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Comparative efficacy of Chinese herbal injections for angina pectoris: A Bayesian network meta-analysis of randomized controlled trials

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ABSTRACT

Objective: The severity of angina pectoris has been recognized. It is believed that Chinese herbal injections have an outstanding clinical effect on this condition. This network meta-analysis was devised to investigate the comparative efficacy of eight Chinese herbal injections (Ciwujia injection, Dazhuhongjingtan injection, Huangqi injection, Shenfu injection, Shengmai injection, Shenmai injection, Shenqi Fuzheng injection, Yiqifumai injection) in the treatment of angina pectoris.

Methods: A literature search was performed in PubMed, Embase, and the Cochrane Library, Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and Chinese Scientific Journal Database from their inception to June 25, 2018. A pre-designed eligibility criterion was utilized in this network meta-analysis, and a methodological quality analysis was conducted. Data analysis was performed by WinGUGS 1.4.3, Stata 13.0 and TSA software, and the odds ratio or mean difference with the 95% credible interval was reported for symptomatic improvement, electrocardiography improvement, fibrinogen, triglyceride and cholesterol. The ranking probability of interventions in various outcomes was also utilized.

Results: A total of 73 randomized controlled trials with 6639 patients were identified. Integrating network meta-analysis results, Shenqi Fuzheng injection plus western medicine therapy and Shenmai injection plus western medicine therapy were shown to be more efficacious than other therapies. In addition, Huangqi injection plus western medicine therapy and Shenmai injection plus western medicine therapy performed well in improving the haemorheology index and serum lipid parameters.

Conclusions: Eligible Chinese herbal injections plus western medicine therapy might have a better impact on angina pectoris patients than western medicine therapy alone. While this study had limitations, the findings should be interpreted with caution. In addition, more high-quality randomized controlled trials with a large sample must be conducted to support this study.

1. Introduction

Coronary heart disease, the most common form of cardiovascular disease, refers to the myocardial dysfunction and/or organic lesions caused by coronary artery stenosis and insufficient blood supply.[1,2] Coronary heart disease represents the leading cause of death worldwide. The global estimate suggests that there are up to 8.14 million coronary heart disease patients and that coronary heart disease accounts for 50 percent of cardiovascular disease-related death and exhibits an upward trend in its prevalence.[3,4] As a common kind of coronary heart disease, angina pectoris (AP) is a clinical syndrome related to recurrent chest pain or chest discomfort resulting from temporary myocardial ischaemia and hypoxia. Patients often suffer from crushing pain that spreads to the end of the shoulder, fingers, or even back.[6–9] These patients are at high risk of acute myocardial infarction, cardiac arrest, and sudden cardiac death.[10] Currently, promoting blood flow and reducing blood oxygen are two steps in AP therapy with ß-blockers, nitrates, calcium channel blockers, angiotensin converting

Abbreviations: AP, angina pectoris; NMA, network meta-analysis; WM, western medicine; RCT, randomized controlled trials; ADRs/ADEs, adverse drug reactions/adverse drug events; OR, odds ratio; MD, mean difference; 95% CI, 95% credible interval; SUCRA, surface under the cumulative ranking area value

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enzyme inhibitors, aspirin, heparin, statins, etc. Due to concerns about undesired and side effects, clinicians have turned their attention to Chinese herbal injections, aiming to explore new treatments for AP in China.[8,10]

According to traditional Chinese medicine theory, AP arises due to *qi* blockage in the chest and heart pain, with the heart as the site of disease; AP is also defined as a deficiency in *qi* and blood caused by six excesses, seven motions, greasy and sweet food, etc.[11,12] Thus, reinforcing *qi* to promote blood circulation is a dominant principal strategy for AP.[12–14] Among various traditional Chinese medicine therapies, Chinese herbal injections have received more consideration because of its characteristics of rapid effect, quick action and remarkable tonic function.[14–16] In this context, this study selected eight regimens of Chinese herbal injection, namely, Ciwujia injection, Dazhuhongjingtan injection, Huangqi injection, Shenfu injection, Shengmai injection, Shenmai injection, Shenqi Fuzheng injection, and Yiqifumai injection, to explore their efficacy in treating AP. All of these treatments were approved by the China Food and Drug Administration.

As a new method of evidence-based medical statistical methods, network meta-analysis (NMA) has gradually been applied in the medical field to synthesize both direct and indirect clinical evidence and perform a ranking analysis of involved interventions.[17] After retrieval, Chinese herbal injections combined with western medicine (WM) therapy were administered to treat AP in the clinic, and efficacy has been observed in several clinical trials and conventional pairwise meta-analyses.[18–24] However, no clinical trials have reported the comparative efficacy between these therapies simultaneously. Thus, it was imperative to conduct a NMA to compare different Chinese herbal injections and offer a comprehensive overview for the selection of an AP treatment. The graphical abstract of this NMA is presented in Fig. 1.

2. Methods

This NMA was performed in accordance with The PRISMA Extension Statement for the Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[25] A completed PRISMA checklist was included as an additional file (supplementary file 1).

2.1. Inclusion and exclusion criteria

All eligible articles must be in accordance with the following criteria: (1) Clinical trials mentioned in articles were described as randomized controlled trials (RCTs) and were not limited to two-arm RCTs. (2) Patients in RCTs were diagnosed with AP by meeting a standard diagnostic criterion. No limitation on gender, nationality, or ethnic origin was applied. (3) Patients in the experiment group received one of the eligible Chinese herbal injections with WM, while patients in the control group received only the same WM or WM plus another Chinese herbal injection. WM therapy included β-blockers, nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors, aspirin, heparin, and statins. Eligible RCTs were retrieved to determine the specific dosage of Chinese herbal injections. (4) Outcomes of each RCT should include at least one of the following indexes: symptomatic improvement, electrocardiography improvement, fibrinogen, triglyceride, and cholesterol. Symptomatic improvement was calculated by this formula: (number of recovery patients / total number of patients) * 100%. Patient recovery was indicated when the number of anginal attacks and nitroglycerine dosage were decreased by 50 percent. Improvement in electrocardiography was calculated by this formula: (number of recovery patients / total number of patients) * 100%. Patient recovery was also indicated when the ischaemic ST-T segment of ECG returned to normal, the ST segment decreased and returned to greater than or equal to 0.05 mV, or the T wave converted to upright. In addition, the incidence of adverse drug reactions/adverse drug events (ADRs/ADEs) was also summarized.

An exclusion criterion was pre-designed as well: (1) The therapy in RCTs should not include rehabilitation therapy, naturopathy, and other Chinese medicine interventions. (2) If the same clinical data were published more than once, the first report would be retained. (3) RCTs with wrong or incomplete data. (4) The article could not be obtained.

