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Traditional Chinese medicine for acute coronary syndrome

A meta-analysis of clinical manifestations and objective indicators

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Abstract

Background: Modern clinical trials and experimental researches of traditional Chinese medicine (TCM) have been conducted for decades and provided support for the prevention and treatment of acute coronary syndrome (ACS). However the level of evidence and the proper application of TCM were still barely satisfactory.

Methods: In this study, we divided ACS into 3 different stages, including unstable angina, acute myocardial infarction, and post myocardial infarction. Then we systematically reviewed and meta-analyzed the existing randomized controlled trials on both clinical manifestations and objective indicators, in these 3 aspects.

Results: The results indicate that TCM can both improve the clinical manifestations and ameliorate the objective parameters in different courses of ACS, including C-reactive protein in unstable angina, left ventricular ejection fraction in acute myocardial infarction and post myocardial infarction. And the incidence of short-term cardiovascular events are lower in TCM intervention group. Some of the improvements lead to potential long-term benefits.

Conclusion: TCM treatment is beneficial to different courses of ACS. To acquire more solid and comprehensive evidence of TCM in treating ACS, more rigorously designed randomized controlled trials with longer follow-up duration are warranted.

Abbreviations: ACS = acute coronary syndromes, AMI = acute myocardial infarction, CD = cardiovascular death, CI = confidence interval, CRP = C-reactive protein, ECG = electrocardiogram, HF = heart failure, IHD = ischemic heart disease, LDL-C = low density lipoprotein-cholesterol, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, PCI = percutaneous coronary intervention, PMI = post myocardial infarction, RCT = randomized controlled trial, RR = relative risk, SMD = standard mean difference, TCM = traditional Chinese medicine, UA = unstable angina.

Keywords: acute coronary syndrome, clinical manifestations, meta-analysis, objective indicators, traditional Chinese medicine

1. Introduction

According to the Global Burden of Death[1] and Roth et al,[2] ischemic heart disease (IHD) is the single most common cause of death worldwide, both in male and female. IHD has caused 116.88 death per million populations in 2017, which has increased 7.51% from 1990.[3] Acute coronary syndrome (ACS) is the unstable and severe stage of IHD. Prompt and proper management of ACS is critical, for that can we prevent long-term

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disability or even death. Yet current circumstance of ACS is far from satisfying. There is a consistent pattern for ACS to be relatively more common in younger than in old people, and the incident rate of ACS is still increasing in many region around the globe.[4] Traditional Chinese medicine (TCM) has shown its possible role in the prevention and management of IHD. Numerous researches were held within the framework of modern medicine, some of which have solid sound of the efficacy of TCM.[5–7]

TCM has a history of more than 2000 years.[8] The understanding and utilization of TCM has always been developing, which was determined by its experience-guiding nature. New generation TCM clinicians have used modern medical equipment to enhance their information acquisition, and established more objective diseases diagnosis and syndrome differentiation criteria. Scientific researches of TCM were launched to elucidate the effectiveness and mechanisms of TCM. TCM, or integrative medicine has help preventing and treating diseases across the world, not just in east of Asia.[9]

Under this circumstance, it is worth to gather the evidence of TCM treating ACS, to provide faith in treating IHD with TCM as primary or alternative therapy, and help decreasing the mortality and morbidity of IHD worldwide. Here, we aim to evaluate the efficacy and potential mechanisms of TCM in different course of ACS. We searched for published studies of randomized controlled trials (RCTs) with relatively fine quality, and systematically assessed the efficacy and safety of TCM therapy for the major clinical stages of ACS, including unstable angina (UA), acute myocardial infarction (AMI), and post myocardial infarction (PMI).

2. Methods

2.1. Search strategy and inclusion/exclusion criteria

Since English and Chinese are the major publication language that TCM related researches used,[10] electronic databases including Medline, EMBASE, the Cochrane Library, the China National Knowledge Internet, the China biology medicine, Wanfang, and VIP databases were searched up to April 1, 2020 for all studies evaluating the effect of TCM on UA, AMI, and PMI. The keywords used in the search were 'traditional Chinese', or 'traditional Chinese medicine', or 'Chinese medicine' in combination with each of the following terms: 'coronary artery', 'coronary heart', 'angina', 'ischemia', 'ischemic', 'acute coronary syndrome', 'myocardial infarction', 'percutaneous coronary intervention', 'coronary artery bypass graft' or 'revascularization'. The specific search algorithms were adjusted for each database. The authors of the articles were contacted for detailed information if necessary.

The studies we included should meet following criteria: study participants were diagnosed as UA or MI, did or did not underwent percutaneous coronary intervention (PCI), coronary artery bypass grafting, or thrombolysis; study should be randomized clinical trial, which compared the efficacy and quantitative parameters of TCM medication with placebo or conventional medication; follow-up in each study should be ≥4 weeks; and study quality was considerably fine, with a Jadad score[11] ≥2 (out of 5). We excluded studies with the following features: studies were nonrandomized or without description of randomization method, studies without definite diagnostic criteria, and studies compared different TCM medications. When 2 articles reported the results from the same research, the articles with more data was included.

Ethical approval was not necessary due to the data we used in this study was extracted from public database.

2.2. Statistical analysis

Data were analyzed using Review Manager v5.3[12] and Microsoft excel 2016. Meta-analysis was conducted if the included studies were no less than 2. For dichotomous outcome the pooled relative risk (RR) with 95% confidence interval (CI) was used as the effect measure. For the continuous outcome, standard mean difference (SMD) was used as the effect measure. The model used to pool the data was random effect model, since the intervention between studies were different.

2.3. Possible mechanisms of traditional Chinese medicine medication

Specific herbs in the TCM formula were documented and evaluated. The frequently used herbs and Chinese patent medicine were described in detail. Mechanism studies of frequently used herbs and patent medicine were searched and summarized.

3. Results

3.1. General information

A flow diagram of the literature search and study selection is shown in Figure 1. We included 43 eligible studies, in which 6 were in English and 37 were in Chinese. The publication date ranged from 2007 to 2020. The participant amount in single group varied from 20 to 2441, the average amount was 105 (the average amount was 50 if one of the largest scale RCT was ruled out). A total of 9035 subjects were included in this research. The quality of the studies were considered mostly moderate, 4 of them had a Jadad score of 5, 6 of them had a Jadad score of 3 to 4, and the rest of them (33 studies) had a Jadad score of 2. Generally, there were 20 studies of UA, 15 studies of AMI, and 8 studies of PMI. The detail information of included studies were listed in Table 1.

3.2. Traditional Chinese medicine for unstable angina

Twenty RCTs (Nos. 1–20) evaluated TCM treating UA were included and assessed. The sample size ranged from 60 to 244 participants, with average of 91.50. The intervention duration ranged from 4 to 24 weeks, with an average of 5.70 weeks. The methodological quality of the included RCTs was generally low. Only 1 of 20 RCTs had a Jadad score of 4 and 3, and the rest of them had score of 2. The major and secondary outcomes we included and assessed for clinical efficacy, angina efficacy, angina frequency, nitrates consumption, electrocardiogram (ECG) efficacy, levels of LDL-C, and C-reactive protein (CRP). One of 20 RCTs compared TCM with placebo, and the rest of them compared TCM with blank intervention, on the basis of conventional therapy, including antiplatelet, beta blocker, anticoagulant, statins, ACEI/ARB, long- or short-active nitrates, hypotensor, and hypoglycemics if necessary.

