Systematic Review and Meta-Analysis

Medicine

OPEN

Safflor yellow treating angina pectoris

A pharmacoeconomic evaluation and network meta-analysis

Liang Lu, MM[a], Yang Li, PhD[a], Qiuchen Jin, BEC[a], Yongfa Chen, PhD[a,*]

Abstract

Background: Coronary heart disease (CHD) is a cardiovascular disease caused by myocardial ischemia. In China, safflor yellow and artemisinin-based combination therapies have been extensively used to treat angina pectoris.

Methods: Efficacies were provided by a network meta-analysis following the PRISMA 2020 checklist. Cost-effectiveness analysis was based on patient perspectives. Two-way and probabilistic sensitivity analyses were conducted to assess the robustness of the study results.

Results: Conventional treatment combined with safflower is a better choice against angina pectoris. Sensitivity analysis showed that the model was sensitive to the treatment efficacy rather than the drug cost.

Conclusion: Conventional treatment combined with safflower injection is suggested to treat angina pectoris. Low molecular weight heparin or compound Danshen-dropping pills can be used to increase the recovery rate of angina pectoris, according to conventional treatment combined with safflower injection.

Abbreviations: CAD = coronary artery disease, CHD = Coronary heart disease, CI = confidence interval, ECG = electrocardiogram, NMA = network meta-analysis, OR = odds ratio, PSA = Probabilistic sensitivity analysis, RCT = randomized controlled trial, SUCRA = The surface under the cumulative ranking curve, WTP = willingness to pay.

Keywords: angina pectoris, cost-effectiveness analysis, network meta-analysis, safflor yellow

1. Introduction

Coronary heart disease (CHD) is the most common heart disease and represents a continuum of diseases. CHD begins with coronary atherosclerosis in the early stages and progresses to established coronary artery disease (CAD), caused by plaque buildup in the walls of the arteries that supply blood to the heart and other parts of the body. Of all the diseases in China, CAD is currently the leading cause of death. As of 2013, the CAD prevalence among people aged 15 and above was 1.23%, 0.81%, and 1.02% for the urban and rural residents and combination, respectively, while the prevalence reached 2.78% in the older population over 60.[1] A recent study on the global burden of disease displayed that China accounted for about 38.2% of the deaths of CHD (ischemic heart disease) worldwide from 1990 to 2017.[2] Meanwhile, the CHD for all cardiovascular diseases elevated from 29% to 37%.[3] Treating angina pectoris is critical to avoiding CHD by preventing acute myocardial infarction. In China, the annual angina pectoris is higher in men than in women aged >40 years.[4] Similarly, in another world, annual angina pectoris in 50-year-old men and women is 0.2% and 0.08%, respectively.

Patients with CHD and angina pectoris frequently manifest anxiety and fear of untimely death. Besides,[5] in patients' self-consciousness, they saw themselves as a burden to their family and others, both physically and financially. In addition to their physical pain, the such psychological condition could result in negative emotions such as anxiety, guilt, and remorse in patients,[6] which would be more likely to lead to acute myocardial infarction or sudden death.[7] Additionally, the irrational drug became increasingly severe due to the increasing number of patients with CHD and angina pectoris saddled the healthcare system with a more social and economic burden. More specifically, CHD accounted for 9.4% of the disability-adjusted life-year loss of the top 10 diseases, ranking first in developed and developing countries.[8] The survey reported that the PCI cases in 2017 were 753142, a 13% increase over 2016, and the cost of hospitalization and medical devices is increasing annually.

Commonly used drugs for treating CHD and angina pectoris include nitrates β-blockers, calcium channel blockers, and antiplatelet agents. However, these drugs always produce side effects. Here, we selected a natural product, safflor yellow, a pigment extracted from the petals of safflor,[9–11] as a treatment drug to assess its efficacy, safety, and cost-effectiveness. Safflor yellow combats cardiovascular disease through various pharmacological effects, such as dilating blood vessels, improving myocardial blood supply, inhibiting platelet aggregation and

LL and YL contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This article does not contain any studies with human or animal subjects.

[a] School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing 211198, Jiangsu, P.R. China.

*Correspondence: Yongfa Chen, School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, P.R. China (e-mail: cyf@cpu.edu.cn).

How to cite this article: Lu L, Li Y, Jin Q, Chen Y. Safflor yellow treating angina pectoris: A pharmacoeconomic evaluation and network meta-analysis. Medicine 2022;101:41(e31036).

Received: 23 March 2022 / Received in final form: 5 September 2022 / Accepted: 7 September 2022

http://dx.doi.org/10.1097/MD.0000000000031036

thrombosis, and anti-oxidation, against cardiovascular disease. This study aimed to identify an optimal treatment plan for safflor yellow injection to guide rational drug use, targeting better allocation of resources and cost savings. To compare the efficacy and safety of safflor yellow injection with the existing angina-pectoris treatments, we conducted stratified research on top of evidence-based medicine using a network meta-analysis followed by pharmacoeconomic evaluation.

2. Methods

We conducted this meta-analysis by the PRISMA 2020 checklist.

2.1. Search strategy

We did a comprehensive search using predefined search terms in PubMed, Cochrane Library databases, Clinical Trials.gov, Chinese National Knowledge Infrastructure, WanFang, VIP databases, and China Biology Medicine Disc (Si-noMed) from January 2005 to December 2019. Keywords included "angina pectoris," "coronary heart disease," "safflor flavin," "safflor yellow injection," and "safflor injection." An advanced search combined with keywords was used to search the Chinese literature. The main search terms were: "stenocardia," "angina pectoris," "coronary heart disease," "safflor flavin," "safflor injection." All prospective studies were included with no linguistic restrictions and were independently screened by 2 reviewers (Lu and Li).

2.2. Inclusion criteria

2.2.1. Study type. Randomized Controlled Trials (RCTs) and retrospective trials.

2.2.2. Participants. All patients were clinically diagnosed with angina pectoris, including stable and unstable angina pectoris caused by aging, abnormal lipid metabolism, hypertension, smoking, diabetes, and other factors.[12]

2.2.3. Interventions. The treatment group was dosed with safflor yellow injection alone, safflor yellow freeze-dried injection product or safflor injection, or safflor yellow combined with conventional treatment or other drugs (low molecular heparin 5000U, carvedilol, levocarnitine injection, atorvastatin calcium tablets, Danshen injection, etc). Conventional treatments with nitrate drugs, β-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers were used when angina pectoris occurred. As a result, these 4 drugs were incorporated into the cost calculation in the following pharmacoeconomic studies.

The control group was given conventional treatment or drugs against angina pectoris, such as compounded Danshen dripping pills, compound Danshen injections, Xiangdan injections, and safflor injections.

2.2.4. Outcomes. The total effective rate was defined based on "Common Guidelines for the Diagnosis and Treatment of Cardiovascular and Cerebrovascular Diseases in China."[13]

(1) judgment criteria for angina pectoris:
- significantly effective: angina pectoris disappears or disappears or the frequency or nitroglycerin consumption is reduced by more than 80% treated for 1 course;
- effective: angina pectoris is largely relieved after 1 course, Nitroglycerin consumption was reduced by over 50%;
- ineffective: times of angina pectoris or nitroglycerin usage was reduced by more than 80%, 50% to 80%, and <50%, respectively.

(2) Criteria for the electrocardiogram (ECG) efficacy:
- significantly effective: the symptoms disappear, the ST segment and T wave of the ECG return to normal, and the exercise test changes from positive to negative;
- effective: symptoms were relieved, the ST segment was low on the ECG, and the T-wave inversion was corrected;
- ineffective: the symptoms were not alleviated, and the ST segment was low on the ECG, or the T-wave inversion was not improved.

2.3. Exclusion criteria

Studies without full-text access, studies with incomplete or severely faulted data, studies with repetitive publications or data, retrospective studies, studies with incomplete or unclear reports on experimental design and results reporting, and animal experiments.

2.4. Literature screening and data extraction

The NoteExpress 3.4.0 software was used for reference management. Two researchers selected the documents independently following the inclusion and exclusion criteria and then extracted the data. The literature extraction data predominantly contained the following information: general information of the study: author, publication time, sample size, age, type of study, etc; treatment: dosage and treatment duration; and outcome indicators: angina pectoris efficacy criteria, ECG, hemorheology indexes, blood lipid improvement, etc.

2.5. Quality assessment

The Cochrane Handbook versions 5.0.1 RCT bias risk assessment tool[14] was applied to weigh the methodological quality of RCTs. Seven domains were integrated into the evaluation: random sequence generation, allocation concealment, blinding method of subjects and researchers, blinding method of the outcome evaluator, incomplete outcome report, selective outcome report, and other biases. Each item was classified as a "low-risk bias," "unclear," or "high-risk bias." Two reviewers conducted data extraction and methodological evaluation. Any inconsistencies were resolved through discussion.

