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Qing-Xin-Jie-Yu Granule for patients with stable coronary artery disease (QUEST Trial): A multicenter, double-blinded, randomized trial

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ABSTRACT

Background and aim: Despite optimal secondary preventive treatment, patients with stable coronary artery disease (SCAD) remain at high risk of cardiovascular events. This multicenter, double-blinded, randomized trial sought to determine whether the addition of Qing-Xin-Jie-Yu Granule (QXJYG), a traditional Chinese medicine prescription, to standard therapy would further reduce risk of cardiovascular events in patients with SCAD.
Methods: A total of 1500 patients with documented SCAD were randomly assigned in a 1:1 ratio to QXJYG or placebo for 6 months, and followed up for another 6 months. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction (MI) and coronary revascularization. Near the end of the trial, but before unblinding, a commonly used composite 'hard' endpoint composed of cardiovascular death, nonfatal myocardial infarction and ischemic stroke was additionally analyzed.
Results: During a median follow-up of 12 months, no significant difference of the primary outcome between the two groups was observed (1.59% vs. 1.62%; hazard ratio, 0.41; 95% CI, 0.13–1.28). However, absolute risk of the composite 'hard' endpoint was reduced by 0.99% (0.31% vs. 1.30%; hazard ratio, 0.06; 95%CI, 0.01 to 0.53). No difference of adverse events between the two groups was observed.
Conclusion: In patients with SCAD, the addition of QXJYG to standard therapy was associated with reduced risk of nonfatal MI and the composite 'hard' endpoint of cardiovascular death, nonfatal MI and stroke. (http://www.chictr.org.cn/showproj.aspx?proj=5200, ChiCTR-TRC-13004370).

1. Introduction

Stable coronary artery disease (SCAD) is the most common type of coronary artery disease.[1,2] Despite proven benefits of the established secondary preventive treatment, 5 to 10% patients suffer adverse cardiovascular events annually, with mortality rates ranging from 1.2 to 2.4%,[3–6] making prognosis improvement for patients with SCAD a hot and unresolved issue. The COMPASS trial[7] evaluated the addition of rivaroxaban, an anticoagulant regimen, to aspirin in patients with SCAD, and found that although compared with aspirin alone, the combination of rivaroxaban and aspirin reduced the composite primary outcome (myocardial infarction, stroke, or cardiovascular death) by 2% (4% vs. 6%), it significantly increased the risk of major bleeding (3% vs. 2%, HR, 1·66, 95% CI, 1·37–2·03, p < 0.0001); Bhatt et al[8] assessed effects of the additional clopidogrel to aspirin in patients with SCAD and found that the addition of clopidogrel only subtly reduced vascular events but greatly increased bleeding risk; Bonaca et al[9] explored effects of the combination of ticagrelor and aspirin in patients with a myocardial infarction more than one year previously, and results showed that ticagrelor reduced the major cardiovascular events by 1.19% but increase the major bleeding incidence by 1.54%. Researchers of CANTOS trial[10] added cankinumab, a fully human monoclonal

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antibody against interleukin-1β, to standard care in patients with previous myocardial infarction and a hs-CRP level of over 2 mg per liter, finding that although cankinumab brought benefits on cardiovascular events, it also increased the incidence of fatal infection; CIRT trial,[11] also targeting inflammation using low dose methotrexate in patients with SCAD, showed that methotrexate did not bring cardiovascular benefits but increased incidence of elevations in liver enzyme and non–basal-cell skin cancers. Moreover, the FOURIER investigators[12] assessed effects of the addition of proprotein convertase subtilisin-kexin type-9 (PCSK-9) inhibitor in patients with atherosclerosis, 80% of which had a history of myocardial infarction, and found that compared with placebo, PCSK-9 inhibitor reduced low density lipoprotein cholesterol (LDL-C) to 30 mg per deciliter (0.78 mmol per liter), and significantly reduced incidence of major cardiovascular events by 1.5%. (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) However, prolonged exposure to extremely low LDL-C aroused great concerns, arguing that extremely low LDL-C could negatively affect neurocognitive function and might result in impaired cellular delivery of fat-soluble vitamins. Besides, PCSK-9 is too costly to be widely applied- costing $14,000 per year.[13] Therefore, there is an urgent need to find a safe and effective therapy to reduce the residual risk of cardiovascular events in patients with SCAD.

Traditional Chinese medicine (TCM) has been widely used in China for more than 2000 years, and is arousing increasing interest globally due to recently emerging evidences[14] Qi-shen-yi-qi dripping pills has been shown to have a similar effect to aspirin in preventing recurrent cardiovascular events in patients with a history of myocardial infarction[15]; Xuezhikang, an extract from red yeast Chinese rice, reduced the incidence of cardiovascular events (nonfatal myocardial infarction and death from coronary heart disease) by 4.7% in patients with previous myocardial infarction[16]; Tongxinluo showed benefits on decreasing infarction area and incidence of myocardial no-reflow after emergency percutaneous coronary intervention (PCI).[17] However, for the more prevalent SCAD, whether TCM would still bring benefits remains unknown. Qing-Xin-Jie-Yu Granule (QXJYG, composed of five herbal granules, *Astragalus membranaceus* [Huangqi], *Salvia miltiorrhiza Bunge* [Danshen], *Ligusticum chuanxiong Hort* [Chuanxiong], *Agastache rugosus* [Huoxiang], and *Coptis chinensis* [Huanglian]) has been applied in clinical practice in China for over 25 years, and analyses of each herbal granule of QXJYG by LC-MSn methods indicated that the main ingredients of QXJYG were saponins, flavones, tanshinones, polyphenols, alkaloids (berberine) and lactones (Figs. S2.1–2.5), all of which have been proven beneficial to cardiovascular disease for their effects of antiatherogensis, cardiac cytoprotection, antioxidant, anti-inflammation, antiapoptosis, vasodilation, or antithrombosis.[18–21] In a small study involving 72 patients with SCAD and elevated level of high-sensitivity C-reactive protein (hs-CRP), we found that QXJYG, compared with placebo, significantly improved angina symptoms and reduced serum level of both hs-CRP and interleukin-6.[22] Yet, no study has been undertaken to assess its benefits on cardiovascular events. Therefore, we conducted this multicenter, double-blinded, randomized trial to assess whether the addition of QXJYG to standard therapy would reduce incidence of cardiovascular events in patients with SCAD.

