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Economic evaluation of isosorbide mononitrate sustained-release capsules for the treatment of angina pectoris

Yuhang Liu [a,b], Jienan Zheng [a,b], Yeyou Xu [a,b], Shuli Zhang [a,b], Yueyun Li [a,b], Hui Zhang [a,b,*]

[a] School of Pharmaceutical Business, Guangdong Pharmaceutical University, Guangzhou, 510006, China
[b] Health Economics and Health Promotion Research Center of Guangdong Pharmaceutical University, Guangdong Pharmaceutical University, Guangzhou, 510006, China

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ABSTRACT

Objective: Systematically evaluate the efficacy of (1) isosorbide mononitrate sustained-release capsules combined with conventional therapy and (2) conventional therapy alone in the treatment of angina pectoris and analyze their economic value to provide evidence and a reference for clinical medication and decision-making.
Methods: Randomized controlled trials on the efficacy of isosorbide mononitrate sustained-release capsules combined with conventional therapy and conventional therapy in the treatment of angina pectoris were searched and abstracted from major Chinese and English literature databases from August 26, 2003 to August 26, 2023, to calculate the rate of improvement in clinical symptoms using isosorbide mononitrate sustained-release capsules combined with conventional therapy (observation group) and using conventional therapy alone (control group). Review Manager 5.4 software was used for meta-analysis, and an economic evaluation was performed using cost-effectiveness analysis (CEA).
Results: The effectiveness rates for clinical symptom improvement were 95% in the observation group and 78% in the control group. According to the meta-analysis results, the efficiency of clinical symptom improvement in the observation group, which received the combination therapy with isosorbide mononitrate sustained-release capsules, was significantly better than that of the control group (OR = 3.38, 95% CI: 2.28 to 4.99, $P < 0.001$). The CEA indicated an incremental cost-effectiveness ratio of 434.12 yuan, and the sensitivity analysis results demonstrated that the evaluation outcomes were stable, suggesting a robust foundation for the study's conclusions.
Conclusions: Compared with conventional therapy alone, isosorbide mononitrate sustained-release capsules combined with traditional treatment have good efficacy and safety in the treatment of angina pectoris and have certain economic advantages.

1. Introduction

Coronary artery atherosclerotic heart disease (coronary heart disease) refers to a heart condition caused by atherosclerosis-caused narrowing or obstructing of the coronary arteries, leading to myocardial ischemia, hypoxia, or necrosis. Atherosclerosis is the most common cause of organ damage. As of 2023, the estimated number of coronary heart disease patients in China was approximately 11.39 million.[1] In clinical practice, coronary heart disease primarily encompasses two subtypes: chronic myocardial ischemia syndrome and acute coronary syndrome (the present manuscript does not encompass an examination of acute coronary syndrome, and thus, further discussion on this topic will not be pursued within the confines of the study). Chronic myocardial ischemia syndrome, also known as stable coronary heart disease, is mostly characterized by stable angina pectoris. Angina pectoris is a clinical syndrome that results from acute or temporary myocardial ischemia and hypoxia caused by inadequate blood supply to the coronary arteries.[2,3] Angina due to coronary heart disease is a common cardiovascular condition encountered in clinical practice that can lead to serious complications such as heart failure, thus posing a significant threat to the patient's life.[4]

Currently, the conventional therapeutic drugs for alleviating angina symptoms in clinical practice include beta-blockers, nitrates, and calcium channel blockers (CCBs). Of these, nitrates function as endothelium-dependent vasodilators that reduce myocardial oxygen demand, improve myocardial perfusion, and alleviate angina symptoms. They are often used in conjunction with beta-blockers or nondihydropyridine

* Corresponding author. School of Pharmaceutical Business, Guangdong Pharmaceutical University, Guangzhou, 510006, China.
E-mail addresses: huizi_zhang@126.com, 19826531981@139.com (H. Zhang).

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CCBs to treat chronic stable angina. The combined antianginal effects of these medications are superior to their individual effects when used alone.[5,6] Isosorbide mononitrate is a nitrate drug and a metabolite of isosorbide dinitrate. It does not undergo a first-pass effect in the liver, is well absorbed after oral administration through the gastrointestinal tract, has a low incidence of adverse reactions, and exhibits relatively little variability in patient response.[7,8] Controlled-release capsules containing isosorbide mononitrate as the primary ingredient, compared with other dosage forms, offer several advantages, including stable in vivo blood drug concentrations, reduced frequency of administration, which leads to improved patient compliance, and high bioavailability. As a result, they are widely used in clinical practice.[9] Several studies have shown that adding controlled-release capsules containing isosorbide mononitrate to conventional therapy can effectively enhance clinical outcomes in treating angina associated with coronary heart disease.[10,11]

