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Outcome measures in clinical trials of traditional Chinese medicine for stable angina pectoris

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Abstract

Objective: This work aimed to present a descriptive analysis of the outcome measures used in clinical trials of traditional Chinese medicine (TCM) for patients with stable angina pectoris, and to provide baseline data for the development of core outcome sets (COSs) for relevant clinical trials.

Methods: Medical databases were searched to identify randomized trials of the effects of TCM for the treatment of stable angina pectoris. Outcome measures of each trial were extracted. Descriptive statistics were used to analyze the baseline characteristics of outcomes in clinical trials of TCM.

Results: 94 randomized trials (with 9,111 participants) involving 79 different outcomes were identified. The mean number of outcomes was 5 (1–21 per trial). The 5 most commonly reported outcomes were efficacy rate of electrocardiogram, efficacy rate of angina pectoris, efficacy rate of TCM syndrome, fasting lipid indices, and withdrawal rate of nitroglycerin. Several challenges were identified: (1) significant heterogeneity of outcomes and differences in the technique and timing of the measurement of the same outcome; (2) transformation of continuous data into categorical data and presented as such in >90% of trials; (3) few trials on the outcomes associated with the advantages and characteristics of TCM; and (4) selective reporting of outcomes.

Conclusions: The outcomes used are excessively heterogenous, and the choice of some outcomes (timing and techniques) for measurement is confusing or inappropriate. Hence, developing and implementing a COS is necessary for greater consistency.

Keywords: Core outcome set, Outcome measures, Randomized trial, Traditional Chinese medicine

1 Introduction

Stable angina pectoris characterized with sensations of burning, severe pain, pressure and other forms of discomfort in the left anterior chest region, or tightness in the throat, greatly comprises patients' life quality and longevity[1]. In United States, stable angina pectoris affected more than 7.8 million people and was reported to have an incidence of more than 0.5 million cases per year[2]. In Europe, the prevalence was estimated to be 10% to 20% of people aged 65 to 74 years[3]. In China, the incidence was 12.4% among men and 3.2% among women, which makes it a serious public health challenge. Current treatment options for stable angina included lifestyle modification, well control of risk factors, pharmacological management, revascularization, and enhanced external counterpulsation[4–5]. Many studies demonstrated that traditional Chinese medicine (TCM) was potential for pain relief and life quality improvement[6–9]. However, the effect of TCM for stable angina was still controversial due to low methodological quality of study design, especially outcome measures[10].

To solve the problem, the development and implementation of a minimum core outcome set (COS) is recommended. A COS represents the minimum that should be measured and reported in all clinical trials for a specific condition to facilitate the comparison and combination of trials while researchers continue to explore other outcomes[11]. In 2010, the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (www.comet-initiative.org) was launched to provide methodological resources to promote the development and uptake of COS[12–13].

Here, we aimed to analyze the outcome measures used in clinical trials of TCM for angina pectoris to clarify existing problems and provide basic data for developing COSs.

2 Methods

2.1 Eligibility criteria

We sought randomized trials that had aimed to evaluate the effects of TCM, irrespective of their use of adequate allocation, concealment, or blinding. Patients recruited into these trials met the diagnosis of stable angina pectoris, characterized by discomfort in the chest, jaw, shoulder, back or arms, typically elicited or aggravated by exertion or emotional stress and relieved by rest or nitroglycerin[14–15]. We did not limit by age, gender, severity or course of disease. The interventions in at least one treatment group in the trials should include Chinese medicines, either Chinese patent medicine or decoction, and we placed no restrictions on the interventions in the control groups.

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2.2 Literature review

Many clinical trials have been published during the past decades, and we used a cluster sampling method to identify eligible articles published in 2010. We searched three Chinese electronic literature databases: Chinese Biomedical Literature Database (SinoMed), China National Knowledge Infrastructure (CNKI), Wanfang Database and PubMed. We developed a broad search strategy combined with hand screening to possibly avoid missing any eligible trials. The search terms were "angina pectoris AND (clinical trial OR clinical observation OR clinical evaluation OR clinical research OR clinical study)". These terms in Chinese were used as free-text words and keywords.

2.3 Literature screening and information extraction

Two authors screened the retrieved records according to the eligibility criteria and extracted information independently. Disagreements in their assessments were resolved by discussion.

The extracted data included: authors, number of participants, age, course of disease, severity of disease, TCM syndrome, type of interventions, course of treatment, study's objectives, outcome measures, time points, and methods of evaluation.

3 Results

Our electronic literature search retrieved 1,249 records. Screening according to the eligibility criteria identified 94 randomized trials as the final sample for this study (Figure 1).

3.1 General characteristics of the included studies

Information of the included studies was summarized in Table 1. In the 94 trials, there were 9,111 patients mostly aged from 40 to 75 years. The sample size ranged from 27 to 439, with a mean of 97.

Thirty-four randomized trials did not report the course of angina. The course of disease in the other 60 studies ranged from 2 days to 20 years. Only 22 trials recorded the angina pectoris classification. Two of these adopted the Chinese angina classification standard, which was divided into mild, moderate, moderate, and severe in accordance with the frequency and duration of angina. The other 20 studies employed the Canada Cardiovascular Society (CCS) classification standard, with grades CCS I–IV.

