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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Traditional Chinese Medicine for Cardiovascular Disease

Evidence and Potential Mechanisms

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ABSTRACT

Traditional Chinese medicine (TCM) has more than 2,000 years of history and has gained widespread clinical applications. However, the explicit role of TCM in preventing and treating cardiovascular disease remains unclear due to a lack of sound scientific evidence. Currently available randomized controlled trials on TCM are flawed, with small sample sizes and diverse outcomes, making it difficult to draw definite conclusions about the actual benefits and harms of TCM. Here, we systematically assessed the efficacy and safety of TCM for cardiovascular disease, as well as the pharmacological effects of active TCM ingredients on the cardiovascular system and potential mechanisms. Results indicate that TCM might be used as a complementary and alternative approach to the primary and secondary prevention of cardiovascular disease. However, further rigorously designed randomized controlled trials are warranted to assess the effect of TCM on long-term hard endpoints in patients with cardiovascular disease. (J Am Coll Cardiol 2017;69:2952–66)

Cardiovascular disease (CVD) is the number 1 cause of death in the world. The World Heart Federation has reported that CVD accounts for 17.3 million deaths/year, and possibly 23.6 million deaths/year by 2030 (1). Because of the unmet needs for CVD control with Western medicine, clinicians have begun to consider the possible role of traditional Chinese medicine (TCM) in the prevention and treatment of CVD, and a number of basic and clinical studies in this field have drawn increasing attention from the cardiovascular community.

TCM, 1 of the intriguing features of traditional Chinese culture, has a history of more than 2,000 years, with both unique theories and rich experience (2). Because of the lack of objective and quantitative evaluation criteria, TCM is considered to be complementary or alternative medicine in most Western countries. However, in China, more than 71.2% of patients who have experienced Western medicine, TCM, and integrative medicine (both Western medicine and TCM) preferred the integrative approach, and 18.7% chose TCM as their favorite (3). Moreover,

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TCM is increasingly welcomed in many developed countries, such as Australia and the United States. Importantly, patients who used more types of TCM tended to use much less Western medicine recommended by current guidelines (4).

Although TCM has had wide applications in many countries, this ancient art is often criticized or even rejected by Western scientists for the following reasons: 1) the TCM formula consists of dozens of ingredients with innumerous chemical molecules, making it difficult, if not impossible, to elucidate the therapeutic mechanism of TCM; 2) currently available TCM medications in China do not undergo the same rigorous approval procedures as Western drugs, so their efficacy and safety cannot be guaranteed; and 3) most clinical studies of TCM were conducted in China by TCM physicians, and very few TCM medications are available in Western countries. Thus, most TCM studies are of poor quality, and the conclusions drawn are not accepted by Western society. To clarify these doubts about TCM, high-quality clinical trials of TCM therapy are needed, and recent progress in randomized controlled trials (RCTs) has spurred the modernization of TCM in China (5). However, most RCTs on TCM have had small sample sizes, used surrogate endpoints, followed study patients for a short period of time, and reported diverse outcomes. Here, we aim to critically evaluate the beneficial and detrimental effects of TCM in patients with CVD, as well as the underlying mechanisms. We searched for the most up-to-date (the past 10 years) published studies of RCTs using pre-defined, strict inclusion and exclusion criteria, and systemically assessed the efficacy and safety of TCM therapy for patients with CVD risk factors (hypertension, dyslipidemia, and diabetes/pre-diabetes) and the 2 major types of CVDs: atherosclerotic cardiovascular disease (ASCVD) and chronic heart failure.

THE SEARCH FOR AND SELECTION OF RCTS

Relevant studies were identified by searching for papers published from January 2006 to 2016 in MEDLINE (Ovid); EMBASE; the Cochrane Library (Cochrane Central Register of Controlled Trials); Global Health, International Pharmaceutical Abstracts; the China National Knowledge Internet; and the China biology medicine, Wanfang, and VIP databases. We also considered published reviews, editorials, and Internet-based sources of information. Because many RCTs on TCM were published in Chinese, published reports in English or Chinese were included. The search algorithm for MEDLINE was as follows: ("traditional Chinese medicine" OR "TCM") AND ("cardiovascular disease" OR "hypertension" OR "blood pressure" OR "dyslipidemia" OR "hyperlipidemia" OR "lipid" OR "diabetes" OR "pre-diabetes" OR "impaired fasting glucose" OR "impaired glucose tolerance" OR "angina" OR "coronary heart disease" OR "coronary artery disease" OR "myocardial infarction" OR "stroke" OR "heart failure") AND ("randomized" OR "randomized controlled trial") AND "blind," with no restriction on subheadings. Similar but adapted search terms were used for other databases of published reports or search engines. The reference lists of all retrieved papers were checked for other potentially relevant citations, and studies not included in the electronic sources mentioned previously were searched manually. Whenever necessary, the authors of the identified papers were contacted for additional information.

We included reports of clinical studies with the following criteria: 1) study patients with a definite diagnosis of essential hypertension, dyslipidemia, diabetes/pre-diabetes, ASCVD, or heart failure who were randomized to receive TCM, contemporary medication, or placebo; 2) sample size in each study group ≥50 cases; 3) follow-up in each study group ≥4 weeks; and 4) quantitative measurements of surrogate endpoints and/or adverse cardiovascular events and/or adverse drug effects available to facilitate outcome analysis. We excluded reports of studies with the following features: 1) studies were nonrandomized and/or non-double-blinded; 2) patients enrolled had no definite diagnosis; 3) studies compared different TCM medications; and 4) studies reported only symptomatic changes of patients, without objective laboratory measurements or physical examination. Methodological quality was evaluated for each study with a Jadad score between 0 (weakest) to 5 (strongest), as described previously (6); any study with a Jadad score <3 was considered to be of poor quality and was excluded. In addition, when 2 papers reported the results of the same study, the paper with less data was excluded.

Finally, we included 56 eligible reports of RCTs: 21 in English (7–27) and 35 in Chinese (28–62). The time of publication of these 56 studies ranged from 2006 to 2016. Overall, there were 8 reports of hypertension, 6 of dyslipidemia, 15 of diabetes/pre-diabetes, 18 of ASCVD, and 9 of chronic heart failure. TCM interventions for each disease were classified into 2 groups: group A, with evidence from 1 or 2 RCTs that assessed the same compound for the same endpoint with a high-quality design (Jadad score: 5); and

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CIMT = carotid intima-media thickness

CVD = cardiovascular disease

FPG = fasting plasma glucose

MI = myocardial infarction

PCI = percutaneous coronary intervention

PG = postprandial glucose

RCT = randomized controlled trial

T2DM = type 2 diabetes mellitus

TCM = traditional Chinese medicine

group B, with evidence from only 1 RCT that had a moderate-quality design (Jadad score: 3 or 4).

TCM FOR RISK FACTORS OF CVD

EFFECT ON HYPERTENSION. Eight RCTs focusing on TCM and essential hypertension were included and assessed (7,8,28-33). The sample size ranged from 102 to 480 participants, and mean follow-up ranged from 4 to 52 weeks. The methodological quality of the included studies was, in general, high: 7 of 8 reports had a Jadad score of 5 (7,8,29-33), and 1 RCT on the Bushenheluo formula had a Jadad score of 3 (28) (Online Table 1).

