Effect of supplementing Qi and promoting blood circulation therapy on left ventricular remodeling: a systematic review and Meta-analysis

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OBJECTIVE: To evaluate the effectiveness of an adjuvant therapy from Traditional Chinese Medicine for supplementing Qi and promoting blood circulation (CMSQPBC) on left ventricular remodeling in patients after myocardial infarction (MI).

METHODS: Randomized controlled trials were identified in the Cochrane Library, Embase, Web of Science, PubMed, China National Knowledge Infrastructure Database, Chinese Biomedical Literature Database, China Science and Technology Journal Database, Wanfang databases, reviews, and reference lists of relevant articles. The weighted mean difference (WMD) was calculated for changes in the left ventricular ejection fraction (LVEF), LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) from baseline to follow-up (> 3 months) by using random-effects Meta-analysis. The primary outcome was change in LVEF, and secondary outcomes were changes in LV dimensions including LVEDV and LVESV.

RESULTS: A total of 10 trials (enrolling 854 participants, median follow-up six months) evaluated the association between CMSQPBC and changes in LV function and volume. Compared with the control group, CMSQPBC significantly improved LVEF (854 patients; WMD: 4.97%, 95% CI: 3.78-6.15; P < 0.001) and attenuated the enlargement of LVEDV (607 patients; WMD: -7.89 mL, 95% CI: -11.54 to -4.24; P < 0.001) and LVESV (364 patients; WMD = -5.80 mL, 95% CI, -9.60 to -2.01; P < 0.01).

CONCLUSION: CMSQPBC may reverse deleterious pathological remodeling after myocardial infarction. Higher quality and more rigorous randomized trials with larger sample sizes are needed to further confirm the findings.

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Keywords: Ventricular remodeling; Myocardial infarction; Reinforcing Qi activating blood; Qi-deficiency blood stasis; Systematic review; Meta-analysis

INTRODUCTION

Adverse left ventricular (LV) remodeling after myocardial infarction often leads to left ventricular hypertrophy, heart failure, and other complications. Traditional Chinese Medicine (TCM) has a long history of treating cardiovascular diseases, including myocardial infarction, with various herbal medicines and therapy approaches. One such approach involves supplementing Qi and promoting blood circulation (CMSQPBC), which is a well-known adjuvant therapy in TCM. This review aims to evaluate the effectiveness of CMSQPBC on left ventricular remodeling in patients after myocardial infarction. The primary outcome is the change in left ventricular ejection fraction (LVEF), and secondary outcomes include changes in LV dimensions such as LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV). The study included 10 randomized controlled trials enrolling 854 participants, with a median follow-up of six months. The results showed that CMSQPBC significantly improved LVEF and attenuated the enlargement of LVEDV and LVESV compared to the control group. These findings support the hypothesis that CMSQPBC may reverse pathological remodeling after myocardial infarction, warranting further high-quality and rigorous randomized trials with larger sample sizes to confirm these findings.
dial infarction (MI) has been demonstrated to be associated with an increased risk for adverse cardiovascular events, whereas the progressive deterioration of cardiac performance is an important warning sign of developing heart failure and a well-documented predictor of cardiac mortality. Several therapeutic approaches have been tried in patients afflicted with acute MI to date, including coronary reperfusion strategies and pharmacological management with angiotensin converting enzyme (ACE) inhibitors, beta-adrenergic blockers, as well as application of electrical cardiac resynchronization. Although numerous clinical trials have already proven that these therapies prevent the continued deterioration of the LV dilatation to a certain degree, the incidences of the adverse LV remodeling are still observed in a substantial proportion of patients after MI. Therefore, there is a constant need for development of novel and more efficient therapies that would reverse LV remodeling.

From the perspectives of Traditional Chinese Medicine (TCM), the point of pathogenesis of MI is mainly "Qi" (vital energy) deficiency and blood stasis, that is, degradation of cardiac function and coronary thrombosis. Our previous epidemiological study demonstrated that in 624 patients with coronary heart disease (CHD) confirmed by angiography, the incidence of Qi-deficiency pattern (83.7%) and blood stasis pattern (91.5%) were generally higher than other TCM symptom patterns. Another analysis including 5284 patients with CHD and also indicated that the top TCM pattern was blood stasis with Qi deficiency (79.3%). Thus, supplementing Qi and promoting blood circulation (SQPBC) reasonably become the key point of the treatment method for CHD. Notably, several clinical trials demonstrated that the administration of CMSQPBC would result in a significant reduction in total serious vascular events and LV remodeling in patients who had experienced documented MI in recent years. However, the sample size of these studies was small, the characteristics of populations were various, and the conclusions were inconsistent. Therefore, the objective of this study was to perform a Meta-analysis of all known clinical trials that reported the effectiveness of CMSQPBC on LV remodeling and evaluate them by LV end-diastolic volumes (LVEDV), LV end-systolic volumes (LVESV) and LV ejection fraction (EF) in patients suffering from MI.