2.6. Statistical methods

A network meta-analysis was utilized for frequency statistics and a Bayesian approach. The frequency statistics approach used statistical samples under hypothesis testing and inference conclusions. The Bayesian approach is flexible and powerful and requires a high degree of statistical knowledge. The frequency statistics method is simple and easily understood (Tian et al, 2014).[15] The Bayesian analysis was performed under Bayesian principles and posterior/prior probability. Studies indicated equivalent reliability between the results of a network meta-analysis of frequency statistics and the Bayesian approach (Carlin et al, 2013).[16] This study implemented a network meta-analysis for research and analysis according to the frequency statistics, a multivariate framework and frequency theory. Stata software (version 14.0) was used for statistical analysis and graphics plotting, applying the mvmeta network and its packages (Tian et al, 2014).[15] The outcome indicators in this study were binary classification variables. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). A network diagram was prepared under the 2-arm data structure to demonstrate the comparative relationships among the different interventions (Zhang et al, 2013).[17] Subsequently, a networked meta-random effect model was constructed to evaluate the model consistency, and then "if plot" command was utilized to assess the inconsistency factor value and conduct the Z test. $P > .05$ indicated consistency, demonstrating better consistency in direct and indirect comparisons (Zhang et al, 2014).[18] The intervention was evaluated for publication bias or small-sample effects by drawing a comparison-correction funnel plot. The surface under the cumulative ranking curve of each intervention (SUCRA) was calculated to predict the ranking of the intervention drug efficacy. The closer the SUCRA value is to 100, the better the intervention is Zeng et al, 2013.[19]

3. Result

3.1. Search results

Of the 79829 related studies identified, 810 retrieved records were screened after removing duplicates and the initial exclusion of invalid literature. Full-text assessment resulted in 42 eligible articles after excluding 768 articles according to this review's inclusion and exclusion criteria, including 41 Chinese studies and 1 English study. The study selection process was performed according to PRISMA guidelines (Fig. 1).

3.2. Study characteristics

The main characteristics of the included studies are summarized in Table 1. The studies were published between 2006 and 2019. Overall, 42 trials[12,20–60] with 4290 angina-pectoris patients were involved in the network meta-analysis, 2273 in the treatment group and 2017 in the control group. The sample sizes of the study participants ranged from 46 to 432. The mean age of the patients across trials fluctuated from 39.8 to 72.7 years, along with a 7 to 14 day treatment duration.

3.3. Risk of bias assessment

The Cochrane risk of bias tool was used to assess the 9 included RCTs. Among the 42 included studies, 11[12,23–25,27,30,34,36,52,56,59] specifically reported the method of random sequence generation. Allocation concealment was adequately described in only a few included studies. All outcomes of the included studies were completed without determining other sources of bias. Overall, these 42 studies showed moderate methodological quality. The details of the bias-risk evaluation for each study are presented in Figure 2.

3.4. Network meta-analysis results

3.4.1. Evidence network diagram. This network meta-analysis (NMA) included 7 safflor yellow-related studies, including its monotherapy and combination with 5 other traditional Chinese medicine injections or conventional treatments for angina pectoris. As is shown in Figure 3, 2 closed loops were formed, focusing on the conventional treatment. 42 RCTs[12,20–60] for angina-pectoris treatment efficiency were estimated according to the efficacy evaluation criteria. ECG effects and

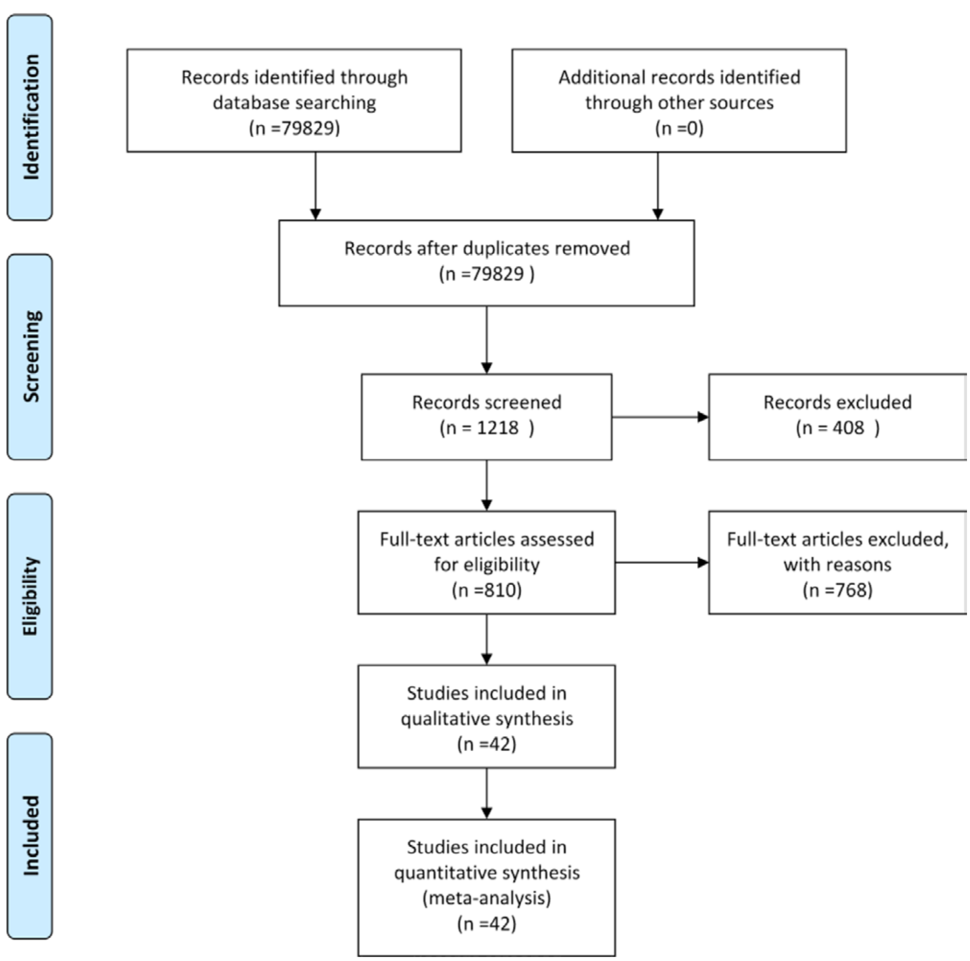

Figure 1. Document screening process.

Table 1

Characteristics of included studies.

