Systematic Review and Meta-Analysis

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Effectiveness and safety of traditional herbal medicine on cardiac arrhythmic condition

A systematic review and meta-analysis of randomized control clinical trial

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Abstract

Introduction: The prevalence of cardiac arrhythmia, which can lead to cardiac death, heart failure, and cardioembolic stroke, is increasing. Although various Western medicines for cardiac arrhythmias have been developed, there are still various difficulties in the management of arrhythmias. Traditional herbal medicines (THM) are widely used to manage arrhythmia in East Asia. Therefore, this study aimed to assess the effectiveness and safety of THM in the treatment of arrhythmia.

Method: Using a systematic review methodology, we searched for randomized clinical trials on herbal medicines for arrhythmia without complications in 4 databases up to September 2022. The literature search was carried out again, targeting papers published until April 2024.We conducted a risk-of-bias assessment and meta-analysis. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: Eighty-two randomized clinical trials were included in this meta-analysis. Total effective rate was significantly better in unspecified arrhythmia (risk ratio [RR]: 1.20, 95% confidence interval [CI]: 1.13–1.26), premature ventricular contraction (RR: 1.29, 95% CI: 1.29–1.33), sinus bradycardia (RR: 1.26, 95% CI: 1.17–1.36), tachycardia (RR: 1.23 95% CI: 1.15–1.32), and atrial fibrillation (RR: 1.17, 95% CI: 1.07–1.27). No severe adverse events were associated with THM. The overall risk of bias was relatively high. The total effective rate was the most frequently assessed clinical outcome variable. Most outcomes were surrogates and not clinical endpoints.

Conclusion: THM, alone or in combination with Western medicine, has therapeutic effects on cardiac arrhythmic diseases. However, additional disease-specific clinical outcome variables are required for further studies on THM. Owing to the low quality of the included studies and their small sample sizes, additional large-scale, long-term follow-up, and well-designed randomized controlled clinical trials are required.

Systematic review registration number: Details of the protocol for this systematic review and meta-analysis were registered on the Open Science Framework (OSF. io). (https://osf.io/7r8kn/).

Abbreviations: AF = atrial fibrillation, CIs = confidence intervals, HR = heart rate, HRV = heart rate variability, PVC = premature ventricular contractions, RCTs = randomized clinical trials, RR = risk ratio, TER = total effective rate, THM = traditional herbal medicine, WM = Western medicine.

Keywords: arrhythmia, herbal medicine, meta-analysis, systematic review, traditional East Asian medicine

1. Introduction

The prevalence of heart disease is increasing. The overall prevalence of arrhythmia was 1%. The incidence rate was observed to significantly increase with age, with a prevalence of 8% in individuals of advanced age (over 80 years).[1] Atrial fibrillation (AF), the most common arrhythmia, is a major factor associated with fatal cardiovascular conditions such as ischemic heart disease,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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cardiovascular disease, and heart failure, without appropriate management.[2] Arrhythmias include various diseases with an abnormal heartbeat, such as AF, paroxysmal supraventricular tachycardia, sinus arrhythmia, ectopic atrial rhythm or wandering pacemaker, atrial premature beat, ventricular premature beat, ventricular tachycardia, and AV block.[3]

In conventional medicine, factor IIa (thrombin) inhibitors (dabigatran) and factor Xa inhibitors (xaban) are used to prevent embolisms caused by arrhythmias. Drug therapies for the management of arrhythmias include lidocaine, amiodarone, and propafenone.[4,5] Non-pharmacological therapies for the management of arrhythmias include pacemakers, catheter ablation, and implantable cardioverter-defibrillators.[6,7] However, these standard treatments have several limitations. Drug therapy is associated with problems such as necessitating lifetime medication for symptom management, rather than curative intent, or adverse effects associated with the drug itself.[8] Even in non-pharmacological therapies such as surgery, if a pacemaker is used, there is a risk of side effects such as making imaging impossible, significantly impeding daily life, and increasing the risk of bleeding.[8] Therefore, the demand for alternative therapies for managing arrhythmias is gradually increasing. In East Asian countries, various complementary and alternative therapies are used to manage arrhythmias.[9]

In East Asian traditional medical records, arrhythmia diseases are already known as slow (迟脉), hesitant (涩脉), skipping (促脉), knotted (结脉), and regularly intermittent pulses (大脉) through pulse diagnosis method from ancient times. In addition, various therapeutic approaches have been suggested, including acupuncture, herbal medicine, and moxibustion.[10] A recent study reported the significance of acupuncture and moxibustion in arrhythmias.[10–13] As such, systematic literature reviews on acupuncture and moxibustion treatment have been continuously published, and research evidence has expanded. However, for traditional herbal medicine (THM) treatment, a systematic literature review of the overall THM for various arrhythmic diseases is still insufficient. Only 1 meta-analysis of specific herbal medicines has been conducted.[14,15] Therefore, this study aimed to examine the effectiveness and adverse events of THM in various arrhythmias in randomized clinical trials (RCTs) using a systematic literature review and meta-analysis methodology. This study examined comprehensive and up-to-date knowledge of THM for arrhythmias for further clinical research and practice. Furthermore, we propose suggestions for future studies by examining the clinical outcome variables and methodological flaws associated with the existing studies.

2. Methods

We conducted a systematic literature review and meta-analysis according to the Cochrane manual.[16,17] The study protocol was prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[16,17] The study protocol was registered in the Open Science Framework (OSF. io). (https://osf.io/7r8kn/). This study was a systematic review of the existing literature and did not require institutional review board approval.

2.1. Eligible criteria for study selection

2.1.1. Definition of disease. Arrhythmia is a condition in which the heart beats irregularly or an abnormal heartbeat appears.[3] In this study, the arrhythmias were primary, and their sub-classifications included tachycardia, bradycardia, AF, ventricular premature contraction, ventricular tachycardia, sinus dysfunction, and atrioventricular conduction block.[18,19] However, secondary arrhythmias occurring due to coronary artery disease, cardiac hypertrophy, and hyperthyroidism were excluded. Patients with arrhythmias after percutaneous coronary intervention were excluded.[20,21] All symptom classifications (syndrome differentiation) in traditional East Asian medicine were permitted.

2.1.2. Types of interventions and comparators. The THM treatment group included herbal medicine monotherapy and combination therapy with Western medicine (WM). Various formulations are available for different types of herbal medicines, such as pills, decoctions, powders, and extracts; however, the administration route is limited to oral drugs. Interventions involving other routes, such as injections, external treatment, intraperitoneal injection, intravenous injection, intramuscular injection, or fumigation treatment, were excluded. In single medicinal herbs, if herbal medicines were not included in the East Asian country's Pharmacopoeia (such as the Korean or Chinese Pharmacopoeia), the research was excluded. For combination therapy with Western and herbal medicines, we included only studies that adopted the same WM between the intervention and control groups. In addition, non-pharmacological treatments such as acupuncture and moxibustion were excluded from this study to explore the effect of THM alone, not with acupuncture nor moxibustion.

2.1.3. Types of outcome measurements. No restrictions exist on the type of clinical outcomes. We extracted every clinical outcome adopted in each clinical trial, including the total effective rate (TER), heart rate (HR) change, electrocardiogram change, and Holter 24-h electrocardiogram results. After investigating the clinical outcomes of each study, a meta-analysis was performed on the outcomes commonly used in several studies.

2.2. Searching strategy and database

We searched the core electronic databases MEDLINE (via PubMed) (https://www.ncbi.nlm.nih.gov/pubmed) and the Cochrane Library (https://www.cochranelibrary.com/) and Embase (https://www.embase.com). In addition, we searched Chinese and Korean DBs such as the China National Knowledge Infrastructure (http://gb.oversea.cnki.net/Kns55/), DBpia (www.dbpia.co.kr), Korean Studies Information Service System (http://kiss.kstudy.com/), OASIS (https://oasis.kiom.re.kr/), and RISS (http://www.riss.kr/index.do). No restrictions exist on the language of the research papers, and the initial search period included publications up to September 2022. With time elapsed since the initial document search, a new search was conducted with a reference point of the end of April 2024.The search strategy and results for each database are described in Supplementary 1A, Supplemental Digital Content, http://links.lww.com/MD/M750 and 1B, Supplemental Digital Content, http://links.lww.com/MD/M751.

2.3. Data collection and analysis

2.3.1. Inclusion and exclusion criteria. Inclusion criteria

1) Research on herbal medicine alone or combination treatment with conventional medication.
2) A study targeting patients diagnosed with primary arrhythmias.
3) A study in which the study design corresponds to a randomized comparative clinical trial.
4) Administration routes were orally prescribed herbal medicine.

Exclusion criteria

1) Non-RCT designs such as animal experiments, case report papers, and review papers.

2) When an invasive herbal medicine administration method was used (pharmacopuncture).
3) Secondary arrhythmias due to organic causes (arrhythmias due to postoperative arrhythmias, heart failure, myocardial infarction, or hyperthyroidism).
4) Research restricted to a specific subgroup (age).

2.3.2. Literature selection. For studies found in the search, duplicate literature was removed using Endnote X9 (Clarivate Analytics, London, United Kingdom). For primary selection, 2 independent authors (J.A. and H.C.) reviewed the titles and abstracts and selected suitable studies. Full texts of the selected primary studies were reviewed and confirmed. In the case of discrepancies, a final decision was made via discussion. Issues that remained unresolved after discussion were assessed by a third reviewer (J.L.).

2.3.3. Data extraction and management. In the final included studies after the selection process, the data extraction and risk-of-bias assessment results were extracted to Excel (Microsoft, Redmond, WA). Data extraction was performed based on the year of publication, study design method, diagnostic criteria, general characteristics of the participants, intervention method of the intervention and control groups, outcome evaluation index, and outcome measurement value.

2.4. Quality assessment

The risk-of-bias assessment was performed using the Cochrane collaboration's "Risk of bias" tool applied to randomized comparative clinical studies (RCTs), referring to Cochrane's systematic literature review guidelines.[16] The risk of bias was evaluated for each item: random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective reporting, and other sources of bias.[15] The risk-of-bias was independently evaluated by 2 researchers (J.A. and H.C.) after discussing the evaluation criteria in advance. If a consensus was not reached, a third researcher (J.L.) intervened.

2.5. Meta-analysis

A meta-analysis was performed to quantitatively synthesize treatment effects by combining several clinical studies on the clinical effects of herbal medicine treatment for arrhythmias. The RevMan (Review Manager version 5.4.1, Cochrane, UK) program was used for meta-analysis. A meta-analysis was conducted when the study design, intervention method, and evaluation tool were appropriate for the quantitative synthesis of studies based on heterogeneity. The risk ratio (RR) was used for dichotomous outcomes, whereas weighted mean differences and 95% confidence intervals (CIs) were used for continuous outcomes. To assess the heterogeneity between studies based on the Higgins I^2 statistic, an $I^2 > 50\%$ indicated heterogeneity between studies. If considerable heterogeneity was identified, a random-effects model was used to synthesize the results.[16]

2.6. Publication bias

A funnel plot was used to visually inspect publication bias in the included studies. Eggar's test was used to analyze publication bias.

3. Results

3.1. Study selection

Among the 2921 articles, 82 were selected. The literature selection process was described using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart criteria (Fig. 1).

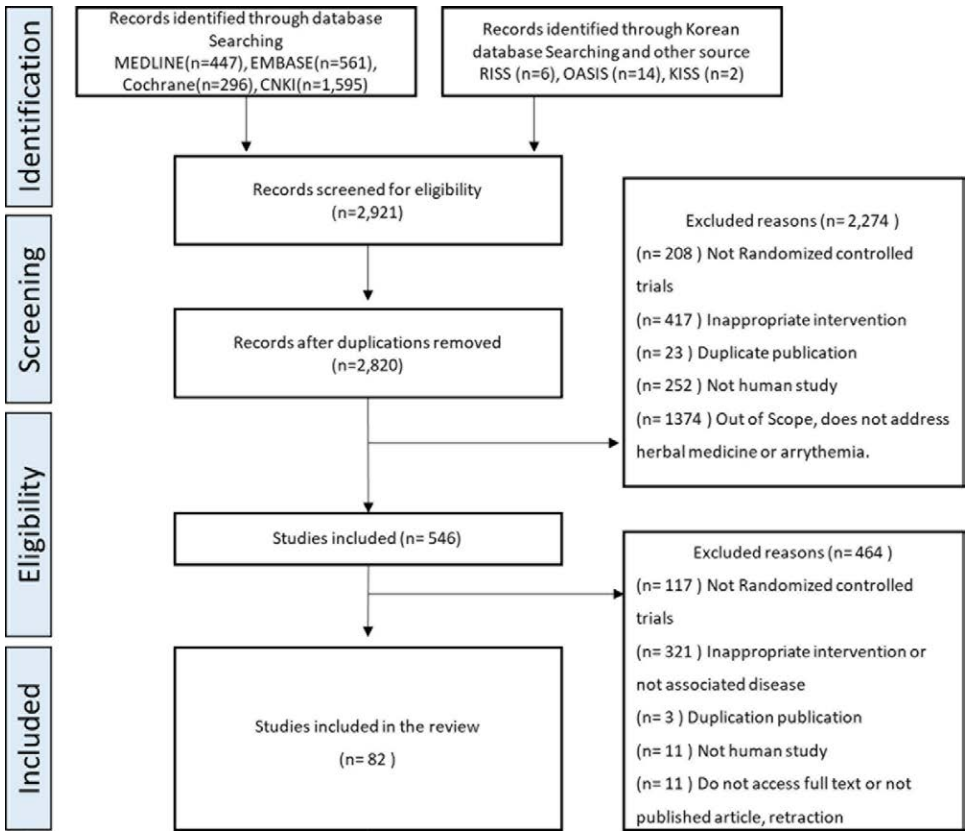

Figure 1. PRISMA flow diagram of the selection process. PRISMA = Preferred Reporting Items for Systematic review and Meta-Analysis.

Table 1

General characteristics of the included trials.