2.2. Search and selection strategy

A comprehensive search to retrieve relevant RCTs was performed through PubMed, Embase, and the Cochrane Library, Chinese Biological Medicine Database, China National Knowledge

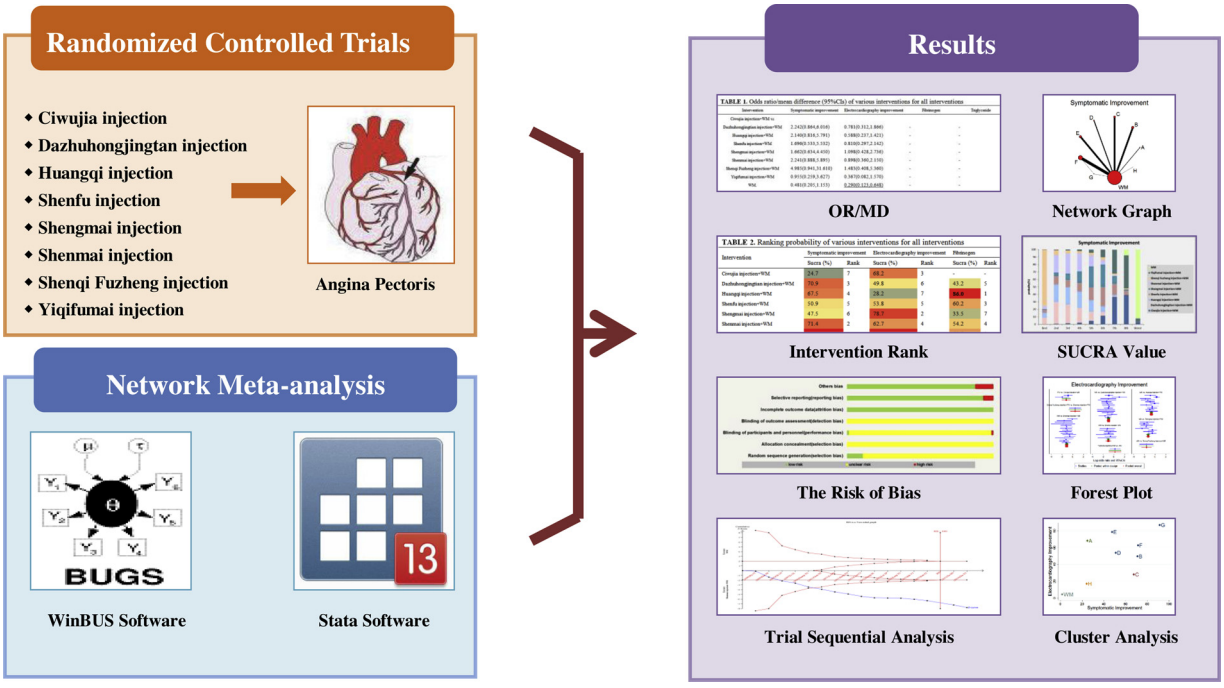

Fig. 1. Graphical abstract for the network meta-analysis.

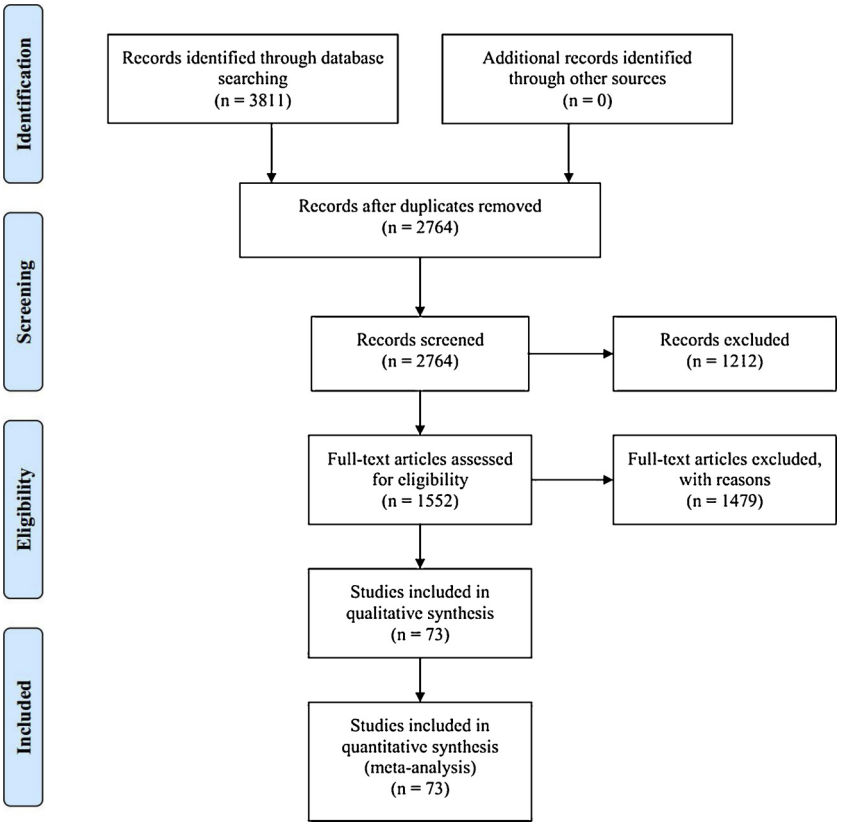

Fig. 2. Flow chart of the search for eligible RCTs.

Infrastructure, Wanfang Database, and Chinese Scientific Journal Database from their inception to June 25, 2018. The method of combining MeSH terms with free terms was utilized. For example, in PubMed, the search strategy was as follows (additional details about retrieval in supplementary file 2).

After duplications were removed, two reviewers scanned the titles and abstracts of all retrieved articles. In addition, the full text of potential articles was obtained for further examination. Any disagreement was resolved by discussion or consultation with a third reviewer.

2.3. Data extraction and quality assessment

The following data were extracted according to the pre-designed form: the first author name, publication year, patient characteristics (sample size, gender, age, patient baseline, and disease duration), details of intervention, duration, outcomes, the RCT design and the domains of risk of bias.

Two independent reviewers evaluated the risk of bias of eligible RCTs with the Cochrane Handbook for Systematic Reviews of Intervention. Seven items were assessed as follows: sequence generation (selection bias), allocation concealment (selection bias), blinding of patients and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each of them was categorized as three levels: “low risk”, “unclear risk” and “high risk”. If the RCTs described a correct and concrete random generation method, implemented blinding and reported complete measure outcomes, the RCT was considered low risk. If not, the RCTs were considered high risk. The RCTs were deemed as unclear risk if the literature did not provide enough information for judgement. Any conflicts during this process were solved by discussion or consultation with a third reviewer.

2.4. Statistical analysis

This NMA introduced a Bayesian framework using WinBUGS 1.4.3 software, Stata 13.0 software and TSA software to calculate the results. Among statistical processes, the random-effects model was selected. The number of iterations was set as 20 0000, the first 10 000 was used for the annealing algorithm in order to eliminate the impact of the initial value. The odds ratio (OR) and mean difference (MD) with the 95% credible interval (95% CI) are presented for binary outcomes and continuous outcomes, respectively. Meanwhile, the ranking probability of each intervention in different outcomes was assessed through the surface under the cumulative ranking area value (SUCRA). Typically, a better treatment was indicated by a higher SUCRA.[26] After determining the SUCRA, a cluster analysis for different outcomes was conducted to identify the most efficacious injection in the treatment of AP.[27] Regarding the optimal intervention, this NMA conducted a trial sequential analysis to verify its stability. Provided that the closed loop of interventions was available, a loop-specific approach was explored to examine the inconsistency of evidence.[28] In addition, publication bias of outcomes included in the above 10 RCTs were checked with a funnel plot. The network graph, the forest plot and the contribution plot were also depicted.

