Systematic review and meta-analysis of randomized controlled trials on Wenxin keli

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Objective: The aim of the study was to evaluate the effectiveness, safety, and cost associated with Wenxin keli in the treatment of cardiovascular diseases based on meta-analysis.

Methods: The terms “Wenxin keli” and “Wenxin” were used as the search terms in the PubMed, ProQuest, Springer, the Cochrane Library, CNKI (China National Knowledge Infrastructure), VIP (Chinese Scientific Journals Database), and Wan fang electronic databases (from January 2000 to October 2015). Relevant print journals and conference papers were also searched. Studies on randomized controlled trials (RCTs) of Wenxin keli used in the treatment of cardiovascular diseases were screened, and its indications were classified. Meta-analysis of these studies was conducted using the RevMan 5.2 software.

Results: A total of 49 RCTs (n=4,610) were included, 29 of which focused on arrhythmia, seven on angina, seven on heart failure, two on viral myocarditis, and four on menopausal syndrome. Analysis of the therapeutic indications of Wenxin keli showed that it was comparatively more curative and effective than other available treatments for cardiovascular diseases.

Conclusion: Wenxin keli showed better clinical efficacy in the treatment of arrhythmia, angina, and heart failure; however, more high-quality evidence is needed to support its use in the clinical setting.

Keywords: Wenxin keli, cardiovascular disease, meta-analysis, systematic review

Introduction
The number of patients affected by cardiovascular disease is steadily increasing because of socioeconomic development and modern lifestyles. A report from the World Health Organization reveals that chronic noncommunicable diseases have now become the leading cause of death worldwide. In 2008, 36 million individuals died of chronic noncommunicable diseases (63% of total deaths), of which 48% died of cardiovascular diseases. In recent years, there has been a shift in the medical paradigm, and cardiovascular and cerebrovascular diseases have now become a serious threat to public health. According to a report on Cardiovascular Diseases in China (2013), presented at the China Heart Congress, about one-fifth of all Chinese adults are currently affected with cardiovascular and cerebrovascular diseases. Furthermore, during the past five years, mortality due to cardiovascular diseases ranks first among all causes of death. Social and economic development has led to dramatic changes in lifestyles, including an increase in energy intake, less manual labor, accelerated pace of life, competitive pressures, and exposure to other risk factors associated with cardiovascular and other chronic noncommunicable diseases, which are causes for concern. Wenxin keli consists of several kinds of Chinese herbs including Huang Jing, Codonopsis, amber, Panax, and nard. Wenxin keli has been used clinically in the treatment of qi and yin deficiency, systolic blood stasis due to restless heart palpitations,
shortness of breath, chest pain, premature ventricular contractions (PVC), and atrial premature beats. It is one of the main forms of treatment for cardiovascular disease in Chinese medicine. In recent years, many researchers have evaluated the use of Wenxin keli in the treatment of cardiovascular disease; however, further evaluation is necessary. Therefore, the present study aimed to conduct a comprehensive evaluation of the efficacy and safety of Wenxin keli, and provide the basis for its use as a medication for cardiovascular disease.

Materials and methods

Literature search
We performed systematic searches for randomized controlled trials (RCTs) designed to evaluate the clinical efficacy of Wenxin keli in CNKI (China National Knowledge Infrastructure), Wan fang, VIP (Chinese Scientific Journals Database), PubMed, the Cochrane Library, Springer, and ProQuest from January 1, 2000 to September 7, 2015 using “Wenxin keli” and “Wenxin” as the search terms.

Inclusion and exclusion criteria
Based on the Cochrane Collaboration Handbook standards, the following inclusion criteria were formulated for the selected literature: all published domestic and international RCTs on Wenxin keli; comparable baseline test data; interventions with individual drugs and Wenxin keli doses of 9 g, three times/day; any particular course of treatment; publications in Chinese and English. Diagnostic criteria used in the present study were based on authoritative Chinese and other countries diagnostic criteria. The exclusion criteria were as follows: duplicate publications, reports of combination therapy effects on treatment, descriptive studies, studies involving animal testing, conflicting before and after data (such as, the sum of the data not matching the total), and reports without statistical indicators.

Quality assessment
Study quality was evaluated with an improved version of the Jadad questionnaire, considering mainly four aspects: 1) random sequence generation (2 points); 2) randomized hiding (2 points); 3) blinding (2 points); 4) a withdrawal period (1 point). Two reviewers independently completed the assessment, and the mean score of the two reviewers was used as the final quality score of the selected studies. In the assessment of RCTs, 1–3 points were considered as low quality, and 4–7 points indicated high quality.