2. Materials and methods

2.1. Study design

Details of the trial design have been previously reported[23] and we only described it in brief. This multicenter, randomized, placebo-controlled trial was conducted at 19 hospitals across mainland China. The full list of hospitals is presented in the *Appendix* (Table S1). The study, registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-13004370), complies with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and the ethics committee at each participating hospital approved the protocol. An independent data and safety monitoring committee blinded to treatment allocation oversaw the trial. The corresponding author takes the responsibility for the accuracy and completeness of the trial data.

2.2. Participants

Patients were eligible if they were between 18–75 years of age with documented SCAD (a history of myocardial infarction 3 months before screening, or PCI one month before screening; or angiography or coronary computed tomographic angiography showing ≥50% stenosis of at least one major coronary artery), and had two or more of the following 4 conditions: a serum hs-CRP level ≥3 mg per liter, a history of hypertension, hyperlipidemia, and diabetes mellitus. Patients were excluded if they were with congenital or rheumatic heart disease or severe heart failure, an uncontrolled severe arrhythmia (including paroxysmal ventricular tachycardia and supraventricular arrhythmia), an uncontrolled blood pressure (systolic blood pressure ≥160 mmHg, or diastolic blood pressure ≥100 mmHg), severe hepatic disease, severe renal disease, or severe hematologic disease, severe mental disorders, or participating in other studies. Detailed exclusion criteria are presented in the *Appendix*. All participants provided written informed consent.

2.3. Randomization, intervention and masking

Patients were randomly assigned using a central computerized randomization system in a 1:1 ratio to receive QXJYG (*Astragalus membranaceus* [Huangqi] 7.5 g, *Salvia miltiorrhiza Bunge* [Danshen] 7.5 g, *Ligusticum chuanxiong Hort* [Chuanxiong] 5 g, *Agastache rugosus* [Huoxiang] 5 g, and *Coptis chinensis* [Huanglian] 2.5 g, produced and packed in a single batch[NO: 1405001 H] by China Resources Sanjiu Medical and Pharmaceutical Co., Ltd., Shenzhen, China) orally after dissolving in 150 ml water, twice daily, or placebo (composed of 10% herbs of QXJYG and 90% starch, identical in color, smell and appearance to QXJYG) for 6 months. Besides, patients in both groups received standard medical therapy, including anti-platelet agents, lipid-lowering agents, renin-angiotensin-aldosterone system blockers, anti-hypertensive agents, and ant-diabetics.[2] Patients were told by study personnel before they gave consent that they would have to take the study drug for 6 months, and that in-person follow-up was required at 3, 6 and 12 and phone call follow-up at 1 and 9 months.

Patients, health-care providers, data collectors, and data analysts were all masked to treatment allocation.

2.4. Outcomes

The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction and coronary revascularization, assessed from the time of randomization until the first occurrence of one of the events. The secondary outcome was a composite of all-cause death, ischemic stroke, and re-admission due to unstable angina, heart failure or malignant arrhythmia (supraventricular and ventricular arrhythmia influencing hemodynamics), also assessed from the time of randomization until the first occurrence of one of the events. Near the end of the trial, but before unblinding, a commonly used objective 'hard' endpoint composed of cardiovascular death, nonfatal myocardial infarction and ischemic stroke [24,25] was additionally analyzed.

Serum level of hs-CRP and lipid profiles were compared between the QXJYG group and the placebo group at month 3, 6 and 12, respectively.

Pre-specified safety variables included major bleeding defined as fatal bleeding, symptomatic bleeding into a critical organ or area, or bleeding leading to hospital visit or admission (Symptomatic bleeding into a critical organ or area included intracranial, intraspinal, intraocular, retroperitoneal, adrenal, intra-articular, pericardial, or intramuscular, or bleeding into the respiratory tract, liver, pancreas, or kidney), and reduction of white blood cell or platelet. Other lab tests

including liver and kidney function, urinalysis, etc. was performed at scheduled time-points.

2.5. Statistical analysis

We estimated the annual event rate for the composite primary outcome in the placebo group to be about 10% [26,27] and a sample size of 1260 would provide a power of 80% to detect an absolute risk reduction of 3% at an α level of 0·05 for QXJYG versus placebo. Considering a maximum dropout rate of 20%, a total of 1512 patients were needed, and finally we decided to recruit 1500 patients.