**METHODS**

**Literature database and search strategies**

We systematically searched published and unpublished RCTs in the following databases: Cochrane Library (Cochrane Database for Systematic Reviews, Cochrane Central Register of Controlled Trials), and Embase (1990 to 2018), ISI Web of Science (1950 to 2018), PubMed (1990 to 2018) databases, China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database (VIP), and Wanfang Databases, using the following terms: "Traditional Chinese Medicine", "Chinese Traditional medicine", "Chinese medicine", "Chinese herb medicine", "Chinese patent medicine", "CMSQPBC therapy", "cardiovascular disease", "coronary artery disease", "myocardial infarction", "acute myocardial infarction", "post myocardial infarction", "heart attack", "heart failure", "left ventricular remodeling", "ventricular remodeling", "ventricular volumes", and "ejection fraction" without language and time limitation. We searched ongoing registered clinical trials on the website of the World Health Organization (WHO) International Clinical Trial Registry Platform (http://apps.who.int/trialsearch/) and international clinical trial registry by the U.S. National Institutes of Health (http://clinicaltrials.gov/). Our entire search ended on December 28, 2018. In addition, we manually searched the reference lists of all original articles, previous systematic reviews and bibliographies of the included studies to avoid missing relevant articles.

The retrieval strategy of each database has slight differences because their different retrieval format requirements. For example, the Cochrane Central Register of Controlled Trials were searched as follows:

1. MeSH descriptor 'Medicine, Chinese Traditional'
2. MeSH descriptor 'Ventricular Remodeling'
3. MeSH descriptor 'Myocardial Infarction'
4. "Traditional Chinese medicine" or 'Chinese Traditional medicine' or 'Chinese medicine' or 'Chinese herb medicines' or 'Chinese patent medicine':ti,ab,kw
5. 'ventricular remodeling' or 'ventricular volumes' or 'myocardial remodeling' or 'ventricle reconstruction' or 'left ventricular remodelling':ti,ab,kw
6. 'myocardial infarction' or 'heart attack' or 'post myocardial infarction' or 'post infarction':ti,ab,kw
7. #1 or #4
8. #2 or #5
9. #3 or #6
10. #7 and #8 and #9

**Study selection**

Two investigators independently reviewed the titles and abstracts of all citations to identify studies reporting the effect of CMSQPBC on ventricular volumes and/or EF in patients with MI. All randomized controlled trials (RCTs) were eligible for inclusion if: (a) they enrolled patients with a diagnosis of MI receiving contemporary evidence-based medical therapy, and randomly allocated patients to receive CMSQPBC or not (the control); (b) the follow-up duration was no less than three months; and (c) the efficacy endpoints (LVEF, LVEDV, or LVESV) were reported. We excluded trials that were not randomized, did not have a usual-care control group, were not intention-to treat or Chinese medicine intervention, and performed less
than 3 months of follow-up duration. Duplicate reports and ongoing studies were also excluded.

**Interventions**

The patients of the control groups were given guideline-recommended regular treatment (RT) with conventional Western conventional medication. The patients in the treatment groups were given CMSQPBC intervention as add-on therapy, which included CMSQPBC prescriptions, Chinese patent herbal oral preparations, and Chinese patent herbal injections. CMSQPBC therapy was defined as the use of common supplemental Qi and blood circulation-promoting prescriptions, based on the Eight Principles plus symptom pattern identification between Qi and blood.14

**Quality evaluation**

Two of the authors independently assessed the methodological quality of the included trials by using standard criteria of the Cochrane risk-of-bias tool, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Disagreements were resolved by consensus.