A unified data extraction sheet was derived, based on blinding characteristics in previously published medical literature, for use by the two reviewers. The information thereby extracted was then cross-checked. The extracted data included:

1) document specifications: first author, publication year, and title;
2) subjects: disease, diagnostic criteria, inclusion and exclusion criteria, sample size, etc;
3) interventions: medication, dosage, route of administration, duration of treatment, etc;
4) results: efficacy indicators.

Statistical analysis
The RevMan 5.2 software, provided by the Cochrane Collaboration, was used to conduct the meta-analysis. Count data were used to determine the odds ratio (OR) and 95% confidence interval (CI) for the efficacy analysis of effect size, whereas measurement data were used to determine the standardized mean difference. Heterogeneity of the included studies was expressed in terms of $P$ and $I^2$. If $P>$0.1 and $I^2<$50%, the result of the test for heterogeneity was considered not statistically significant, and the fixed effects model was used for meta-analysis. For contrast, the random effects model was also applied to the data when $P\leq0.1$ and $I^2\geq50%$.

Results

Retrieval results and quality assessment
We searched 2,970 potentially relevant articles in CNKI, 3,488 in Wan fang, 2,393 in VIP, and two each in PubMed, Springer, the Cochrane Library, and ProQuest. We retrieved 2,274 reports after reading the abstracts, and reports involving animal studies, pharmacological studies, and systems analyses were excluded. After screening the full texts of 663 documents that were selected following application of the inclusion and exclusion criteria, 29 studies on arrhythmia were included, of which nine were on PVC, seven on angina, seven on heart failure, two on viral disorders, and four on climacteric syndrome, as shown in Figure 1 and Table 1.

The quality assessment of the studies was performed by two independent reviewers. Of the 49 studies included (Figure 1 and Table 1), only two studies were found to be of high quality (4 points). The results of specific assessment are presented in Table 1.

Results of meta-analysis

Meta-analysis of Wenxin keli in the treatment of arrhythmia

Clinical efficacy
There were 29 reports on the use of Wenxin keli in the treatment of arrhythmia, including nine on PVC. The results showed that Wenxin keli exhibited better clinical efficacy in
Meta-analysis of the effects of Wenxin keli

“Wenxin keli” and “Wenxin” used as keywords in searchable databases

CNKI (n=2,970)  VIP (n=3,488)  WF (n=2,393)  PubMed, ProQuest, Springer, Cochrane (n=2)

Screening based on title and abstract, and the following exclusion criteria: animal testing, nonrandomized controlled trials, and systematic reviews

Filter document number (n=2,274)

Further multiplex screening, excluding duplicate publications, those that did not meet specific standards, and those that satisfied the criteria without the required index text

Literature review for meta-analysis (n=49)

Syndrome classification

Arrhythmia (n=29)  Angina (n=7)  Heart failure (n=7)  Viral myocarditis (n=2)  Climacteric syndrome (n=4)

Figure 1 Study selection steps.

Abbreviations: CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journals Database; WF, Wan fang.