According to the intention-to-treat principle, we analyzed patients in the groups to which they were randomly allocated. Continuous variables were presented as the mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical variables of baseline characteristics as frequency and percentages. The comparability of baseline characteristics between the two groups was assessed using a two-sample Student's *t*-test for continuous variables and the chi-square test or Wilcoxon test for categorical variables. Data was censored for patients lost to follow-up on the last day their status was known. Cumulative event rates of the primary and secondary outcomes in the QXJYG and the placebo groups were estimated using the Kaplan-Meier method, and differences between the curves were tested using the log-rank test. The crude and adjusted hazard ratio (HR) and its 95% confidence interval (CI) was estimated using a Cox proportional hazard model, adjusting for predefined 12 baseline characteristics known as risk factors including sex, age, smoking status, systolic blood pressure, previous myocardial infarction, previous stroke, hypertension, diabetes, hyperlipidemia, peripheral atherosclerosis, baseline levels of hs-CRP and low-density lipoprotein (LDL) cholesterol. The adjusted analysis was defined as the primary analysis.[28] For all analyses, we used two-sided *P* values and took $P < 0{\cdot}05$ to be significant. All statistical analyses were performed with SPSS 20 software (International Business Machines, Armonk, NY, USA).

For the primary outcome, we did three pre-specified and subgroup analyses based on baseline hs-CRP (< 3 vs. ≥ 3 mg per liter), sex (men vs. women) and the presence or absence of diabetes. And to assess consistency of the main findings, we did post-hoc subgroup analyses according to different baseline characteristics.

3. Results

Between March, 2014, and July, 2017, a total of 7543 patients underwent screening at 19 centers across mainland China, and finally 1500 patients were enrolled and randomized with 750 assigned to QXJYG and 750 to placebo (Fig. 1). The median follow-up was 12 months. The patients' distribution is shown in the *Appendix* (Table S1). By the end of follow-up, 66 (8.7%) patients in the QXJYG group and 71 (9.5%) patients in the placebo group discontinued the trial ($P = 0.65$, Fig. 2). Detailed reasons for the discontinuation were out of contact (39 in QXJYG group and 41 in placebo group) or withdrawal for constipation (one in QXJYG group), mild abdominal pain (3 in the placebo group), unwilling to continue the medicine (10 in QXJYG group and 11 in placebo group), deeming the medicine ineffective (3 in QXJYG group and 5 in placebo group). The rest 24 patients withdrew without giving any reasons (13 in QXJYG group and 11 in placebo group).

Baseline characteristics were similar across the study groups and are presented in Table 1. The mean age of the patients was 60.3 years, 449 (30%) were women, 306 (20.4%) were current smokers, 582 (38.8%) had diabetes mellitus, 1059 (70.6%) had hypertension, 1039 (68.6%) had dyslipidemia, 600 (40.0%) had a history of myocardial infarction, 757 (54.5%) had undergone PCI and 54 (3.6%) coronary artery bypass grafting before randomization, 175 (11.7%) had a history of stroke, 351 (23.4%) had peripheral artery diseases. At baseline, antiplatelet agents were taken by 1222 (81.5%) of the patients, lipid-lowering agents by 921 (61.4%), inhibitors of the renin–angiotensin system by 405 (27.0%), beta-blocker by 572 (38.1%), nitrates by 206 (13.7%). Warfarin was taken by 9 patients (0.6%) complicated with atrial fibrillation and no new anticoagulants were taken. Median hs-CRP level at trial entry was 1.28 mg per liter and the median LDL cholesterol level was 2.16 mmol per liter.

3.1. Effects on clinical endpoints

Fig. 2A shows Kaplan-Meier event rates for the primary outcome at one year. The primary outcome occurred in 5 patients (0.67%) assigned to QXJYG and 10 patients (1.33%) assigned to placebo (cumulative event rates, 1.59% vs.1.62%; covariate adjusted HR, 0.41; 95%CI, 0.13–1.28; $P = 0.13$) (Table 2). Across all subgroups, the findings were generally consistent with primary outcome (Fig. 3).

With regard to the three components of the primary outcome, a significant reduction of nonfatal myocardial infarction was observed with one (0.13%) occurred in the QXJYG group and 5 (0.67%) in the placebo group (cumulative event rates, 0.16% vs. 0.82%; adjusted HR, 0.82; 95%CI, 0.01 to 0.95; $P = 0.045$); There were 5 (0.67%) coronary revascularization in the QXJYG and 6 (0.80%) in the placebo group (cumulative event rates, 1.59% vs. 0. 97%; adjusted HR, 0.83; 95%CI, 0.22–3.03; $P = 0.77$); No cardiovascular death occurred in the QXJYG group and one (0.13%) occurred in the placebo group.

The pre-specified secondary outcome occurred in 10 (1.33%) patients in the QXJYG group and 19 (2.53%) patients in the placebo group, showing a reduction trend in the QXJYG (cumulative event rates, 1.59% vs.3.90%; adjusted HR, 0.45; 95%CI, 0.19–1.06; $P = 0.07$) (Fig. 2B. Table 2).

For the composite 'hard' endpoint composed of cardiovascular death, nonfatal myocardial infarction and ischemic stroke, we found that QXJYG significantly lowered the incidence of this composite 'hard' endpoint, with 2 (0.29%) patients in the QXJYG group and 8 (1.18%) patients in the placebo group, with an absolute risk reduction of 0.99% (cumulative event rates 0.31% vs. 1.30%; HR,0.25; 95%CI, 0.05–1.18; adjusted HR, 0.06; 95%CI, 0.01 to 0.53; $P = 0.012$),(Fig. 2C, Table 2). The number need to treat (NNT) is 101 for the 'hard' endpoint, which means that the treatment of 101 patients with QXJYG will prevent one 'hard' endpoint within one year.

