Efficacy and safety of Shexiang Baoxin pill (MUSKARDIA) in patients with stable coronary artery disease: a multicenter, double-blind, placebo-controlled phase IV randomized clinical trial

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Abstract

Background: The Shexiang Baoxin Pill (MUSKARDIA) has been used for treating coronary artery disease (CAD) and angina for more than 30 years in China. Nevertheless, methodologically sound trials on the use of MUSKARDIA in CAD patients are scarce. The aim of the study is to determine the effects of MUSKARDIA as an add-on to optimal medical therapy (OMT) in patients with stable CAD.

Methods: A total of 2674 participants with stable CAD from 97 hospitals in China were randomized 1:1 to a MUSKARDIA or placebo group for 24 months. Both groups received OMT according to local tertiary hospital protocols. The primary outcome was the occurrence of a major adverse cardiovascular event (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke. Secondary outcomes included all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for unstable angina or heart failure, peripheral revascularization, angina stability and angina frequency.

Results: In all, 99.7% of the patients were treated with aspirin and 93.0% with statin. After 2 years of treatment, the occurrence of MACEs was reduced by 26.9% in the MUSKARDIA group (MUSKARDIA: 1.9% *vs.* placebo: 2.6%; odds ratio = 0.80; 95% confidence interval: 0.45–1.07; $P = 0.2869$). Angina frequency was significantly reduced in the MUSKARDIA group at 18 months ($P = 0.0362$). Other secondary endpoints were similar between the two groups. The rates of adverse events were also similar between the two groups (MUSKARDIA: 17.7% *vs.* placebo: 17.4%, $P = 0.8785$).

Conclusions: As an add-on to OMT, MUSKARDIA is safe and significantly reduces angina frequency in patients with stable CAD. Moreover, the use of MUSKARDIA is associated with a trend toward reduced MACEs in patients with stable CAD. The results suggest that MUSKARDIA can be used to manage patients with CAD.

Trial registration: chictr.org.cn, No. ChiCTR-TRC-12003513

Keywords: MUSKARDIA; Stable coronary artery disease; Angina; Major adverse cardiovascular event

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Introduction

Cardiovascular diseases (CVDs) are the leading causes of death in many countries, accounting for 31.5% of deaths worldwide and 45% of all deaths due to non-communicable diseases. The combined use of aspirin and statin is a standard (and effective) secondary prevention approach to reduce the risk of cardiovascular events in patients with stable coronary artery disease (CAD).[1-4] Nevertheless, some residual cardiovascular risks persist.[5-7] Moreover, many patients with CAD in China, particularly females, are intolerant to aspirin because of gastrointestinal reaction, exacerbated respiratory disease, gout, or hyperuricemia.[8-10] Therefore, novel approaches are urgently needed to reduce the residual CAD risk and as eventual alternatives for patients with intolerance to standard drugs.

Traditional Chinese medicine (TCM) may be a potential add-on treatment and has long been used for treating CAD, which is considered as heart Yang deficiency resulting from Qi inadequacy.[11,12] Shexiang Baoxin Pill (MUSKARDIA) has been used to treat CAD and angina for more than 35 years in China. MUSKARDIA is composed of bioactive components, including muscone, ginsenosides, storax, bufadienolides, cinnamic acid, arenobufagin, and borneol.[13-16] Preliminary studies have indicated that MUSKARDIA dilates coronary arteries[17] and increases coronary blood flow, relieving the symptoms of angina.[13,18] Nevertheless, there are few methodologically sound trials that have been conducted on the use of MUSKARDIA in patients with CAD.

Therefore, the aim of this multicenter, double-blind, placebo-controlled, phase IV, randomized clinical trial (RCT) was to examine the long-term efficacy, safety, and compliance of MUSKARDIA as an add-on treatment to optimal medical therapy (OMT) in patients with stable CAD.

Methods

Design and oversight

The MUSKARDIA trial is a randomized, double-blinded, placebo-controlled, phase IV trial conducted at 97 sites in China (chictr.org.cn, ChiCTR-TRC-12003513). The trial was designed and led by an executive steering committee. The protocol and amendments were approved by the ethics committee at each participating center. Written informed consent was obtained from all patients before enrollment. The funder (Shanghai Hutchison Pharmaceuticals) had no role in the study design or in the collection, analysis, and reporting of data. Data were reviewed regularly throughout the trial by an independent data and safety monitoring committee.