Stud ID	Disease	Sample size (TG:CG) 1. Initial 2. Final	Age (yr) mean ± SD or range	Experimental group (Herbal Medicine)	Frequency and total treatment duration	Control group	Outcome measurements
Unspecified arrythmia							
Dai 2011[22]	Arrythmia	1. 84 (44:40) 2. 84 (44:40)	T: 64.5 ± 8.1 C: 63.2 ± 8.4	Jianpizishen-Tang (健脾滋肾)	bid 4 wk	Isosorbide nitrate 10 mg tid, aspirin 100 mg tid, and metoprolol tartrate 12.5 mg tid	1. TER; 2. 24 Holter-TER
Dong 2009[23]	Arrhythmia	1. 60 (30:30) 2. 60 (30:30)	T: 56 C: 52	Fumai-Tang (复脉汤)	bid, 4 wk	Propafenone 150 mg	1. TER
Fan 2019[24]	Arrhythmia	1. 106 (53:53) 2. 90 (45:45)	T: 48.61 ± 2.32 C: 47.59 ± 3.21	Chaihujialungguomuli-Tang (柴胡加龙骨牡蛎汤)	bid, 4 wk	Anti-arrhythmia medication	1. TER
Huang 2005[25]	Arrhythmia	1. 120 (60:60) 2. 120 (60:60)	N/A	Sicai-Tang (四参汤)	tid	Conventional Western medicine for arrhythmia	1. TER, 2. HR
Li 2004[26]	Arrhythmia	1. 80 (42:38) 2. 80 (42:38)	46	Wenxinkeli (稳心颗粒)	tid, 2 wk	Propafenone 150 mg	1. TER
Li 2016[27]	Arrythmia	1. 60 (30:30) 2. 60 (30:30)	T: 61.93 ± 9.51 C: 60.50 ± 9.96	Qingrehuatananshen-Fang (清热化痰安神方)	bid 4 wk	Betaloc 12.5–25 mg, bid, 14 d	1. TER; 2. HR; 3. Number of PVC; 4. LFT (ALT, AST)
Chen 2012[28]	Arrhythmia	1. 140 (70:70) 2. 140 (70:70)	T: 66.4 ± 7.9 C: 64.8 ± 8.1	Cansongyangxinjiaonang (参松养心胶囊)	tid, 4 wk	Methotrexate 100 mg, bid, 4 wk	1. TER
Xueyuan 2013[29]	Arrhythmia	1. 300 (150:150) 2. 300 (150:150)	58	Zhigancaozhongyao-Tang (炙甘草中药汤)	bid, 2 wk	Propafenone, mexiletine, and betaloc	1. TER
Shi 2018[30]	Arrhythmia	1. 90 (45:45) 2. 90 (45:45)	T: 65.21 ± 2.53 C: 65.21 ± 2.53	Yangxin-Tang (养心汤)	bid, 4 wk	(Diuretics) spironolactone 20–80 mg/d; (angiotensin receptor antagonists) valsartan dispersible tablets 40–120 mg/d; (nitrates) isosorbide mononitrate	1. TER, 2. Blood Pressure
Shu 2016[31]	Arrythmia (Heart energy deficiency)	1. 50 (25:25) 2. 50 (25:25)	T: 51 ± 8.6 C: 52 ± 9.1	Wuweizi-Tang (五味子汤)	tid, 2 wk	Amiodarone 200 mg, tid, 2 wk	1. TER
Danqian 2008[32]	Arrhythmia	1. 100 (50:50) 2. 100 (50:50)	T: 57.3 ± 11.70 C: 55.8 ± 13.20	Wenxinkeli (稳心颗粒)	tid, 4 wk	Propafenone 150 mg, tid, 4 wk	1. TER, 2. Blood Test (TC, LDL)
Wang 2011[33]	Arrhythmia (timidity due to deficiency of heart qi)	1. 68 (34:34) 2. 68 (34:34)	T: 45.79 ± 14.01 C: 45.38 ± 12.84	Zhenxin-dan (镇心丹)	tid, 4 wk	Mexiletine 150 mg, tid, 4 wk	1. TER, 2. Holter, 3. Urinary test, LFT, RFT
Wang 2015[34]	Arrhythmia	1. 160 (80:80) 2. 160 (80:80)	T: 64.5 C: 65.5	Zhigancao-Tang (炙甘草汤)	qid, 2 wk	Bradycardia: lidocaine and amiodarone Premature atrial contraction: diazepam, propranolol, amiodarone, and oryzanol Fibrillation: digoxin, cediline, and diuretics	1. TER
Wang 2017[35]	Arrhythmia	1. 100 (50:50) 2. 100 (50:50)	57.5	Zhigancao-Tang jiajian (炙甘草汤加减)	bid, 2 wk	Metoprolol 6.25 mg, bid, 2 wk	1. TER
Zhang 2001[36]	Arrhythmia	1. 80 (48:32) 2. 80 (48:32)	T: 47.3 C: 47.8	Xinjiningjiaonang (心疾宁胶囊)	3 g tid, 4 wk	Propranolol 10 mg, tid, 4 wk	1. TER, 2. HRV
Zhang 2007[37]	Arrhythmia (timidity due to deficiency of heart qi)	T: 201(101:100) C: 201(101:100)	46.0 ± 13.8	Pinglufu-Fang (平律复方)	20 mL, tid, 2 wk	Propafenone 50 mg, tid, 2 wk	1. TER
Zhang 2014[38]	Arrhythmia	1. 80 (40:40) 2. 80 (40:40)	T: 39.7 ± 16.4 C: 41.5 ± 17.1	Canweifumai-Tang (参味复脉汤)	bid, 4 wk	Amiodarone 0.4–0.6 g (d)	1. TER

(*Continued*)

Table 1

(*Continued*)

Stud ID	Disease	Sample size (TG:CG) 1. Initial 2. Final	Age (yr) mean ± SD or range	Experimental group (Herbal Medicine)	Frequency and total treatment duration	Control group	Outcome measurements
Zhang 2018[39]	Arrhythmia	1. 100 (50:50) 2. 100 (50:50)	69.32 ± 7.65	Guizhigancaolonggumuli-Tang jiajian (桂枝甘草龙骨牡蛎汤加减)	bid, 30 d	Amiodarone, tid, 30 d	1. TER
Zhang 2020[40]	Arrhythmia	1. 90 (45:45) 2. 90 (45:45)	T: 51.63 ± 8.05 C: 51.47 ± 8.29	Guipi-Tang (归脾汤)	bid, 30 d	Potassium and magnesium aspartate propafenone, betaloc (not specific)	1. TER
Zhao 2019[41]	Arrhythmia	1. 112 (58:54) 2. 112 (58:54)	T: 55.67 ± 5.63 C: 56.34 ± 3.88	Baoxinfulu-Tang (保心复律汤)+Betaloc 12.5 mg	bid, 2 wk	Betaloc 12.5 mg, bid, 2 wk	1. TER
Zhou 2016[42]	Sinus bradycardia	1. 54 (29:25) 2. 54 (29:25)	T: 54.1 ± 1.9 C: 55.8 ± 1.5	Zhigancao-Tang (炙甘草汤)	bid, 1 mo	Atropine 0.3 mg, tid, 1 mo	1. TER
PVC							
Bo 2009[43]	PVC	1. 100 (50:50) 2. 100 (50:50)	56.2	Wenlu-Tang (稳律汤)	tid 21 d	Propafenone 150 mg tid, 21 d	1. TER; 2. 24 Holter-Number of PVC
Hua 2015[44]	PVC	1. 1200 (600:600) 2. 1072 (536:535)	T: 53.7 ± 12.2 C: 53.9 ± 11.8	Wenlu-Tang (稳律汤)	9 g/each, tid, 4 wk	Placebo	1. ECG, 2. Holter
Lai 2015[45]	PVC	1. 80 (40:40) 2. 80 (40:40)	T: 51.4 ± 6.9 G: 52.2 ± 7.3	Wuweizi-Tang (五味子汤)	bid, 2 wk	Amiodarone 0.2 g tid, 2 wk	1. TER, 2. Number of PVC
Li 2000[46]	PVC	1. 164 (86:78) 2. 164 (86:78)	T: 46 ± 6.8 C: 56 ± 5.7	Jiawei-Zhigancao-Tang (加味炙甘草汤)	tid, 4 wk	Ethmozine 200 mg, tid, 4 wk	1. TER
Li 2010[47]	PVC	1. 75(45:30) 2. 72(44:28)	T: 53.6 ± 10.5 C: 52.8 ± 12.8	Yixin-Fang (益心方)	qid 3 mo	Amiodarone 200 mg, bid, 14 d -> 100 mg, bid, 3 mo	1. TER; 2. HR; 3. Holter - Number of PVC; 4. PR time (ms), QRS time (ms), QTC time (ms)
Li 2014[48]	PVC	1. 60 (30:30) 2. 60 (30:30)	T: 66.7 ± 5.5 C: 67.6 ± 5.6	Zhongyao-Fufang-Tang (中药复方汤) + Amiodarone 0.2 g	bid, 4 wk	Amiodarone 0.2 g, bid, 4 wk	1. TER, 2. ECG
Li 2018[49]	PVC (Qi deficiency and phlegm and blood stasis type)	1. 62 (31:31) 2. 59 (30:29)	T: 55.73 ± 10.84 C: 55.93 ± 11.13	Diaoluningji-Tang (调律宁悸汤)	bid 2 wk	Metoprolol 47.5 mg, qid, 2 wk	1. Holter, 2. TER
Li 2020[50]	PVC (Qi and Yin deficiency)	1. 86 (43:43) 2. 83 (41:42)	T: 53.68 ± 13.845 C: 54.74 ± 15.177	Shengmai-yinjiawei (生脉饮加味)	bid, 4 wk	Metoprolol 47.5 mg, qid, 4 wk	1. TER; 2. Holter; 3. LFT, RFT
Liang 2020[51]	PVC	1. 144 (76:68) 2. 136 (71:65)	T: 62 ± 11 C: 63 ± 12	Danggui-fumai-Tang (當歸復脈湯) + Metoprolol 12.5 mg	tid, 12 wk	Metoprolol 12.5 mg + Placebo	1. TER, 2. Holter
Zhao et al 2019[52]	PVC	1. 72 (36:36) 2. 72 (36:36)	T: 46.32 ± 12.84 C: 49.87 ± 9.12	Yangxintongmai-Fang (养心通脉方)	qid, 2 wk	Western medicines for cardiovascular disease	1. TER, 2. ECG
Wang 2011[53]	PVC	1. 100 (50:50) 2. 100 (50:50)	T: 55.35 ± 2.24 C: 55.22 ± 2.15	Wenxinkeli (稳心颗粒)	tid, 4 wk	Propafenone 150 mg	1. TER; 2. Blood Test; 3. Number of PVC
Wang 2015[54]	PVC (Yin asthenia causing fire type)	1. 60 (30:30) 2. 60 (30:30)	T: 54.4 ± 8.31 C: 54.6 ± 7.41	Ziyinqinghuodingji-Fang (滋阴清火定悸方)	tid, 4 wk	Propafenone 100 mg, tid, 4 wk	1. TER, 2. LFT
Wang 2016[55]	Senile ventricular arrhythmia	1. 84 (42:42)x 2. 84 (42:42)	61.53 ± 10.26	Zhigancao-Tangkeli (炙甘草汤颗粒)	9 g, tid, 4 wk	Amiodarone 200 mg, qid, 4 wk	1. TER, 2. HR
Wang 2019[56]	PVC (deficiency of Qi and Yin)	1. 100 (50:50) 2. 100 (50:50)	N ± A	Dingxin-Fang (定心方)	bid, 4 wk	Mexiletine 50 mg 4 tablets, tid, 4 wk	1. TER, 2. Holter - Number of PVC
Wang 2021[57]	PVC	1. 107 (56:51) 2. 107 (56:51)	T: 67.38 ± 8.74 C: 66.59 ± 9.25	Yangxindingjijiaonang (养心定悸胶囊)	6 tablet each, qid, 1 mo	Amiodarone 600 mg for 1st 5 d and reduce 200 mg, tid metoprolol tartrate 25 mg, bid	1. TER, 2. Holter

(*Continued*)

Table 1

(*Continued*)

Stud ID	Disease	Sample size (TG:CG) 1. Initial 2. Final	Age (yr) mean ± SD or range	Experimental group (Herbal Medicine)	Frequency and total treatment duration	Control group	Outcome measurements
Xia 2019[58]	PVC	1. 60 (30:30) 2. 60 (30:30)	T: 87.60 ± 1.77 C: 87.53 ± 1.74	Bailing-jiaonang (百令胶囊) + Bisoprolol 2.5 mg	3 tablet each, tid, 1 mo	Bisoprolol 2.5 mg, qid, 1 mo	1. TER, 2. Number of PVC
Xu 2016[59]	PVC	1. 60 (30:30) 2. 60 (30:30)	T: 35.73 ± 6.92 C: 34.47 ± 7.31	Shuganxiehuo-Fang (疏肝泻火方)	bid, 4 wk	Betaloc 23.75 mg, 4 wk	1. TER, 2. Holter—Number of PVC
Yin 2017[60]	PVC (Qi and Yin deficiency)	1. 40 (20:20) 2. 40 (20:20)	T: 62.5 ± 17.47 C: 63.5 ± 16.49	Fufang-guanbaifu-Tang (复方关白附汤)	qid, 4 wk	Metoprolol 47.5 mg, qid, 4 wk	1. TER, 2. Holter—Number of PVC
Zou 2011[61]	PVC	1. 188 (96:92) 2. 173 (89:84)	T: 44.70 ± 14.77 C: 45.17 ± 13.18	Cansongyangxinjiaonang (参松养心胶囊) + Mexiletine 450 mg	4 capsule tid, 8 wk	Mexiletine 450 mg	1. ECG; 2. Holter; 3. TER
Sinus bradycardia							
Chen 2012[28]	Sinus bradycardia	1. 86 (43:43) 2. 86 (43:43)	T: 64.99 ± 10.44 C: 64.84 ± 6.31	Zenglufumai-Tang (增率复脉汤)	tid, 3 wk	Placebo	1. TER, 2. ECG
Guo 2013[62]	Sinus bradycardia	1. 60 (30:30) 2. 60 (30:30)	T: 54 ± 5.6 C: 55 ± 5.2	1.Xuefuzhuyu-Tang (血府逐瘀汤) 2. Wendantang-he-guaweijianbaibanxia-Tang (温胆汤合瓜蒌建白半夏汤) 3. Shengmaisan-he-renshenyangying-Tang (生脉散合人参养营汤) 4. Canfutang-he-youguiyin (参附汤合右归饮)	tid 5 wk	Atropine 0.3 mg, tid 5 wk	1. Resting HR; 2. Average HR; 3. Slowest HR
Huang 2018[63]	Sinus bradycardia	1. 72 (36:36) 2. 72 (36:36)	N/A	Yiqishugan-Fang (益气疏肝方)	bid, 4 wk	Atropine 0.3 mg, tid, 4 wk	1. TER, 2. HR
Li 2014[64]	Sinus bradycardia	1. 84 (42:42) 2. 84 (42:42)	T: 55 C: 54.5	Yiqishenglu-Tang (益氣升率湯)	bid, 4 wk	Albuterol 2 mg, Atropine 0.3 mg, Q10 10 mg, tid, 4 wk	1. TER, 2. HR, 3. ECG (PR time, QRS time)
Li 2019[65]	Sinus bradycardia	1. 60 (40:20) 2. 60 (40:20)	T: 63.93 ± 7.09 C: 64.20 ± 6.34	Canxianshengmaikoufu-Tang (参仙升脉口服汤)	bid, 12 wk	Placebo	1. Holter
Lin 2015[66]	Sinus bradycardia (blood deficiency type)	1. 60 (30:30) 2. 60 (30:30)	T: 50.7 ± 11.14 C: 51.5 ± 10.1	Shengyu-Tang (圣愈汤)	bid 2 wk	Salbutamol 2.4 mg, tid,	1. TER
Liu 2014[67]	Sinus bradycardia	1. 219 (124:117) 2. 241 (115:104)	N/A	Cansongyangxinjiaonang (参松养心胶囊)	tid, 4 wk	Placebo	1. TER; 2. ECG; 3. Lab Test
Shi 2019[68]	Sinus bradycardia	1. 100 (50:50) 2. 100 (50:50)	T: 56.71 ± 2.13 C: 56.50 ± 2.12	Yangxin-Tang (养心汤)	bid, 4 wk	Atropine 0.3 mg, tid, 4 wk	1. TER
Wang 2011[69]	Sinus bradycardia (Yang deficiency and blood statsis)	1. 99 (66:33) 2. 99 (66:33)	N ± A	Mahuangfuzixixin-Tang (麻黄附子细辛汤加减)	bid, 4 wk	Atropine 0.3 mg tid, 4 wk	1. TER, 2. Holter - Total beat
Wei 2015[70]	Sinus bradycardia	1. 80 (40:40) 2. 80 (40:40)	86.4 ± 7.2	Xinbao pill (心宝丸)	10 tablet each, tid, 12 wk	Placebo	1. TER
Yang 1999[71]	Sinus bradycardia	1. 82 (42:40) 2. 82 (42:40)	T: 49.2 ± 12.6 C: 48.6 ± 11.7	Traditional Chinese Medicine	tid, 1 mo	Atropine 0.6 mg, tid, 1 mo	1. TER, 2. HR