There were 37 trials (39.4%) that applied TCM syndrome in their eligibility criteria. There were six types of TCM syndrome: blood stasis (33 trials), phlegm-heat, damp stagnation, deficiency in the heart and spleen, deficiency in *qi* and *yin*, and deficiency in the heart (*yang*).

We divided interventions in the experimental groups into two categories: decoction of prescriptions (water extract of herbal pieces) and Chinese patent medicine (drugs with fixed ingredients and dosage, and approved for sale by the China Food and Drug Administration). There were 37 trials (39.4%) of decoctions and 57 trials (60.6%) that tested the effects of Chinese patent medicines (including injections in 18 trials and oral liquid in 39 trials).

The duration of treatment in 4 trials was not reported. The treatment duration ranged from 10 days to 2 years in the rest 90 trials as follows: treatment duration in 25 trails was 2 weeks, treatment duration in 45 trials was 4 weeks, and treatment duration in 10 trials was 6 to12 weeks, treatment duration in 1 trial was 2 years.

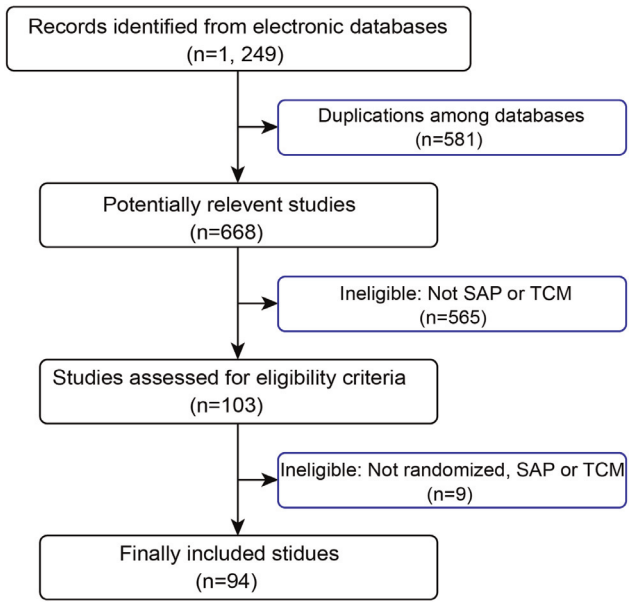

Figure 1. Flow diagram of literature screening. SAP: Stable angina pectoris; TCM: Traditional Chinese medicine.

3.2 Outcomes

Here, 79 different outcome measures were used in the 94 trials, including 14 qualitative outcomes and 65 quantitative outcomes. The following is a summary of the characteristics and problems of the outcome measures.

Physical examinations included heart rate, blood pressure, electrocardiogram (ECG), Holter, Treadmill exercise testing, and ultrasound (heart, carotid artery, and brachial artery).

Biochemical tests included fasting lipid (including levels of total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, apolipoprotein A, apolipoprotein B), fasting or post plasma glucose, adiponectin, Von Willebrand Factor, interleukin-6, nitric oxide, endothelin, C-reactive protein, high sensitive C-reactive protein, tumor necrosis factor, brain natriuretic peptide, vascular endothelial growth factor, matrix metalloproteinases-9, activated partial thromboplastin time, prothrombin time, fibrinogen, thromboxane B_2, platelet aggregation rate, P-selection, basic fibroblast growth factor, hemodynamic indices, liver function (alanine transaminase, aspartate aminotransferase, etc.), renal function (blood urea nitrogen, serum creatinine, etc.), and routine blood (red blood cell count, white blood cell count, platelet count, etc.) tests.

Most of the trials have reported efficacy rates, including efficacy rates of ECG, angina pectoris, TCM syndrome, individual symptoms of TCM (refers to each TCM symptom, such as chest pain), TCM symptoms (refers to all TCM symptoms including chest pain, fatigue, dyspnea, etc.), symptoms of angina, angina pectoris classification, overall response, angina symptoms scores decreased, and

Table 1

General characteristic of included studies.

