Safflor yellow treating angina pectoris
A pharmacoeconomic evaluation and network meta-analysis

Liang Lu, MMa, Yang Li, PhDa, Qiuchen Jin, BEECa, Yongfa Chen, PhDa,*

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. 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. Meanwhile, the CHD for all cardiovascular diseases elevated from 29% to 37%. 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. 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, 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, which would be more likely to lead to acute myocardial infarction or sudden death. 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, CAD accounted for 9.4% of the disability-adjusted life-year loss of the top 10 diseases, ranking first in developed and developing countries. The survey reported that the PCI cases in 2017 were 755142, 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, 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...
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.

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.”

(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, 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 outcome indicators were binary classification variables. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CI). 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). 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.

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 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 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 for angina-pectoris treatment efficiency were estimated according to the efficacy evaluation criteria. ECG effects and
## Table 1
Characteristics of included studies.

| Study          | Sample size | Age | Interventions in the treatment group | Interventions in the control group | Treatment Duration | Outcome indexes | Study Design | Adverse reactions |
|----------------|-------------|-----|--------------------------------------|-------------------------------------|--------------------|-----------------|--------------|------------------|
| Battel 2014    | 36          | 55.8 ± 7.3 | 54.6 ± 8.6 | CT + SYI 100 mg | CT | No | RCT | Not reported |
| Cui Xiaochun 2019 | 46          | 57.8 ± 6.2 | 57.8 ± 6.2 | CT + safflower yellow sodium chloride injection 100 mL | CT | No | RCT | Yes |
| Han Biaoding 2013 | 60          | 58.8 | 66.2 | CT + 100 mL safflower yellow sodium chloride injection | CT | No | RCT | Yes |
| Jin Chao 2010 | 65          | 57.10 ± 5.22 | 57.45 ± 6.67 | CT + 150 mg SYI | CT | No | RCT | No |
| Zhou Wenjun 2014 | 40          | 61.12 ± 5.43 | 61.12 ± 5.43 | CT + SYI 100 mg | CT | No | RCT | Yes |
| Fang Xiang 2017 | 52          | 65.3 ± 12.8 | 66.4 ± 11.3 | CT + SYI 100 mg | CT | No | RCT | No |
| Fang Kai 2017 | 24          | 58.22 ± 5.14 | 59.46 ± 6.47 | CT + SYI 150 mg | CT | No | RCT | No |
| Huang Bo 2016 | 26          | 60.78 | 62.5 | CT + SYI 100 mg | CT | No | RCT | No |
| Xu Xiangmei 2017 | 59          | 58.23 ± 6.10 | 59.05 ± 7.22 | CT + SYI 100 mg | CT | No | RCT | Yes |
| Lu Junfang 2014 | 43          | 58.0 ± 7.4 | 57.7 ± 7.7 | CT + SYI 100 mg | CT | No | RCT | No |