(*Continued*)

Table 1

(*Continued*)

Stud ID	Disease	Sample size (TG:CG) 1. Initial 2. Final	Age (yr) mean ± SD or range	Experimental group (Herbal Medicine)	Frequency and total treatment duration	Control group	Outcome measurements
Yang 2017[72]	Sinus bradycardia	1. 64 (32:32) 2. 64 (32:32)	T: 49.7 ± 7.1 C: 51.9 ± 6.7	Xinbao pill (心宝丸)	tid, 12 wk	Atropine 0.5–1 mg, tid 12 wk	1. TER
Yao 2000[73]	Sinus bradycardia	1. 41 (21:20) 2. 41 (21:20)	T: 61 ± 6.1 C: 60 ± 5.2	Wenshenhuoxie-Zhongyao (温肾活血中药)	bid, 1 mo	Relevant Western drug (not specific)	1. TER, 2. HR
Yu 2013[74]	Sinus bradycardia	1. 120 (60:60) 2. 120 (60:60)	T: 54.1 ± 2.6 C: 52.8 ± 7.3	Xinbao pill (心宝丸)	3 tablets each, tid, 3 mo	Atropine 0.3 mg, tid, 3 mo	1. TER, 2. HR
Zhan 2013[75]	Sinus bradycardia	1. 60 (30:30) 2. 60 (30:30)	T: 65.17 ± 5.21 C: 68.5 ± 5.32	Zhigancao-Tang (炙甘草汤)	4 wk	Amiodarone 200 mg, tid, 4 wk	1. TER; 2. HR; 3. QT time
Zhang 2012[76]	Sinus bradycardia	1. 96 (48:48) 2. 96 (48:48)	T: 55 ± 7.0 C: 56 ± 7.2	Traditional Chinese Medicine (No name)	3 mo	Group 1 Adenosine triphosphate 20 mg 3 times/d Group 2 Aspirin 25 mg 3 times/d isosorbide mononitrate 10 mg 3 times/d captopril, 12.5 mg 3 times/d	1. TER, 2. Holter
Zhang 2016[77]	Sinus bradycardia	1. 50 (25:25) 2. 50 (25:25)	T: 55 C: 54	Cansongyangxinjiaonang (参松养心胶囊)	qid, 15 d	Atropine (Muscle Injection/if HR < 40/min) Observation (if HR > 50/min)	1. TER
Zhang 2019[78]	Sinus bradycardia	1. 333 (167:166) 2. 303 (147:156)	T: 56.2 ± 12.2 C: 57.2 ± 11.3	Cansongyangxinjiaonang (参松养心胶囊)	4 tablet each, tid, 8 wk	Placebo	1. ECG; 2. HR; 3. Blood Test
Zhao 2019[52]	Sinus bradycardia	1. 76 (57:19) 2. 76 (57:19)	T: 55.312 G: 53.9	Fudingzhaomai-Tang (扶正助脉方)	bid, 45 d	Atropine 0.3 mg, tid, 45 d	1. TER, 2. HR
Zhu 2014[79]	Sinus bradycardia	1. 100 (50:50) 2. 100 (50:50)	T: 52.2 ± 5.6 C: 51.8 ± 6.3	Xinbao pill (心宝丸)	240 mg, tid, 3 mo	atropine 0.3 mg, tid, 3 mo	1. TER, 2. HR
Tachycardia							
Hou 2018[80]	Tachycardia	T: 60 (30:30) C: 60 (30:30)	T: 60.10 ± 14.01 C: 62.87 ± 11.75	Ningjikeli (宁悸颗粒) 25 mg + Metoprolol 12.5 mg	bid, 4 wk	Placebo	1. TER; 2. Frequency; 3. HRV
Li 2008[81]	Tachycardia	1. 122 (62:60) 2. 122 (62:60)	T: 43.2 C: 49.2	Yiqishengmai-Tang (益气生脉汤)	tid, 12 wk	Mexiletine 150–250 mg, tid, 4 wk	1. TER
Liang 2008[82]	Tachycardia	1. 60 (30:30) 2. 60 (30:30)	T: 48.1 ± 13.1 C: 51.9 ± 15.0	Pingxindingji-Tang (平心定悸汤)	bid, 1 mo	Propafenone 150 mg tid, 1 mo	1. TER
Tao 2012[83]	Tachycardia	1. 95 (48:47) 2. 95 (48:47)	T: 40.6 ± 3.8 C: 39.2 ± 3.3	Qinggandingji-Tang (清肝定悸汤) 200 mL + Metoprolol 12.5 mg	bid, 4 wk	Metoprolol 12.5 mg	1. TER
Wei 2011[84]	Tachycardia	1. 60 (30:30) 2. 60 (30:30)	T: 54.3 ± 17.61 C: 52.93 ± 15.55	Cansongyangxinjiaonang (参松养心胶囊) + Mexiletine	Cansongyangxinjiaonang(参松养心胶囊) 4ea, tid Mexiletine 150 mg, tid 8 wk	Mexiletine 150 mg, tid, 8 wk	1. TER, 2. HR,3. ECG, 4. HRV
Xu 2009[85]	Tachycardia	1. 68 (38:30) 2. 68 (38:30)	T: 53.1 C: 53.7	Kucanpingxin-Tang (苦参平心汤)	bid, 4 wk	Propafenone	1. TER; 2. HR; 3. ECG
Yan 2005[86]	Tachycardia	1. 180 (120:60) 2. 180 (120:60)	T: 50.30 ± 14.37 C: 51.43 ± 13.46	Fulu-yin (复律饮)	tid, 2 wk	Propafenone 150 mg	1. TER
Yang 2018[87]	Tachycardia (Qi and Yin deficiency)	1. 80 (40:40) 2. 80 (40:40)	T: 54.92 ± 8.45 C: 54.19 ± 8.66	Pingxindingji-Tang (平心定悸汤)	bid, 16 wk	Propafenone 100–200 mg	1. TER
Zhang 2019[88]	Tachycardia	1. 78 (39:39) 2. 78 (39:39)	T: 54.26 ± 7.22 C: 54.48 ± 7.18	Sicanyinyansheng-Fang (四参饮衍生方) +atenolol 12.5 mg	bid, 1 mo	Atenolol 12.5 mg, bid, 4 wk	1. TER; 2. HRV; 3. BP

(*Continued*)

Table 1

(*Continued*)

Stud ID	Disease	Sample size (TG:CG) 1. Initial 2. Final	Age (yr) mean ± SD or range	Experimental group (Herbal Medicine)	Frequency and total treatment duration	Control group	Outcome measurements
AF							
Cui 2021[89]	AF (kidney deficiency and blood stasis type)	T: 65 (33:32) C: 65 (33:32)	T: 61.91 ± 10.85 C: 60.38 ± 9.25	Guzhifulingwanjiajian (桂枝茯苓丸加减)	4 wk	Metoprolol 23.75 mg, qid, 4 wk Warfarin 1.5 mg, qid, 4 wk	1. TER, 2. HR, 3. IL-6
Li 2006[90]	AF	1. 106(46:30:30) 2. 106 (46:30:30)	62.8	Zhigancao-Tang (炙甘草汤) + amiodarone	150 mg tid 7 d -> 150 mg qd 3 mo	Amiodarone 200 mg, tid, 7 d -> 200 mg, qid, 7 d	1. TER
Li 2012[91]	AF	1. 60 (30:30) 2. 60 (30:30)	T: 54.80 ± 7.52 C: 55.60 ± 5.54	Yangxinfumai-Tang (养心复脉汤)	Bid	Standard Western Medicine Treatment	1. TER; 2. HR (Average); 3. HR (24h); 4. Size of LV
Liang 2014[92]	AF	1. 84 (42:42) 2. 84 (42:42)	71.31 ± 7.91	Changhuwendan-tang (菖琥温胆汤)	bid 1 mo	Metoprolol, 1 mo	1. TER
Yang 2017[93]	AF (qi and yin deficiency)	1. 70 (35:35) 2. 65 (35:30)	T: 55.83 ± 6.5 C: 57.07 ± 6.5	Jiaweidingxin-Tang (加味宁心汤) + amiodarone	bid, 6 mo	Amiodarone 0.2 g tid -> (5 d after bid)-> (5 d after qid), 6 mo	1. TER, 2. HR
Wang 2010[94]	AF	1. 70 (35:35) 2. 70 (35:35)	T: 61.3 ± 5.4 C: 63.1 ± 6.2	Fumaikeli (复脉颗粒)	tid, 3 wk	Amiodaron 200 mg tid (1st week)-> bid (2nd week) -> qid (3rd week)	1. TER
Wang 2011[95]	AF	1. 205 (106:99) 2. 205 (106:99)	T: 58.0 ± 12 C: 63.0 ± 9	Cansongyangxinjiaonang (参松养心胶囊) + Propafenone	4 tablet each, tid, 8 wk	Propafenone	1. TER
Wang 2017[96]	AF	1. 60 (30:30) 2. 59 (29:30)	T: 51.6 ± 10.30 C: 50.9 ± 10.36	Canguihuxin-Tang (参桂护心湯) + Ammonium hydrochloride 200 mg	tid, 4 wk	Ammonium hydrochloride 200 mg (1st week) -> 100 mg (other wk), tid, 4 wk	1. ECG; 2. HR; 3. Blood Test (PT, APTT)
Wang 2019[97]	AF	1. 60 (30:30) 2. 60 (30:30)	N ± A	Dingxin-Fang (定心方)+WM	bid, 4 wk	WM	1. TER, 2. HR
Xiao 2021[98]	AF	1. 110 (55:55) 2. 110 (55:55)	T: 52.56 ± 8.92 C: 52.84 ± 8.37	Cansongyangxinjiaonang (参松养心胶囊)	4 tablet each, tid, 6 mo	Low-dose antiarrhythmic drugs and anticoagulants (not specific)	1. Frequency
Xu 2019[99]	AF (Qi stagnation and blood stasis)	1. 66 (33:33) 2. 66 (33:33)	T: 64.97 ± 5.987 C: 64.91 ± 7.195	Dingxindingjijiaonang (宁心定悸胶囊)	0.4 g *3 capsule, tid, 4 wk	Metoprolol 47.5 mg, qid, 4 wk	1. TER; 2. Average HR; 3. INR
Zhang 2018[100]	AF	1. 41 (20:21) 2. 41 (20:21)	T: 71 ± 12 C: 72 ± 13	Wenxinkeli (稳心颗粒)	Wenxinkeli (稳心颗粒) 9 g/each + amiodarone 200 mg, tid, 4 wk	Amiodarone 200 mg, tid, 4 wk	1. TER, 2. ECG, 3. Holter, 4. SONO
Zhuang 2018[101]	AF (qi and yin deficiency and blood stasis syndrome)	1. 60 (30:30) 2. 60 (30:30)	T: 26.73 ± 15.16 C: 24.37 ± 11.18	Dingxin-Fang (定心方)	bid, 4 wk	Metoprolol 23.75 mg, qid, 4 wk	1. TER, 2. Holter - Total beat

AF = atrial fibrillation, C = control group, ECG = electrocardiogram, HR = heart rate, HRV = heart rate variability, LV = left ventricle, N/A = not applicable, N/S = no specific events reported, NR = not reported, PVC = premature ventricular contraction, SONO = sonography, T = treatment group, TER = total effective rate.

3.2. Characteristics of the included studies

All clinical studies were published in China. The general characteristics of the included studies are summarized in Table 1.

3.2.1. Included disease. Of the 82 studies, 20 were conducted without categorizing specific arrhythmias using the word "arrhythmia." In the remaining studies, 13 had AF or paroxysmal AF, 21 had bradycardia arrhythmia or sinus bradycardia, 9 had rapid arrhythmia or tachyarrhythmia, and 19 had ventricular arrhythmia or premature ventricular contractions (Table 1).

3.2.2. Interventions. Fifteen studies used a combination therapy group (THM and WM) and the control as the WM alone group. In the 59 RCTs, the THM-alone group (treatment group) was compared with the WM-alone group (control group). Eight studies compared the THM and WM groups with the Placebo THM and WM groups. Regarding conventional medications, propafenone was used in 14 RCTs, amiodarone in 13, atropine in seven, beta-blockers in five, mexiletine in six, salbutamol in one, ethmozine in one, and methotrexate in one. Six studies did not mention specific WM drugs in the control group and only mentioned that they used standard treatments. Detailed information on the herbal prescriptions, treatment duration, and composition of the herbal medicines is shown in Supplementary 2A, Supplemental Digital Content, http://links.lww.com/MD/M752 and 2B, Supplemental Digital Content, http://links.lww.com/MD/M753. The most frequently used medicinal herb for arrhythmia treatment was Ophiopogonis Radix (Maidong, 麦冬, 64 times), Radix Astragali (Huangqi, 黄芪, 32 times), Ginseng Radix et Rhizoma (Renshen, 人蔘, 32 times), Salviae Miltiorrhizae Radix et Rhizoma (Danshen, 丹参, 32 times), Glycyrrhizae Radix et Rhizoma Praeparata cum Melle (Zhigancao, 炙甘草, 29 times), and Schisandrae Fructus (Wuweizi, 五味子, 27 times).