Pharmacoeconomics is an interdisciplinary field that studies how to maximize health improvements within the constraints of limited healthcare resources.[12] In recent years, China has continuously strengthened the significant role of pharmacoeconomic evaluations in healthcare decision-making. Pharmacoeconomic evaluations and their evidence play an increasingly important role in various areas, including formulating the National Essential Medicines Policy, centralizing drug procurement with volume-based incentives, providing guidance on rational drug use in clinical practice, and adjusting the national medical insurance drug list. Evaluation methods include cost, cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses.[13,14] As the effectiveness of isosorbide mononitrate medication has increasingly been clinically validated, some studies have conducted economic evaluations of isosorbide mononitrate medications; however, most of these focus on tablets,[15–17] with relatively limited literature evaluating sustained-release capsule formulations. Sustained-release capsules are widely used in clinical practice and have been chosen as products for national procurement. Isosorbide mononitrate sustained-release capsules have comprehensive quality assurance and supply guarantee measures, as well as substitute supply processes. Moreover, the medication's costs are relatively low, enhancing its clinical accessibility.[18] Due to its unique clinical efficacy and good accessibility, pharmacoeconomic evaluations of isosorbide mononitrate sustained-release capsules can provide scientific support for centralized procurement, medical insurance decision-making, and clinical use. Based on this, the study extracted effectiveness data of isosorbide mononitrate sustained-release capsules for treating stable angina pectoris using meta-analysis and subsequently evaluated their cost-effectiveness through a decision tree model and cost-effectiveness analysis (CEA). This study provides scientific evidence for the rational clinical use of these drugs to treat angina in patients with coronary heart disease and to support medical insurance decision-making regarding these drugs.

2. Materials and methods

2.1. Inclusion and exclusion criteria for the literature

Inclusion criteria: (1) The study subjects were patients diagnosed with angina pectoris based on clinical assessments, all of whom met the relevant diagnostic and treatment criteria for angina pectoris and the indications for drug treatment. There were no restrictions regarding ethnicity, gender, or age and no limit on the number of cases. In the event of duplicate publications, data from the most comprehensive source were used; (2) The treatment regimen is derived from a randomized controlled trial (RCT) for angina that uses controlled-release capsules of isosorbide mononitrate in combination with conventional medications or solely conventional medications such as beta-blockers, low-dose aspirin, CCBs, and nitroglycerin, regardless of whether the studies included in the research employed blinding methods. The language is limited to Chinese and English; (3) According to the medication plan, the subjects were divided into an observation group and a control group. The observation group received conventional therapy combined with isosorbide mononitrate sustained-release capsules as the intervention, while the control group received only conventional medications as the intervention, with specific dosages and administration protocols determined by the type of medication; (4) The study includes efficacy evaluation indicators and presents the evaluation results.

Exclusion criteria: (1) During the literature review, two similar studies from the same institution were identified, and the data from one of the studies was excluded; (2) The quality of the literature was assessed using Lichtenstein's criteria and additional customized criteria. Studies with low quality, incomplete data, those from which it was impossible to calculate the data, and those with unclear data descriptions were excluded; (3) Patients with other diseases in addition to coronary heart disease were excluded; (4) Non-RCT studies, studies with improper randomization, and studies that were only available as abstracts without full text versions were excluded to ensure the quality and reliability of the research; (5) Reviews, master's and doctoral theses, conference papers, book chapters, and other similar texts were excluded.

2.2. Literature search

The Cochrane Central Register of Controlled Trials, PubMed, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang Database, VIP Chinese Science and Technology Journals Database, and the China Biology Medicine database were searched using computer-based methods. The literature retrieval period for all databases spanned from their inception to July 2023. The process of literature screening is illustrated in Fig. 1. The search terms are as follows:

P: Coronary disease, coronary diseases, disease, coronary, diseases, coronary, coronary heart disease, coronary heart diseases, disease, coronary heart, diseases, coronary heart, heart disease, coronary, heart diseases, coronary; I: Isosorbide mononitrate SR capsules, isosorbide-5-mononitrate SR capsules; S: Randomized controlled trial, randomized, placebo, RCT.

The language is restricted to Chinese and English only. Two evaluators independently assessed the search strategy, and any discrepancies were resolved through discussion or coordination with a third party professional.

