Systematic Review / Meta-analysis

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Efficacy, safety, and economy of shensongyangxin capsules for the treatment of coronary heart disease arrhythmia: a meta-analysis of randomized controlled trials

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Background: Shensong Yangxin Capsules (SSYX) is a proprietary Chinese medicine commonly, used in the treatment of arrhythmia. In recent years, a flurry of randomized controlled trials of SSYX was reported in the treatment of Coronary heart disease arrhythmia in China. However, these experiments have not been systematically evaluated by economics. The purpose of this study was to assess the efficacy, safety, and economy of the SSYX in the treatment of arrhythmia in patients with coronary heart disease.
Methods: With "Shensong Yangxin Capsules" "Coronary Heart Disease" "Coronary Atherosclerotic Heart Disease"and "Arrhythmia" as the subject words, the relevant journals and conference papers were searched manually in China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP, PubMed, Web Of Science, CBM, Embase and The Cochrane Library. The literature of randomized controlled trials of SSYX in the treatment of coronary heart disease arrhythmia was searched until November 2022. All data were analyzed using RevMan 5.3 Sotware and combined with cost-effectiveness for economic evaluation.
Results: Twenty randomized controlled trials were included in this study, with a total of 2011 cases. The meta-analysis showed that the therapeutic effect of SSYX-metoprolol is superior to that of metoprolol alone. SSYX is superior to amiodarone in improving the total clinical effective rate, reducing the incidence of adverse reactions, and reducing the junction premature beats. There was no significant difference between the SSYX and amiodarone in the curative effect of ECG, ventricular premature complexes, and atrial premature beats. The results of pharmacoeconomics show that SSYX has a cost-effectiveness advantage in treating coronary heart disease arrhythmia. Single-factor sensitivity analysis also confirmed the stability of the results. In summary, SSYX has a curative effect, safety, and economy in treating coronary heart disease arrhythmia.

Keywords: amiodarone, arrhythmia, coronary heart disease, metoprolol, Shensong Yangxin capsules, traditional Chinese medicine

Introduction

Coronary heart disease is a heart disease caused by coronary artery disease. According to statistics, 40% of patients with cardiovascular disease are caused by coronary heart disease. Arrhythmia is myocardial ischaemia and hypoxia caused by coronary atherosclerosis, resulting in cardiac abnormalities[1], and the incidence of arrhythmias increases with the increase of the incidence of coronary heart disease[2,3]. According to statistics, at least 1 million people die of coronary heart disease in China every year. Arrhythmia is a common cause of death in coronary heart disease, and more than 75% of patients with coronary heart disease are accompanied by arrhythmia. Patients with mild arrhythmias of coronary heart disease have palpitation, chest tightness, palpitation, shortness of breath, severe precordial pain, dyspnoea, and even heart failure, resulting in death. According to

HIGHLIGHTS

- In terms of methodology, this study adopts the method of literature research, which saves the cost of drug research, provides a reference for pharmacoeconomic data analysis, and can effectively provide some economic analysis for patients in clinical drug use.
- Shensong Yangxin Capsules has a cost-effectiveness advantage in treating coronary heart disease arrhythmia.
- Shensong Yangxin Capsules has a curative effect, safety, and economy in treating coronary heart disease arrhythmia.

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the survey, 80% of sudden death patients in the United States are related to arrhythmias[4].

The prevalence of arrhythmias in coronary heart disease is increasing year by year, which affects human health and increases the economic burden. According to the literature, the annual hospitalization cost of coronary heart disease management is about C$2.2 billion or more, and the average annual medication costs were C$1593 per patient in Canada; patients with arrhythmia account for 32% of the total population, and the annual economic burden is about $17.3 billion in Brazil; in 2021, there were 194 patients (with an average age of 82.6 years), and the average hospitalization time was 11.3 days, the economic cost related to admission of each patient was €6,892.15 in Europe.[5–7]. At present, the effect of conventional western medicine in the treatment of arrhythmia in coronary heart disease is not good, often with fatigue, sinus bradycardia, sudden drop in blood pressure, diarrhoea, and other adverse reactions[8,9]. Shensong Yangxin Capsules (SSYX) has a good effect in the treatment of arrhythmia in coronary heart disease. It can effectively improve[10] the symptoms of chest tightness and palpitation and reduce the incidence of adverse reactions.

SSYX is a kind of Chinese patent medicine, widely using in the treatment of arrhythmia in China[11]. It composed of ingredients are Ginseng Radix et Rhizoma, Ophiopogon japonicus, Cornus officinalis, Salvia miltiorrhiza, Semen Ziziphi Spinosae (parched), Herba Taxilli, Radix Paeoniae Rubra, Eupolyphaga Seu Steleophaga, Gan Song, Coptidis Rhizoma, Fructus Schisandrae Chinensis and Os Draconis. SSYX can replenish qi, nourish yin, promote blood circulation, clear heart and soothe nerves. It can be used for treating coronary heart disease, such as ventricular arrhythmia due to deficiency of both qi and yin, and heart collateral stasis. Symptoms include palpitation, shortness of breath and fatigue, aggravation of movement, chest tightness and pain, insomnia and dreams, night sweats, tiredness and laziness. The overall ingredient of SSYX was listed in Table 1 and Chinese herbal medicine diagram of SSYX was showed in Fig. 1.

In the past decade, dozens of randomized controlled trials have reported the use of SSYX in the treatment of coronary heart disease arrhythmia. In a long-term toxicity (3 months) study, it was found[12] that the maximum oral tolerance of SSYX in mice was 524 times the clinical dose, and there were no significant effects on 10 biochemical indicators such as rat body weight, electrocardiogram, blood cell count, and heart, liver, and kidney function. No pathological changes were observed in various organs under the microscope. Studies have shown that SSYX can effectively improve clinical efficacy and reduce a series of adverse reactions[13,14]. During the observation period of 600 patients, only one case of mild gastric distension occurred, and the symptoms disappeared without treatment and did not affect the patient. No other adverse reactions were observed. However, there is still insufficient evidence to support its use. Therefore, we conducted a meta-analysis to evaluate the effectiveness, safety, and economy of SSYX in the treatment of coronary heart disease arrhythmia.

Materials and methods

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Supplemental Digital Content 1, http://links.lww.com/MS9/A89) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines, Supplemental Digital Content 2, http://links.lww.com/MS9/A90[15].

Retrieval method

Use “Shensong Yangxin Capsules,” “Coronary Heart Disease” and “Arrhythmia” “Coronary Atherosclerotic Heart Disease”as the subject words to comprehensively search the China Knowledge Infrastructure Databases, Wanfang database, China Science and Technology Journal Database, PubMed, Web Of Science, Embase, China Biomedical database web and The Cochrane Library databases until November 2022, combined with manual retrieval of related journals and conference papers.