3. Results

3.1. Study identification and characteristics of the included studies

Out of 3811 articles from 7 databases, 1552 remained after duplications, reviews, unrelated studies and animal experiments were removed. Moreover, 1479 articles were excluded because of the following reasons: (1) Not an RCT or an RCT with the wrong randomization (n = 16); (2) Retrospective study (n = 5); (3) Intervention was not in accordance with the inclusion criteria (n = 928); (4) Disease did not

meet the inclusion criteria (n = 473); (5) Outcomes missed the inclusion criteria (n = 27); (6) Repeated data (n = 11); (7) Wrong data (n = 1); and (8) Full-text articles of the RCTs could not be obtained (n = 18). Ultimately, 73 two-arm RCTs conducted in China from 1998 to 2018 were included in this NMA. The selection process is illustrated in Fig. 2, and the included RCTs list is shown in supplementary file 3.

A total of 6639 patients (3433 patients in the experimental group, 3206 patients in the control group) with AP were included in this NMA. Male patients accounted for approximately 61.6% of the total study population, and the majority of them were middle-aged and elderly people. Nine comparisons were evaluated: Ciwujia injection + WM vs. WM (n = 2), Dazhuhongjingtian injection + WM vs. WM (n = 18), Huangqi injection + WM vs. WM (n = 12), Shenfu injection + WM vs. WM (n = 8), Shengmai injection + WM vs. WM (n = 10), Shenmai injection + WM vs. WM (n = 18), Shenqi Fuzheng injection + WM vs. WM (n = 1), Shenqi Fuzheng injection + WM vs. Shenmai injection + WM (n = 1), and Yiqifumai injection + WM vs. WM (n = 3). WM therapy comprised ß-blockers, nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors, aspirin, heparin, statins, etc. The eligible Chinese herbal injections were given via intravenous drip once a day, except in one RCT, which did not report the method of administration. The duration of treatment ranged 7–28 days, with most studies administering the treatment for 14 days. In terms of outcomes, 67.1% of RCTs reported symptomatic improvement, 84.9% of RCTs tested electrocardiography improvement, 16.4% RCTs investigated fibrinogen, and 9.6% RCTs measured triglyceride and cholesterol. Additionally, 11 RCTs adopted dialectical theory based on traditional Chinese medicine theory in treating AP. The detailed characteristics of included RCTs are demonstrated in supplementary file 3, and the network graphs for various outcomes are illustrated in Fig. 3.

3.2. Quality assessment

Overall, the quality of included RCTs was moderate. Low-risk items were as follows: (1) 8 RCTs in selection bias (stated adopted random number table or drawing method). (2) 1 RCT in performance bias (assigned clinician outside of the RCT to conduct the treatment and kept researchers and patients blinded as much as possible). (3) 73 RCTs in attribution bias (reported outcomes data completely). (4) 68 RCTs in reporting bias (reported all outcomes as designed). (5) 64 RCTs in other bias (reported the baseline of RCTs). High risk items: (1) 1 RCT in performance bias (utilized single blinding method because the colour and usage of Chinese herbal injections had a potential possibility of being detected). (2) 5 RCTs in reporting bias (did not report all outcomes as designed). (3) 9 RCTs in other bias (did not report the baseline data of RCTs). Unclear risk items were as follows: the remaining RCTs were considered to have “unclear risk” due to insufficient information. The detailed graphical results are presented in Fig. 4.

3.3. Symptomatic improvement

A total of 49 RCTs reported symptomatic improvement (Ciwujia injection + WM vs. WM (n = 2), Dazhuhongjingtian injection + WM vs. WM (n = 9), Huangqi injection + WM vs. WM (n = 8), Shenfu injection + WM vs. WM (n = 4), Shengmai injection + WM vs. WM (n = 9), Shenmai injection + WM vs. WM (n = 14), Shenqi Fuzheng injection + WM vs. WM (n = 1), Shenqi Fuzheng injection + WM vs. Shenmai injection + WM (n = 1), Yiqifumai injection + WM vs. WM (n = 1). Apart from Ciwujia injection and Yiqifumai injection, other injections plus WM therapy were superior to WM therapy alone, and the difference was statistically significant. Table 1 shows the following results: Dazhuhongjingtian injection + WM vs. WM (OR = 0.216, 95% CI: 0.135-0.332), Huangqi injection + WM vs. WM (OR = 0.225, 95% CI: 0.142-0.350), Shenfu injection + WM vs. WM (OR = 0.287, 95% CI: 0.128-0.607), Shengmai injection + WM vs. WM (OR = 0.290, 95% CI: 0.188-0.440), Shenmai injection + WM vs. WM (OR = 0.214, 95% CI: 0.144-0.310), and Shenqi Fuzheng injection + WM vs. WM (OR = 0.098, 95% CI: 0.019-0.405). With respect to ranking probabilities, Shenqi Fuzheng injection + WM performed well due to a higher SUCRA (91.3%), while Shenmai injection + WM (71.4%) ranked second and Dazhuhongjingtian injection + WM (70.9%) ranked third. The SUCRA and graphical representations are shown in Table 2 and Fig. 5, respectively. In addition, the forest plot for symptomatic improvement is shown in Fig. 6.

