

# Traditional Chinese medication for cardiovascular disease

Pan-Pan Hao, Fan Jiang, Yu-Guo Chen, Jianmin Yang, Kai Zhang, Ming-Xiang Zhang, Cheng Zhang, Yu-Xia Zhao and Yun Zhang

**Abstract** | Traditional Chinese medication (TCM) is increasingly used to treat cardiovascular disease (CVD) in China and some other Asian countries. However, therapeutic efficacy and adverse effects of TCM are difficult to evaluate because few large-scale, randomized controlled trials (RCTs) enrolling patients with CVD have been performed. In this Review, we critically examine the current evidence on the cardiovascular effects of TCM. We reviewed 68 RCTs that included a total of 16,171 patients. The methodological quality of the trials was generally low. Only three reports described adverse cardiovascular events specifically, although in most studies TCM was associated with significant improvements in surrogate end points for hypertension, coronary heart disease, cardiac arrhythmias, and heart failure. The risk of adverse effects was not increased compared with no intervention, placebo, or Western medications. However, whether TCM is effective in reducing the all-cause or cardiovascular mortality in patients with CVD remains unknown and must be tested in large-scale RCTs with adverse cardiovascular events as primary end points.

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## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. The annual global CVD mortality is predicted to be 23.6 million by 2030.<sup>1</sup> Although a number of Western medications have been effective in reducing all-cause or CVD mortality, a substantial proportion of patients remains at a high risk of cardiovascular events.<sup>2</sup> Therefore, a broader range of therapeutic agents than is currently available is needed to reduce the residual risks of CVD.

Traditional Chinese medication (TCM) has been developed over >2,000 years, and has increased in popularity in both Asian and Western countries in the past few decades.<sup>3</sup> In a 2004 national survey of Chinese patients who had received Western medicine, TCM, and integrative medicine (TCM and Western medicine combined), 71.2% preferred integrative medicine and 18.7% preferred TCM.<sup>4</sup> In another national survey performed in secondary and tertiary hospitals in China, among 2,712 outpatients undergoing treatment for coronary heart disease (CHD), only 3.1% received TCM alone, 30.0% received integrative medicine, and 66.9% received only Western medicine.<sup>5</sup> TCM treatment was most likely to be used by patients with a long history of CHD or with a history of stroke. Importantly, in patients who used TCM, the number of Western medications used decreased with increasing numbers of TCMs.

In the USA, >15 million people use herbal remedies or high-dose vitamins, at a cost of >US\$34 billion per year, and the numbers of visits to complementary and

alternative medicine practitioners far exceed those to primary physicians.<sup>6</sup> In view of the increased use of complementary medicine in the USA, in 2005, the ACC published a Complementary Medicine Expert Consensus Document.<sup>7</sup> In Australia, in a 2011 national survey of 2,540 adults aged >50 years, respondents were asked to list chronic conditions and treatment experiences, including from where they had received advice or treatment. Overall, 8.8% of respondents reported seeing complementary and alternative medicine practitioners in the previous 3 months.<sup>8</sup> In addition, 65–69% of the Australian population reportedly uses complementary and alternative medicines, particularly to alleviate chronic or recurrent conditions.<sup>9</sup> Furthermore, herbal remedies have been approved to treat CVD in Germany and Japan.<sup>3</sup>

Despite the widespread use of TCM, a lack of scientific evidence exists to indicate whether TCM has beneficial roles in the treatment of CVD. Randomized controlled trials (RCTs) are taken to be the gold standard of testing efficacy and safety of therapies for a wide spectrum of diseases and for informing therapeutic guidelines. RCTs have spurred on the modernization of TCM in China. Many TCM physicians advocate rigorous testing of the efficacy and safety of these medicines in RCTs,<sup>4</sup> although some believe that the principle of RCTs is against the doctrine of TCM as personalized medicine. Because RCTs of TCM have just started to be performed in China, most use surrogate end points, and have small sample sizes, short follow-up, and diverse outcome results. In this Review, we critically examine the available evidence from RCTs on the effects of TCM in patients with CVD.