Author	Intervention	T/C	Ages	Course of disease	Treatment duration
Gao H	Danshen powder injection	106/220	55–75; 49–76; 50–70	3–6 ys; 2–5 ys; 1–6 ys	NA
Guo TJ	Xuesaitong injection	50/50	40–82; 40–81	NA	2 ws
Han Y	Shenmai injection	45/45	41–78; 40–76	1.5–12 ys; 1.5–13 ys	2 ws
Huang YG	Shenmai injection	45/45	56.7 ± 11.9; 57.2 ± 12.3	9.7 ± 5.4 ys; 9.3 ± 5.6 ys	10 days
Li S	Safflower yellow injection	39/38	60 ± 2.3; 59 ± 1.6	NA	2 ws
Li YF	Danhong injection	30/30	40–75	NA	2 ws
Liu HD	Danhong injection	160/140	60 ± 12	11 ± 8 ys	2 ws
Liu Q	Shuxuening injection	64/63	57 ± 9; 58 ± 8	5.9 ± 2.4 ys; 6.5 ± 2.7 ys	4 ws
Lu GL	Danshen injection	43/40	62.3 ± 7.6; 63.7 ± 5.7	NA	4 ws
Lv WZ	Sodium ferulate injection	38/38	46–76; 45–70	NA	2 ws
Meng ZP	Danhong injection	50/50	47–72; 49–70	NA	2 ws
Miao Y	Safflower yellow injection	330/109	NA	NA	2 ws
Ruan ZW	Xuesaitong injection	50/100	45–70; 46–71; 44–69	1–10 ys; 1.5–9 ys; 1–9 ys	2 ws
Wang Q	Guanxinning injections	40/40	48–72; 50–69	NA	2 ws
Wu CF	Puerarin injection	36/32	45–76; 46–78	NA	2 ws
Yan F	Ginkgo biloba injection	60/30	64.4 ± 3.1; 61.6 ± 4.7	5.4 ± 1.2 ys; 4.8 ± 1.3 ys	2 ws
Yang JF	Danhong injection	80/80	62.5 ± 8.5; 62.3 ± 8.9	12.4 ± 3.3 ys; 11.5 ± 2.8 ys	2 ws
Zhang HF	Sodium ferulate (Danggui and Chuanxiong) injection	60/59	59 ± 5.25; 60 ± 5.12	NA	2 ws
Zhang L	Shuxuening injection	30/30	69 ± 5.8; 68 ± 4.6;	NA	2 ws
Zhang SQ	Astragalus injection	50/50	57.4 ± 4.12	NA	3 ws
Zhao HY	Ginseng saponins for injection	27/28	18–70	NA	2 ws
Cao XB	Xinsaitong capsule	30/30	65.50 ± 4.50; 64.28 ± 3.72	6.80 ± 4.20 ys; 6.72 ± 4.46 ys	8 ws
Chai WL	Yangxinshi tablet	44/52	49–67; 50–69	NA	8 ws
Che F	Tongsaimai tablet	42/40	64	0.5–1.3 ys	0.5 y
Duan SY	Xuezhikang capsule	26/25	46–75	0.6–20 ys; 2 ms–17 ys	2 ys
Gao F	Shexiang baoxin pills	40/40	NA	NA	4 ws
Guo BY	Curcumin capsule	60/60	57.4 ± 5.4; 56.3 ± 6.0	NA	4 ws
He MM	Shenzhi tongmai capsule	14/13	60.02 ± 7.31; 57.5 ± 4.79	33.4 ± 4.3 ys; 33.3 ± 7.9 ys	4 ws
He TH	Naoxintong capsule	40/40	37–72; 42–73	12 ± 4 ys; 8 ± 1.5 ys	4 ws
Hu JH	Shexiang baoxin pills	25/25	42–68; 43–69	1 ms–6 ys; 2 ms–8 ys	4 ws
Huang CL	Tongxinluo capsule	50/36	53.2; 56.6	2 ws–2 ms	4–6 ws
Hui JK	Yangxinshi tablet	288/132	52.48 ± 8.31; 53.36 ± 4.58	8.36 ± 2.24 ys; 8.06 ± 4.32 ys	4 ws
Jia ZM	Xinyue capsule	50/48	NA	2–9 ys; 3–10 ys	8 ws
Jiang YS	Tongxinluo capsule	43/43	50 ± 10;	10 ± 3 ys; 10 ± 4 ys	4 ws
Jin ZX	Tongxinluo capsule	30/30	51.4 ± 10.4; 53.1 ± 10.2	10.4 ± 3.4 ys; 9.5 ± 3.6 ys	4 ws
Li GW	Mailuotong tablet	198/66	NA	NA	4 ws
Li GJ	Guanxin Shutong capsule	60/60	61 ± 7; 56 ± 9	9 ± 3 ys; 8 ± 5 ys	4 ws
Li H	Tongxinluo capsule	62/60	45–75; 46–74	6.4 ys; 6.3 ys	12 ws
Li WA	Ginkgolides drop pills	55/55	55.21 ± 6.7; 55.32 ± 7.3	7.01 ± 3.21 ys; 6.93 ± 3.45 ys	NA
Li XH	Tongxinluo capsule	64/64	41–76; 48–76	NA	4 ws
Li XH	Qishen capsule	32/32	62–78	6–15 ys	6 ws
Li ZM	Xihuang pill	30/30		57.23 ± 6.07 ys; 58.72 ± 7.35 ys	4 ws
Liao YX	Tongxinluo capsule	40/20	60–75	5.1 ± 4.1 ys; 5.2 ± 4.3 ys	5 ws
Ling Y	Yangxinshi tablet	23/23	52.23 ± 6.94	NA	3 ms
Liu YG	Guanxin danshen drop pills	34/69	45–75	1–5 ys	1 m
Pu JC	Danshen pills and Ginkgo leaf tablets	50/150	58 ± 10	NA	4 ws
Shang JJ	Xuezhitong capsule	33/32	55–73	0.5–12 ys	8 ws
Su X	Compound salvia tablet and Shenshao tablet	25/17	62.96 ± 8.52; 59 ± 3.84	3.65 ± 2.51 ys; 2.65 ± 1.8 ys	NA
Sun JH	Shexiang baoxin pills	50/50	42–75; 43–76	1 ms–8 ys; 2 ms–7 ys	4 ws
Wang GY	Shenmaikang capsule	15/15	NA	NA	4 ws
Wang J	Xintongkang capsule	43/40	47–78; 45–75	3 ms–26 ys; 3 ms–24 ys	4 ws
Xu M	Shexiang baoxin pills	42/41	67.54 ± 4.27; 67.09 ± 4.45	NA	3 ms
Yang XH	Tongxinluo capsule	18/18	57 ± 18	NA	2 ws
Yu CY	Yindan xinnaotong capsule	50/30	48–65	5.6 ± 1.1 ys	4 ws
Yuan M	Xinmaikang capsule	30/30	44–70	0.1–20 ys	4 ws
Zhang WG	Yixinkang capsule	25/25	61 ± 5.5	NA	4 ws
Zhu H	Shexiang baoxin pills	100/100	65.7 ± 11.1; 66.9 ± 8.9	NA	0.5 y
Cao Q	Decoction of herbal prescription	30/30	62.67 ± 9.64; 61.97 ± 8.94	NA	12 ws

