

BMJ Open Effectiveness and safety of oral Chinese patent medicines as adjuvant treatment for unstable angina pectoris on the national essential drugs list of China: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Achieving efficacious and safe treatments for unstable angina pectoris (UAP) is still a challenging clinical problem. The availability of different oral Chinese patent medicines frequently poses a practical challenge to clinicians, namely, which one to choose as first-line regimen for treatment. This study aims to examine the comparative effectiveness and safety of oral Chinese patent medicines for UAP on the national essential drugs list of China.

Methods and analysis We will conduct a network meta-analysis (NMA) of all randomised controlled trials to evaluate the use of oral Chinese patent medicines as adjuvant for the treatment of UAP. We will explore eight electronic databases from their inception to June 2018 and search for grey literature. Primary outcomes include mortality and the cardiovascular events. Secondary outcomes include: (1) symptom improvement; (2) ECG improvement; (3) frequency of acute angina attack; (4) duration of angina; (5) adverse effects. Two independent authors will screen titles and abstracts, review full texts, extract data, assess the risk of bias using the Cochrane risk of bias tool and assess the quality of evidence and strength of the recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). If adequate data are available, NMA will be performed with Bayesian analysis methods.

Ethics and dissemination The NMA will help us to reduce the uncertainty of interventions and help clinicians to make optimal and more accurate therapeutic decisions for adults with UAP. Therefore, we will publish the findings of this study in a peer-reviewed journal. No ethics approval is necessary for this study based on the nature of its design.

Trial registration number CRD42018092822.

INTRODUCTION

Unstable angina pectoris (UAP) is a transitory and critical syndrome, characterised by severe transient myocardial ischaemia.¹ UAP is a type

Strengths and limitations of this study

- This network meta-analysis will provide evidence of the comparative effectiveness and safety of oral Chinese patent medicines for unstable angina pectoris on the national essential drugs list of China for the first time.
- This network meta-analysis will be based on a comprehensive search strategy and selection of studies; data extraction and estimation of quality will be performed independently by two reviewers to ensure the integrity and authenticity of all relevant studies.
- We will assess the quality of evidence and the strength of recommendations for the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.
- This review will not cover medical databases in other languages (such as Japanese and Korean), so a language bias may exist.

of acute coronary syndrome, which is very common and often quite serious. In 2014, there were 24 000 UAP principal diagnosis discharges and the corresponding number of inpatient hospital discharges was 382 000 unique hospitalisations for UAP when secondary discharge diagnoses were included in the USA.² More importantly, UAP is easily exacerbated into acute myocardial infarction, ischaemic death and severe cardiac arrhythmias which can lead to sudden death.²⁻⁴ Therefore, we must keep in mind that treatment should begin immediately after the onset of UAP.

Recent studies have shown that the main mechanism underlying UAP initiation was plaque rupture or erosion with overlying thrombosis. This process is mainly related to

vascular endothelial injury, the inflammatory response, platelet activation and aggregation and other relevant factors.^{5–7}

Multiple treatment regimens and drugs are recommended in various clinical guidelines, including invasive strategies, conservative treatment, anti-ischaemic therapy, nitroglycerin, antiplatelet therapy, aspirin, beta blockers and so on.^{8–10} Among them, conservative treatment was performed in 76.2% of the patients with UAP. Although conservative treatment was used in patients with normal coronary angiogram, still in 77.7% of UAP with high-risk criteria it was performed.¹¹ The aim of these treatments is to improve quality of life by reducing angina attacks and prevent cardiovascular events as well as death. However, not all of these treatments are useful for UAP. The ProAcor Study showed that 1-year mortality was still up to 7.6% and at 1-year cardiac events were noted in 14.9% even in very standard and reasonable treatments.¹² And drawbacks such as drug resistance and adverse effects are issues too.¹³ Achieving safe and effective treatments for UAP is still a challenging clinical problem.