**Data extraction**

All literature searches were independently reviewed by two investigators to identify relevant trials that met the inclusion criteria. Disparities were resolved by discussion. Relevant data regarding study design, population characteristics (age, gender, and onset of MI), treatment regimen, CMSQPBC treatment protocol, control intervention, LVEF and LV volumes, and brain natriuretic peptide (BNP) or N-terminal-pro-BNP (NT-pro-BNP) were extracted (as available) from individual studies. Clinical trials with multiple publications, sequential follow-up durations or different outcome indicators were considered single studies. When necessary, original investigators were contacted to clarify data or provide additional data.

**Data analysis**

For each study, data regarding changes from baseline to follow-up of LVEF, LVEDV and LVESV in both the Chinese medicine and control groups were used to calculate weighted mean differences (WMD) and 95% confidence interval (CI) by using a random-effect (DerSimonian and Laird) model. Missing standard deviations were imputed according to the Cochrane Handbook for Systematic Review of Intervention. Statistical heterogeneity of treatment effects between studies was formally tested by Cochran’s test (P < 0.05). The I² statistic was also examined to measure the proportion of total variation due to heterogeneity beyond chance, and I² > 75% was considered to indicate significant heterogeneity between the trials.15 Sensitivity analyses were performed to evaluate the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the pooled (mean difference) MD estimates for the remaining studies. All statistical analyses were performed with Review Manager software (RevMan, version 5.1, Nordic Cochrane Centre, Copenhagen, Denmark).

**RESULTS**

**Outcomes of the search**

Overall, 1768 citations were identified in a combined search of the Cochrane Library, ISI Web of Science, EMBASE, PubMed, CNKI, CBM, VIP, and Wanfang databases and from a manual approach (search of previous studies cited in previous reviews and of references listed in the identified articles); of which 563 were initially excluded as duplicates. After reading the titles and abstracts, 1079 citations were further excluded because they were not pertinent (Figure 1). Among the 126 articles retrieved in completed form, 51 were excluded because the average duration from initial treatment to follow-up evaluation was less than three months, five were excluded because the sample size of the trial was less than 50, and 24 were excluded because the investigated irrelevant primary or secondary outcomes. In addition, 36 studies were excluded because they combined other TCM therapies in the intervention group. Ultimately, 10 trials with 854 subjects were included in our Meta-analysis.

**Characteristics of the studies obtained**

The descriptive information of the included trials and subjects in the analysis are shown in Table 1. All 10 trials were RCTs conducted in mainland China mainland and published between 2005 and 2016. The intention-to-treat principle was used in analysis of the majority of the included studies, but this was not clearly indicated in a number of small studies.16,17 The sample size ranged from 60 to 186, with a mean size of 86. The mean age of the participants was 59.5 years, and 69.4% were male. All patients enrolled were diagnosed with MI based on the criteria of the American College of Cardiology/American Heart Association (ACC/AHA) 2004 guidelines for the management of patients with ST-elevation myocardial infarction, and the 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction, or the 2010 Chinese guideline for the management of ST-elevation myocardial infarction.18,19 The diagnostic criteria for TCM symptom pattern (Qi-deficiency and blood stasis pattern) were those according to the 2002 Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine. Treatment duration of CMSQPBC ranged from three to 12 months. The median follow-up duration was six months (range: three months to 12 months). LV parameters data at baseline and follow-up was measured by echocardiogra-
phy in all 10 studies. No significant difference on baseline was identified in any of the studies, including the type and severity of coronary lesion. With regard to medical therapy, use of anti-platelet agents, beta-blockers, ACE-inhibitors, angiotensin II receptor blockers (ARBs), and lipid-lowering agents were similar between control and CMSQPBC groups within each study, although rates did vary across studies. Furthermore, the impact of reperfusion strategies on changes in LVEF and volume appeared to be unrelated to variations in medical therapy between studies.

Data quality evaluation
The judgments about each risk-of-bias item for each included study are presented in Figure 2. The majority of the included trials were evaluated be of generally poor methodological quality according to the predefined quality evaluation criteria. The randomized allocation of participants was mentioned in all trials. However, only six trials\cite{16,20-25} stated the methods for sequence generation by a random number table. Only did one study\cite{17,24} declare the use principle of double blind and concealment of allocation. A total of two studies\cite{16,24} reported adequate details about withdrawals or dropouts, whereas the others did not address this issue. None of the studies had a pretrial estimation of sample size. Generally, insufficient information was provided to determine whether the study was conducted properly.