(*continued*)

Table 1
(continued).

Author	Intervention	T/C	Ages	Course of disease	Treatment duration
Ceng ZQ	Decoction of herbal prescription	38/34	51–71; 53–70	3.2–19 ys; 3.6–19.6 ys	4 ws
Chen PL	Decoction of herbal prescription	45/45	59.2±3.5; 58.8±3.3	10.2±4.1 ys; 10±3.9 ys	3 ws
Chen W	Decoction of herbal prescription	40/40	49–71	NA	2 ws
Ding D	Decoction of herbal prescription	30/30	61.67±9.13, 59.4±10.47	11.2±7.35 ys;10.37±5.97 ys	4 ws
Dong SY	Decoction of herbal prescription	70/70	58.31±9.72; 58.36±8.68	4 ms–11 ys; 4 ms–11.8 ys	6 ws
Huang ZP	Decoction of herbal prescription	42/42	68.5±14.4; 67.9±14.8	3.28±2.94 ys; 3.18±2.98 ys	4 ws
Jiang JC	Decoction of herbal prescription	10/20	56.5±6.03; 53.2±6.05; 53.9±7.4	NA	8 ws
Lang T	Decoction of herbal prescription	30/30	NA	NA	4 ws
Li Y	Decoction of herbal prescription	31/32	49.6±6.9; 51.3±6.8	5.3±1.1 ys; 4.9±1.3 ys	4 ws
Li Y	Decoction of herbal prescription	90/30	45–75	NA	4 ws
Li GH	Decoction of herbal prescription	30/30	46–79; 42–80	1–23 ys; 1–20 ys	2 ws
Li SS	Decoction of herbal prescription	30/21	59.47±4.98; 59.67±5.98	7.6±4.84 ys; 5.28±4.77 ys	4 ws
Li SJ	Decoction of herbal prescription	30/30	64.1±3.8; 62.5±4.9	NA	4 ws
Li ZZ	Decoction of herbal prescription	36/33	74.56±9.62	NA	2 ws
Liao YX	Decoction of herbal prescription	52/26	58.2±8.2; 57.1±8.4	4.6±3.1 ys; 4.5±2.9 ys;	7 ws
Li ZZ	Decoction of herbal prescription	41/41	57.2±12.1	6.6±4.7 ys	4 ws
Ma CZ	Decoction of herbal prescription	30/30	40–75	NA	2 ws
Qi S	Decoction of herbal prescription	30/30	63.87±4.43; 63.70±5.03	NA	2 ms
Qin Y	Decoction of herbal prescription	30/30	56.4±14.5; 55.8±15.1	6.12±4.87 ys; 6.31±4.65 ys	4 ws
Sun TS	Decoction of herbal prescription	60/60	60.17±6.43; 60.29±7.2	4 ms–10 ys; 3 ms–11 ys	4 ws
wsang Y	Decoction of herbal prescription	42/41	50–75; 56–73	5 ms–12 ys; 6 ms–11 ys	4 ws
wsang CH	Decoction of herbal prescription	68/52	52.9±9.6; 53±9.8	2 ms–5 ys; 2 ms–6 ys	2 ws
wsu H	Decoction of herbal prescription	40/40	67.3±12.74; 65.8±13.25	6.5±2.66 ys; 5.8±1.93 ys	4 ws
Xia JL	Decoction of herbal prescription	45/45	52.84±6.06; 54±6.37	5.74±3.89 ys; 5.28±3.8 ys	4 ws
Xiu Y	Decoction of herbal prescription	45/32	40–78	3 ms–30 ys, 3 ms–20 ys	4 ws
Yang F	Decoction of herbal prescription	30/30	61.38±6.65; 62.73±7.86	9.72±4.36 ys; 9.35±5.85 ys	4 ws
Yu DM	Decoction of herbal prescription	30/30	61.3±5.35; 62.7±4.76	7.21±2.79 ys; 8.53±3.08 ys	4 ws
Yu HW	Decoction of herbal prescription	25/25	72.3±5.82; 70.25±5.4	5 ms–30 ys; 3 ms–32 ys	4 ws
Yu RF	Decoction of herbal prescription	38/38	53±7.8; 52±7.6	3.5±1.3 ys; 2.9±1.1 ys	2 ws
Yu CJ	Decoction of herbal prescription	58/57	56.54±6.42; 56.52±6.41	4 ms–6 ys	2 ws
Zhang HY	Decoction of herbal prescription	30/30	40–78; 40–79	1–20 ys	NA
Zhang JM	Decoction of herbal prescription	30/25	58.47±6.6; 58.12±6.71	5.63±3.14 ys; 5.08±2.94 ys	4 ws
Zhang LL	Decoction of herbal prescription	30/30	NA	NA	4 ws
Zhao DY	Decoction of herbal prescription	49/49	36–74; 38–76	NA	2 ws
Zhou HT	Decoction of herbal prescription	30/30	52.24±5.84; 52.76±6.96	4.45±1.07 ys; 4.15±1.33 ys	4 ws
Zhou YX	Decoction of herbal prescription	80/76	58.31±8.72; 58.36±8.68	2.85±2.42 ys; 3.1±2.6 ys	4 ws