The Key Laboratory of Cardiovascular Remodelling and Function Research, Chinese Ministry of Education and Chinese Ministry of Health, Qilu Hospital, Shandong University, 107 Wen Hua Xi Road, Jinan, Shandong 250012, China (P.-P.H., F.J., Y.-G.C., J.Y., K.Z., M.-X.Z., C.Z., Y.-X.Z., Y.Z.).

Correspondence to: Y.-X.Z. [yxzhao@sdu.edu.cn](mailto:yxzhao@sdu.edu.cn)

## Competing interests

The authors declare no competing interests.

**Key points**

- Compared with no intervention or placebo, traditional Chinese medication (TCM) lowers blood pressure, reduces coronary event rates in patients with myocardial infarction, and lessens angina and myocardial ischaemia severity
- TCM has antitachycardic and antibradycardic effects in patients with cardiac arrhythmias, compared with no intervention or placebo
- The severity of cardiac dysfunction was ameliorated with TCM in patients with heart failure compared with no intervention or placebo
- Compared with Western medication, TCM has similar therapeutic effects in patients with hypertension and better effects in patients with angina pectoris or cardiac arrhythmias
- Adverse effect rates were similar between TCM and control groups, similar between TCM and Western medication in patients with hypertension, but lower for TCM in patients with coronary heart disease
- The quality of studies is poor, and large-scale, high-quality randomized clinical trials are needed to clarify whether TCM can contribute to reducing all-cause mortality and major adverse cardiovascular events

**Search strategy and selection criteria**

We searched for published reports with particular characteristics. Firstly, we identified study populations with definite diagnoses of essential hypertension, CHD, arrhythmias, or heart failure (HF) made with accepted Western medicine methods, and in which the efficacy of TCM had been assessed. These assessments were: measurement of blood pressure before and after treatment for hypertension; electrocardiography at rest or under stress for CHD; 24 h dynamic electrocardiography for cardiac arrhythmias; and left ventricular systolic and/or diastolic function or measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for HF. All clinical indicators were compared with no intervention or placebo, or Western medications. Secondly, the sample size in each study group was  $\geq 50$ . Thirdly, follow-up duration was  $\geq 4$  weeks. Finally, the studies included quantitative assessment of hard end points, such as death and nonfatal myocardial infarction (MI), and/or surrogate end points, such as blood pressure, electrocardiographic changes, or left ventricular function, and/or drug-related adverse effects. We excluded studies that had a nonrandomized design, or in which investigators enrolled patients with no definite CVD diagnosis, compared different TCMs only, or reported only symptomatic changes without objective measurements. We assessed methodological quality of studies with the Jadad score; a score  $< 2$  indicated very poor quality and these RCTs were excluded.<sup>10–12</sup> If multiple articles reported results from the same study, those with fewer data were excluded.

P.-P.H. and Y.-G.C. extracted data and assessed quality independently. Any disagreements were resolved by a third author (C.Z.). Extracted information (first author's surname, year of publication, number of enrolled patients, age, sex, CVD diagnosis, medications in each group, follow-up duration, end points, and adverse effects) was summarized on standardized reporting forms. Absolute numbers were calculated when only percentages were reported.

Of 1,541 eligible reports identified, 68 RCTs satisfied our criteria (Figure 1). Six were published in English<sup>13–18</sup> and 62 in Chinese,<sup>19–80</sup> from 1998 to 2014. The studies