As early as 3000 years ago, Chinese medicine has already appeared and encompasses unique theories for aetiology, pathogenesis, diagnosis and treatment.^{14 15} A review has indicated that traditional Chinese medicine (TCM) could be used as a complementary and alternative approach in the primary and secondary prevention of cardiovascular disease.¹⁶ In the developing and developed world, an increasing number of people accept TCM as an alternative to conventional treatments.^{17 18} Oral Chinese patent medicine is an important part of TCM. And Chinese patent medicines are a kind of TCM products, which is commercialised and approved by the State Drug Supervision and Administration Department. In order to prevent and treat diseases, TCM products are processed into certain dosage forms using TCM as raw material and the theory of TCM as guide. Common dosage forms include injection, oral liquid dosage forms (solution, suspension, emulsion) and oral solid dosage forms (powder, capsule, tablet, pill).¹⁹ Oral Chinese patent medicine is the collective name of the latter two. And it has been used in clinical practice for the treatment of UAP in East and South Asia, such as China, Japan and Korea.^{20–22}

Several systematic reviews have been conducted to examine the comparative effectiveness and safety of single oral Chinese patent medicines for UAP.^{23–25} As the number of oral Chinese patent medicines increases, the required number of pairwise systematic reviews would increase exponentially. Pairwise meta-analysis of multiple treatments is laborious and time-consuming. In addition, because different head-to-head oral Chinese patent medicines trials are scarce, these systematic reviews have not focused on any head-to-head comparisons of different oral Chinese patent medicines. Although these studies confirm that a single oral proprietary Chinese medicine is effective against UAP, the availability of different oral Chinese patent medicines frequently poses a practical

challenge to clinicians, namely, which one to choose as first-line regimen for treatment.

The use of network meta-analysis (NMA) allows the direct and indirect comparison of different oral Chinese patent medicine therapeutic options for UAP in terms of safety and effectiveness. It is a highly valuable tool allowing indirect comparisons of multiple interventions to estimate their safety and effectiveness and rank them.²⁶ Based on these reasons, we decided to conduct a NMA comparing oral Chinese patent medicines for UAP on the national essential drugs list of China, to examine their relative effectiveness and safety.

OBJECTIVE

This NMA aims to examine the safety and effectiveness of oral Chinese patent medicines for UAP on the national essential drugs list of China.

METHODS AND ANALYSIS

Our NMA protocol has been registered on the PROSPERO international prospective register of systematic reviews (ID=CRD42018092822). Our protocol has been prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.²⁷ The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Healthcare Interventions.²⁸

Eligibility criteria

Type of study

We will include all relevant randomised controlled trials (RCTs) regardless of blinding and concealment, as RCT is regarded as the gold criterion for examining interventions. Cross-over and cluster randomised trials will also be included. Quasi-RCTs will be excluded such as those allocating using the number of medical records. We will not include studies with the high risk of bias, such as only one researcher or the research sites are community or low level hospitals.

Types of participants

Adults (aged ≥18 years) with UAP diagnosed according to the standards revised by ‘Nomenclature and criteria for diagnosis of ischaemic heart disease’ released by WHO in 1979²⁹ and ‘diagnosis and treatment of UAP’ released by Chinese Society of Cardiovascular Diseases of Chinese Medical Association in 2000³⁰ and 2007³¹ will be included. According to the risk stratification of UAP, current guidelines recommend invasive treatment regimens first for very-high-risk or high-risk patients.^{9 10} So, those very-high-risk or high-risk patients will be excluded. Patients who have undergone coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), with acute myocardial infarction or other deadly serious diseases,

such as cancer, will be excluded, because the risk of these patients is significantly different from that of the patients with UAP.^{9,10} We will not apply restrictions with regard to gender, ethnic origin or other characteristics.

Types of interventions

Interventions involving any oral Chinese patent medicines for the treatment of UAP are eligible. These oral Chinese patent medicines could be used in combination with routine treatment regardless of dose, duration, preparation form and manufacturer. The control groups include routine treatment or another oral Chinese patent medicine plus routine treatment. The following groups are eligible: Oral Chinese patent medicine+routine treatment versus another oral Chinese patent medicine+routine treatment and Oral Chinese patent medicine+routine treatment versus routine treatment. Routine treatment includes anti-ischaemia, antiplatelet, anticoagulation, lipid-lowering and so on. As for the usage of the treatment, including the selection of the timing of intervention during UAP treatment, follow the guidelines. But the two groups of routine treatment must be the same in the same RCT. We are interested in comparing the following drugs: Shengmai Yin, Wenxinkeli, Xueshuantongjiaonang, Xuesaitongjiaonang, Yinxingye, Yindanxinnaotongruanjiaonang, Shexiangbaoxinwan, Naoxintongwan, Xinmainingjiaonang, Xueshuanxinmainingjiaonang, Shensongyangxinjiaonang, Yixinshujiaonang, Guanxinsuhewan, Diaoxinxuekangjiaonang, Tongxinluojiaonang, Dengzhanhuasupian, Naoankeli, Maixuekangjiaonang, Xuefuzhuyuan, Fufangdanshen, Suxiaojiuxinwan, Xinkeshu, NuodiKangjiaonang and so on.¹⁹ Since there are many dosage forms of a drug, such as Shengmai Yin including Shengmai Yinjiaonang and Shengmai Yinkeli, we use Shengmai Yin as a unified substitute and separate them if necessary. **Figure 1** shows the network of all possible pairwise comparisons among the eligible interventions. We anticipate that any patient who meets all inclusion criteria is equally to be randomised to any of the interventions in the synthesis comparator set. Trials which allow rescue medications will be included so long as these are equally provided among the randomised arms. If Chinese patent medicines (such as suxiaojiuxinwan) were used as rescue medications in a study, and the intervention measures were not this medicine in the study, this study would be excluded. Trials that only compare different oral Chinese patent medicines without routine treatment or self-made proprietary Chinese patent medicines will be excluded.