Fifteen RCTs had reported the clinical efficacy after intervention. Meta-analysis had shown significant difference of RR (1.20, 95% CI 1.13–1.28) (Fig. 2A). As for the angina efficacy, 7 RCTs were included in the meta-analysis and had shown significant

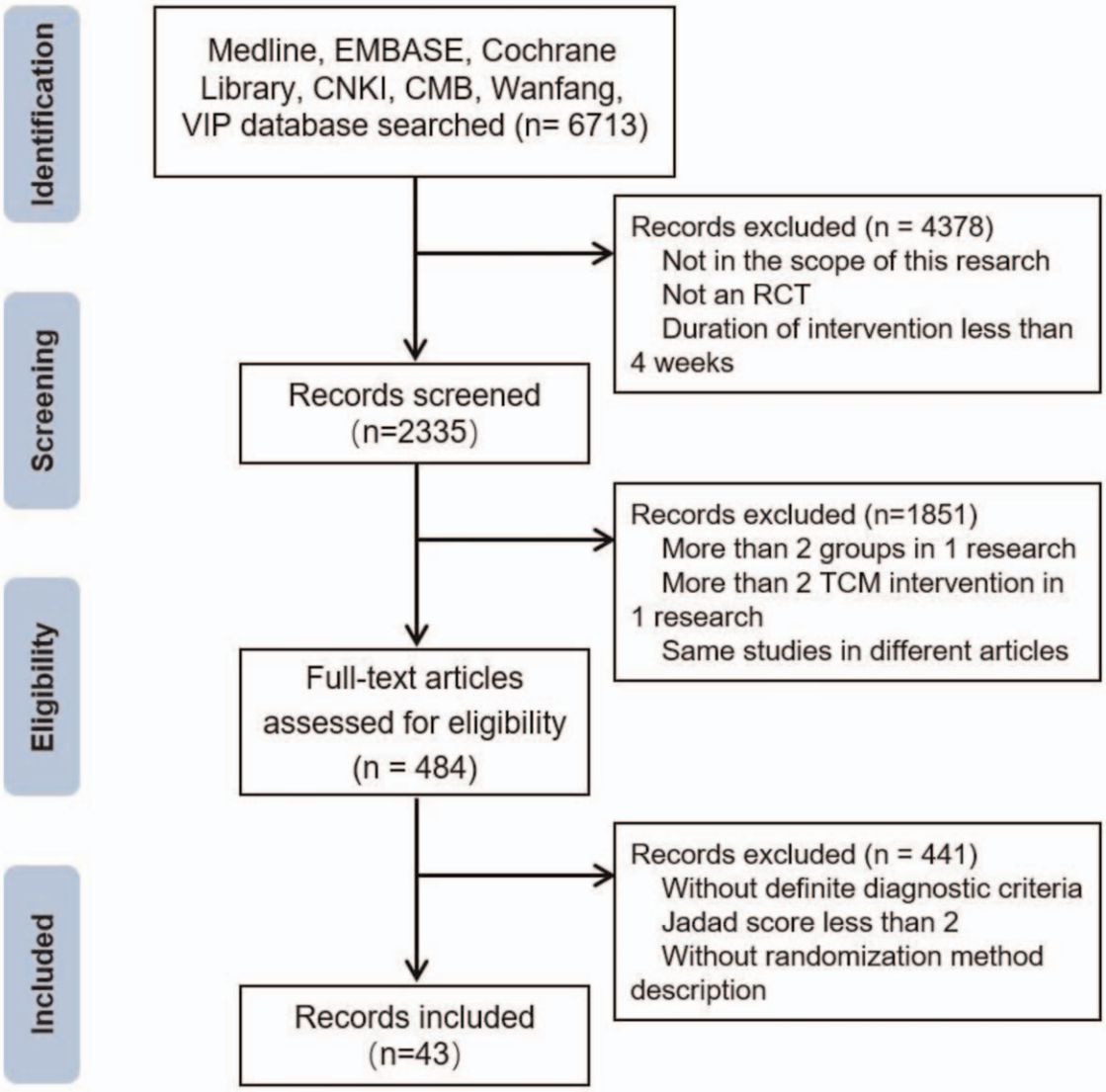

Figure 1. Flow diagram of the RCT inclusion process. RCT = randomized controlled trial.

difference of RR (1.20, 95% CI 1.09–1.32) (Fig. 2B). The RCTs documented angina frequency and nitrates consumption were relatively fewer (2 RCTs in each comparison). Meta-analysis conducted in these 2 comparison showed significant difference in RR (angina frequency: −1.95, 95% CI −2.41 to −1.49; nitrates consumption: −2.12, 95% CI −3.02 to −1.22) (Fig. 2C and D). These analyses indicated TCM could improve the clinical efficacy of UA, probably by ameliorate the manifestation of angina and reduce the angina frequency and consumption of nitrates.

Nine RCTs had documented the ECG efficacy after intervention. Meta-analysis showed significant improvement of TCM in ECG, with RR of 1.22 and 95% CI 1.11 to 1.35 (Fig. 3A). ECG efficacy indicated that TCM can improve unstable angina in the aspect of ECG.

As for the laboratory parameters, low density lipoprotein-cholesterol (LDL-C) and CRP were synthetize respectively. Meta-analysis shown significant difference in CRP (−0.92, 95% CI −1.50 to −0.35) (Fig. 3C) but not in LDL-C (0.12, 95% CI −0.75 to 0.99) (Fig. 3B). Meta-analyses of 2 out of 3 RCTs that LDL-C included showed no significant difference either. Data of other conventional cholesterol was not sufficient enough for systematic review in these 20 RCTs concerning UA. The efficacy of TCM for cardiovascular diseases risk factors in UA needs more evidence to be proved.

3.3. Traditional Chinese medicine for acute myocardial infarction

Fifteen RCTs (Nos. 21–35) evaluated TCM treating AMI were included and assessed. All the participants in every RCTs were diagnosed myocardial infarction with formally published criteria. The intervention time nodes were around the AMI and coronary recanalization. Respectively, 2 RCTs were 30 minutes to 2 days before recanalization; 1 RCTs were 12 to 55 days after recanalization; 12 RCTs were immediately after recanalization. The sample size ranged from 40 to 219 participants, with average of 109.93. Three of them compared TCM with placebo, with the basis of antiplatelet, anticoagulant, beta blocker, and ACEI. The intervention duration ranged from 4 to 24 weeks, with average of 8.13 weeks. The methodological quality of the included RCTs

Table 1

Details of included studies.

