovery; KDZ, Kudiezi injection; NA, not applicable; OR, odds ratio; SM, Shenmai injection; SXN, Shuxuening injection; SYM-I, symptomatic improvements; SYM-R, symptomatic recovery.

### 3.3.3 Sample sizes, the average ages and follow-up periods as potential moderators in meta-regression

We conducted the meta-regression on included RCTs that showed the heterogeneity (i.e.  $I^2 > 30\%$  or significant difference among subgroups) based on sample sizes, dosages, averages ages, the proportion of female participants and follow-up periods. Sample sizes, the average ages and follow-up periods seemed to be associated with the efficacy estimates (Table 4), while the impact of average ages on ECG-I of Huangqi (*Astragalus*) injection ( $\beta = -0.0988$ ,  $p = 0.0131$ ) should be carefully interpreted as the average age was a study characteristic rather than an individual characteristic.

Table 4  
The results of meta-regression on groups with statistical heterogeneity

Treatment-comparator	Outcomes	$\beta_1$	$p_1$	$\beta_2$	$p_2$	$\beta_3$	$p_3$	$\beta_4$	$p_4$	$\beta_5$	$p_5$
SXN-CT	SYM-I	0.0037	0.0243*	0.0084	0.3750	-0.0128(10)	0.6884	3.217(11)	0.1072	-0.0971	0.0656
XST-CT	SYM-I	0.0006	0.9186	0.0008	0.2554	0.0006	0.9186	-0.0154	0.5039	-4.0786	0.0634
SM-CT	SYM-R	0.0029	0.7196	-0.0015	0.9049	-0.0882	0.3505	-0.9451	0.7441	-0.1193	0.2238
DSDf-CT	SYM-R	-0.0011	0.3772	-0.0004	0.7963	0.0091	0.7991	3.2246	0.0784	0.1799	0.6544
DZXX-CT	SYM-R	0.0086	0.5968	-0.0461	0.1443	0.0066	0.9054	5.5184	0.4501	0.0602	0.9429
SXN-CT	SYM-R	0.0026	0.4021	0.0203	0.0805	-0.0261	0.5118	0.0349	0.9915	-0.0049	0.9541
HHH-CT	ECG-I	0.0032	0.5691	-0.0046	0.5233	-0.0680	0.2724	0.1480	0.9672	-0.1361	0.0482*
HQ-CT	ECG-I	-0.0154	0.0308*	-0.0145	0.5547	-0.0988	0.0131*	-0.1706	0.9259	0.0001	0.9880
HHH-CT	ECG-R	0.0039	0.2191	-0.0033	0.5134	-0.0039	0.9282	-3.6930	0.1286	-0.0630	0.1906
HHH-DS	ECG-R	0.0015	0.0607	0.0041	0.4838	6.2020	0.0560	-0.0737	0.7121	NA	NA
KDZ-CT	ECG-R	-0.0077	0.4225	-0.0102	0.5962	-0.0091(8)	0.7972	2.3411(9)	0.2366	-0.3712	0.4601
DH-CT	ECG-R	0.0000	0.9926	0.0063	0.5684	0.0165(37)	0.2948	0.3299(40)	0.7717	0.0992	0.0673
CT, conventional treatments; DH, Danhong injection; DS, Danshen ( <i>Salvia miltiorrhiza</i> ) injection; DSDf, Danshenduofen ( <i>Salvianolate</i> ) injection; DZXX, Dengzhanxixin ( <i>Erigeron breviscapus</i> ) injection; ECG-I, electrocardiography improvement; ECG-R, electrocardiography recovery; HHH, Honghuang huangsesu ( <i>Safflower yellow</i> ) injection; HQ, Huangqi ( <i>Astragalus</i> ) injection; KDZ, Kudiezi injection; NA, not applicable; SM, Shenmai injection; SXN, Shuxuening injection; SYM-I, symptomatic improvements; SYM-R, symptomatic recovery; XST, Xuesaitong injection;											
$\beta_1$ , coefficient of sample sizes; $\beta_2$ , coefficient of dosages of the intervention; $\beta_3$ , coefficient of average age; $\beta_4$ , coefficient of the proportion of female; $\beta_5$ , coefficient											
of follow-up periods.											
*, statistical significance.											
The result in the bracket of the coefficient estimate was the number of included studies with the available covariates.											

### 3.3.4 Substantial publication bias among included RCTs

Seven pairwise meta-analyses including 157 RCTs on symptomatic outcome data and 10 pairwise meta-analyses including 114 RCTs on electrocardiography outcome data showed a significant publication bias. All but four adjusted ORs with the trim-fill methods [36] and the Copas methods [37] were no more than the overall results (Supplement 6).

## 3.4 Results of network meta-analysis

Symptomatic outcome data were reported in 317 RCTs and electrocardiography outcome data were reported in 252 RCTs (Supplement 13). Evidence networks on symptomatic and electrocardiography outcomes were presented in Fig. 2.