NA: Not available; T/C: Treatment/control; m: Month; ms: Months; ws: Weeks; y: Year; ys: Years.

TCM symptoms scores decreased as well as rates of nitroglycerin withdrawal and clinical efficacy.

The most frequently used outcome was the efficacy rate of ECG, which was reported in 69 trials. The most common outcome measures in the included trials are shown in Table 2. These were the efficacy rate of ECG, efficacy rate of angina pectoris, efficacy rate of TCM syndrome, fasting lipid indices, withdrawal rate of nitroglycerin, total scores of TCM syndrome, rate of clinical efficacy, nitroglycerin consumption, hemodynamic indices, endothelin, efficacy rate of individual symptoms of TCM, and frequency of angina attack.

Many trials included two or more of the five most common outcome measures (Table 3). For example, ECG efficacy and angina pectoris curative effect were both used in 52 trials (55.3%), while 27 studies (28.7%) applied efficacy rates of ECG, angina pectoris, and TCM syndrome to evaluate the effects and mechanism of the tested interventions. The efficacy rates of ECG, angina pectoris, and TCM syndrome, and the withdrawal rate of nitroglycerin consumption were used together in 17 studies (18.1%). All the five most common outcomes were used together in eight trials (8.5%).

3.3 Problems with the outcome measures

3.3.1 Number of outcomes used

The number of outcomes in the 94 trials ranged from 1 to 21 per trial, with a mean of 5. The combination of outcomes also varied across the trials.

3.3.2 Outcomes evaluated at different time points

Table 4 shows the time point for the measurement of selected outcomes, and how much variation there was in these. For instance, ECG efficacy was assessed at nine different time points by 65 studies: 10 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, and 3 months; with 77% of the trials evaluating the ECG at 2 weeks and 4 weeks.

For the efficacy rate of angina pectoris, the evaluation time point was not clear in three trials, although 10 different time points were used in the other 54 trials, varying from 2 weeks to 2 years. Approximately one third of the trials assessed it at 2 weeks.

For the efficacy rate of TCM syndrome, the evaluation points ranged from 2 weeks to 3 months, with 2 weeks (26% of trials) and 4 weeks (57%) being the most common.

Table 2

The most common outcomes used in the included trials.

Outcome	No. (%) of trials
Efficacy rate of ECG	69 (73.4%)
Efficacy rate of angina pectoris	57 (60.6%)
Efficacy rate of TCM syndrome	35 (37.2%)
Fasting lipid indices	27 (28.7%)
Withdrawal rate of nitroglycerin	21 (22.3%)
Total scores of TCM syndrome	12 (12.8%)
Rate of clinical efficacy	11 (11.7%)
Nitroglycerin consumption	10 (10.6%)
Hemodynamic indices	10 (10.6%)
Endothelin	10 (10.6%)
Efficacy rate of individual symptoms of TCM	9 (9.6%)
Frequency of angina attack	8 (8.5%)

ECG: Electrocardiogram; TCM: Traditional Chinese medicine.

Fasting lipid indices were measured at five different time points: 2 weeks, 4 weeks, 8 weeks, 3 months, and 2 years; with >60% of the trials measuring blood lipid indices after 4 weeks of treatment.

Additionally, 21 studies used withdrawal rate of nitroglycerin as an outcome, with evaluations at 2, 4, 8 weeks, and 2 years.

The time point at which outcomes are measured should consider the characteristics of the disease, outcomes, and interventions, as well as the feasibility of measuring the outcome in the trial. Moreover, although many trials used evaluation time points between 4 and 8 weeks after treatment, the wide variability makes it difficult to compare, contrast, and combine the findings of different studies when considering the effects of the same interventions on the same outcomes.

3.3.3 Outcomes evaluated using different standards

In addition to the heterogeneity in the time points at which outcomes were measured, there was also a large amount of variability in how they were measured. For instance, there were 10 different methods to measure the efficacy rate of ECG and 16 different evaluation criteria for the efficacy rate of angina pectoris. For total scores of TCM syndrome, there were five evaluation standards and the same number of evaluation standards was adopted to assess the withdrawal rate of nitroglycerin consumption. When the same outcome is evaluated by different standards, this increases the heterogeneity among clinical trials, which might result in different data and different conclusions, thereby hindering meta-analyses and affecting the value of the individual trials[16].