Inclusion criteria

Trial design: randomized controlled trials. (2) Participants: All the enroled participants were required to meet the current or past definitions of coronary heart disease arrhythmias. (3) Intervention measures: the experimental group was treated with SSYX and SSYX-metoprolol, and the control group was treated with amiodarone and metoprolol alone. The primary treatment of the two groups was similar, including angiotensin-converting enzyme inhibitors, β-blockers, diuretics, nitrates, and so on. (4) Efficacy indicators: the leading efficacy indicators include clinical efficacy, ECG efficacy, and adverse reactions, and secondary efficacy indicators include the frequency of ventricular premature complexes (VPCs), the

Table 1

Overview ingredient of Shensong Yangxin Capsule.

Chinese name	Pharmaceutical name	Species	Family
Renshen	Ginseng Radix et Rhizoma	Panax ginseng C.A.Mey	Araliaceae
Maidong	Radix Ophiopogonis	Ophiopogon japonicus (Thunb.) ker gawl	Liliaceae
Shanzhuyu	Corni fructus	Cornus oj-jZcinalis sieb. etZucc	Cornaceae
Sangjisheng	Taxilli herba	Taxillus chinensis (DC.) danser	Loranthaceae
Tubiechong	Eupolyphaga	Eupolyphaga sinensis walke	Eupolyphaga
Chishao	Paeoniae Radix Rubra	Paeonia veitchii lynch	Ranunculaceae
Huanglian	Coptidis Rhizoma	Coptis chinensis franch., coptis deltoidea	Ranunculaceae
Nanwuweiwi	Schisandrae sphenantherae	Schisandra sphenanthera Rehder and E.H.Wils	Magnoliaceae
Longgu	Os draconis	Fossils of bones of elephant, rhinoceros or horse	—
Danshen	Salvia miltiorrhiza	Salvia miltiorrhiza Bge	Labiatae
Suanzaoren (Chao)	Semen Ziziphi Spinosae (parched)	Ziziphus jujuba Mill.var.spinosa	Buckthorn
Gansong	—	Nardostachyos Radix Et Rhizoma	Honeysuckle

Figure 1. Chinese herbal medicine diagram of Shensong Yangxin Capsules.

frequency of atrial premature beats (APBs), the frequency of junction premature beats (JPBs).

Exclusion criteria

(1) Repeatedly published literature. (2) The literature of animal experiments. (3) The literature of review, descriptive research, and case report. (4) Literature lacking data and related indicators. (5) Does not accord with the following curative effect basis of arrhythmia of coronary heart disease: Significantly effective; after treatment, chest tightness and palpitation symptoms were significantly improved, and the number of premature beats was 90% less than before. Effective; after treatment, chest tightness and palpitation symptoms have been improved, and the number of premature beats is 50% less than in the past—90%. Ineffective; after treatment, palpitation and chest tightness symptoms were not improved, and the number of premature beats decreased by 50% less than before.

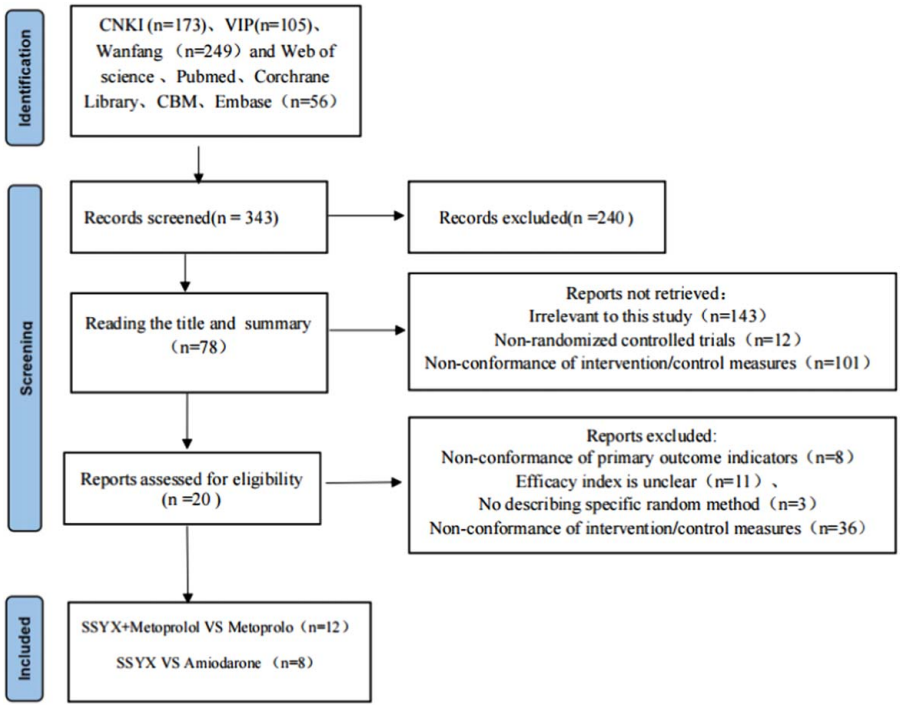

Figure 2. Flow chart of the search for eligible randomized controlled trials. CNKI, China National Knowledge Infrastructure; SSYX, Shensong Yangxin Capsules.

Table 2

Characteristic of included studies.