### 3.4.1 Best treatments on primary outcomes

The network meta-analysis for symptomatic outcomes included 23 TCMLs with 31593 participants. Comparative efficacy among treatments on symptomatic outcomes was displayed in Fig. 3. Except for Xinmailong, Xiangdan and Mailuoning injection, other TCMLs showed better efficacy than conventional treatments on SYM-I (Fig. 2(a)). Ciwujia injection had the first rank on SYM-I according to the P-score (OR = 7.59, 95% CI: 2.85–20.21). Ciwujia injection was superior to other treatments in improving anginal symptoms, although only 3 RCTs on Ciwujia injection were incorporated into this network meta-analysis. We found substantial inconsistency in the overall network ( $Q = 2379.9, p < 0.0001$ ). According to the heat plot (Supplement 8), the inconsistency was mainly contributed by the comparison of Danshen (*Salvia miltiorrhiza*) injections and conventional treatments, in which there was a statistically significant inconsistency between the direct and indirect comparison ( $z = -4.1, p < 0.0001$ ).

The network meta-analysis for electrocardiography outcomes included 21 TCMLs with 26243 participants. Comparative efficacy among treatments on electrocardiographic outcomes was displayed in Fig. 4. All but Danshen (*Salvia miltiorrhiza*) injection showed a better performance than conventional treatments on ECG-I (Fig. 2(c)). Gualoupi (*Pericarpium Trichosanthis*) injection had the first rank on ECG-I (OR = 7.48, 95% CI: 4.68–11.95). Gualoupi (*Pericarpium Trichosanthis*) injection was superior to other TCMLs in improving electrocardiography, while only 4 RCTs on

Gualoupi (*Pericarpium Trichosanthis*) injection were incorporated into this network meta-analysis. There was substantial inconsistency in the overall network ( $Q = 1062.58, p < 0.0001$ ). The heat plot (Supplement 8) indicated the inconsistency was mainly contributed by the comparison of Honghua huangsesu (Safflower yellow) injection and conventional treatments, in which there was a statistically significant inconsistency between the direct and indirect comparison ( $z = 3.34, p = 0.0008$ ).

### 3.4.2 Best treatments of secondary outcomes

Comparative efficacy among treatments on SYM-R was displayed in Fig. 3. Eighteen TCMI for angina pectoris had better performance than conventional treatments on SYM-R (Supplement 9). Honghua (Safflower) injection was ranked as the best treatment in terms of SYM-R (OR = 2.98, 95% CI: 2.98–4.38). Significant inconsistency was identified with the total Q statistic of 2379.9 ( $p < 0.0001$ ) in the overall network of SYM-R.

Comparative efficacy among treatments on ECG-R was displayed in Fig. 4. Except for Shenqi fuzheng, Xiangdan and Danshen (*Salvia miltiorrhiza*) injection, other TCMI performed better on ECG-R (Supplement 9). Gualoupi (*Pericarpium Trichosanthis*) injection was ranked as the best treatment in terms of ECG-R (OR = 3.29, 95% CI: 2.09–5.17). Significant inconsistency was identified with the total Q statistic of 1115.82 ( $p < 0.0001$ ) in the overall network of ECG-R.

### 3.4.3 Preferable TCMI with robust superiority in ranking of treatments

As a statistical difference was observed in subgroup analysis based on conventional treatments (Table 3), we removed the RCTs comparing Dengzhanxixin (*Erigeron breviscapus*) or Danhong injection with conventional treatments (monotherapy or combinational therapy) to perform the sensitivity analysis. According to subgroup and sensitivity analysis (Supplement 10), Hongjingtian (*Rhodiola*), Honghua huangsesu (Safflower yellow) injection on SYM-I as well as Honghua (Safflower) injection on SYM-R always showed the superiority to other TCMI, they were identified as the preferable treatments in improving anginal symptoms; Gualoupi (*Pericarpium Trichosanthis*) and Honghua (Safflower) injection both on ECG-I and ECG-R always showed the superiority to other TCMI, they were identified as the preferable treatments in improving electrocardiography.

## 3.5 Low or very low quality of the evidence

The quality of direct evidence was assessed as low or very low with the GRADE approach [15]. Risk of bias was deemed as very serious for the generally poor quality of included RCTs, all evidence was thus downgraded to low. Then heterogeneity ( $I^2 > 30\%$  or statistical difference in subgroup analysis), imprecision (the number of included studies less 5 or the 95% CI covering the threshold 1) and publication bias (significant results of Egger's test or Begg's test) further rated down the quality of evidence to very low (Supplement 11). The proportion of very low quality of direct evidence on outcome measures were 59.26% (SYM-I), 66.67% (SYM-R), 75.86% (ECG-I) and 62.07% (ECG-R).

According to GRADE-NMA approach [16, 17], very low quality of direct evidence on preferable treatments caused indirect evidence very low. Due to little head-to-head evidence of TCMI, indirect evidence contributed to the very low quality of the comparative evidence on the preferable treatments. Hongjingtian (*Rhodiola*) injection on SYM-I included 8.7% low quality and 91.3% very low quality of comparative evidence, and the quality of the comparative evidence on other preferable treatments was very low.