TCM herbs commonly used to treat hypertension include Ramulus Uncariae cum Uncis (*Uncaria rhynchophylla* [Miq.] Miq. ex Havil.), milkvetch root (*Astragalus membranaceous* [Fisch.] Bunge), *Achyranthes bidentata* Bl., *Ligusticum wallichii* (Rhizoma Ligustici Chuanxiong), tall gastrodia tuber (*Gastrodia elata* Bl.), Radix Rehmanniae (*Rehmannia glutinosa* [Gaetn.] Libosch. ex Fisch. et Mey.), and glossy privet fruit (Fructus Ligustri Lucidi), which have been found to be effective in lowering blood pressure (BP).

Data summaries for the high-quality RCTs of TCM interventions for hypertension are listed in **Figure 1**. TCM interventions in Group A for hypertension included Tiankuijiangya tablet, Zhongfujiangya capsule, Qiqilian capsule, Jiangya capsule, Jiangyabao tablet, and TCM acupuncture. Efficacy and safety of Tiankuijiangya in hypertensive patients were examined in an RCT involving 6 centers. A total of 8 weeks of treatment with Tiankuijiangya resulted in a statistically significant lowering of morning systolic blood pressure (SBP) by 17.64 mm Hg and diastolic blood pressure (DBP) by 11.85 mm Hg from baseline (both $p < 0.05$), with statistical significance compared with placebo (both $p < 0.05$). The incidence of adverse effects was 3.13% (5 of 160) in the Tiankuijiangya group and 2.50% (2 of 80) in the placebo group (30). A total of 418 hypertensive patients were randomized to Zhongfujiangya ($n = 314$) and benazepril ($n = 104$) groups in another multicenter RCT. Zhongfujiangya treatment for 4 weeks lowered 24-h average SBP by 10.67 mm Hg and DBP by 7.49 mm Hg from baseline (both $p < 0.01$). The BP-lowering effect of Zhongfujiangya was similar to that of benazepril ($p = 0.661$ for SBP and $p = 0.409$ for DBP) (33). The rate of effective response to treatment with the Qiqilian capsule, defined as a reduction of DBP ≥10 mm Hg or to normal range and/or SBP ≥30 mm Hg, was higher than that with placebo ($p < 0.05$) (31). In 1 RCT, compared with placebo, the Jiangya capsule significantly lowered SBP ($p < 0.05$), but not DBP ($p > 0.05$) (29). In another study, the Jiangya capsule was compared with placebo and nimodipine. The Jiangya capsule lowered 24-h average and day-average SBP (both $p < 0.05$), but not DBP or night-average SBP (both $p > 0.05$), compared with placebo, with no substantial difference in SBP or DBP between Jiangya and nimodipine treatment (both $p > 0.05$) (7). Although the effective response to treatment with Jiangyabao tablet in the daytime did not differ from that with placebo ($p > 0.05$), both SBP and DBP were significantly lower with Jiangyabao than with placebo at night (both $p < 0.05$) (32). No serious drug-related adverse effects occurred after treatment with Tiankuijiangya, Zhongfujiangya, Qiqilian, Jiangya, or Jiangyabao.

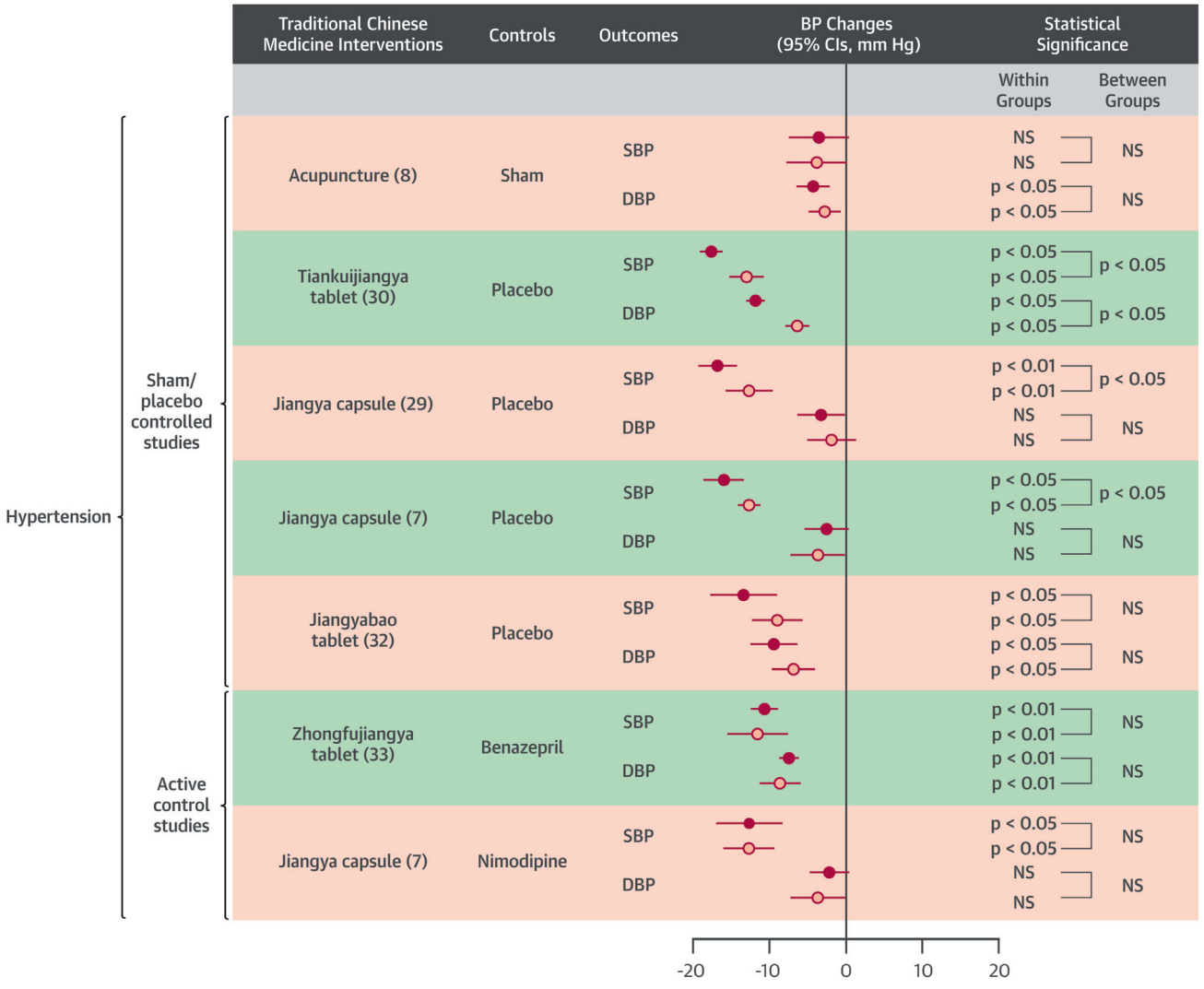
The SHARP (Stop Hypertension with the Acupuncture Research Program) pilot trial used rigorous methodology and principles of TCM acupuncture to examine the effect of acupuncture on hypertension in a relatively large sample of participants ($n = 192$). Participants were randomly assigned to active or invasive sham acupuncture twice weekly for 6 weeks. During the first 10 weeks after random assignment, BP was monitored every 2 weeks, and the mean BP decrease from baseline to 10 weeks did not differ significantly between participants with active (individualized and standardized) versus sham acupuncture (SBP: −3.56 mm Hg vs. −3.84 mm Hg; $p = 0.90$; DBP: −4.32 mm Hg vs. −2.81 mm Hg; $p = 0.16$). No treatment effects were evident after 12 months. The results did not reveal any benefit of active acupuncture for controlling hypertension relative to invasive sham acupuncture (8).