Table 1 Basic characteristics of included studies

| Study                        | Indications | Number of cases (test/control groups) | Treatment (days) | Interventions | Control drug | Outcomes | Jadad score |
|------------------------------|-------------|---------------------------------------|------------------|---------------|--------------|----------|-------------|
| Gao4                         | Arrhythmia  | 48/48                                 | 28               | Wexin keli    | Propafenone  | 1, 4     | 2           |
| Liu et al7                   | Arrhythmia  | 75/75                                 | 28               | Wexin keli    | Propafenone  | 1        | 2           |
| Wang6                        | Arrhythmia  | 60/60                                 | 28               | Wexin keli    | Propafenone  | 1, 4     | 2           |
| Cui10                        | Arrhythmia  | 60/60                                 | 28               | Wexin keli    | Propafenone  | 1, 2     | 2           |
| Li et al10                   | Arrhythmia  | 48/35                                 | 28               | Wexin keli    | Propafenone  | 1, 2, 3  | 1           |
| Xie11                        | Arrhythmia  | 34/32                                 | 28               | Wexin keli    | Propafenone  | 1, 4     | 2           |
| Zou and Zhao15               | Arrhythmia  | 102/101                               | 28               | Wexin keli    | Propafenone  | 1        | 2           |
| Wang13                       | Arrhythmia  | 75/75                                 | 28               | Wexin keli    | Propafenone  | 1, 4     | 2           |
| Lou14                        | Arrhythmia  | 53/50                                 | 28               | Wexin keli    | Propafenone  | 1        | 2           |
| Shi15                        | Arrhythmia  | 32/30                                 | 28               | Wexin keli    | Propafenone  | 1, 4     | 2           |
| Wang14                       | Arrhythmia  | 58/64                                 | 28               | Wexin keli    | Propafenone  | 2, 4     | 2           |
| Jin and Huang17              | Arrhythmia  | 20/20                                 | 28               | Wexin keli    | Propafenone  | 3        | 3           |
| Xue18                        | Arrhythmia  | 126/72                                | 28               | Wexin keli    | Propafenone  | 3        | 3           |
| Ren and Qiao19               | Arrhythmia  | 43/21                                 | 28               | Wexin keli    | Propafenone  | 3        | 3           |
| Wu and Yue20                 | Arrhythmia  | 48/33                                 | 28               | Wexin keli    | Propafenone  | 3        | 2           |
| Li and Shen21                | Arrhythmia  | 40/37                                 | 28               | Wexin keli    | Amiodarone   | 1, 4     | 2           |
| Wang22                       | Arrhythmia  | 46/30                                 | 28               | Wexin keli    | Amiodarone   | 1, 4     | 2           |
| Pang23                       | Arrhythmia  | 56/58                                 | 28               | Wexin keli    | Amiodarone   | 1, 4     | 2           |
| Xu et al24                   | Arrhythmia  | 68/61                                 | 28               | Wexin keli    | Amiodarone   | 1, 4     | 2           |
Table 1 (Continued)

| Study             | Indications                  | Number of cases (test/control groups) | Treatment (days) | Interventions                      | Control drug                  | Outcomes | Jadad score |
|-------------------|------------------------------|---------------------------------------|------------------|------------------------------------|-------------------------------|----------|-------------|
| Xia et al         | Arrhythmia                   | 50/50                                 | 28               | Wenxin keli                        | Amiodarone                    | 1, 4     | 2           |
| Sun et al         | PVC                          | 32/31                                 | 28               | Wenxin keli                        | Propafenone                   | 1, 2, 3   | 2           |
| Wu et al          | PVC                          | 54/35                                 | 28               | Wenxin keli                        | Propafenone                   | 1, 2     | 2           |
| Wang et al        | PVC                          | 60/30                                 | 28               | Wenxin keli                        | Propafenone                   | 1, 2     | 2           |
| Guo et al         | PVC                          | 53/53                                 | 28               | Wenxin keli                        | Propafenone                   | 1, 2, 3   | 2           |
| Jin et al         | PVC                          | 60/30                                 | 28               | Wenxin keli                        | Propafenone                   | 1, 2, 3   | 2           |
| Zhang et al       | PVC                          | 39/38                                 | 28               | Wenxin keli                        | Propafenone                   | 2, 3     | 2           |
| Li et al          | PVC                          | 32/32                                 | 28               | Wenxin keli                        | Propafenone                   | 3, 2     | 2           |
| Wang et al        | PVC                          | 60/60                                 | 28               | Wenxin keli                        | Propafenone                   | 2, 3     | 2           |
| Yan et al         | PVC                          | 60/60                                 | 28               | Wenxin keli                        | Propafenone                   | 2, 3     | 2           |

Notes: 1, clinical efficacy; 2, ECG efficacy; 3, clinical symptoms of heart palpitations, shortness of breath, dizziness, insomnia, chest tightness, etc; 4, adverse reactions.

| Study             | Indications                  | Number of cases (test/control groups) | Treatment (days) | Interventions                      | Control drug                  | Outcomes | Jadad score |
|-------------------|------------------------------|---------------------------------------|------------------|------------------------------------|-------------------------------|----------|-------------|
| Yu et al          | Angina                       | 40/35                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Shu and Li        | Angina                       | 37/37                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Ye et al          | Angina                       | 36/36                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Wei et al         | Angina                       | 50/50                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Yuan et al        | Unstable angina              | 47/47                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 4     | 2           |
| Wei and Deng      | Unstable angina              | 50/50                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 3     | 2           |
| Yuan and Wei      | Unstable angina              | 80/80                                 | 28               | Conventional treatment +           | Wenxin keli                   | 1, 3, 4  | 2           |

Notes: 1, angina pectoris; 2, ECG efficacy; 3, changes in the indicator lipids; 4, adverse reactions.