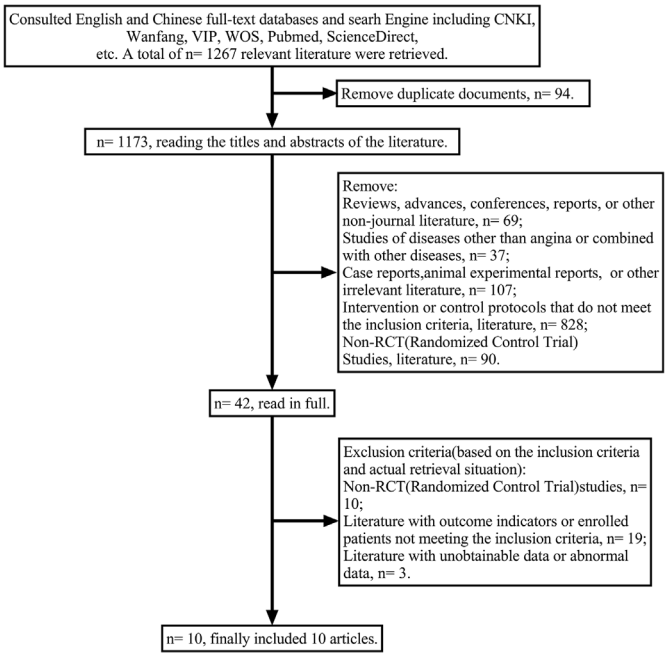

Fig. 1. Literature screening process.

2.3. Literature screening and data extraction

Two evaluators independently reviewed the titles, abstracts, and full texts of the identified literature, screened them against the inclusion and exclusion criteria, and extracted the data using a predesigned form.[19] After the screening was completed, a cross-check was conducted, and any discordant opinions were resolved through discussion or by consulting a third party, resulting in the final selection of the included studies.

2.4. Literature quality assessment

The methodological quality of the included studies was assessed with the bias risk evaluation criteria for RCTs outlined in the *Cochrane Handbook*, version 5.4.[20] The criteria include:

(1) randomization method
(2) allocation concealment
(3) blinding
(4) completeness of outcome data
(5) selective reporting of study results
(6) other sources of bias (such as early termination of trial and baseline inconsistencies)

Each criterion was evaluated as "yes" (indicating low bias), "no" (indicating high bias), or "unclear" (indicating bias uncertainty or a lack of relevant information).

2.5. Pharmacoeconomic evaluation

2.5.1. Research perspective

Pharmacoeconomic evaluations commonly include societal and healthcare system perspectives. This study adopts the healthcare system perspective for analysis. The study duration is 90 days, nondiscounted. Table 1 shows the analysis framework.

2.5.2. Evaluation method

CEA is better suited for evaluating short-term medical interventions[18] because it links health improvements directly to costs, helping decision-makers make rational healthcare decisions with limited resources. Additionally, CEA accounts for the health effects of specific patient populations, thereby supporting personalized medicine. This study uses CEA for its pharmacoeconomic evaluation. The therapeutic regimen for the control group, as recommended by the guidelines,[6] includes general treatment measures and drug therapy with aspirin (either clopidogrel and aspirin tablets, compound acetylsalicylic acid tablets, or aspirin tablets) at a dose of 80 mg/day; metoprolol tartrate tablets with an initial dose of 100 mg/day for the first 7 days of the study, subsequently adjusted to a maintenance dose of 100–200 mg/day taken twice daily; amlodipine besylate starting at a dose of 5.0 mg/day for the first 7 days of the study, with potential dosage increases up to a maximum of 10 mg/day (uniformly set at 7.5 mg/day in this study); and nitroglycerin tablets administered at 0.25–0.50 mg per dose, repeated every 5 min、as needed (set at four doses based on the literature in this study). Prices are based on the average values derived from data for 2021–2023 published by Yaozh.com.

The treatment group received isosorbide mononitrate sustained-release capsules at doses of 40 mg/day or 50 mg/day. The treatment period corresponds to the median therapy duration of the study, which is 90 days. The cost reference is based on median winning bid prices for drugs published by the China Drug Wisdom Network in 2023. Isosorbide mononitrate sustained-release capsules are produced by Zhuhai Rundu Pharmaceutical Co., Ltd., with a specification of 40 mg/box at 24.6 yuan/box (30 capsules); aspirin enteric-coated tablets are produced by Shiyao Group Ouyi Pharmaceutical Co., Ltd., with a specification of 0.1 g/tablet at 17.45 yuan/box (36 tablets); amlodipine besylate and atorvastatin calcium tablets are produced by Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd., with a specification of 5 mg each of amlodipine besylate (calculated as amlodipine) and atorvastatin calcium (calculated as atorvastatin) per tablet, packaged as 10 mg × 14 tablets/box at 36.67 yuan/box; nitroglycerin tablets are produced by BeijingYimin Pharmaceutical Co., Ltd., with a specification of 500 μg at 38 yuan/box. Please refer to Table 2 for further detail. Direct costs other than drug costs are assumed to be generally consistent and thus only drug costs are considered. As the simulation period does not exceed 1 year, costs require no discounting, and none is applied. Treatment effectiveness is evaluated based on improvements in angina symptoms as indicated by meta-analysis results. Outcomes are rated 1 for effective and 0 for noneffective.