Types of outcome measures

UAP has the highest risk of myocardial infarction and death within 2 months after the onset of disease.³² It is of great value to pay attention to the efficacy of this period. Thus, the time point we need is within 2 months of onset and those patients with the course of disease within 2 months will be enrolled.

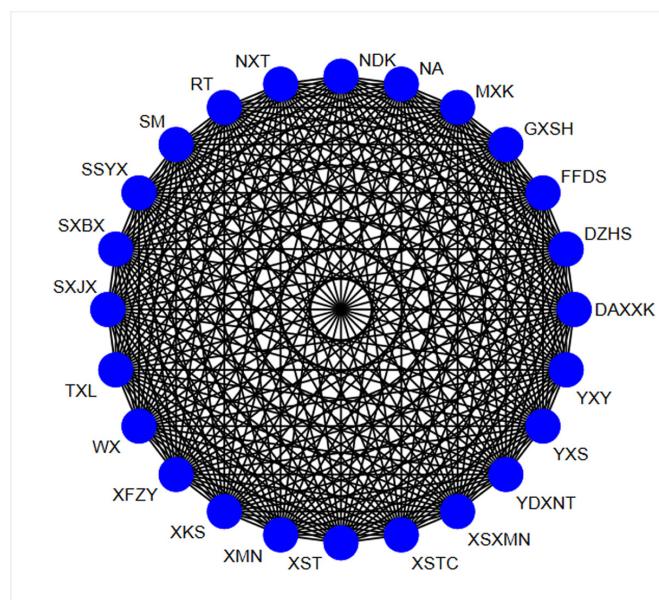


Figure 1 Network of all possible pairwise comparisons between the eligible interventions. DAXXK, Diaoxinxuekangjiaonang+RT; DZHS, Dengzhanhuasupian+RT; FFDS, Fufangdanshen+RT; GXSH, Guanxinsuhewan+RT; MXK, Maixuekangjiaonang+RT; NA, Naoankeli+RT; NDK, NuodiKangjiaonang+RT; NXT, Naoxintongwan+RT; RT, Routine treatment; SM, Shengmai Yin+RT; SSYX, Shensongyangxinjiaonang+RT; SXBX, Shexiangbaoxinwan+RT; SXJX, Suxiaojiuxinwan+RT; TXL, Tongxinluojiaonang+RT; WX, Wenxinkeli+RT; XFZY, Xuefuzhuyuan+RT; XKS, Xinkeshu+RT; XMN, Xinmainingjiaonang+RT; XST, Xuesaitongjiaonang+RT; XSTC, Xueshuantongjiaonang+RT; XSXMN, Xueshuanxinmainingjiaonang+RT; YDXNT, Yindanxinnaotongruanjiaonang+RT; YXS, Yixinshujiaonang+RT; YXY, Yinxingye+RT.

Primary outcomes

The mortality

It is defined as the proportion of patients who die for any reason during the treatment (within 2 months).

The cardiovascular events

The proportion of patients with cardiovascular events (within 2 months). The cardiovascular events include endpoints fatal versus nonfatal of events (eg, myocardial infarction (MI)), different types of events (eg, Q-wave versus non-Q-wave MI), bleeding, stroke, transient ischemic attack (TIA) and other important cardiovascular outcomes (eg, CABG and PTCA).