| Study             | Indications                  | Number of cases (test/control groups) | Treatment (days) | Interventions                      | Control drug                  | Outcomes | Jadad score |
|-------------------|------------------------------|---------------------------------------|------------------|------------------------------------|-------------------------------|----------|-------------|
| Yu et al          | Chronic heart failure        | 37/35                                 | 56               | Conventional treatment +           | Wenxin keli                   | 1, 2, 3   | 4           |
| Yang and Dong     | Chronic heart failure        | 40/40                                 | 56               | Conventional treatment +           | Wenxin keli                   | 1, 3, 4   | 2           |
| Kong et al        | Chronic heart failure        | 30/30                                 | 56               | Conventional treatment +           | Wenxin keli                   | 2, 4, 6   | 2           |
| Xu et al          | Chronic heart failure        | 37/35                                 | 56               | Conventional treatment +           | Wenxin keli                   | 3, 4     | 2           |
| Hu et al          | Chronic heart failure        | 50/48                                 | 56               | Conventional treatment +           | Wenxin keli                   | 4, 2     | 2           |
| Yu et al          | Congestive heart failure     | 35/37                                 | 56               | Conventional treatment +           | Wenxin keli                   | 1, 2, 3, 5| 2           |
| Wang et al        | Congestive heart failure     | 35/35                                 | 56               | Conventional treatment +           | Wenxin keli                   | 1, 2, 4, 6, 7| 2        |

Notes: 1, clinical efficacy; 2, TCM syndromes; 3, clinical echocardiography; 4, plasma BNP values; 5, heart rate; 6, 6-minute walking distance measurement; 7, adverse reactions.

| Study             | Indications                  | Number of cases (test/control groups) | Treatment (days) | Interventions                      | Control drug                  | Outcomes | Jadad score |
|-------------------|------------------------------|---------------------------------------|------------------|------------------------------------|-------------------------------|----------|-------------|
| Yang et al        | Children with viral myocarditis | 34/34                                | 14               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Deng et al        | Children with viral myocarditis | 30/28                                | 14               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |

Notes: 1, clinical efficacy; 2, creatine kinase (CK-MB) change; 3, adverse reactions.

| Study             | Indications                  | Number of cases (test/control groups) | Treatment (days) | Interventions                      | Control drug                  | Outcomes | Jadad score |
|-------------------|------------------------------|---------------------------------------|------------------|------------------------------------|-------------------------------|----------|-------------|
| Liu and Ren       | Climacteric syndrome        | 60/58                                 | 84               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Lei et al         | Climacteric syndrome        | 42/38                                 | 84               | Conventional treatment +           | Wenxin keli                   | 1, 2     | 2           |
| Li and Miao       | Climacteric syndrome        | 33/33                                 | 60               | Wenxin keli                        | Oryzanol + propanolol + vitamin B complex | 1, 2     | 2           |
| Hu et al          | Climacteric syndrome        | 25/23                                 | 60               | Wenxin keli                        | Oryzanol + propanolol + vitamin B complex | 1, 2     | 2           |

Notes: 1, clinical efficacy; 2, adverse reactions.

Abbreviations: BNP, brain natriuretic peptide; CK-MB, creatine kinase MB isoenzyme; ECG, electrocardiogram; PVC, premature ventricular contractions; TCM, traditional Chinese medicine.
the treatment of arrhythmia (OR = 1.74, 95% CI [1.28, 2.35], \( P=0.0003 \); Figure 2) compared to propafenone. Also, in comparison to amiodarone, Wenxin keli again exhibited better clinical efficacy in the treatment of arrhythmia (OR = 2.28, 95% CI [1.33, 3.89], \( P=0.003 \); Figure 3).

Five studies considered the use of Wenxin keli in the treatment of PVC. The meta-analysis showed that it exhibited better clinical efficacy than propafenone (OR = 2.92, 95% CI [1.72, 4.96], \( P<0.0001 \); Figure 4).

### Efficacy of Wenxin keli on electrocardiogram

Three studies reported on the efficacy of Wenxin keli on electrocardiogram (ECG). Meta-analysis of the random effects model showed no significant difference between Wenxin keli and propafenone in the treatment of arrhythmia based on the ECG (OR = 2.15, 95% CI [0.58, 7.97], \( P=0.25 \); Figure 5).

Eight studies reported on the use of Wenxin keli in the treatment of PVC. The meta-analysis showed that Wenxin keli showed better efficacy than propafenone based on the ECG (OR = 2.19, 95% CI [1.45, 3.30], \( P=0.0002 \); Figure 6).