3.3.4 Transformation of continuous data into categorical data

Continuous data of outcomes in the included studies were often transformed into categorical data for the purposes of analyses, often using self-determined cut-off points. Most of the trials have reported these transformed, categorical data only without the original continuous data. It was reported that categorical data was inferior to continuous

Table 3

Combinations of the 5 most common outcomes.

Outcome combinations	No. (%) of trials
Two outcomes together	
Efficacy rate of ECG, efficacy rate of angina pectoris	52 (55.3%)
Efficacy rate of ECG, efficacy rate of TCM syndrome	30 (31.9%)
Efficacy rate of angina pectoris, efficacy rate of TCM syndrome	30 (31.9%)
Efficacy rate of ECG, fasting lipid indices	23 (24.5%)
Efficacy rate of ECG, withdrawal rate of nitroglycerin	20 (21.3%)
Efficacy rate of TCM syndrome, withdrawal rate of nitroglycerin	19 (20.2%)
Efficacy rate of angina pectoris, withdrawal rate of nitroglycerin	19 (20.2%)
Efficacy rate of angina pectoris, fasting lipid indices	19 (20.2%)
Efficacy rate of TCM syndrome, fasting lipid indices	14 (14.9%)
Withdrawal rate of nitroglycerin, fasting lipid indices	12 (12.8%)
Three outcomes together	
Efficacy rate of ECG, efficacy rate of angina pectoris, efficacy rate of TCM syndrome	27 (28.7%)
Efficacy rate of ECG, efficacy rate of TCM syndrome, withdrawal rate of nitroglycerin	18 (19.1%)
Efficacy rate of angina pectoris curative effect, efficacy rate of TCM syndrome, withdrawal rate of nitroglycerin	18 (19.1%)
Efficacy rate of ECG, efficacy rate of angina pectoris, withdrawal rate of nitroglycerin	18 (19.1%)
Efficacy rate of ECG efficacy, efficacy rate of angina pectoris, fasting lipid indices	17 (18.1%)
Efficacy rate of angina pectoris, efficacy rate of TCM syndrome, fasting lipid indices	13 (13.8%)
Efficacy rate of ECG efficacy, efficacy rate of TCM syndrome, fasting lipid indices	12 (12.8%)
Efficacy rate of ECG efficacy, fasting lipid indices, withdrawal rate of nitroglycerin	11 (11.7%)
Efficacy rate of angina pectoris, fasting lipid indices, withdrawal rate of nitroglycerin	10 (10.6%)
Efficacy rate of TCM syndrome, fasting lipid indices, withdrawal rate of nitroglycerin	10 (10.6%)
Four outcomes together	
Efficacy rate of ECG efficacy, efficacy rate of angina pectoris, Efficacy rate of TCM syndrome, withdrawal rate of nitroglycerin	17 (18.1%)
Efficacy rate of ECG efficacy, efficacy rate of angina pectoris, Efficacy rate of TCM syndrome, fasting lipid indices	11 (11.7%)
Efficacy rate of ECG efficacy, efficacy rate of TCM syndrome, fasting lipid indices, withdrawal rate of nitroglycerin	9 (9.6%)
Efficacy rate of angina pectoris, efficacy rate of TCM syndrome, fasting lipid indices, withdrawal rate of nitroglycerin	9 (9.6%)
Efficacy rate of ECG efficacy, efficacy rate of angina pectoris, fasting lipid indices, withdrawal rate of nitroglycerin	9 (9.6%)
All five outcomes together	8 (8.5%)

ECG: Electrocardiogram; TCM: Traditional Chinese medicine.

Table 4

Measurement points of outcomes.

Evaluation points	No. (%) of trials
Efficacy rate of ECG	69
Unknown	4 (5.8%)
10 days after treatment	1 (1.4%)
2 weeks after treatment	19 (27.5%)
3 weeks after treatment	1 (1.4%)
4 weeks after treatment	34 (49.3%)
5 weeks after treatment	1 (1.4%)
6 weeks after treatment	1 (1.4%)
7 weeks after treatment	1 (1.4%)
8 weeks after treatment	5 (7.2%)
3 months after treatment	2 (2.9%)
Efficacy rate of angina pectoris	57
Unknown	3 (5.3%)
2 weeks after treatment	17 (29.8%)
3 weeks after treatment	2 (3.5%)
4 weeks after treatment	25 (43.9%)
5 weeks after treatment	1 (1.8%)
6 weeks after treatment	1 (1.8%)
7 weeks after treatment	1 (1.8%)
8 weeks after treatment	4 (7%)
3 months after treatment	1 (1.8%)
6 months after treatment	1 (1.8%)
2 years after treatment	1 (1.8%)
Efficacy rate of TCM syndrome	35
Unknown	2 (5.7%)
2 weeks after treatment	9 (25.7%)
4 weeks after treatment	20 (57.1%)
8 weeks after treatment	3 (8.6%)
3 months after treatment	1 (2.9%)
Fasting lipid indices	27
Unknown	1 (3.7%)
2 weeks after treatment	2 (7.4%)
4 weeks after treatment	17 (63%)
8 weeks after treatment	4 (14.8%)
3 months after treatment	2 (7.4%)
2 years after treatment	1 (3.7%)
Withdrawal rate of nitroglycerin consumption	21
Unknown	2 (9.5%)
2 weeks after treatment	2 (9.5%)
4 weeks after treatment	15 (71.4%)
8 weeks after treatment	1 (4.8%)
2 years after treatment	1 (4.8%)

ECG: Electrocardiogram; TCM: Traditional Chinese medicine.

outcomes[17]. The transformed categorical data with self-determined cut-off points in different trials could not be combined or compared[18].