2.5.3. Evaluation model

The decision tree model is primarily used to assess the cost-effectiveness of short-term treatment regimens. As angina is a short-term, episodic condition, this study uses a decision tree model to perform an economic evaluation. Effectiveness indicators are derived through meta-analysis, and relevant parameters for outcomes, costs, and transition probabilities are subsequently collected. These parameters are used to conduct pharmacoeconomic evaluations with the decision tree model. The model's structure and parameters are outlined in Fig. 2.

2.5.4. Statistical processing

Microsoft Excel 2020 was used for statistical analysis and chart creation. Frequency distribution and percentages describe the data, while line graphs and bubble charts illustrate the characteristics of evidence distribution. The meta-analysis was conducted using Review Manager (RevMan) 5.4 statistical software. For count data, the relative risk or odds ratio (OR) was used as the effect size measure, and for continuous data, the mean difference was employed. The results were expressed using each effect measure along with its corresponding 95% confidence interval (CI). Clinical heterogeneity checking (Q test) was initially performed. If there was no heterogeneity among the study results ($P > 0.1$, $I^2 < 50\%$), a fixed-effect model was used for the meta-analysis. If there was heterogeneity among the study results ($P < 0.1$, $I^2 \geq 50\%$), a

Table 1
Pharmacoeconomic analysis framework.

Health economics evaluation elements	Content description
Treatment group	Isosorbide mononitrate Sustained-Release capsules + Standard treatment protocol control group
Control group	Standard treatment
Protocol perspective	From the perspective of chinese healthcare
Evaluation method	CEA
Time horizon	90d
Health database	Treatment effects: Meta-analysis
Costs	Direct medical costs only, including: Drug treatment expenses
Outcome indicators	Effectiveness ICER
Willingness-to-Pay (WTP) threshold	Three times the per capita gross domestic product (GDP), calculated based on 2022 figures of 85,698 yuan/person
Discount rate	No discounting
Uncertainty analysis	One-way sensitivity analysis Probability sensitivity analysis

Table 2
Costs of various medications.

Project (Drug name)	Specification (mg)	Unit price (Yuan)	Annual cost (Yuan)
Isosorbide mononitrate sustained-release capsules	40.0/50.0	0.24	73.8
Aspirin tablets	100.0	0.48	43.2
Atorvastatin calcium tablets	5.0/10.0	0.52	235.7
Nitroglycerin tablets	0.5	0.38	1.5

Source: www.yaozh.com.

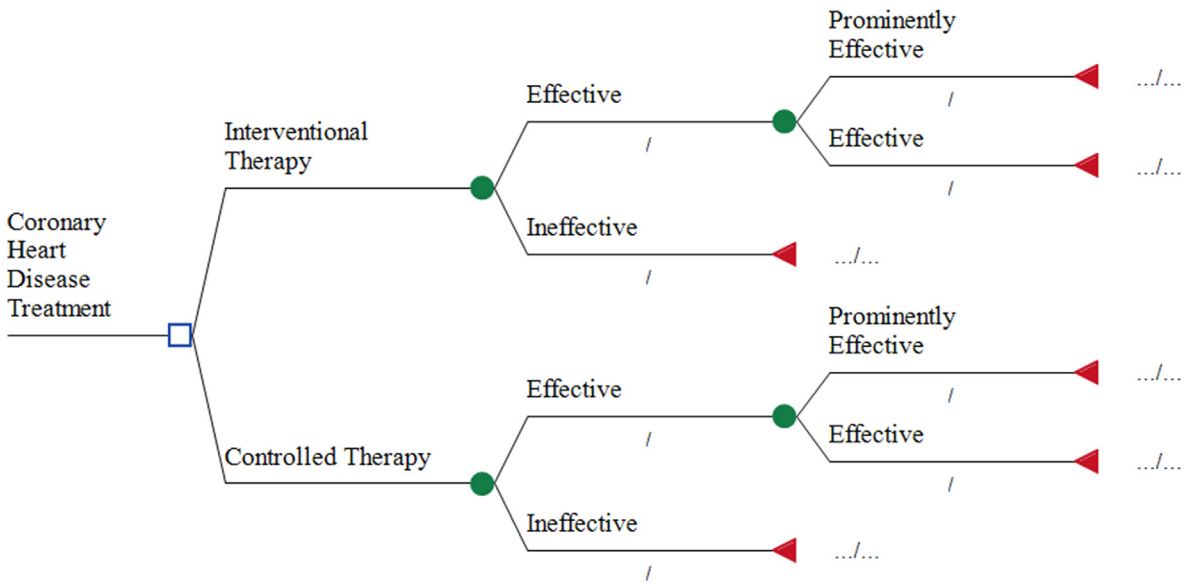

Fig. 2. Structure of decision tree model.

random-effects model was used for the meta-analysis. In cases where the data source was unavailable, descriptive analysis was employed.[29] A significance level of $P < 0.05$ indicated a statistically significant difference.