Study	Sample size T	Sample size C	Age T	Age C	Interventions in the treatment group	Interventions in the control group	Treatment Duration	Outcome indexes	Study Design	Adverse reactions (Yes/No)
Battel 2014	36	36	55.8 ± 7.3	54.6 ± 8.6	CT + SYI 100 mg	CT	14d	①②	RCT	Not reported
Cui Xiuchun 2019	46	46	57.8 ± 6.2	57.8 ± 6.2	CT + safflor yellow sodium chloride injection 100 mL	CT	14d	①②③	RCT	Yes
Han Biaoding 2013	60	60	58.8	66.2	CT + 100 mL safflor yellow sodium chloride injection	CT	14d	①②③	RCT	Yes
Jin Chao 2010	65	65	57.10 ± 5.22	57.45 ± 6.67	CT + 150 mg SYI	CT	14d	①②④	RCT	No
Zhou Wenjun 2014	40	40	61.12 ± 5.43	61.12 ± 5.43	CT + SYI 100 mg	CT	14d	①②④⑤	RCT	Yes
Fang Xiang 2017	52	50	65.3 ± 12.8	66.4 ± 11.5	CT + SYI 150 mg	CT	14d	①②④⑤⑥⑦	RCT	No
Fang Kai¥ 2019	24	24	58.22 ± 5.14	59.46 ± 6.47	CT + SYI 150 mg	CT	14d	①③	RCT	No
Huang Bo 2016	26	26	60-75	60-75	CT + SYI 100 mg	CT	14d	①②③	RCT	No
Xu Xiangmei 2017	59	55	58.23 ± 6.10	59.05 ± 7.22	CT + SYI 100 mg	CT	14d	①②③⑦	RCT	Not reported
Lv Junfang 2014	43	43	58.0 ± 7.4	57.7 ± 7.7	CT + SYI 100 mg	CT	14d	①②	RCT	No
Wang ¥¥ 2012	32	32	56.4	55.4	CT + SI 20 mL	CT	14d	①②③	RCT	No
Li Yingchun 2018	59	59	54.35 ± 11.64	55.48 ± 11.16	CT + SYI 150 mg	CT	14d	①②③	RCT	Not reported
Liu Hua 2017	31	31	63.5 ± 4.2	64.2 ± 3.2	CT + SYI 100 mg	CT	14d	①②	RCT	Not reported
XuZhi 2018	50	50	59.2 ± 3.4	58.5 ± 3.2	SYI 100 mg + CT	CT		①②④	RCT	Not reported
Wu Juan 2014	60	60	54-78	54-78	CT + SYI 0.15 g	CT	14d	①②③	RCT	Not reported
Wang Chengjun 2011	54	54	70.6 ± 9.2	72.7 ± 7.2	CT + SYI 80 mg	CT	14d	①②③	RCT	Not reported
Liu Jianhong 2009	28	20	62	63	CT + SYI 50 mg	CT	10d	①②③	RCT	No
Wang Jun2 014	35	35	68	68	CT + SYI 100 mg + L-C3g	CT	10d	①②	RCT	No
Huang Lumei 2017	56	56	69.13 ± 6.24	68.26 ± 5.47	CT + SYI 100 mg + L-C 3 g	CT	14d	①②③	RCT	No
Wu Haokun 2017	39	39	61.5 ± 8.4	60.0 ± 8.2	CT + safflor yellow sodium chloride injection 100 mL + CD 10 mg	CT	14d	①②③	RCT	No
Zhang Yulei 2007	83	69	63.5	64.5	CT + H5000U + SI 20 mL	CT	14d	①②	RCT	Yes
Zu Guoyou 2010	37	35	41.3	39.8	CT + H4100U + SI 100 mg	CT	7d	①②⑦	RCT	Yes
Huang Liuxiang 2014	45	45	64.7 ± 6.5	65.2 ± 6.7	CT + safflor yellow sodium chloride injection 100 mL + SMI 60 mL	CT	14d	①②③	RCT	No
Ji Kaifeng 2012	36	36	58.8 ± 13.5	59.4 ± 14.3	CT + SYI 100 mg + AC 20 mg	CT	14d	①②	RCT	Not reported
Li Dan 2016	23	23	/	/	CT + SI 40 mL + DS	CT	14d	①②	RCT	No
Wu Shuqi 2016	24	24	/	/	CT + SI 20 mL + DS	CT	14d	①②⑦	RCT	No
Su Wenjie 2016	50	50	56.2 ± 2.6	56.2 ± 2.6	CT + SI 30 mL	CT	14d	①②	RCT	Yes
Chen Wenbin 2013	50	50	55.7 ± 2.3	55.7 ± 2.3	CT + SI 30 mL	CT	14d	①②	RCT	No
Cao Xuehui 2012	78	78	54.6	55.3	CT + SI 30 mL	CT	14d	①②	RCT	Not reported
Hou Mingying 2013	65	65	59.3 ± 10.8	58.6 ± 10.2	CT + SYI 100 mg	CT	14d	①②③⑦	RCT	No
Wang Yingjie 2013	60	56	64.5	65.2	CT + SYI 100 mg	CT	14d	①②③	RCT	Not reported
Li Xiaojun 2013	46	46	55.5 ± 5.6	55.5 ± 5.6	SYI 20 mL	CT	14d	①②	RCT	No
Zhu Xiaofeng 2012	107	108	18-70	18-70	SYI 250 mg	SI 15 mL	14d	①②④⑧⑨	RCT	Yes
Zhang Qiong	323	100	18-70	18-70	SYI 80 mg	DSI 20 mL	14d	①②③	RCT	No
Wu Changyan 2014	35	35	63.51	62.58	CT + SYI 100 mg	CT + salvianolate injection 200 mg	14d	①②	RCT	Yes
Qi Yongjun 2014	48	48	544 ± 3.2	53.2 ± 4.5	CT + SI 30 mL	CT + DSI 30 mL	14d	①②	RCT	Yes
Wang Qiang 2012	30	30	59	59	SYI 150 mg	DSI 14 mL	14d	①②	RCT	Not reported
Wang Ying 2016	30	30	40-70	41-75	SYI 150 mg	DSI	14d	①	RCT	Not reported
Shi Hua 2012	50	50	39-70	39-71	SYI 80 mg	DSI 20 mL	14d	①②	RCT	No
Ji Hongbin 2015	100	100	55.32 ± 2.66	55.32 ± 2.66	Safflor yellow freeze-dried powder injection 100 mg	XDI 20 mL	14d	①②	RCT	No
Gao Linlin 2007	34	34	58.97 ± 5.96	58.48 ± 7.97	SYI 120 mg	XDI 10 mL	14d	①②③④⑧	RCT	No
ShenLin 2006	24	24	/	/	SYI 100 mg	XDI 10 mL	14d	①②③④⑧	RCT	Not reported

(A) Due to the different purity of safflor injection and safflor yellow injection, they should be distinguished; (B) The safflor yellow sodium chloride injection is prepared by adding sodium chloride to the safflor yellow injection for dilution. Therefore, only safflor yellow injection was included in the network meta-analysis.

AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

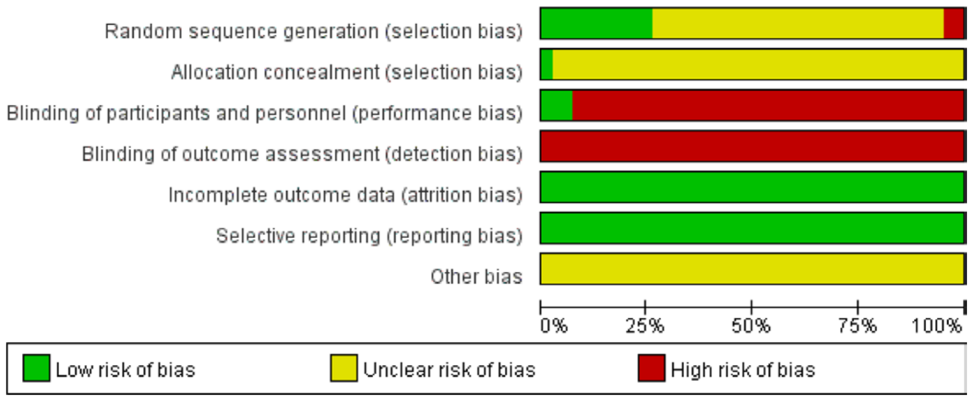

Figure 2. Bias risk of included studies.

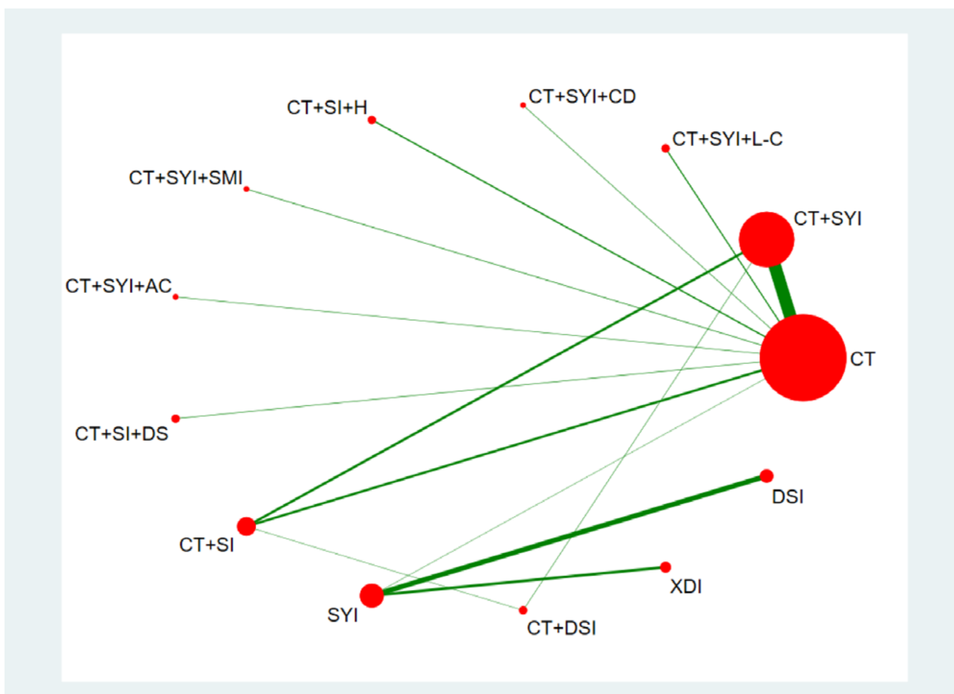

Figure 3. Evidence network plot. AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

hemorheological indicators were included in 40 RCTs[12,20–24,26–55,57–60] and 19 RCTs,[20,21,25–30,33–35,37,38,41,48,49,52,59,60] respectively.

3.4.2. Test for heterogeneity. Two triangular closed loops appeared during the intervention. LOOP was used to construct the inconsistency test chart, calculate the inconsistency factor, and conduct the Z test. The Z value finalized that Loop (CT + SYI-CT + SI-CT + DSI) *P* = .446 and Loop (CT-CT + SYI-CT + SI) *P* = .584, demonstrating no inconsistency results.

3.4.3. Publication bias. Eleven studies were included in the funnel plot for publication bias analysis. The funnel plot showed an asymmetric distribution of points and indicated the possibility of publication bias and minor study effects.

3.4.4. Network meta-analysis of drug efficacy for angina pectoris treatment. 42 RCTs demonstrated the clinical treatment efficacy against angina pectoris. A comparison of these results is presented in Table 2. Compared with the conventional treatment group, the CT + SI + H group showed the highest treatment efficacy (OR = 9.62, 95% CI [3.84, 24.05]), and the DSI group displayed the most modest treatment effect (OR = 0.85, 95% CI [0.16, 4.64]).

3.4.5. SUCRA curves of treatment efficacy. The SUCRA values from probability ranking are listed in Table 3. CT + SI + H had the highest rank probability of treatment success rate. The rank probability of the treatments based on SUCRAs is shown in Figure 4, demonstrating similarity to the ranking of the effective NMA results (Table 3).

3.5. Adverse reactions

Nine studies[20,21,23,39,40,45,51,53,54] including 1045 patients demonstrated the adverse events occurrences. Mild venous inflammation was observed in 2,[45] disappearing after needle removal and not significantly affecting treatment. In addition, 2 patients in the control group developed an allergic reaction. One study[40] indicated that the treatment and control groups resulted in

Table 2

Network meta-analysis results comparing the clinical effectiveness.