3.4. Electrocardiography improvement

Electrocardiography improvement was measured in 62 RCTs

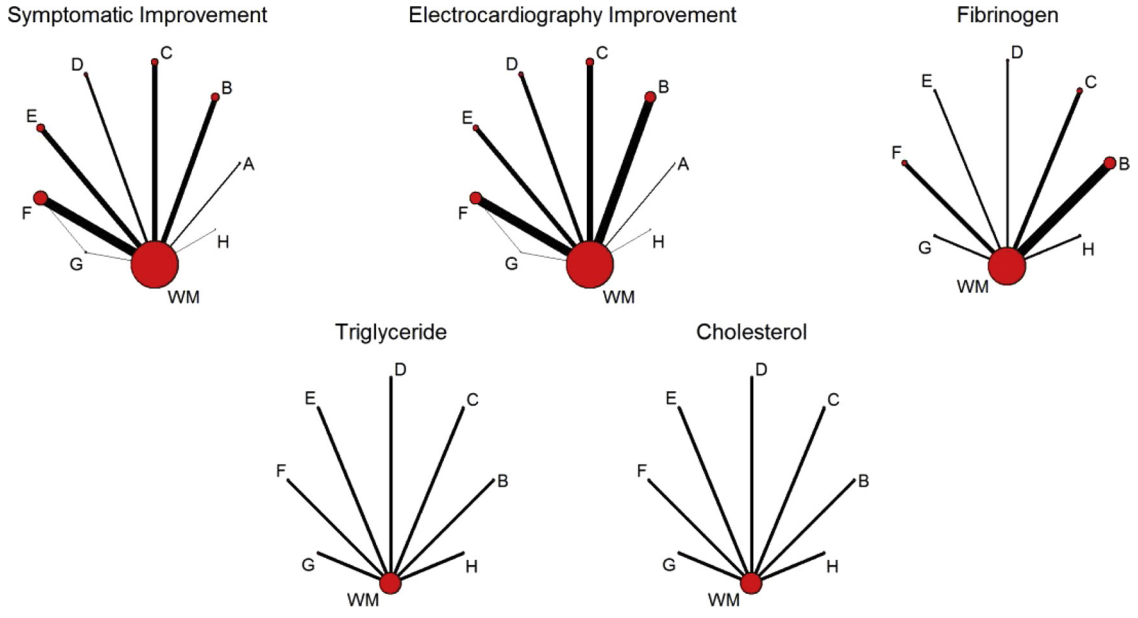

Fig. 3. Network graph for symptomatic improvement, electrocardiographic improvement, fibrinogen, triglyceride and cholesterol.
Note: A: Ciwujia injection + WM; B: Dazhuhongjingtian injection + WM; C: Huangqi injection + WM; D: Shenfu injection + WM; E: Shengmai injection + WM; F: Shenmai injection + WM; G: Shenqi Fuzheng injection + WM; H: Yiqifumai injection + WM.

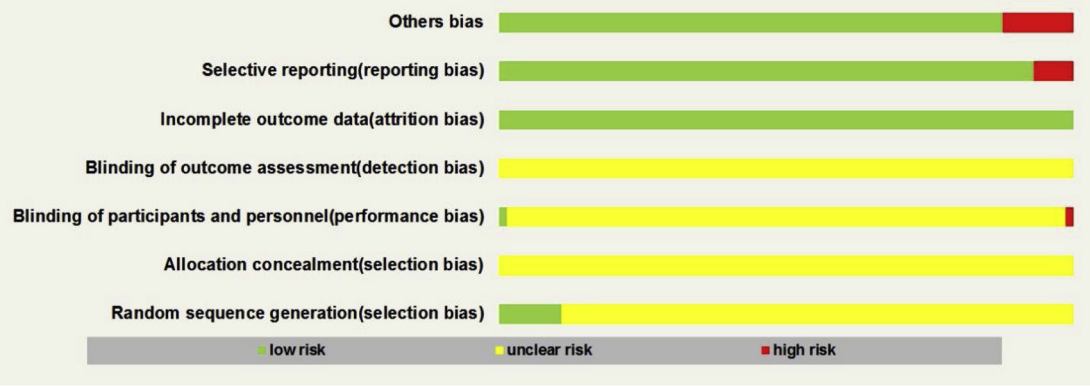

Fig. 4. Risk of bias graph.

(Ciwujia injection + WM vs. WM (n = 2), Dazhuhongjingtian injection + WM vs. WM (n = 15), Huangqi injection + WM vs. WM (n = 11), Shenfu injection + WM vs. WM (n = 7), Shengmai injection + WM vs. WM (n = 8), Shenmai injection + WM vs. WM (n = 16), Shenqi Fuzheng injection + WM vs. WM (n = 1), Shenqi Fuzheng injection + WM vs. Shenmai injection + WM (n = 1), Yiqifumai injection + WM vs. WM (n = 1)). Except for Yiqifumai injection, the other injections plus WM therapy were statistically better than WM therapy alone in promoting electrocardiography improvement. Table 1 shows the following results: Ciwujia injection + WM vs.

Table 1
Odds ratio/mean difference (95%CIs) of all interventions.