No.	First author	Title	Journal	Publication Year	TCM intervention	T (n)	Control intervention	C (n)	Duration (week)	Jadad Score
Unstable angina										
1	Liu Yunfang	Effects of Quyu xiaoban capsules on clinical outcomes and platelet activation and aggregation in patients with unstable angina pectoris	J Altern Complement Med	2007	Quyu Xiaoban Capsule	41	Placebo	44	4	4
2	He Qingyong	Effect of Yiqi Yangyin Decoction on the quality of life of patients with unstable angina pectoris	Chin J Integr Med	2010	Yiqi Yangyin Decoction	54	NA	54	4	3
3	Zuo Ping	Clinical observation of guanxin kangfu decoction in the treatment of unstable angina pectoris	Journal of traditional Chinese medicine	2010	Guanxinkangfu Decoction	34	NA	32	4	2
4	Duan Xuezhong	Observation on the efficacy of maianshu granules in the treatment of unstable angina pectoris	Chinese emergency department of traditional Chinese medicine	2011	Maianshu Granule	30	NA	30	4	2
5	Lian Jianhong	Effect of yiyuan tongmai prescription on hs-crp and il-6 in unstable angina pectoris	Chinese journal of practical medicine	2011	Yiyuantongmai Decoction	30	NA	30	4	2
6	Lu Qiangyi	Curative effect observation on 30 cases of unstable angina pectoris treated with traditional Chinese and western medicine	New Chinese medicine	2011	Wendan Decoction	30	NA	30	4	2
7	Wang Lingjun	Effect of guanmai ling fang on endothelial function in patients with unstable angina pectoris with qi stagnation and blood stasis	Liaoning journal of traditional Chinese medicine	2011	Guanmailing Decoction	30	NA	30	4	2
8	Wang Zerui	Xintongning in the treatment of unstable angina: 244 cases of clinical research	Jilin Journal of traditional Chinese medicine	2012	Xintongning Liquid	124	NA	120	4	2
9	Lu Wentao	Curative effect of snakegourd tablets on blood stasis and collaterals obstruction in unstable angina pectoris	New Chinese medicine	2013	Danlou Tablet	44	NA	44	4	2
10	Zhang Dawei	Clinical efficacy of yixinshu capsule in the treatment of unstable angina pectoris caused by coronary heart disease and its effect on heart rate variability	Journal of cardiovascular and cerebrovascular diseases	2013	Yixinshu Capsule	79	NA	79	4	2
11	Zhang Yue	A randomized parallel control study of buxu huoxue quyu prescription combined with western medicine in the treatment of unstable angina pectoris	Journal of internal medicine of traditional Chinese medicine	2014	Buxuhuoxuequyu Decoction	40	NA	40	4	2
12	Li Hongying	Curative effect of qishen danzhi decoction on unstable angina pectoris	Emergency of Chinese traditional medicine	2015	Qishendanzhi Decoction	52	NA	54	4	2
13	Li Jun	Randomized controlled study on the treatment of unstable angina pectoris with wenxin decoction	Chinese journal of experimental pharmacology	2016	Wenxin Decoction	118	NA	110	8	2
14	Mao Xiangping	Effect of xintai on p-selectin and TXB_2 in patients with unstable angina pectoris syndrome of qi stagnation and blood stasis	Science and technology of traditional Chinese medicine	2016	Xintongtai Granule	30	NA	30	12	2
15	Sheng Hanen			2016	Guifulizhong Pill	49	NA	49	6	2

(*continued*)

Table 1
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No.	First author	Title	Journal	Publication Year	TCM intervention	T (n)	Control intervention	C (n)	Duration (week)	Jadad Score
		Clinical study on guifuli zhongwan in the treatment of xinshen Yang deficiency syndrome of unstable angina pectoris	Journal of traditional Chinese medicine							
16	Cao Lei	Protective effect of traditional Chinese medicine on vascular endothelium in patients with unstable angina pectoris	World journal of traditional Chinese medicine	2017	Yiqihuayu Decoction	80	NA	80	4	2
17	Liu Jing	Effect of heat-clearing, detoxification and blood-activating method on endothelial function in patients with unstable angina pectoris	Chinese emergency department of traditional Chinese medicine	2017	Qingrejieduhuoxue Decoction	40	NA	40	4	2
18	Yang Yue	Curative effect of combined traditional Chinese and western medicine in the treatment of unstable angina pectoris	Shandong journal of traditional Chinese medicine	2017	Buyanghuanwu Decoction	30	NA	30	4	2
19	Yin Junyan	Clinical observation on the treatment of unstable angina pectoris of qi deficiency and blood stasis syndrome with supplementing Qi and activating blood circulation	Chinese folk therapy	2019	Yiqihuoxue Decoction	30	NA	30	24	2
20	Yang Cui	Clinical study on the treatment of unstable angina pectoris with Yiqiwenyanghuoxue decoction	Chinese Journal of Integrative Medicine on Cardio-/ Cerebrovascuiar Disease	2020	Yiqiwenyanghuoxue Decoction	30	NA	30	4	2
Acute myocardial infarction										
21	Zhang Haitao	No-reflow protection and long-term efficacy for acute myocardial infarction with Tongxinluo: a randomized double-blind placebo-controlled multicenter clinical trial (ENLEAT Trial)	Chin Med J (Engl)	2010	Tongxinluo Capsule	108	Placebo	111	24	4
22	Long Weiping	Effect of yixinyin on TCM syndrome and left heart function after PCI in patients with acute myocardial infarction	Journal of hunan university of traditional Chinese medicine	2013	Yixinyin Decoction	30	NA	30	12	2
23	Li Shujian	28 cases of cardiac insufficiency after successful thrombolytic therapy of acute myocardial infarction with integrated traditional Chinese and western medicine	Liaoning journal of traditional Chinese medicine	2014	Yixinfumai Decoction	28	NA	31	4	2
24	Lu Jianqi	Study on the clinical effect of anxin granule combined with tirofiban in patients with acute myocardial infarction after PCI	Chinese journal of traditional Chinese medicine	2014	Anxin Granule	60	NA	60	4	3
25	Guo Xiaoming	Analysis on the curative effect and quality of life of acute myocardial infarction treated with traditional Chinese and western medicine	Journal of clinical medicine	2015	Danhong Injection	55	NA	55	4	2
26	Jiang Lei	Clinical effect of tongxin fang on phlegm and blood stasis in patients with acute myocardial infarction and its effect on MPO	Journal of hunan university of traditional Chinese medicine	2015	Xintong Decoction	20	NA	20	4	2
27	Zhang Aizhi	Clinical observation on the treatment of 38 cases of acute	Chinese medicine guide	2015	Shenqifumai Decoction	38	NA	38	4	3

(*continued*)

Table 1
(continued).

No.	First author	Title	Journal	Publication Year	TCM intervention	T (n)	Control intervention	C (n)	Duration (week)	Jadad Score
		myocardial infarction with qi deficiency and blood stasis by shenqi fumai recipe								
28	Zuo Weihui	Clinical study on treating acute myocardial infarction by invigorating qi, activating blood circulation and tongluo method combined with intravenous thrombolysis	Journal of traditional Chinese medicine	2015	Yiqihuoxuetongluo Decoction	51	NA	51	4	2
29	Wang Lei	Efficacy of Danlou tablet in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: results from a multicentre, placebo-controlled, randomized trial	Evid Based Complement Alternat Med	2016	Danlou Tablet	109	Placebo	110	12	5
30	Mao Shuai	Traditional Chinese medicine, Danlou tablets alleviate adverse left ventricular remodeling after myocardial infarction results of a double-blind, randomized, placebo-controlled, pilot study	BMC Complement Altern Med	2016	Danlou Tablet	44	Placebo	44	12	5
31	Guo Daoqun	Clinical efficacy and safety of integrated traditional Chinese and western medicine in the treatment of acute myocardial infarction patients with coronary heart disease	Medical review	2016	Zhongyao Decoction	65	NA	65	4	2
32	Yang Guangming	Clinical study of Tongxinluo capsule in the treatment of inflammatory response after PCI in patients with acute myocardial infarction	Journal of Hubei University of Nationalities	2018	Tongxinluo Capsule	43	NA	43	12	2
33	Li Junlong	Effect of Yixinhuoxue Pill on the clinical effect and heart function of patients with acute ST segment elevation myocardial infarction and Qi-Yin deficiency syndrome after percutaneous coronary intervention	Journal of Traditional Chinese Medicine	2019	Yixinhuoxue Pill	83	NA	83	4	2
34	Liu Shili	The effect of Tongmaijiangzhuo Decoction on cardiac function and vascular endothelial function in patients with acute myocardial infarction after PCI	Journal of Liaoning University of Traditional Chinese Medicine	2019	Tongmaijiangzhuo Decoction	48	NA	48	12	2
35	Xu Weiwei	Clinical study of Tongxinluo capsule combined with tirofiban in the treatment of acute myocardial infarction during PCI	New Chinese medicine	2019	Tongxinluo Capsule	39	NA	39	8	2
Post myocardial infarction										
36	Lu Zongliang	Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction	Am J Cardiol	2008	Xuezhikang Capsule	2429	Placebo	2441	216	5
37	Zhang Hongxing	The prevention and treatment effect of guanxin danshen dropping pills on restenosis after coronary heart disease stent implantation	Shandong pharmaceutical	2014	Guanxindanshen Dripping Pill	30	NA	30	24	2

(*continued*)

Table 1
(continued).