## 4. Discussion

A total of 475 RCTs with 48511 participants were available in this network meta-analysis. Our study found that: (1) pairwise comparisons suggested TCMI were associated with greater effects in the treatment of angina pectoris; (2) significant publication bias was detected in 59.52% (157/317) of included studies on symptomatic outcomes and 45.23% (114/252) of included studies on electrocardiography outcomes, and almost all adjusted results were no more than overall efficacy estimates; (3) the network meta-analysis with substantial inconsistency showed Hongjingtian (*Rhodiola*), Honghua huangsesu (Safflower yellow) and Honghua (Safflower) injection showed greater efficacy than other TCMI in improving anginal symptoms and Gualoupi (*Pericarpium Trichosanthis*) and Honghua (Safflower) injection showed greater efficacy than other TCMI in improving electrocardiography; (4) the overall quality of included RCTs was poor due to the integrity issues, furthermore, the quality of evidence was rated low or very low.

The protocol of systematic reviews and meta-analyses that reported the designs and methodologies before conduct would enhance the study designs and transparency, hence the reliability and reproducibility of evidence [21]. Our study was impartial, valid and reliable in compliant with the pre-specified protocol [24, 25]. Previous network meta-analyses [19, 20] without protocols did not identify the limitations which included PRISMA-discrepancy, inappropriate model selection based on heterogeneity test, inadequate statistical analysis, and lack of evidence assessment (Supplement 12). Therefore, their results and conclusions [19, 20] were biased and untrustworthy. Our study conducted a rigorous and comprehensive network meta-analysis in accordance with the PRISMA statements [21–23] and the pre-specified protocol [24, 25]. We employed the random-effects model for data synthesis with an assumption of different populations among eligible RCTs [29]. In our study, the robustness of overall results was tested by subgroup analysis, sensitivity analysis, meta-regression and publication bias analysis. Quality assessment of the evidence with the GRADE approach [15–17] would help inform the strength of clinical recommendations. This study provided the best evidence to evaluate the efficacy of TCMI for angina pectoris.

Publication bias must be taken seriously, as it would threaten the validity of conclusions from meta-analyses [47]. All available evidence in this meta-analysis were from published RCTs. There was significant publication bias in 157 RCTs on symptomatic outcomes and 114 RCTs on electrocardiography outcomes. Publication bias explained why small studies could observe larger effects, which was also known as the small-study effects [48]. Since the median sample size in this study was merely 86, the effect sizes tended to be overestimated on the account of the small-study effects. The greater efficacy of Kudiezi injection ECG-R (Table 3) and the efficacy of Huangqi (Astragalus) injection on ECG-I (Table 4) in smaller studies showed the potential publication bias among their included studies, while meta-regression analysis suggested a positive association between the efficacy of Shuxuening injection on SYM-I and sample sizes (Table 4,  $\beta = 0.0037$ ,  $p = 0.0243$ ). According to subgroup analysis (Table 3, Supplement 10), Shuxuening injection has more efficacious on symptomatic outcomes in treating unstable angina pectoris. Studies [49, 50] found that Ginkgo biloba extracts of Shuxuening injection improved the imbalance between nitric oxide and endothelin-1 in patients with coronary artery disease, resulting in exerting vasodilating effects and promoting the coronary blood flow. Antiplatelet therapy— aspirin seemed the optimal treatment for unstable angina pectoris [51]. Ginkgolide from Shuxuening injection was demonstrated as the antagonist for platelet activating factor (PAF) that induced platelet aggregation [52]. Shuxuening injection could reduce the PAF level to inhibit thrombosis [53]. In addition, statistically insignificant results by Begg's test[34] or Egger's test[35] cannot confirm the nonentity of publication bias, because the power of two tests was limited for meta-analyses with fewer than 10 included studies[54], thereby results that did not found significant publication bias should be cautiously interpreted.

The quality of the included studies in meta-analyses has been always emphasized [55]. Poor RCTs not only wasted precious resources, but also made the findings hardly reproduce and even misled healthcare decision-making. RCTs with unclear randomization, allocation concealment, or blinding methods tended to exaggerate the estimate of treatment effect [56, 57]. Of included RCTs in this study, only 2 RCTs [42, 43] reported detailed methods, such as random allocation, blind design, withdraw of participants and statistical analysis plan. Other included RCTs lacked adequate information on implementation. Eighty-four RCTs reported vague random sequence generation; 26 RCTs reported blind methods but lacked the information on specific process; 16 RCTs reported the number of drop-out cases (Supplement 5). The overall quality of the included RCTs was poor. RCTs with inappropriate randomization or blinding methods would pose a risk of 7%-23% exaggeration on the treatment effect [58, 59], the true effects of TCMI might be smaller than our efficacy estimates.

The quality of RCTs on TCMI has always been problematic [60–62], while its impact on the certainty of evidence has rarely been taken into consideration. According to the GRADE approach [15–17], "very serious" risk of bias from poor quality of included RCTs rated down the certainty of all direct evidence, further restricting the indirect evidence that initiated from the quality of direct evidence. As a result, the low quality of included RCTs would degrade the certainty of evidence both from pairwise and network meta-analysis.

Quality of network evidence summarized the certainty of each inter-comparison. In this study with 24 TCMI included, it was a great challenge to undertake the evidence assessment 288 times on each outcome measure. We were more concerned about the quality of the evidence of preferable treatments, because it could be inappropriate to recommend a higher ranked treatment with low quality of evidence [63]. Very low quality of network evidence indicated the comparative efficacies of preferable TCMI were substantially different from the true effect.