Included studies	Sample size (E/C)	Sex (M/F)	Age (E/C)	Intervention (E)	Intervention (C)	Course (days)	Outcomes
Song *et al.*[17]	50/50	60/40	(68 ± 3)/(68 ± 4)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	①③
Xu[19]	50/50	64/63	(67.98 ± 6.44)/(68.34 ± 6.21)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	①④⑤⑥
Zhu[21]	54/54	61/67	(51.4 ± 8.2)/(51.8 ± 7.8)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	①③
Li[22]	61/61	74/48	(62.96 ± 6.31)/(62.53 ± 6.45)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	①⑤
Li[23]]	50/50	53/47	(64.8 ± 4.3)/(65.5 ± 3.7)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	①
Zhang[24]	43/43	59/27	(58.6 ± 4.2)/(58.6 ± 4.2)	Metoprolol 25 mg Tid + SSYX 1.2 g Tid	Metoprolol 25 mg Tid	28	③
Dong[27]	53/53	59/47	(65.52 ± 2.41)/(65.15 ± 2.54)	Metoprolol 47.5 mg Qd + SSYX 1.2 g Tid	Metoprolol 47.5 mg Qd	28	①③④
Peng[18]	72/72	71/73	(63.28 ± 9.03)/(62.49 ± 9.11)	Metoprolol 47.5 mg Qd + SSYX 1.2 g Tid	Metoprolol 47.5 mg Qd	28	①③⑤
Qu *et al.*[20]	40/40	46/34	(47.4 ± 14.5)/(45.2 ± 16.1)	Metoprolol 47.5 mg Qd + SSYX 1.2 g Tid	Metoprolol 47.5 mg Qd	28	①③⑤
Luo*et al.*[26]	41/41	50/32	(71.8 ± 3.2)/(71.4 ± 3.2)	Metoprolol 47.5 mg Qd + SSYX 1.2 g Tid	Metoprolol 47.5 mg Qd	30	①③⑤
Sun[16]	63/63	79/47	(64.0 ± 4.8)/(63.6 ± 4.7)	Metoprolol 23.75 mg Qd + SSYX 1.2 g Tid	Metoprolol 23.75 mg Qd	28	①③④⑤⑥
Tian[25]	40/40	46/34	(43.8 ± 11.2)/(39.7 ± 14.3)	Metoprolol 12.5 mg Bid + SSYX 1.6 g Tid	Metoprolol 25 mg Tid	90	①④⑤⑥
Yu[28]	80/80	120/40	(74.2 ± 8.1)/(72.8 ± 8.9)	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days, 25 mg Qd 14 d	28	③④⑤⑥
Wu *et al.*[29]	50/50	53/47	NR	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days, 25 mg Qd 14 days	28	①②③
Li *et al.*[30]	40/40	60/20	(74.2 ± 8.1)/(72.8 ± 8.9)	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days, 25 mg Qd 14 days	28	③④⑤⑥
Liang *et al.*[31]	40/35	63/12	(63 ± 5)/(64 ± 5)	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 21 days	28	①②
Wang *et al.*[32]	20/20	28/12	(68 ± 6)/(69 ± 6)	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days, 25 mg Qd 14 days	28	①④⑤
Huang[33]	65/65	77/53	(65.5 ± 2.5)/(63.8 ± 2.3)	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 21 days	28	①②③④⑤⑥
Dong[34]	45/45	52/38	NR	SSYX 1.6 g Tid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days,25 mg Qd 14 days	28	③
Xing *et al.*[35]	51/51	58/44	72.8/73.5	SSYX 1.2 g Qid	Amiodarone 25 mg Tid 7 days, 25 mg Bid 7 days, 25 mg Qd 14 days	84	①③

①effective rate;②electrocardiogram;③adverse events;④the frequency of ventricular premature complexes;⑤the frequency of atrial premature beats;⑥the frequency of junction premature beat.

Bid, two times a day; C, control group; E, experimental group; F, female; M, man; NR, not reported; Qd, one time a day; SSYX, Shensong Yangxin Capsule; Tid, three times a day; Y, years.

Data extraction

The two researchers, respectively, extract, input, and check the data. The extracted information includes inclusion-exclusion criteria, diagnostic criteria, clinical efficacy indicators, adverse reactions, and so on. Any disagreements were resolved by a third researcher.

Quality assessment

The methodological quality of included randomized controlled trials (RCTs) was assessed using the Cochrane risk-of-bias tool. The main contents of the evaluation were the generation of random sequences, distribution concealment, the blindness of researchers and subjects, blind evaluation of study outcomes, the integrity of outcome data, and selective research reports. Whether there are seven aspects such as other bias, each element is divided into three levels: "low risk," "high risk," and "unclear." "low risk" refers to the low possibility of bias; "high risk" refers to the high probability of bias; "unclear" refers to the unclear degree of the possibility of bias. If there is a situation where there is no consensus, the third researcher will negotiate and solve the problem.

Determine cost analysis and cost-effectiveness analysis

The cost of this study refers to the cost of the drug regimen, excluding indirect costs, hidden costs, and adverse reaction costs. The drug prices of the test group and the control group come from the 315 websites. The meta-analysis of total clinical efficacy was combined with the direct cost of metoprolol and amiodarone for pharmacoeconomic evaluation. If there was a statistical difference ineffectiveness, the trial group used cost-effectiveness analysis; if there was no statistical difference in efficacy between the two groups, the minimum cost was used.

Statistical analysis

Meta-analysis of drug efficacy was carried out with ReviewManager 5.3 software, for dichotomy results, Risk Ratio (RR) is used, and 95% CI table is used for effect quantity show. For the products of continuous variables, the changed scores are used for meta-analysis. For continuous outcomes, the Change Score was used to conduct the meta-analysis, and the Change Score was estimated according to the SD of the pre-intervention data and post-intervention data by using the following formula provided by the Cochrane Handbook.

$$SD^2change = SD^2pre + SD^2post - 2 \times Corr \times SDpre \times SDpost$$

$$Corr = 0.8$$

The change score is expressed as mean difference (MD) or standard MD (SMD), with a CI of 95%. In this meta-analysis, VPCs, APBs, and JPBs were expressed as MD or SMD, and the total effective rate and adverse reactions were described as RR. Cochrane I^2 statistics were used to evaluate the heterogeneity of the study. The data with low heterogeneity ($I^2 > 50\%$) were analyzed by the fixed-effect model, while the random effect model analyzed those with low heterogeneity ($I^2 > 50\%$). The sensitivity analysis of the data with high heterogeneity ($I^2 > 50\%$) was carried out to determine the heterogeneity source. A funnel chart test evaluated the potential publication bias

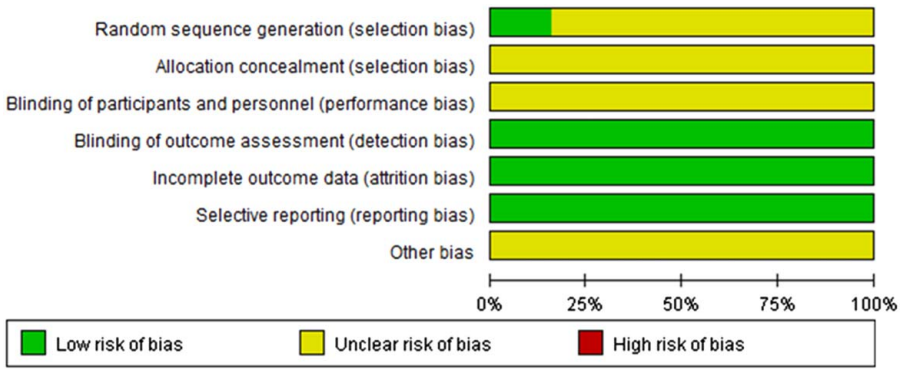

Figure 3. Rist-of-bias graph.