3.3.5 Limited dimension of outcomes

All the included trials reported outcomes from physical and chemical examinations, which might be of much more relevance to physicians, than to patients and decision makers. Only three studies assessed the quality of life, with either SF-36 or disease-specific scale Seattle Angina Questionnaire, and important cardiovascular events were reported in only five trials. Furthermore, important endpoints, which need long-term follow-up, were measured after 8 to 12 weeks of treatment. None of the trials reported on health economics. In general, the results presented for these TCM trials provide inadequate evidence for patients, decision makers, insurance companies, and other stakeholders.

3.3.6 Lack of outcomes linked with TCM symptoms

According to the theory of TCM, a basic principle is to apply treatment according to syndrome differentiation. Change in TCM symptoms is also an important indicator for the evaluation of Chinese medicine. In this sample, 12 trials (15.2%) used total score of TCM syndrome, and nine (11.4%) adopted efficacy rate of individual symptoms of TCM. Only six of the 79 different outcomes reported in the 94 trials discussed the changes of the TCM symptoms before and after treatment.

3.3.7 Reporting bias

Incomplete outcome reporting is likely to have been common. All the trials reported positive results in favor of TCM, and because none of the trials provided information on prospective registration, it is not possible to assess the extent of unreported or changed outcomes. This might be a particular problem, considering that 38 trials (40.4%) did not report anything on adverse events or adverse drug reactions. Although the other 56 trials (59.6%) reported on these outcomes, 42 trials declared no adverse events or adverse drug reactions. Finally, 11 studies aimed to identify the safety of interventions, but none used specific outcomes related to safety.

4 Discussion

Recently, the World Health Organization (WHO) reported that herbal medicine has been used by >80% of people at some time in their life[19–20]. Its use is the highest in low- and middle-income countries, such as India, Brazil, and Africa. In China, >50% of patients use herbs after the onset of angina[21]. However, the underlying evidence base for many of these treatments is weak, despite the 1993 publication of research guidelines by the WHO for evaluating the safety and efficacy of herbal medicines[22]. This suggests a considerable uncertainty of the effects of herbal medicines, including TCM, and the poor methodological quality of clinical trials of TCM makes it difficult to use their findings in practice.

Randomized trials and systematic reviews of these trials are accepted as the most robust design for assessing the effects of interventions and minimizing bias and have been widely used in clinical trials of TCM. In contrast, insufficient attention has been paid to the outcome measures in clinical trials[23]. This is an important gap because, alongside the use of appropriate methods for the conduct of randomized trials, the selection of appropriate outcomes is crucial to the design of a trial if it is to influence future practice.

The problem with outcomes that we have identified in this review of randomized trials are serious and have been noted in other areas of health and social care[23]. We found specific problems in the choice of outcomes in these clinical trials of TCM for stable angina pectoris, such as the lack of long-term evaluation time points, the loss of information through the transformation of continuous data to categorical data, the lack of outcomes linked with TCM symptoms, and the risk of reporting bias. All those problems hindered comparison and synthesis across studies, then limited clinical practice of interventions.

In TCM theory, syndrome reflected pathological changes in disease, at a certain stage[24]. Syndrome included clinical symptoms, tongue manifestation and

pulse condition. Different outcomes linked with TCM symptoms were measured including TCM symptoms score (primary symptoms and secondary symptoms), TCM syndrome efficacy (single or multiple items). Furthermore, these outcomes were poorly reported.

Reporting bias refers to only publishing a subset of the original variables recorded for a study[25], and usually harm related outcomes were missing or partially reported[26]. Reporting bias is most easily judged if the study protocol is available for comparing what the researcher planned to measure and what they reported. It had an impact on people's understanding of the study findings, and was an essential problem to solve.

Outcome measures should be relevant to the aim of a specific study and reflect the value of different stakeholders. In 2012, the American Heart Association published a guideline for stable ischemic heart disease[27] which identified the goals of treatment for stable angina pectoris: (a) reducing premature death induced by cardiovascular events, (b) decreasing complications such as acute coronary syndrome, heart failure, (c) improving quality of life, (d) relieving or removing the clinical symptoms caused by angina, and (e) minimizing medical costs. Clinical trials of stable angina should adopt appropriate outcomes in these different domains to evaluate the effects of interventions, including TCM.

A powerful approach to address the problems that we have highlighted in the selection, measurement, and reporting of outcomes is the development of a COS, which would be used, as a minimum, in all clinical trials for a particular health condition. The COMET Initiative is helping to facilitate this[28–30] and our study highlights the need to establish a scientific and rational COS for randomized trials of TCM for stable angina pectoris.