Study population

Patients aged ≥18 years were eligible for the study if they presented with stable ischemic myocardial symptoms for at least 1 month and had at least one of the following events according to their hospital records or follow-up/health examination report: (1) history of acute myocardial infarction (MI) over 6 months; (2) history of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) over 6 months; and (3) epicardial coronary stenosis of ≥ 50% in at least one major branch as indicated by coronary computed tomography (CT) angiography or coronary angiography. The key exclusion criteria were: (1) patients preparing to receive PCI or CABG; (2) serious CVDs (sustained severe angina [Canadian Cardiovascular Society IV], refractory heart failure, cardiogenic shock, severe aortic stenosis, or aortic insufficiency; (3) severe respiratory diseases; (4) diabetes with inadequate glycemic control (fasting blood glucose > 200 mg/dL or 11.1 mmol/L for more than twice within 1 month before enrollment); (5) hypertension with inadequate blood pressure control (systolic pressure ≥180 mmHg or diastolic pressure ≥110 mmHg before enrollment); (6) severe liver or kidney disease; or (7) any other severe diseases such as malignant tumor, severe anemia, or severe renal artery stenosis. Detailed inclusion and exclusion criteria are listed in Supplementary Table S1, http://links.lww.com/CM9/A396.

Randomization and blinding

Patients were randomly assigned 1:1 to receive oral MUSKARDIA (Hehuang Pharmaceutical Co., Shanghai, China) or placebo for 24 months. Central randomization with a block size of four was used to generate grouping codes. No stratification was applied. The codes were prepared in sealed envelopes and opened after a patient met the eligibility criteria and signed the consent form. The placebo had the exact same appearance and taste as the MUSKARDIA (bitter, black-brown, lustrous pill) and was kindly donated by the Shanghai Hutchison Pharmaceuticals Company. The patients, investigators, and core study staff were blinded to treatment allocation.

Treatment

Before the initiation of trial drug administration, all study patients entered a 28-day run-in period during which they received standard therapy for stable CAD according to the guidelines. Patients were then allocated to either oral MUSKARDIA (two pills, three times daily, 135 mg in total) or placebo (two pills, three times daily, 135 mg in total). The patients were instructed to take medications about 30 min after each meal. Patients continued with the study medication for 24 consecutive months or until the development of a major adverse event (AE). Interruption of the study drug for more than 14 consecutive days was considered as a protocol violation. Patients were allowed to receive other prescription medication, except TCM, for CVDs. The participants were followed up at 1, 3, 6, 9, 12, 18, and 24 months.

Endpoints and assessments

The primary composite efficacy endpoint was the occurrence of a major adverse cardiovascular event (MACE), defined as cardiovascular death, non-fatal MI, or non-fatal stroke. The secondary endpoints included all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization

for unstable angina or heart failure and coronary angioplasty (PCI or CABG), patient compliance, angina stability and angina frequency. All primary and secondary endpoint events were adjudicated by a blinded, independent clinical endpoint committee. Compliance was defined as the proportion of prescribed medication taken by the patients. Angina stability and angina frequency were assessed with the Seattle Angina Questionnaire. Other prespecified exploratory endpoint measures consisted of liver and renal functions and concomitant medication.

Safety endpoints comprised the number of total AEs and severe AEs (SAEs) by 24 months. Vital signs and electrocardiogram were assessed at each visit, whereas the physical examination and laboratory parameters were assessed every 6 months.

Statistical analysis

According to the ACTION[19] and EUROPA[20] studies, an event rate of 5.0% per year was estimated for the placebo (control) group. With a planned sample size of 2700, the overall study would have 80% power at a two-sided α of 0.05 to detect a 30% relative risk reduction in the MUSKARDIA group. All reported P values were two-sided. $P < 0.05$ was considered statistically significant.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, NY, USA). For variables not normally distributed, medians and interquartile ranges were reported; otherwise, means and standard deviations were reported.