| Wang Y' 2012 | 32          | 56.4 | 55.4 | CT + S 20 mL | CT | No | RCT | No |
| Li Yingchun 2018 | 59          | 54.35 ± 11.64 | 55.48 ± 11.16 | CT + SYI 100 mg | CT | No | RCT | Yes |
| Liu Hua 2017 | 31          | 63.5 ± 4.2 | 64.2 ± 3.2 | CT + SYI 100 mg | CT | No | RCT | Yes |
| Xu Zhi 2018 | 50          | 59.2 ± 3.4 | 58.3 ± 3.2 | SYI 100 mg + CT | CT | No | RCT | Yes |
| Wu Juan 2014 | 60          | 54.78 | 54.78 | CT + SYI 15 g | CT | No | RCT | Yes |
| Wang Chengjun 2011 | 54          | 70.8 ± 9.2 | 72.7 ± 7.2 | CT + SYI 80 mg | CT | No | RCT | Yes |
| Liu Jianhong 2009 | 28          | 62 | 63 | CT + SYI 50 mg | CT | No | RCT | No |
| Wang Jun 2014 | 35          | 68 | 68 | CT + SYI 100 mg | CT | No | RCT | No |
| Huang Lumei 2017 | 56          | 69.13 ± 6.24 | 68.26 ± 5.47 | CT + SYI 100 mg + L-C | CT | No | RCT | No |
| Wu Haokun 2017 | 39          | 61.5 ± 8.4 | 60.0 ± 8.2 | CT + safflower yellow sodium chloride injection 100 mL | CT | No | RCT | No |
| Zhang Yuexun 2007 | 83          | 63.5 | 64.5 | CT + H5000U + S 20 mL | CT | No | RCT | Yes |
| Zu Guoyou 2010 | 37          | 41.3 | 39.8 | CT + H4100U + S 100 mg | CT | No | RCT | Yes |
| Huang Liuxiang 2014 | 45          | 64.7 ± 6.5 | 65.2 ± 6.7 | CT + safflower yellow sodium chloride injection 100 mL + SMJ 60 mL | CT | No | RCT | Yes |
| Ji Kafeng 2012 | 36          | 58.8 ± 13.3 | 59.4 ± 14.3 | CT + SYI 100 mg + AC 20 mg | CT | No | RCT | Yes |
| Li Dan 2016 | 23          | / | / | CT + S 40 mL + DS | CT | No | RCT | No |
| Wu Shuqin 2016 | 24          | / | / | CT + S 20 mL + DS | CT | No | RCT | No |
| Su Wenjie 2016 | 50          | 56.2 ± 2.6 | 56.2 ± 2.6 | CT + S 30 mL | CT | No | RCT | No |
| Chen Wenzhen 2013 | 50          | 55.7 ± 2.3 | 55.7 ± 2.3 | CT + S 30 mL | CT | No | RCT | Yes |
| Cao Xuehui 2012 | 78          | 54.6 | 55.3 | CT + S 30 mL | CT | No | RCT | No |
| Hou Mingying 2013 | 65          | 59.3 ± 10.8 | 58.6 ± 10.2 | CT + SYI 100 mg | CT | No | RCT | No |
| Wang Yingjie 2013 | 60          | 64.5 | 65.2 | CT + SYI 100 mg | CT | No | RCT | No |
| Li Xiaojun 2013 | 46          | 55.5 ± 5.6 | 55.5 ± 5.6 | CT + SYI 20 mL | CT | No | RCT | No |
| Zhu Xiaofeng 2012 | 107         | 18-70 | 18-70 | SYI 250 mg | SI 15 mL | No | RCT | No |
| Zhang Qiong 2014 | 323         | 100 | 100 | CT + SYI 80 mg | DSI 20 mL | No | RCT | No |
| Wu Changyan 2014 | 35          | 63.51 | 62.58 | CT + SYI 100 mg | CT + salvianolate injection 200 mg | CT + DSI 30 mL | No | RCT | No |
| Qi Yongjun 2014 | 48          | 544 ± 3.2 | 53.2 ± 4.5 | CT + S 30 mL | CT + DSI 30 mL | No | RCT | No |
| Wang Qiang 2012 | 30          | 59 | 59 | SYI 150 mg | DSI 14 mL | No | RCT | No |
| Wang Jing 2013 | 30          | 40-70 | 41-75 | SYI 150 mg | DSI 150 mg | No | RCT | No |
| Shi Hua 2012 | 50          | 39-79 | 39-71 | SYI 80 mg | DSI 20 mL | No | RCT | No |
| Ji Hongbin 2015 | 100         | 55.32 ± 2.66 | 55.32 ± 2.66 | Safflower yellow freeze-dried powder injection 100 mg | XDI 20 mL | No | RCT | No |
| Gao Linlin 2007 | 34          | 58.97 ± 5.96 | 58.48 ± 7.97 | SYI 120 mg | XDI 10 mL | No | RCT | No |
| ShenLin 2006 | 24          | / | / | SYI 100 mg | XDI 10 mL | No | RCT | No |