2.6. Meta-analysis

2.6.1. Basic information on the included literature (see Table 3)

2.6.2. Methodological quality assessment of included studies

All included studies were assessed using the Cochrane bias risk assessment tool in the RevMan 5.4 software, encompassing seven aspects:

(1) Generation of random sequence (selection bias)
(2) Allocation concealment (selection bias)
(3) Blinding of all study participants and personnel (performance bias)
(4) Blinding of outcome assessment (detection bias)
(5) Completeness of outcome data (attrition bias)
(6) Selective reporting (reporting bias)
(7) Others

As shown in Fig. 3, 10 studies employed some form of randomization for allocation. Of these, six mentioned randomization without specifying the method, one's method was unclear, and the three remaining studies specified their methods. All 10 studies used allocation concealment. It was unclear whether blinding was implemented in seven studies, three of which used single-masked methods. Nine studies had no missing data, and thus, the remaining study had missing data. Selective reporting was not identified in four studies, but it was present in six studies. Three studies had no other biases, while it remained unclear whether biases were present in the other seven studies (see Fig. 3).

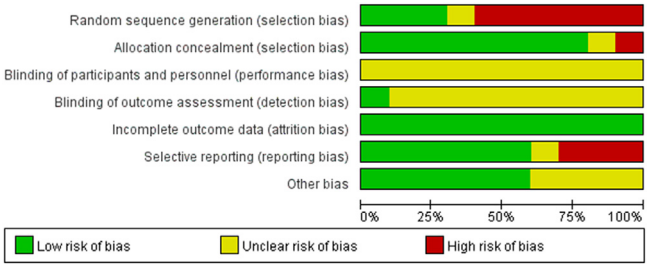

Fig. 3. Risk bias assessment of the included literature.

Table 3
Summary of included economic evaluations.

The first author and the year of publication	Number of cases (Treatment group/ Control group)	Age (Year)		Duration of illness (Year)		Duration of treatment (Day)
		Treatment group	Control group	Treatment group	Control group	
Weng 2019[21]	70/70	45.9 ± 4.2	43.6 ± 3.8	2.0–10.0	2.0–11.0	30
Gao 2019[22]	40/40	65.9 ± 3.8	64.2 ± 3.4	/	/	90
Reng 2017[23]	62/62	52.3 ± 6.0	54.2 ± 9.0	6.3 ± 1.0	6.1 ± 3.2	/
Geng 2017[24]	39/39	65.4 ± 3.4	65.0 ± 3.7	/	/	28
Luo 2015[25]	90/90	46.7 ± 2.5	47.2 ± 2.6	5.3 ± 0.7 (1–14)	5.2 ± 0.6 (1–13)	30
Yan 2014[26]	39/39	68.3 ± 1.1	68.4 ± 1.2	4.8 ± 0.6 (1–18)	4.9 ± 0.7 (1–16)	30
Meng 2014[27]	50/50	45.6 ± 2.5	47.5 ± 1.3	/	/	60
Weng 2014[28]	200/200	/	/	/	/	/
Liu 2017[29]	70/70	46.7 ± 2.5	47.2 ± 2.6	5.3 ± 0.7 (1–14)	5.2 ± 0.6 (1–13)	/
Wang 2016[30]	31/31	57.8 ± 9.0	58.2 ± 9.4	/	/	60

Note:/= data not found.

2.6.3. Publication bias and heterogeneity assessment

This study covered 10 pieces of literature on angina pectoris (References 21to30), thus permitting an analysis of publication bias for the logarithm of the OR of the total effective rate for angina pectoris, as well as its standard error. Fig. 4 shows the distribution of literature on treating angina pectoris with isosorbide mononitrate-containing controlled-release capsules in conjunction with conventional therapy, which is largely symmetrical and thus suggests only minimal publication bias. The included literature demonstrates good homogeneity[31]; however, overall heterogeneity is relatively high, with a Q value of 0.297 (> 0.05) and an I^2 of 60.4%, as shown in Fig. 5.

2.6.4. Effectiveness rate and subgroup analysis of effectiveness rate

The results of the random-effects model meta-analysis demonstrate a statistically significant difference for improvements in clinical symptoms between the case and control groups[32] [OR = 3.38, 95% CI (2.28, 4.99), $P < 0.001$]. The meta-analysis results indicate that the experimental group has a higher effectiveness rate than that of the control group. For details, please refer to Fig. 6. Because of the high heterogeneity of the included studies, a subgroup analysis was conducted based on the intervention measures.[31] Fig. 7 presents the results of this analysis.