The consistency is the statistical manifestation of transitivity in the network meta-analysis[40]. We identified significant inconsistencies in network meta-analysis on all outcome measures. Thus, it seems not plausible to hold the transitivity assumption. We did not rate down the quality of indirect efficacy estimates by intransitivity because the evidence had downgraded to very low by imprecision. The efficacy of TCMI for angina pectoris was evaluated with direct evidence because direct evidence does not rely on the transitivity assumption [64]. Direct evidence was mainly assessed as very low, there was a substantial difference between the true effect and the efficacy estimate. Although meta-analysis suggested a better performance of TCMI in treating angina pectoris, we have very little confidence in these efficacy estimates.

Making healthcare decisions was complicated, not only depending on the efficacy of treatments. It was insufficient to recommend optimal treatments according to the ranking of comparative efficacy in previous network meta-analyses [19, 20]. Decision-makers not only considered the overall trade-off between the efficacy and safety of interventions but also were influenced by the certainty of evidence. A lower-ranked intervention with high quality evidence might be more preferable than a higher-ranked intervention with low quality evidence for patients and clinicians [63]. TCMI with better performance but low quality evidence, for instance, Xinmailong injection ( $OR_{SYM-I} = 8.21$ , 95% CI: 1.41–47.66) and Huangqi injection ( $OR_{SYM-R} = 2.98$ , 95% CI: 0.88–10.09), might not be preferred interventions with respect to symptomatic outcomes (Table 1). Also, drug safety should be considered in treatment selection. Adverse drug reaction (ADR) on TCMI accounted for over 50% of total ADRs on TCMI [65, 66], while 46.32% (220/475) included RCTs did not provide any information on ADRs. Safety risks of TCMI should be carefully concerned when referring to our findings for clinical decision-making.

The major strength of the present study was assessing the certainty of evidence. The certainty of evidence allowed readers' critical appraisal for the research which was helpful in the management of healthcare. According to the GRADE approach [15–17], we developed an association between the low quality of RCTs on TCMI with the certainty of comparative efficacy for the first time, which suggested the confidence of estimated efficacy. Secondly, rigorous methodologies were enhanced by the comprehensive literature search and adequate statistical analyses. This study included all available treatments to provide the most comprehensive and rigorous evidence of TCMI in treating angina pectoris.

Moreover, our methodologies in compliance with the PRISMA statement [21–23] promised to be a reference in evaluating the efficacy of TCMs for other diseases.

Limitations of available data should be noted. Only 17.35% (55/317) of included studies on symptomatic data and 25% (63/252) of included studies on electrocardiographic data were head-to-head comparison trials. This network of TCMI for angina pectoris was mainly determined by indirect comparison of TCMI with conventional treatments, which introduced imprecision and intransitivity in the comparative efficacies. Secondly, the treatment efficacy with sparse RCTs always had the wide confidence interval reflecting highly uncertain. With two RCTs [67, 68] for inclusion, Xinmailong injection showed extremely efficacious on SYM-I (Table 1, OR = 8.21, 95% CI: 1.41–47.66). But pairwise comparisons with less than 5 included RCTs hardly assessed the robustness of overall results. It seemed that the uncertainty of effect size had little impact on the ranking of treatments based on P-scores. Overall network meta-analysis on SYM-R showed the Xinmailong injection was as effective as conventional treatments (OR = 7.91, 95% CI: 0.79–79.1) despite its fifth ranking (Supplement 9). We performed subgroup and sensitivity analysis of network meta-analysis to determine the preferable treatments with robust effect sizes.

## 5. Conclusion

The overall efficacy estimates showed TCMI were associated with beneficial effects for angina pectoris, however, low quality of current evidence cannot support the superiority of TCMI in treating angina pectoris.

## Abbreviations

ADR, Adverse drug reaction; CI, confidence interval; CNKI, China National Knowledge Infrastructure Library; ECG-I, electrocardiography improvement; ECG-R, electrocardiography recovery; GRADE, Grading of Recommendations and Assessment, Development, and Evaluation; NMPA, National Medical Products Administration; OR, odds ratio; PAF, platelet activating factor; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; RCT, randomized controlled trial; RoB 2, revised Cochrane's risk of bias tool for randomized trials; SYM-I, symptomatic improvement; SYM-R, symptomatic recovery; TCM, traditional Chinese medicines; TCMI, traditional Chinese medicine injection.

## Declarations

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### Authors' contributions

Conceptualization: SW Leung and Y Jia; Methodology: S Leung, Y Jia and G Gao; Investigation and formal analysis: G Gao; Validation: Y Jia and SW Leung; Writing – original draft: G Gao; Writing – review and editing: SW Leung, Y Jia and G Gao; Funding acquisition: S Leung and Y Jia.