CT + SI + H	**0.70 (0.14,3.55)**	**0.55 (0.11,2.86)**	**0.45 (0.16,1.27)**	**0.41 (0.06,2.66)**	**0.44 (0.08,2.32)**	**0.41 (0.11,1.58)**	**0.34 (0.13,0.88)**	**0.30 (0.06,1.43)**	**0.17 (0.02,1.20)**	**0.11 (0.03,0.46)**	**0.09 (0.01,0.61)**	**0.10 (0.04,0.26)**
1.42 (0.28,7.17)	CT + SI + DS	0.79 (0.12,5.29)	0.64 (0.15,2.65)	0.58 (0.07,4.79)	0.63 (0.09,4.29)	0.59 (0.11,3.07)	0.48 (0.12,1.86)	0.43 (0.07,2.68)	0.24 (0.03,2.14)	0.15 (0.03,0.88)	0.13 (0.01,1.09)	0.15 (0.04,0.56)
1.80 (0.35,9.30)	1.27 (0.19,8.51)	CT + SYI + CD	0.81 (0.19,3.45)	0.74 (0.09,6.18)	0.79 (0.11,5.54)	0.74 (0.14,3.98)	0.60 (0.15,2.42)	0.55 (0.09,3.47)	0.30 (0.03,2.76)	0.20 (0.03,1.14)	0.16 (0.02,1.40)	0.19 (0.05,0.73)
2.22 (0.78,6.29)	1.56 (0.38,6.47)	1.23 (0.29,5.24)	CT + SI	0.91 (0.17,5.00)	0.98 (0.22,4.27)	0.92 (0.30,2.75)	0.74 (0.46,1.21)	0.68 (0.18,2.58)	0.37 (0.06,2.28)	0.24 (0.08,0.73)	0.20 (0.03,1.15)	0.23 (0.14,0.38)
2.44 (0.38,15.80)	1.71 (0.21,14.06)	1.35 (0.16,11.28)	1.10 (0.20,6.02)	SYI	1.07 (0.13,9.12)	1.00 (0.15,6.73)	0.82 (0.16,4.27)	0.74 (0.10,5.76)	0.41 (0.21,0.77)	0.27 (0.04,1.92)	0.22 (0.13,0.35)	0.25 (0.05,1.29)
2.27 (0.43,12.00)	1.60 (0.23,10.95)	1.26 (0.18,8.81)	1.02 (0.23,4.47)	0.93 (0.11,7.93)	CT + SYI + AC	0.94 (0.17,5.14)	0.76 (0.18,3.14)	0.69 (0.11,4.47)	0.38 (0.04,3.54)	0.25 (0.04,1.47)	0.20 (0.02,1.80)	0.24 (0.06,0.95)
2.43 (0.63,9.32)	1.71 (0.33,8.95)	1.35 (0.25,7.21)	1.09 (0.36,3.28)	1.00 (0.15,6.68)	1.07 (0.19,5.86)	CT + SYI + L-C	0.81 (0.29,2.27)	0.74 (0.15,3.61)	0.41 (0.05,3.02)	0.26 (0.06,1.17)	0.21 (0.03,1.53)	0.25 (0.09,0.68)
2.98 (1.14,7.79)	2.10 (0.54,8.20)	1.65 (0.41,6.64)	1.34 (0.82,2.19)	1.22 (0.23,6.40)	1.31 (0.32,5.42)	1.23 (0.44,3.42)	CT + SYI	0.91 (0.25,3.26)	0.50 (0.08,2.93)	0.32 (0.11,0.98)	0.26 (0.05,1.47)	0.31 (0.23,0.41)
3.28 (0.70,15.40)	2.31 (0.37,14.30)	1.82 (0.29,11.50)	1.48 (0.39,5.63)	1.35 (0.17,10.47)	1.44 (0.22,9.32)	1.35 (0.28,6.61)	1.10 (0.31,3.94)	CT + SYI + SMI	0.55 (0.06,4.69)	0.36 (0.07,1.91)	0.29 (0.04,2.38)	0.34 (0.10,1.18)
5.99 (0.83,43.20)	4.21 (0.47,38.01)	3.32 (0.36,30.48)	2.70 (0.44,16.61)	2.46 (1.30,4.66)	2.64 (0.28,24.62)	2.47 (0.33,18.38)	2.01 (0.34,11.82)	1.82 (0.21,15.62)	XDI	0.65 (0.08,5.21)	0.53 (0.24,1.17)	0.62 (0.11,3.59)
9.18 (2.16,39.10)	6.46 (1.13,36.86)	5.09 (0.87,29.69)	4.13 (1.36,12.52)	3.77 (0.52,27.24)	4.04 (0.68,24.09)	3.78 (0.85,16.82)	3.08 (1.02,9.26)	2.80 (0.52,14.93)	1.53 (0.19,12.25)	CT + DSI	0.81 (0.11,6.21)	0.96 (0.31,2.93)
11.30 (1.64,77.69)	7.95 (0.92,68.70)	6.27 (0.71,55.11)	5.09 (0.87,29.75)	4.64 (2.89,7.43)	4.97 (0.56,44.52)	4.66 (0.66,33.08)	3.79 (0.68,21.15)	3.44 (0.42,28.20)	1.89 (0.85,4.17)	1.23 (0.16,9.40)	DSI	1.18 (0.22,6.41)
9.62 (3.84,24.05)	**6.76 (1.78,25.63)**	**5.33 (1.37,20.78)**	**4.33 (2.64,7.09)**	**3.95 (0.77,20.12)**	**4.23 (1.06,16.97)**	**3.96 (1.48,10.60)**	**3.22 (2.42,4.28)**	**2.93 (0.84,10.16)**	**1.60 (0.28,9.23)**	**1.05 (0.34,3.21)**	**0.85 (0.16,4.64)**	CT

CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

bleeding, slightly longer coagulation time, and slightly reduced platelet count after treatment. One study[39] reported that 3 cases of acute myocardial infarction occurred in the control group without inducing death among the adverse reactions in the circulatory system. Five studies[20,21,39,53,54] indicated other adverse reactions, including insomnia, nausea, dizziness, nausea, pruritus, rash, hypotension, head swelling, and muscle aches. All adverse reactions returned to normal after continued or discontinued observation. The results show that safflor yellow injection is effective and safe for treating angina pectoris, with few adverse reactions.

Table 3

Probability ranking of clinical effectiveness evaluation in 13 angina-pectoris treatments.

Treatment	SUCRA	Rank	Ranking of the results of the network meta-analysis effectiveness
CT	12.1	13	13
CT + SYI	48.5	8	8
CT + SYI + L-C	59.3	7	6
CT + SYI + CD	68.6	3	3
CT + SI + H	89.4	1	1
CT + SYI + SMI	46.5	9	9
CT + SYI + AC	61.4	6	5
CT + SI + DS	77.8	2	2
CT + SI	65	4	4
SYI	63.1	5	7
CT + DSI	15.1	11	11
XDI	31.1	10	10
DSI	12.2	12	12

CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

4. Pharmacoeconomic evaluation

4.1. Research perspective

This analysis was done from the perspective of patients with angina.[61] The calculation of the implicit cost was not contained due to its complication. This study is a retrospective analysis, so the differences between indirect and hidden costs are too significant. Therefore, we only involved the direct costs of different treatment schemes.

4.2. Methods

4.2.1. Decision tree model. This study used a decision tree model to analyze the cost and effect of 13 treatment options for angina included in the network meta-analysis. Efficacy and safety indicators were obtained using meta-analysis to comprehensively evaluate the economics of 13 treatment regimens. The structure of the decision-tree model is shown in Figure 5. The model primarily assessed the short-term economy, and the time horizon for this analysis was 1 treatment course (14 days).