Secondary outcomes

Symptom improvement

Measured by the total number of patients who had a remission of symptoms (including chest distress, shortness of breath and hypodynamia) between baseline and the end of treatment (within 2 months) on any standardised rating scale.

ECG improvement

Measured by the total number of patients who had a remission of ECG between baseline and the end of treatment

Table 1 Characteristics of the outcome measures

Outcomes	Measurement of variables (units)	Statistical estimates and measurement of association
Primary		
Mortality	Number of deaths	OR (95% CrI)
Cardiovascular events	Number of MI, CABG or PTCA	OR (95% CrI)
Secondary		
Symptom improvement	Number of improvement	OR (95% CrI)
ECG improvement	Number of ECG improvement	OR (95% CrI)
Frequency of acute angina attacks	Number of acute angina attacks	MD (95% CrI)
Duration of angina	Time of angina	MD (95% CrI)
Adverse effects	Side effects: toxic response, discontinuation, digestive symptoms, headache and dizziness so on.	OR or MD (95% CrI)

95%CrI, 95% credibility interval; MD, mean difference; OR, odds ratio.

(within 2 months). Remission is defined as that the ECG returned to 'approximately normal', reached 'normal ECG' or the ST segment reduced by more than 0.05 mV.³³

Frequency of acute angina attacks

It is defined as number of angina attacks within a specified period of time (a day or a week).

Duration of angina

It is defined as average time of angina attack within prescribed time.

Adverse effects

Measured by the total number of patients who suffered from those adverse effects between baseline and the end of treatment (within 2 months). The adverse effects include bleeding events, toxic response, discontinuation, digestive symptoms, headache, dizziness and so on.

The study with incorrect, incomplete or unavailable data of outcomes will be excluded. The definitions of the outcomes are described in table 1. Those outcome measures including mortality, the cardiovascular events, symptom improvement, ECG improvement, frequency of acute angina attacks and duration of angina will be used to assess for effectiveness and safety assessment will be measured by incidence and severity of adverse effects. See figure 2 for full details about the data selecting and extraction of outcome (decision tree).

Search methods for the identification of studies

Search strategies have been developed through the liaison with Xiao-feng Du who is an experienced librarian at Liaoning University of Traditional Chinese Medicine Library. We will explore the following eight electronic databases: PubMed, CNKI, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library,

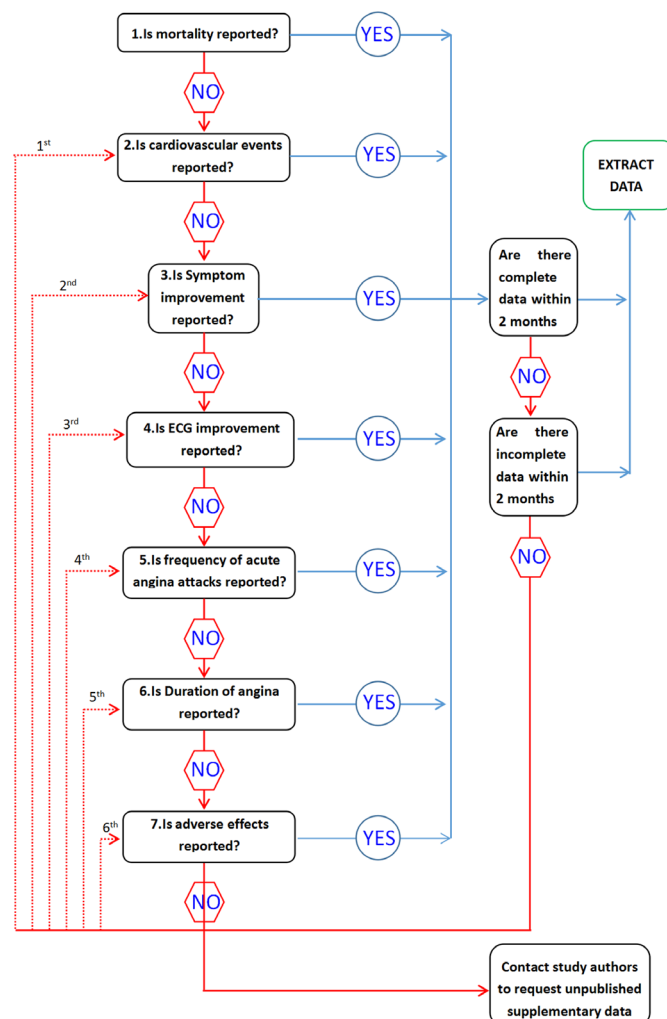


Figure 2 Decision-tree for data selecting and extraction of outcome.