A post-hoc analysis of a composite of all clinical outcomes including all-cause death, non-fatal myocardial infarction, ischemic stroke, revascularization and re-admission for unstable angina, heart failure or malignant arrhythmia showed a significant lower event rate in the QXJYG group than in the placebo group, with 13 (1.9%) patients in QXJYG group and 25 (3.68%) patients in placebo group (2.84% vs. 4.89%; adjusted HR, 0.43; 95%CI, 0.21 to 0.90; $P = 0.025$) (Fig. 2D, Table 2).

3.2. Effects on Hs-CRP and lipid profiles

No significant reduction was observed on the serum level of hs-CRP (Fig. 4 and Table 2) and lipid profiles in the QXJYG group compared with the placebo group (Tables S3–6).

3.3. Safety

No bleeding events, events of white blood cell or platelet reduction or other serious events that needed medical treatment occurred during the 12 months follow-up, and 12 (1.6%) mild adverse events were reported in the QXJYG group and 23 (3.1%) in the placebo group, with no significant difference between the two groups ($P = 0.06$) (Table S7). Most of the mild adverse events were slight gastrointestinal symptoms including mild diarrhea, constipation, mild abdominal pain, and mild nausea. Of all patients suffered these adverse events, only one (0.1%) patient in the QXJYG group discontinued the study due to constipation and 3 patients in placebo group discontinued the study due to abdominal pain, constipation and mild edema of the lower limbs,

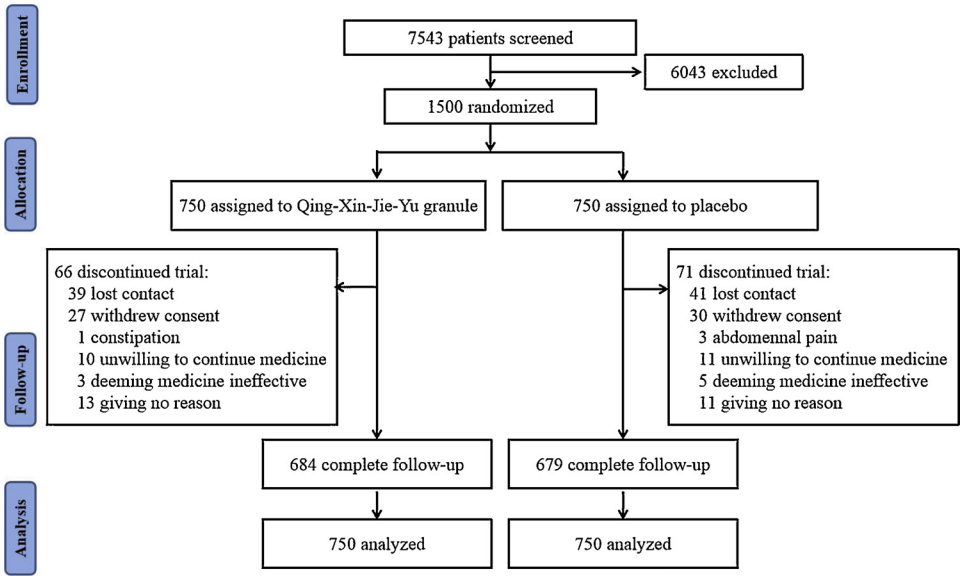

Fig. 1. Study Flow Chart. The flow chart illustrated the number of patients in each group throughout the study.