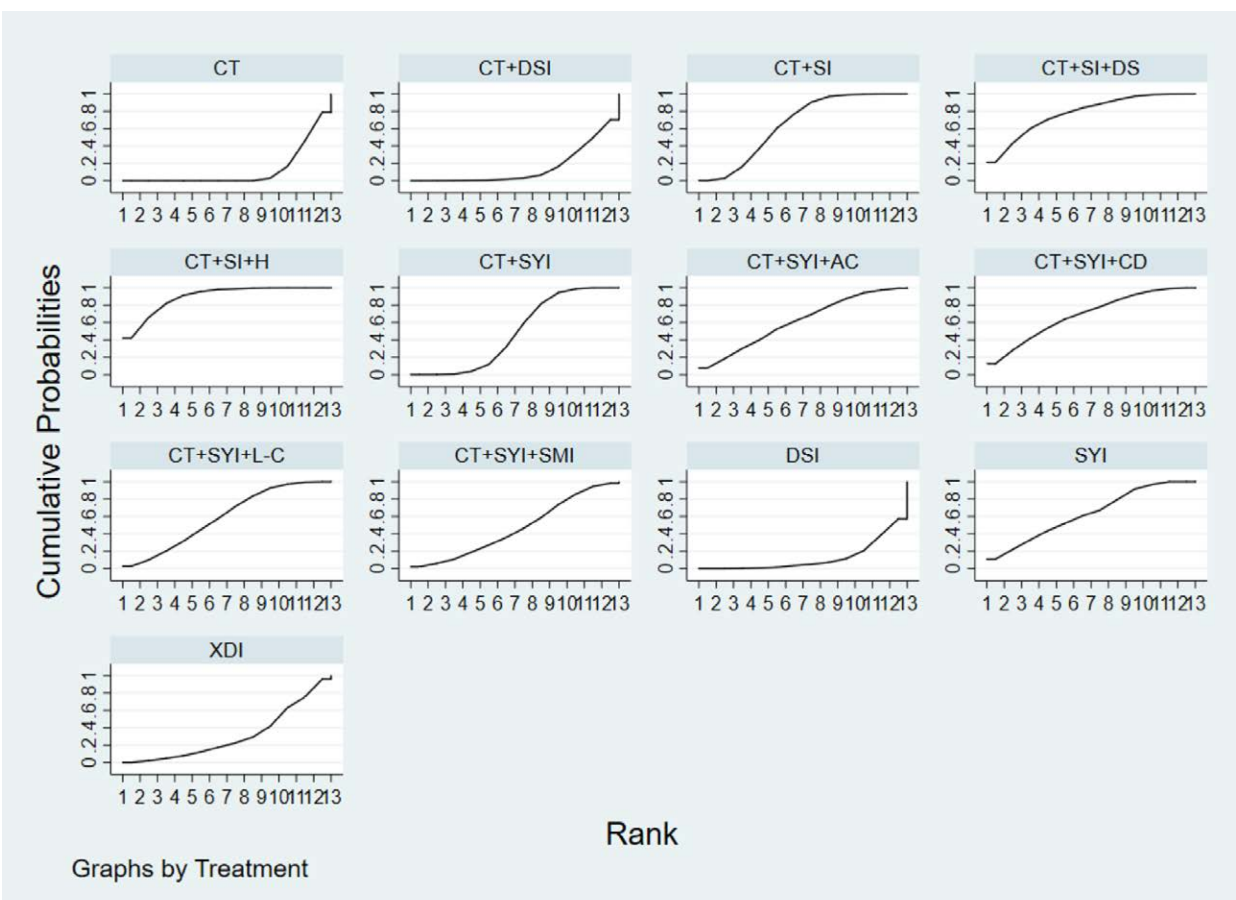

Figure 4. SUCRA curves of 13 treatment interventions. AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

Table 4

Clinical efficacy and ranking of 13 angina-pectoris treatments.

No.	Treatment	Effectiveness	Efficiency ranking	SUCRA rank	Efficient result ordering in network meta-analysis
1	CT	74.86%	12	13	13
2	CT + SYI	91.78%	6	8	8
3	CT + SYI + L-C	93.41%	4	7	6
4	CT + SYI + CD	92.31%	5	3	3
5	CT + SI + H	94.98%	1	1	1
6	CT + SYI + SMI	91.11%	9	9	9
7	CT + SYI + AC	91.67%	7	6	5
8	CT + SI + DS	93.66%	3	2	2
9	CT + SI	94.76%	2	4	4
10	SYI	91.24%	8	5	7
11	CT + DSI	80.76%	10	11	11
12	XDI	77.49%	11	10	10
13	DSI	69.40%	13	12	12

CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

4.2.2. Statistical analysis. In pharmacoeconomic evaluation, cost-effectiveness analysis calculated the incremental cost-effectiveness ratio. Cyclone plots were drawn by single factor sensitivity analysis, probability sensitivity analysis was carried out by Monte Carlo simulation, and acceptable cost effect curves were drawn.[62] TreeAge 2011 was used to construct a decision tree model for cost-effectiveness and sensitivity analyses.

4.2.3. Effectiveness. The studies included in the economic evaluation were similar to the network meta-analysis. We obtained the effective rates of 13 treatment regimens according to the proportion of each study shown in the forest map in the meta-analysis and weighting the treatment efficiency of angina patients. The results showed that the efficiency ranking and the score ranking of SUCRA in the NMA were similar, indicating that the efficiency from the weighted calculation was reasonable and could be included in the economic-evaluation calculation (Table 4).

4.2.4. Cost. Cost estimation was based on the patient perspective. We assumed that the direct and indirect costs of the 13 interventions were the same, that direct medical costs caused the differences in total costs, and that the cost of the conventional treatment was identical for each treatment regimen. In addition, this study's effective components of safflower yellow injection and safflower injection are consistent. However, they were produced by different manufacturers, were differentiated in the network meta-analysis and discriminated in the cost calculation. We adopted a discount rate of 5% for the cost data and discounted uniformly until early 2020.

(1) Drug cost

We utilized the most common drug retail prices and the lowest to the highest manufacturers' retail prices for the sensitivity analysis. When calculating the total drug cost of the 13 treatment schemes, the weighted drug amount was calculated by multiplying the cost of various drugs or injections in the included literature by the weight obtained from the meta-analysis and the drug cost of the treatment scheme was unified. The costs of the 10 drugs are shown in Table 5. The weighted dosages of the 13 treatment regimens are listed in Table 6.

The cost of 1 course of treatment, including Aspirin enteric-coated tablets, Propranolol tablets, Nitroglycerin tablets and Nifedipine sustained-release tablets for conventional treatment, was ¥13.09, ¥13.72, ¥1.68, and ¥17.08, respectively, and the total cost of 1 course of conventional treatment was ¥45.57.[63] The discounted cost of conventional treatment was ¥50.24.

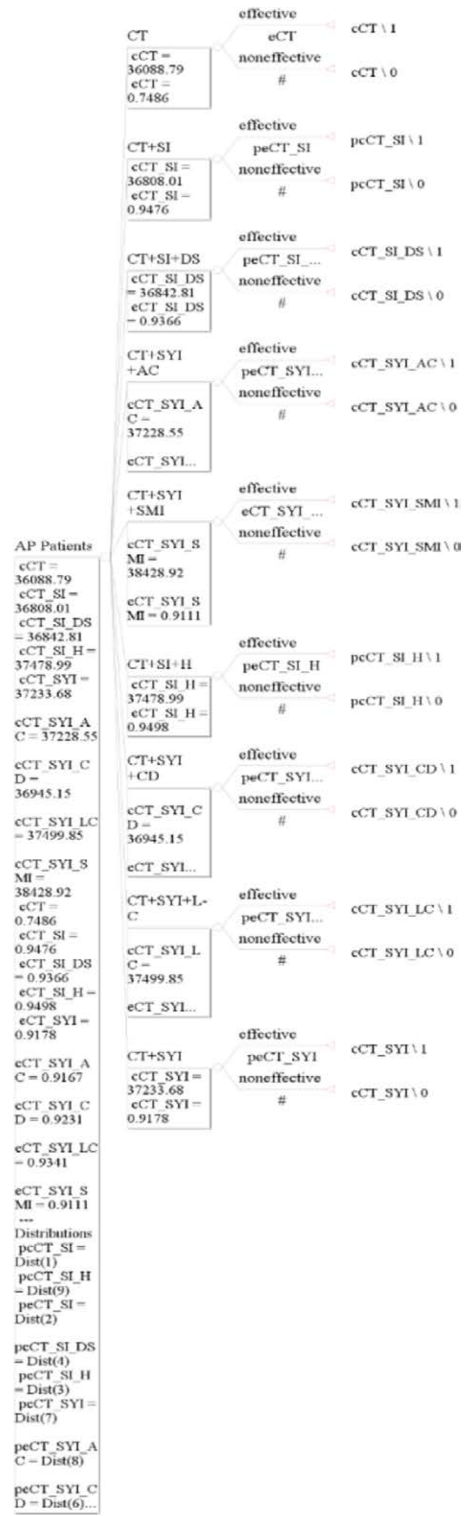

Figure 5. Decision tree model. The decision tree model was used to analyze the cost-effectiveness of 13 treatment options for angina included in the network meta-analysis. The specific treatment protocols and their cost are shown in this figure. The time horizon for this analysis is 1 treatment course (14 days). AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

(2) Other costs

The cost of injection mainly includes the cost of materials, such as disposable infusion tubes and syringes used for intravenous injection, and the cost of intravenous injection. The latest medical service fees published by the Beijing Medical Insurance Bureau include ¥5.5 for intravenous injection and ¥7 for intravenous infusion.[64] The total intravenous infusion material fee was ¥8.00 and the total amount of intravenous infusion material fee was ¥2.40.[65] After discounting, the average value is ¥14.3/day. In addition, the cost of examination items during the entire course of treatment for patients with angina includes the cost of blood, urine, stool routine, liver and kidney function, and electrocardiogram before treatment. The cost of laboratory tests and electrocardiograms was obtained from Jianwei Xuan et al[66] The average price of medical services was obtained from the website of the local Health Commission. Discount calculation results for inspection cost of ¥373.6. Zhang et al[67] summarized the costs of diagnosing and treating CHD in 26 sample hospitals from 2014 to 2016 and found that the average hospitalization cost for angina patients was ¥26745.12. Zhao et al[12] studied CHD in 237 tertiary hospitals in Beijing in 2014 and found that the average hospitalization cost of patients with unstable angina was ¥26482.41. The average cost of hospitalization calculated after discount is ¥34811.63.