### Secondary outcomes

Five studies reported on the effect of Wenxin keli treatment on secondary efficacy variables in PVC. Heterogeneity was minimal; thus, the fixed effects model was applied to the study that reported on secondary efficacy variables, in addition to dizziness. The results showed that Wenxin keli exhibited better efficacy, in addition to dizziness (Table 2).

### Adverse reactions

A total of eleven studies reported adverse reactions in the treatment of arrhythmia. Wenxin keli showed a lower incidence of adverse reactions, with reports of mild adverse reactions and favorable clinical application and safety, in comparison to both propafenone and amiodarone (Figures 7 and 8).

Six studies reported on adverse reactions in the treatment of PVC. Meta-analysis of the fixed effects model showed that Wenxin keli exhibited a lower incidence of adverse reactions (OR = 0.32, 95% CI [0.16, 0.64], \( P=0.001 \); Figure 9) compared to amiodarone.

### Publication bias

A funnel plot (Figure 10) showed that the studies reporting the use of Wenxin keli in the treatment of arrhythmia, included in the analysis, were substantially symmetric. This suggests less publication bias in these reports. According to the Cochrane Handbook, funnel plot analysis should not be performed for other indications if there are less than ten studies.

### Meta-analysis of Wenxin keli in the treatment of angina

**Angina pectoris**

Six reports, included in the analysis, reported on the use of Wenxin keli in the treatment of angina pectoris, of which three specifically focused on angina and three on unstable angina. Meta-analysis of the fixed effects model showed that the clinical efficacy of Wenxin keli combined with conventional therapy in the treatment of angina was significantly better than conventional therapy alone (OR = 3.12, 95% CI [1.77, 5.52], \( P=0.0001 \); Figure 11). The clinical efficacy of Wenxin keli combined with conventional therapy in the treatment of unstable angina was also significantly better than conventional therapy alone (OR = 3.97, 95% CI [1.92, 8.22], \( P=0.0002 \); Figure 12).

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### Table 2: Adverse reactions

| Study or subgroup | Experimental Events | Total | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI |
|------------------|---------------------|-------|----------------|-------|------------|-------------------------------|-------------------------------|
| Cui\(^6\)        | 44                  | 60    | 44             | 60    | 18.1       | 1.00 (0.45, 2.25)             |                               |
| Gao\(^6\)        | 41                  | 48    | 41             | 48    | 9.2        | 1.00 (0.32, 3.11)             |                               |
| Li et al\(^10\)  | 42                  | 48    | 35             | 48    | 5.6        | 2.42 (0.77, 7.60)             |                               |
| Liu et al\(^10\) | 62                  | 75    | 75             | 48    | 12.9       | 2.68 (1.25, 5.74)             |                               |
| Lou\(^13\)       | 46                  | 53    | 42             | 50    | 8.8        | 1.55 (0.42, 3.76)             |                               |
| Shi\(^13\)       | 30                  | 32    | 25             | 30    | 2.5        | 3.00 (0.54, 16.81)            |                               |
| Wang\(^13\)      | 69                  | 75    | 75             | 75    | 2.3        | 3.63 (1.35, 9.76)             |                               |
| Wang\(^6\)       | 51                  | 60    | 51             | 60    | 11.8       | 1.00 (0.37, 2.72)             |                               |
| Xie\(^11\)       | 30                  | 34    | 20             | 32    | 3.7        | 4.50 (1.27, 15.96)            |                               |
| Zhou and Zhao\(^12\) | 86                | 102   | 82             | 101   | 20.0       | 1.25 (0.60, 2.59)             |                               |
| **Total (95% CI)** | **587**            | **566** | **436**     |   | **100**    | **1.74 (1.28, 2.35)**        |                               |

**Figure 2: Meta-analysis of Wenxin keli and propafenone in the treatment of arrhythmia.**

**Abbreviations:** CI, confidence interval; M–H, Mantel–Haenszel.
### Figure 3 Meta-analysis of Wenxin Keli and Amiodarone in the Treatment of Arrhythmia.