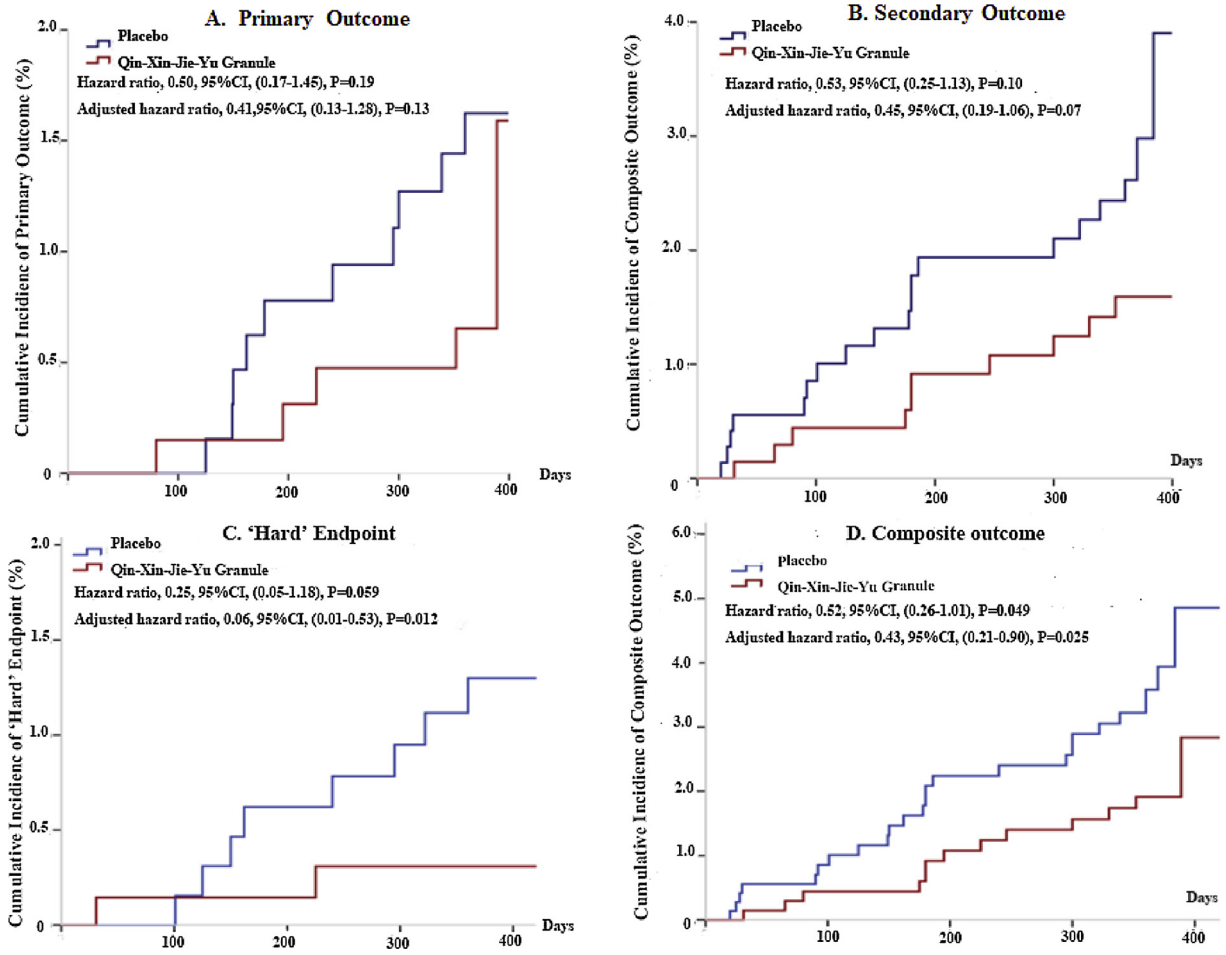

Fig. 2. Kaplan–Meier Curves for Clinical Outcomes. Kaplan-Meier survival curves comparing QXJYG and placebo for (A) primary outcome, comprising cardiovascular death, nonfatal myocardial infarction and coronary revascularization; (B) secondary outcome, including all-cause death, ischemic stroke, and re-admission due to unstable angina, heart failure or malignant arrhythmia; (C) 'Hard' endpoint, consisting of cardiovascular death, nonfatal myocardial infarction and ischemic stroke; and (D) composite outcomes, comprising all-cause death, non-fatal myocardial infarction, ischemic stroke, revascularization and re-admission for unstable angina, heart failure or malignant arrhythmia cardiac death. CI = confidence interval; QXJYG = Qing-Xin-Jie-Yu Granule.

Table 1
Baseline Characteristics of Patients Receiving Qing-Xin-Jie-Yu granules or Placebo.

Characteristic	QXJYG (n = 750)	Placebo group (n = 750)	*P*
Demographics			
Male-no. (%)	523 (69.73)	528 (70.40)	0.78
Age-yrs.	60.63 ± 8.95	60.03 ± 8.82	0.16
BMI (kg/m^2)	25.09 (23.15-27.06)	24.89 (23.18-27.01)	0.77
Risk factors			
Current smoking-no. (%)	154 (20.53)	152 (20.27)	0.90
Diabetes-no. (%)	291 (38.80)	291 (38.80)	1.00
Hypertension-no. (%)	527 (70.27)	532 (70.93)	0.78
Dyslipidemia-no. (%)	524 (69.87)	515 (68.67)	0.82
Past medical history-n (%)			
Stroke	79 (10.53)	96 (12.80)	0.17
Ischemic stroke	72 (9.60)	89 (11.87)	0.16
Hemorrhagic stroke	3 (0.40)	2 (0.27)	0.65
Peripheral atherosclerosis	179 (23.87)	172 (22.93)	0.67
Previous myocardial infarction	307 (41.20)	293 (38.80)	0.46
History of PCI	394 (52.53)	363 (48.40)	0.11
History of CABG	23 (3.20)	31 (4.00)	0.27
Laboratory measurements-median (IQR)			
Hs-CRP (mg/L)	1.31 (0.50-3.03)	1.21 (0.60-2.94)	0.67
Fasting plasma glucose (mmol/L)	5.69 (5.10-6.86)	5.72 (5.04-6.91)	0.47
Total cholesterol (mmol/L)	3.85 (3.29-4.50)	3.94 (3.35-4.66)	0.06
LDL cholesterol (mmol/L)	2.14 (1.66-2.75)	2.19 (1.70-2.82)	0.10
HDL cholesterol (mmol/L)	1.11 (0.94-1.32)	1.10 (0.94-1.31)	0.70
triglyceride (mmol/L)	1.38 (1.01-1.94)	1.45 (1.05-2.02)	0.16
Medication before randomization-n (%)			
≥1 antiplatelet therapy	600 (80.00)	622 (82.93)	0.14
Aspirin	545 (72.67)	568 (75.73)	0.18
Clopidogrel	314 (41.87)	306 (40.80)	0.68
Ticagrelor	23 (3.07)	20 (2.67)	0.64
Dual antiplatelet therapy	279 (37.20)	271 (36.13)	0.67
Lipid-lowering agents	472 (62.93)	449 (59.87)	0.22
Statin	470 (62.67)	448 (59.73)	0.24
Beta-blocker	269 (35.87)	303 (40.40)	0.07
Angiotensin-converting enzyme inhibitor	93 (12.40)	93 (12.40)	1.00
Angiotensin II receptor blocker	105 (14.00)	114 (15.20)	0.51
Nitrates	96 (12.80)	100 (13.33)	0.76
Calcium channel blockers	100 (13.33)	123 (16.40)	0.10
Warfarin	3(0.4)	6(0.8)	0.51