No.	First author	Title	Journal	Publication Year	TCM intervention	T (n)	Control intervention	C (n)	Duration (week)	Jadad Score
38	Fan Shiping	Effect of modified buyang huawu decoction on ventricular remodeling and expression of mirna-21 and gdf-15 in patients with myocardial infarction	Liaoning journal of traditional Chinese medicine	2016	Jiaweibuyanghuanwu Decoction	50	NA	50	16	2
39	Li Hui	Clinical study of naoxintong capsule combined with western medicine in the treatment of patients after PCI	Liaoning journal of traditional Chinese medicine	2016	Buchangnaoxintong Capsule	60	NA	60	4	2
40	Wang Kaili	Clinical observation on 32 cases of restenosis after PCI intervention with huxinkang tablets for coronary heart disease	Hunan journal of traditional Chinese medicine	2016	Huxinkang Tablet	32	NA	30	24	2
41	Zhai Ying	Clinical study on the treatment of angina pectoris after coronary intervention by invigorating qi, nourishing Yin and activating blood circulation	Modern remote education of traditional Chinese medicine	2016	Yixinzhitong Decoction	34	NA	34	4	2
42	Chen Shaojun	Therapeutic effect of yiwenyang huoxue tongluo drugs on angina pectoris after PCI in elderly patients over 80 years old	World journal of traditional Chinese medicine	2017	Yiqiwenyanghuoxuetongluo Decoction	32	NA	33	8	3
43	Zhou Yuanshen	Effect of xintongguan Granule on heart function in patients with heart failure after acute myocardial infarction	Chin J Integr Med	2019	Xintongguan Granule	30	Placebo	30	12	5

TCM = traditional Chinese medicine.

was moderate. Two of 15 RCTs had a Jadad score of 5, 1 had a Jadad score of 4, 2 had score of 3, and 10 had score of 2. The major and secondary outcomes we included and assessed were clinical efficacy, major adverse cardiovascular events (MACE), cardiovascular death (CD), and left ventricular ejection fraction (LVEF), according to the data in RCTs we included.

Ten of 15 RCTs had reported the clinical efficacy after intervention. Participants in 1 of the RCTs underwent thrombolysis, and in another RCTs, participants underwent PCI. Meta-analysis had shown significant difference of RR (1.15, 95% CI 1.08–1.21) (Fig. 4A). This result indicated that TCM can improve the clinical efficacy of AMI.

The average follow-up duration of these RCTs were 8.13 weeks (4–24 weeks), hence the short-term outcomes would be the major concern of TCM intervention in these RCTs. Six of the RCTs had documented incidence of MACE in each group after intervention. Meta-analysis showed significant difference of RR (0.55, 95% CI 0.41–0.74) (Fig. 4B). As for CD, meta-analysis also showed significant difference of RR (0.35, 95% CI 0.16–0.76) (Fig. 4C). Five of the RCTs had also documented the LVEF after intervention. Data was pooled together and synthetized, the results favored TCM group (SMD 0.94, 95% CI 0.22–1.66) (Fig. 4D). Research had shown that the 30-day cardiac mortality rate in ST elevated myocardial infarction patients was 7.3% even underwent PCI, the 1-year cardiac mortality rate was 8.4%, with a <1.5% annual risk of successive cardiac death.[13] Reducing the short-term cardiac mortality rate in AMI patients is vital to control the over-all outcomes of MI patients. Cardiac mortality rate in TCM group is 4.1%. The results in these research indicated that TCM may be a key role in this goal.

3.4. Traditional Chinese medicine for post myocardial infarction

PMI is usually reckoned as 4 to 8 weeks after AMI. If the patient survive from AMI and/or cardiac shock, malignant arrhythmia, cardiac remodelling, and coronary collateral circulation establishment should be the major physiopathological process.[14,15] Prompt and adequate intervention can boost the cardiac rehabilitation and prolong life expectancy.[16] Eight RCTs (Nos. 36–43) evaluated TCM treating PMI were included and assessed. All the participants experienced AMI 1 to 12 months before inclusion, despite recanalization or not. The sample size ranged from 60 to 4870 participants, with average of 675.63 (average of 76.43 if the largest scale RCT was ruled out). The intervention duration ranged from 4 to 216 weeks, with average of 38.5 weeks (average of 13.14 if the largest scale RCT was ruled out). The methodological quality of the included RCTs was generally low. Two of 8 RCTs had a Jadad score of 5, 1 had a Jadad score of 3, and 5 had score of 2. The major and secondary outcomes we included and assessed were clinical efficacy, angina efficacy, LVEF, and MACE.

Five of 8 RCTs had reported the clinical efficacy after intervention. All of them compared TCM with blank intervention, with the basis of antiplatelet, beta blocker, statins, ACEI/ARB, and nitrates. Meta-analysis had shown significant