**Abbreviations:** CI, confidence interval; M–H, Mantel–Haenszel.

| Study or subgroup | Experimental Events | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| Li and Shen      | 34                  | 40             | 31    | 37         | 26.4                       |
| Pang             | 53                  | 56             | 47    | 58         | 13.5                       |
| Wang             | 38                  | 46             | 23    | 30         | 26.4                       |
| Xia              | 48                  | 50             | 43    | 50         | 9.4                        |
| Xu et al         | 62                  | 68             | 48    | 61         | 24.4                       |

**Total (95% CI):**

- Total events: 235
- Heterogeneity: $\chi^2=3.30, df=4 (P=0.51); I^2=0$
- Test for overall effect: $Z=3.01 (P=0.003)$

### Figure 4 Meta-analysis of Wenxin Keli and Propafenone in the Treatment of PVC.

**Abbreviations:** CI, confidence interval; PVC, premature ventricular contractions; M–H, Mantel–Haenszel.

| Study or subgroup | Experimental Events | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| Wu               | 51                  | 54             | 23    | 31         | 10.1                       |
| Wang             | 53                  | 60             | 21    | 30         | 20.4                       |
| Sun              | 29                  | 32             | 23    | 31         | 13.7                       |
| Jin              | 53                  | 60             | 21    | 30         | 20.4                       |
| Guo              | 46                  | 53             | 43    | 53         | 35.4                       |

**Total (95% CI):**

- Total events: 232
- Heterogeneity: $\chi^2=2.52, df=4 (P=0.64); I^2=0$
- Test for overall effect: $Z=3.97 (P=0.0001)$

### Figure 5 Meta-analysis of Wenxin Keli and Propafenone in the Treatment of Arrhythmia.

**Abbreviations:** CI, confidence interval; M–H, Mantel–Haenszel.

| Study or subgroup | Experimental Events | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| Cui              | 54                  | 60             | 39    | 60         | 33.7                       |
| Li et al         | 43                  | 48             | 25    | 35         | 31.2                       |
| Wang             | 44                  | 58             | 53    | 64         | 35.1                       |

**Total (95% CI):**

- Total events: 141
- Heterogeneity: $\chi^2=1.07, df=2 (P=0.007); I^2=80$
- Test for overall effect: $Z=1.15 (P=0.25)$

### Figure 6 Meta-analysis of Wenxin Keli and Propafenone in the Treatment of PVC.

**Abbreviations:** CI, confidence interval; PVC, premature ventricular contractions; M–H, Mantel–Haenszel.

| Study or subgroup | Experimental Events | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| Guo              | 60                  | 65             | 62    | 65         | 15.2                       |
| Jin              | 53                  | 60             | 24    | 30         | 11.9                       |
| Li               | 28                  | 32             | 24    | 32         | 9.6                        |
| Sun              | 23                  | 32             | 22    | 31         | 20.0                       |
| Wang             | 58                  | 60             | 44    | 60         | 4.7                        |
| Wu               | 48                  | 54             | 25    | 35         | 10.7                       |
| Yan              | 55                  | 60             | 45    | 60         | 12.0                       |
| Zhang et al      | 33                  | 39             | 32    | 38         | 15.9                       |

**Total (95% CI):**

- Total events: 358
- Heterogeneity: $\chi^2=11.77, df=7 (P=0.11); I^2=41$
- Test for overall effect: $Z=3.73 (P=0.0002)$
Table 2: Meta-analysis of secondary efficacy variables in treatment of arrhythmia

| Outcomes            | Number of included studies | Number of cases | Heterogeneity | Model | Meta-analysis |
|---------------------|---------------------------|-----------------|---------------|-------|--------------|
|                     |                           |                 |               |       | OR (95% CI)  |
|---------------------|---------------------------|-----------------|---------------|-------|--------------|
| Palpitations        | 4                         | 383             | 0%            | 0.99  | Fixed        |
| Chest tightness     | 5                         | 451             | 0%            | 0.70  | Fixed        |
| Restless sleep      | 4                         | 373             | 0%            | 0.50  | Fixed        |
| Dizziness           | 4                         | 379             | 55%           | 0.09  | Random       |
| Shortness of breath | 5                         | 462             | 0%            | 0.94  | Fixed        |

Abbreviations: CI, confidence interval; OR, odds ratio.

Figure 7: Meta-analysis of Wenxin keli, propafenone, and associated adverse reactions on arrhythmia.

Figure 8: Meta-analysis of Wenxin keli, amiodarone, and associated adverse reactions on arrhythmia.

Figure 9: Meta-analysis of Wenxin keli, propafenone, and associated adverse reactions on PVC.

Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
ECG efficacy
Two studies reported on the efficacy of Wenxin keli in the treatment of angina based on the ECG. Meta-analysis of the fixed effects model showed that the efficacy of Wenxin keli combined with conventional therapy was not significantly different from that of the conventional therapy alone (OR =2.02, 95% CI [0.65, 6.24], \( P=0.22 \); Figure 13).

Adverse reactions
Three studies mentioned the development of adverse reactions to Wenxin keli in the treatment of angina, two of which could not be compared because the experimental and control groups were not described separately. The latter test group and six cases (15%) in the control group exhibited no adverse reactions.