EMBASE, Web of Science, Wanfang Database, VIP, SinoMed, from their inception to June 2018. The search will be conducted in English and Chinese. We will use a combination of Medical Subject Heading and free-text terms including various synonyms for UAP, Traditional Chinese Medicine and oral Chinese patent medicines on the national essential drugs list of China (table 2 details the search strategy for PubMed). We will also search ongoing trial registers in the trial registry websites (such as the Chinese Clinical Trial Registry and the US National Institutes of Health resource) to obtain grey literature. At the same time, we will also plan to perform a manual search for the reference lists of reviews captured by the initial searches. There will be no restrictions on date limit, country, publication status or year of publication.

Data collection

Selection of studies

NoteExpress literature management software (v3.2.0.7103) will be used to manage all studies.³⁴ First, the software will be used to classify and organise the preliminary literature and exclude the repeated collection of literature. Second, two independent review

Table 2 Details of the search strategy for PubMed

No.	Search item
#1	Angina, Unstable[MeSH Terms]
#2	Anginas, Unstable[Title/Abstract] OR Angina Pectori, Unstable[Title/Abstract] OR Angina Pectoris, Unstable[Title/Abstract] OR Unstable Angina Pectori[Title/Abstract] OR Unstable Angina[Title/Abstract] OR Angina at Rest[Title/Abstract] OR Angina, Preinfarction[Title/Abstract] OR Anginas, Preinfarction[Title/Abstract] OR reinfarction Angina[Title/Abstract] OR Variant Angina Pectoris[Title/Abstract] OR Prinzmetal's Angina[Title/Abstract] OR Angina, Prinzmetal's[Title/Abstract] OR Prinzmetals Angina[Title/Abstract] OR Prinzmetal Angina[Title/Abstract] OR Angina, Prinzmetal[Title/Abstract]
#3	#1 OR #2
#4	Medicine, Chinese Traditional[MeSH Terms]
#5	Medicine, Chinese Traditional[Title/Abstract] OR Traditional Chinese Medicine[Title/Abstract] OR Chung I Hsueh[Title/Abstract] OR Hsueh, Chung I[Title/Abstract] OR Traditional Medicine,Chinese[Title/Abstract] OR Zhong Yi Xue[Title/Abstract] OR Chinese TraditionalMedicine[Title/Abstract] OR Chinese Medicine, Traditional[Title/Abstract] OR Drugs, Chinese Herbal[Title/Abstract] OR Chinese Drugs, Plant[Title/Abstract]OR Chinese Herbal Drugs[Title/Abstract] OR Herbal Drugs,Chinese[Title/Abstract] OR Plant Extracts, Chinese[Title/Abstract] OR ChinesePlant Extracts[Title/Abstract] OR Extracts, Chinese Plant[Title/Abstract]
#6	#4 OR #5
#7	shengmai[Title/Abstract] OR wenxin[Title/Abstract] OR xueshuantong[Title/Abstract] OR xuesaitong[Title/Abstract] OR yinxingye[Title/Abstract] OR yindan xinnaotong[Title/Abstract] OR shexiangBaoxin[Title/Abstract] OR naoxintong[Title/Abstract] OR xinmaining[Title/Abstract] OR xueshuan xinmaining[Title/Abstract] OR shensongyangxin[Title/Abstract] OR yixinshu[Title/Abstract] OR guanxinsuhe[Title/Abstract] OR diao xinxuekang[Title/Abstract] OR xinxuekang[Title/Abstract] OR tongxinluo[Title/Abstract] OR dengzhanhuasu[Title/Abstract] OR naoan[Title/Abstract] OR maixuekang[Title/Abstract] OR xuefu zhuyu[Title/Abstract] OR fufangdanshen[Title/Abstract] OR compound danshen[Title/Abstract] OR suxiaojiuxin[Title/Abstract] OR xinkeshu[Title/Abstract]
#8	#6 OR #7
#9	randomised controlled trial[Publication Type]
#10	controlled clinical trial[Publication Type]
#11	randomised[Title/Abstract]
#12	randomly[Title/Abstract]
#13	#9 OR #10 OR #11 OR #12
#14	#3 AND #8 AND #13