### Availability of data and materials

Data extracted or analysis in our study are provided in the supplementary files.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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## Figures

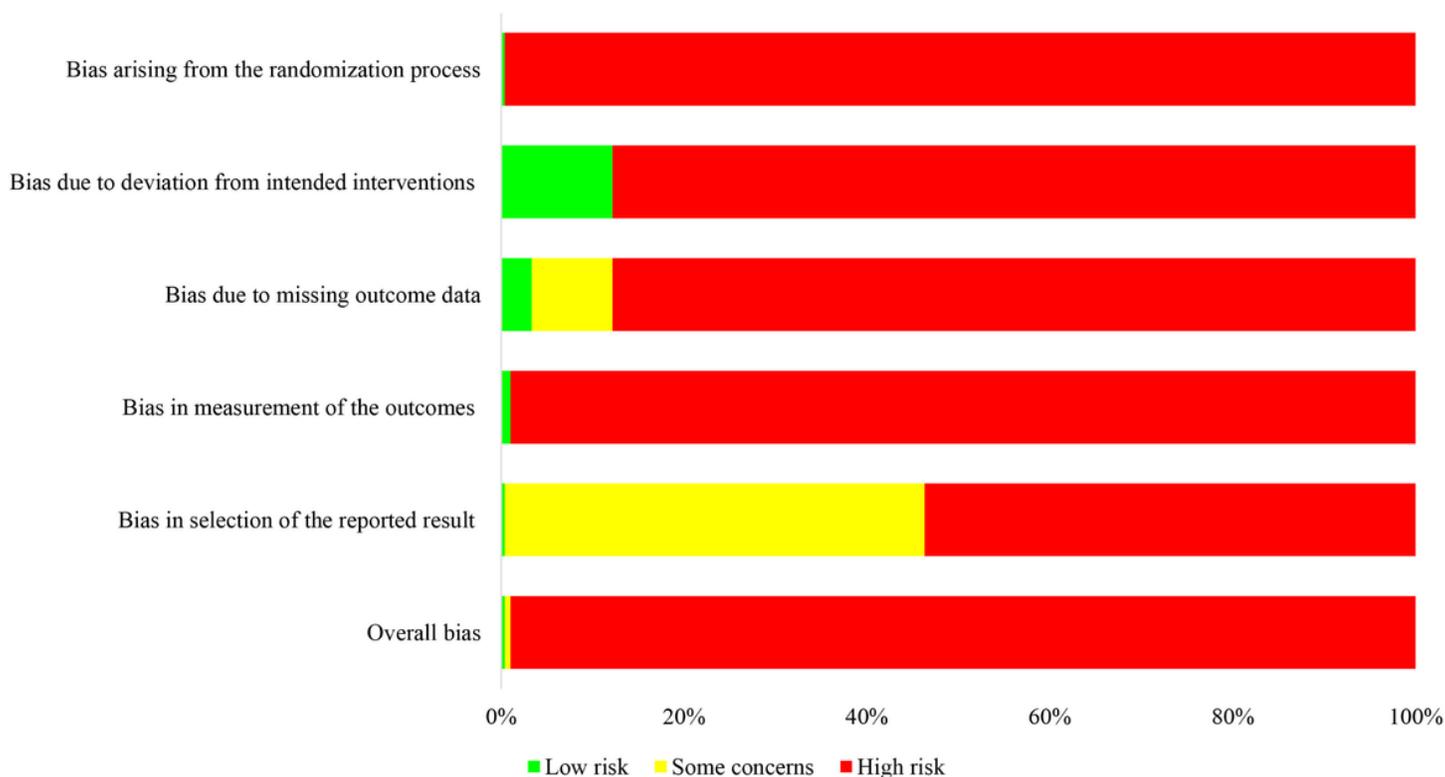


Figure 1

Risk of bias across the included RCTs using the revised Cochrane's tool.



Figure 2

Summary of network meta-analysis on primary outcomes. (a) The ranked forest plots on the primary outcome of SYM-I; (b) Network evidence for symptomatic outcomes; (c) The ranked forest plots on the primary outcome of ECG-I; (d) Network evidence for electrocardiographic outcomes. For the sections (b) and (d), the size of the circle weighted by the number of included studies, the width of the line weighted by the inverse standard error of the comparison.