Meta-analysis of Wenxin keli in the treatment of heart failure
Clinical efficacy
Two studies reported on the clinical efficacy of Wenxin keli in the treatment of chronic heart failure. Meta-analysis showed that Wenxin keli combined with conventional treatment showed no greater clinical efficacy (OR =2.62, 95% CI [0.91, 7.56], \( P=0.07 \); Figure 14) compared to the conventional treatment group.

Secondary efficacy variables
Analysis of secondary efficacy end points showed that Wenxin keli combined with conventional treatment showed better efficacy in left ventricular ejection fraction (LVEF) values, plasma brain natriuretic peptide (BNP) levels, and stroke volume (Table 3).

Meta-analysis of Wenxin keli in the treatment of viral infections
Clinical efficacy
Two studies reported on the clinical efficacy of Wenxin keli in the treatment of viral infections. Meta-analysis showed that Wenxin keli combined with conventional treatment exhibited better clinical efficacy (OR =4.89, 95% CI [1.30, 18.38], \( P=0.02 \); Figure 15) compared to conventional treatment.

Adverse reactions
Two studies investigated adverse reactions associated with Wenxin keli in the treatment of viral infections. No adverse reactions were reported in either study, suggesting the safety of Wenxin keli.

Meta-analysis of Wenxin keli in the treatment of climacteric syndrome
Clinical efficacy
Four studies reported on the clinical efficacy of Wenxin keli in the treatment of climacteric syndrome, of which two compared Wenxin keli combined with conventional therapy to conventional therapy alone, and the other two compared Wenxin keli to a combination of oryzanol, propranolol, and vitamin B complex. Meta-analysis showed that in comparison to conventional treatment alone, Wenxin keli combined

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Oddsratio \( \text{M–H, fixed, 95% CI} \) |
|-------------------|---------------------|----------------|------------|---------------------------------|
| Shu and Li\(^a\)  | 28                  | 20             | 34.7       | 2.64 (0.98, 7.12)               |
| Wei et al\(^a\)   | 45                  | 50             | 25.0       | 3.86 (1.28, 11.64)              |
| Ye et al\(^a\)    | 32                  | 36             | 19.0       | 4.00 (1.15, 13.95)              |
| Yu et al\(^a\)    | 36                  | 40             | 21.3       | 2.25 (0.60, 8.46)               |
| Total (95% CI)    | 163                 | 158            | 100        | 3.12 (1.77, 5.52)               |

Total events 141
Heterogeneity: \( \chi^2=0.63, df=3 (P=0.89); P=0% \)
Test for overall effect: \( Z=3.92 (P<0.0001) \)

Figure 11 Meta-analysis of Wenxin keli and propafenone in the treatment of angina.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
Table 3: Meta-analysis of secondary efficacy variables in treatment of heart failure

| Outcomes               | Number of included studies | Number of cases | Heterogeneity | Model       | Meta-analysis           |
|------------------------|---------------------------|-----------------|---------------|-------------|-------------------------|
| LVEF values            | 4                         | 310             | 57%           | Random      | 0.76 (0.41, 1.12)       |
|                        |                           |                 |               |             | <0.0001                 |
| Plasma BNP levels      | 3                         | 238             | 99%           | Random      | -5.92 (-9.70, -2.14)    |
|                        |                           |                 |               |             | 0.002                   |
| Stroke volume          | 3                         | 212             | 29%           | Fixed       | 0.50 (0.18, 0.83)       |
|                        |                           |                 |               |             | 0.002                   |

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; LVEF, left ventricular ejection fraction; MD, mean difference.
with conventional treatment exhibited better clinical efficacy in the treatment of climacteric syndrome (OR = 3.67, 95% CI 1.88, 7.18, \( P = 0.0001 \); Figure 16). In comparison to the control drug (propranolol + oryzanol + vitamin B), Wenxin keli showed better clinical efficacy (OR = 7.82, 95% CI [2.92, 20.95], \( P = 0.0001 \); Figure 17).

### Adverse reactions

No adverse reactions were reported in the literature regarding the use of Wenxin keli in the treatment of climacteric syndrome. Thus, comparisons between any control and corresponding experimental groups were not possible.