The sole TCM medication in group B was Bushenheluo formula. Bushenheluo formula significantly lowered SBP ($p < 0.05$), but not DBP ($p > 0.05$), compared with placebo. The safety profile was similar in the 2 treatment groups (28).

Thus, current evidence indicates that some TCM medications, such as Tiankuijiangya, Zhongfujiangya, Qiqilian, Jiangya, and Jiangyabao, have certain antihypertensive effects and a good safety profile, and may likely serve as an alternative approach for patients who are intolerant of or cannot afford Western medications. However, their long-term effects on BP and cardiovascular events are still unclear.

EFFECT ON DYSLIPIDEMIA. In the 6 eligible RCTs for treating dyslipidemia with TCM, the following TCM formulations were compared with placebo: Xiaoyujiangzhi capsule, Propolis and ginkgo extract, glossy ganoderma and sea cucumber extract, Jiangzhitongluo capsule, and *Salvia miltiorrhiza* and *Pueraria lobata* capsule; Zhibitai capsule was compared with

FIGURE 1 Data Summaries From the High-Quality RCTs of TCM Interventions for Hypertension



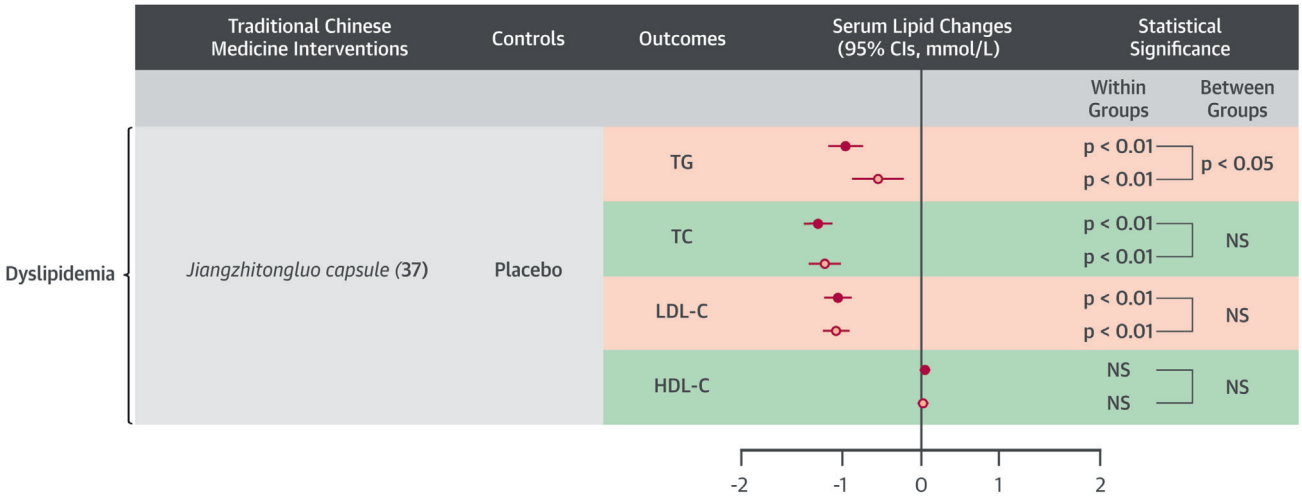
Filled circles = treatment; **open circles** = control; **numbers in parentheses** = reference numbers. BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; NS = not significant; RCT = randomized controlled trial; SBP = systolic blood pressure; TCM = traditional Chinese medicine.

atorvastatin (9,34-38). The sample size ranged from 106 to 288, and the mean follow-up duration was 6 to 52 weeks. The methodological quality of the included studies was, in general, low: only 1 of 6 reports had a Jadad score of 5 (37), and the other 5 had Jadad scores of 3 or 4 (9,34-36,38) (Online Table 2).

Some TCM herbs, including red sage root (Radix *Salvia miltiorrhiza*), maybush (*Crataegus pinnatifida* Bunge), rhizoma alismatis (*Alisma plantago-aquatica* Linn.), largehead atractylodes rhizome (Rhizoma Atractylodis Macrocephalae), ginkgo (*Ginkgo biloba* L.), glossy ganoderma (*Ganoderma lucidum*), and curcuma root (Radix Curcumae) have been found effective in lowering serum lipid levels.

The sole TCM medication in group A for dyslipidemia was the Jiangzhitongluo capsule. In this RCT, 138 patients with triglycerides >1.7 mmol/l and low-density lipoprotein cholesterol (LDL-C) >3.37 mmol/l were randomized to Jiangzhitongluo (n = 69) or placebo (n = 69) treatment in addition to atorvastatin treatment in both groups. A total of 8 weeks of treatment with the Jiangzhitongluo capsule significantly lowered serum triglyceride levels ($p < 0.05$), but did not alter the serum levels of total cholesterol,

FIGURE 2 Data Summary From the High-Quality RCT of Jiangzhitongluo Capsule for Dyslipidemia



Filled circles = treatment; **open circles** = control; **number in parenthesis** = reference number. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol; TG = triglycerides; other abbreviations as in Figure 1.

LDL-C, and high-density lipoprotein cholesterol (HDL-C) (all $p > 0.05$), compared with placebo (37). The adverse effects with the Jiangzhitongluo capsule were aminotransferase abnormality and gastrointestinal discomfort, but the incidence of these adverse effects did not differ between Jiangzhitongluo and placebo treatment. Figure 2 summarizes the data from this trial.

TCM medications in group B for dyslipidemia included *Salvia miltiorrhiza* and *Pueraria lobata* capsule, Zhibitai capsule, Xiaoyujiangzhi capsule, Propolis and ginkgo extract, and glossy ganoderma and sea cucumber extract. One RCT with a Jadad score of 3 evaluated the antiatherosclerotic efficacy and safety of *Salvia miltiorrhiza* and *Pueraria lobata* capsule in 165 post-menopausal women from 47 to 65 years of age with borderline hypercholesterolemia. After 6 months of treatment, the percent change of carotid intima-media thickness (CIMT) from baseline measured by high-resolution ultrasonography, a surrogate endpoint of atherosclerosis, was significantly less in patients receiving the capsule than in those receiving placebo (−0.57% vs. −0.03%; $p = 0.028$). Decreases in serum LDL-C and total cholesterol levels were also greater in patients receiving the capsule than placebo. *Salvia miltiorrhiza* and *Pueraria lobata* capsule was well tolerated, with no adverse effects (9). In another RCT with a Jadad score of 4, 240 patients 55 to 72 years of age with dyslipidemia were randomized to either Zhibitai ($n = 120$) or atorvastatin ($n = 120$). Zhibitai treatment for 8 weeks decreased triglycerides by 0.45 mmol/l, total cholesterol by 1.68 mmol/l, and LDL-C by 1.27 mmol/l, and increased HDL-C by 0.66 mmol/l from baseline (all $p < 0.05$). Levels of triglycerides, total cholesterol, LDL-C, and HDL-C, and drug-related adverse effects did not differ between the Zhibitai and atorvastatin treatment groups (all $p > 0.05$) (38). Moreover, serum levels of triglycerides and total cholesterol were lowered with the Xiaoyujiangzhi capsule, Propolis and ginkgo extract, or glossy ganoderma and sea cucumber extract as compared with placebo (all $p < 0.05$). However, these RCTs did not measure CIMT and failed to increase HDL-C levels without overt drug-related adverse effects (34-36).

Thus, available data suggest that some TCM medications, such as the Jiangzhitongluo capsule, *Salvia miltiorrhiza* and *Pueraria lobata* capsule, and Zhibitai capsule, have a potent lipid-lowing effect and may serve as an alternative to Western medications for the treatment of dyslipidemia. However, whether these salutary effects may translate into reduction of cardiovascular events awaits further high-quality, large-scale RCTs using hard outcome endpoints.