Effects of CMSQPBC on LV function
Compared with the control group, the CMSQPBC interventions significantly improved post-infarction LVEF by 4.97% (10 trials; 854 patients; 95% CI: 3.78-6.15; \(P < 0.000\ 01\); Figure 3) during mean six-month follow up, this analysis demonstrated substantial heterogeneity (\(I^2 = 70\%\), \(P < 0.01\)).\cite{16,17,20-27} Subsequently, a sensitivity analyses was performed to identify the potential source of heterogeneity. Exclusion of each study conducted did not change the pooled results. However, the heterogeneity was significantly offset when excluding two trials.\cite{16,25} The observed heterogeneity could be attributable to different CMSQPBC (including formulation, dosage, administration, and duration of treatments) and different medical research methods were used in the studies, and how the studies were conducted in these two studies. Visual inspection of the funnel plots on data from 10 studies revealed asymmetrical variables, indicating potential risk of publication bias. The reasons might lie in clinical trials with negative results that are difficult to publish.

**Effects of CMSQPBC on LV dilation**
Moreover, the benefits associated with CMSQPBC treatment by attenuating the enlargement of LVEDV and LVESV were observed in this Meta-analysis. A total of six trials\cite{17,20-25,24,26,27} with 607 participants, evaluated the association between CMSQPBC therapy and changes in LVEDV in patients after MI. In an overall pooled estimate, compared with the control group, CMSQPBC decreased the LVEDV change from baseline to follow-up (WMD = -7.89 mL, 95% CI: -11.54 to -4.24; \(P < 0.001\); Figure 4). Slight heterogeneity for this outcome was found (\(I^2 = 38\%\), \(P = 0.15\)). A total of three trials\cite{20,23,26} with 364 participants evaluated the association between CMSQPBC therapy and
## Table 1 Basic characteristics of the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (C/I)</th>
<th>Mean age (years)</th>
<th>Men (%)</th>
<th>Reperfusion strategy</th>
<th>CMSQPBC intervention (key components)</th>
<th>Method to evaluate LV parameters</th>
<th>Mean follow-up (months)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fun SP et al 2016&lt;sup&gt;6&lt;/sup&gt;</td>
<td>MI 50/50</td>
<td>57.5</td>
<td>68</td>
<td>NR</td>
<td>Buycang Huanwu decoction: Huangqi (Radix Astragali Mongolici), Honghua (Flos Carthami), Chuaxiong (Rhizoma Chuanxiong), Danggui (Radix Angelicae Sinensis)</td>
<td>Echo</td>
<td>4</td>
<td>Cardiac function/structure, miRNA-21, NT-ProBNP</td>
</tr>
<tr>
<td>Chen S 2015&lt;sup&gt;1&lt;/sup&gt;</td>
<td>STIMI 30/30</td>
<td>65.99</td>
<td>66.6</td>
<td>PCI</td>
<td>Qishen Yiqi dripping pills: Huangqi (Radix Astragali Mongolici), Danshen (Radix Salviae Miltiorrhizae), Sanqi (Radix Notoginseng), Jiangxiang (Lignum Dalbergiae Odoriferae), Qili Qiangxin pills: Huangqi (Radix Astragali Mongolici), Renshen (Radix Ginseng), Honghua (Flos Carthami), Danshen (Radix Salviae Miltiorrhizae), Zexie (Rhizoma Alismatis)</td>