All efficacy and safety analyses were performed in the full analysis set (FAS) / safety set (SS), defined as randomized patients who received at least one dose of study medication. The analysis of the primary endpoint was based on Kaplan-Meier estimates of cumulative incidence. The hazard ratio and 95% confidence interval (CI) were estimated based on Cox proportional hazards models. All-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for unstable angina or heart failure and peripheral revascularization, compliance, angina stability and angina frequency were compared between the two groups using the independent sample t test or Pearson chi-square test or Fisher exact test, as appropriate. The odds ratio (OR) was calculated by logistic regression. All statisticians were blinded to group allocation.

Results

Study population

A total of 2674 patients from 97 centers were enrolled and randomized between July 2011 and August 2015. At one site with only one patient enrolled, the patient dropped out before the run-in period for logistic reasons. The study flowchart is shown in Supplementary Figure 1, http://links.lww.com/CM9/A396. No unblinding in response to AE was undertaken before the data lock. Further, 2673 patients received a study drug: 1342 in the MUSKARDIA group and 1331 in the placebo group. The mean age of the total population was 63.8 years; 70.8% were male. The overall baseline aspirin was 99.7%. The overall statin use was 93.0%. In addition, 31.6% of the patients were under isosorbide mononitrate medication at enrollment. The Seattle Angina Questionnaire showed that the frequency of angina at baseline was similar in the two groups (MUSKARDIA: 20.1%; controls: 19.4%). As shown in Table 1, all baseline characteristics were comparable between groups.

Efficacy endpoints

The incidence of the primary endpoint (MACE) was 1.9% (26/1335) in the MUSKARDIA group compared with 2.6% (34/1327) in the placebo group at 24 months (OR = 0.80; 95% CI: 0.45–1.07; $P = 0.2869$). From 18 months, the Kaplan-Meier curves of the two groups diverged, with a 26.9% reduction in the occurrence of MACE in the MUSKARDIA group after 2 years of treatment compared with the placebo group [Figure 1]. For every 1000 CAD patients, there were, on average, 3.5 fewer MACEs were reported in the MUSKARDIA group per year. The comparisons of the occurrence rates of MACE at different time points are listed in Supplementary Table S2, http://links.lww.com/CM9/A396.

In terms of person-year analysis for the primary endpoint the occurrence rates of MACE were 1.2% (27.0/2232.5) in the MUSKARDIA group and 1.6% (35.0/2209.6) in the placebo group (OR = 0.70; 95% CI: 0.44–1.18; $P = 0.1986$). The subgroup analysis showed that MUSKARDIA was superior to placebo in females and in the body mass index (BMI) < 24 kg/m^2 subgroups [Figure 2].

For individual MACE endpoints, there were no significant differences in all-cause mortality (0.37% in the MUSKARDIA group *vs.* 0.23% in the placebo group), non-fatal MI (0.97% in the MUSKARDIA group *vs.* 1.51% in the placebo group), and non-fatal stroke (0.67% in the MUSKARDIA group *vs.* 0.90% in the placebo group). The detailed comparisons on efficacy endpoints are shown in Supplementary Table S3, http://links.lww.com/CM9/A396. At 18 months, the MUSKARDIA group had significantly higher scores than the placebo group for angina stability ($P = 0.0458$) and angina frequency ($P = 0.0362$). No significant differences were observed in angina stability ($P = 0.9104$) and angina frequency ($P = 0.0742$) at 24 months [Figure 3]. Treatment compliance was similar between groups, with 84.5% the patients in the MUSKARDIA group and 82.0% in the placebo group achieving ≥70% compliance in FAS [Supplementary Table S4, http://links.lww.com/CM9/A396].

Safety endpoints and key laboratory results

In the SS, 236 patients (17.7%) in the MUSKARDIA group had at least 1 AE, which could be compared with 231 patients (17.1%) in the placebo group ($P = 0.8785$). The total numbers of AEs were 443 in the MUSKARDIA group and 477 in the placebo group. SAEs occurred in 47 patients (3.5%) in the MUSKARDIA group and 41 patients (3.1%) in the placebo group. Table 2 summarizes the centrally adjudicated clinical events, clinical AEs, and laboratory abnormalities.

Table 1: Baseline characteristics of patients with coronary artery disease in the full analysis set.