4.3. Results

4.3.1. Base-case results. We selected studies with effective rates of more than 90% (including conventional treatment) for economic evaluation. As shown in Table 7, CT + SI was the most cost-effective treatment.

Table 5

Cost price and maximum/minimum value of 10 drugs.

Generic name	Cost/¥	Maximum	Minimum
Safflower yellow pigment injection	36.97/50 mg*1	79.9	20.5
Safflower injection	8.95/5 mL*1	12.6	2.21
Levocarnitine injection	13/g*1	23	8.7
Carvedilol	40.33/20 mg*10 pieces	48	7.2
Low molecular weight heparin	63.5/0.6 mL:6150AXaIU*2	118.96	29.96
Shenmai injection	36/20 mL*4	77.54	24.04
Atorvastatin calcium tablets	26.15/10 mg*7 pieces	60	3.88
Compound salvia miltiorrhiza drop pills	28.53/27 mg*180 tablets	45	18
Salvia miltiorrhiza injection	45.05/10 mL*6	54	27.24
Xiangdan injection	6.24/10 mL*1	16	1.38

(A) All data come from 315 medicine price inquiry net https://www.315jiage.cn. (B) Maximum, minimum and cost of the exact drug specifications.

Table 6

Weighted dose and cost of 13 treatment options.

NO.	Treatment	Weighted dose	Cost/¥	Maximun	Minimum
1	CT	——	36088.79	——	——
2	CT + SYI	CT + SYI (110.6 mg)	37233.68	38563.13	36723.63
3	CT + SYI + L-C	CT + SYI (100 mg) + L-C (3 g)	37499.85	39291.99	37028.19
4	CT + SYI + CD	CT + SYI (80 mg) + CD (10 mg)	36945.15	37912.15	36553.03
5	CT + SI + H	CT + SI (20 mL) + H (0.6 mg)	37478.99	38459.83	36631.99
6	CT + SYI + SMI	CT + SYI (80 mg) + SMI (60 mL)	38428.92	41135.23	37557.67
7	CT + SYI + AC	CT + SYI (100 mg) + AC (20 mg)	37228.55	38565.99	36678.31
8	CT + SI + DS	CT + SI (30 mL) + DS (1粒)	36842.81	37150.69	36275.83
9	CT + SI	CT + SI (28.7 mL)	36808.01	37101.33	36088.79
10	CT + DSI	CT + DSI (30 mL)	36404.14	36466.79	36279.47

CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

Table 7

Base-case analysis results.

No.	Treatment	Effectiveness	Incremental effectiveness	Cost	Incremental cost	ICER
1	CT	74.86%	——	36088.79	——	——
2	CT + SYI	91.78%	0.1692	37233.68	1144.89	6766.47
3	CT + SYI + L-C	93.41%	0.1855	37499.85	1411.06	7606.79
4	CT + SYI + CD	92.31%	0.1745	36945.15	856.36	4907.50
5	CT + SI + H	94.98%	0.2012	37478.99	1390.20	6909.54
6	CT + SYI + SMI	91.11%	0.1625	38428.92	2340.13	14400.79
7	CT + SYI + AC	91.67%	0.1681	37228.55	1139.76	6780.25
8	CT + SI + DS	93.66%	0.188	36842.81	754.02	4010.74
9	CT + SI	94.76%	0.199	36808.01	719.22	3614.18

CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, ICER = incremental cost-effectiveness ratio, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

4.3.2. Two-way sensitivity analysis. It was assumed that the efficacy rate of the 9 treatment regimens fluctuated by 5%. The cost was analyzed sensitively according to the highest and lowest manufacturer retail price, assuming that WTP was GDP per capita in 2018. As shown in Figure 6, the parameter with the most significant impact on the results was the treatment efficiency of the CT + SI group.

4.3.3. Probabilistic sensitivity analysis (PSA). The results of the PSA based on 1000 Monte Carlo simulations are presented in the cost-effectiveness scatter plot below (Fig. 7). The efficiency and the cost were presumed to be a beta distribution and a triangular distribution, respectively. The patient's WTP changed from 0 to ¥198018. The acceptable cost effect curve is shown in Figure 7. The probability of cost-effectiveness of CT + SI gradually increased with the WTP threshold and exceeded CT when the WTP reached ¥19801.8. When the WTP is higher than ¥39603.6, the CT + SI probability representing a more economical scheme was reduced; however, it was still greater than 50%. The results of the PSA were consistent with the base-case results (Fig. 8).

5. Discussion

The clinical outcome of angina is influenced by many factors, such as patient age, surgical operation, complications, and drug type. Specifically, angina pectoris is more likely to be cured with medications than other diseases, such as myocardial infarction, with higher mortality in CHD. Currently, the leading therapeutic method used in China is pharmacotherapy. Meanwhile, the primary indication of safflower is angina, consistently demonstrating excellent treatment efficacy. Therefore, it is significant to study the efficacy and cost-effectiveness of safflower-related treatment regimens for clinical guidance.

Network meta-analysis was used to indirectly evaluate the efficiency of 13 treatments for angina patients. The bayesian method was utilized to assess the cost-effectiveness of 9 treatments indirectly. Compared with conventional treatment regimens, the treatment combined with safflower indicated improved effects, and the combination with Danshen-dropping pills demonstrated the most effective treatment potency. Moreover, the addition of other drugs, such as low molecular heparin, carvedilol, and l-carnitine injection, to the combination allowed higher efficacy and cost-effectiveness due to improving curative effect and reducing dosage and drug cost compared with the conventional treatment and routine treatment combined with safflower flavin.

The study limitations are as follows: The recovery cost from angina not mentioned in the included studies was not reflected. This might affect the evaluation when calculating the cost of a 1-course -treatment (14 days). The final Cochrane score of the included studies was low, resulting in insufficient information to judge the study quality, such as randomization, allocation, concealment, and blinding. Frequency-based meta-analysis was used for indirect comparisons; therefore, the efficiency ranking may be biased. However, certain studies indicated that the frequency-based and Bayesian network meta-analyses were comparable. The included studies were all published but lacked gray documents, such as special reports and unpublished materials. The studies lacked long-term follow-up

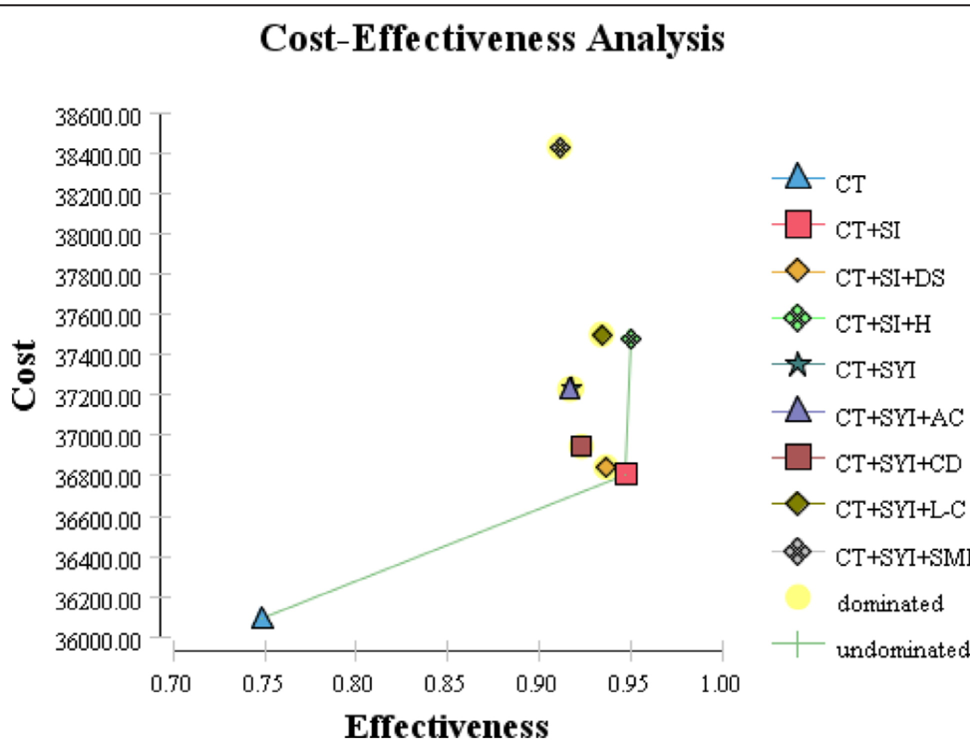

Figure 6. Sensitivity analysis on cost and effective rate. eCT_SI = effective rate of combined therapy of conventional treatment and Safflor injection, eCT_SI_H = effective rate of combined therapy of conventional treatment and Safflor injection and low molecular heparin, eCT_SI_DS = effective rate of combined therapy of conventional treatment and Safflor injection and compound Danshen drip pill, eCT_SYI_LC = effective rate of combined therapy of conventional treatment and safflor yellow injection and L-Carnitine injection, eCT_SYI_CD = effective rate of combined therapy of conventional treatment and safflor yellow injection and carvedilol, cCT_SI = cost of combined therapy of conventional treatment and Safflor injection, eCT_SYI = effective rate of combined therapy of conventional treatment and safflor yellow injection, eCT_SYI_AC = effective rate of combined therapy of conventional treatment and safflor yellow injection and atorvastatin calcium tablets, cCT_SI_H = cost of combined therapy of conventional treatment and Safflor injection and low molecular heparin, eCT_SYI_SMI = effective rate of combined therapy of conventional treatment and safflor yellow injection and Shenmai injection, eCT = effective rate of conventional treatment, cCT_SYI_SMI = cost of combined therapy of conventional treatment and safflor yellow injection and Shenmai injection, eCT_SYI_LC = effective rate of combined therapy of conventional treatment and safflor yellow injection and L-Carnitine injection.