<td>Echo</td>
<td>6</td>
<td>Cardiac function/structure, BNP</td>
</tr>
<tr>
<td>Mei FG et al 2014&lt;sup&gt;3&lt;/sup&gt;</td>
<td>AMI 34/34</td>
<td>59</td>
<td>66.2</td>
<td>PCI</td>
<td>Tongxinluo capsules: Renshen (Radix Ginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>6</td>
<td>Cardiac function/structure, BNP</td>
</tr>
<tr>
<td>Tian ST et al 2014&lt;sup&gt;4&lt;/sup&gt;</td>
<td>AMI 30/30</td>
<td>54.7</td>
<td>65.3</td>
<td>PCI</td>
<td>Tongxinluo capsules: Renshen (Radix Ginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>3</td>
<td>Left heart function, quality of life, NT-proBNP, MACE, SAQ, Inflammatory cytokines</td>
</tr>
<tr>
<td>Yang W et al 2012&lt;sup&gt;5&lt;/sup&gt;</td>
<td>AMI 29/30</td>
<td>65</td>
<td>59.3</td>
<td>PCI</td>
<td>Qishen Yiqi dripping pills: Huangqi (Radix Astragali Mongolici), Danshen (Radix Salviae Miltiorrhizae), Sanqi (Radix Notoginseng), Jiangxiang (Lignum Dalbergiae Odoriferae), Qili Qiangxin pills: Huangqi (Radix Astragali Mongolici), Renshen (Radix Ginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>6</td>
<td>LV wall motion, LVEDV, LVEF</td>
</tr>
<tr>
<td>Xie D et al 2011&lt;sup&gt;1&lt;/sup&gt;</td>
<td>STEMI 42/40</td>
<td>51</td>
<td>51.2</td>
<td>NR</td>
<td>Qishen Yiqi dripping pills: Huangqi (Radix Astragali Mongolici), Danshen (Radix Salviae Miltiorrhizae), Sanqi (Radix Notoginseng), Jiangxiang (Lignum Dalbergiae Odoriferae), Qili Qiangxin pills: Huangqi (Radix Astragali Mongolici), Renshen (Radix Ginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>12</td>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Du WX et al 2010&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AMI 92/94</td>
<td>69</td>
<td>64.5</td>
<td>NR</td>
<td>Tongxinluo capsules: Renshen (Radix Ginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>12</td>
<td>PIINP, BNP, LV function/structure</td>
</tr>
<tr>
<td>Wang G et al 2007&lt;sup&gt;7&lt;/sup&gt;</td>
<td>AMI 34/34</td>
<td>57.9</td>
<td>89.7</td>
<td>PCI</td>
<td>Yixintong capsules: Huangqi (Radix Astragali Mongolici), Renshen (Radix Ginseng), Danshen (Radix Salviae Miltiorrhizae), Sanqi (Radix Notoginseng), Shuizhi (Hirudo), Quanxie (Scorpio), Wugong (Scolopendra, Hirudo), Chishao (Radix Paeoniae Rubra)</td>
<td>Echo</td>
<td>6</td>
<td>PIINP, BNP, LV function/structure</td>
</tr>
<tr>
<td>Zhang L 2006&lt;sup&gt;9&lt;/sup&gt;</td>
<td>AMI 31/32</td>
<td>57</td>
<td>79.4</td>
<td>PCI</td>
<td>Echo</td>
<td>3</td>
<td>LV wall motion, LVEDV, LVEF</td>
<td></td>
</tr>
<tr>
<td>You S et al 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>STEMI 52/60</td>
<td>57.9</td>
<td>82.1</td>
<td>PCI/ fibrinolytic therapy</td>
<td>Echo, SPECT</td>
<td>6</td>
<td>LV wall motion, LVEDV, LVEF</td>
<td></td>
</tr>
</tbody>
</table>