BMI = body-mass index; CABG = coronary-artery bypass grafting; hs-CRP = high sensitivity C-reactive protein; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; QXJYG = Qing-Xin-Jie-Yu Granule.

respectively; the rest patients suffering adverse events all continued the study drug and the symptoms relieved without special medical treatment. The lab tests of liver and kidney function showed no significant or abnormal changes at 6 months and at the end of the study (Table S8).

4. Discussion

In this trial, no significant reduction of the primary outcome (cardiovascular death, non-fatal myocardial infarction, and revascularization) and a reduction trend of the secondary outcome (all-cause death, ischemic stroke, and re-admission for unstable angina or heart failure or malignant arrhythmia) were observed in the QXJYG group. Nonetheless, the composite 'hard' endpoint (cardiovascular death, nonfatal myocardial infarction, and ischemic stroke) analyzed at end of the present trial but before unblinding and all outcomes (all-cause death, non-fatal myocardial infarction, stroke, revascularization, other thromboembolic events and re-admission for unstable angina, heart failure and malignant ventricular or supraventricular arrhythmia) were significantly reduced by QXJYG. Kaplan-Meier estimates indicated that 101 patients would be needed to be treated with QXJYG for 6 months to avoid one 'hard' endpoint within one year.

Despite widespread optimal secondary prevention, risk of cardiovascular events remains high,[2,26,27] making the improvement of prognosis for patients with SCAD challenging and urging. Researchers have made lots of efforts trying to reduce the residual risk in patients with SCAD, but no results of these attempts were completely satisfying with various safety concerns. However, we found in the present study that QXJYG was associated with lower incidence of the composite 'hard' endpoint (cardiovascular death, nonfatal myocardial infarction, and ischemic stroke) and non-fatal myocardial infarction without increasing any adverse events. Considering that this improvement in clinical outcomes arose on top of optimal medical care in the population of SCAD, our finding is well worth notice and may provide a promising therapy to further reduce the high residual risks of cardiovascular events in patients with SCAD.

Safety of Chinese herbal medicine, especially the herb-drug interaction, has been concerned by many researchers and practitioners. Danshen, ingredient of QXJYG, is documented to have major interactions with anticoagulant or antiplatelet drugs for its intrinsic anticoagulant or antiplatelet properties,[29,30] which, theoretically, may increase bleeding risk in patients who are co-administrated with QXJYG and anticoagulant or antiplatelet agents. However, no bleeding events were observed in our study, despite that 81.5% patients were taking at least one antiplatelet agent with 36.67% were taking dual antiplatelet agents. Therefore, impressively, our study ensured the safety of combination of QXJYG and antiplatelet agents. The combination of Danshen with other herbs according to TCM theory may account for this result. Drug interaction between QXJYG and warfarin needs to be further explored since only 9 patients (3 in the QXJYG group) were taking warfarin.

When devising the protocol, we thought that the need for coronary revascularization was likely to indicate deterioration of the macrovascular and would respond to treatment in a similar way to stroke and myocardial infarction. However, the truth is that coronary revascularization is in a large part affected by the decision of cardiologists and patients themselves in SCAD, and this may account for our findings regarding the primary outcome and the composite 'hard' endpoint: when we replaced the outcome of coronary revascularization with ischemic stroke, a more objective indicator of deterioration of the macrovascular, in the 'hard' endpoint, a significant reduction of 0.99% in the QXJYG group was observed.

In this trial, we found no significant reduction of hs-CRP levels with QXJYG, which might due to the rather low hs-CRP level at randomization, only 1.28 mg per liter. In CANTOS, the reduction of hs-CRP was dose-dependent and the largest reduction was observed with 300 mg cankinumab, from 4.13 to 1.30 mg per liter at 3-month, and then increased slightly to 1.90 mg per liter at 48-month, which implied that a serum level of hs-CRP lower than 1.28 is hard to achieve.[10] Therefore, to estimate effects of QXJYG on inflammation, we'd better target patients with obviously elevated baseline hs-CRP levels in future study.

The event rates in the placebo group in our study was much lower than that in the REACH Registry study[26,27] and other studies with similar population,[7,31] which might due to the following reasons: First, compared with REACH Registry study, patients enrolled in our study were at relatively low risk. For example, the mean age in the REACH Registry study was 68 years, with 43.88% complicated by diabetes mellitus, 81.72% by hypertension, while in our study, the mean age was 60 years, 38.80% complicated by diabetes mellitus, 70.60% by hypertension. Second, advances in new secondary prevention medications, such as ticagrelor,[32] might have reduced the incidence of cardiovascular events.

Atherosclerosis has long been considered a chronic inflammatory disease triggered by the accumulation of cholesterol-containing LDL particles on the arterial wall, and inflammatory reactions may accelerate disease progression by increasing plaque instability, resulting in

Table 2
Clinical outcomes of Qing-Xin-Jie-Yu Granule in patients with stable coronary diseases.