Intervention	Symptomatic improvement	Electrocardiography improvement	Fibrinogen	Triglyceride	Cholesterol
Ciwujia injection + WM *vs.*					
Dazhuhongjingtian injection + WM	2.242(0.864,6.016)	0.781(0.312,1.866)	–	–	–
Huangqi injection + WM	2.140(0.816,5.791)	0.588(0.237,1.421)	–	–	–
Shenfu injection + WM	1.696(0.533,5.532)	0.810(0.297,2.142)	–	–	–
Shengmai injection + WM	1.662(0.634,4.450)	1.098(0.428,2.736)	–	–	–
Shenmai injection + WM	2.241(0.888,5.895)	0.898(0.360,2.150)	–	–	–
Shenqi Fuzheng injection + WM	4.985(0.941,31.610)	1.483(0.408,5.360)	–	–	–
Yiqifumai injection + WM	0.955(0.259,3.627)	0.367(0.082,1.570)	–	–	–
WM.	0.481(0.205,1.153)	0.290(0.123,0.648)	–	–	–
Dazhuhongjingtian injection + WM *vs.*					
Huangqi injection + WM	0.958(0.507,1.805)	0.751(0.475,1.218)	1.572(-0.480,3.873)	0.122(-8.989,9.264)	0.180(-9.090,9.516)
Shenfu injection + WM	0.751(0.313,1.856)	1.037(0.559,1.958)	0.607(-2.163,3.383)	−0.227(-10.010,9.518)	−0.734(-10.390,8.950)
Shengmai injection + WM	0.743(0.399,1.376)	1.407(0.832,2.410)	−0.307(-2.372,2.011)	0.295(-8.872,9.460)	0.602(-8.518,9.783)
Shenmai injection + WM	1.002(0.559,1.802)	1.147(0.731,1.807)	0.479(-3.304,4.263)	0.817(-8.409,10.060)	1.174(-8.054,10.540)
Shenqi Fuzheng injection + WM	2.190(0.492,11.970)	1.896(0.688,5.421)	0.706(-2.296,3.768)	2.200(-7.081,11.430)	1.928(-7.181,11.070)
Yiqifumai injection + WM	0.428(0.143,1.266)	0.470(0.134,1.654)	−0.142(-3.735,3.380)	−0.002(-9.330,9.331)	−0.129(-9.476,9.305)
WM.	0.216(0.135,0.332)	0.371(0.268,0.510)	−0.545(-2.040,0.969)	0.014(-6.569,6.562)	−0.161(-6.648,6.388)
Huangqi injection + WM *vs.*					
Shenfu injection + WM	0.783(0.324,1.964)	1.381(0.727,2.603)	−0.950(-3.890,1.733)	−0.371(-9.964,9.273)	−0.931(-10.660,8.744)
Shengmai injection + WM	0.775(0.414,1.442)	1.871(1.090,3.212)	−1.872(-4.171,0.369)	0.168(-8.850,9.118)	0.427(-8.788,9.645)
Shenmai injection + WM	1.047(0.588,1.918)	1.527(0.947,2.418)	−1.104(-5.049,2.609)	0.686(-8.404,9.703)	0.990(-8.352,10.360)
Shenqi Fuzheng injection + WM	2.295(0.516,12.560)	2.516(0.897,7.266)	−0.864(-4.015,2.073)	2.069(-7.022,11.050)	1.745(-7.456,10.940)
Yiqifumai injection + WM	0.446(0.151,1.341)	0.626(0.175,2.201)	−1.711(-5.404,1.737)	−0.131(-9.306,8.958)	−0.323(-9.751,9.157)
WM.	0.225(0.142,0.350)	0.494(0.345,0.686)	−2.112(-3.851,-0.684)	−0.109(-6.486,6.182)	−0.349(-6.942,6.270)
Shenfu injection + WM *vs.*					
Shengmai injection + WM	0.988(0.397,2.345)	1.358(0.687,2.689)	−0.921(-3.627,2.018)	0.543(-9.127,10.150)	1.354(-8.205,10.990)
Shenmai injection + WM	1.337(0.545,3.131)	1.107(0.588,2.057)	−0.156(-4.335,4.084)	1.061(-8.626,10.770)	1.911(-7.765,11.630)
Shenqi Fuzheng injection + WM	2.948(0.562,17.920)	1.828(0.601,5.678)	0.102(-3.371,3.593)	2.447(-7.330,12.220)	2.684(-6.928,12.270)
Yiqifumai injection + WM	0.568(0.160,1.993)	0.453(0.120,1.708)	−0.751(-4.746,3.144)	0.240(-9.577,10.030)	0.625(-9.245,10.440)
WM.	0.287(0.128,0.607)	0.358(0.207,0.607)	−1.163(-3.489,1.155)	0.258(-7.027,7.542)	0.565(-6.561,7.728)
Shengmai injection + WM *vs.*					
Shenmai injection + WM	1.354(0.767,2.404)	0.815(0.477,1.382)	0.774(-3.160,4.521)	0.525(-8.586,9.658)	0.545(-8.648,9.742)
Shenqi Fuzheng injection + WM	2.964(0.679,15.790)	1.344(0.467,4.002)	1.009(-2.139,3.971)	1.910(-7.212,10.990)	1.325(-7.828,10.360)
Yiqifumai injection + WM	0.573(0.195,1.719)	0.335(0.092,1.198)	0.164(-3.503,3.601)	−0.302(-9.465,8.919)	−0.746(-10.110,8.594)
WM.	0.290(0.188,0.440)	0.264(0.171,0.397)	−0.221(-2.030,1.260)	−0.278(-6.664,6.140)	−0.771(-7.173,5.622)
Shenmai injection + WM *vs.*					
Shenqi Fuzheng injection + WM	2.177(0.530,11.140)	1.650(0.632,4.457)	0.253(-4.119,4.574)	1.381(-7.829,10.530)	0.777(-8.543,9.946)
Yiqifumai injection + WM	0.427(0.146,1.238)	0.409(0.117,1.441)	−0.587(-5.343,4.109)	−0.823(-10.060,8.463)	−1.287(-10.730,8.170)
WM.	0.214(0.144,0.310)	0.323(0.234,0.444)	−1.030(-4.506,2.546)	−0.799(-7.272,5.719)	−1.323(-7.941,5.287)
Shenqi Fuzheng injection + WM *vs.*					
Yiqifumai injection + WM	0.194(0.028,1.098)	0.247(0.053,1.174)	−0.849(-5.021,3.311)	−2.196(-11.400,7.052)	−2.060(-11.370,7.258)
WM.	0.098(0.019,0.405)	0.196(0.072,0.514)	−1.256(-3.886,1.336)	−2.187(-8.645,4.341)	−2.095(-8.508,4.322)
Yiqifumai injection + WM *vs.*					
WM.	0.504(0.183,1.349)	0.788(0.233,2.642)	−0.418(-3.579,2.82)	0.023(-6.551,6.607)	−0.036(-6.805,6.749)

Table 2
Ranking probability of all interventions.

Intervention	Symptomatic improvement		Electrocardiography improvement		Fibrinogen		Triglyceride		Cholesterol	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
Ciwujia injection+WM	24.7	7	68.2	3	-	-	-	-	-	-
Dazhuhongjingtian injection+WM	70.9	3	49.8	6	43.2	5	44.6	5	45.1	5
Huangqi injection+WM	67.5	4	28.2	7	**86.0**	1	46.1	4	47.6	4
Shenfu injection+WM	50.9	5	53.8	5	60.2	3	42.7	7	37.2	8
Shengmai injection+WM	47.5	6	78.7	2	33.5	7	48.8	3	53.9	3
Shenmai injection+WM	71.4	2	62.7	4	54.2	4	56.4	2	60.9	2
Shenqi Fuzheng injection+WM	**91.3**	1	**87.0**	1	61.9	2	**73.9**	1	**71.5**	1
Yiqifumai injection+WM	24.1	8	17.2	8	40.4	6	44.5	6	43.7	6
WM.	1.6	9	4.4	9	20.5	8	42.8	8	40.1	7

WM (OR = 0.290, 95% CI: 0.123-0.648), Dazhuhongjingtian injection + WM vs. WM (OR = 0.371, 95% CI: 0.268-0.510), Huangqi injection + WM vs. WM (OR = 0.494, 95% CI: 0.345-0.686), Shenfu injection + WM vs. WM (OR = 0.358, 95% CI: 0.207-0.607), Shengmai injection + WM vs. WM (OR = 0.264, 95% CI: 0.171-0.397), Shenmai injection + WM vs. WM (OR = 0.323, 95% CI: 0.234-0.444), and Shenqi Fuzheng injection + WM vs. WM (OR = 0.196, 95% CI: 0.072-0.514). Ranking analysis indicated that Shenqi Fuzheng injection + WM was the optimal combination with a probability of 87.0%; other beneficial interventions were Shengmai injection + WM (78.7%) and Shenqi Fuzheng injection + WM (68.2%) (Table 2 and Fig. 5). In addition, the forest plot for symptomatic improvement is shown in Fig. 6.

3.5. Fibrinogen

Fibrinogen was identified in 12 RCTs (Dazhuhongjingtian injection + WM vs. WM (n = 4), Huangqi injection + WM vs. WM (n = 2), Shenfu injection + WM vs. WM (n = 1), Shengmai injection + WM vs. WM (n = 1), Shenmai injection + WM vs. WM (n = 2), Shenqi Fuzheng injection + WM vs. WM (n = 1), Yiqifumai injection + WM vs. WM (n = 1)). Huangqi injection + WM vs. WM (OR= -2.112, 95% CI: -3.851-0.648) showed a statistically significant difference (Table 1). The ranking analysis indicated that Dazhuhongjingtian injection + WM was the favourable intervention (86.0%) (Table 2).

3.6. Triglyceride and cholesterol

The efficiency of decreasing triglyceride and cholesterol was estimated in 7 RCTs (Dazhuhongjingtian injection + WM vs. WM (n = 1), Huangqi injection + WM vs. WM (n = 1), Shenfu injection + WM vs. WM (n = 1), Shengmai injection + WM vs. WM (n = 1), Shenmai injection + WM vs. WM (n = 1), Shenqi Fuzheng injection + WM vs. WM (n = 1), Yiqifumai injection + WM vs. WM (n = 1)). According to Table 1, there was no significant difference between each comparison. Based on ranking analysis, Shenqi Fuzheng injection + WM was the optimum treatment for these two indexes (Table 2).