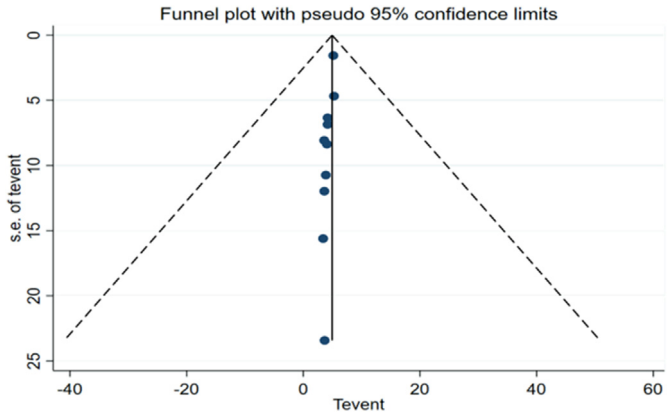

Fig. 4. Funnel plot for the publication bias of the included literature.

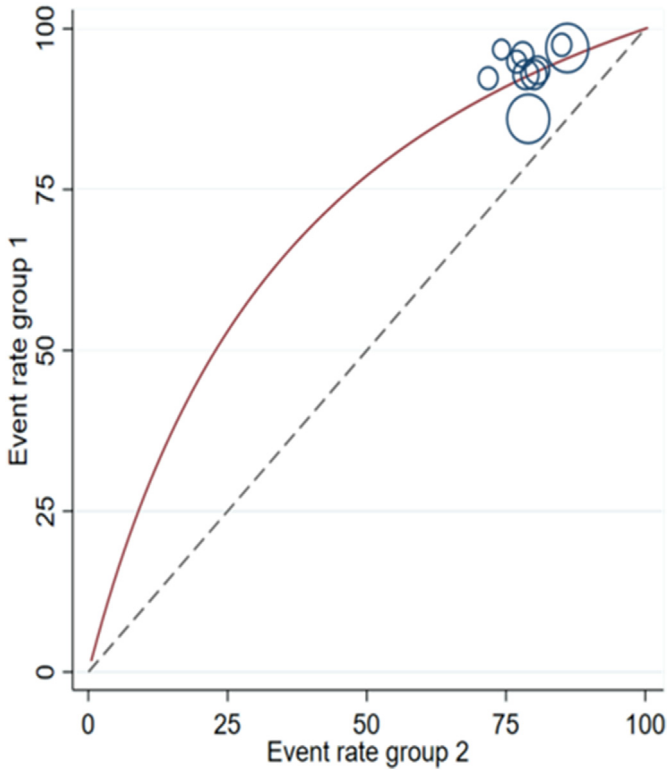

Fig. 5. Heterogeneity evaluation of included literature.

3. Pharmacoeconomic evaluation

3.1. Cost-effectiveness analysis

According to the results of the meta-analysis, the angina symptom improvement rates for each group were determined using weighted averages from the literature.[33] After the weighted calculation, the efficacy rates were 95% for the intervention group and 78% for the control group. Using drug cost (C) and weighted symptom improvement efficacy rate (E) as reference indicators, the cost-effectiveness ratio and incremental cost-effectiveness ratio (ICER) were calculated. The results show an ICER of 434.12 yuan. This reflects that for each additional treatment with isosorbide mononitrate-containing controlled-release capsules, there is an associated increase in expenditure of 434.12 yuan when compared to the conventional therapy group, as outlined in Table 4, without prejudice to the actual outcomes achieved.

3.2. Sensitivity analysis

The respective results of the univariate and the probabilistic sensitivity analyses are displayed in Figs. 8 and 9. Fig. 8 indicates that the results are significantly affected by (1) the efficacy rate of conventional therapy and (2) the costs and efficacy rate of controlled-release capsules containing isosorbide mononitrate. The results of the univariate sensitivity analysis indicate that the three factors above do not affect the outcomes when altered. Fig. 9 shows that controlled-release capsules containing isosorbide mononitrate exhibit superior cost-effectiveness when the willingness-to-pay value exceeds 434.12 yuan. These results closely align with the findings from the CEA, indicating good stability in the outcomes.[34]

4. Discussion

Angina is chest pain experienced by patients with coronary heart disease under specific triggers.[5] The primary goal of treating angina in coronary heart disease is to alleviate pain.[35,36] Sustained-release capsules containing isosorbide mononitrate, a long-acting nitrate drug, effectively prolong cardiac protection for the long-term treatment and prevention of angina. Its combined use with other treatments can significantly improve patients' symptoms.[37,38]