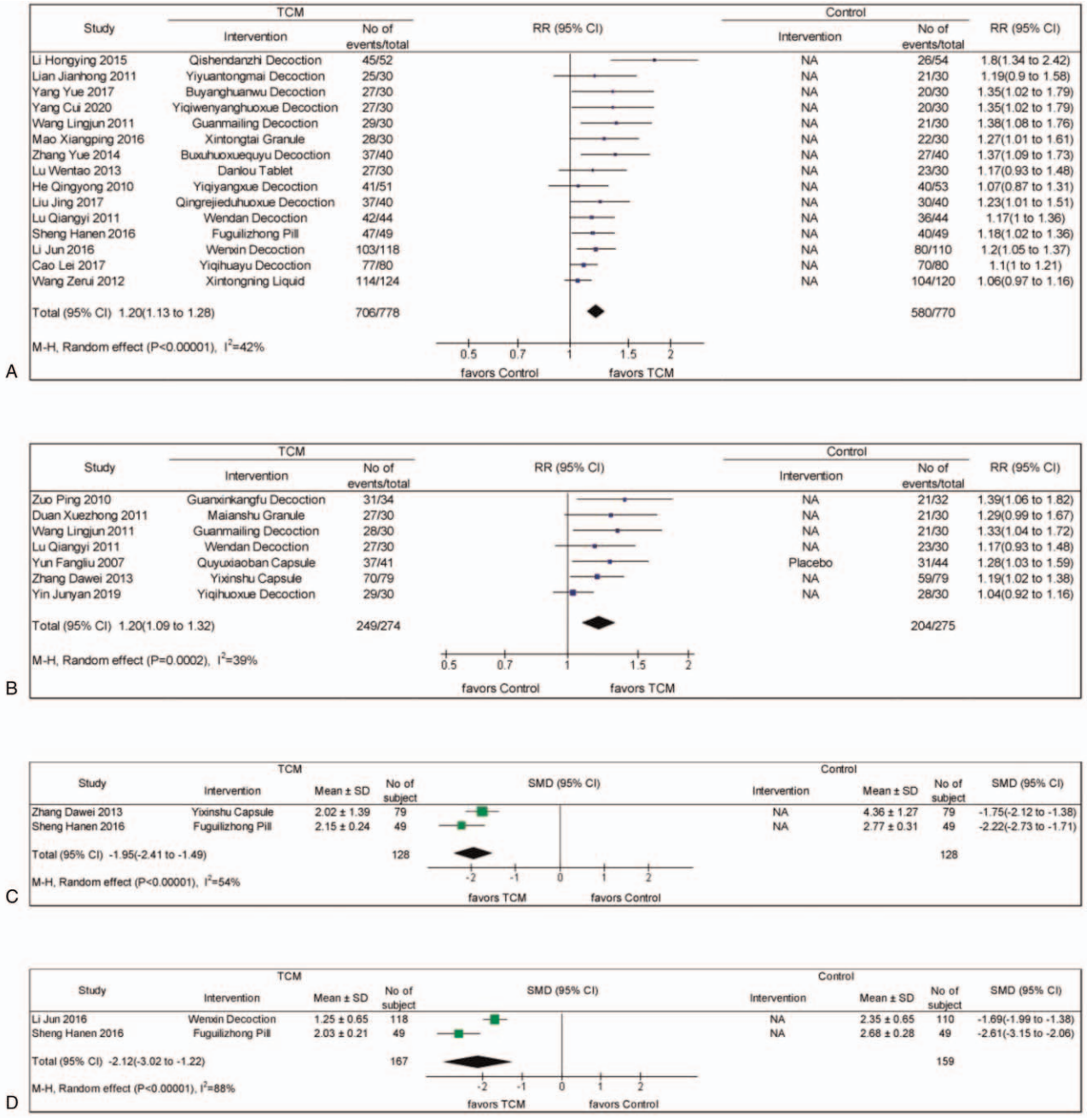

Figure 2. Clinical and angina efficacy comparison between TCM group and control group in UA. A: Clinical efficacy comparison between TCM group and control group. B: Angina efficacy comparison between TCM group and control group. C: Angina frequency comparison between TCM group and control group. D: Nitrates consumption comparison between TCM group and control group. CI = confidence interval, RR = relative risk, TCM = traditional Chinese medicine, UA = unstable angina.

difference of RR (1.28, 95% CI 1.15–1.42) (Fig. 5A). Three RCTs were included in the meta-analysis of angina efficacy, and had shown significant difference of RR (1.48, 95% CI 1.23–1.78) (Fig. 5B). This result indicated that TCM can improve the clinical and angina efficacy of PMI.

LVEF reflects the pumping function of left ventricular. Size of infarct myocardium, formation of ventricular aneurysm, ventricular remodeling, arrhythmia, and cardiac rehabilitation are the detrimental and beneficial factors of remaining LVEF. Four RCTs documented LVEF after intervention. Meta-analysis showed that in LVEF, TCM achieved significant improvement compared to blank intervention (SMD 0.34, 95% CI 0.06–0.63) (Fig. 5C). As for MACE in PMI after intervention, the incidence rate in TCM group was 5.18%, compared to 8.04% in control group (RR 0.56, 95% CI 0.32–0.97) (Fig. 5D). TCM has significant effect on reducing incidence rate of MACE.

3.5. Pharmacological effects and possible mechanisms of traditional Chinese medicine medication

The clinical trials we summarized above have proven the effectiveness of TCM in different stages of ACS. The majority

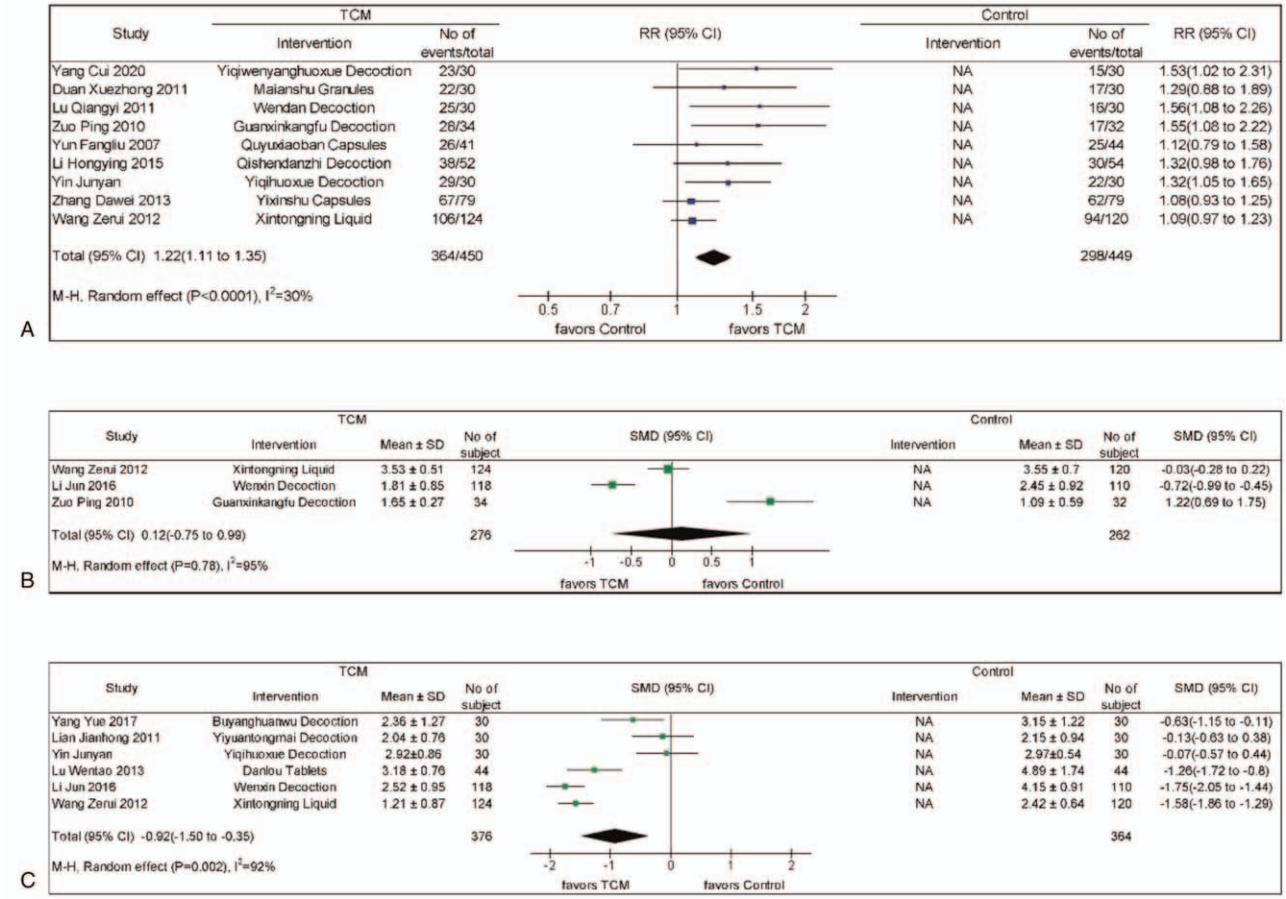

Figure 3. Objective parameters comparison between TCM group and control group in UA. A: ECG comparison between TCM group and control group. B: LDL-C comparison between TCM group and control group. C: CRP comparison between TCM group and control group. CI = confidence interval, CRP = C-reactive protein, ECG = electrocardiogram, LDL-C = low density lipoprotein-cholesterol, RR = relative risk, SMD = standard mean difference, TCM = traditional Chinese medicine, UA = unstable angina.