3.7. Cluster analysis

The cluster analysis based on SUCRA is illustrated in Fig. 7. First, the cluster analysis was towards all eligible interventions tested for both symptomatic improvement and electrocardiography improvement. Subsequently, cluster analyses were performed between these two outcomes and others. The eight eligible interventions for which effects on triglyceride and cholesterol were investigated also underwent a cluster analysis. Among all eligible comparisons, Shenqi Fuzheng injection + WM therapy was overall outstanding, while Huangqi injection + WM exhibited a superior effect to other therapies in reducing fibrinogen, and Shenmai injection + WM exhibited a better impact on lowering serum lipids.

3.8. Trial sequential analysis

In accordance to the trial sequential analysis, evidence on Shenqi Fuzheng injection + WM was insufficient, and a larger sample size was needed to support the findings regarding symptomatic improvement and electrocardiography improvement. While the evidence on Shenmai injection + WM was stable with the existing sample size in these two outcomes, the evidence on Huangqi injection + WM and Shenmai injection + WM in fibrinogen, triglyceride, and cholesterol outcomes was insufficient and needed a larger sample size for support. The graphic presentation is shown in Fig. 8.

3.9. Publication bias

Publication bias was expressed by funnel plots for symptomatic improvement, electrocardiography improvement and fibrinogen. Visual inspection showed asymmetry in these outcomes, whereas several included RCTs were displayed outside of the lines. Thus, the potential publication bias did exist (Fig. 9).

3.10. Inconsistency test

Loop-specific analysis did not find any inconsistency in symptomatic

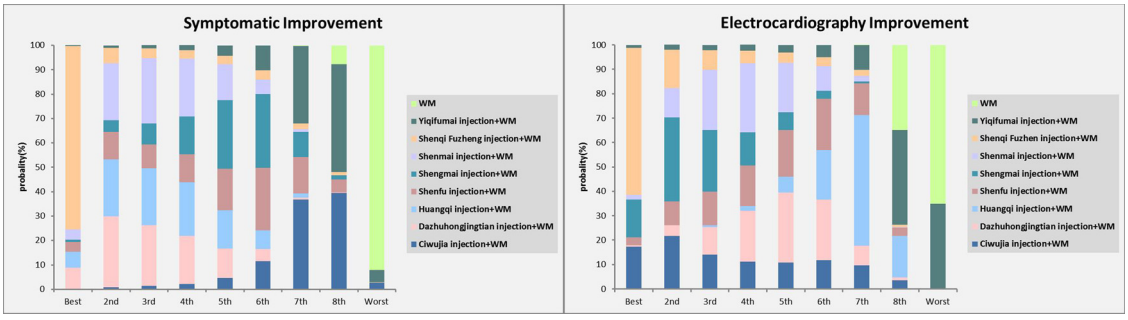

Fig. 5. Plot of the surface under the cumulative ranking curves for all treatments based on symptomatic improvement and electrocardiography improvement.

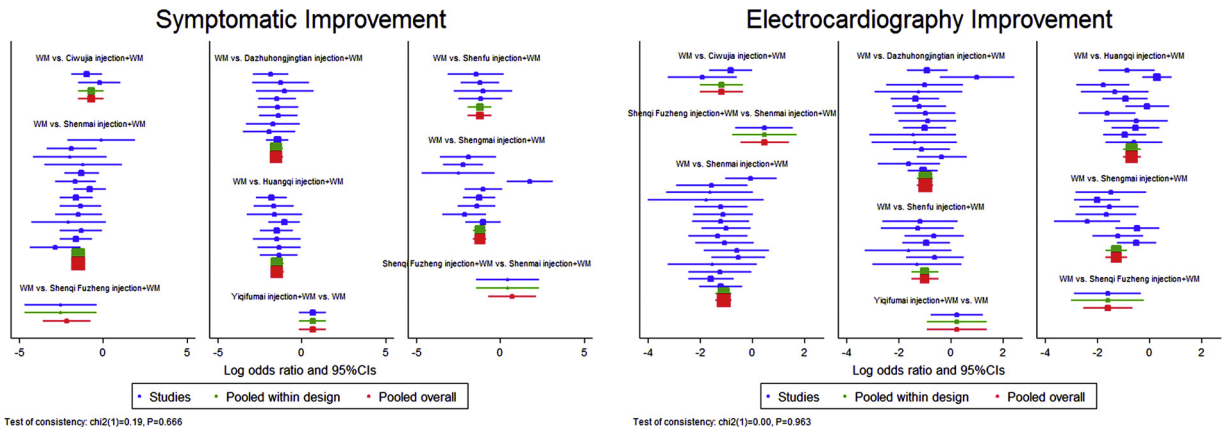

Fig. 6. Network forest plot for symptomatic improvement and electrocardiography improvement.

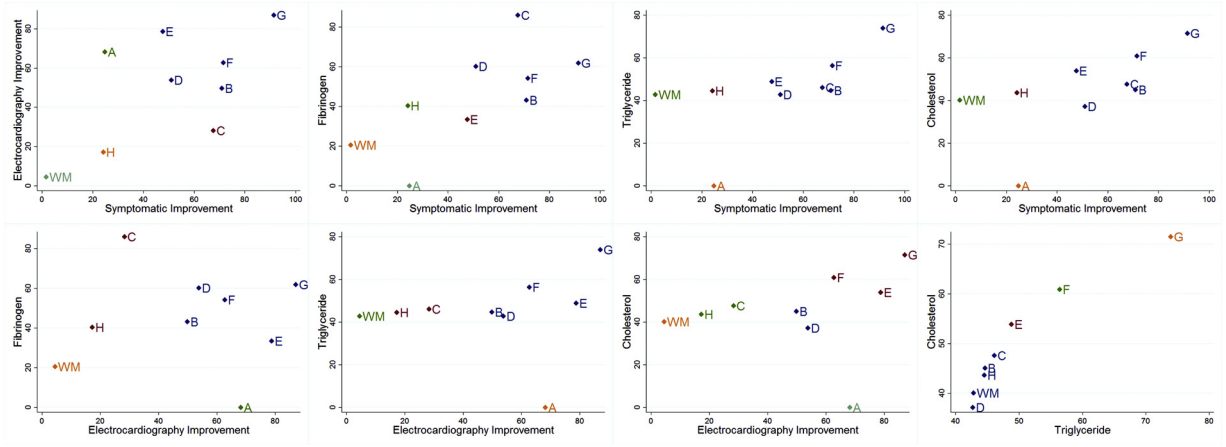

Fig. 7. Plots of the cluster analyses for all types of outcomes.
Note: A: Ciwujia injection + WM; B: Dazhuhongjingtian injection + WM; C: Huangqi injection + WM; D: Shenfu injection + WM; E: Shengmai injection + WM; F: Shenmai injection + WM; G: Shenqi Fuzheng injection + WM; H: Yiqifumai injection + WM.

improvement and electrocardiography improvement. The p-value of the loop of Shenmai injection + WM-Shenqi and Fuzheng injection + WM-WM was above 0.05, and the inconsistency factors were 0.630 (0.00, 3.49) and 0.049 (0.00, 1.76), respectively, showing that the direct and indirect evidence were consistent.