3.2.3. Treatment regimen. Of the 78 studies in which dose information was specified, 35 reported doses 3 times per day (TID), 37 twice per day (bid), and six four times per day (QID). Among the 79 studies, 2 weeks were adopted in 13 RCTs, 3 weeks in 3 RCTs, 1 month in 44 RCTs, 1–2 months in 2 RCTs, 2 months in 4 RCTs, and 3 months in 10 RCTs. One study implemented treatments for 16 weeks (4 months), and 2 studies used treatments for 6 months (Table 1).

3.2.4. Applied outcomes. TER was the most common clinical outcome variable (77 RCTs) and HR (26 RCTs). Among studies that used Holter electrocardiography, 13 measured the number of premature ventricular contractions (PVC). Among the studies using electrocardiography, 7 measured PR time, 5 measured QRS time, and 8 measured QTc time. Three studies measured the total HR over 24 hours, and 1 study measured the size of the left ventricle using ultrasound. Three studies measured HR variability, 2 measured tachycardia, and one measured general arrhythmia (Table 1).

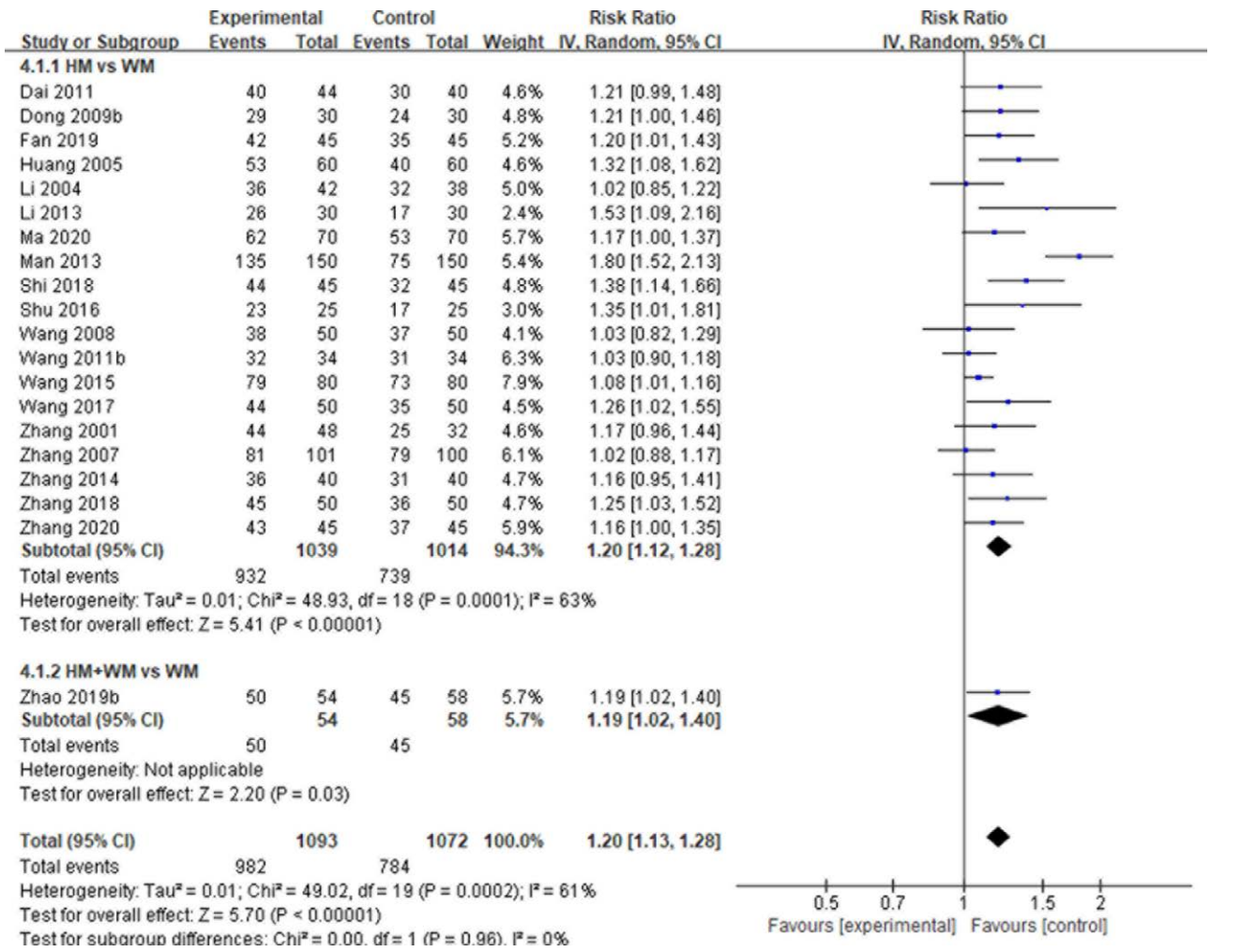

Figure 2. Meta-analysis of TER on patients with arrhythmia between the intervention and control groups. HM = herbal medicine, TER = total effective rate, WM = Western medicine.

3.3. Clinical effectiveness of herbal medicine in cardiac arrhythmia

TER was used as the primary outcome measure. To analyze the treatment effect, the literature was classified into separate diseases such as arrhythmia, sinus bradycardia, tachycardia, AF, and PVC. The results were classified by comparing the effects of HM + WM versus placebo HM + WM, HM + WM versus WM, and HM versus WM.

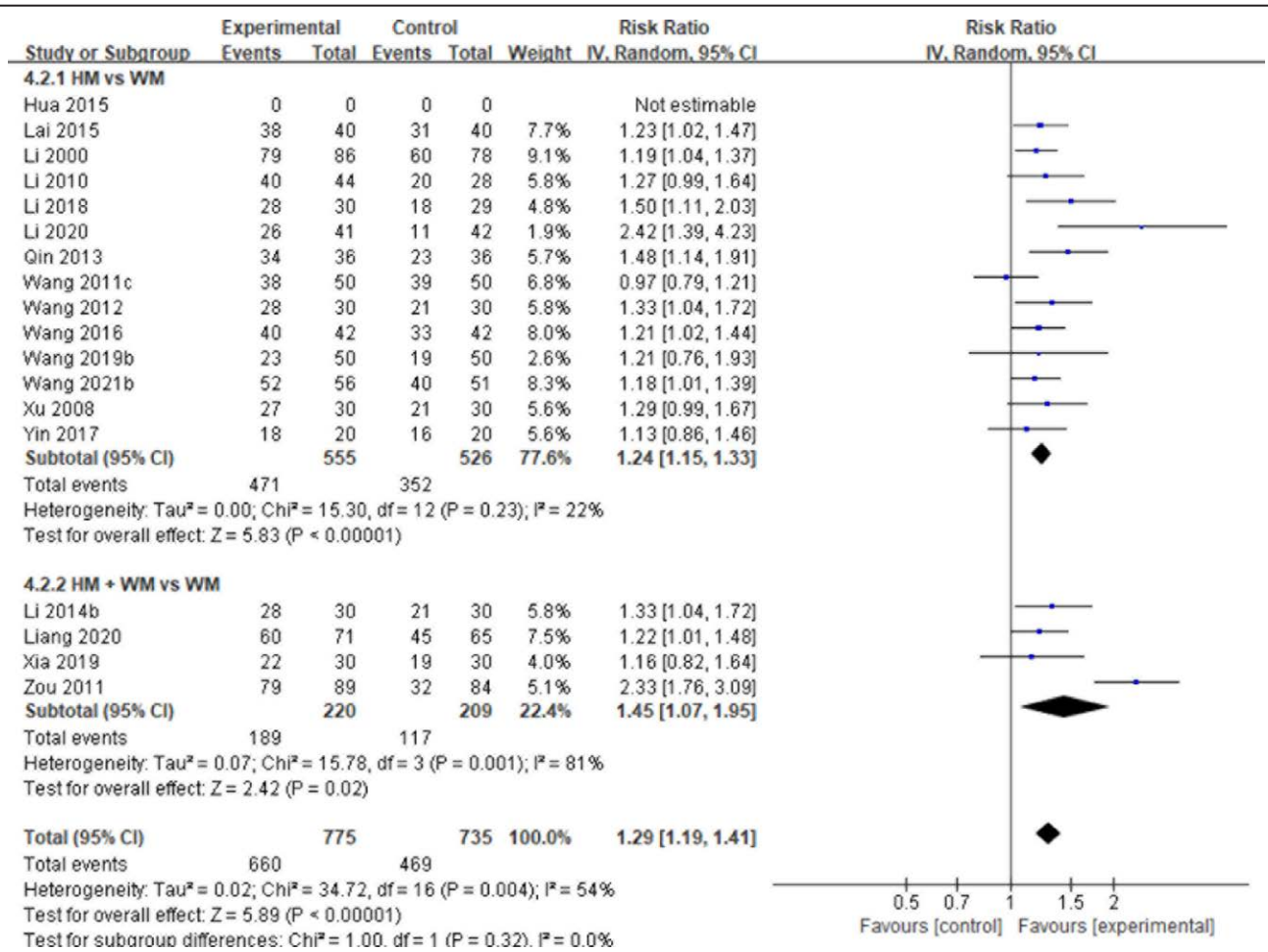

Figure 3. Meta-analysis of TER on patients with PVC between the intervention and control groups. HM = herbal medicine, PVC = premature ventricular contraction, TER = total effective rate, WM = Western medicine.

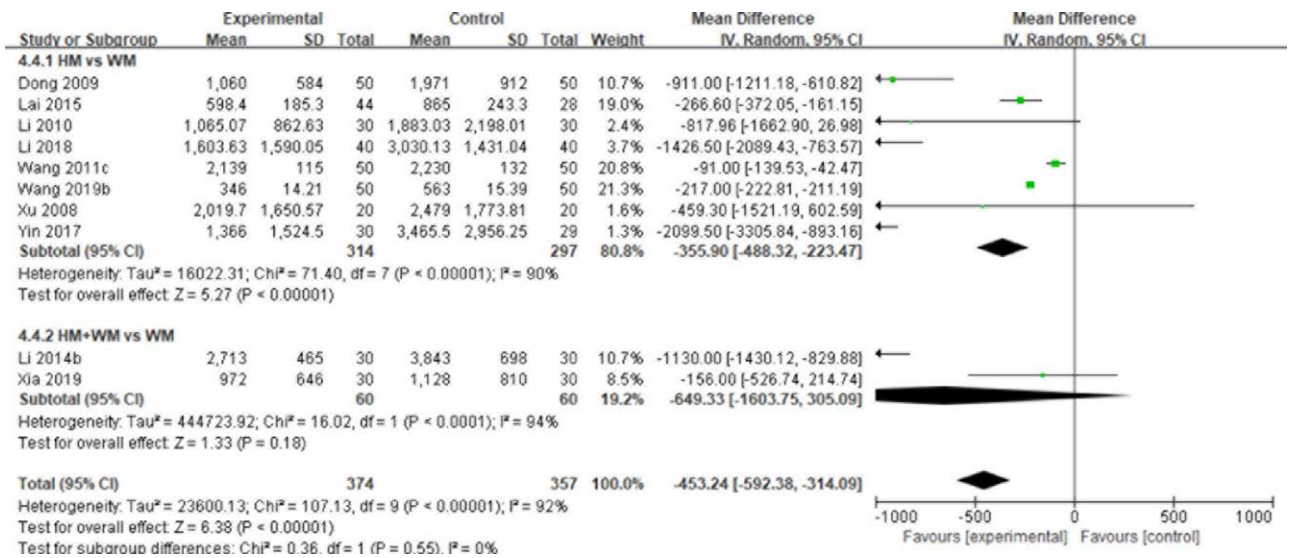

Figure 4. Meta-analysis of the number of PVC on patients with PVC between the intervention and control groups. HM = herbal medicine, PVC = premature ventricular contraction, WM = Western medicine.

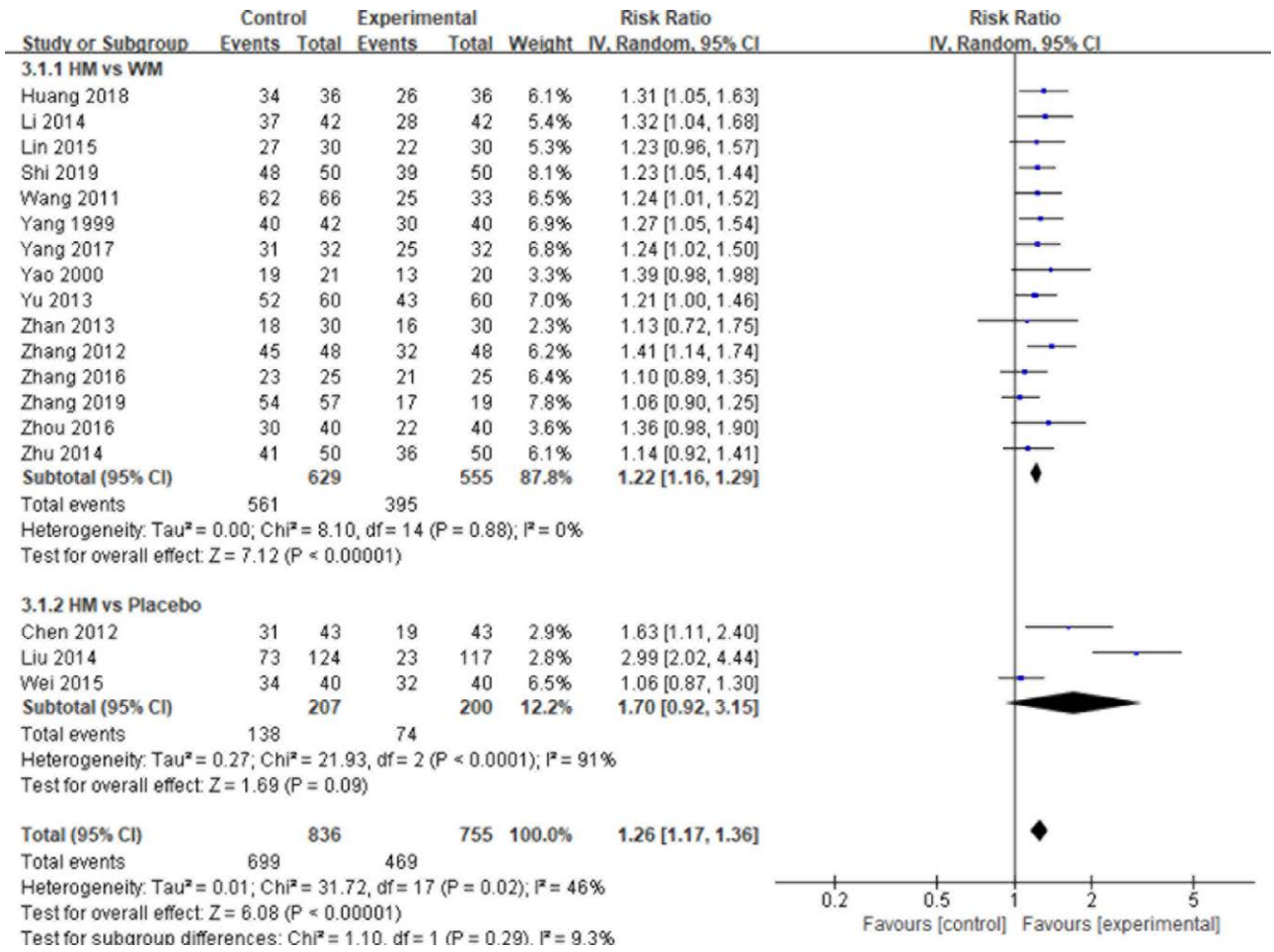

Figure 5. Meta-analysis of TER on patients with sinus bradycardia between the intervention and control groups. HM = herbal medicine, TER = total effective rate, WM = Western medicine.