of them used herbal formula as intervention. We documented and screened out the most frequently used herbs in these RCTs, the top 5 herbs were listed in Table 2, along with the main components, beneficial effects and potential mechanisms. The most frequently used herb for ACS is Chuanxiong Rhizoma. Tetramethylpyrazine is the main component of Chuanxiong Rhizoma. Chuanxiong Rhizoma is known as its effects of vasodilation, antiplatelet, inhibition of vascular smooth muscle cell proliferation etc. It might exert these beneficial effects by inhibiting the activity of Endothelin 1 (ET-1) and nitric oxide, inhibiting calcium mobilization from both the extracellular medium and intracellular stores, inhibiting calcineurin activity and reducing efos and proliferation cell nuclear antigen expression.[17,18] Astragalus membranaceus is well reckoned as one of the tonic herbs. Its main component is astragaloside. The beneficial effects of Astragalus membranaceus include immunomodulatory, anti-inflammation, antioxidation, antiautophagy, and it is reportedly that it can preserve cardiac function.[19–21] Radix Salviae can reduce the levels of tumor necrosis factor-alpha (TNF-α), IL-6, and MDA, enhance capacities of antioxidant enzymes and prevent myocardium cell apoptosis, activate ERK and PKB and downregulate the levels of TNF-α and angiotensin II, and inhibit H2O2-induced ROS production.[22,23]

Chinese patent medicines is widely used in TCM practice. Chinese patent medicines are studied thoroughly before and after public utilization. Among these included RCTs, the most studied Chinese patent medicines were summarized (Table 3). Danlou tablet can decreased the expressions of inflammation cytokines by down regulating NF-κB singling pathway and accelerated cholesterol effluent through activating PPARα/ABCA1 signaling pathway; inhibit EGFR phosphorylation and lower the expression of TNF-α, IL-6 and MMP9, decrease the expression levels of ox-LDL and MDA, and increase the expression of SOD.[28–31] Yixinshu capsule can attenuate ET-1 induced contraction dysfunction and BNP elevation, attenuate myocardial ischemia/reperfusion injury.[32–36] Xuezhikang capsule is extracts of red yeast, it contains natural statins. Other than lipid lowering effect, it can also inhibit TLR4/NF-κB signaling pathway, inhibit 7-KC-induced upregulation of apoptosis, protein expression of apoptotic markers (cleaved caspase-3 and cleaved PARP), and NF-κB activation.[41–44]

3.6. Evaluation of adverse events

Two researches of UA and 2 of AMI had documented adverse events. The incidence of adverse events between TCM and control groups was not significantly different (RR: 1.08, 95% CI: 0.52–2.25) (Table 4), which implied that TCM is generally safe.

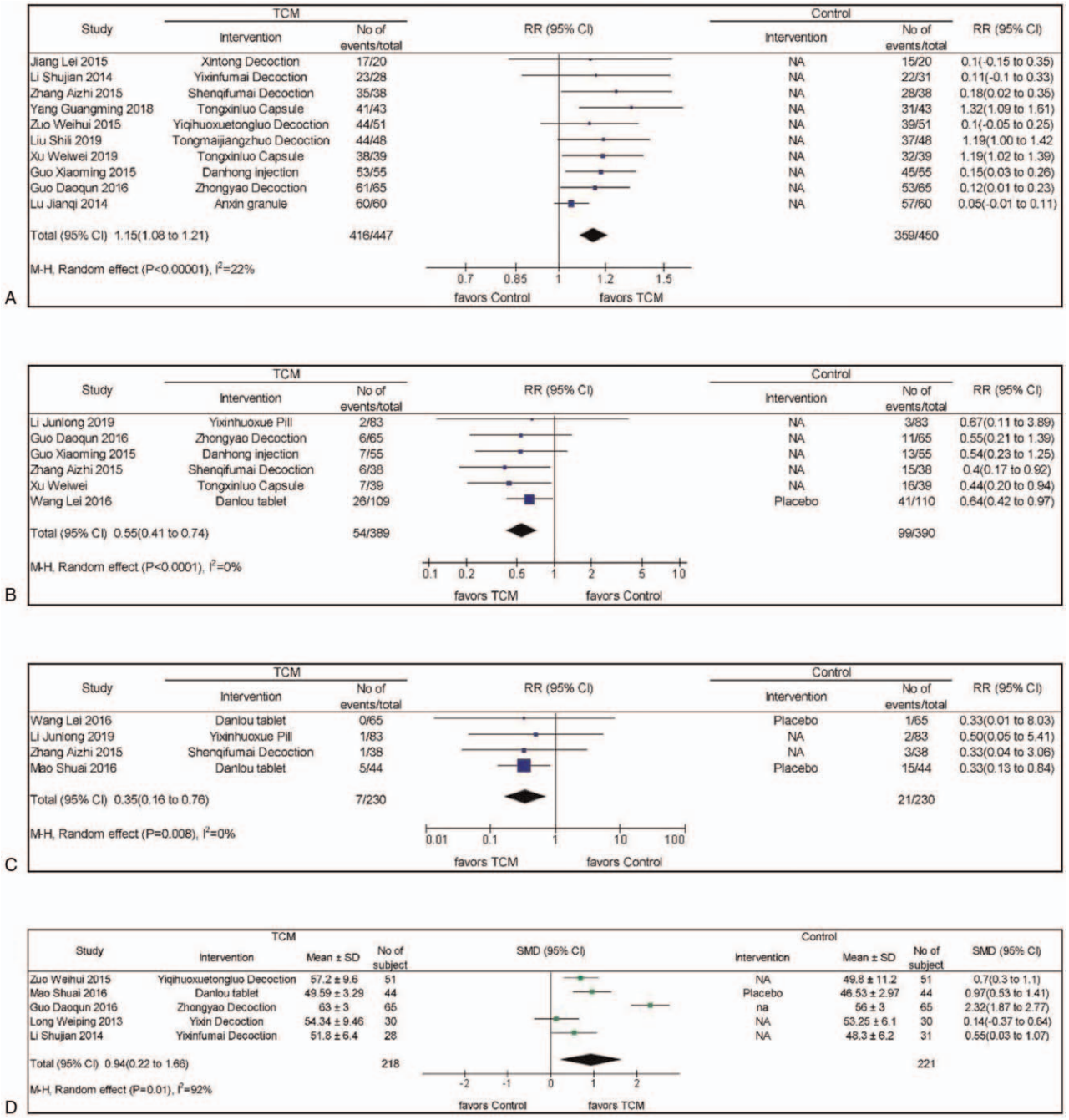

Figure 4. Clinical efficacy and objective parameters comparison between TCM group and control group in AMI. A: Clinical efficacy comparison between TCM group and control group. B: Incidence of MACE comparison between TCM group and control group. C: Incidence of cardiac death comparison between TCM group and control group. D: LVEF comparison between TCM group and control group. AMI = acute myocardial infarction, CI = confidence interval, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, RR = relative risk, SMD = standard mean difference, TCM = traditional Chinese medicine.