Clinical outcomes	QXJYG Group (n = 750)	Placebo Group (n = 750)	HR (95%CI)	Adjusted HR (95%CI) *	P value†	Adjusted P value*
	n (%) ‡					
Primary outcome (cardiovascular death, nonfatal myocardial infarction and coronary revascularization)	5 (1.59)	10 (1.62)	0.50 (0.17-1.45)	0.41 (0.13-1.28)	0.19	0.13
Cardiovascular death	0 (0.00)	1 (0.16)	0.02 (0-150027.35)	0.09/	0.32	0.95
Non-fatal myocardial infarction	1 (0.16)	5 (0.82)	0.20 (0.02-1.72)	0.82 (0.01-0.95)	0.10	0.045§
Coronary revascularization	5 (1.59)	6 (0.97)	0.82 (0.25-2.7)	0.83 (0.22-3.03)	0.75	0.77
PCI	5 (1.59)	4 (0.63)	1.23 (0.33-4.59)	1.43 (0.35-5.92)	0.76	0.62
CABG	0 (0.00)	2 (0.34)	0.02/	0.00/	0.16	0.85
Secondary outcome (all-cause death, ischemic stroke, and re-admission due to unstable angina, heart failure or malignant arrhythmia)	10(1.59)	19 (3.90)	0.53 (0.25-1.13)	0.45 (0.19-1.06)	0.10	0.07
All-cause death	0 (0.00)	1 (0.16)	0.02 /	0.09/	0.32	0.95
Ischemic stroke	1 (0.14)	2 (0.32)	0.50 (0.05-5.55)	0.00 (0.00-3273178124.30)	0.57	0.61
Re-admission due to unstable angina, heart failure or malignant arrhythmia	9 (1.60)	16 (3.44)	0.56 (0.25-1.27)	0.59(0.21-1.41)	0.16	0.23
Composite 'hard' endpoint (cardiovascular death, nonfatal myocardial infarction and ischemic stroke)	2 (0.31)	8 (1.30)	0.25 (0.05-1.19)	0.06 (0.01-0.53)	0.059	0.012§
All outcomes‖	13 (2.84)	25 (4.86)	0.52 (0.26-1.01)	0.43 (0.21-0.90)	0.0497§	0.025§

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; QXJYG = Qing-Xin-Jie-Yu Granule.

/ unavailable.

‖ All outcome included all-cause death, non-fatal myocardial infarction, stroke, revascularization, other thromboembolic events and re-admission for unstable angina, heart failure and malignant ventricular or supraventricular arrhythmia.

* Adjusted for sex, age, smoking status, systolic blood pressure, previous myocardial infarction, previous stroke, hypertension, diabetes, hyperlipidemia, peripheral atherosclerosis, baseline levels of hs-CRP and LDL cholesterol.

† Log-rank test, unadjusted.

‡ Kaplan-Meier cumulative event rates.

§ $P < 0.05$.