From the perspective of the healthcare system,[39] this study conducted a CEA of combining controlled-release capsules containing isosorbide mononitrate with conventional treatment for patients with angina pectoris secondary to coronary heart disease using a decision tree model. The results indicate an ICER for the observation group of 434.12 yuan. Thus, compared with the control group, the average additional cost per day for each angina pectoris treatment cycle in the observation group was 4.82 yuan. According to the *China Health Statistics Yearbook 2022*, China's per capita gross domestic product (GDP) for 2022 was 85,698 yuan, or 234.79 yuan per day.[40] Therefore, the cost increase was significantly less than the per capita GDP, indicating a relative economic advantage for the combination of controlled-release capsules containing isosorbide mononitrate compared with conventional treatment alone. This conclusion can serve as a reference for clinical staff to provide rational drug use for patients.

Based on the assessment of the risks of bias in the literature for this study, publication bias and attrition bias are relatively low. In contrast, selection bias is relatively high, with 60% of the literature evidencing a high risk of bias. Consequently, a limitation of this study is the relatively low quality of the included literature.[41] Additionally, the CEA includes only drug costs and does not take into account other medical expenses,

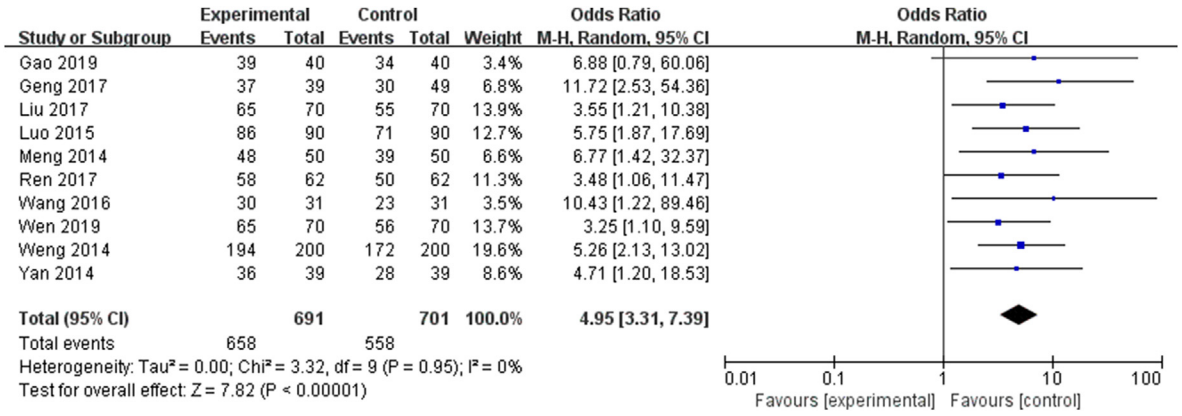

Fig. 6. Forest plot of meta-analysis of efficacy between two groups of angina patients.