CT	0.190(0.035)	0.248(21.28)	0.650(2.82)	0.200(15.20)	0.370(24.05)	0.290(22.83)	0.260(11.63)	0.250(16.34)	0.210(12.57)	0.180(13.22)	0.180(11.30)	0.340(18.66)	0.250(16.39)	2.200(13.53)	0.330(15.75)	0.340(17.76)	0.210(14.38)	0.220(15.32)	0.220(15.32)	0.770(42.40)	0.130(0.126)	0.310(23.04)	0.130(0.144)
1.201.29(3)	CW	1.840(69.94)	<b>4.961(92.18)</b>	1.500(55.47)	2.070(87.09)	2.210(86.07)	1.490(49.43)	1.750(61.50)	1.500(52.40)	1.360(43.77)	1.360(44.16)	2.500(81.39)	1.800(65.51)	16.710(92.90)	2.520(70.03)	2.500(77.85)	1.560(55.49)	1.600(59.75)	1.610(58.40)	<b>5.821(85.18)</b>	0.960(81.70)	2.340(85.44)	1.010(21.49)
1.201.84(25)	DH	<b>2.001(67.50)</b>	0.810(61.10)	1.520(92.24)	1.200(61.66)	0.810(47.41)	0.950(61.42)	0.860(41.53)	0.740(52.04)	0.740(41.27)	1.400(72.73)	1.020(65.42)	0.970(59.19)	1.370(63.14)	1.400(67.21)	0.850(57.24)	0.910(62.13)	0.800(61.29)	<b>3.161(72.80)</b>	0.520(65.22)	1.270(91.75)	0.500(16.91)	
1.150(96.17)	<b>0.350(14.87)</b>	<b>0.570(47.69)</b>	DS	<b>0.360(22.61)</b>	<b>0.560(36.90)</b>	<b>0.440(32.82)</b>	<b>0.360(17.65)</b>	<b>0.350(22.55)</b>	<b>0.320(18.50)</b>	<b>0.270(19.49)</b>	<b>0.260(16.49)</b>	<b>0.520(27.10)</b>	<b>0.360(23.69)</b>	3.170(22.52)	0.510(22.19)	0.520(25.10)	<b>0.310(21.67)</b>	<b>0.340(22.82)</b>	<b>0.350(22.50)</b>	1.170(62.23)	0.190(62.19)	<b>0.470(33.67)</b>	<b>0.260(60.72)</b>
1.330(91.26)	0.710(21.18)	1.150(91.43)	<b>2.001(62.50)</b>	DSD	<b>1.871(143.00)</b>	1.400(99.19)	1.000(55.82)	1.170(71.88)	1.000(57.19)	0.910(60.18)	0.920(51.66)	1.700(63.47)	1.260(75.13)	11.180(72.17)	1.690(71.01)	1.720(83.75)	1.040(66.16)	1.120(71.77)	1.090(70.71)	<b>3.892(61.54)</b>	0.640(66.52)	<b>1.871(62.31)</b>	0.470(19.24)
1.710(21.42)	0.540(20.43)	0.870(63.21)	<b>1.541(82.19)</b>	0.760(52.10)	DZH	0.760(47.13)	<b>0.550(26.10)</b>	0.620(35.11)	0.570(28.14)	<b>0.490(25.82)</b>	<b>0.490(25.80)</b>	0.920(41.20)	0.870(37.24)	5.970(38.94)	0.90(36.20)	0.920(40.22)	0.560(32.97)	0.600(35.90)	0.580(34.01)	<b>2.001(62.31)</b>	0.340(61.50)	0.840(51.38)	0.560(16.14)
1.971(56.17)	0.600(21.55)	0.970(76.12)	<b>1.721(92.21)</b>	0.840(63.11)	DZXX	<b>0.600(37.12)</b>	0.760(49.12)	0.720(38.15)	0.620(40.95)	0.620(34.13)	1.170(58.28)	0.860(50.14)	1.140(48.75)	1.170(54.52)	0.710(41.12)	0.760(48.21)	0.740(47.17)	0.740(47.17)	<b>2.441(58.15)</b>	0.430(64.43)	1.060(71.59)	0.460(13.64)	
1.710(83.90)	0.830(30.24)	1.340(91.97)	<b>2.361(58.50)</b>	1.160(76.77)	1.530(92.43)	1.380(82.14)	GLP	1.170(62.27)	1.060(82.13)	0.910(49.69)	0.920(44.83)	1.780(75.41)	1.200(62.53)	11.190(68.17)	1.690(63.48)	1.780(76.24)	1.040(51.89)	1.120(62.11)	1.090(58.20)	<b>3.891(58.71)</b>	0.640(66.83)	1.570(86.27)	0.470(17.42)
1.710(21.27)	0.520(20.13)	0.840(63.14)	<b>1.491(87.20)</b>	0.730(52.04)	0.970(63.48)	0.870(61.25)	0.630(39.10)	GN	0.910(61.79)	0.780(47.20)	0.760(41.50)	1.400(69.16)	1.080(61.93)	9.570(61.15)	1.440(59.56)	1.480(65.34)	0.890(51.51)	0.960(57.62)	0.940(55.58)	<b>3.331(74.40)</b>	0.550(65.66)	1.340(84.15)	0.560(16.12)
1.902(62.40)	0.910(31.40)	1.470(92.10)	<b>2.001(74.80)</b>	1.270(83.90)	<b>1.491(82.77)</b>	1.510(97.23)	1.100(64.80)	<b>1.741(82.81)</b>	HH	0.840(47.57)	0.870(48.17)	1.630(63.85)	1.190(52.43)	16.550(65.87)	1.960(74.30)	1.630(65.66)	0.980(50.92)	1.060(57.97)	1.030(51.01)	<b>3.871(68.36)</b>	0.610(66.40)	1.480(72.77)	0.460(16.40)
1.910(91.84)	0.740(21.91)	1.190(91.53)	<b>2.101(62.70)</b>	1.030(71.40)	1.370(93.02)	1.240(89.16)	0.890(57.19)	1.410(98.03)	0.810(53.24)	HHH	1.010(55.85)	1.190(92.30)	1.390(83.13)	12.280(78.19)	1.850(77.45)	1.960(86.45)	1.150(71.85)	1.240(73.97)	1.200(75.92)	<b>4.271(88.38)</b>	0.760(77.20)	<b>1.721(82.41)</b>	0.740(21.67)
1.201.96(34)	0.760(26.91)	1.130(71.60)	<b>2.011(53.60)</b>	0.980(64.53)	1.300(82.12)	1.170(74.81)	0.850(52.40)	1.340(82.15)	0.770(45.12)	0.950(61.40)	HT	1.880(81.42)	1.370(70.70)	12.140(75.99)	1.810(74.82)	1.870(77.44)	1.130(62.13)	1.220(65.28)	1.190(62.22)	<b>4.221(92.31)</b>	0.760(77.17)	1.760(91.06)	0.740(19.81)