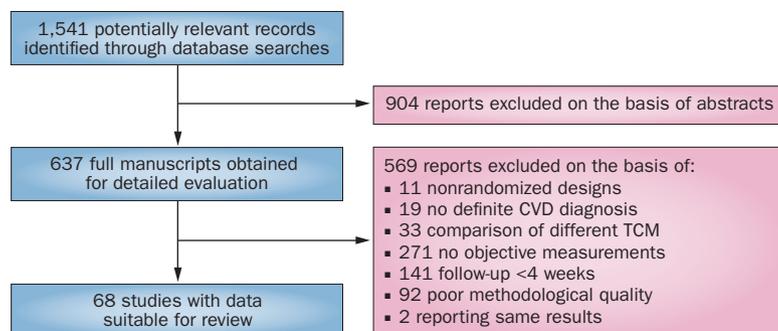
involved a total of 16,171 patients. 10 reports were concerned with hypertension,<sup>19–28</sup> 31 with CHD,<sup>13–15,29–56</sup> 14 with cardiac arrhythmias,<sup>16,17,57–68</sup> and 13 with HF.<sup>18,69–80</sup> The sample sizes ranged from 100 to 4,870 participants and the mean follow-up ranged from 4 to 234 weeks. The methodological quality of studies was generally low, with only 14 (21%) having a Jadad score  $\geq 3$ . Only three reports, all published in English, described adverse cardiovascular events.<sup>13–15</sup> Few reports provided laboratory measurements for drug-related adverse effects; adverse effects, including treatment-related symptoms and signs, were described in some. Full characteristics of the included studies are provided in [Supplementary Table 1 online](#).

**Hypertension**

Essential hypertension has become an epidemic disease, and is the most important risk factor for CHD and stroke in China.<sup>81</sup> China has an estimated 200 million individuals with hypertension, which accounts for  $\sim 20\%$  of the total burden of hypertension worldwide.<sup>81</sup> However, awareness of the disease, treatment rates, and control rates are low (30.2%, 24.7%, and 6.1%, respectively).<sup>81</sup> By comparison, the control rate of hypertension in the USA is 36.8%.<sup>82</sup> The main reason for the low control rate of hypertension in China is that more than one Western medicine drug is needed to normalize blood pressure in most patients, which constitutes a large economic burden to patients in rural areas, whereas in major cities the control rate of hypertension can be as high as 26.8%.<sup>83</sup> Another major issue is that patients with hypertension often have multiple risk factors, such as hyperglycaemia, hyperlipidaemia, or target-organ damage (for example, carotid artery atherosclerosis and microproteinuria) that might add further economic burden. One important advantage of TCM is that patients are treated holistically and, therefore, TCM uses medications aimed at multiple targets, which might help to improve compliance.<sup>3</sup> Another advantage is that the medications used are much lower in price than Western medicine drugs in China.<sup>84,85</sup>

TCM ingredients commonly used to treat hypertension include dogbane (*Apocynum venetum*) leaf, *Prunellae* sp. flowers, chrysanthemum (generally *Chrysanthemum morifolium* or *Chrysanthemum indicum*) flower and red ochre (ochre and haematite). Patients with hypertension had oxidative stress, which can lead to vascular endothelial injury and inflammatory reaction and contribute to the progression of atherosclerosis.<sup>86</sup> In a 2013 meta-analysis, the decoction of tall gastrodia (*Gastrodia elata*) and *Uncaria tomentosa* significantly increased superoxide dismutase levels and attenuated oxidative stress in patients with hypertension when compared with Western medication, although blood pressure did not differ between groups.<sup>87</sup>

In the RCTs we assessed for this Review, 1,658 patients with hypertension (966 [58%] men, age 26–91 years) were enrolled, and diagnosed according to the 1999 WHO/International Society of Hypertension guidelines and the 1999 Chinese guidelines on the prevention and treatment of hypertension and updated editions (2004, 2005, 2006, and 2010), dependent on the date of



**Figure 1** | Selection of randomized, controlled trials. Abbreviations: CVD, cardiovascular disease; TCM, traditional Chinese medication.

publication. All 10 reports of hypertension were published in Chinese and all had a low Jadad score except one, which had a score of 3.<sup>19</sup> In addition, hard end points, such as all-cause mortality or major adverse cardiovascular events, were not evaluated. Consequently, whether TCM can improve the long-term outcome of patients with hypertension remains unknown.