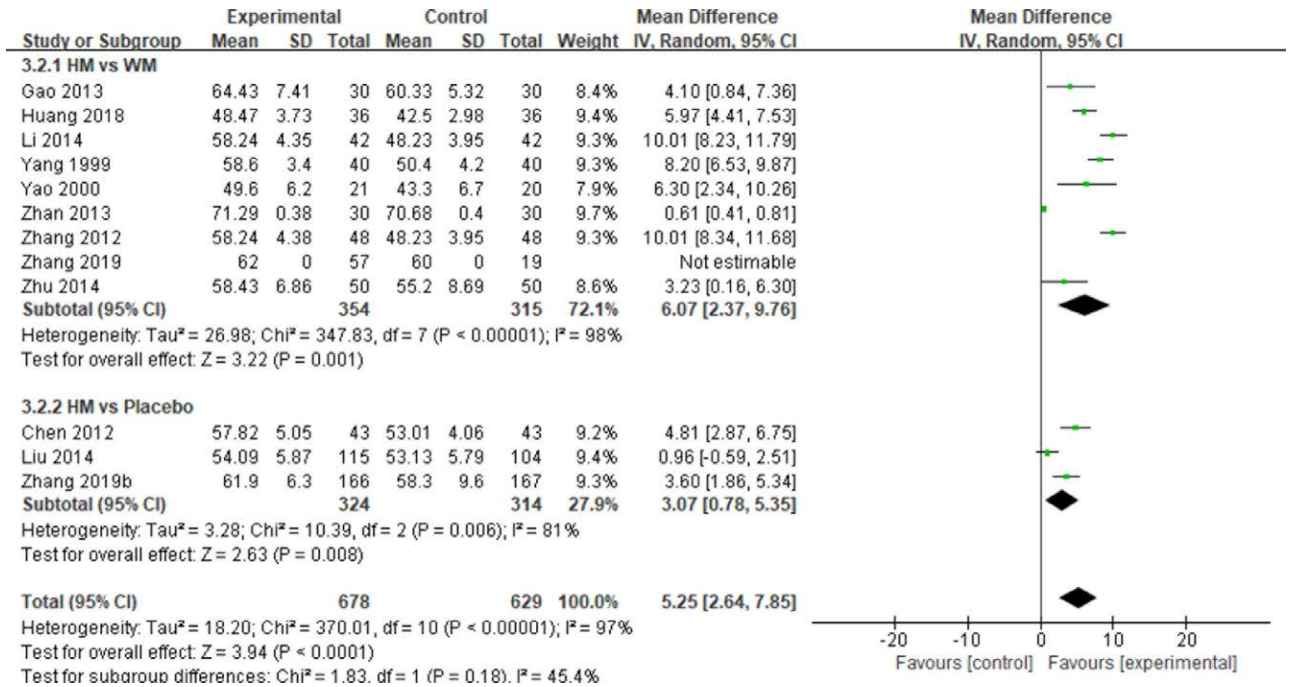

Figure 6. Meta-analysis of HR on patients with sinus bradycardia between the intervention and control groups. HM = herbal medicine, HR = heart rate, WM = Western medicine.

3.3.1. (Unspecified) arrhythmia. Among 20 RCTs for the unspecified arrhythmia subtype, the TER of the HM-only group or the HM + WM combined group was significantly higher than that of the WM group (RR: 1.20, 95% CI: 1.13–1.26, I^2 = 0%). In the HM versus WM design (19 RCTs), TER in the HM group was significantly higher than that in the WM group (RR: 1.20, 95% CI: 1.12–1.28). Only 1 study compared HM + WM with WM alone. The TER of the HM combined group was significantly higher than that of the WM group (RR: 1.20, 95% CI: 1.02–1.40) (Fig. 2). The meta-analysis results for HR are represented in Supplementary 3A, Supplemental Digital Content, http://links.lww.com/MD/M754.

3.3.2. Premature ventricular contractions. Among the 18 RCTs for PVC treatment, the TER of the HM-only group or the HM + WM combined group was significantly higher than that of the WM group (RR: 1.29, 95% CI: 1.15–1.33). In 14 RCTs comparing HM and WM, the TER was significantly higher in the HM group (RR, 1.24; 95% CI: 1.15–1.33). In the HM + WM versus WM alone group design (4 RCTs), the TER of the combined group was higher than that of the WM alone group (RR: 1.45, 95% CI: 1.07–1.95) (Fig. 3). The HR was not significantly different (Supplementary 3B, Supplemental Digital Content, http://links.lww.com/MD/M754).

In 10 RCTs, the number of PVC was measured using a 24-h Holter electrocardiogram. The HM group or HM + WM combined group showed fewer times on average than that of the WM group (MD: −453.24, 95% CI: −592.38 to −314.09) (Fig. 4). Liang 2020's study discussed only the average number of PVCs and did not provide the standard deviation; thus, they were excluded from the meta-analysis. In the HM versus WM design (8 RCTs), the number of PVCs was less than that in the WM group (MD: −355.90, 95% CI: −488.32 to −223.47). In the HM + WM versus the WM design, the difference was not significant.

3.3.3. Sinus bradycardia. Among the 18 studies targeting patients with bradycardia, the TER of the HM group was significantly higher than that of the WM group (15 RCTs) or the placebo HM group (3 RCTs) (RR: 1.26, 95% CI 1.17–1.36). In 15 RCTs comparing HM versus WM designs, the TER was higher in the HM group (RR, 1.22; 95% CI: 1.16–1.29). In the 3 RCTs using HM + WM versus placebo HM + WM designs, the TER was not significantly different (Fig. 5).

HR was measured in 12 RCTs among the 18 RCTs involving patients with bradycardia. The HR of the HM group was significantly higher than that of the WM group (6 RCTs) or the placebo HM group (3 RCTs). (MD: 5.25, 95% CI: 2.64–7.85). In 9 RCTs using the HM versus WM design, the HR was higher in the HM group than that in the WM group (MD: 6.07, 95% CI: 2.37–9.7). In 3 RCTs using HM + WM versus placebo HM + WM design, HR was higher in the HM group (MD: 3.07, 95% CI: 0.78–5.35) (Fig. 6).

3.3.4. Tachycardia. The overall meta-analysis of 9 RCTs revealed that HM treatment resulted in a higher TER than that in the control group (RR, 1.23; 95% CI: 1.15–1.32). In the HM versus WM group design (5 RCTs), the HM group showed a higher TER than that of the WM group (RR: 1.19, 95% CI: 1.09–1.29). In the case of the HM + WM versus WM group design (3 RCTs), TER was higher in the HM + WM group than that in the WM group (RR: 1.29, 95% CI: 1.12–1.48). In 1 study comparing HM + WM versus HM placebo + WM, the TER in the HM group was higher than that in the placebo HM group (RR: 1.86, 95% CI 1.24–2.79) (Fig. 7).

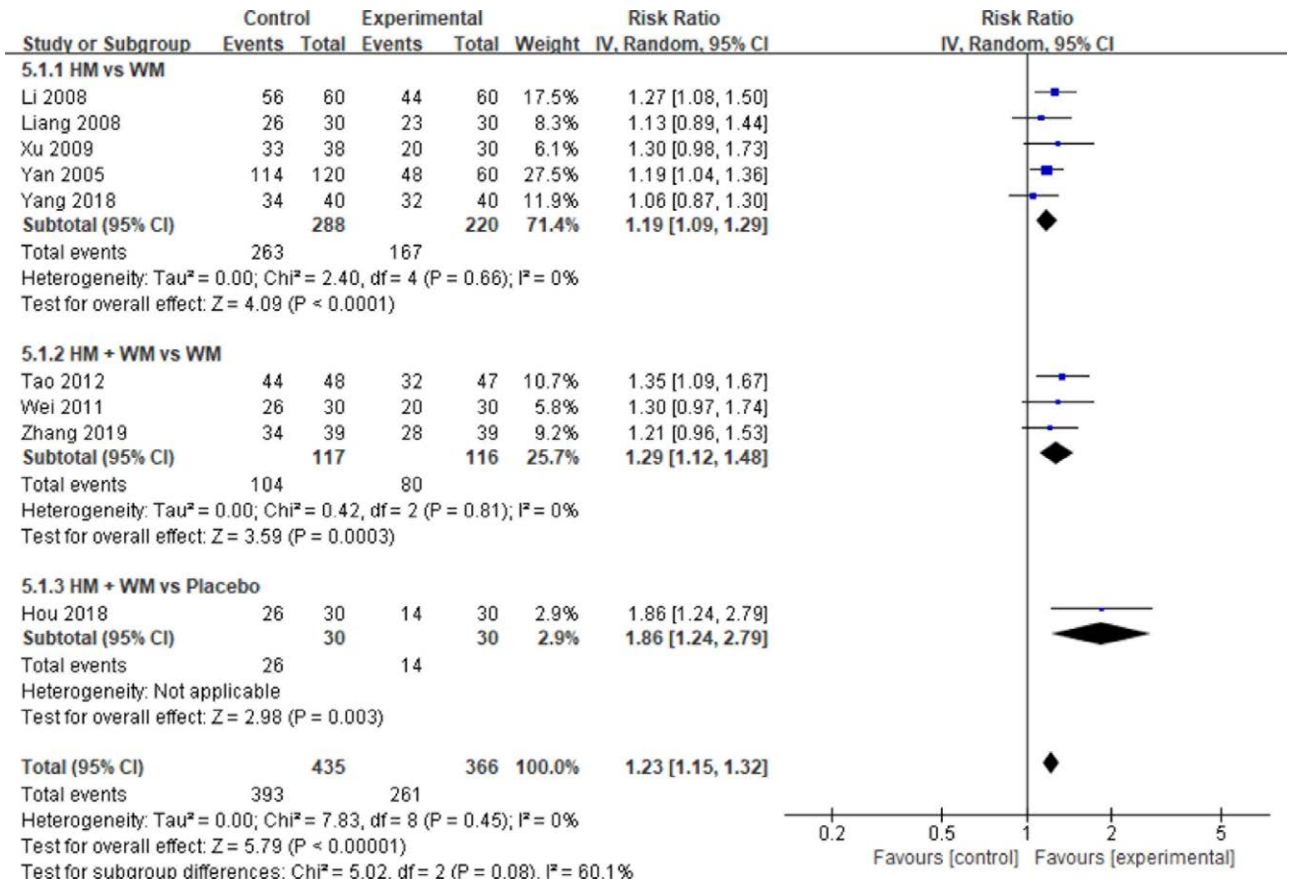

Figure 7. Meta-analysis of TER on patients with tachycardia between the intervention and control groups. HM = herbal medicine, TER = total effective rate, WM = Western medicine.

Outcome variables using electrocardiogram and HR variability, such as PR time, QT time, standard deviation of all NN intervals, and standard deviation of the averages of NN intervals, are represented in Supplementary 3C–G, Supplemental Digital Content, http://links.lww.com/MD/M754.

3.3.5. Atrial fibrillation. Thirteen studies included patients with AF. In 12 RCTs, the TER, HM alone, or HM + WM group showed better TER than that in the control group (RR: 1.17, 95% CI: 1.07–1.27). In the HM versus WM group design, TER was higher than that in the WM group (RR: 1.21, 95% CI: 1.04–1.41). In the HM + WM versus WM design, TER was higher in the HM + WM group than that in the WM group (RR: 1.13, 95% CI: 1.03–1.24) (Fig. 8).

Six studies used the HR/min as the outcome. HM with WM or HM alone showed decreased HR/min (RR: −6.97, 95% CI: −10.77 to −3.17). In 3 RCTs that adopted the HM versus WM design, the HM group had a lower HR than that of the WM group (RR: −7.93, 95% CI: −14.42 to −1.43). In the other 3 RCTs that used the HM + WM versus WM design, the HM + WM group showed less HR than that of the WM group (RR: −5.93, 95%

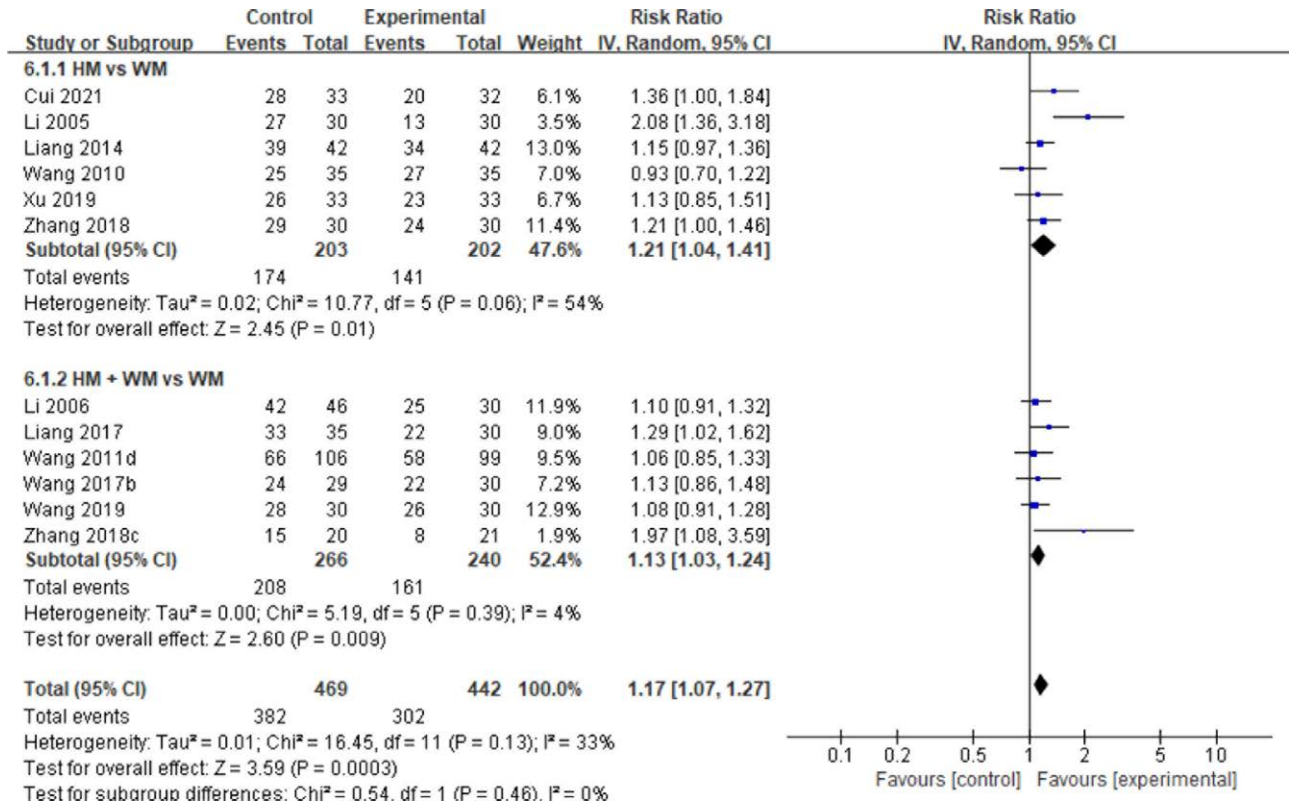

Figure 8. Meta-analysis of TER on patients with atrial fibrillation between the intervention and control groups. HM = herbal medicine, TER = total effective rate, WM = Western medicine.