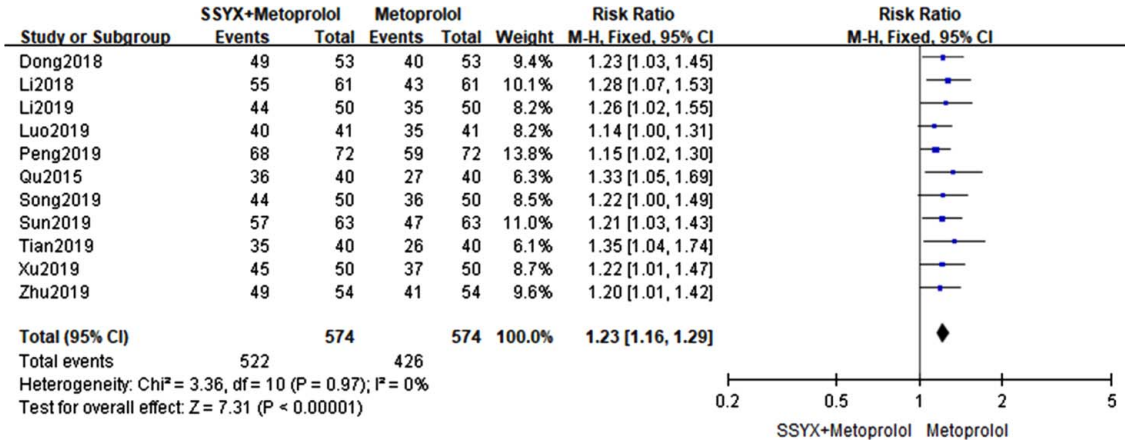

Figure 4. Forest plot of comparison: SSYX-metoprolol vs. metoprolol alone: the total effective rate. SSYX, Shensong Yangxin Capsules.

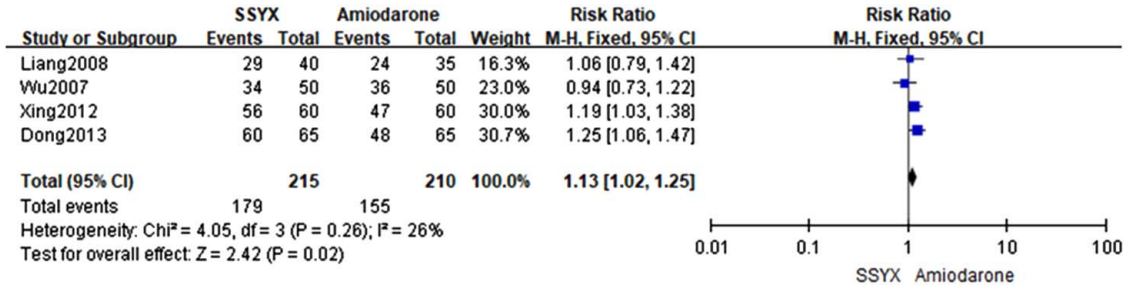

Figure 5. Forest plot of comparison: SSYX vs. amiodarone: the total effective rate ECG. SSYX, Shensong Yangxin Capsules.

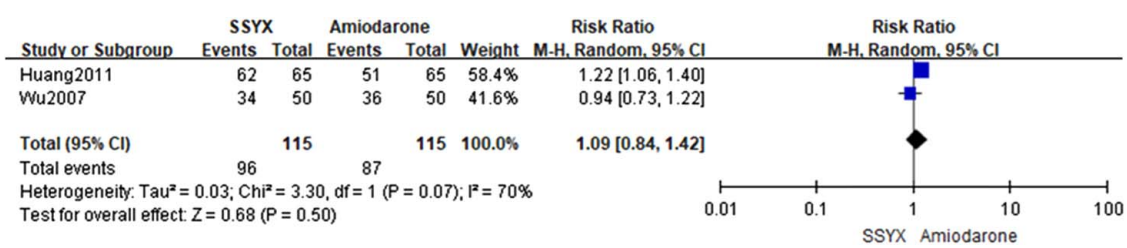

Figure 6. Forest plot of comparison: SSYX vs. amiodarone: ECG. SSYX, Shensong Yangxin Capsules.

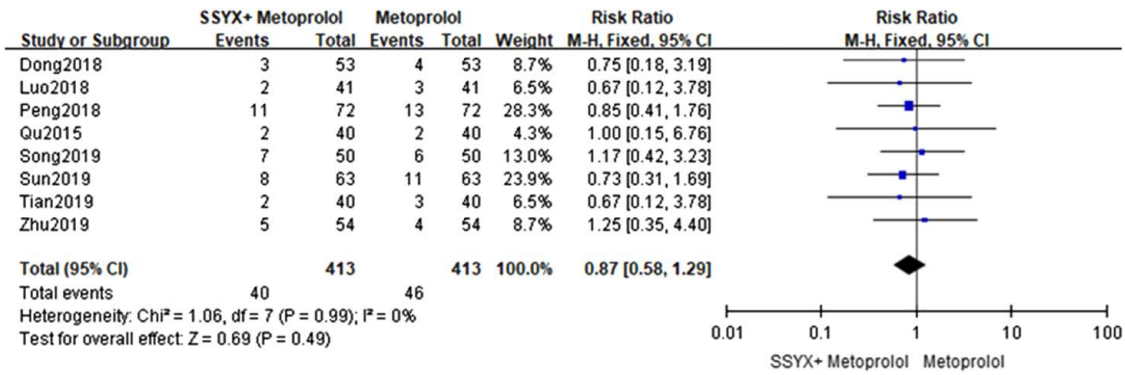

Figure 7. Forest plot of comparison: SSYX-metoprolol vs. metoprolol alone: ADRs. ADR, adverse reaction; SSYX, Shensong Yangxin Capsules.

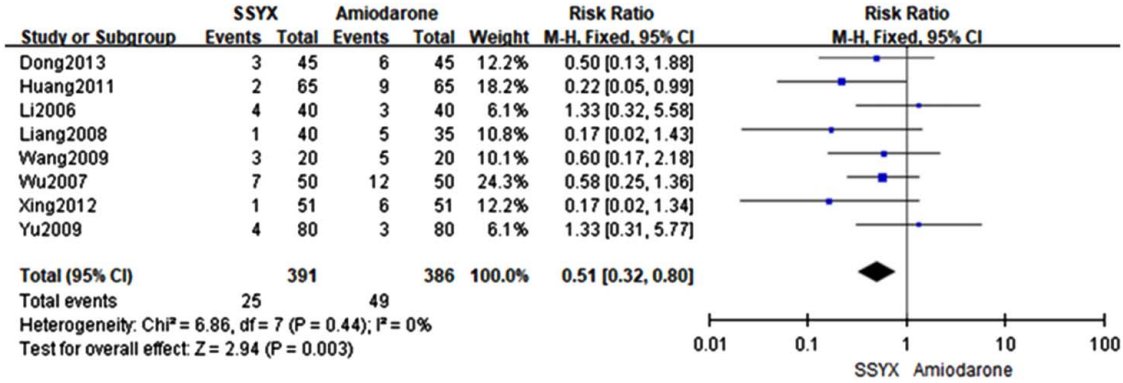

Figure 8. Forest plot of comparison: SSYX vs. amiodarone: ADRs. ADR, adverse reaction; SSYX, Shensong Yangxin Capsules.