4. Discussion

Clinical efficacy, or the amelioration of symptoms, is one of the major evaluation of TCM intervention, according to its natural characteristics. More and more clinical and experimental evidence has been revealed to support the utilization of TCM as primary or complementary therapy for diseases, and show that TCM can both ameliorate clinical symptoms and improve objective parameters. According to the Guiding Principles for Clinical Research of New Chinese Medicines (published by State Drug Administration of China in 2002), clinical efficacy evaluation is based on patient self-reported severity of various clinical symptoms to form a disease assessment scale. With this equipment allows researchers assess the clinical efficacy in a more quantitative way, especially in some diseases which clinical manifestations play important role in the management and patient satisfaction.[50,51]

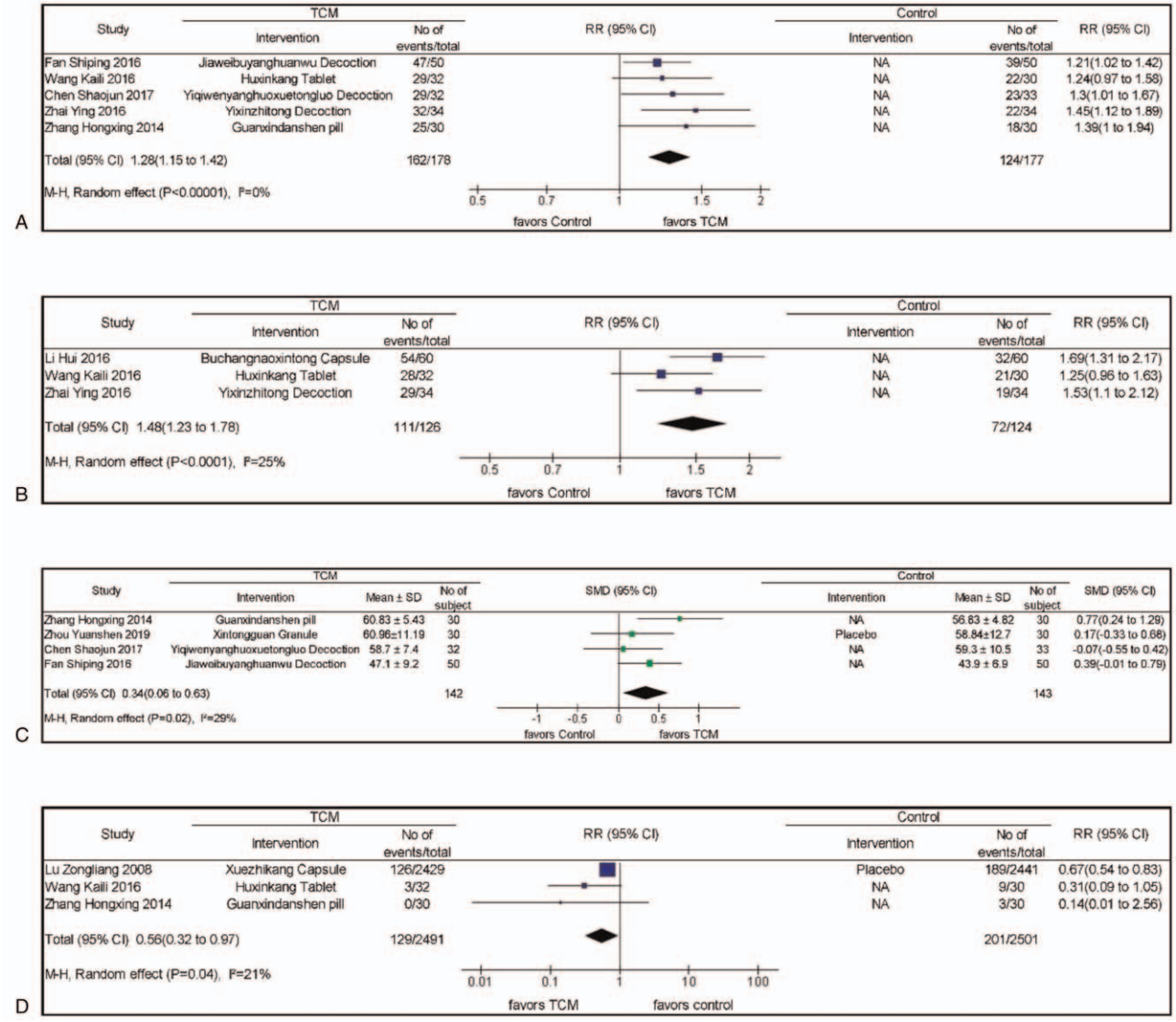

Figure 5. Clinical efficacy and objective parameters comparison between TCM group and control group in PMI. A: Clinical efficacy comparison between TCM group and control group. B: Angina efficacy comparison between TCM group and control group. C: LVEF comparison between TCM group and control group. D: Incidence of MACE comparison between TCM group and control group. CI = confidence interval, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, RR = relative risk, SMD = standard mean difference, TCM = traditional Chinese medicine.

As we mentioned above, we value the clinical efficacy comparison after intervention. 'Effective' was defined as the total score of symptoms reduced over 50% after intervention in the RCTs we included. Of all the aspects of ACS this research concerned, TCM achieved better clinical efficacy, with RR ranged between 1.15 and 1.28. The evaluation and the results of angina efficacy were similar to clinical efficacy in these analyses, and were corroborated by the analyses of angina frequency and nitrates consumption. Considering almost every RCT was conducted on the basis of conventional treatment in both TCM group and control group, it is safe to say that TCM can improve clinical efficacy as complementary to western medicine. The improvement of clinical efficacy was coincided with previous reports.[50–53]

As the clinical efficacy was improved, objective parameters were altered in these RCTs. The secondary outcomes we synthesized and analyzed were affected by RCTs we included. In the aspect of UA, only LDL-C and CRP were pooled and analyzed. In the aspect of AMI and PMI, MACE and CD were more important to assess the value of TCM intervention. MACE and CD are more likely to happen closer to the onset of MI.[13] It is vital to control recurrent cardiovascular events in patients experienced MI. These analyses indicated that TCM can reduce the incidence rate of MACE and CD both in acute and nonacute stage of MI.

LVEF reflects the pumping function of left ventricular. Local myocardial damage or long-term myocardium ischemia can lead to the reduction of LVEF. LVEF was documented in AMI and PMI related RCTs. Level of LVEF is one of the major diagnostic and stratification biomarkers for heart failure (HF). All-cause mortality is generally higher in HF with reduced ejection fraction than HF with preserved ejection fraction.[54] Meta-analyses of

Table 2

The top 5 frequently used herbs.

Herb	Main components	Beneficial effects	Potential mechanisms	References
Chuanxiong Rhizoma	Tetramethylpyrazine	Vasodilation; antiplatelet; antioxidation; inhibit vascular smooth muscle cell proliferation; antiatherogenesis; anti-inflammatory response; reduce Ischemia-Reperfusion Injury	Inhibits the activity of ET-1 and NO; inhibits calcium mobilization from both the extracellular medium and intracellular stores, inhibits the vWF-mediated process of platelet thrombus formation; inhibition of calcineurin activities and the reduction in e-fos and proliferation cell nuclear antigen expression; promotes the activity of SOD and GSH-Px and decreases that of MDA, LDH, creatinine kinase, tumor necrosis factors-α, and IL-6.	[17,18]
Astragalus membranaceus	Astragaloside	Anti-inflammation; antioxidation; immunomodulatory; antiautophagy; preserve cardiac function	Decrease TNF-α release, cycloxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, nitrotyrosine formation, NF-κB activation, and reactive oxygen species (ROS) release; induce the activation and migration, and monocyte maturation of peripheral blood mononuclear cells	[19–21]
Radix Salviae	Tanshinone	Antiapoptosis; antioxidation; anti-inflammation	Reduce the levels of TNF-α, IL-6 and MDA; increase the activity of SOD; enhance capacities of antioxidant enzymes and prevent myocardium cell apoptosis; activating ERK and PKB and downregulate the levels of TNF-α and angiotensin II, and inhibit H_2O_2-induced ROS production	[22,23]
Radix Paeoniae Rubra	Paeoniflorin	Anti-ischemia; antiapoptosis; antithrombosis	Increased SOD, CAT, and GSH-Px activities, and reduced MDA and LPO levels; decrease of endoplasmic reticulum stress-related factors PERK, XBP-1, ATF-6, and CHOP protein expression levels while an increase of GRP78 and MVD expression; downregulate the levels of MMP-9, PAI-1, NMDAR1 and upregulate the levels of TIMP-1, PA, and VEGF	[24,25]
Safflower	Crocin	Antiatherosclerosis; lipid-lowering; antiischemia; antioxidation; reduce ischemia–reperfusion injury; antiplatelet; antiapoptosis	Reduce fat and cholesterol absorption by inhibiting pancreatic lipase; increase the activities of SOD and catalase in the liver; increase the activity of NOS and the content of NO in cells, to protect endothelial cells from injury; inhibit collagen induced platelet aggregation and viscosity; decrease the levels of IL-1β, IL-6, TNF-α, COX-2 and iNOS, and enhance the phosphorylation of JAK2/STAT3 pathway	[26,27]

LVEF in AMI and PMI had provided evidence for the TCM potential long-term protection for ACS.