The therapeutic effects of TCM were compared with no intervention or Western medications. The following TCMs were compared with blank control: decoction of tall gastrodia and *Uncaria tomentosa*,<sup>19</sup> *Rehmannia* sp. bolus plus decoction of tall gastrodia and *Uncaria tomentosa*,<sup>20</sup> decoctions of *Pinellia ternata* plus *Atractylodes macrocephala* rhizome, tall gastrodia plus *Alisma* sp.,<sup>21</sup> *erbai jiangya*,<sup>22</sup> and *sini*,<sup>23</sup> and one mixed TCM formula.<sup>24</sup> In the studies of Western medications, decoction of tall gastrodia and *Uncaria tomentosa* was compared with nitrendipine<sup>25,26</sup> or captopril,<sup>27</sup> and compound *qima* capsules were compared with nifedipine.<sup>28</sup>

TCM treatment was associated with significantly lowered systolic and diastolic blood pressures compared with no intervention in four of the six studies (mean 22.38 mmHg versus 17.40 mmHg for systolic blood pressure; 15.45 mmHg versus 10.34 mmHg for diastolic blood pressure). Treatment-related adverse effects were reported in two studies, and were dry cough, dry mouth, sleepiness, dizziness, constipation, nausea, vomiting, and anorexia.<sup>19,22</sup> The incidence of adverse effects was similar for tall gastrodia and *Uncaria tomentosa* and no intervention control,<sup>19</sup> but was lower than with the no intervention control in patients receiving *erbai jiangya* decoction.<sup>22</sup>

In comparisons of TCM and Western medication, treatment with decoction of tall gastrodia and *Uncaria tomentosa* was associated with significantly lowered systolic and diastolic blood pressure compared with captopril,<sup>27</sup> but not nitrendipine.<sup>25,26</sup> When compared with compound *qima* capsules, nifedipine had great reduction on diastolic blood pressure, but similar effects on systolic blood pressure.<sup>28</sup> Drug-related adverse effects were reported in two studies.<sup>27,28</sup> A dry mouth was reported by those taking compound *qima* capsules, and facial flushing and oedema with nifedipine, but the incidence did not differ significantly between groups.<sup>28</sup> In another study participants reported a dry cough, rash, and oedema with captopril, and dry cough and rash with decoction of

tall gastrodia and *Uncaria tomentosa*, but the incidence in the TCM group was significantly lower than that in captopril group.<sup>27</sup> Therefore, TCM might have moderate antihypertensive effects and seem to be well tolerated.

## CHD

Mortality related to CVD is rapidly escalating in China; an estimated 3 million Chinese people die from CHD and stroke each year, which equates to one death every 10 s. However, even in large hospitals in China, almost one-third of outpatients receive TCM for CHD.<sup>6</sup> Chinese herbs commonly used to treat angina pectoris include red sage (*Salvia miltiorrhizae*) root, safflower (*Carthamus tinctorius*) flowers, chuanxiong rhizome (*Ligusticum wallichii*), pollen from *Typhaceae* sp., roots from *Curcuma* sp., and macrostem onion (*Allium macrostemon*).

In the studies we assessed, 9,209 patients with CHD were enrolled (age 28–88 years), diagnosed according to the Chinese guidelines on the prevention and treatment of CHD 1997 or 2007 edition, dependent on the publication date. 28 reports were published in Chinese<sup>29–56</sup> and three in English.<sup>13–15</sup> Only eight studies were of good quality, having a Jadad score of 3–5.<sup>13–15,29–33</sup> All-cause mortality and major adverse cardiovascular events were investigated in only three studies.<sup>13–15</sup>

The most important TCM trial that used major adverse cardiovascular events as an end point was a secondary prevention study, CCSPS,<sup>13</sup> in which the effects of *xuezhikang*, a partially purified extract of red yeast rice, on serum lipid levels and cardiovascular end points were evaluated in Chinese patients with a history of MI. Patients were randomly assigned to receive placebo ( $n = 2,441$ ) or *xuezhikang* ( $n = 2,429$ ) daily and were followed up for a mean of 4.5 years. The primary end point was a major coronary event, including death from CHD and nonfatal MI. The incidence of the primary end point was 10.4% in the placebo group and 5.7% in the *xuezhikang* group, which equates to absolute and relative decreases of 5% and 45%, respectively. *Xuezhikang* treatment was also associated with significantly decreased cardiovascular and all-cause mortality (30% and 33%, respectively) and need for coronary revascularization (33% decrease). Serum levels of total and LDL cholesterol and triglycerides were lower in the *xuezhikang* group than in the placebo group, and HDL cholesterol levels were elevated. *Xuezhikang* treatment was deemed safe and well tolerated. This multicentre, randomized, double-blind, placebo-controlled trial clearly demonstrated that long-term treatment with *xuezhikang* significantly prevented the occurrence of coronary events in patients with previous MI. Several ingredients are used in this treatment, of which lovastatin, although quantitatively predominant, is unlikely to account solely for the favourable plasma lipid-lowering and the rather striking cardiovascular benefit found.<sup>13,88</sup> Other components, such as lovastatin hydroxy acid, plant sterols, isoflavones, and isoflavone glycosides, are likely to have contributed to the results.<sup>13,88</sup> Furthermore, TCM for supplementing *qi*, nourishing *yin*, and activating blood circulation have been associated with improved cardiac function, reduced symptom and sign scores, and reduced