EFFECT ON DIABETES. In patients with type 2 diabetes mellitus (T2DM), TCM treatment was compared with placebo in 7 RCTs (10-12,39-42) and with Western medications in 3 RCTs (13,43,44); 6 of the 10 RCTs had a Jadad score of 5 (10-13,39,40). The sample size ranged from 108 to 800, and mean follow-up ranged from 4 to 78 weeks (Online Table 3).

TCM medications in group A for T2DM were the Xiaoke pill, Tangminling pill, Jinlida granule, Jianyutangkang tablet, 6-ingredient rehmannia pill, and Folium ginkgo tablet. In a multicenter RCT with a noninferiority design, a total of 800 T2DM patients with inadequate glycemic control (fasting plasma glucose [FPG]: 7 to 13 mmol/l and glycosylated hemoglobin [HbA_{1c}] 7% to 11%), of whom one-half were drug-naïve and one-half were already on metformin treatment, were randomized to Xiaoke and glibenclamide groups in a 1:1 ratio. Xiaoke treatment significantly reduced the risk of hypoglycemia (drug-naive patients in the Xiaoke arm were 38% less likely to have any hypoglycemia than those in the glibenclamide arm [$p = 0.024$]; the average annual rate of hypoglycemia in the Xiaoke arm was 62% lower than that in the glibenclamide arm in the patients previously treated with metformin monotherapy [$p = 0.003$]) and improved glycemic control similar to glibenclamide treatment. No serious adverse events were reported with either Xiaoke or glibenclamide treatment (13). In a large-scale RCT with a Jadad score of 5, a cohort of 480 overweight patients with early-stage T2DM (35 to 65 years of age, HbA_{1c} ≥7.0%, FPG 7.0 to 13.9 mmol/l or 2-h postprandial glucose [PG] >11.1 mmol/l, body mass index [BMI] ≥24 kg/m^2) were randomized into Tangminling or placebo groups in a 3:1 ratio. After 12 weeks of treatment, HbA_{1c} was reduced by 1.02% and 0.47% in the Tangminling and placebo groups, respectively. FPG was decreased by 0.8 ± 0.1 mmol/l in the Tangminling group, whereas it increased by 0.2 ± 0.2 mmol/l in the placebo group. Two-hour PG declined by 2.7 ± 0.3 mmol/l and 0.9 ± 0.4 mmol/l in the Tangminling and placebo groups, respectively (all $p < 0.05$). Tangminling treatment improved β-cell function, which was more prominent in patients with higher baseline HbA_{1c} levels. In addition, body weight, BMI, and waist circumference in the Tangminling group were reduced, and the symptoms related to diabetes were attenuated (10). In another multicenter RCT with a Jadad score of 4, a total of 210 overweight patients with early-stage T2DM were randomized into high-dose Tangminling (12 g), low-dose Tangminling (6 g), or placebo groups in a 1:1:1 ratio for 12 weeks. Both high- and low-dose Tangminling treatment significantly reduced HbA_{1c}, FPG, 2-h PG, BMI, and waist circumference compared with placebo treatment (all $p < 0.05$) (41). There was no significant difference in the type and frequency of adverse reactions between Tangminling and placebo treatments (10,41). In a multicenter RCT with a Jadad score of 5, 192 patients with T2DM (2-h PG 7.8 to 11.1 mmol/l and FPG >7.0 mmol/l) were randomly allocated to receive either Jinlida granule or placebo in addition to metformin treatment in a 1:1 ratio. After 12 weeks of treatment, HbA_{1c} decreased by 0.92% and 0.53% in the Jinlida and placebo groups, respectively ($p < 0.01$). There was a significant difference in the reduction of FPG between the 2 groups (−1.34 ± 1.70 mmol/l in the Jinlida group vs. −0.73 ± 1.70 mmol/l in the placebo group) and 2-h PG (−2.95 ± 3.99 mmol/l in the Jinlida group vs. −1.57 ± 4.34 mmol/l in the placebo group; both $p < 0.01$). The Jinlida group also showed improved β-cell function. No serious adverse events were reported with either Jinlida or placebo treatment (11). In another RCT with a Jadad score of 3, 280 patients with T2DM were randomized into Jinlida and metformin groups in a 1:1 ratio for 8 weeks. Jinlida reduced HbA_{1c}, FPG, and 2-h PG levels compared with metformin (all $p < 0.05$), without drug-related side effects (44). In a 3-center RCT, 150 patients with diabetes based on metformin treatment were randomized to receive the Jianyutangkang tablet ($n = 79$) or placebo ($n = 71$). After 26 weeks of treatment, FPG levels decreased by 2.0 ± 0.4 mmol/l and 1.4 ± 0.4 mmol/l in the Jianyutangkang and placebo groups, respectively ($p < 0.05$). HbA_{1c} levels were also significantly decreased in the Jianyutangkang group (−0.8 ± 0.2%) compared with the placebo group (−0.6 ± 0.2%) ($p < 0.05$). There were no adverse effects in either group during follow-up (12). By contrast, HbA_{1c}, FPG, 2-h PG levels, and insulin resistance did not differ between the 2 treatment groups, 1 with 6-ingredient rehmannia pill and Folium ginkgo tablet, and another with placebo (all $p > 0.05$) (39,40).

TCM medications in group B for T2DM were Jintangning capsule and Tangke capsule. A total of 480 T2DM patients were randomized into Jintangning ($n = 360$) and acarbose ($n = 120$) groups for 4 weeks of treatment in a phase III RCT with a Jadad score of 3. Jintangning treatment decreased FPG by 13.5%, 2-h PG by 20%, and HbA_{1c} by 5.6% from baseline (all $p < 0.0001$), and improved glycemic control similar to acarbose treatment (43). In another RCT with a Jadad score of 3, compared with placebo, Tangke capsule decreased 2-h PG ($p = 0.045$), but not HbA_{1c} or FPG levels (both $p > 0.05$) (42).

A total of 5 RCTs comparing TCM with placebo for pre-diabetes treatment were included and assessed (14,15,45-47), and the Jadad scores were 5 in 2 RCTs (14,45) and 4 in the other 3 RCTs (15,46,47). The sample size ranged from 122 to 420, and mean follow-up ranged from 12 to 104 weeks (Online Table 3).

TCM medications in group A for pre-diabetes included the Tangzhiping capsule and Tianqi capsule. In 1 RCT, 140 individuals with impaired glucose tolerance were randomized to a Tangzhiping ($n = 70$) or placebo ($n = 70$) group for 2 years.

The Tangzhiping group exhibited lower average annual morbidity from diabetes compared with the placebo group (5.39% vs. 11.72%; $p < 0.05$). No drug-related adverse events were reported in either group (45). In another multicenter RCT, a total of 420 individuals (mean age 52.4 years) with impaired glucose tolerance were randomized to Tianqi or placebo groups in a 1:1 ratio for 12 months of treatment. Of these patients, 389 completed the trial (198 in the Tianqi group and 191 in the placebo group), and Cox proportional hazards model analysis showed that Tianqi reduced the risk of diabetes by 32.1% compared with placebo ($p < 0.05$). No severe adverse events occurred (14). Data from the high-quality RCTs of TCM interventions for diabetes and pre-diabetes are summarized in **Figure 3**.