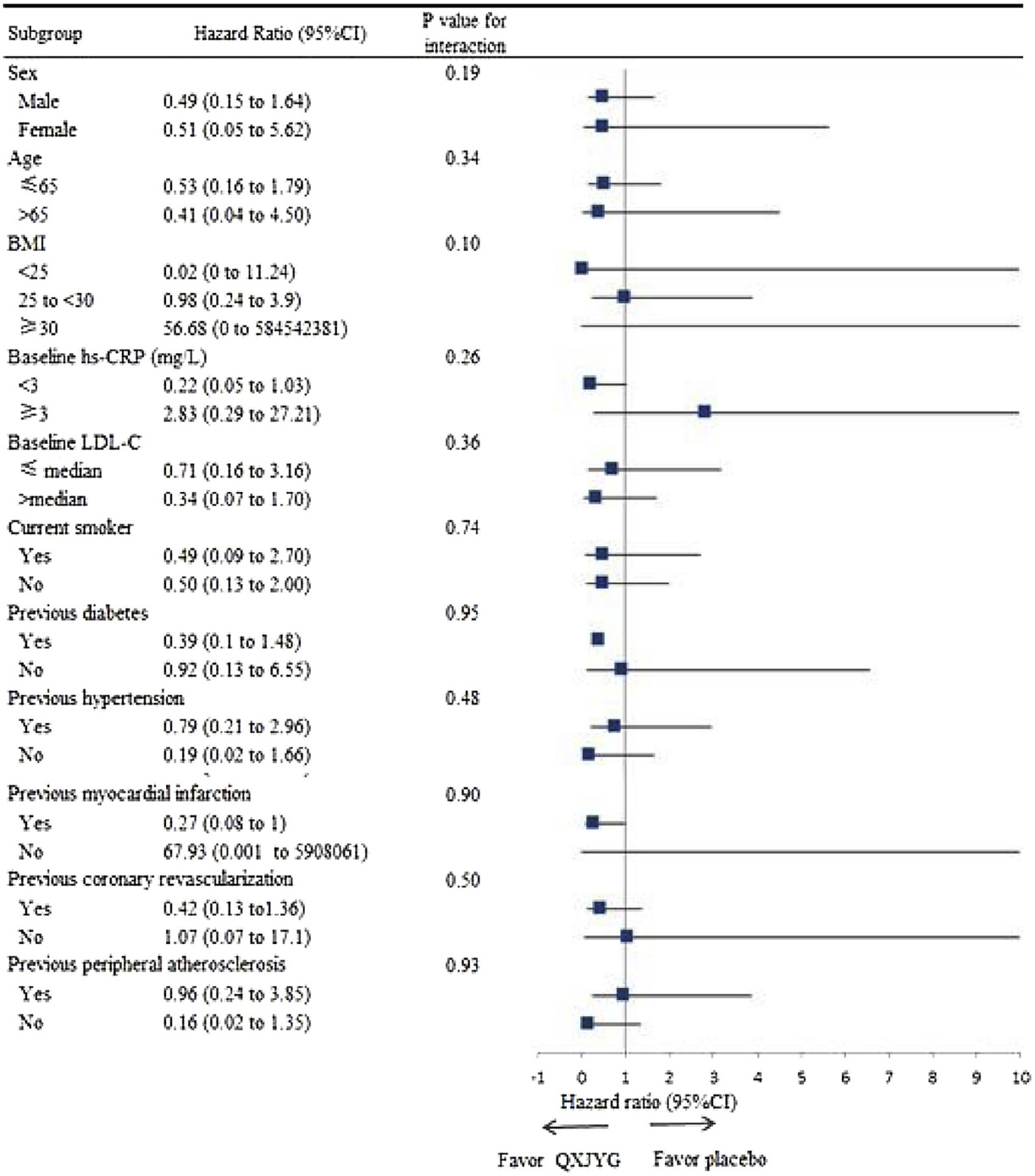

Fig. 3. Subgroup analysis of primary outcome. Across all subgroups, the incidence of primary outcome consistently did not differ between the QXJYG and the placebo group. BMI = body mass index; CI = confidence interval; C-reactive protein; hs-CRP = high-sensitivity; LDL-C = low-density lipoprotein cholesterol; QXJYG = Qing-Xin-Jie-Yu Granule.

plaque rupture and clinical events.[33–35] Recently published CANTOS study moves the inflammatory hypothesis of coronary artery disease forward and indicates that anti-inflammatory therapy reduces cardiovascular events.[10,11] Considering results of our previous small clinical study showing that QXJYG effectively reduced plasma inflammatory factors, we speculate that the anti-inflammatory effects might be one of the key mechanisms for cardiovascular protective effects of QXJYG. Moreover, a network analysis indicated that QXJYG have pleiotropic effects, probably offering anti-inflammatory, anti-platelet, plasma lipid-regulating effects, etc.[36]

This trial has some limitations. Event rates in this trial were lower than expected, which made our trial underpowered to detect a significant effect of QXJYG on the primary outcome. Nonetheless, the significant between-group difference observed on the 'hard' endpoint provided us great impetus to conduct further researches on QXJYG. Besides, although we widely recruited patients from 19 hospitals across China, they are all Chinese, which may limit generalization of our finding.

5. Conclusion

In patients with SCAD, the addition of QXJYG to standard therapies

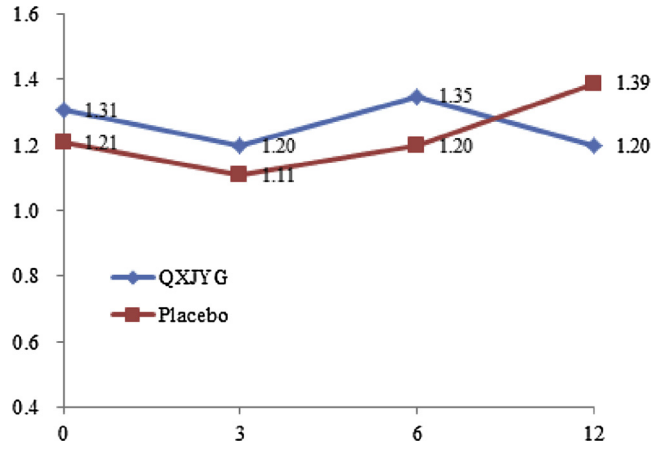

Fig. 4. Effects of Qing-Xin-Jie-Yu Granule on serum level of hs-CRP. Compared with placebo, QXJYG did not significantly decreased hs-CRP level at 3, 6 or 12 months. hs-CRP = high-sensitivity C-reactive protein; QXJYG = Qing-Xin-Jie-Yu Granule.

was associated with a lower rate of myocardial infarction and the 'hard' endpoint composed of cardiovascular death, non-fatal myocardial infarction, and ischemic stroke than placebo.

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Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Jingen Li: Formal analysis, Investigation, Data curation, Writing - original draft. **Zhuye Gao:** Investigation, Supervision, Writing - review & editing. **Lijing Zhang:** Investigation, Writing - review & editing. **Shengyao Li:** Investigation, Writing - review & editing. **Qiaoning Yang:** Investigation, Writing - review & editing. **Qinghua Shang:** Investigation, Writing - review & editing. **Xiang Gao:** Investigation, Data curation, Writing - review & editing. **Hua Qu:** Investigation, Writing - review & editing. **Jie Gao:** Investigation, Writing - review & editing. **Lixiao Shi:** Investigation, Writing - review & editing. **Yue Liu:** Investigation, Writing - review & editing, Supervision. **Jianpeng Du:** Investigation, Writing - review & editing. **Hao Xu:** Conceptualization, Methodology, Writing - review & editing. **Dazhuo Shi:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Project administration, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.102209.

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