authors (Peng Xu and Kun Dong) will screen the titles and abstracts of each study retrieved to identify relevant studies based on the eligibility criteria. Then, we will obtain the full text of all the studies potentially suitable for the NMA and review them for further assessment. In this process, the two people will screen the titles, abstracts and the full text of each study, respectively, make decisions independently and then compare their selection of studies. Once the conclusions of the two evaluators are inconsistent, the differences are resolved through discussion. If the agreement cannot be reached, we will seek the help of a third author (Guan-lin Yang or Zhe Zhang) for judgement and arbitration. And if the disagreement is caused by insufficient information of the literature, it is necessary to classify the literature into the category of waiting for evaluation and then decide whether the literature should be included after sufficient additional information is added. In an excluded studies list, we will report the reasons for exclusion of studies in the full-text review.

A flowchart that depicts the search process, including a reference list of all excluded studies, will be included. The proposed structure for the flowchart is shown in figure 3.

Data extraction and management

Data from the studies will be extracted by two review authors (Peng Xu and Kun Dong) independently using a pretested Microsoft Excel data extraction form. The data items we plan to extract include:

1. Study characteristics (including authors, journal, publication year, method of randomisation and blinding method).
2. Participants (sample size, age, duration of disease, disease diagnostic criteria, type of UAP and symptoms and signs).
3. Intervention (type of therapy, dosage forms, clinical doses and course of treatment).
4. Control (type of therapy, the course of treatment, dosage forms and clinical doses).
5. Outcomes (results, types of outcome measures and adverse events).

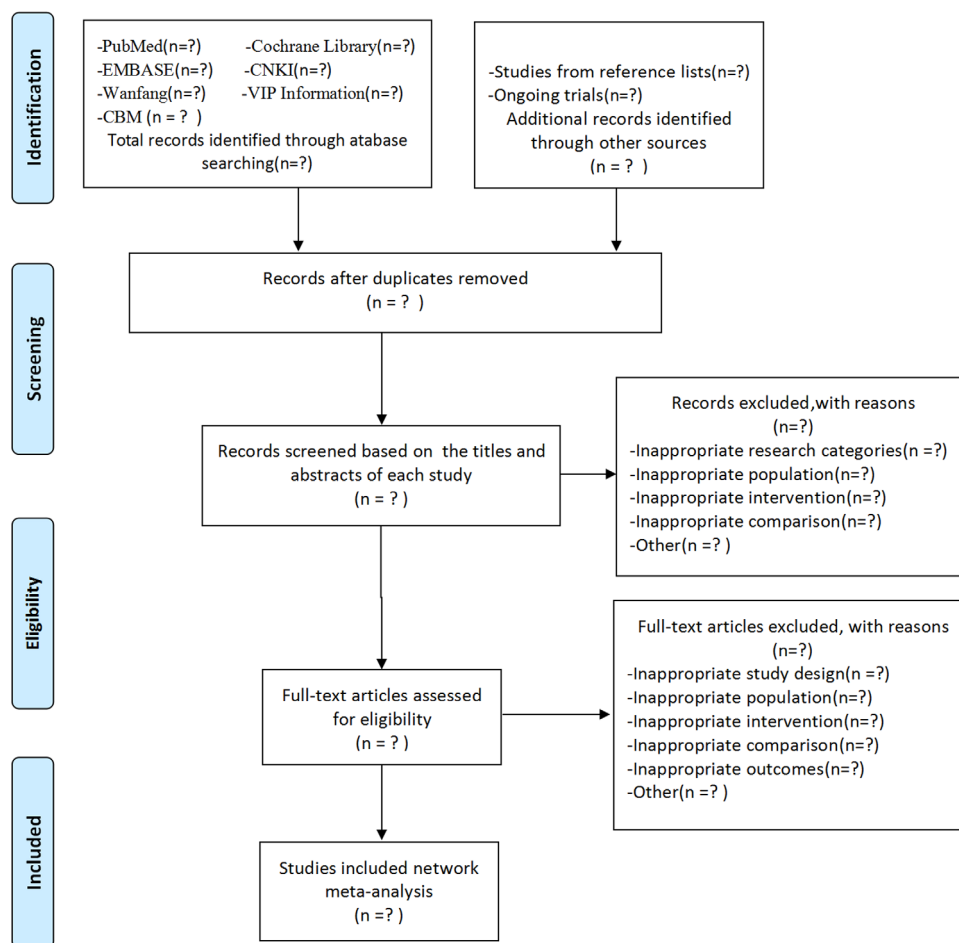


Figure 3 Proposed flowchart to depict the search process.