The mechanisms of TCM treating ACS have been summarized. To date researches results indicated that TCM treatment exerts its efficacy in ACS mostly by anti-inflammation, antioxidation, antiplatelet, antiapoptosis, ameliorate atherosclerosis, etc. The ways to achieve these beneficial effects are complex, and the therapeutic targets of single herb or patent medicine are multiple. The evidence we gathered is not sufficient enough to elucidate how TCM can achieve clinical manifestations and objective parameters improvements. Hence, further and more thorough investigation on promising TCM treatment is needed.

Studies both in English and in Chinese were screened and included. The methodology quality of RCTs we included was considered moderate, as we ruled out all the RCTs with Jadad score less than 2, those without definite randomization method were excluded, either. Primary and secondary endpoints we included and analyzed were based on the disease features and the included RCTs.

There were some potential limitations and sources of variability to this review: the individual RCTs differed in baseline characteristics, especially some baseline parameters such as LVEF, and the baseline western medication; the follow-up duration was moderate to short, the sample size was relatively small; heterogeneity was considered moderate to high between studies in some of the comparison. Baseline, follow-duration and sample size inconsistence may contribute to it; and most of the RCTs compared TCM with blank intervention, only a few had used placebo. TCM decoction and some patent medicine are mostly highly-scented, it is difficult to produce satisfying placebo. To eliminate these limitations and enhance the reliability, further rigorously designed RCTs with larger scale and multiple centers are needed.

5. Conclusions

Our meta-analysis of data from RCTs supports the use of TCM in different stages of ACS. TCM can both improve the clinical manifestations and ameliorate the objective parameters. Some of the improvements lead to potential long-term benefits. To acquire more solid and comprehensive evidence of TCM in treating ACS, larger scaled, multi-centered, double-blinded RCTs with reliable placebo and longer follow-up duration are needed.

Table 3

The most studied Chinese patent medicines.

Chinese patent medicine	Major components	Beneficial effects	Potential mechanisms	Reference
Danlou tablet	Gallic acid, danshensu, 5-hydroxymethyl-2-furaldehyde, puerarin, mirificin, daidzin, paeoniflorin, rosmarinic acid, salvianolic acid B, salvianolic acid A and tanshinone IIA	Anti-inflammatory and antioxidative effects; attenuate atherosclerosis; lower elevated levels of cTnI and reduce incidence of MACE in non-ST elevation ACS patients	Decrease the expressions of inflammation cytokines by down regulating NF-κB singling pathway and accelerate cholesterol effluent through activating PPARα/ABCA1 signaling pathway; inhibit EGFR phosphorylation and lower the expression of TNF-α, IL-6, and MMP9, decrease the expression levels of ox-LDL and MDA, and increase the expression of SOD	[28–31]
Yixinshu capsule	(Z)-Ligustilide, salvianic acid A, salvianolic acid A, salvianolic acid B, and rosmarinic acid	Attenuate ET-1-induced contraction dysfunction, BNP elevation; antioxidation, antiapoptosis and DNA repair; attenuate myocardial ischemia/reperfusion injury	Suppress mitochondrial mediated apoptosis and upregulating liver-X-receptor α; upregulate endogenous nuclear receptors including LXRα, PPARα, PPARβ, and ERα	[32–36]
Danhong injection	Danshensu, salvianolic acids, protocatechuic aldehyde, rosmarinic acid, caffeic acid, tanshinone ll A and cryptotanshinone	Inhibition of oxidative stress and inflammatory responses, anticoagulation, antithrombotic effects, reduction of apoptosis, blood pressure-lowering, relaxation of blood vessels, and pro-angiogenesis	Inhibit the activation of NF-κB; decreasing caspase-3 activity; Nrf2 activation; enhancing stromal cell-derived factor-1 (SDF1)/CXC chemokine receptor 4 (CXCR4) signaling; alleviation of Ca2+ overload and ROS content, thereby suppressing the opening of the mitochondrial permeability transition pore (mPTP)	[37,38]
Shenmai injection	Ginsenosides Rb1, Rb2, Rb3, Rc, Rd, S-Rg3, R-Rg3 and notoginsenoside R1, ginsenosides Re, Rf, Rg1, S-Rg2, R-Rg2	Alleviation of hypoxia/reperfusion injury; regulation of inflammatory mediators.	Decrease mitochondrial mass and cytosolic Ca2+, increase mitochondrial membrane potential and mitochondrial morphology, inhibition of excessive mitochondria fission and increased mitochondrial fusion; nomalize the expression of IKK-α, iNOS, and NO	[39,40]
Tongxinluo capsule	Peoniflorin, ginsenoside Rg1, ginsenoside Rb1, jujuboside A and jujuboside B	Aameliorate myocardial ischemia/reperfusion injury; stabilize atherosclerotic plaque; attenuate vasoconstriction	Activate Parkin-mediated mitophagy and downregulating ubiquitin-proteasome system; enhance PPAR-gamma expression and suppressing NF-kappaB activity; increase nNOS expression in the collared carotid artery through activation of ERK1/2 signaling; inhibition of endothelial-to-mesenchymal transition; angiopoietin-like 4-mediated protection of endothelial barrier integrity via PPAR-α pathway	[41–45]
Xuezhikang capsule	Monacolin J, K, L, acid form, lactone form, dehydromonacolin	Lipid lowering effects; anti-inflammation; antiapoptosis; suppress vulnerable plaque progression and rupture; antiatherosclerosis	Inhibit TLR4/NF-κB signaling pathway; inhibit 7-KC-induced upregulation of apoptosis, protein expression of apoptotic markers (cleaved caspase-3 and cleaved PARP), and NF-κB activation	[46–49]

Table 4

Adverse events.

	TCM		Control			
Study	Intervention	No. of AEs/total	Intervention	No. of AEs/total	RR (95% CI)	Types of AEs
UA						
Li Hongying 2015	Shenqidanzhi Decoction	1/52	NA	1/54	1.04 (0.07, 16.17)	Thirst in TCM group (1); dizziness and headache in Control group (1)
Li Jun 2016	Wenxin Decoction	11/118	NA	9/110	1.14 (0.49, 2.64)	Nausea (3), mild headache (3), and loose stool (5) in TCM group; headache (9) in Control group
AMI						
Wang Lei 2016	Danlou Tablet	2/109	Placebo	0/110	5.05 (0.25, 103.89)	Nausea and diarrhea (2) in TCM group
Yang Guangming 2018	Tongxinluo Capsule	1/43	NA	3/43	0.33 (0.04, 3.08)	Stomach ache (1) in TCM group; stomach ache (3) in Control group
Total no. of AEs		15/322		13/317		
Incidence of total AEs					1.08 (0.52, 2.25)	

AEs = adverse events, AMI = acute myocardial infarction, RR = relative risk, TCM = traditional Chinese medicine, UA = unstable angina.

Author contributions

JL, XL, and JD designed and supervised the study. YH and TL carried out the search and screening criteria. MS, ZW, KW, JC, QZ, and MC performed literature search, screening, and data collection. JL, YH, and YW drafted the manuscript and XL, JD revised it.

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