1.201.20(79)	0.870(21.91)	1.080(63.10)	<b>1.911(33.30)</b>	0.940(53.66)	1.250(72.53)	1.020(62.09)	0.810(42.17)	1.260(70.37)	0.740(38.43)	0.910(51.63)	0.960(51.85)	IQ	1.730(33.14)	6.470(39.07)	0.980(34.79)	1.000(38.24)	0.800(29.27)	0.630(31.37)	0.630(31.33)	2.290(93.47)	0.370(63.67)	0.910(45.84)	0.360(16.10)
1.831(31.14)	0.560(21.50)	0.910(65.27)	<b>1.901(62.81)</b>	0.760(54.15)	1.040(66.19)	0.960(61.39)	0.460(41.12)	1.070(70.14)	0.620(37.02)	0.760(51.11)	0.800(41.13)	KDZ	8.850(56.41)	1.340(53.30)	1.370(59.10)	1.370(59.10)	1.370(59.10)	1.370(59.10)	1.370(59.10)	<b>3.871(68.36)</b>	0.510(65.50)	1.240(74.20)	0.530(14.99)
0.690(19.24)	0.210(61.03)	0.340(81.23)	0.600(16.19)	0.300(81.00)	0.300(81.47)	0.350(81.29)	<b>0.250(49.97)</b>	0.400(81.15)	<b>0.280(60.89)</b>	0.290(81.05)	0.300(81.14)	MLN	1.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)	0.150(01.24)
1.800(91.47)	0.530(18.12)	0.890(68.73)	1.370(83.10)	0.770(91.53)	1.020(62.12)	0.920(61.84)	0.670(31.42)	1.050(52.11)	0.610(28.34)	0.730(71.50)	0.780(37.07)	0.620(35.92)	0.980(47.04)	2.010(62.00)	SF	1.020(34.04)	0.620(25.51)	0.600(27.62)	0.600(27.58)	2.010(62.00)	0.380(63.47)	0.930(92.20)	0.400(91.77)
1.911(31.24)	0.610(21.72)	0.970(91.44)	<b>1.711(62.80)</b>	0.950(61.40)	1.120(63.11)	1.010(59.73)	0.730(39.16)	1.060(62.05)	0.670(36.24)	0.820(48.14)	0.860(44.87)	1.080(61.87)	2.890(71.31)	1.160(69.25)	SOM	0.800(27.15)	0.600(29.45)	0.600(29.41)	2.260(88.75)	0.370(63.15)	0.910(82.96)	0.360(16.10)	
1.611(96.43)	0.810(30.10)	1.260(91.54)	<b>2.261(65.14)</b>	1.120(79.50)	1.490(92.24)	1.330(92.91)	0.860(61.55)	1.510(82.00)	0.830(54.11)	1.040(51.10)	1.170(81.22)	1.020(62.19)	3.700(71.30)	1.450(71.97)	1.310(72.32)	SNN	1.000(65.79)	1.000(65.79)	1.000(65.79)	1.000(65.79)	1.000(65.79)	1.000(65.79)	1.000(65.79)
1.201.72(9)	0.760(27.18)	1.130(81.40)	<b>1.991(47.71)</b>	0.960(71.35)	1.290(81.94)	1.160(82.64)	0.840(55.10)	1.340(91.96)	0.760(50.19)	0.950(67.13)	0.990(63.56)	1.040(57.18)	1.240(82.18)	3.310(89.12)	1.270(63.56)	1.150(66.22)	0.800(60.29)	SNT	0.970(59.61)	<b>3.471(76.96)</b>	0.570(66.87)	1.400(89.19)	0.460(16.10)
1.410(88.09)	0.740(28.92)	1.190(91.55)	<b>2.110(62.10)</b>	0.970(81.04)	1.230(81.72)	1.090(81.72)	0.890(57.40)	1.410(97.06)	0.810(51.20)	0.900(70.40)	1.050(67.64)	1.060(61.99)	1.310(87.90)	3.500(92.34)	1.340(66.70)	1.220(70.11)	0.920(65.13)	1.060(74.51)	SXT	<b>3.501(76.14)</b>	0.580(66.03)	1.430(92.24)	0.620(17.25)
1.220(76.90)	0.730(31.06)	<b>0.69(37.97)</b>	1.670(65.76)	0.520(31.87)	0.670(39.12)	<b>0.620(37.17)</b>	<b>0.490(25.80)</b>	0.710(42.10)	<b>0.420(22.79)</b>	<b>0.510(30.80)</b>	<b>0.530(29.87)</b>	0.560(27.14)	0.870(39.11)	1.770(45.76)	0.680(30.52)	0.620(31.22)	<b>0.470(27.81)</b>	<b>0.530(30.81)</b>	<b>0.510(30.80)</b>	XZ	1.610(62.70)	<b>0.460(16.10)</b>	<b>0.460(16.10)</b>
1.901(44.24)	0.880(26.95)	1.430(66.19)	<b>2.011(55.50)</b>	1.240(92.10)	1.460(72.50)	1.470(66.20)	1.070(52.52)	1.690(75.84)	0.970(42.68)	1.200(54.60)	1.260(54.26)	1.260(54.26)	4.200(94.17)	1.610(59.41)	1.460(69.63)	1.110(62.52)	1.270(56.85)	1.200(54.69)	2.370(95.84)	XML	2.440(24.24)	1.050(81.47)	
1.710(32.09)	0.520(20.14)	0.840(63.15)	<b>1.491(51.92)</b>	<b>0.750(55.97)</b>	0.970(66.41)	0.870(64.13)	<b>0.640(41.97)</b>	1.000(71.41)	<b>0.570(37.60)</b>	<b>0.610(42.96)</b>	0.740(48.11)	0.760(44.10)	0.930(61.36)	2.470(87.90)	0.950(48.80)	0.860(51.46)	<b>0.650(47.92)</b>	0.700(54.03)	<b>0.710(54.07)</b>	1.400(82.30)	0.590(27.10)	SXT	0.430(11.45)
1.270(96.87)	0.760(26.03)	1.270(47.40)	2.240(83.67)	1.100(63.00)	1.460(52.09)	1.310(48.50)	0.950(33.72)	1.500(54.14)	0.860(30.40)	1.060(39.22)	1.120(39.20)	1.170(38.95)	1.400(53.94)	3.700(74.18)	1.430(44.65)	1.260(43.88)	0.980(35.73)	1.120(41.11)	1.060(39.54)	2.100(71.22)	0.890(25.09)	1.510(58.94)	YQFM