TCM medications in group B for pre-diabetes were Tianqijiangtang capsule, Jinqijiangtang tablet, and Yitangkang granule. In a multicenter RCT, 122 patients with impaired glucose tolerance and metabolic syndrome (mean age 52.9 years) were randomly assigned to receive Tianqijiangtang capsule ($n = 63$) or placebo ($n = 59$) for 12 months. Cox regression analysis revealed that Tianqijiangtang treatment reduced the risk of diabetes by 55.6% compared with placebo ($p < 0.05$) (46). In a multicenter RCT, 362 participants with pre-diabetes (mean age 54.5 years) were randomized to the Jinqijiangtang tablet ($n = 182$) or placebo ($n = 180$) groups. After 12 months of intervention and a 12-month follow-up, Jinqijiangtang tablet significantly reduced the incidence of diabetes (20.3% in the Jinqijiangtang group vs. 32.8% in the placebo group; $p < 0.05$) and increased the pre-diabetes to normal reversion rate (45.1% in the Jinqijiangtang group vs. 30% in the placebo group; $p < 0.05$), without drug-related adverse reactions (15). In addition, compared with placebo, Yitangkang granule decreased 2-h PG in patients with BMI ≥25 kg/m^2 ($p < 0.01$), but not HbA_{1c} or FPG levels (both $p > 0.05$) (47).

Taken together, these data suggest that some TCM medications, such as Xiaoke, Tangminling, Jinlida, and Jianyutangkang, have a potent therapeutic effect on glycemic control and/or β-cell function in patients with T2DM, and some other TCM medications, such as Tangzhiping and Tianqi, might prevent the progression of pre-diabetes to diabetes. However, whether they can improve the long-term outcomes of these patients remains unknown.

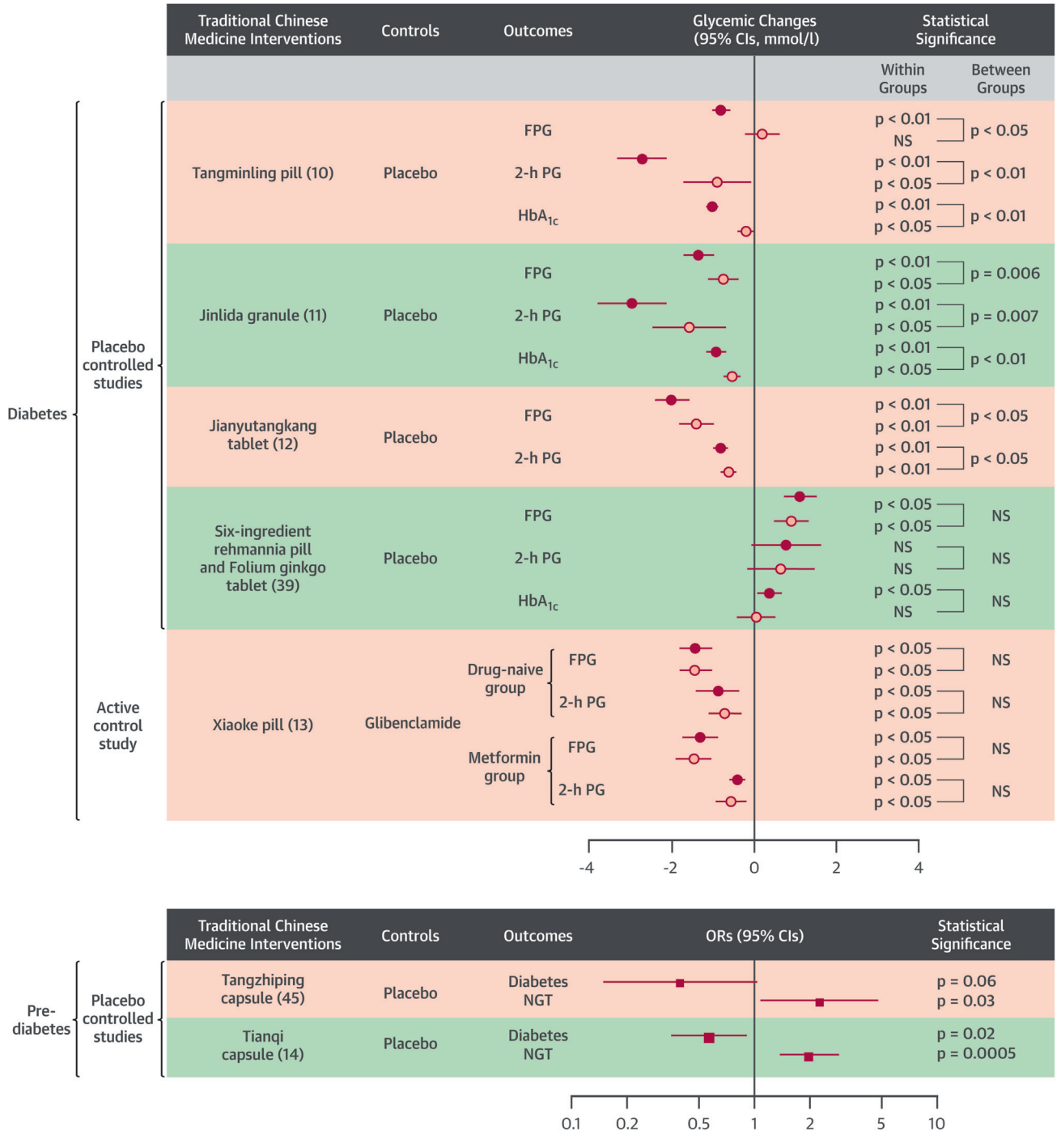
TCM FOR ASCVD

Clinical ASCVD consists of stable angina pectoris, acute coronary syndrome, history of myocardial infarction (MI) or arterial revascularization, stroke, transient ischemic attack, and peripheral arterial diseases (63). A number of TCM medications have been used to treat these diverse clinical syndromes. In patients with coronary artery disease (CAD), TCM herbs, such as red sage root (Radix *Salvia miltiorrhiza*), Ligusticum wallichii (Rhizoma Ligustici Chuanxiong), safflower (Flos Carthami), and curcuma root (Radix Curcumae) have proven effective in improving angina symptoms and clinical outcomes. We included and assessed 13 RCTs focusing on TCM and CAD; Jadad scores were 5 for 3 RCTs (18,20,21), 4 for 3 RCTs (17,19,53), and 3 for 7 RCTs (16,48–52,54). The sample size ranged from 100 to 4,870, and follow-up ranged from 4 weeks to 4.5 years (Online Table 4). Data from the high-quality RCTs of TCM interventions for ASCVD are summarized in the **Central Illustration**.

TCM medications in group A for CAD included the Xuezhikang capsule, Qishenyiqi dripping pill, and Shenzhuguanxin granule. The Chinese Coronary Secondary Prevention Study investigated the effect of Xuezhikang, a partially purified extract of red yeast rice, on serum lipid levels and cardiovascular endpoints in patients with previous MI. A total of 4,870 patients (mean age 58.9 years) were randomly assigned to receive placebo ($n = 2,441$) or Xuezhikang capsule ($n = 2,429$). After a mean follow-up of 4.5 years, the incidence of primary cardiovascular events was significantly lower with Xuezhikang treatment than with placebo (5.7% vs. 10.4%; $p < 0.05$). Serum levels of total cholesterol, LDL-C, and triglycerides were lower and HDL-C levels were higher with Xuezhikang than with placebo treatment (all $p < 0.001$). Xuezhikang was deemed safe and well tolerated, with no treatment-related serious adverse events reported (20). This study was compelling due to its large sample size, long duration of follow-up, and use of cardiovascular events as an outcome endpoint. One RCT assessed the efficacy and safety of the Qishenyiqi dripping pill for secondary prevention of MI. The result showed that Qishenyiqi and aspirin had similar effects in preventing the recurrence of vascular events in patients with previous MI, and that Qishenyiqi treatment produced fewer adverse effects than aspirin. This study was compelling for its large sample size, long duration of follow-up, and use of cardiovascular events as an outcome endpoint. However, the event rates in both groups were insufficient to generate a firm conclusion (21). In addition, compared with placebo, Shenzhuguanxin treatment improved angina symptoms, but did not reduce cardiovascular events in patients with CAD (18,48).