(A) Due to the different purity of safflower injection and safflower yellow injection, they should be distinguished; B) The safflower yellow sodium chloride injection is prepared by adding sodium chloride to the safflower yellow injection for dilution. Therefore, only safflower 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; XDI = Xiangdan injection; SI = safflower injection; SMJ = Shenmai injection; SYI = safflower yellow injection; XDI = Xiangdan injection.
hemorheological indicators were included in 40 RCTs\cite{12,20-24,26-55,57-60} and 19 RCTs\cite{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\cite{20,21,23,39,40,45,51,53,54} including 1045 patients demonstrated the adverse events occurrences. Mild venous inflammation was observed in 2\cite{45} disappearing after needle removal and not significantly affecting treatment. In addition, 2 patients in the control group developed an allergic reaction. One study\cite{46} indicated that the treatment and control groups resulted in
### Table 2

Network meta-analysis results comparing the clinical effectiveness.

|                 | CD    | CT + SI + H | CT + SI + DS | CT + SI + CD | CT + SI + SYI + CD | CT + SI + XDI | CT + SI + SMI | CT + SYI + CD | CT + SYI + DSI | CT + SYI + XDI | CT + SYI + SMI |
|-----------------|-------|-------------|--------------|--------------|-------------------|--------------|--------------|--------------|----------------|----------------|---------------|
| **0.45**        | 1.42  | 1.07        | 1.60         | 1.02         | 0.93              | 1.07         | 1.23         | 0.91         | 1.07           | 0.91           | 0.79          |
| **0.05**        | 0.70  | 0.79        | 0.81         | 0.74         | 0.79              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.40**        | 0.55  | 0.58        | 0.81         | 0.74         | 0.79              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.06**        | 0.45  | 0.63        | 0.74         | 0.74         | 0.79              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.40**        | 0.34  | 0.59        | 0.60         | 0.60         | 0.74              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.30**        | 0.04  | 0.48        | 0.60         | 0.60         | 0.74              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.08**        | 0.04  | 0.43        | 0.60         | 0.60         | 0.74              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.18**        | 0.08  | 0.24        | 0.32         | 0.32         | 0.41              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.10**        | 0.04  | 0.15        | 0.20         | 0.20         | 0.26              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.05**        | 0.03  | 0.16        | 0.20         | 0.20         | 0.26              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |
| **0.03**        | 0.02  | 0.19        | 0.24         | 0.24         | 0.26              | 0.91         | 0.98         | 0.92         | 0.94           | 0.81           | 0.75          |

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.

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).

Table 3

| Treatment | SU CRA | 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                                                           |
| DSI       | 31.1   | 10   | 10                                                           |

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 4. SU CRA 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.
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.
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. 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. 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. 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. 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          | 139/10 mL*1 | 23      | 5.7     |
| Carvedilol                       | 40.33/20 mg*10 pieces | 48      | 7.2     |
| Low molecular weight heparin     | 63.5/0.6 mL*10000 U*1 | 118.96  | 29.98   |
| 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. (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/¥     | Maximum | 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 | 36533.03 |
| 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) | 38428.82   | 41135.23 | 37557.67 |
| 7   | CT + SYI + AC              | CT + SYI (100 mg) + AC (20 mg) | 37229.55   | 38565.99 | 36878.31 |
| 8   | CT + SI + DS               | CT + SI (30 mL) + DS (1 ml) | 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        | 7066.79 |
| 4   | CT + SYI + CD | 92.31%       | 0.1746                     | 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                     | 37229.55 | 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 ¥198018. 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.

![Cost-Effectiveness Analysis](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_SIYL LC = effective rate of combined therapy of conventional treatment and safflor yellow injection and L-Carnitine injection, eCT_SIYL 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_SIYL = effective rate of combined therapy of conventional treatment and safflor yellow injection and carvedilol, eCT_SIYL AC = effective rate of combined therapy of conventional treatment and safflor yellow injection and atorvastatin calcium tablets, eCT_SIYL H = cost of combined therapy of conventional treatment and Safflor injection and low molecular heparin, eCT_SIYL SMI = effective rate of combined therapy of conventional treatment and safflor yellow injection and Shenmai injection, eCT = effective rate of conventional treatment, cCT_SIYL SMI = cost of combined therapy of conventional treatment and safflor yellow injection and Shenmai injection, eCT_SIYL LC = effective rate of combined therapy of conventional treatment and safflor yellow injection and L-Carnitine 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.
[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. Pharmacoeconomic 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.