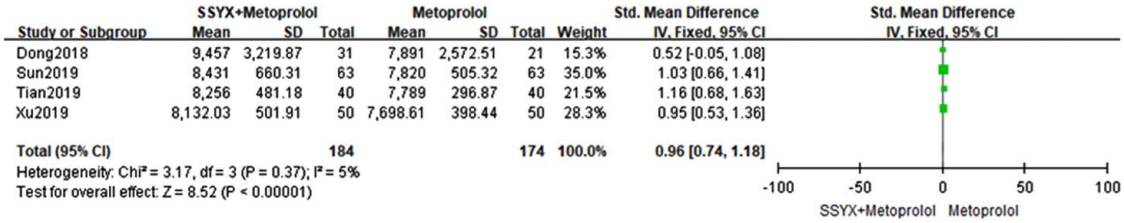

Figure 9. Forest plot of comparison: SSYX-metoprolol vs. metoprolol alone: VPCs. SSYX, Shensong Yangxin Capsules; VPC, ventricular premature complex.

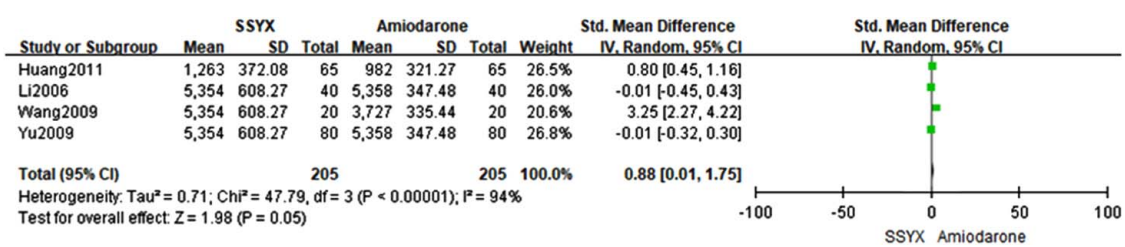

Figure 10. Forest plot of comparison: SSYX vs. amiodarone: VPCs. SSYX, Shensong Yangxin Capsules; VPC, ventricular premature complex.

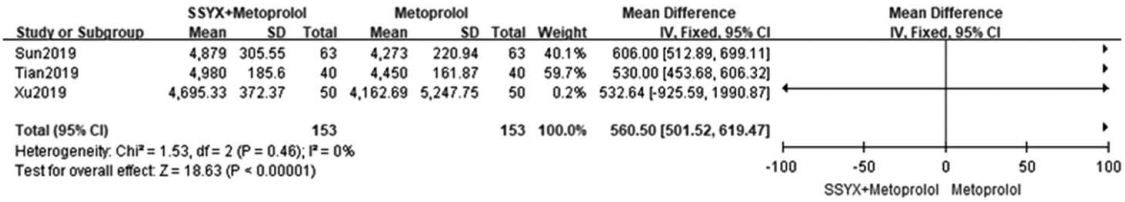

Figure 11. Forest plot of comparison: SSYX-metoprolol vs. metoprolol alone: APBs. APB, atrial premature beat; SSYX, Shensong Yangxin Capsules.

of the results. If the funnel diagram is asymmetrical, there is a publication bias between these studies.

Results

Literature inclusion process

Five hundred fifty-six kinds of literature were searched, including 226 repetitive literature, 253 articles that were not consistent with articles and abstracts, and 58 types. Finally, 20 RCTs[16–36] were eligible for this meta-analysis, which were carried out in China between 2010 and 2022. The flow chart of the research strategy is shown in Fig. 2.

Study characteristics

Nineteen RCTs with 1925 coronary heart disease arrhythmias patients accorded with the eligibility criteria, including 965 patients in the experimental groups and 960 patients in the control groups, 60.99% of the participants were male, most of them belonged to the elderly, and there was no significant difference between the two groups ($P > 0.05$). Metoprolol 25 mg Tid combined with SSYX 1.2 g Tid for 28 days accounted for 50%, metoprolol 25 mg Tid for 28 days accounted for 50%, SSYX 1.6 g Tid for 28 days accounted for 87.5%, amiodarone 25 mg Tid for 7 days, 25 mg Bid for 7 days, 25 mg Qd for 14 days, accounting for 62.5%, Table 2.

Quality evaluation

Use the Cochrane bias risk assessment tool to evaluate the quality of each study, (1) Selection bias (generation of random sequence): In 4 randomized controlled experiments[18,19,24,25], the random method uses the random number table method, and the risk bias is "low risk." Other randomized controlled trials only involve randomization, and there is no precise randomization method, so the risk bias is "unclear risk." (2) Selection bias (allocation concealment): In all the included literature, there is no information about allocation concealment, so the selection bias is "unclear risk." (3) Implementation bias (trial blindness to investigators and subjects): All studies did not provide information on blinding, so the performance bias was evaluated as "unclear risk." (4) Measurement bias (blind evaluation of research outcome): The results of randomized controlled trials included in the study are not affected by the blinding of the researcher's results, so measurement bias is "low risk." (5) Follow-up bias (completeness of the outcome data): The data of the randomized controlled trials included in the study all show completeness, so the follow-up bias is "low risk." (6) Reporting bias (selective reporting of research results): Considering that a complete trial report cannot be obtained, the selection bias is "unclear." (7) Other biases: Since other biases are not mentioned in the study, they are considered "low risk." The risk assessment included in the literature, Fig. 3.

Outcomes

The total effective rate

Eleven studies mentioned the clinical efficacy of SSYX-metoprolol versus metoprolol alone in the treatment of coronary heart disease arrhythmia[16–23,25–28]. No statistically significant heterogeneity was found in analyses ($I^2 = 0\%$), and a fixed-effect model was used for statistical analysis. The meta-analysis results showed that SSYX-Metoprolol had better clinical efficacy than metoprolol in the treatment of coronary heart disease arrhythmia [RR = 1.23, 95% CI (1.16, 1.30), $P < 0.00001$], as shown in Fig. 4.