incidence of major adverse cardiovascular events in patients with acute coronary syndromes after successful percutaneous coronary intervention.<sup>14</sup>

For angina pectoris, in the 13 RCTs that used no intervention or placebo, TCMs used included *buyang huanwu*, *yiqi yangyin*, snakegourd fruit plus macrostem onion plus *Pinellia ternata*, *qingre jiedu huoxue jianpi*, *ershen* pseudoginseng, *xuefu zhuyu*, *shugan yiqi tongyu*, *zhuyu*, *buqi huayu*, and *sini* decoctions and *maixuekang*, *tongxinluo*, *yiqi tongmai*, and *guanxin tongluo* capsules.<sup>15,29,34–44</sup> In the 16 studies in which TCM was compared with Western medication, the following comparisons were made: compound *danshen* dripping pills with isosorbide dinitrate;<sup>30–32,45,46</sup> *Zhuyu* decoction with aspirin,  $\beta$ -blockers, and angiotension-converting-enzyme inhibitors or angiotensin-receptor blockers;<sup>33</sup> *yiqi tongmai* capsules with isosorbide dinitrate plus diltiazem;<sup>47</sup> *shenhong* (dried *Panax ginseng*, *Salvia miltiorrhiza*, and *Rhodiola rosea*) *huazhuo tongluo* granules with isosorbide mononitrate;<sup>48</sup> *ziyin qianyang huoxue* formula with isosorbide dinitrate plus captopril;<sup>49</sup> musk *baoxin* pills with isosorbide dinitrate;<sup>50</sup> *xuefu zhuyu* decoction with isosorbide dinitrate;<sup>51</sup> *shugan yiqi tongyu* decoction with aspirin, clopidogrel, isosorbide dinitrate, and metoprolol;<sup>52</sup> *buqi huayu* decoction with isosorbide mononitrate;<sup>53</sup> *guanxin tongluo* capsules with isosorbide mononitrate;<sup>54</sup> TCM hot compress with isosorbide mononitrate;<sup>55</sup> and *sini* decoction with ferulic acid.<sup>56</sup> An effective response to treatment was defined as reduced Canadian angina classification by at least one grade and improvement in depressed ST segment by  $\geq 1$  mm (or  $\geq 0.5$  mm) on electrocardiography, at rest or under stress.

In nine studies in which no intervention control or placebo was used, effective response rates were significantly higher in the TCM group than in the control group. The effective response rate and incidence of important clinical events did not differ between patients receiving *yiqi yangyin* decoction and blank control.<sup>15</sup> Treatment-related adverse effects were insomnia with *yiqi yangyin* decoction<sup>15</sup> and headache with *hewei jiangzhuo* formula.<sup>36</sup> Adverse effect rates did not differ significantly between the TCM and control groups.

In most studies to compare TCM and Western medication, the effective response rate was higher in the TCM groups. However, the effective response rates did not differ between red ginseng *huazhuo tongluo* granules,<sup>48</sup> *xuefu zhuyu* decoction,<sup>51</sup> or *guanxin tongluo* capsules,<sup>54</sup> and nitrates. Moreover, the frequency of adverse effects was lower with TCM than with Western medication. Adverse effects included rash, facial flushing, headache, sensation of 'head fullness', dizziness, palpitations, abdominal discomfort, and body pain for nitrates; lip numbness, abdominal discomfort, and dizziness for musk *baoxin* pills; and abdominal discomfort for compound *danshen* dripping pills. TCM treatment, therefore, had similar antianginal effects to Western medication and might be an alternative option for patients. High-quality, large-scale RCTs (similar to CCSPS<sup>13</sup>) are required before any definite conclusions can be drawn as to whether TCM treatment can improve long-term outcomes in patients with angina.