Notes: AMI: acute myocardial infarction; CMSQPBC: Chinese medicine for supplementing Qi and promoting blood circulation; EF: ejection fraction; LV: left ventricular; LVESV: left ventricular end-systolic volume; LVEDV: left ventricular end-diastolic volume; MACE: major adverse cardiac event; NYHA: New York Heart association functional classification; NT-proBNP: N-terminal pro-brain natriuretic peptide; NR: not reported; PCI: percutaneous coronary intervention; SAQ: Seattle Angina Questionnaire; SPECT: single photon emission computed tomography; STEMI: ST segment elevation myocardial infarction. C/I: control group and CMSQPBC intervention group.
Mao S et al. / Systematic Review

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

<table>
<thead>
<tr>
<th>Low risk of bias</th>
<th>Unclear risk of bias</th>
<th>High risk of bias</th>
</tr>
</thead>
</table>

Figure 2 Risk of bias summary

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TCM+RT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan SP 2016</td>
<td>5.9</td>
<td>5.66</td>
<td>50</td>
<td>1.8</td>
<td>4.43</td>
<td>50</td>
<td>10.3%</td>
<td>4.10 [2.11, 6.09]</td>
<td></td>
</tr>
<tr>
<td>Chen S 2015</td>
<td>10.3</td>
<td>5.97</td>
<td>30</td>
<td>3.23</td>
<td>5.15</td>
<td>30</td>
<td>8.0%</td>
<td>7.07 [4.25, 9.99]</td>
<td></td>
</tr>
<tr>
<td>Mei FG 2014</td>
<td>7.3</td>
<td>6.14</td>
<td>34</td>
<td>5.6</td>
<td>3.69</td>
<td>34</td>
<td>9.1%</td>
<td>1.70 [0.71, 2.71]</td>
<td></td>
</tr>
<tr>
<td>Tian ST 2014</td>
<td>4.57</td>
<td>2.72</td>
<td>30</td>
<td>2.43</td>
<td>2.95</td>
<td>30</td>
<td>12.0%</td>
<td>2.14 [0.70, 3.58]</td>
<td></td>
</tr>
<tr>
<td>Yang W 2012</td>
<td>14.4</td>
<td>8.44</td>
<td>30</td>
<td>9</td>
<td>3.81</td>
<td>29</td>
<td>9.8%</td>
<td>5.00 [2.83, 7.17]</td>
<td></td>
</tr>
<tr>
<td>Xie DX 2011</td>
<td>9.2</td>
<td>5.28</td>
<td>38</td>
<td>2.8</td>
<td>2.66</td>
<td>40</td>
<td>10.7%</td>
<td>6.40 [4.53, 8.27]</td>
<td></td>
</tr>
<tr>
<td>Du WX 2010</td>
<td>6.6</td>
<td>6.68</td>
<td>94</td>
<td>0.8</td>
<td>5.53</td>
<td>92</td>
<td>11.0%</td>
<td>5.80 [4.04, 7.56]</td>
<td></td>
</tr>
<tr>
<td>Wang G 2007</td>
<td>5.01</td>
<td>4.81</td>
<td>34</td>
<td>-0.79</td>
<td>4.91</td>
<td>34</td>
<td>9.4%</td>
<td>5.80 [3.49, 8.11]</td>
<td></td>
</tr>
<tr>
<td>Zhang L 2006</td>
<td>5.1</td>
<td>4.88</td>
<td>32</td>
<td>-1.4</td>
<td>4.87</td>
<td>31</td>
<td>9.1%</td>
<td>6.50 [4.09, 8.91]</td>
<td></td>
</tr>
<tr>
<td>You SJ 2005</td>
<td>5.01</td>
<td>4.81</td>
<td>60</td>
<td>-0.79</td>
<td>4.91</td>
<td>52</td>
<td>10.9%</td>
<td>5.80 [3.99, 7.61]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>432</td>
<td></td>
<td>422</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>4.97 [3.78, 6.15]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.50; Ch² = 30.38, df = 9 (P = 0.0004); I² = 70%
Test for overall effect: Z = 8.24 (P < 0.0001)

Figure 3 Forest plot of weighted mean differences in left ventricular ejection fraction in patients treated with CMSQPBC compared with controls
CM: Chinese medicine for supplementing Qi and promoting blood circulation; RT: guideline-recommended regular treatment with modern conventional medication; CI: confidence intervals; SD: standard deviation.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TCM+RT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan SP 2016</td>
<td>-18</td>
<td>17.08</td>
<td>50</td>
<td>-2.3</td>
<td>17.09</td>
<td>50</td>
<td>17.2%</td>
<td>-15.70 [-22.40, -9.00]</td>
<td></td>
</tr>
<tr>
<td>Xie DX 2011</td>
<td>-18</td>
<td>17.08</td>
<td>38</td>
<td>-11.8</td>
<td>16.44</td>
<td>40</td>
<td>13.9%</td>
<td>-6.20 [-13.65, 1.25]</td>
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<tr>
<td>Du WX 2010</td>
<td>-8</td>
<td>17.27</td>
<td>94</td>
<td>-2.6</td>
<td>15.54</td>
<td>92</td>
<td>34.5%</td>
<td>-5.40 [-10.12, -0.68]</td>
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</tr>
<tr>
<td>Wang G 2007</td>
<td>7.3</td>
<td>16.77</td>
<td>34</td>
<td>15.35</td>
<td>20.83</td>
<td>34</td>
<td>9.5%</td>
<td>-8.06 [-17.04, 0.94]</td>
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<tr>
<td>Zhang L 2006</td>
<td>18.46</td>
<td>16.98</td>
<td>32</td>
<td>20.78</td>
<td>19.28</td>
<td>31</td>
<td>9.5%</td>
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<tr>
<td>You SJ 2005</td>
<td>7.1</td>
<td>16.82</td>
<td>60</td>
<td>15.95</td>
<td>20.81</td>
<td>52</td>
<td>15.4%</td>
<td>-8.85 [-15.93, -1.77]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>308</td>
<td></td>
<td>299</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>-7.77 [-10.54, -4.99]</td>
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<td></td>
</tr>
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</table>

Heterogeneity: Ch² = 8.03, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 5.49 (P < 0.0001)

Figure 4 Forest plot of weighted mean differences in left ventricular end-diastolic volume in patients treated with CMSQPBC compared with controls
CM: Chinese medicine for supplementing Qi and promoting blood circulation; RT: guideline-recommended regular treatment with modern conventional medication; CI: confidence intervals; SD: standard deviation.