Two reviewers (Peng Xu and Kun Dong) will perform data extraction independently. Any disagreement will be resolved through discussion or consultation with a third author (Guan-lin Yang). We will contact original authors through email to request any missing information that may affect eligibility.

Dealing with missing data

We will try to get missing data by contacting research authors and discuss the reasons, extent, nature and how to deal with missing data in each study. For the dichotomous outcome, we will conduct sensitivity analyses using best-worst case scenario analysis to explore the potential impact of the missing data. For continuous outcomes, participants with missing outcome data will be excluded from the analysis.

Assessment of risk of bias in the included studies

The risk of bias will be performed by two raters independently (Zhen Hua and Feng-ting Zhai) based on the Cochrane risk of bias tool.³⁵ It includes seven specific domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete outcome data, (6) selective reporting and (7) other bias. We will manage to reach consensus between two raters

on condition that there are any disagreement when assessing the risk of bias of the studies. If necessary, a third rater (Guan-lin Yang or Zhe Zhang) will resolve the disagreement.

Data analysis

Pairwise meta-analyses

For each direct treatment comparison, if no less than two RCTs, we will perform pairwise meta-analyses. We will use the OR to assess the effect size of dichotomous variables, while the effect size of continuous variables will be assessed using the mean difference (MD), if these continuous variables are reported using the same scale, standardised mean difference otherwise, both with 95% CrI (see figure 1). Given that the methodological and clinical heterogeneity among the included studies will create statistical heterogeneity in turn, the random-effects (RE) model will be used to pool direct evidence for every direct treatment comparison. Because methodological and clinical diversity always exist in pairwise meta-analysis, obviously statistical heterogeneity is inevitable.³⁶ And we will assess the heterogeneity both within and across those treatment comparisons by calculating the I^2 and visual inspection of forest plots within every pairwise comparison. The interpretation of I^2 will be based on

the thresholds level as set forth in the Cochrane Collaboration.³⁷ If there is important heterogeneity that influences result, we will perform meta-regression to examine potential effect moderators such as age of participants, sample size, duration of disease, course of treatment and study quality and so on. It is generally known that TCM research always involves the problem of syndrome differentiation and treatment.³⁸ The oral Chinese patent medicines in the study were mainly for promoting blood circulation and removing blood stasis, benefiting Qi and nourishing Yin, regulating Qi and broadening chest to relieve pain.³⁹ Besides, there are three types of UAP (rest angina pectoris, new-onset angina pectoris and accelerated angina pectoris) and the severity of each type is different. To avoid the bias, we will do subgroup analysis of syndrome types and types of UAP or perform meta-regression of syndrome types and types of UAP as potential effect moderators. Moreover, if there is considerable heterogeneity, especially when the direction of the effect is inconsistent, which indicates that the quantitative synthesis is inappropriate, we will do a general statistical description.

Network meta-analyses

Given that we expect between-study heterogeneity, we will perform a RE NMA. Considering that some of the therapeutic regimens available to treat UAP have not been compared in head-to-head RCT studies, we anticipate that some of the potential comparisons between the interventions will not have direct evidence. The common comparator will be routine treatment for UAP as it is the current criteria of treatment. If any trial forms nodes which are not connected to the network, we will exclude them. With the lack of direct evidence for the potential comparisons, we will perform adjusted indirect comparisons which will provide an estimate of the treatment effect. In the case of direct evidence, the NMA will be based on a mixed treatment comparison model generation and it will provide a combined estimate including direct comparison and indirect comparison evidence.⁴⁰ We will perform the NMA using Markov Chain Monte Carlo method in a Bayesian hierarchical framework. And effect sizes will be reported using the OR or MD along with 95% CrI. A network diagram will be generated for each outcome. The network diagram is made up of lines and dots. In the diagram, the dots will represent every intervention, and the size of the dot will mean the amount of participants. The lines will indicate direct comparisons between different interventions and the thickness of the line will mean the amount of studies.⁴¹ For each outcome, we will present the contribution plots, which exposit the contribution of each direct comparison to the entire network as well as for each network estimate.⁴² The main characteristics of NMA are ranking analysis having the ability to rank the various treatments for each outcome. The surface under the cumulative ranking curve (SUCRA) values and the mean ranks will be used to rank the probabilities.⁴³ The SUCRA values may range from 0% to 100%, and

the higher predicted value indicates that the treatment regimen is more effective.