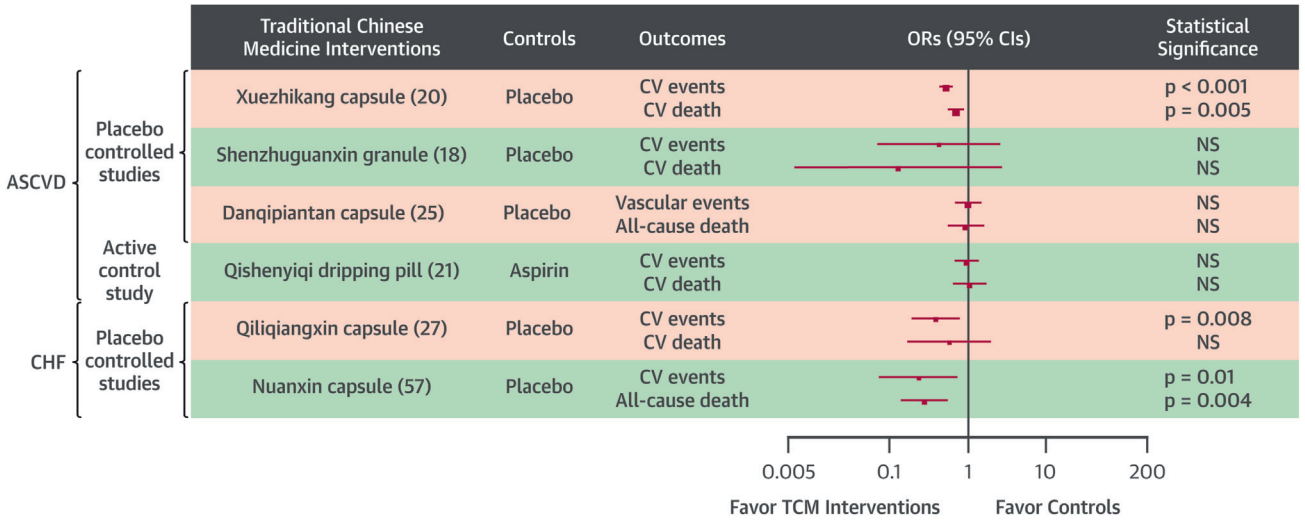
TCM medications in group B for CAD included the Xiongshao capsule, *Salvia miltiorrhiza* and *Pueraria*

FIGURE 3 Data Summaries From the High-Quality RCTs of TCM Interventions for Diabetes and Pre-Diabetes



Filled circles = treatment; **open circles** = control; **numbers in parentheses** = reference numbers. FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; NGT = normal glucose tolerance; OR = odds ratio; PG = postprandial glucose; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Traditional Chinese Medicine Interventions for ASCVD and CHF: Data Summaries of the High-Quality RCTs**



Hao, P. et al. J Am Coll Cardiol. 2017;69(24):2952–66.

Numbers in parentheses = reference numbers. ASCVD = atherosclerotic cardiovascular disease; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; NS = not significant; OR = odds ratio; RCT = randomized controlled trial; TCM = traditional Chinese medicine.

lobata capsule, Tongxinluo capsule, compound red sage root tablet, Xinyue capsule, Kedaling tablet, Propolis flavonoid dripping pill, Tongmaiyangxin pill, Wufuxinnaoqing capsule, and Guanxinzhitong topical ointment. These RCTs showed that Xiongshao, *Salvia miltiorrhiza* and *Pueraria lobata*, Tongxinluo, compound red sage root, and Xinyue were compellingly efficacious in improving hard and/or surrogate endpoints. One RCT showed that 6 months of treatment with Xiongshao ameliorated restenosis (24.1% in the Xiongshao group vs. 48.5% in the placebo group; $p < 0.05$) and decreased cardiovascular events with borderline statistical significance (11.7% in the Xiongshao group vs. 27.6% in the placebo group; $p = 0.051$) after percutaneous coronary intervention (PCI), compared with placebo, with no drug-related adverse events (53). In 1 double-blind, parallel-group RCT, patients with CAD were randomized to receive adjunct treatment with *Salvia miltiorrhiza* and *Pueraria lobata* combined or placebo, followed by optional open-label treatment with *Salvia miltiorrhiza* and *Pueraria lobata*. Brachial flow-mediated dilation and CIMT were measured by ultrasonography. Treatment with *Salvia miltiorrhiza* and *Pueraria lobata* improved flow-mediated dilation and CIMT, and was well tolerated in this study (16). One RCT showed that the Tongxinluo capsule reduced myocardial no-reflow and infarction area, and improved myocardial perfusion after primary PCI for acute MI, which was evaluated by electrocardiography, single-photon emission computed tomography, and coronary angiography. Severe adverse events did not differ between the 2 treatment groups (19). The results from another RCT indicated that combination therapy with compound red sage root tablet and Xinyue capsule significantly improved myocardial perfusion, compared with placebo, in patients undergoing primary PCI for MI (54).

Several RCTs showed that treatment with Kedaling, Propolis flavonoids, Tongmaiyangxin, Wufuxinnaoqing, and Guanxinzhitong reduced the frequency and severity of anginal attack as well as consumption of nitroglycerin, and improved ischemic electrocardiographic changes at rest in patients with stable angina compared with placebo. However, stress electrocardiographic or imaging tests were not performed in these RCTs, leading to less convincing efficacy. Treatment-related adverse events did not differ between these TCM and placebo groups (17,49–52).

Five RCTs comparing TCM with placebo for ischemic stroke were assessed; Jadad scores were 5 in 2 trials (22,25) and 4 in the other 3 (23,24,55). The sample size ranged from 100 to 1,100, and follow-up ranged from 4 to 104 weeks (Online Table 4).

TCM medications in group A used for ischemic stroke included the Sanchitongshu capsule (Radix/Rhizoma notoginseng extract) and Danqipiantan capsule. A multicenter RCT enrolled 140 patients with ischemic stroke who were assigned to receive Sanchitongshu capsule (Radix/Rhizoma notoginseng extract) (n = 71) or placebo capsule (n = 69) treatment. Sanchitongshu capsule significantly ameliorated neurological deficit and daily activity compared with placebo. Adverse reaction rates were similar with both treatments (22). In a large RCT of TCM involving 880 patients with ischemic stroke and follow-up of 24 months, the probability of achieving functional independence, as defined by a modified Rankin scale, was significantly increased with Danqipiantan treatment at 6 months and persisted up to 18 months after stroke compared with placebo. However, the difference was not significant at 24 months. In addition, the total mortality and incidence of vascular events were similar between the Danqipiantan and placebo groups (25).