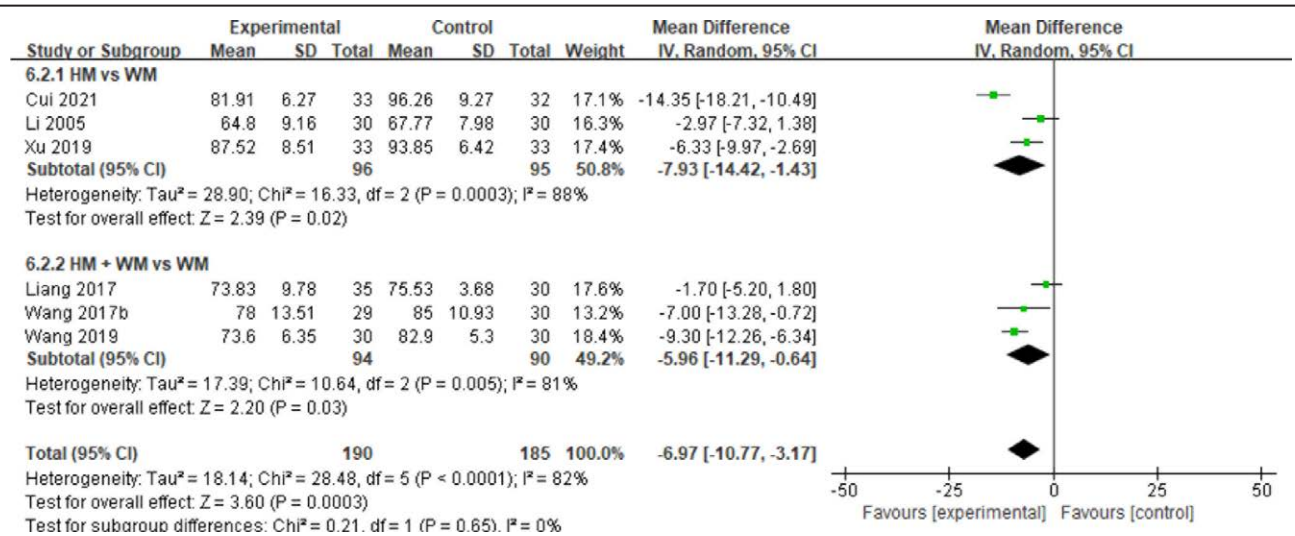

Figure 9. Meta-analysis of heart rate on patients with atrial fibrillation between the intervention and control groups. HM = herbal medicine, WM = Western medicine.

Table 2

Detailed information of adverse events.

First author	Diseases	Herbal medicine	Adverse events (T vs C)	Design
Dai 2011[22]	Arrythmia	Jianpizishen-Tang (健脾滋肾)	T: N/S vs C: Bradycardia 3	HM vs WM
Fan 2019[24]	Arrhythmia	Chaihujialungguomuli-Tang (柴胡加龙骨牡蛎汤)	T: Nausea 1 vs C: Vomit 1	HM vs WM
Li 2004[26]	Arrhythmia	Wenxinkeli (稳心颗粒)	T: Dizziness 2, Nausea 4. vs C: Bradycardia 2, Low BP 1, Dizziness 4, Nausea 1	HM vs WM
Wang 2008[32]	Arrhythmia	Wenxinkeli (稳心颗粒)	T: mild headache 2 vs C: Dizziness & Nausea 2, Bradycardia 3, Low BP 1	HM vs WM
Zhang 2007[37]	Arrhythmia	Pinglufu-Fang (平律复方)	T: N/S vs C: Headache 1, Nausea 1, Heart discomfort 1	HM vs WM
Zhang 2018[100]	Arrhythmia	Guizhigancaolonggumuli-Tang jiajian (桂枝甘草龙骨牡蛎汤加减)	T: Constipation 2, Nausea 1 vs C: Constipation 2, Nausea 2, thyroidism 1	HM vs Placebo
Zhao 2019[88]	Arrhythmia	Baoxinfulu-Tang (保心复律汤)+Betaloc 12.5 mg + Betaloc 12.5 mg	T: Nausea 1, Dizziness 1, Dyspepsia 1 vs C: Diarrhea 3, Tachycardia 2, Low BP 1	HM + WM vs WM
Hua 2015[44]	PVC	Wenxinkeli (稳心颗粒)	T: Gastrointestinal symptoms 1, Headache 1, Dizziness 1 vs C: Abdominal discomfort 1, Gastrointestinal symptoms 1, Palpitation 1, Osphyalgia 1	HM vs Placebo
Li 2018[49]	PVC	Diaoluningji-Tang (调律宁悸汤)	T: N/S vs C: Dry mouth and Insomnia 1, Dyspepsia 1	HM vs WM
Li 2020[50]	PVC	Shengmaiyinjiawei (生脉饮加味)	Abnormal LFT T: 3/41 vs C: 13/42 Abnormal RFT T: 17/41 vs C: 15/42	HM vs WM
Wang 2011[53]	PVC	Wenxinkeli (稳心颗粒)	T: Constipation 1 vs C: Low BP 1, Bradycardia 1	HM vs WM
Wang 2021[57]	PVC	Yangxindingjijiaonang (养心定悸胶囊)	T: Low BP 1, Dizziness 1 vs C: Low BP 2, Nausea 2, Arrhythmia 1	HM vs WM
Guo 2013[62]	Sinus Bradycardia	1. Xuefuzhuyu-Tang (血府逐瘀汤) 2. Wendantang-he-guaweijianbaibanxia-Tang (温胆汤合瓜蒌建白半夏汤) 3. Shengmaisan-he-renshenyangying-Tang (生脉散合人参养营汤) 4. canfutang-he-youguiyin (参附汤合右归饮)	T: Dry Mouth 2 case vs C: Urinary discomfort 1, Dry skin 4, Tachycardia 4, Fever 2 ($P < .05$)	HM vs WM
Liu 2014[67]	Sinus bradycardia	Cansongyangxinjiaonang (参松养心胶囊)	T: 1 vs C: 5	HM vs Placebo
Yang 2017[72]	Sinus Bradycardia	Xinbaopill (心宝丸)	T: N/S vs C: Nausea 1, sensitive feeling 2	HM vs WM
Zhang 2019[88]	Sinus bradycardia	Cansongyangxinjiaonang (参松养心胶囊)	T: 20 vs C: 23	HM vs Placebo
Hou 2018[80]	Tachycardia	Ningjikeli (宁悸颗粒) 25 mg + Metoprolol 12.5 mg	T: Gastrointestinal tract discomfort 1 vs C: Headache 2	HM + WM vs WM + Placebo
Li 2008[81]	Tachycardia	Yiqishengmai-Tang (益气生脉汤)	T: N/S vs C: Nausea and Gastric discomfort 2	HM vs WM
Liang 2008[82]	Tachycardia	Pingxindingji-Tang (平心定悸汤)	T: Diarrhea 2 vs C: Sinus bradycardia 2, Sinus arrest 1, Gastrointestinal discomfort 2	HM vs WM
Wei 2011[84]	Tachycardia	Cansongyangxinjiaonang (参松养心胶囊) + Mexiletine	T: Gastrointestinal tract discomfort 1, Headache 1 vs C: Dry cough 1, Gastrointestinal tract discomfort 1	HM + WM vs WM
Xu 2009[85]	Tachycardia	Kucaopingxin-Tang (苦参平心汤)	T: Dyspepsia 1 vs C: Dizziness 2, Nausea 1	HM vs WM
Yang 2018[87]	Tachycardia	Pingxindingji-Tang (平心定悸汤)	T: Diarrhea 2 vs C: Diarrhea 2, Dry mouth 3, Numbness of Face and lip 4, Nausea 1	HM vs WM
Yang 2017[93]	AF	Jiaweidingxin-Tang (加味宁心汤) + amiodarone	T: N/S vs C: 3 Sinus bradycardia and 2 patients with transaminase increased more than 3 times and withdrew from the trial	HM + WM vs WM
Wang 2011[69]	AF	Cansongyangxinjiaonang (参松养心胶囊) + Propafenone	T: Gastric discomfort 1, Nausea 1 vs C: Constipation 1, Dizziness 1, Nausea 1, Gastric discomfort 1, Tachycardia 1, rash 1	HM + WM vs WM
Xiao 2021[98]	AF	Cansongyangxinjiaonang (参松养心胶囊)	T: Palpitation 1, Dizziness 1, Chest discomfort 1 vs C: Palpitation 1, Dizziness 1	HM vs WM
Xu 2019[99]	AF	Dingxindingjijiaonang (宁心定悸胶囊)	T: Abnormal Urinary test result 1 vs C: Abnormal Urinary test result 1	HM vs WM

AF = atrial fibrillation, C = control group, ECG = electrocardiogram, HM = herbal medicine, N/A = not applicable, N/S = none specific events reported, PVC = premature ventricular contraction, SONO = sonography, T = treatment group, TER = total effective rate, WM = Western medicine.

CI: −11.29 to −0.64) (Fig. 9). Decreased HR can be interpreted that HM has a positive effect of HM on AF.[102]

3.4. Safety

Among the 82 studies included in this review, only 37 reported adverse events. Of the 37 studies, 11 reported no adverse events in either the intervention or control group. Adverse reactions were reported in 26 studies, 6 of which reported no adverse effects in the intervention group. Among the side effects reported in the treatment group, nausea was the most common (7 cases), followed by gastrointestinal discomfort (4 cases), dizziness (4 cases), headache (3 cases), dry mouth (3 cases), anorexia (dyspepsia) (3 cases), and constipation (2 cases). The adverse effects of individual studies are reported in detail in Table 2. No serious adverse events associated with HM were reported.

3.5. Risk of bias

The overall risk of bias across the articles reviewed in this study is shown in Figure 10 and Supplementary 4, Supplemental Digital Content, http://links.lww.com/MD/M755. As many studies have compared herbal medicine monotherapy, herbal medicine, and Western medicine combination therapy, the risk of bias for blinding was "high." In addition, many studies often graded allocation concealment and random sequence generation as "unclear" due to ambiguous descriptions. The risk of bias was "low" for the remaining items.

3.6. Publication bias

Publication bias was evaluated by visual inspection using a funnel plot (Supplementary 5A–O, Supplemental Digital Content, http://links.lww.com/MD/M756). Visual inspection revealed that the possibility of publication bias was relatively low.

4. Discussion

4.1. Summary of findings

This study investigated RCTs of herbal prescriptions for arrhythmias. A total of 82 studies were included in this systematic review and meta-analysis. Our results showed that the TER for unclassified arrhythmias, PVC, sinus bradycardia, tachycardia, and AF was higher in the HM group than that in the control group. The results of the analysis of the individual arrhythmia types were as follows. The number of 24-h PVCs was significantly lower in the intervention group than that in the control group. In patients with sinus bradycardia, the HR was higher in the intervention group than that in the control group. In studies involving patients with tachycardia, the HR was significantly lower in the HM group than that in the control group. Additionally, autonomic parameters, such as standard deviation of all NN intervals, were higher in the intervention group than that in the control group. In studies of patients with AF, the HR and ECG indices related to the risk of AF were lower in the intervention group than those in the control group. No serious adverse events associated with the herbal medicine treatments have been reported.

4.2. Debates: implication for clinical practice and theoretical basis

Arrhythmia is one of the 3 major heart diseases with an increasing incidence worldwide. Western medical treatments for arrhythmia include anticoagulants and antiarrhythmic drugs. If the drugs are ineffective, radiofrequency catheter ablation or pacemakers are used. Amiodarone is a widely used conventional medication to treat tachycardia; however, it has been associated with adverse effects, such as sinus bradycardia and toxicity in several studies.[103, 104] Non-pharmacological treatment for arrhythmia may lead to complications, such as postoperative infections, and can cause difficulties in postoperative magnetic resonance imaging. Moreover, the eligibility criteria for non-pharmacological treatment are limited.[104] However, traditional East Asian medicines have a long history of treating cardiac disease. Various studies have reported the effects of herbal medicine, acupuncture, moxibustion, and external preparations for the treatment of symptoms related to arrhythmias, such as fatigue, chest pain, and anxiety.[44, 105, 106] However, previous systematic reviews and meta-analyses of herbal medicines on arrhythmias only investigated individual-specific herbal prescriptions or a certain subtype of arrhythmia, leading to a lack of a comprehensive overview of arrhythmia treatment with HTM.[11, 107] Therefore, this study provides quantitative evidence on the effects of herbal medicines on arrhythmia treatment for clinicians. The results of this study will be helpful in the decision-making of traditional medicine physicians treating cardiac disorders. However, our study did not focus on specific subgroups (by sex or age). Therefore, further studies are warranted to identify subgroup effects. Regarding safety, among the 37 studies, only 11 reported no adverse events in either the intervention or control group. Most reported adverse events were digestive system side effects, and no serious adverse events were observed.