Assessment of inconsistency

Inconsistency is differences between indirect and direct effect estimates for the same comparison, including loop inconsistency and design inconsistency.⁴⁴ We will use the node-splitting method to evaluate the inconsistency between direct and indirect evidence locally. If $p > 0.05$, it suggests consistency between direct and indirect evidence. As we all know, tests for inconsistency have low power,⁴⁵ and recent evidence has shown that only 2%–14% of evidence loops reported in the medical literature are expected to be inconsistent.^{46 47} Therefore, we must be cautious to interpret the statistical inference about inconsistency.

Assessment of reporting bias

A comparison-adjusted funnel plot and funnel plot for each treatment comparison and outcome (at least 10 trials⁴⁸ will be constructed to assess the small-study effects and potential publication bias).⁴⁹ And Egger's test will be used to assess the symmetry of the funnel plot.⁴⁹ For the funnel plot, the horizontal axis will represent the difference between effect sizes and the comparison-specific summary effect. Due to the lack of small-study effects or publication bias, the comparison-adjusted funnel plot should be symmetric around the zero line.

Model implementation

In our NMA, we will fit our model using WinBUGS 14.3⁵⁰ and Stata 14.0. The RE model with vague priors for multiarm trials will be used.⁴³ We will use a Markov chain Monte Carlo method called Gibbs sampling to estimate the model parameters. Convergence will be found to be adequate after running 1000 samples. These samples are discarded as 'burn-in', and posterior summaries will be based on 100 000 subsequent simulations. Production of network graphs, contribution plots and result figures and analyses for statistical evaluation of the inconsistency will be carried out in Stata 14.0 by the mvmeta and network command.⁴⁴ We will also duplicate all analyses of the primary outcomes using the netmeta package in R software.⁵¹

Quality of evidence

We will assess the quality of evidence and the strength of recommendations for the main outcomes using the GRADE guidelines.⁵² There are five factors that can reduce the quality of evidence: study limitations (risk of bias), inconsistency, indirectness, publication bias and imprecision. Correspondingly, three factors can improve the quality of evidence: residual confounding, dose-response gradient and large magnitude of effect. The quality of evidence will be graded in four levels: very low, low, moderate, high. This step will be conducted using GRADEprofiller (GRADEpro3.6software).

Patient and public involvement

No patients or public involvement will be involved in this study.

DISCUSSION

The proposed NMA will provide evidence of the comparative effectiveness and safety of oral Chinese patent medicines for UAP on the national essential drugs list of China. As we have seen, this NMA will be the first NMA in this respect. Because the findings of our study could be used to provide clinical recommendations for adults with UAP, it will interest a broad audience, including cardiologists, practice guideline developers, decision makers, researchers, policymakers and patients.

However, this NMA will have some limitations. Chinese medicine is widely used in China and also in East Asian countries, such as Korea and Japan. However, we will not search medical databases in languages such as Japanese and Korean, so excluding those studies may lead to language bias. In addition, the problem of clinical heterogeneity should not be ignored. If the scope of included studies is small, the ability to explore heterogeneity and conduct meta-regression could be limited. Moreover, we do not limit the dose and duration of the intervention, so we anticipate the dose and duration of the intervention in different clinical studies cannot be absolutely unified; however, the inconsistency will be reduced by setting subgroups or conducting meta-regression.

Nevertheless, this study is expected to provide a ranking of oral Chinese patent medicines for UAP. Based on this ranking of medicines, clinicians will make more accurate and optimal treatment decisions for adults with UAP. We will publish the findings and results of this study in a peer-reviewed journal.

ETHICS AND DISSEMINATION

Because of the nature of the study, no ethical approval and no informed consent are required. We will publish the findings and results of this study in a peer-reviewed journal.

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Contributors GY, ZZ and ZH conceptualised and designed the study. ZH and F-TZ drafted the manuscript protocol, and this was revised by ZZ, PX, CG and JT. The search strategy was developed by XD. The selection criteria, data abstraction criteria and risk of bias assessment strategy were developed by all of the authors. CG, FZ and S-JL will perform the search strategy, and PX and KD will screen the potential studies, and ZH and F-TZ will assess the risk of bias. JT provided statistical expertise. All the reviewers have read and approved the final manuscript.

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