Four studies mentioned that SSYX vs. amiodarone in the treatment of coronary heart disease arrhythmia[28,30,33,34], No statistically significant heterogeneity was found in analyses ($I^2 = 0\%$), and a fixed-effect model was used for statistical analysis. The meta-analysis results showed that SSYX had better clinical efficacy than amiodarone in the treatment of coronary heart disease arrhythmia [RR = 1.13, 95% CI (1.02, 1.25), $P = 0.02$], Fig. 5.

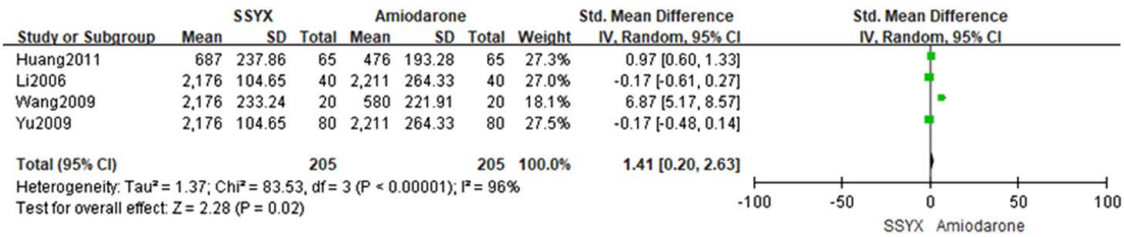

Figure 12. Forest plot of comparison: SSYX vs. amiodarone: APBs. APB, atrial premature beat; SSYX, Shensong Yangxin Capsules.

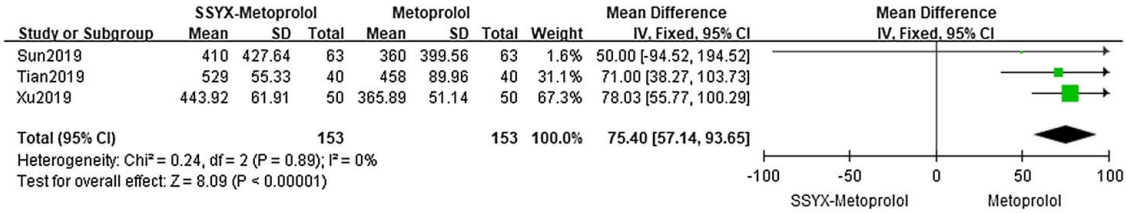

Figure 13. Forest plot of comparison: SSYX-metoprolol vs. metoprolol alone: JPBs. JPB, junction premature beat; SSYX, Shensong Yangxin Capsules.

ECG

Two studies mentioned the effect of SSYX on the treatment of coronary heart disease arrhythmia[29,33] on ECG. After the heterogeneity test, the heterogeneity is considerable ($I^2 = 70\%$). The random-effects model was adopted. The meta-analysis results showed that SSYX and amiodarone were not statistically significant on the treatment of coronary heart disease arrhythmia on ECG [RR = 1.09, 95% CI (0.84, 1.42), $P = 0.50$], Fig. 6.

Adverse reactions (ADRs)

Nine studies mentioned the adverse effects of SSYX -metoprolol in the treatment of coronary heart disease arrhythmia[16–18,20,21,25,27,28]. No statistically significant heterogeneity was found in analyses ($I^2 = 0\%$), and a fixed-effect model was used for statistical analysis. The meta-analysis results showed that SSYX-metoprolol had a lower incidence of ADRs than metoprolol in the treatment of coronary heart disease and arrhythmia [RR = 0.88,95% CI (0.60, 1.28), $P = 0.50$], Fig. 7.

Eight studies mentioned the adverse effects of SSYX vs. amiodarone in the treatment of coronary heart disease arrhythmia[28,30–36]. No statistically significant heterogeneity was found in analyses ($I^2 = 0\%$), and a fixed-effect model was used for statistical analysis. The meta-analysis results showed that SSYX was safer than amiodarone alone in the treatment of coronary heart disease arrhythmia [RR = 0.51, 95% CI (0.32, 0.80), $P = 0.003$], Fig. 8.

Ventricular premature complexes

Four studies mentioned the number of VPCs of SSYX-metoprolol to treat coronary heart disease arrhythmia with metoprolol[16,19,25,27]. No statistically significant heterogeneity was found in analyses ($I^2 = 5\%$), and a fixed-effect model was used for statistical analysis. The meta-analysis results showed that SSYX-metoprolol was more effective in reducing the VPCs compared with Metoprolol alone [SMD = 0.96, 95% CI (0.74, 1.18), $P < 0.00001$], Fig. 9.

Four studies mentioned that SSYX vs. amiodarone in the treatment of coronary heart disease arrhythmia in the number of VPCs[29,31–33], high heterogeneity ($I^2 = 94\%$), using random-effects. The meta-analysis results showed that SSYX and amiodarone were not statistically significant in reducing the VPCs [SMD = 0.88, 95% CI [0.01,1.75, $P = 0.05$], Fig. 10.

Atrial premature beats

Three studies mentioned that SSYX-metoprolol in the treatment of coronary heart disease arrhythmia with APBs[16,19,24], low heterogeneity ($I^2 = 0\%$), fixed-effect model, The meta-analysis results showed that SSYX-metoprolol was better than metoprolol in reducing the APBs [MD = 560.50, 95% CI (501.52, 619.470), $P < 0.00001$], Fig. 11.

Four studies mentioned that SSYX vs. amiodarone in the treatment of coronary heart disease arrhythmia with APBs[28,30,32,33], high heterogeneity ($I^2 = 96\%$), using random-effects model, The meta-analysis results showed that SSYX and amiodarone were not statistically significant in reducing the APBs [SMD = 0.88, 95% CI (0.01,1.75), $P = 0.05$], Fig. 12.

Junction premature beats

Three studies mentioned that SSYX-metoprolol in the treatment of coronary heart disease arrhythmia with JPBs[16,19,25], low heterogeneity ($I^2 = 0\%$), using a fixed-effect model, The meta-analysis results showed that SSYX-metoprolol was more effective than metoprolol in reducing the JPBs [MD = 75.40,95% CI (57.14, 93.65), $P < 0.00001$], Fig. 13.