Figure 3

The results of network meta-analysis on symptomatic outcomes Comparative efficacies on SYM-I are presented in the right upper half, and comparative efficacies on SYM-R are presented in the left lower half. Text in bold indicated significant results.

CT	0.390(23.67)	0.350(31.84)	0.840(71.02)	0.320(25.84)	0.370(17.50)	0.370(31.05)	0.130(08.21)	0.340(25.07)	0.260(18.38)	0.310(26.38)	0.300(23.39)	0.360(27.67)	0.450(34.85)	0.410(18.94)	0.310(18.82)	0.320(23.44)	0.280(07.62)	0.320(27.38)	0.340(21.85)	0.650(43.74)	0.390(32.48)
1.971(17.33)	CW	0.900(51.57)	<b>2.261(28.79)</b>	0.810(45.44)	0.940(50.75)	0.950(54.16)	<b>0.340(17.70)</b>	0.840(46.62)	0.660(34.28)	0.800(45.41)	0.760(42.18)	0.910(50.66)	1.140(62.10)	1.050(39.28)	0.790(37.16)	0.820(44.54)	0.510(15.79)	0.820(46.43)	0.840(42.77)	1.440(79.26)	1.000(56.78)
1.901(82.15)	0.970(57.64)	DH	<b>2.442(41.30)</b>	0.900(61.18)	1.040(75.14)	1.060(84.13)	<b>0.380(24.61)</b>	0.960(61.30)	0.740(49.11)	0.890(71.13)	0.850(64.13)	1.010(74.18)	1.270(81.74)	1.170(51.71)	0.880(51.50)	0.920(65.10)	0.570(18.78)	0.910(71.12)	0.960(58.19)	<b>1.001(18.17)</b>	1.120(81.41)
1.030(17.12)	<b>0.520(31.87)</b>	<b>0.540(45.65)</b>	DS	<b>0.370(28.48)</b>	<b>0.430(30.60)</b>	<b>0.430(34.54)</b>	<b>0.150(09.25)</b>	<b>0.390(28.50)</b>	<b>0.300(20.45)</b>	<b>0.360(29.45)</b>	<b>0.350(26.47)</b>	<b>0.410(31.56)</b>	<b>0.520(38.67)</b>	0.480(21.11)	<b>0.360(21.62)</b>	<b>0.370(27.52)</b>	<b>0.230(07.73)</b>	<b>0.370(30.46)</b>	<b>0.390(24.64)</b>	<b>0.650(40.88)</b>	<b>0.450(35.58)</b>
1.610(35.21)	0.860(49.15)	0.890(69.11)	<b>1.601(28.21)</b>	DSD	1.150(78.71)	1.170(87.59)	<b>0.420(28.77)</b>	1.060(71.54)	0.820(52.28)	0.960(74.12)	0.930(67.13)	1.120(78.61)	1.410(97.63)	1.300(55.07)	0.970(55.72)	1.020(69.15)	0.630(20.09)	1.000(75.14)	1.060(62.18)	<b>1.771(24.5</b>	

electrocardiography recovery; GLP, Gualoupi (*Pericarpium trichosanthis*) injection; GXN, Guanxinning injection; HH, Honghua (Safflower) injection; HHH, Honghua huangsesu (Safflower yellow) injection; HJT, Hongjingtian (*Rhodiola*) injection; HQ, Huangqi (*Astragalus*) injection; KDZ, Kudiezi injection; MLN, Mailuoning injection; RCT, randomized controlled trials; SF, Shenfu injection; SM, Shenmai injection; SGM, Shengmai injection; SQ, Shenqi fuzheng injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; SYM-I, symptomatic improvement; SYM-R, symptomatic recovery; XD, Xiangdan injection; XML, Xinmailong injection; XST, Xuesaitong injection; YQFM, Yiwifumai injection.

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