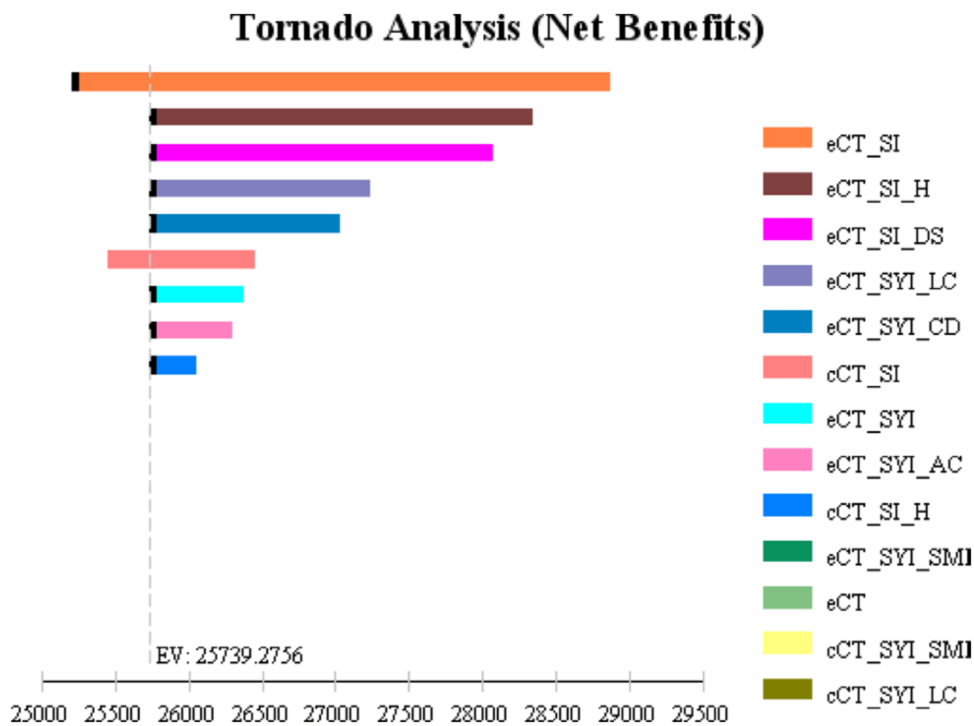

Figure 7. Cost-effectiveness acceptability curve. AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

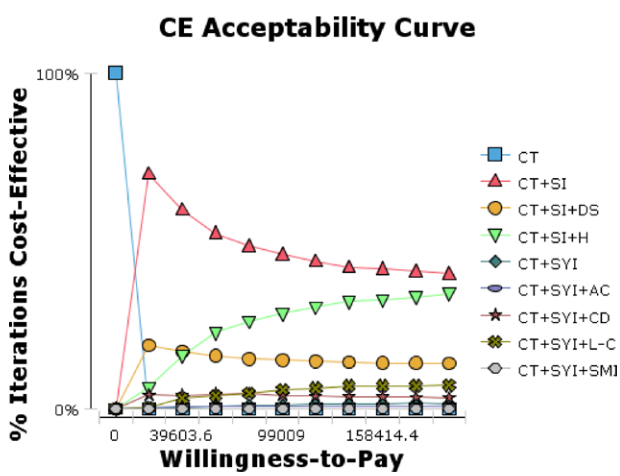

Figure 8. Cost-effectiveness of screening options. AC = atorvastatin calcium tablets, CD = carvedilol, CT = conventional treatment, DS = compound Danshen drip pill, DSI = (compound) Danshen injection, H = low molecular heparin, L-C = L-Carnitine injection, SI = safflor injection, SMI = Shenmai injection, SYI = safflor yellow injection, XDI = Xiangdan injection.

monitoring in terms of safety, poorly assessing the long-term risk of safflower. More high-quality clinical data are required to confirm our findings.

6. Conclusion

This study used various analytical methods to conduct a multilevel analysis of 13 treatment regimens related to safflower against angina from evidence-based medicine and economic evaluation. From the perspective of evidence-based medicine, the CT + SI + H group had the best treatment efficacy. The CT + SI group was the most cost-effective, combined with the cost data. Yet, CT + SI + DS was recommended as the best treatment choice due to the advantages of efficiency and cost-effectiveness. Sensitivity analysis showed that the model was sensitive to the treatment effectiveness instead of the drug cost. Therefore, we recommend a combination of conventional treatment and safflower injection to treat angina pectoris. Of note, adding low molecular weight heparin or compound Danshen-dropping pills to the combination could improve efficacy and cost-effectiveness. Indeed, more clinical trials are needed to support our conclusions due to the limited data.

Acknowledgments

The authors thank Dr He and Dr Du for linguistic assistance.

Author contributions

Conceptualization: Yongfa Chen, Liang Lu.
Data curation: Qiuchen Jin.
Formal analysis: Liang Lu.
Methodology: Liang Lu, Yang Li.
Software: Yang Li.
Supervision: Yongfa Chen.
Writing – original draft: Liang Lu.
Writing – review & editing: Liang Lu.

References

[1] National Health and Family Planning Commission Expert Committee on Rational Use of Drugs, Chinese Pharmacists Association. Guidelines for rational use of drugs for coronary heart disease (Second Edition). Chin J Med Front. 2018;10:7–136.
[2] Chen WW, Gao RL, Liu LS, et al. Summary of “Chinese Cardiovascular Disease Report 2018”. Chin J Circulation. 2017;32:521–30.
[3] Safiri S, Karamzad N, Singh K, et al. Burden of ischemic heart disease and its attributable risk factors in 204 countries and territories, 1990-2019. Eur J Prev Cardiol. 2021;2:420–31.
[4] Xi XQ. Influence of psychological nursing on anxiety and depression and nursing satisfaction of patients with angina pectoris. Chin J Mod Drug Appl. 2019;13:184–5.