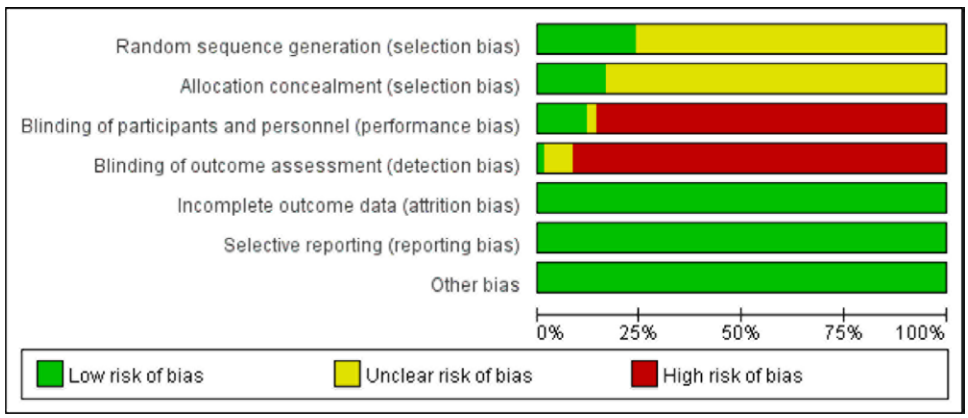

Figure 10. Risk-of-bias graph: a systematic review of the authors' judgments regarding each risk-of-bias item presented as percentages across all included trials using the Cochrane risk-of-bias tool (n = 82).

The herbs most commonly used for treating arrhythmia include Opiopogonis radix (Maidong), Radix Astragali (Huangqi), Ginseng Radix et Rhizoma (Renshen), Salviae Miltiorrhizae (Danshen), Glycyrrhizae Radix et Rhizoma Praeparata cum Melle (Zhigancao), and Schisandrae Fructus (Wuweizi). These medicinal herbs are widely used in TEAM to manage heart diseases. Sheng-Mai-San, a representative TCM prescription for cardiac disease composed of Maidong, Renshen, and Wuweiz, is effective against myocardial ischemic injury.[108] Renshen is well known for its effects on cardiovascular diseases, including arrhythmia, by regulating Ca^{2+} channels.[109, 110] Zhigancao acts on the HERG (K+) channels of cardiomyocytes to control abnormal heartbeats, such as tachycardia. Wuweizi regulates NCOR2 and NFAT expression to repair heart cell damage. Gosam contains oxymatrine, which protects blood vessels and acts on calcium and potassium channels, thereby improving heart function.[111, 112]

4.3. Suggestions for further research

In most studies, the only reported outcome variable was TER, and no specific clinical outcome was adequate for specific arrhythmia subtypes. Disease-specific clinical endpoints that require long-term follow-up should be included in RCTs.[113] In future studies, long-term follow-up of clinical endpoints related to AF, such as cardiac death, stroke, heart failure, hospitalization, and emergency room visits, should be considered. Moreover, various core outcome sets have been developed for herbal medicine studies on heart disease.[114] Future herbal medicine studies should adopt core outcome sets related to AF.

In a few studies, inappropriate electrophysiological indices were used. Increased PR and QTc times on ECG were associated with increased AF risk. However, in such cases, PR and QTc time are used as indicators of risk rather than as indicators of treatment effects.[115–117] In our review, studies used PR and QTc time to determine the effect of herbal medicine on AF, which is not an appropriate index for the treatment effect. Autonomic parameters such as HR variability, which are associated with long-term prognosis, can be considered. In future studies, qualitative research methodologies should be considered to explain changes in the QoL and satisfaction of participants, which will promote an in-depth understanding of the effects and expectations of TEAM management.[118]

Several problems have been identified in disease diagnosis. In our meta-analysis, 20 studies defined arrhythmia without specific definitions or subtypes, such as AF and sinus bradycardia. In future studies, arrhythmia subtypes should be classified in greater detail. Regarding the treatment regimens, most studies adopted standardized and semi-standardized prescriptions. Therefore, more pragmatic clinical trials on the effects of traditional medicine therapy are needed.[119–122] Several studies have not mentioned adverse events, emphasizing the importance of reporting the safety of the intervention. Cases have been reported in which the indiscriminate use of THM without proper diagnosis and prescription by a traditional practitioner resulted in liver damage. Furthermore, future studies should conduct adverse event reporting using standardized questionnaires to distinguish cases or concerns regarding DILI from existing natural medicines.[123, 124]

4.4. Limitations and strengths

This study has several limitations. We did not analyze the specific formulation effects of herbal medicines such as liquids, extracts, and powders. In future studies, we could adopt a network meta-analysis method to explore the treatment effects according to the formulation and administration route. However, we did not compare the effects of the herbal prescriptions. Based on these results, we evaluated the effects of each herbal medicine using a network meta-analysis method in further study. In addition, only a small number of studies on the specific outcomes of specific arrhythmia subtypes were included. Finally, the follow-up periods of the included studies were relatively short. Real-world studies are required to overcome the limitations associated with the length of each clinical trial.

However, this study had several strengths. To the best of our knowledge, this is the first study to comprehensively review the effects and safety of various herbal medicines on AF. In a previous study on sinus bradycardia, only 6 herbal prescriptions were investigated.[124] In previous studies, only specific herbal prescriptions were evaluated, whereas various herbal prescriptions were included in this study. In other studies, there were certain flaws in the search strategy that just used "AF" and "Chinese Medicine" as the search terms to generate search formulas, which limited the number of studies included.[15, 125, 126] In our study, a wider range of search strategies was applied.

5. Conclusion

Various herbal medicines have clinical advantages in improving arrhythmia-related symptoms. Herbal medicine combination therapy may be an effective addition to the currently available conventional arrhythmia medications without severe adverse events. Therefore, future studies should adopt disease-specific outcome variables. Considering the low methodological quality of individual studies, large-scale, long-term follow-up, and rigorous clinical studies on the effects of herbal medicine on arrhythmia are warranted. Our results provide useful fundamental data for future study design by researchers and decision-making by clinicians.

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Writing – review & editing: Jong-Min Yun, Jungtae Leem.

References

[1] Yang N, Kim M, Choi D, Han C. One case of Bradyarrhythmia treated with (炙甘草湯) and acupuncture. J Int Korean Med. 2010;31:183–9.
[2] Jong B. Mechanism of atrial fibrillation. Korean J Med. 2011;81:4.
[3] Antzelevitch C, Burashnikov A. Overview of basic mechanisms of cardiac arrhythmia. Card Electrophysiol Clin. 2011;3:23–45.
[4] Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. Circulation. 1999;100:2025–34.
[5] Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJV, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation. JACC Heart Fail. 2013;1:21–8.
[6] Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J. 2007;29:155–65.
[7] Freedman B, Lip GYH. "Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation. Thromb Haemost. 2016;116:587–9.
[8] Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102:1796–805.
[9] Kanmanthareddy A, Reddy M, Ponnaganti G, et al. Alternative medicine in atrial fibrillation treatment – yoga, acupuncture, biofeedback and more. J Thorac Dis. 2015;7:8.
[10] Lee B, Hwang J, Kwon J. The effect of moxibustion treatment for cardiac arrhythmia: a systematic review. J Korean Med. 2019;40:99–111.

[11] Liu J, Li SN, Liu L, et al. Conventional acupuncture for cardiac arrhythmia: a systematic review of randomized controlled trials. Chin J Integr Med. 2018;24:218–26.
[12] VanWormer AM, Lindquist R, Sendelbach SE. The effects of acupuncture on cardiac arrhythmias: a literature review. Heart Lung. 2008;37:425–31.
[13] Li Y, Barajas-Martinez H, Li B, et al. Comparative effectiveness of acupuncture and antiarrhythmic drugs for the prevention of cardiac arrhythmias: a systematic review and meta-analysis of randomized controlled trials. Front Physiol. 2017;8:358.
[14] Jian X, Luo Y, Wang X, et al. Investigating the efficiency and tolerability of traditional Chinese formulas combined with antiarrhythmic agents for paroxysmal atrial fibrillation: a systematic review and Bayesian network meta-analysis. Phytomedicine. 2022;94:153832. https://pubmed.ncbi.nlm.nih.gov/34781230/
[15] Dong Y, Liao J, Yao K, Jiang W, Wang J. Application of Traditional Chinese Medicine in treatment of atrial fibrillation. Evid-Based Complementary Altern Med. 2017;2017:1–11.
[16] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. 674. https://training.cochrane.org/handbook/current
[17] Kim S, Park J, Seo H, Shin C. NECA's Guidance for Undertaking Systematic Reviews and Meta-analyses for Intervention.
[18] Khan AH, Hussain M, Malik MK. Arrhythmia classification techniques using deep neural network. Complexity. 2021;2021:1–10.
[19] Rajkumar A, Ganesan M, Lavanya R. Arrhythmia classification on ECG using Deep Learning. In: 2019 5th International Conference on Advanced Computing & Communication Systems (ICACCS). IEEE; 2019:365–369.
[20] Lubitz SA, Yin X, Rienstra M, et al. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham heart study. Circulation. 2015;131:1648–55.
[21] Sacchetti A, Moyer V, Baricella R, Cameron J, Moakes M. Primary cardiac arrhythmias in children. Pediatr Emerg Care. 1999;15:95–89.
[22] Dai Y, Huang X. Clinical observation on the treatment of senile ischemic arrhythmia by strengthening the spleen and nourishing the kidney. Inner Mongolia Tradit Chin Med. 2011;30:30.
[23] Dong B, Song T. Clinical study of Wenlu decoction in the treatment of ventricular arrhythmia with Yin deficiency and fire excess syndrome. J Pract Chin Med. 2009;23:12–4.
[24] Fan X. Therapeutic observation of 106 cases of cardiac arrhythmia treated by traditional Chinese medicine Chaihu Jia Longgu Muli Decoction. Wisdom Health. 2019;5:115–6.
[25] Huang J, Sun L, You C. Sixty cases of arrhythmia treated by Sishen decoction. J Cardiovasc Cerebrovasc Dis Integr Tradit Chin Western Med. 2005;13:908–9.
[26] Li K. Efficacy and safety of Wenxin granules in the treatment of arrhythmia. Chin Clin. 2004;32:47–8.
[27] Li X. Clinical study on the treatment of phlegm-heat disturbed heart-type tachyarrhythmia with Qingre Huatan Anshen Recipe. Master. Shandong University of Traditional Chinese Medicine. 2016.
[28] Chen J. Clinical study of Zengrate Fumai Decoction in the treatment of bradyarrhythmia and its effect on heart rate variability. Master's thesis. Beijing University of Chinese Medicine. China. 2012.
[29] Xueyuan W. Analysis of the clinical efficacy of 150 cases of cardiac arrhythmia treated with integrated traditional Chinese and Western medicine. Seek Med Ask Med. 2013;11:31.
[30] Shi Z, Hu P, Shi L. Evaluation of the efficacy of traditional Chinese medicine Yangxin Decoction in the treatment of arrhythmia. Latest Med Inform Digest. 2018;72:236–7.
[31] Shu Z. A clinical study on the treatment of arrhythmia with Qi deficiency with modified Schisandra Decoction. Cardiovasc Dis Integr Tradit Chin Western Med. 2016;4:195–6.
[32] Danqian W. A clinical study on the treatment of premature ventricular contractions with traditional Chinese medicine Wenxin granules and cardiac rhythmpine. Master's thesis. Hubei university of Chinese medicine. 2008.
[33] Wang L. Clinical study of Zhenxin Dan in the treatment of premature ventricular contractions (deficiency of heart and timidity). Master. Chengdu University of Traditional Chinese Medicine. 2011.
[34] Wang Z. Analysis of the clinical efficacy of 160 cases of arrhythmia treated with integrated traditional Chinese and Western medicine. Med Equip. 2015;28:60–1.
[35] Wang Y. Clinical observation on the effect of traditional Chinese medicine prescriptions on the treatment of arrhythmia. Chin Med Theory. 2017;182:192–3.
[36] Zhang N, Yin C, Xue J, Guan L, Wei X, Shao H. Clinical observation of Xinjining capsule in the treatment of 48 cases of ventricular arrhythmia. J Tradit Chin Med. 2001;42:537–8.
[37] Zhang J, Wang J, Li X, Xiong Y, Liu M. Efficacy observation of Pinglu compound prescription in the treatment of ventricular arrhythmia. Modern Chin Med. 2007;27:1–2.
[38] Zhang H, Shi Z. Shenwei Fumai Decoction in the treatment of 80 cases of arrhythmia. Western Chin Med. 2014;27:62–3.
[39] Zhang G. Clinical effect of modified Guizhi Gancao Longgu Muli Decoction in the treatment of arrhythmia. TCM Chin Med. 2018;34:127–8.
[40] Zhang Y. Effect of Guipi Decoction in the treatment of arrhythmia. Wisdom Health. 2020;17:181–2.
[41] Zhao Y, Gao T, Yang C. Clinical observation on the treatment of arrhythmia with Baoxin Fulu Decoction combined with Betaloc in the treatment of arrhythmia. Wisdom Health. 2019;5:135–8.
[42] Zhou J, Yang G. Clinical efficacy of Zhigancao decoction in the treatment of bradyarrhythmias. Clin J Chin Med. 2016;8:38–9.
[43] Bo D, Tingting S. Clinical study of Wenlu decoction in the treatment of ventricular arrhythmia with Yin deficiency and fire excess syndrome. J Pract Chin Med. 2009;23:12–4.
[44] Hua W, Gao RL, Zhao BC, et al. The efficacy and safety of wenxin keli in patients with frequent premature ventricular contractions: a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. Chin Med J (Engl). 2015;128:2557–64.
[45] Lai Y, Wen P, Zhou Y. Curative effect observation of 40 cases of arrhythmia with deficiency of Qi in the treatment of 40 cases of arrhythmia with modified Schisandra Decoction. Yunnan Chin J Tradit Chin Med. 2015;36:40–1.
[46] Li J, Yang L, Hou X. Clinical observation of Jiawei Zhigancao Decoction combined with etmothiazide in the treatment of premature beats. Shanghai J Tradit Chin Med. 2000;9:15–6.
[47] Li S. Observation and research on the curative effect of Yiqi Huoxue Tongluo method in the treatment of frequent premature ventricular contractions. Master. Guangzhou University of Traditional Chinese Medicine. 2010.
[48] Li W. Analysis of the effect of integrated traditional Chinese and Western medicine on patients with ventricular arrhythmia. China Health Industry. 2014;1:184–5.
[49] Li S. Clinical observation of Tiaolu Ningjin Decoction in the treatment of ventricular arrhythmia (ventricular premature and paroxysmal ventricular tachycardia) due to qi deficiency and phlegm and blood stasis. Master. Henan University of Traditional Chinese Medicine. 2018.
[50] Li P. Clinical observation of Shengmaiyin in the treatment of premature ventricular contraction (Qi-yin deficiency type). Master. Changchun University of Traditional Chinese Medicine. 2020.
[51] Liang B, Zou FH, Fu L, Liao HL. Chinese herbal medicine Dingji Fumai decoction for ventricular premature contraction: a real-world trial. Biomed Res Int. 2020;2020:5358467.
[52] Zhao Z, Liang J, Liu X, Xu Y, Tan Y. Clinical observation on the treatment of bradyarrhythmia due to yang deficiency and blood stasis with Fuzheng Zhumai prescription. Psychol Monthly. 2019;14:10–1.
[53] Wang H. Interventional study of Buchang Wenxin Granule on premature ventricular contractions. World Chinese Medicine. Master's thesis. Chengdu University of Chinese medicine. 2011.
[54] Wang L. Clinical study of Ziyin Qinghuo Dingji prescription in the treatment of ventricular premature beats due to yin deficiency and fire. Master. Shandong University of Traditional Chinese Medicine. 2015.
[55] Wang X. Efficacy analysis of integrated traditional Chinese and Western medicine in the treatment of elderly ventricular arrhythmia. Clin J Chin Med. 2016;34:92–3.
[56] Wang C, Chi Y, Zhang Y. Clinical observation of Dingxin prescription in the treatment of premature beats due to deficiency of both Qi and Yin. Zhonghua J Tradit Chin Med. 2019;37:742–5.
[57] Wang C, Wang Q. Effects of Yangxin Dingpal Capsules on TCM syndromes in patients with premature ventricular contractions. World Chin Med. 2021;16:155–59.
[58] Xia J, Zhao D, Chen T, Xu Y, Yu H. Efficacy of Bailing Capsules combined with Bisoprolol in the treatment of premature ventricular contractions and the improvement of TCM symptoms. Integr Chin Western Med Cardiovasc Dis. 2019;7:146–7.
[59] Xu S. Clinical study on the treatment of functional premature ventricular contractions with liver stagnation and fire syndrome with Shugan Xiehuo Recipe. Master. Shandong University of Traditional Chinese Medicine. 2016.
[60] Yin J. Clinical study on Fufang Guanbaifu Decoction in the treatment of atrial premature beat due to deficiency of both Qi and Yin. Master. Nanjing University of Traditional Chinese Medicine. 2017.
[61] Zou JG, Zhang J, Jia ZH, Cao KJ. Evaluation of the traditional Chinese Medicine Shensongyangxin capsule on treating premature ventricular