3.11. Safety

In terms of safety, 21 RCTs did not have any ADRs during treatment, and 13 RCTs reported ADRs. Meanwhile, the remaining RCTs did not report ADRs/ADEs in their publications. Among 13 RCTs, 12 RCTs administered WM in the control group, and one administered Shenmai injection + WM. Two of the RCTs administered Dazhuhongjingtian injection + WM in the treatment group: in Liu's research, the control

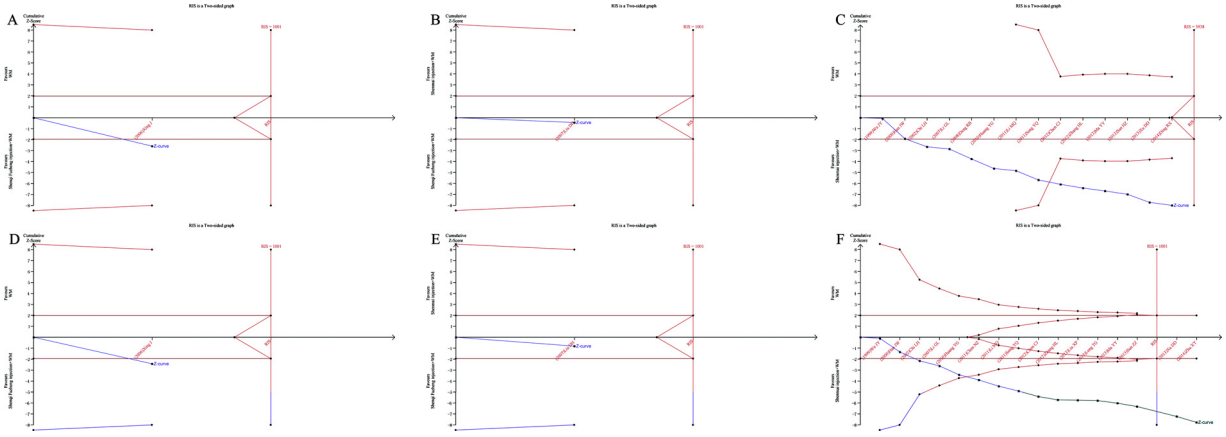

Fig. 8. Plot of trial sequential analysis for symptomatic improvement and electrocardiography improvement.
Note: A-C: trial sequential analysis for symptomatic improvement; D-F: trial sequential analysis for electrocardiography improvement.

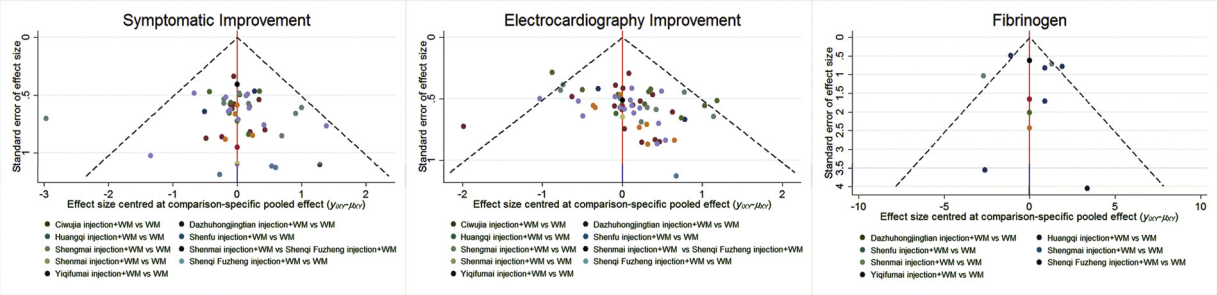

Fig. 9. Funnel plot of symptomatic improvement, electrocardiography improvement and fibrinogen.

group reported 1 case of dropsy and 1 case of headache; and in Qin's research, the treatment group reported 1 case of nausea and vomiting and 1 case of dizziness, while in the corresponding control group, 3 cases of nausea and vomiting, 2 cases of light dizziness, 3 cases of headache were reported. Two of the RCTs administered Huangqi injection + WM in the treatment group: in Zhao's research, the treatment group reported 2 cases of skin allergy; and in Shao's research, the treatment group reported 1 case of fever and 2 cases of dizziness. Two of the RCTs administered Shenfu injection + WM in the treatment group: in Wang's research, the treatment group reported 2 cases of xerostomia and dysphoria; and in Su's research, the treatment group reported 1 case of light headache and dysphoria, while its corresponding control group reported 8 cases of light headache. One of the RCTs administered Shengmai injection + WM in the treatment group: in Liang's research, the treatment group reported 1 case of flush, and its corresponding control group reported 1 case of headache. Five of the RCTs administered Shenmai injection + WM in the treatment group: in Wu's research, the control group reported 6 cases of ADRs but did not report the specific situation; in Chi's research, the treatment group and the control group reported 5 cases and 4 cases of headache and dizziness; in Sun's research, the treatment group and the control group reported 3 cases and 1 case of stomach disorder; in Ding's research, the treatment group reported 1 case of dizziness, 1 case of debilitation and 2 cases of flush, while its corresponding control group reported 1 case of debilitation and 1 case of flush; and in Zhu's research, the treatment group reported 1 case of headache and 1 case of flush, while its corresponding control group reported 2 cases of headache and flush. In addition, one of the RCTs administered Shenqi Fuzheng injection + WM in the treatment group and Shenmai injection in the control group: in Liu's group, the treatment group reported 2 cases of fullness in the head. All the symptoms were treated and did not affect the results.

A total of 12 RCTs utilized Chinese herbal injection exceeding the recommended dosage: 5 RCTs did not report ADRs (1 RCT utilized Dazhuhongjingtian injection + WM in the treatment group, 3 RCTs utilized Huangqi injection + WM in the treatment group, and 1 RCT utilized Shengmai injection + WM in the treatment group) and 2 RCTs utilized Huangqi injection + WM in the treatment group and reported ADRs. In addition, the remaining RCTs did not report ADRs/ADEs in their publications. The detailed information is shown in supplementary file 3.

A total of 23 RCTs utilized Chinese herbal injection with solutions not congruent with specifications: 10 RCTs did not report ADRs (6 RCTs utilized Dazhuhongjingtian injection + WM in the treatment group, 1 RCTs utilized Shengmai injection + WM in the treatment group, 2 RCT utilized Shenmai injection + WM in the treatment group and 1 RCT utilized Yiqifumai injection + WM in the treatment group), while 2 RCTs utilized Shenfu injection + WM in the treatment group and reported ADRs. In addition, the remaining RCTs did not report ADRs/ADEs in their publications. The detailed information is shown in supplementary file 3.