Three studies mentioned that SSYX vs. amiodarone in the treatment of coronary heart disease arrhythmia with JPBs[28,30,33].There was significant heterogeneity in the three studies ($I^2 = 97\%$), and a sensitivity analysis was conducted by excluding the studies one by one, The heterogeneity between the studies was significantly reduced after removing the study reported by Huang[33] ($I^2 = 0\%$) As shown in Table 2, the amiodarone dose in the study[33] was different from the other two

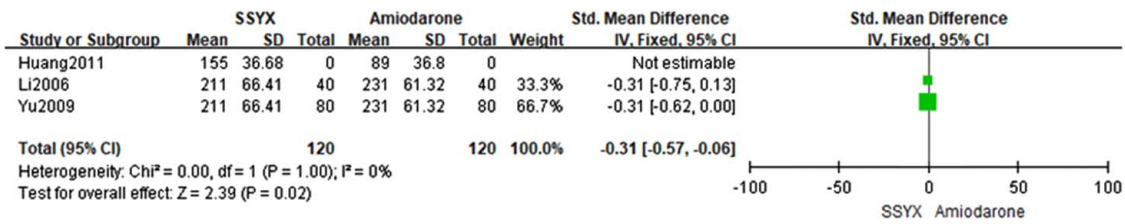

Figure 14. Forest plot of comparison: SSYX vs. amiodarone: JPBs. JPB, junction premature beat; SSYX, Shensong Yangxin Capsules.

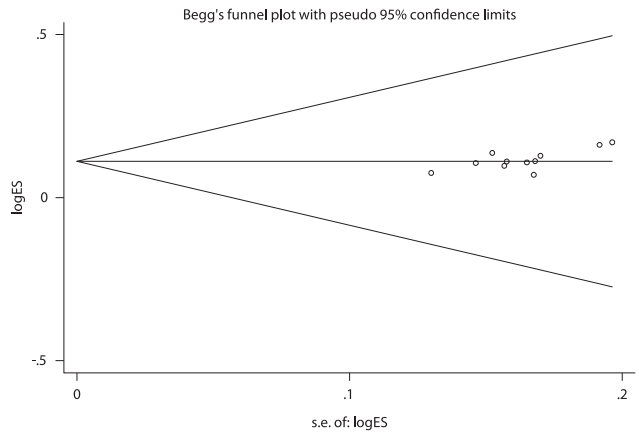

Figure 15. Begg's funnel plot of the total effective rate:SSYX-metoprolol vs. Metoprolol. SSYX, Shensong Yangxin Capsules.

studies, which might contribute to the heterogeneity. A fix-effect model was used for meta-analysis after removing the study[33]. The meta-analysis results showed that SSYX were more effective in reducing the JPBs compared with amiodarone alone [SMD = – 0.31, 95% CI(– 0.57, – 0.06), $P = 0.02$], Fig. 14.

Publication bias of outcomes

The publication bias adopts the Begg test, and the total effective rate of the Begg test is 0.014 ($P < 0.05$), indicating that these studies have publication bias, as shown in Fig. 15. The total effective Begg funnel chart is visually asymmetric, meaning that these studies have publication bias. The tendency may be the small sample size of the randomized trial and the inadequate quality assessment of the Chinese literature and methodology.

Cost-effectiveness analysis

Through the literature treatment plan, the use of SSYX [manufacturer; Beijing Yiling Pharmaceutical Co., Ltd., approval number; National Medicine Zhunzi Z20103032] accounted for 50%[16–19,21,23–27], use SSYX [Shijiazhuang Yiling Pharmaceutical Co., Ltd., Z20030058] accounted for 20%[22,27,30,34]. Other studies did not mention; Metoprolol tartrate [AstraZeneca Pharmaceutical Co., Ltd.] Produced by the company, batch number: 180206, specification: 25 mg) accounted for 25%[16,17,25–27]. Other studies did not mention; amiodarone [Hangzhou Sinoferi Minsheng Pharmaceutical Co., Ltd., approval number: National Medicine Standard The word H19993254] accounts for 10%[30,34]. Other studies have not mentioned it. Metoprolol 25 mg Tid combined with SSSYX 1.2 g Tid for 28 days accounted for 50%, Metoprolol 25 mg Tid for 28 days accounted for 50%; SSYX 1.6 g Tid for 28 days accounted for 87.5%, Amiodarone 25 mg Tid for 7 days, 25 mg Bid for seven days, 25 mg Qd for 14 days, accounting for 62.5%. The cost of the medicine = the unit price of the drug (yuan/box) × the number of containers used in 28 days, calculate the cost. The weighted average effective rate of the included studies is used to obtain the effect data of each group of drugs. The data of this effect and the cost of the drugs are used for economic evaluation and analysis, as shown in Table 3, Fig. 16.

$$\text{Medicine cost}_{(\text{SSYX+Metoprolol})} = 3 \times 3 \times 28 \div 36 \times 29.29 + \text{A}_{(\text{Metoprolol})} = 205.03 + \text{A yuan}$$

$$\text{Medicine cost}_{(\text{Amiodarone})} = (3 \times 7 + 2 \times 7 + 1 \times 14) \div 20 \times 21.99 = 53.88 \text{ yuan}$$

$$\text{Medicine cost}_{(\text{SSYX})} = 3 \times 4 \times 28 \div 36 \times 29.29 = 273.37 \text{ yuan.}$$

The results showed that the total effective rate of SSXY-metoprolol in the treatment of coronary heart disease arrhythmia increased by 1 unit, the cost increased by 12.21 yuan; Compared with amiodarone in the treatment of arrhythmia of coronary heart disease, the total clinical effective rate and electrocardiogram effect of SSYX increased by 1 unit, the cost increased by 23.73 yuan and 34.03 yuan. In the incremental cost-effectiveness ratio (ICER), according to WHO's recommendation on pharmaceutical economic evaluation[36], ICER < per capita GDP, and the increased price cost was entirely acceptable; Per capita GDP < ICER <3 times per capita GDP, the price increase was allowable; ICER > three times per capita GDP, the increased price was not worth it. Based on the fact that China's per capita GDP will exceed 80976 yuan in 2021 released by the National Bureau of Statistics, this study concluded that SSYX was worth treating coronary heart disease arrhythmia based on the control drug and had a better effect.

Single-factor sensitivity analysis

In this study, the price of drugs and the efficacy of drugs are the major factors that affect this study, and also the most direct factors that affect the incremental cost. Under the condition of keeping other efficacy indicators unchanged, the sensitivity analysis of drug prices is carried out by single factor, and the price of drugs is reduced by 10% to cope with the fluctuation of cost-effectiveness. Single-factor sensitivity analysis shows that a 10% drop in the price of the drug has little effect on the curative effect of the drug. Single-factor sensitivity confirms the stability of the results, as shown in Table 4.

Table 3

Cost-effectiveness analysis

Intervention	C	E_1 (%)	E_2 (%)	Analytical method	ΔC	ΔE_1	ΔE_2	ΔC /ΔE1	ΔC /ΔE2
SSYX + Metoprolol	205.03 + A	90.72	—	CEA	205.03	16.78	—	12.21	—
Metoprolol	A	73.94	—	CEA					
SSYX	273.37	83.4	81.7	CEA	219.49	9.25	6.45	23.73	34.03
Amiodarone	53.88	74.15	75.25	CEA					

A, metoprolol drug cost; C, drug cost; CEA, cost-effectiveness analysis; E_1, clinical effective rate; E_2, ECG effective rate; SSYX, Shensong Yangxin Capsule.