In China, TCM is widely used to treat or prevent ischaemic stroke, especially stroke related to atherosclerosis. Eight medications (milk vetch [*Astragalus membranaceus*] root, *mailuoning*, *Ginkgo biloba*, ligustrazine, *danshen* agents, *xuesetong*, puerarin, and *Acanthopanax* [*Eleutherococcus senticosus*]) were studied more often and in greater numbers of patients than other TCMs, but the evidence of efficacy and adverse effects was poor for ischaemic stroke.<sup>89</sup>

### Cardiac arrhythmias

Cardiac arrhythmias, including paroxysmal atrial fibrillation, frequent atrial or ventricular premature beats, and bradycardia–tachycardia syndrome, are common clinical diseases. Other causes of arrhythmias are sick sinus syndrome and atrioventricular block. Patients with paroxysmal atrial fibrillation are at increased risk of HF and thromboembolism. Although atrial or ventricular premature beats without concomitant organic cardiac disease might not require treatment, studies have revealed a potential role of frequent atrial or ventricular premature beats in the pathogenesis of cardiomyopathy.<sup>90</sup>

We identified studies that included a total of 3,060 patients with arrhythmias (age 15–86 years); 12 reports were published in Chinese<sup>57–68</sup> and two in English.<sup>16,17</sup> Only three studies were of good quality, with a Jadad score of 3–5.<sup>16,17,57</sup> In addition, major adverse cardiovascular events were not evaluated. Whether TCM treatment can improve the long-term outcome of patients with cardiac arrhythmias, therefore, remains unknown.

Diagnosis of cardiac arrhythmias was based on electrocardiographic or 24 h dynamic electrocardiographic recordings. TCMs, including fried *Glycyrrhizae uralensis* decoction, *yangxue fumai* decoction, decoctions of bupleurum root (*Bupleurum chinense*) plus *longmu*, and *shensong yangxin* and *anfuer* capsules were compared with no intervention or placebo in four studies.<sup>16,17,58,59</sup> In 11 RCTs involving Western medications, *shensong yangxin* capsules were compared with mexiletine<sup>16</sup> or bisoprolol,<sup>57</sup> *wenxin* granules with propafenone<sup>60–62</sup> or mexiletine,<sup>63</sup> *jianxin pinglu* pills with amiodarone,<sup>64</sup> *huangyangning* with propafenone,<sup>65</sup> decoction of bupleurum root plus *longmu* with Western medications (including lidocaine, procainamide, quinidine, potassium chloride, propranolol, and/or phenytoin),<sup>66</sup> *anfuer* capsules with mexiletine,<sup>67</sup> and *dingxin* granules with mexiletine.<sup>68</sup>

Effective response to treatment was defined as: a 50% reduction in ectopic beats recorded by 24 h dynamic electrocardiography in patients with atrial or ventricular premature beats; arrhythmic episodes in 1 month reduced by 50% or the ventricular rate recorded by 24 h dynamic electrocardiography reduced by 20% in patients with paroxysmal atrial fibrillation; and the average heart rate on 24 h dynamic electrocardiography increased by 10% in patients with bradycardia. In studies to compare TCM with no intervention or placebo, the effective response rate was significantly higher in all TCM groups than in control groups. Treatment-related adverse effects included abdominal discomfort and dizziness for fried *Glycyrrhizae uralensis* decoction,<sup>58</sup> and abdominal discomfort,

headache, and dizziness for *yangxue fumai* decoction,<sup>59</sup> but the rates did not differ significantly between the treatment and control groups. In studies involving Western medication, the effective response rate was also higher in the TCM groups in eight studies and did not differ in three.<sup>61,62,68</sup> Fewer treatment-related adverse effects were reported with *jianxin pinglu* pills than with amiodarone,<sup>64</sup> with *anfuer* capsules than with mexiletine,<sup>67</sup> with *wenxin* granules plus oryzanol than with propafenone,<sup>62</sup> and with dingxin granules than with mexiletine.<sup>68</sup> Notably, two studies had a Jadad score of 5 and were published in English, which suggested good quality.<sup>16,17</sup> On the basis of these findings, we suggest that TCM might be useful as a complementary or alternative approach in the treatment of cardiac arrhythmias, particularly in patients with bradycardia–tachycardia syndrome.