4. Discussion

AP, a severe form of cardiovascular disease accompanied by a high mortality rate and poor life quality, has attracted great awareness from society and the clinic.[5] Among various treatments, Chinese herbal injections have been recommended as complementary and alternative regimens and attained desired efficacy, as proven by many clinical trials and systematic reviews.[18–24] As this NMA sought to identify potential regimens, 73 RCTs with 6639 patients were included to analyse the comparative effectiveness of Chinese herbal injections simultaneously with the absence of direct comparison. Nine treatments were compared in this NMA, namely, Ciwujia injection + WM vs. WM, Dazhuhongjingtian injection + WM vs. WM, Huangqi injection + WM vs. WM, Shenfu injection + WM vs. WM, Shengmai injection + WM vs. WM, Shenmai injection + WM vs. WM, Shenqi Fuzheng injection + WM vs. WM, Shenqi Fuzheng injection + WM vs. Shenmai injection + WM, and Yiqifumai injection + WM vs. WM.

Four principal findings provided new evidence on the efficacy of Chinese herbal injections for treating AP: (1) Integrating NMA results and cluster analysis, all eligible Chinese herbal injections plus WM therapy were associated with significantly greater clinical improvement than WM therapy alone. (2) Among eligible Chinese herbal injections, Shenqi Fuzheng injection plus WM therapy and Shenmai injection plus WM therapy exhibited a better effect than other interventions. Meanwhile, Huangqi injection plus WM therapy and Shenmai injection plus WM therapy exerted an outstanding impact on the haemorheology index and serum lipid parameter by reducing fibrinogen, triglyceride and cholesterol levels. (3) Trial sequential analysis and publication bias analysis indicated that the sample size needed to be extended to attain a rigorous conclusion. (4) Some included RCTs did not strictly adhere to specifications and reported less safety, causing difficulty in ascertaining conclusions on safety due to insufficient information.

Shenqi Fuzheng injection is a kind of Chinese herbal injection extracted from Dangshen (*CODONOPSIS RADIX*) and Huangqi (*ASTRAGALI RADIX*), whose major ingredients are lobetyolin, astragaloside and so on.[29] By combining these two tonic herbal medicines, the ability to reinforce healthy *qi* will be enhanced.[29,30] Pharmacological experiments confirmed that Shenqi Fuzheng injection led to dilation of coronary arteries, reducing coronary artery perfusion resistance. This treatment can also decrease cardiac oxygen consumption to prevent myocardial reperfusion injury and protect ischaemic myocardium.[30,31] The Shenmai injection contains Hongshen (*GINSENG RADIX ET RHIZOMA RUBRA*) and Maidong (*Ophiopogonis radix*) and has an outstanding capacity to reinforce *qi* and replenish *yin* to generate body fluids. Its major ingredients are ginsenoside, Panaxatriol, Ophiopogonone, etc. Pharmacological studies have suggested that Shenmai injection has the ability to expand blood vessels and increase blood flow as well as protect the metabolic activity and microcirculation under ischaemia and hypoxia conditions.[32] In addition, several conventional pairwise meta-analyses have been conducted and demonstrated that Shenmai injection plus WM therapy is beneficial to improving symptoms and electrocardiographic parameters.[19,33,34] Huangqi injection is

made of extracts of Huangqi (*ASTRAGALI RADIX*), and its dominant component is astragaloside. Pharmacological experiments showed that Huangqi injection could dilate blood vessels, reduce the platelet adhesion rate, improve microcirculation and protect cardiac cells.[23,35] Additionally, several conventional pairwise meta-analyses indicated that Huangqi performed well in improving symptoms and electrocardiographic parameters in AP patients.[23,35,36]

Apart from efficacy, the safety of Chinese herbal injections in the treatment of AP should be considered an important issue. Approximately 50 percent of included RCTs do not report on safety in their publications, leading to the lack of attention to drug safety among clinicians. By one estimate, ADRs usually occur within 30 min after treatment with Chinese herbal injections, and thus, attention should be focused on this period of time.[37] Moreover, it is the responsibility of clinicians to inform patients of potential ADRs when they receive Chinese herbal injections for the first time.[38] Meanwhile, approximately 50 percent of included RCTs utilized dosages or solutions not in accordance with specifications. Although no study demonstrated a certain relation between these two factors and ADRs, deviation from drug specifications may increase the risk of ADRs.[39,40]

Though previous conventional pairwise meta-analyses drew similar conclusions as this NMA, several merits need to be highlighted. The Bayesian model, the most applicable approach for multiple-intervention NMAs, was used for the first time to evaluate the efficacy of Chinese herbal injections in the treatment of AP. The application of this model addressed the absence of direct comparison of Chinese herbal injections and revealed a favourable intervention by ranking analysis of various outcomes. Further, a comprehensive retrieval and a pre-designed inclusion criterion ensured the lowest possible degree of clinical heterogeneity. Moreover, the method of trial sequential analysis decreased the incidence of random error to confirm the stability of the NMA and offered a required sample size for follow-up study.[17]

However, there were several unavoidable limitations in this NMA. First, the design of the included RCTs was poor. The small percentage of RCTs using a random number table and other low-risk methods was associated with an exaggerated curative effect and decreased reliability of the evidence.[16,41] Second, the majority of included RCTs did not perform a dialectical analysis. Chinese herbal injections exerted their pharmacological effect under the viewpoints of traditional Chinese medicine and must be utilized through dialectics, which could provide an innovative perspective for secondary research of the literature.[16] If included patients are diagnosed and treated in accordance with dialectics, the systematic reviews would synthesize the outcome data as different types of syndrome and offer a more pointed guideline for the clinic. Third, the outcomes of this NMA did not address the quality of life of patients. Multi-dimensional quality of life assessments can show a trend of AP prevention and can reflect curative effects and prognoses.[42] Given this information, the RCTs conducted in the future should be perfected in relevant areas. We also propose several suggestions towards RCTs on Chinese herbal injections in the treatment of AP. First, RCTs should be registered in advance to ensure the transparency of the trial process. Second, the implementation of RCTs should adhere to the latest clinical diagnosis and treatment guidelines. Third, clinicians should report the status of patients with as much detail as possible, including information on cardiac classification and dialectical condition, which can provide not only a holistic view of the disease progression but also offer an innovative perspective for systematic reviews.

5. Conclusion

In summary, these findings indicate that Chinese herbal injections plus WM therapy might have a positive influence on AP patients and may significantly outperform WM therapy alone. These results suggest that Shenqi Fuzheng injection plus WM therapy and Shenmai injection plus WM therapy are potentially the preferred interventions for AP. In addition, Huangqi injection plus WM therapy and Shenmai injection plus WM therapy performed pretty well in improving the haemorheology index and serum lipid parameters. Because of several limitations, the findings should be interpreted with caution. More large-scale and multi-centre RCTs are imperative to confirm the results of this NMA.

Authors' contributions

W J-R and W K-H: Conception and design of the network meta-analysis; W K-H, L X, Z S-X, N M-W, L S-Y, M Z-Q and G X-Y: Performance of the network meta-analysis; W K-H, S H-C and W J-R : Quality assessment of the network meta-analysis; W K-H, D X-J and Z D: Analysis of study data; and W K-H and D X-J: Writing of the paper. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that there are no competing interests in any aspects of this study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.01.019.

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