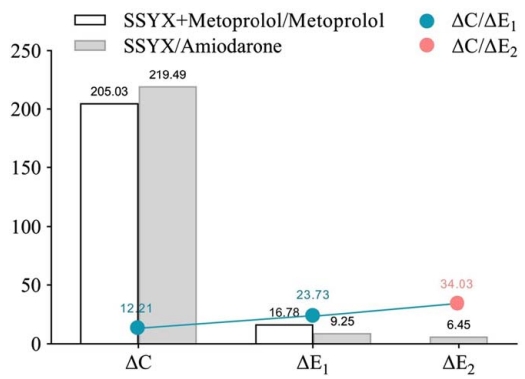

Figure 16. SSYX cost-effectiveness analysis. SSYX, Shensong Yangxin Capsules.

Discussion

Efficacy statement of SSYX

The prevalence of coronary heart disease is increasing year by year. Arrhythmia is a common complication, which is mainly caused by the increase of Ca^{2+} concentration and the decrease of K^+ concentration in ischaemic myocardium, resulting in abnormal bioelectrical activity of myocardium. Western medicine has limitations in drug therapy and non-drug therapy. Amiodarone and metoprolol are often used to treat arrhythmia in coronary heart disease. Studies have shown[37,38] that amiodarone and metoprolol can improve arrhythmia by inhibiting Ca^{2+} pathway, but the effect of using it alone is not good and it will lead to adverse reactions, so it needs to be used in combination with other important drugs. SSYX has the effects of invigorating qi, nourishing yin, promoting blood circulation, dredging collaterals, clearing heart-fire and tranquilizing mind, and its mechanism of action is to resist arrhythmia by inhibiting Na^+, K^+, and Ca^{2+} channels. According to relevant study[39], it can reduce Na^+ current and L-type calcium channel current peak value, inhibit myocardial cell remodelling, and have a blocking effect on multi-ion channels[40], improves cardiac load, and prolongs the duration of action potentials to prevent arrhythmia; SSYX can also inhibit arrhythmia by inhibiting the effect of the fast sodium channel, L-type calcium channel, and potassium channel, accelerate the inactivation process of KVI.4ΔN potassium channel current, and slow down the recovery after the inactivation of KVI.4ΔN channel, and significantly inhibit the current of KVI.4ΔN potassium channel to anti-arrhythmia[41]. In addition, SSYX in the inhibition of sodium ion flow, promote potassium ion outflow, reduce the automaticity of cardiomyocyte, and prolong the potential action time of atrial muscle, ventricular muscle, and conduction system achieve the effect of anti-arrhythmia.

Conclusion

The meta-analysis showed that the therapeutic effect of SSYX-metoprolol is superior to that of metoprolol alone. SSYX is superior to amiodarone in improving the total clinical effective rate, reducing the incidence of ADRs, and reducing the JPBs. There was no significant difference between the SSYX and amiodarone in the curative effect of ECG, VPCs, and APBs. The results of pharmacoeconomics show that SSYX has a cost-effectiveness advantage in treating coronary heart disease arrhythmia. Single-factor sensitivity analysis also confirmed the stability of the results. However, since the weighted ECG efficacy of SSYX and amiodarone was not significantly different, the cost was slightly higher for each additional unit of efficacy. Single-factor sensitivity analysis also confirmed the stability of the results. In summary, SSYX has a curative effect, safety, and economy in treating coronary heart disease arrhythmia.

Significance of research

At present, the safety of traditional Chinese medicine has been controversial. There are 13 articles in the literature about the adverse reactions of SSYX in the treatment of coronary heart disease arrhythmias, such as headache, nausea, atrioventricular block, and bradycardia. However, these uncomfortable symptoms will disappear with the continuation of treatment. Meta-analysis showed that the adverse reaction effect of SSYX-metoprolol and SSYX was lower than that of metoprolol and amiodarone alone. In summary, SSYX has a curative effect, safety, and economy in treating coronary heart disease arrhythmia.

Limitation

First of all, the quality of the included randomized controlled trials is poor, and the literature is Chinese. However, all patients were randomly assigned to different groups, with only three articles describing the use of random number tables without mention of participant withdrawal and loss of follow-up, which may affect the accuracy of the results. Secondly, this study does not consider hidden costs, indirect costs, and adverse reaction costs, so it has some limitations on the financial consequences of this study. Finally, the risk of publication bias is high, which may have a particular impact on the results, some of the trials were small sample studies with positive findings.

Table 4

Sensitivity analysis

Intervention	C	E1 (%)	E_2 (%)	Analytical method	ΔC	ΔE_1	ΔE_2	ΔC /ΔE1	ΔC /ΔE2
SSYX + Metoprolol	184.77 + a	90.72	—	CEA	184.77	16.78	—	11.01	—
Metoprolol	a	73.94	—	CEA					
SSYX	246.03	83.4	81.7	CEA	197.54	9.25	6.45	21.35	30.63
Amiodarone	48.49	74.15	75.25	CEA					

a, Metoprolol reduces drug cost by 10%; C, drug cost; CEA, cost-effectiveness analysis; E1, clinical effective rate; E2, ECG effective rate; SSYX, Shensong Yangxin Capsule.

Prospect

In terms of methodology, this study adopts the method of literature research, which saves the cost of drug research, provides a reference for pharmacoeconomic data analysis, and can effectively provide some economic analysis for patients in clinical drug use. However, due to the poor quality of the included literature methodology, it will have a particular impact on the results of this study; the effects of Meta-analysis are affected by the quality of included randomized trials, and the methodological quality of a single randomized controlled trial affects the results. Therefore, we will have many high-quality samples to conduct a prospective multicenter randomized, double-blind trial to evaluate the efficacy, safety, and economy of SSYX to treat coronary heart disease arrhythmias. And further pharmacoeconomic research.

Ethical approval and consent to participate

Not applicable as it is meta-analysis study.

Consent for publication

Not applicable as it is meta-analysis study.

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Author contribution

Topic selection and design: L.M., L.L. and S.M.; Data analysis: F.M. and F.M.; Manuscript writing: L.M.; Final manuscript: L.M.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

1. Name of the registry: We register this systematic review on PROSPERO.
2. Unique Identifying number or registration ID: CRD42021 246631.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/

Guarantor

The guarantor for this article is: Luyao Ma.

Data availability statement

The original contributions in the research report are included in the article or supplementary materials. For further inquiries, please contact the corresponding author directly.

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