contractions: a randomized, double-blind, controlled multicenter trial. Chin Med J (Engl). 2011;124:76–83.
[62] Geng N, Du L, Wang G, Wang L, Li D. Clinical study on treating sinus Bradycardia with Traditional Chinese Medicine Fuxinmai Capsule. ITCM 2006;23:32–3.
[63] Huang J. Clinical study on 68 cases of bradyarrhythmia treated by nourishing qi and soothing liver. Inner Mongolia Tradit Chin Med. 2018;8:31–2.
[64] Li X. Treatment of bradyarrhythmia with traditional Chinese medicine. Modern Health. 2014;14:257–8.
[65] Li J. A pilot trial of Shenxian Shengmai Oral Liquid in the treatment of bradyarrhythmias. Master's thesis, Beijing University of Chinese medicine, Beijing, China. 2019.
[66] 林海飞,黄丽娜. 圣愈汤治疗气血两虚型缓慢性心律失常临床观察. 中华中医药学刊. 2015;33:1244–6.
[67] Liu Y, Li N, Jia Z, Lu F, Pu J. Chinese medicine shensongyangxin is effective for patients with bradycardia: results of a randomized, double-blind, placebo-controlled multicenter trial. Evid Based Complement Altern Med. 2014;2014:605714.
[68] Shi Z, Shi L, Hu P. Analysis of the curative effect of traditional Chinese medicine Yangxin Decoction in the treatment of bradyarrhythmia. Journal of Clinical Medical Literature. 2019;6:85–6.
[69] Wang H. Clinical study on the treatment of bradyarrhythmia with Yang deficiency and blood stasis syndrome with Mahuang Fuzi Xixin Decoction. Master. Changchun University of Traditional Chinese Medicine. 2011
[70] Wei D, Zhou H, Xia X, Hu J. A preliminary study on the efficacy of Xinbao Pill in the treatment of elderly patients with sinus bradycardia. Chin Commun Phys. 2015;31:93–4.
[71] Yang D, Liu A. Treatment of bradyarrhythmia with integrated traditional Chinese and Western medicine. Pract Clin Rescue Integr Tradit Chin Western Med. 1999;6:67–8.
[72] Yang Z. Clinical observation of Xinbao Pill in the treatment of bradyarrhythmia. China Contin Med Educ. 2017;25:107–9.
[73] Yao H. Clinical observation on the treatment of bradyarrhythmia by warming the kidney and activating blood. J Clinic Healthcare. 2000;3:14–5.
[74] Yu Q. Clinical observation of Xinbao Pill in the treatment of 60 cases of slow arrhythmia. JGCTCM. 2013;35:31–3.
[75] Zhan P. Theoretical and clinical research of Zhigancao decoction in the treatment of senile bradyarrhythmia. Master's thesis. Shandong University of Traditional Chinese Medicine. 2013.
[76] Zhang C. Clinical observation on the treatment of bradyarrhythmia with integrated traditional Chinese and western medicine. China Modern Doctor. 2012;50:82–4.
[77] Zhang Y. Observation on the curative effect of Shensong Yangxin Capsule in the treatment of bradyarrhythmia. Integr Chin Western Med Cardiovasc Electronic J. 2016;4:30–1.
[78] Zhang F, Zou J, Yu H, et al. Acute efficacy of a traditional Chinese medicine for treatment of frequent premature ventricular contractions in patients with concomitant sinus bradycardia: results from a double-blind, placebo-controlled, multicentre, randomized clinical trial. Evid Based Complement Alternat Med. 2019;2019: 3917282.
[79] Zhu H, Zhang C. Clinical observation of Xinbao Pill in the treatment of 50 cases of bradyarrhythmia. Chin Med Res. 2014;35: 105–6.
[80] Hou J. Clinical study of Ningjin Granules in the treatment of tachyarrhythmia of Qi deficiency and fire exuberance. Master's thesis. Beijing University of Traditional Chinese Medicine. 2018.
[81] Li X. Efficacy analysis of Yiqi Shengmai Decoction in the treatment of tachyarrhythmia. China Med Herald. 2008;5:81–2.
[82] Liang W. Clinical study of Pingxin Dingji decoction in the treatment of tachyarrhythmia of Qi and Yin deficiency type. Master. Shandong University of Traditional Chinese Medicine. 2011.
[83] Tao Y. Treatment of 48 cases of benign tachyarrhythmia with integrated traditional Chinese and Western medicine. Jiangxi Chin Med. 2012;43:41–2.
[84] Wei X. Clinical observation on the efficacy and safety of Shensong Yangxin capsule combined with mexiletine in the treatment of Tachy ventricular arrhythmia. Master. Nanjing University of Traditional Chinese Medicine. 2011.
[85] Xu D. Clinical observation of Kushen Pingxin decoction in the treatment of 38 cases of tachyarrhythmia. Guiding J Tradit Chin Med Pharm. 2009;15:24–6.
[86] Yan X. Observation on the curative effect of Fuluyin in the treatment of tachyarrhythmia. Chin Med Emerg. 2005;14:12–3.
[87] Yang T. Clinical study of Pingxin Dingji Decoction in the treatment of tachyarrhythmia with deficiency of both Qi and Yin. China Modern Dist Educ Tradit Chin Med. 2018;16:89–90.
[88] Zhang Y. Clinical study of Sishenyin derivative formula combined with atenolol on tachyarrhythmia. Liaoning J Tradit Chin Med. 2019;46:2371–4.
[89] Cui F. Clinical efficacy of Guizhi Fuling Pills in the treatment of paroxysmal atrial fibrillation due to kidney deficiency and blood stasis. Master's thesis. Shanxi University of Traditional Chinese Medicine. 2021.
[90] Li J, Hou Y. Zhigancao Decoction combined with amiodarone in the treatment of paroxysmal atrial fibrillation. Xinjiang Chin Med. 2006;24:10–1.
[91] Li H. Efficacy observation of Yangxin Fumai Decoction in the treatment of paroxysmal atrial fibrillation with Qi deficiency and blood stasis syndrome. Master. Shandong University of Traditional Chinese Medicine. 2012.
[92] Liang Y, Wu R. Clinical observation of Changhu Wendan decoction in the treatment of paroxysmal atrial fibrillation with phlegm and fire disturbing heart type. Shaanxi Univ Tradit Chin Med J. 2014;37:42–3.
[93] Yang L. Clinical observation of Jiawei Ningxin Decoction in the treatment of paroxysmal atrial fibrillation with Qi and Yin deficiency syndrome. Master's thesis. Hunan University of Traditional Chinese Medicine. 2017.
[94] Wang J. Curative effect observation of Fumai granules in the treatment of atrial fibrillation. Master's thesis. Guangzhou University of Chinese medicine. 2010
[95] Wang A, Pu J, Qi X, et al. Evaluation of shensongyangxin capsules in the treatment of paroxysmal atrial fibrillation: a randomized, double-blind and controlled multicenter trial. Zhonghua Yi Xue Za Zhi. 2011;91:1677–81.
[96] Wang C. Clinical Observation of Shengui Huxin Decoction in the Treatment of Atrial Fibrillation and Its Effect on Coagulation Function. Master's thesis. Heilongjiang University of Traditional Chinese Medicine. China. 2017.
[97] Wang C, Chi Y, Zhang Y. Clinical observation of Dingxin prescription in the treatment of permanent atrial fibrillation with dyslipidemia. Liaoning J Tradit Chin Med. 2019;46:1202–4.
[98] Xiao J, Fu J, Li X, Ji D, Chen J. Clinical efficacy and safety analysis of Shensong Yangxin capsule in the treatment of hypertension complicated with paroxysmal atrial fibrillation. Western Chin Med. 2021;34:110–2.
[99] Xu H. Clinical study of Ningxin Dingji Capsule in the treatment of persistent atrial fibrillation with Qi stagnation and blood stasis syndrome. Master's thesis. Shanxi University of Traditional Chinese Medicine. 2019.
[100] Zhang N, Tse G, Dahal S, et al. Efficacy of Wenxin Keli Plus amiodarone versus amiodarone monotherapy in treating recent-onset atrial fibrillation. Cardiol Res Pract. 2018;2018:6047271.
[101] Zhuang Z. Clinical observation of Dingxin prescription in the treatment of permanent atrial fibrillation with qi-yin deficiency and blood stasis. Master. Liaoning University of Traditional Chinese Medicine. 2018.
[102] Holmqvist F, Kim S, Steinberg BA, et al.; ORBIT-AF Investigators. Heart rate is associated with progression of atrial fibrillation, independent of rhythm. Heart. 2015;101:894–9.
[103] Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T–U waves precede torsades de pointes in long QT syndrome. J Am Coll Cardiol. 2009;54:143–9.
[104] Connolly SJ, Camm AJ, Halperin JL, et al.; PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011;365:2268–76.
[105] Jeong G, Kim Y, Kwon J, Kim K. A investigation into arrhythmia between East and West medicine. J Intern Korean Med 2000;21:747–63.
[106] Zhang F, Zou J, Yu H, et al. Acute efficacy of a traditional Chinese medicine for treatment of frequent premature ventricular contractions in patients with concomitant sinus bradycardia: results from a double-blind, placebo-controlled, multicentre, randomized clinical trial. Evid Based Complement Altern Med. 2019;2019:1–8.
[107] Fei Y, Fei R, Zhang J, Sun Y, Yu Q. Systematic evaluation of efficacy and safety of acupuncture treatment for patients with atrial fibrillation. Open Access Maced J Med Sci. 2019;7:461–6.
[108] Li F, Fan XX, Chu C, Zhang Y, Kou JP, Yu BY. A strategy for optimizing the combination of active components based on Chinese medicinal formula Sheng-Mai-San for myocardial ischemia. Cell Physiol Biochem. 2018;45:1455–71.

[109] Lee CH, Kim JH. A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. J Ginseng Res. 2014;38:161–6.
[110] Beik A, Joukar S, Najafipour H. A review on plants and herbal components with antiarrhythmic activities and their interaction with current cardiac drugs. J Tradit Complement Med. 2020;10:275–87.
[111] Yong-gang C, Shan J, Lei L, et al. Antiarrhythmic effects and ionic mechanisms of oxymatrine from Sophora flavescens: antiarrhythmic effects of oxymatrine. Phytother Res. 2010;24:1844–9.
[112] Hu S, Zuo H, Qi J, Hu Y, Yu B. Analysis of effect of Schisandra in the treatment of myocardial infarction based on three-mode gene ontology network. Front Pharmacol. 2019;10:232.
[113] Lee JM, Lee SMK, Leem J, et al. Effects of acupuncture on cardiac remodeling in patients with persistent atrial fibrillation: results of a randomized, placebo-controlled, patient- and assessor-blinded pilot trial and its implications for future research. Medicina (Mex). 2021;58:41.
[114] Zhang M, Chua HZ, Zhang J, et al. Developing a core outcome set on traditional Chinese medicine (COS-TCM) for chronic heart failure (CHF): a study protocol. BMJ Open. 2021;11:e047148.
[115] Cheng M, Lu X, Huang J, Zhang S, Gu D. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies: PR interval and atrial fibrillation. J Cardiovasc Electrophysiol. 2015;26:36–41.
[116] Zhang N, Gong M, Tse G, et al. Prolonged corrected QT interval in predicting atrial fibrillation: a systematic review and meta-analysis. Pacing Clin Electrophysiol. 2018;41:321–7.
[117] Mandyam MC, Soliman EZ, Alonso A, et al. The QT interval and risk of incident atrial fibrillation. Heart Rhythm. 2013;10:1562–8.
[118] Lee SMK, Leem J, Park JH, et al. Close look at the experiences of patients enrolled in a clinical trial of acupuncture treatment for atrial fibrillation in Korea: a qualitative study nested within a randomised controlled trial. BMJ Open. 2017;7:e013180.
[119] Lee H, Kim TH, Leem J. Acupuncture for heart failure: a systematic review of clinical studies. Int J Cardiol. 2016;222:321–31.
[120] Leem J. Does acupuncture reduce the risk of acute myocardial infarction? Integr Med Res. 2016;5:165–8.
[121] Leem J. Is acupuncture effective for functional recovery in ischemic stroke? Integr Med Res. 2015;4:185–8.
[122] Leem J. Does acupuncture increase the risk of bleeding in patients taking warfarin? Integr Med Res. 2015;4:119–21.
[123] Tarantino G, Pezzullo MG, di Minno MN, et al. Drug-induced liver injury due to "natural products" used for weight loss: a case report. World J Gastroenterol. 2009;15:2414–7.
[124] Danan G, Teschke R. RUCAM in Drug and herb induced liver injury: the update. Int J Mol Sci . 2015;17:14.
[125] Liu S, Tian G, Chen J, et al. Traditional Chinese Medicine for bradyarrhythmia: evidence and potential mechanisms. Front Pharmacol. 2018;9:324.
[126] Lei Y, Tang Y, Huang L, He P. Systematic review and meta-analysis on efficacy of traditional Chinese medicine for atrial fibrillation through cluster analysis. Ann Palliat Med. 2021;10:8982–90.