Changes in LVESV. In an overall pooled estimate, compared with the control group, patients in the CMSQPBC therapy group had significantly greater reduction in LVESV from baseline to follow-up (WMD = -5.80 mL, 95% CI: -9.60 to -2.01; P < 0.01; Figure 5). Low heterogeneity for this outcome was found (heterogeneity test: I² = 41%, P = 0.18).

Effects of CMSQPBC on serum indicators
Of these 10 studies, six studies (552 patients) reported a change of serum BNP or NTpro-BNP concentration after CMSQPBC treatment. Pooling the results of the qualified trials revealed that treatment with CMSQPBC induced a significant reduction in serum BNP or NTpro-BNP (SMD, -0.46; 95% CI, -0.63 to -0.29; P < 0.000 01; Figure 6) compared to regular therapy, with no evidence of heterogeneity or publication bias (I² = 0).

Safety and adverse events
CMSQPBC treatment was well tolerated in the enrolled patients. No severe adverse events occurred in the CMSQPBC groups compared with the control groups. This systematic review suggested that CMSQPBC might be a safe approach in managing cardiac remodeling after myocardial infarction; no trials reported adverse events contributed by CMSQPBC.
The main finding of this study was that CMSQPBC significantly improved LV contractility and attenuated the detrimental expansion after MI, with an increase in LVEF of about 5% as well as a decreased LVEDV and LVESV. There was a suggestion of the potential superiority of CMSQPBC treatment, as an adjuvant therapy, concerning LV remolding in post-infarction patients with Qi-deficiency and blood stasis pattern.

Despite advances in pharmacological management and reperfusion strategies that have resulted in an increasing proportion of MI survivors, adverse LV remodeling and subsequent heart failure remains a major cause of mortality and disability. None of the current therapies completely addresses the underlying process of adverse remodeling. Over the course of years of clinical practice, numerous of Chinese herbs and formulas that would exert cardio-protective effects received a great deal of attention and have been tested for their abilities in alleviating symptoms of heart failure, myocardial infarction, angina pectoris, systemic hypertension, and other cardiovascular conditions. Based on epidemiologic study and the basic theories of TCM, Qi deficiency with blood stasis pattern together has been identified as a major TCM symptom pattern among patients suffering from MI. None of the current therapies completely addresses the underlying process of adverse remodeling.