### Discussion

Wenxin keli consists primarily of Codonopsis, Huang Jing, Panax, amber, nard, and other traditional Chinese herbs. It represents the first broad-spectrum treatment capable of affecting multiple ion channels (Na\(^+\), K\(^+\), and Ca\(^{2+}\)) that can also significantly improve heart function (without causing arrhythmias), heart palpitations, chest tightness, and other associated symptoms. Modern pharmacological studies have confirmed that Codonopsis contains inulin and amino acids, and that it exerts anti-platelet aggregation, enhances immunity, and improves myocardial contractile effects.\(^{55}\) Huang Jing exhibits lipid-lowering and anti-atherosclerotic effect, reduces blood pressure, and increases coronary blood flow.\(^{56}\) Panax can increase coronary blood flow, inhibit self-discipline of the ectopic pacemaker sinus node, reduce myocardial oxygen consumption, improve microcirculation, and regulate myocardial ischemia and hypoxia.\(^{56}\) Nard plays a role in relieving depression, and pharmacological experiments show that it contains valerian ketones. These compounds can combine with specific proteins via ion channels in the myocardial cell membrane to reduce myocardial cell automaticity, extend the atrial action potential of ventricular muscle and conduction system time, interrupt reentry, and eliminate arrhythmias.\(^{57}\) The therapeutic index of Wenxin keli on the heart, kidneys, and liver was within normal limits. Wenxin keli can enhance immune function, without causing significant adverse reactions, and shows no evidence of the side effects of myocardial ischemia and arrhythmia. It is therefore considered to be safe and effective.\(^{3}\)

### Limitations

Among the studies included in the meta-analysis, only two of them that had higher scores on the Jadad questionnaire were used to evaluate the quality, thereby potentially affecting the strength of the results. There were fewer documents available for some of the indications analyzed, and some studies had smaller sample sizes. Both of these factors represent limitations of the present study.

No standards for RCTs have been published in People’s Republic of China; therefore, allocation concealment and blinding were rarely mentioned in the studies included in the analysis. Thus, it is possible that most of the original

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**Table 1**

| Study or subgroup | Experimental Events | Total | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI |
|------------------|--------------------|-------|----------------|-------|------------|-------------------------------|-------------------------------|
| Lei\(^{32}\)     | 37                 | 42    | 21             | 38    | 35.7       | 4.36 (1.49, 12.82)             | 3.29 (1.39, 7.76)             |
| Liu and Ren\(^{31}\) | 50               | 60    | 35             | 58    | 64.3       |                               |                               |
| **Total (95% CI)** | **102**           | **96** | **Total events** | **100** |            |                               |                               |

Heterogeneity: \( \chi^2 = 0.16, \, df = 1 \) \( (P = 0.69) \), \( I^2 = 0\%

Test for overall effect: \( Z = 3.80 \) \( (P = 0.0001) \)

**Figure 16** Meta-analysis of Wenxin keli combined with conventional treatment for climacteric syndrome. Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

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**Table 2**

| Study or subgroup | Experimental Events | Total | Control Events | Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI |
|------------------|--------------------|-------|----------------|-------|------------|-------------------------------|-------------------------------|
| Hu\(^{34}\)     | 22                 | 25    | 15             | 23    | 59.6       | 3.91 (0.89, 17.19)             | 13.57 (3.44, 53.57)           |
| Li and Miao\(^{32}\) | 30               | 33    | 14             | 33    | 40.4       |                               |                               |
| **Total (95% CI)** | **58**           | **56** | **Total events** | **100** |            |                               |                               |

Heterogeneity: \( \chi^2 = 1.46, \, df = 1 \) \( (P = 0.23) \), \( I^2 = 32\%

Test for overall effect: \( Z = 4.09 \) \( (P = 0.0001) \)

**Figure 17** Meta-analysis of Wenxin keli in the treatment of climacteric syndrome. Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
reports were inconclusive and the results were of low quality, thereby increasing bias. To address the aforementioned limitations and verify the results of the present study, additional high-quality RCT studies that employ larger sample sizes are required.

Conclusion
Based on the available evidence, meta-analysis is an effective method to prove the safety and efficacy of a particular treatment. The results of meta-analysis allow physicians and patients to choose the most effective treatment.

For systematic reviews of Wenxin keli in the treatment of cardiovascular disease, we used the indicators of angina pectoris total efficiency, ECG total efficiency, and adverse outcomes for comparison with the control groups that were treated with propafenone and amiodarone. The findings observed in the treatment of arrhythmia, PVC, angina pectoris, heart failure, viral myocarditis, and climacteric syndrome, among others, were derived from 49 studies. Overall, these studies reported favorable effects of Wenxin keli, regardless of whether it was used directly or as an adjuvant therapy. Furthermore, a low incidence of adverse reactions was evident among the studies analyzed.

Disclosure
The authors report no conflicts of interest in this work.

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