A major problem in the treatment of cardiac arrhythmias is that almost all Western antiarrhythmic medications have notable adverse effects, and some drugs might be proarrhythmic. Treatment of bradycardia–tachycardia syndrome is particularly difficult, and many patients with this syndrome require pacemaker implantation combined with antiarrhythmic drugs.<sup>91</sup> Therefore, further exploration of the possible role of TCM in the treatment of cardiac arrhythmias is urgently needed.

TCMs commonly used to normalize heart rate or rhythm in patients with tachyarrhythmias include coptis (*Coptis chinensis*) root, scutellaria (*Scutellaria baicalensis*) root, and spikenard (*Nardostachys jatamansi*) root. Similarly, some TCMs are useful in normalizing heart rate or rhythm in patients with bradycardia; examples are aconite root, ginseng (*P. ginseng*), cinnamon bark and twigs (*Cinnamomum* sp.), and *Ganoderma lucidum*. TCM formulas containing mixtures of these herbs, therefore, might have both antibradycardic and antitachycardic effects. For example, *shensong yangxin* capsules were associated with reductions in premature ventricular beats in patients with or without organic heart disease in a multicentre, randomized, double-blind, placebo-controlled trial.<sup>16</sup> Similarly in another multicentre, randomized, double-blind, placebo-controlled trial, these capsules were efficacious in increasing heart rate in patients with sick sinus syndrome or atrioventricular block.<sup>17</sup> Although the exact mechanisms underlying TCM-mediated antibradycardic and antitachycardic effects are unknown, rapid and slow heart rate might be possible to control in the same patient.

### Heart failure

Chronic HF is clinically associated with high morbidity and mortality and constitutes a substantial burden on health-care systems. The investigators in an epidemiological study of 15,518 Chinese adults in 2000 reported an HF prevalence of 0.9%, or >10 million patients, in China.<sup>92</sup> The prognosis of patients with chronic HF has improved during the past 2 decades because of increased use of angiotensin-converting-enzyme inhibitors, angiotensin-receptor antagonists,  $\beta$ -blockers, and mineralocorticoid-receptor antagonists. Nonetheless, the prevalence of HF continues to rise, largely because of

the improved survival of patients after acute coronary syndromes and expanding populations exposed to HF risks because of increasing age and/or adoption of Western lifestyles in some countries. To reduce the high morbidity and mortality associated with HF, new therapeutic approaches are needed. Some TCMs are used to improve cardiac function in patients with HF, such as astragalus (*Astragalus membranaceus*) root, lepidium seed (*Lepidium* sp. and *Descurainia* sp.), fuling (*Wolfiporia extensa*, also known as *Poria cocos*), and ginseng (*P. ginseng*).

We found studies involving a total of 2,244 patients with HF (age 32–87 years); 12 reports were published in Chinese<sup>69–80</sup> and one in English.<sup>18</sup> Jadad scores were generally low, except for one report that had a score of 3,<sup>69</sup> and one with a score of 5.<sup>18</sup> In addition, hard end points, such as all-cause mortality or major adverse cardiovascular events, were not evaluated. Whether TCM improves the long-term outcome of patients with heart failure, therefore, remains unknown.