TCM medications in group B for ischemic stroke included the Naoxinduotai capsule, Ginkgo tablet, and Dihuangyinzi tablet, which were more effective in improving neurological dysfunction than placebo, without analysis of cardiovascular events or measurement of cerebral perfusion. The results of 1 RCT showed that treatment with the Naoxinduotai capsule significantly improved neurological function and Barthel index compared with placebo in patients with ischemic stroke (55). Ginkgo tablet was compared with placebo in an RCT that enrolled 102 patients with acute ischemic stroke. Multivariate regression adjusted by age and sex revealed a significant decrease in U.S. National Institutes of Health Stroke Scale score with ginkgo compared with placebo; thus, administration of ginkgo was recommended after acute ischemic stroke (23). Another RCT enrolled patients with recent ischemic stroke to assess the efficacy and safety of the Dihuangyinzi tablet on functional outcome. All patients received Dihuangyinzi or placebo tablet treatment. Fugl-Meyer Assessment score and Barthel index showed greater improvement with the Dihuangyinzi tablet than with placebo (24).

In summary, treatment with some TCM medications might be effective in alleviating angina symptoms, myocardial perfusion abnormalities, or neurological deficit in patients with CAD or ischemic stroke, and Xuezhikang might reduce cardiovascular events in patients after MI. However, more high-quality, large-scale RCTs are required before any definite conclusions can be drawn as to whether TCM treatment can improve the long-term outcomes of patients with ASCVD.

TCM FOR CHRONIC HEART FAILURE

We included and assessed 9 RCTs (26,27,56–62) that enrolled 100 to 512 patients with heart failure and had mean follow-ups ranging from 4 to 52 weeks; the Jadad score was 5 in 4 RCTs (26,27,57,59), 4 in 2 RCTs (60,61), and 3 in 3 RCTs (56,58,62) (Online Table 5). The effective response to treatment, defined as an increase of ≥1 in New York Heart Association (NYHA) functional class, was evaluated in 6 RCTs.

TCM medications in group A used for chronic heart failure included the Qiliqiangxin capsule, Nuanxin capsule, Shencaotongmai granule, and Yangxinkang tablet, which were proven efficacious in improving hard and/or surrogate endpoints. The efficacy and safety of the Qiliqiangxin capsule were compared with placebo in an RCT enrolling 512 patients with chronic heart failure (mean age 57.3 years). After 12 weeks of treatment, the Qiliqiangxin capsule significantly reduced the level of N-terminal pro-B-type natriuretic peptide compared with placebo (mean percent reduction: 24.7% vs. 0.0%; $p = 0.002$). Qiliqiangxin treatment had superior performance to placebo in altering NYHA functional classification, left ventricular ejection fraction (LVEF), 6-min walking distance, quality of life, and composite cardiac events. Moreover, the analysis of drug-induced adverse events and treatment withdrawal revealed no difference between the 2 treatments (27). This study was compelling due to its large sample size and use of cardiovascular events as an outcome endpoint. However, the 12-week follow-up duration was relatively short. The possible mechanisms underlying the beneficial effects of Qiliqiangxin on cardiac remodeling may involve regulating the balance between proinflammatory and anti-inflammatory cytokines in cardiomyocytes, as well as down-regulating the cardiac chymase signaling pathway and angiotensin II production (64). In an RCT with a Jadad score of 5, 150 patients with chronic heart failure (mean age 69.7 years) were randomly assigned to receive either Nuanxin capsule or placebo in a 1:1 ratio for 24 weeks. The Nuanxin group exhibited a lower rehospitalization rate (23.9% vs. 53.4%; $p < 0.05$) and incidence of acute heart failure (22.5% vs. 42.5%; $p < 0.05$), as well as a higher effective response rate (78.9% vs. 64.4%; $p < 0.05$) than the placebo group. There was no significant difference in death or drug-related side effects between the 2 groups (57). In another RCT with a Jadad score of 3, a cohort of

100 patients with chronic heart failure (mean age 65.9 years) was randomly assigned to receive either Nuanxin capsule or placebo in a 1:1 ratio for 12 months. Nuanxin treatment significantly increased the effective response rate (89.6%) compared with placebo (72.3%), without drug-related side effects (56). A multicenter RCT enrolling 280 patients with chronic heart failure (mean age 65.6 years) showed that the effective response rate and LVEF were greater with Shencaotongmai than with placebo after 12 weeks of treatment, and the incidence of adverse drug reaction was similar with both treatments (59). In addition, the effective response and improvement of physical signs were greater with the Yangxinkang tablet than with placebo, with no adverse reactions (26). The **Central Illustration** summarized data from the high-quality RCTs of TCM interventions for chronic heart failure.

TCM medications in group B used for chronic heart failure included the Yiqihuayu capsule, Qiangxintongmai granule, Yangxin decoction, and Zhuangshenling formula. Yiqihuayu, Qiangxintongmai, and Yangxin were confirmed to be efficacious in improving surrogate endpoints in patients with chronic heart failure (58,60,62). Compared with placebo, Yiqihuayu capsule significantly improved NYHA functional classification and LVEF, without drug-related side effects in either group (58). Both 6-min walking distance and quality of life were significantly improved with Qiangxintongmai treatment relative to placebo (60). Moreover, the effective response and improvement of physical signs were greater with Yangxin decoction than with placebo treatment (62). In addition, hot compresses with Zhuangshenling formula conferred a higher effective response rate and lower B-type natriuretic peptide level than placebo, but no difference in 6-min walking distance was found between the 2 treatments (61).

Taken together, these data suggest that some TCM medications, such as Qiliqiangxin, Nuanxin, Shencaotongmai, and Yangxinkang, might be effective in improving cardiac remodeling and function in patients with chronic heart failure, with a good safety profile. However, the effect of TCM medications on the long-term outcomes of these patients remains obscure.

POTENTIAL LIMITATIONS OF AVAILABLE RCTS

First, most RCTs of TCM were flawed due to small sample sizes and the assessment of surrogate endpoints, leaving the therapeutic effect of TCM on hard endpoints in most patients with CVDs an open question. Second, although in most studies the placebo was identical in size and shape to the corresponding TCM medications, and in 1 study sham acupuncture was described as insertion of acupuncture needles at non-TCM sites (8), there was no information in some studies on the quality of placebo used and how effectively it was formulated to resemble or conceal the active TCM medications. Third, publication bias might be present due to only positive results being published, beneficial effects being achieved by experienced TCM practitioners, results being published only in TCM journals, and lack of data provided about potential drug interactions, among other factors.

PHARMACOLOGICAL EFFECTS OF TCM INGREDIENTS ON CVD AND POTENTIAL MECHANISMS

A battery of compounds, including various polyphenols, terpenoids, saponins, and alkaloids (Online Table 6), has been isolated from TCMs and shown to have beneficial effects in the cardiovascular system (**Table 1**) (65-67). Polyphenols are abundant in many TCMs used for treating hypertension and CAD, and their cardiovascular protective actions have been mainly ascribed to their antioxidant, anti-inflammatory, hypolipidemic, and anticytotoxic effects (68-71). For example, the flavonoid baicalein (from *Scutellaria baicalensis*) is a potent antioxidant with antithrombotic and anti-inflammatory effects in endothelial cells, and antihypertensive effects in vivo (72). Baicalin, the glycoside of baicalein, can protect cardiomyocytes in vitro by interfering with endoplasmic reticulum stress-induced apoptosis (73). Similarly, curcumin from Radix Curcumae exerts antithrombotic and antiatherogenic effects (74), at least in part by repressing the activity of the proinflammatory transcription factor nuclear factor-κB (75). Curcumin may prevent the development of cardiac hypertrophy and failure by inhibiting the acetyltransferase enzyme CBP/p300 (76).