The review was conducted using robust and established methodology, but has limitations. Our study is based on a cluster sampling literature review, we only included clinical trials published in Chinese journals and PubMed in 2010, only researchers' and clinicians' viewpoints on outcomes were referenced, while patients and other stakeholders were not considered; secondly, only studies in English and Chinese were included. Thus, outcomes reported in other languages could have been omitted. therefore, a selection bias may influence our findings. Further follow-up studies will be done to support our findings.

Conflict of interest statement

None.

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Author contributions

Dongmei Xing performed the literature search and data analysis, and worked on the manuscript. Mingjun Zhu designed the study and prepared the first version of this manuscript. Dongmei Xing and Chunxiang Liu screened literature for inclusion and abstracted data. Hui Wang contributed to the data analysis.

Ethical approval of studies and informed consent

Not applicable.

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References

[1] Ohman EM. CLINICAL PRACTICE. Chronic stable angina. *N Engl J Med* 2016;374 (12):1167–1176.
[2] Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation* 2020;141 (9):e139–e596.
[3] Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris. *Eur Heart J* 2006;27: 1341–1381.
[4] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines on the diagnosis and management of chronic coronary syndromes: the task force for diagnosis and management of chronic coronary syndromes of the European society of cardiology (ESC). *Eur Heart J* 2020;41:407–477.
[5] McKenna C, Hawkins N, Claxton K, et al. Cost-effectiveness of enhanced external counterpulsation (EECP) for the treatment of stable angina in the United Kingdom. *Int J Technol Assess Health Care* 2010;26 (2):175–182.
[6] Zhao L, Li D, Zheng H, Chang X, et al. Acupuncture as adjunctive therapy for chronic stable angina: a randomized clinical trial. *JAMA Intern Med* 2019;179 (10):1388–1397.
[7] Sun MY, Miao Y, Jin M, et al. Effect and safety of Guanxinning Tablet for stable angina pectoris patients with Xin (Heart)-blood stagnation syndrome: a randomized, multicenter, placebo-controlled trial. *Chin J Integr Med* 2019;25 (9):684–690.
[8] Yang G, He H, Li H, et al. Effects of Danlou tablet for the treatment of stable angina pectoris: a study protocol of a randomized, double-blind, and placebo-controlled clinical trial. *Medicine (Baltimore)* 2020;99 (49):e23416.
[9] Zhang L, Zhang J, Chen J, et al. Clinical research of traditional Chinese medicine needs to develop its own system of core outcome sets. *Evid Based Complement Alternat Med* 2013; 2013:202703.
[10] Li Y, Zhang L, Lyu S, et al. Efficacy and safety of oral Guanxinshutong capsules in patients with stable angina pectoris in China: a prospective, multicenter, double-blind, placebo-controlled, randomized clinical trial. *BMC Complement Altern Med* 2019;19 (1):1–9.
[11] Williamson PR, Altman DG, Bagley H, et al. The COMET handbook: version 1.0. *Trials* 2017;18 (3):1–50.
[12] Kirkham JJ, Gargon E, Clarke M, et al. Can a core outcome set improve the quality of systematic reviews?—a survey of the Coordinating Editors of Cochrane Review Groups. *Trials* 2013;14 (1):1–5.
[13] COMET initiative. https://www.comet-initiative.org/. Accessed March 1, 2020.
[14] Valgimigli M, Biscaglia S. Stable angina pectoris. *Curr Atheroscler Rep* 2014;16 (7):422.
[15] Duan SY. The Combination of Traditional Chinese Medicine and West Medicine in Treatment of Chronic Stable Angina Pectoris. Beijing: Beijing University of Chinese Medicine; 2010.
[16] Tovey D. The impact of Cochrane Reviews. Cochrane Database Syst Rev. 2010 (7): ED000007.
[17] D'Amico G, Abraldes JG, Rebora P, et al. Ordinal outcomes are superior to binary outcomes for designing and evaluating clinical trials in compensated cirrhosis. *Hepatology* 2020;72 (3):1029–1042.
[18] Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *BMJ* 1998;317:1181–1184.
[19] World Health Organization. WHO traditional medicine strategy: 2014-2023. https://www.who.int/publications/i/item/9789241506096. Accessed March 1, 2020.
[20] World Health Organization. The use of herbal medicines in primary health care. https://www.who.int/publications/i/item/SEA-HSD-322. Accessed March 1, 2020.

[21] Cai M, Zhao HS, Sun JY. Survey of TCM application status on secondary prevention of coronary heart disease. *Beijing J Tradit Chin Med* 2013;32 (5):343–345.
[22] World Health Organization. Legal status of traditional medicine and complementary. https://www.who.int/publications/i/item/WHO-EDM-TRM-2001.2. Accessed February 20, 2020.
[23] Kirkham J, Gorst S, Altman DG, et al. COS-STAR: a reporting guideline for studies developing core outcome sets (protocol). *Trials* 2015;16 (1):1–6.
[24] World Health OrganizationWHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region. Geneva, Switzerland: World Health Organization; 2007.
[25] Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005;330 (7494):753.
[26] Saini P, Loke YK, Gamble C, et al. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ* 2014;349:g6501.
[27] Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60 (24):e44–e164.
[28] Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: its role in improving Cochrane Reviews. *Cochrane Database Syst Rev* 2012;(5):ED000041.
[29] Gargon E. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative. *Maturitas* 2016;91:91–92.
[30] Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86–89.

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