Diagnosis of HF followed the Chinese guidelines on the prevention and treatment of heart failure published in 1997 and updated in 2007, depending on the study publication date. TCMs assessed in these studies included *qiangxin kangshuai*, *lixin*, *shenqi yangxin*, modified *baoyuan* decoction and *xinshuai* decoction, and *qili qiangxin* and *qianglixin* capsules, compared with no intervention or placebo in all 13 studies. The effective response to treatment was defined as an increase of at least one NYHA functional class. The effective response rate was higher in TCM than in control groups in all but three studies.<sup>70–72</sup> In these studies, before treatment, the mean left ventricular ejection fraction measured by 2D echocardiography was 36.5% in the control and TCM groups, and after treatment was 43.5% and 49.0%, respectively. The E/A ratio (a marker of left ventricular diastolic function) was much higher in patients treated with TCM than in controls. Only three reports gave data on 6 min walking distance, which showed significant improvement after TCM relative to control.<sup>18,73,74</sup> The level of NT-proBNP in serum was measured in only one study,<sup>18</sup> and a greater reduction was seen after treatment with TCM than with placebo. The level of B-type natriuretic peptide in serum was measured in another study<sup>72</sup> and did not differ between groups before treatment, but was significantly lower in the TCM group after treatment. The treatment-related adverse effects reported were nausea, vomiting, and abnormal liver function for both TCM and blank control or placebo groups, but the rates did not differ significantly between groups.

The largest multicentre, randomized, double-blind, placebo-controlled clinical trial was designed to compare the efficacy and safety of *qili qiangxin* capsules with placebo in 512 patients with chronic HF.<sup>18</sup> The primary end point was a reduction or percentage change in NT-proBNP level during 12 weeks of treatment. Reductions from baseline were seen in the TCM and placebo groups, but were greater in the TCM group. Additionally, NYHA functional class, left ventricular ejection fraction, 6 min walking distance, and quality of life were improved more in the TCM group than in the placebo group.<sup>18</sup>

**Conclusions**

Compared with blank control or placebo, TCM was efficacious in lowering blood pressure in patients with hypertension, reducing the occurrence of coronary events in patients with previous MI (especially *xuezhikang*), attenuating the severity of angina and MI, inhibiting arrhythmic episodes—including both tachycardia and bradycardia (especially *shensong yangxin* capsules), and improving cardiac function in patients with HF (especially *qili qiangxin* capsules). Compared with Western medication, TCM had similar therapeutic effects in patients with hypertension and possibly a better effects in patients with angina pectoris and cardiac arrhythmias. In most studies, adverse effects with TCM did not occur significantly more frequently than those seen with controls or Western medication. Nevertheless, the methodological quality of most studies included in this Review was low, and many investigators did not assess major adverse cardiovascular events or laboratory measurements of adverse effects. High-quality, large-scale RCTs should, therefore, be undertaken before any definite conclusions can be drawn as to whether TCM treatment can improve the long-term outcome of patients with CVD.

**Review criteria**

We searched MEDLINE (Ovid), EMBASE, the Cochrane Library (Cochrane Central Register of Controlled Trials), Global Health, International Pharmaceutical Abstracts, the China National Knowledge Internet, China Biology Medicine Database, VIP database for Chinese technical periodicals, and the grey literature (SIGLE) databases for relevant randomized, controlled trials. We also considered published review articles, editorials, and Internet-based sources of information (<http://www.ClinicalTrials.gov>, <http://www.clinicaltrialsresults.org>, and <http://www.theheart.org>). We considered publications in either English or Chinese. In MEDLINE our search terms were “traditional Chinese medicine”, “traditional Chinese medication”, or “TCM” in combination with “cardiovascular disease”, “hypertension”, “angina”, “coronary heart disease”, “coronary artery disease”, “myocardial infarction”, “arrhythmia”, or “heart failure”, together with “randomized” or “randomized controlled trial”, with no restriction on subheadings. We adapted search terms for use in databases and search engines. For the PubMed search, we used either the Latin name of the plant or the generic name of the known compound, in combination with “cardiovascular”. We checked the reference lists of retrieved articles for further potential citations. We primarily focused on articles published after 1 January 1998.

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## Author contributions

P.P.H., Y.-X.Z., and Y.Z. made substantial contribution to discussion of the article content, wrote, reviewed, and edited the manuscript before submission. Y.-G.C., K.Z., M.-X.Z., C.Z. wrote, reviewed and edited the manuscript before submission. J.Y. made substantial contribution to discussion of the content and wrote the manuscript. F.J. made substantial contribution to discussion of the content.