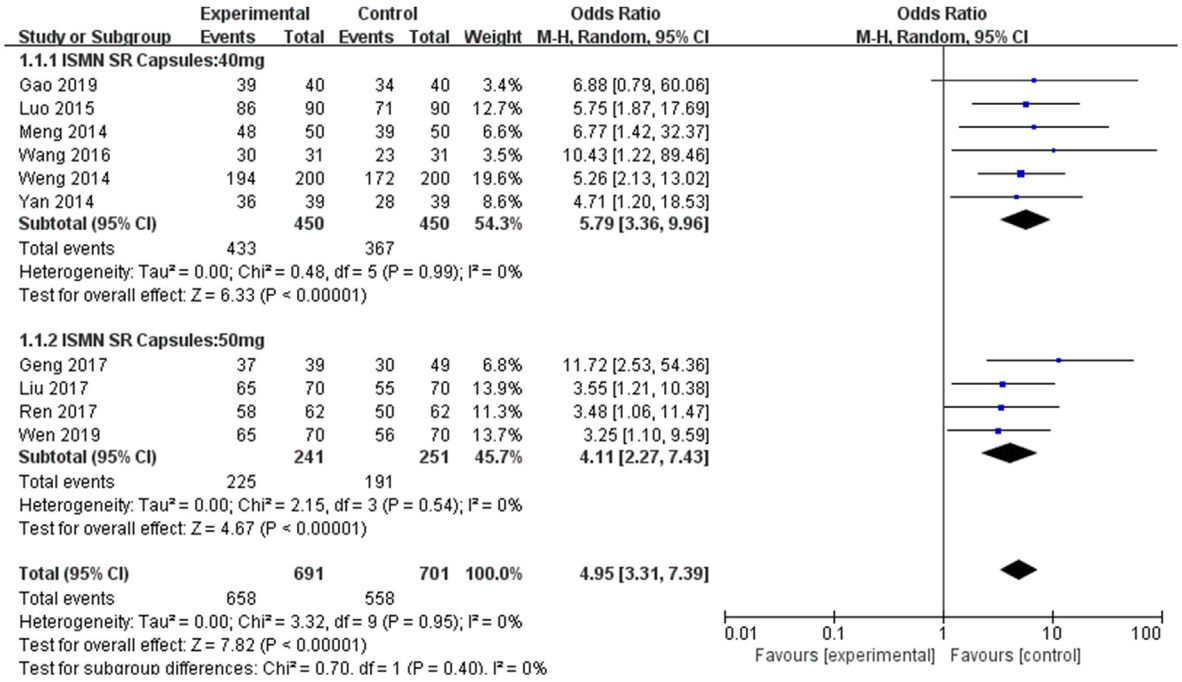

Fig. 7. Subgroup meta-analysis result of efficacy.

Table 4
Results of cost-effectiveness analysis in two groups.

Group	C (Yuan)	E	C/E	ΔC/ΔE
Treatment group	354.22	0.95	372.86	434.12
Control group	280.42	0.78	359.51	–

indirect costs, or costs associated with adverse drug reactions. However, given the minimal impact of isosorbide mononitrate drugs on medical costs beyond the costs of the drugs themselves and the relatively mild adverse reactions, the associated expenses can be considered negligible.[42]

In summary, the combined use of controlled-release capsules containing isosorbide mononitrate, compared to the use of beta-blockers, aspirin, and CCBs alone, demonstrates superior efficacy and economic advantages when added to conventional medication. However, there currently needs to be more high-quality research, specifically large-scale RCTs, on controlled-release capsules containing isosorbide mononitrate. Therefore, further real-world studies on this medication are necessary, and a greater number of high-quality literature sources should be

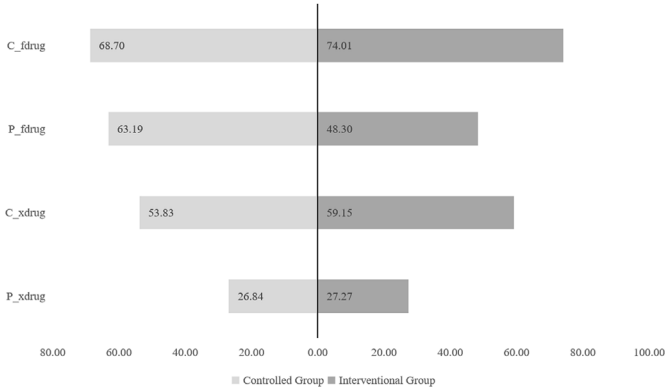

Fig. 8. Cyclonic map of symptom improvement rate in angina pectoris patients (net benefit). Note: C_xdrug refers to the controlled group drug cost, P_fdrug refers to the efficacy rate in the Intervention group, P_xdrug refers to the efficacy rate in the controlled group, and C_fdrug refers to the drug cost in the Intervention group.

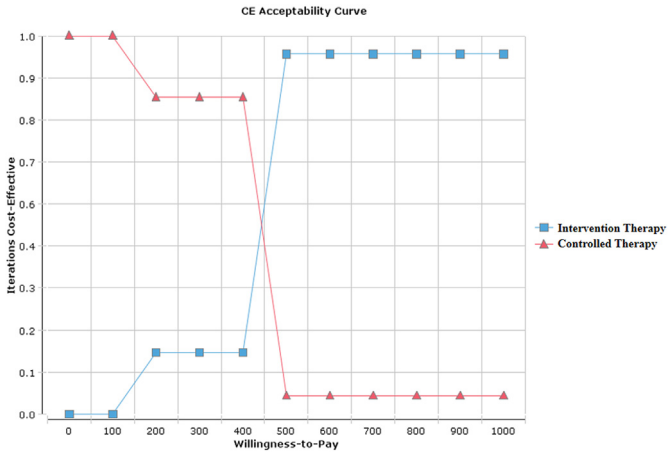

Fig. 9. Cost-effectiveness acceptability curve.

included in evaluations to improve the scientific rigor and precision of the research findings.

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CRediT authorship contribution statement

Yuhang Liu: Writing – review & editing, Methodology, Formal analysis. **Jienan Zheng:** Methodology, Formal analysis. **Yeyou Xu:** Writing – review & editing, Methodology. **Shuli Zhang:** Writing – review & editing, Writing – original draft. **Yueyun Li:** Writing – review & editing, Writing – original draft. **Hui Zhang:** Supervision, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhip.2024.04.003.

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