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trix.41 Because the optimal proportions of these ECM components eventually determine the beneficial healing of the infarcted myocardium, we speculate that addition of CMSQPBC to the classic Western pharmacological therapy of MI patients likely shifted the initial adverse remodelling processes toward the ultimate regeneration and formation of the more elastic post-infarct scars, complying with the action of the initially injured hearts and preserving global contractility and compliance.42 Recent research has found that Qishen Yiqi dripping pills can act in rats with MI by different targets of the renin-angiotensin-aldosterone system (RAAS), especially on renin and Ang II, ACE/ACE2, and AT1/AT2, eventually decreasing the levels of matrix metalloproteinase-9 and transforming growth factor-β, which is believed to contribute significantly to the improvement of cardiovascular function and myocardial remodelling.42,43 (b) Myocardial ischemia/reperfusion injury is another primary reason for heart failure despite optimal revascularization. Myocardial ischemia followed by subsequent reperfusion can cause profound damage to cardiac myocytes through enhanced oxidative stress and intracellular Ca++ overload, resulting in structural and functional remodelling of myocytes and extracellular matrix (ECM) components.44 It has been confirmed that Tongxinluo reduces reperfusion injury through the preservation of endothelial nitric oxide synthase (eNOS) activity, protection of cardiac microvascular endothelial cells by activating the MEK/ERK pathway, which play important roles in restoring myocardial microcirculation, secreting cytokines involved in cardiac metabolism, growth, contractile performance, and rhythmicity.45 In addition, data has been confirmed that cardioprotection Qishen Yiqi dripping pill offer against ischemia/reperfusion injury by amelioration of multiple mitochondrial dysfunctions.45,46 (c) Accumulating evidence reveals that myocardial inflammation plays an important role in the development of cardiac hypertrophy and dysfunction during MI. It has been shown that Buyang Huanwu decoction,47 Qili Qiangxin48,49 and Tongxinluo50 improved cardiac function after acute myocardial infarction due to markedly lowering proinflammatory factors [such as tumor necrosis factor-α (TNF-α)] expression, and elevating anti-inflammatory factors [such as insulin-like growth factor 1 (IGF-1)] in the myocardium. Furthermore, Qili Qiangxin has been shown to be effective in the treatment of chronic heart failure after myocardial infarction through increasing cardiac contractility and kidney blood flow and regulating inflammatory responses.47 (d) Recently, considerable attention has been focused on the potential for cardiomyocytes to proliferate, which could induce myocardial regeneration and might play a role in the treatment of cardiac remodelling. It has been reported that reduction in the expression of C/EBPβ, a transcription factor, and elevation of its negatively regulated molecule CITED4 resulted in cardiomyocyte proliferation and differentiation.41 Qili Qiangxin was demonstrated to reduce C/EBPβ and increased CITED4 expression in the hearts of mice, which correlated with improved cardiac function and resistance to pathological changes induced in the heart by pressure overload.51 Furthermore, knockdown CITED4 decreased the Qili Qiangxin-induced cardioprotection, which means this agent exerts beneficial effects on the heart via, at least in part, C/EBPβ/CITED4-dependent cardiomyocyte proliferation. In addition, Tongxinluo was reported to improve cardiac function and ameliorates ventricular remodelling in mice models of MI through enhancing angiogenesis.52 (e) Although the causal role of autophagy in the pathogenesis of adverse cardiac remodelling is not completely understood, increased autophagy has been certified in myocardial damage which may contribute to the progression of heart failure.53 Recent results showed that both Qili Qiangxin54,55 and Tongxinluo56 treatment significantly suppressed the excessive increases in cardiomyocyte autophagy in mice after experimental MI, suggesting that these CMSQPBC drugs abrogated the development of cardiac remodelling and dysfunction, at least in part, through reduction of excessive cardiomyocyte autophagy. (f) Because cardiomyocyte apoptosis plays a causal role in contractile dysfunction and heart failure, increased apoptosis of cardiac myocytes may be a potential mechanism of the impaired contractility in mice during a long period of hemodynamic overload.57 Cardiomyocyte apoptosis was observed to decrease significantly in QiliQiangxin-treated mice compared with vehicle-treated ones after chronic pressure overload, indicating that this CMSQPBC regimen may protect the heart against cardiomyocyte apoptosis.58,59 (g) Microvascular obstruction, though to be associated with a lower ejection fraction, increased ventricular volumes and infarct size, and induced a greater risk of major adverse cardiac events in patients with MI.60 Excessive platelet activation when it adheres to impaired vessels plays a key role in the pathogenesis of microembolization. Studies show that the vast majority of CMSQPBC, Buyang Huanwu decoction, Qishen Yiqi dripping pills and Tongxingluo capsules, can reduce the platelet aggregation rate and P-selection expression significantly in patients or animal models with thromboembolic diseases.61,62

The limitations of this review are as follows. First, we established rigorous criteria for included and excluded studies in the Meta-analysis; therefore, this study yielded the conclusions from a relatively small population. Moreover, most of these enrolled studies did not include formal sample size estimation, which may run the risk of overestimating CMSQPBC intervention benefits. Second, the clinical heterogeneity compromised the validity of the included studies. There were large variations in the formulation, dosage, administration, and duration of treatments of the CMSQPBC in these included studies. Third, because studies with negative results are less published, publication bias inevitable.
bly exists. In addition, the protocols of some included studies were not available, which makes it difficult to evaluate the bias of some studies correctly. There were few details about concealment of allocation, blinding method, withdrawals, or dropouts in these trials, which suggests a potential risk of bias. Finally, all the studies were conducted in mainland China, and the source of experimental data is quite narrow; thus, the interpretation of the positive findings of treatment with CMSQPBC should be made with caution.

In conclusion, despite the positive findings from the study, it is premature to draw the conclusion that CMSQPBC administration led to definite improvement of LVESV and LVSDV in patients following MI, because of the heterogeneity of the included studies and small number of trials in this Meta-analysis. More well-designed trials are required to further confirm our findings.

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