[5] James Z, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psycho-Oncol. 2001;10:19–28.
[6] Yang H, Wu QW. Research progress on influencing factors and intervention strategies of cancer patients' self-perceived burden. Chin Nurs Manage. 2012;3:95–7.
[7] Li M, Ma YW. The influence of TCM emotional intervention on self-perceived burden of patients with unstable angina. Chin J Health Psychol. 2014;22:355–6.
[8] Hu SL. Research on the Burden of Disease (Part 1). Health Econ Res. 2005;5: 23–28.
[9] Cardiovascular Branch of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiovascular Disease. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndrome (2016). Chin J Cardiovas Dis. 2017;5:359–76.
[10] Li ZY, Tu XH. Progress in pharmacological research of safflower yellow pigment. Chin New Drugs Clin Pharmacol. 2005;016:153–6.
[11] Wang SY. Application research of budget impact analysis in the selection of medical insurance drug list for unstable angina pectoris. (Doctoral dissertation). 2019:31–2.
[12] Bater. Clinical observation of 72 cases of angina pectoris of coronary heart disease treated by safflor yellow combined with isosorbide mononitrate. Chin Ethnic Folk Med. 2014;18:66–66.
[13] Department of Medical Administration, Ministry of Health of the People's Republic of China. Guidelines for the diagnosis and treatment of common cardiovascular and cerebrovascular diseases in China. Beijing: Science Press. 2000;59–60.
[14] Higgins JPT, Altman DG, Peter CG, et al. The cochrane collaboration's tool for assessing risk of bias in randomized trials. BMJ (online). 2011;11:343–51.
[15] Tian JH, Li L, Yang KH. The realization of frequency statistical method meshed Meta analysis in STATA software. Chin J Evid Based Pediatr. 2014;9:472–4.
[16] Carlin BP, Hong H, Shamliyan TA, et al. Case study comparing bayesian and frequentist approaches for multiple treatment comparisons. Rockville, MD: Agency for Healthcare Research & Quality. 2013.
[17] Zhang C, Xu C, Zeng XT. The drawing of the network relationship diagram in the network meta analysis. Chin J Evid Based Med. 2013;13:1382–6.
[18] Zhang C, Yan JZ, Sun F, et al. Identification and treatment of the consistency of mesh meta-analysis. Chin J Evid Based Med. 2014;14:884–8.
[19] Zeng XT, Xu C, Zhang C, et al. Implementation of mesh meta-analysis in stata software. Chin J Evid Based Med. 2013;13:1387–91.
[20] Cui XC, Yin WB, Liao ZT, et al. Clinical study of safflor yellow sodium chloride injection combined with propranolol in the treatment of coronary heart disease angina pectoris. Modern Med Clin. 2019;8:2287–92.
[21] Han BD. Observation on the efficacy of safflower yellow sodium chloride injection in the treatment of coronary heart disease and angina pectoris. China Modern Med Appl. 2013;7:98–9.
[22] Jin C. Treatment of 65 cases of unstable angina with safflower yellow pigment. China Emerg Tradit Chin Med. 2010;19:1952–3.
[23] Zhou WJ, Feng J. Clinical observation of safflower yellow in the treatment of unstable angina pectoris. Drug Eval Res. 2014;37:548–50.
[24] Fang X, Li X, Liu XH. Clinical observation of safflor yellow in the treatment of elderly diabetic nephropathy patients with acute myocardial infarction. China Pharmacy. 2017;28:4140–3.
[25] Fang KY, Kang JQ, Ding ZS, et al. The effect of safflower yellow injection in adjuvant treatment of coronary heart disease and angina pectoris and its influence on the hemorheology of patients. J Chronic Dis. 2019;20:1060–1061 + 1064.
[26] Huang B. Observation of the clinical efficacy of safflower yellow injection combined with western medicine in the treatment of unstable angina pectoris. (Doctoral dissertation). 2016:14–6.
[27] Xu XM, Wang XY, Liu SG, et al. The clinical effect of safflower yellow injection in the treatment of angina pectoris and the study of its protective effect on the heart of patients. Chin Herb Med. 2017;9:2209–11.
[28] Lu JF, Liu JB. Clinical observation of safflower yellow injection in the treatment of unstable angina pectoris of coronary heart disease. China Practical Med. 2014;36:153–5.
[29] Wang YY, Jin L. The effect of safflower injection in the auxiliary treatment of coronary heart disease and angina pectoris. People's Military Surgeon. 2012;10:972–3.
[30] Li YC. The effect of alprostadil injection combined with safflower yellow in the treatment of unstable angina pectoris of coronary heart disease. Henan Med Res. 2018;16:2994–6.
[31] Liu H. The clinical value of combining safflor yellow on the basis of conventional western medicine in the treatment of coronary heart disease and angina pectoris. Inner Mongolia Tradit Chin Med. 2017;4:83.
[32] Xu Z. Clinical observation of safflower yellow for injection in the treatment of patients with coronary heart disease and angina pectoris of heart blood stasis syndrome. Heilongjiang Med. 2018;1:34–6.
[33] Wu J. Evaluation of the effect of safflor yellow on stable angina pectoris of coronary heart disease. Inner Mongolia Tradit Chin Med. 2014;33:26–7.
[34] Wang CJ, Cai ZR, Mao YJ, et al. Clinical observation and prognostic analysis of safflower yellow in the treatment of unstable angina pectoris in the elderly. Chin Med Guide 2011;09:187–8.
[35] Liu JH, Hou XJ. The effect of safflower yellow injection on unstable angina pectoris. J Integr Tradit Chin West Med Cardio-Cerebrovasc Dis. 2009;6:109–10.
[36] Wang J. Safflower yellow injection combined with L-carnitine in the treatment of fatigue angina. J Integr Tradit Chin West Med Cardio-Cerebrovasc Dis. 2014;12:115–6.
[37] Huang LM, Shi LP, Zhao FL, et al. Safflower yellow injection combined with L-carnitine in the treatment of 56 cases of stable angina pectoris of elderly coronary heart disease. China Emerg Tradit Chin Med. 2017;26:473–5.
[38] Wu HK, Fan T, Zhao YQ. The effect of carvedilol combined with safflor yellow sodium chloride injection on patients with unstable angina pectoris of coronary heart disease. Practical J Cardiovasc Pneumal Vasc Dis. 2017;12:162–4.
[39] Zhang YL, Ouyang L. Low molecular weight heparin combined with safflower injection in the treatment of 83 cases of angina pectoris. Intern Med. 2017;002:556–7.
[40] Zu GY, Na HJ, Guo X. Observation on the effect of low molecular weight heparin combined with safflower yellow in the treatment of unstable angina pectoris. North China National Defense Med. 2010;22:427–9.
[41] Huang LX, Wang M. Treatment of 45 cases of unstable angina pectoris of Qi deficiency and blood stasis type with safflower yellow pigment and Shenmai injection. Hunan J Tradit Chin Med. 2014;30:38–40.
[42] Ji KF. Clinical observation of safflor yellow combined with atorvastatin calcium tablets in the treatment of unstable angina pectoris. Chin Comm Phys. 2012;14:94–94.
[43] Li D. Clinical analysis of Honghua injection combined with compound Danshen dripping pills in the treatment of unstable angina pectoris. Guide to China Med. 2016;14:225.
[44] Wu SQ. Clinical observation of safflower injection in the treatment of angina pectoris. China Med Guide 2016;14:203–4.
[45] Su WJ, Zhong ZH. Clinical analysis of Honghua injection in the treatment of coronary heart disease and angina pectoris. Electronic J Integr Tradit Chin West Med Cardiovasc Dis. 2016;4:66–7.
[46] Chen WB, Xue ML, Shan SL. Analysis of the clinical efficacy of safflower injection in the treatment of coronary heart disease and angina pectoris. China Health Ind. 2013;17:74 + 76.
[47] Cao XH. Clinical efficacy analysis of safflower injection in the treatment of coronary heart disease and angina pectoris. Contemp Med. 2012;10:682–682.
[48] Hou MY. The therapeutic effect of safflower yellow for injection combined with aspirin and clopidogrel on unstable angina pectoris. J Integr Tradit Chin West Med Cardio-Cerebrovasc Dis. 2013;4:109–10.
[49] Wang YJ. The clinical efficacy of safflower yellow in the treatment of unstable angina pectoris. China Mod Med Appl. 2013;16:125.
[50] Li XA. randomized parallel controlled study of safflower yellow in the treatment of angina pectoris of coronary heart disease with blood stasis. J Pract Tradit Chin Intern Med. 2013;27:23–5.
[51] Zhu XF, Zhang RH, Wang TC, et al. A multi-center randomized controlled clinical study of safflower yellow freeze-dried powder injection for the treatment of stable angina pectoris of coronary heart disease with heart and blood stasis syndrome. Chin Patent Med. 2012;04:13–8.
[52] Zhang Q, Peng JH, Zhang XN. A clinical study of Safflower yellow injection in treating coronary heart disease angina pectoris with Xin-blood stagnation syndrome. Chin J Integr Med. 2005;11:222–5.
[53] Wu CY. Observation on the curative effect of safflower yellow in the treatment of coronary heart disease and angina pectoris. China Urban Rural Enterp Health. 2014;3:112–3
[54] Qi YJ. Observation on the clinical efficacy of safflower injection in the treatment of 48 cases of coronary heart disease and angina pectoris. China Med Guide. 2014;26:286–7.
[55] Wang Q. Observation on the efficacy of clinical injection of safflor yellow in the treatment of 60 cases of coronary heart disease and angina pectoris. Beifang Pharmacy. 2012;7:51.
[56] Wang Y. Observation on the efficacy of clinical injection of safflower yellow in the treatment of angina pectoris of coronary heart disease in 60 cases. Digest of World Latest Med Info. 2016;71:358.

[57] Shi H. Analysis of the curative effect of safflower yellow in the treatment of coronary heart disease and angina pectoris. J Contemp Med. 2012;10:157–8.
[58] Ji HB. Clinical study of safflower yellow lyophilized powder injection for the treatment of stable angina pectoris of coronary heart disease with heart and blood stasis syndrome. Electronic J Integr Tradit Chin West Med Cardiovasc Dis. 2015;3:160 + 162.
[59] Gao LL. Clinical study of safflower yellow injection in the treatment of coronary heart disease angina pectoris (heart blood stasis syndrome). Changchun University of Traditional Chinese Medicine (Doctoral dissertation). 2007:31–7.
[60] Shen L, He Y, Xu YJ. Clinical observation on the treatment of coronary heart disease and angina with safflower yellow pigment for injection. Chin Patent Med. 2006;8:1154–6.
[61] Qi FJ, Lu JL, Feng S, et al. Common costs and their measurement methods in pharmacoeconomic evaluation. Shanghai Med. 2015;1:7–9.
[62] Guan X, Li HC, Shao RJ, et al. Systematic review and cost-effectiveness analysis of triple therapy of omeprazole and esomeprazole in the treatment of peptic ulcer. Chin J Hospital Pharmacy. 2019;39:502–7.
[63] Feng S, Hu M. Pharmaccoeconomic evaluation of Danshen ligustrazine injection versus salvia miltiorrhiza polyphenolate injection in the treatment of coronary heart disease and angina pectoris. J Pharm Pract. 2018;36:147–55.
[64] Beijing Municipal Medical Insurance Bureau. Anonymous. 2020. Available at: http://ybj.beijing.gov.cn/. [Access date 2020.6.12].
[65] Li J. Cost-Effectiveness analysis of five therapeutic schemes in treatment of unstable angina pectoris. China Pharm. 2011;020:50–1.
[66] Xuan JW, Huang M, Lu YJ, et al. Economic evaluation of Safflower yellow injection for the treatment of patients with stable angina pectoris in China: a cost-effectiveness analysis. J Altern Complement Med. 2018;6:564–9.
[67] Zhang XX, Zhao X, Cheng W. Research on inpatient diagnosis and treatment expenses of coronary heart disease in 26 hospitals in Beijing. China Health Econ. 2019;38:52–6.