Tanshinones from *Salvia miltiorrhiza* are a representative example of terpenoids with cardiovascular protective effects in TCM (77). *Salvia miltiorrhiza* is used for angina pectoris in TCM. Evidence from experimental studies and clinical trials has demonstrated that tanshinones may prevent atherogenesis and pathological cardiac hypertrophy (77,78). Tanshinones have antioxidant effects that can inhibit lipid peroxidation; they can also suppress vascular inflammation and platelet aggregation (77). Tanshinones may protect against myocardial ischemia by promoting angiogenesis and reducing apoptosis (79,80).

TABLE 1 Representative Examples of Major Cardiovascular Effects of TCM Ingredients and Potential Mechanisms

Bioactive Ingredients	Representative Herbs	Related Formulations	Beneficial Effects	Potential Mechanisms	Experimental Models Used	Ref. #
Polyphenols						
Baicalein/baicalin	*Scutellaria baicalensis*	Not available	Antioxidant; anti-inflammatory; antithrombotic; improving endothelial function; cardiac cytoprotective; antihypertensive	Free-radical scavenging; inhibiting xanthine oxidase; inhibiting lipoxygenase; inhibiting endoplasmic reticulum stress-induced apoptosis	Cell cultures; rodent models	(72,73)
Curcumin	Radix Curcumae	*Jiangzhitongluo* capsule	Antithrombotic; antiarrhythmic; antiatherogenic; cardiac cytoprotective	Inhibiting NF-κB; inhibiting the acetyltransferase enzyme CBP/p300; improving intracellular Ca^{2+} handling	Cell cultures; rodent models	(74–76)
Terpenoids						
Tanshinones	Radix *Salviae miltiorrhizae*	*Salvia miltiorrhiza and Pueraria lobata* capsule; *Jinlida* granule; *Tangzhiping* capsule; compound red sage root tablet; *Qiliqiangxin* capsule; *Shencaotongmai* granule; *Qiangxintongmai* granule	Antiatherogenic; cardiac cytoprotective; antioxidant; anti-inflammatory; antithrombotic	Inhibiting the calcineurin/NFAT pathway; antiapoptosis	Cell cultures; rodent models	(77,78)
Saponins						
Ginsenosides	Radix Ginseng	*Jinlida* granule; *Tianqi* capsule; *Tongxinluo* capsule; *Qiliqiangxin* capsule; *Shencaotongmai* granule; *Qiangxintongmai* granule	Vasorelaxant; antioxidant; anti-inflammatory; hypoglycemic; cardiac cytoprotective; proangiogenic	Activating protein kinase A; stabilizing hypoxia-inducible factor-1; activating the PI3K/Akt pathway; inhibiting NF-κB	Cell cultures; ex vivo experiments; rodent models; human studies	(81,82,85)
	Radix Ginseng Rubra	*Nuanxin* capsule				
Astragaloside	*Radix astragali*	*Qiqilian* capsule; *Xiaoke* pill; *Tianqijiangtang* capsule; *Tianqi* capsule; *Jinqijiangtang* tablet; *Qiliqiangxin* capsule; *Yiqihuayu* capsule; *Shencaotongmai* granule; *Qiangxintongmai* granule	Cardiac cytoprotective	Maintaining mitochondrial homeostasis; activating PI3K/Akt	Cell cultures	(87)
Alkaloids						
Berberine	*Rhizoma coptidis*	*Qiqilian* capsule; *Tangminling* pill; *Jinlida* granule; *Tangzhiping* capsule; *Tianqijiangtang* capsule; *Tianqi* capsule; *Jinqijiangtang* tablet	Positive inotropic; vasodilator; cardiac cytoprotective; antiapoptotic	Blocking K^+ channels; activating AMP-activated protein kinase and PI3K/Akt pathways	Cell cultures; ex vivo experiments; rodent models	(89,90)
Matrine/ oxymatrine	Radix *Sophorae flavescentis*	Not available	Cardiac cytoprotective	Promoting hERG-mediated K^+ conductance; increasing hERG expression; down-regulating angiotensin-converting enzyme, transforming growth factor-β, and collagens; inhibiting mitogen-activated protein kinases; up-regulating expression of β3-adrenoreceptors, endothelial nitric oxide synthase, and antiapoptotic proteins	Cell cultures; rodent models	(92,93)

AMP = adenosine monophosphate; Ca^{2+} = calcium ion; hERG = human ether-a-go-go-related gene; K^+ = potassium ion; NF = nuclear factor; NFAT = nuclear factor of activated T cells; PI3K = phosphatidylinositol 3-kinase; TCM = traditional Chinese medicine.

Saponins (ginsenosides) are the major active ingredients of ginseng. Ginsenosides are thought to be responsible for the vasorelaxant, antioxidant, anti-inflammatory, and hypoglycemic activities of ginseng (81,82). Ginseng is frequently used for heart failure. Indeed, some experimental studies found that certain ginsenosides may prevent cardiomyocyte apoptosis in a protein kinase A-dependent manner (83). Saponins, including ginsenosides, also exhibit anti-inflammatory, antiapoptotic, and proangiogenic

activities; some of these effects are likely to be mediated by activation of the phosphatidylinositol 3-kinase/Akt pathway (84–87).

Alkaloids with cardiovascular protective effects include *Uncaria* alkaloids (from Ramulus Uncariae cum Uncis), berberine (from Rhizoma Coptidis), and matrine/oxymatrine (from Radix *Sophorae flavescentis*). Ramulus Uncariae cum Uncis is 1 of the herbs present in the Tiankuijangya tablet, and it turns out to contain potent *Uncaria* alkaloids that can exert cardiovascular effects via regulation of calcium and potassium channels, neurotransmitter transport, and metabolism (88). Berberine has positive inotropic effects (attributable to blockade of delayed rectifier and adenosine triphosphate-sensitive potassium channels), and vasodilator and antiapoptotic effects (by activating 5′ adenosine monophosphate-activated protein kinase and PI3K-Akt pathways) (89,90). Berberine (91) and matrine/oxymatrine (92,93) can alleviate cardiac remodeling and retard the development of heart failure. These beneficial effects of the alkaloids are associated with changes in multiple signaling pathways in failing hearts, including down-regulated expression of angiotensin-converting enzyme, transforming growth factor β1, and collagens; reduced activation of mitogen-activated protein kinases; and up-regulation of β3-adrenoreceptors, endothelial nitric oxide synthase, and the anti-apoptotic protein Bcl-2.

Of note, one should bear in mind that TCM medications are usually prescribed as complex formulae, which are often further manipulated by the practitioner on a personalized basis. Moreover, most active ingredients isolated from TCM may target multiple molecules or pathways. Not surprisingly, we are facing immense challenges in interpreting the observed therapeutic benefits of TCMs with contemporary pharmacological approaches by pinpointing individual compounds and their molecular targets. Establishing a causal relationship between the observed cellular or molecular actions of TCM and their overall beneficial effects on CVD from current published reports is difficult, especially in the context of the single compound-single target paradigm (94).

CONCLUSIONS

Current evidence from RCTs indicates that some TCM medications might be effective in control of cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes/pre-diabetes, and exert beneficial effects on ASCVD and chronic heart failure. The pharmacological effects and the underlying mechanisms of some active ingredients of TCM medications have been elucidated. Thus, some TCM medications might be used as a complementary and alternative approach for primary and secondary prevention of cardiovascular disease. However, further rigorously designed RCTs are warranted to evaluate the effect of TCM on total mortality or major adverse cardiovascular events in patients with cardiovascular disease.

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KEY WORDS Chinese herbal drugs, dyslipidemia, heart failure, hypertension, randomized controlled trials as topic, type 2 diabetes mellitus

APPENDIX For supplemental tables, please see the online version of this article.