Variables	Placebo ($n=1327$)	MUSKARDIA ($n=1335$)
Age		
Mean (SD)	63.7 (9.9)	63.9 (9.8)
< 65 years, *n* (%)	682 (51.4)	696 (52.1)
≥65 years, *n* (%)	645 (48.6)	639 (47.9)
Males, *n* (%)	935 (70.5)	951 (71.2)
History of coronary disease, mean (SD), years	3.0 (3.7)	3.0 (3.8)
BMI, mean (SD), kg/m^2	24.5 ± 3.0	24.5 ± 3.0
Systolic blood pressure, mean (SD), mm Hg	127.6 (12.8)	127.9 (13.0)
Diastolic blood pressure, mean (SD), mm Hg	76.0 (8.4)	75.8 (8.4)
Medical history, *n* (%)		
Diabetes	376 (28.3)	340 (25.5)
Hypertension	764 (57.6)	742 (55.6)
Chronic kidney disease	417 (33.5)	445 (35.7)
Atrial fibrillation	9 (0.7)	10 (0.7)
Heart failure	3 (0.2)	5 (0.4)
Baseline medication, *n* (%)		
Aspirin	1322 (99.6)	1331 (99.7)
Statins	1238 (93.3)	1237 (92.7)
Isosorbide mononitrate	416 (31.3)	426 (31.9)
Clopidogrel	674 (50.8)	702 (52.6)
β-blockers	981 (73.9)	997 (74.7)
CCB	463 (34.9)	480 (36.0)
ARB	395 (29.8)	377 (28.2)
ACEI	381 (28.7)	379 (28.4)
Anti-angina drugs	78 (5.9)	68 (5.1)
SAQ quality of life, mean (SD)		
Physical limitation	81.1 (17.1)	80.1 (17.4)
Angina stability	61.0 (22.8)	62.5 (22.8)
Angina frequency	82.3 (20.1)	82.3 (19.4)
Satisfaction with treatment	74.0 (15.0)	73.5 (14.9)
Cognition of disease	59.4 (20.8)	59.8 (20.0)

ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; BMI: Body mass index; CCB: Calcium channel blocker; MUSKARDIA: Shexiang Baoxin Pill; SAQ: Seattle angina questionnaire; SD: Standard deviation.

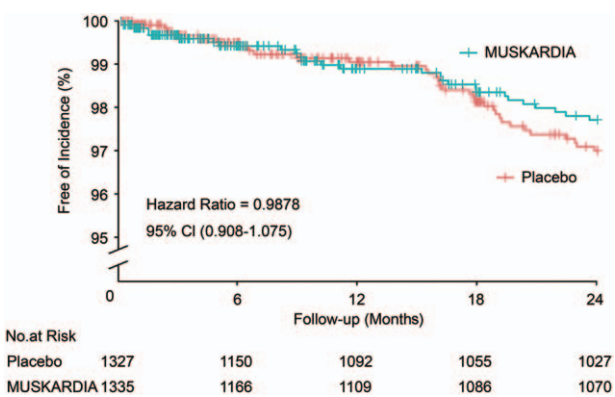

Figure 1: Cumulative Kaplan-Meier estimates of the time to the first major adverse cardiovascular event. No significant difference was observed between the Shexiang Baoxin Pill and placebo groups during the 24-month trial period ($P=0.2215$). A trend of gradual curve diversion emerged after 18 months of treatment.

Discussion

TCM has long been used to treat CAD in China. However, the evidence regarding the efficacy and safety from large scale RCTs is lacking. Therefore, this study aimed to determine the effects of MUSKARDIA on stable CAD as an add-on to OMT by enrolling 2673 patients with stable CAD from 97 sites across China. Our results showed that add-on MUSKARDIA to standard aspirin and statin in patients with stable CAD was safe and significantly reduced angina frequency at 18 and 24 months. In addition, a trend towards reduced MACE was observed in the MUSKARDIA group.

The bioactive components of MUSKARDIA include muscone, ginsenosides, storax, bufadienolides, cinnamic acid, arenobufagin, and borneol.[13,14,16] Muscone has been shown to have beneficial effects on cardiac remodeling in animal models of CAD.[21] Bufadienolides are compounds that are toxic at high doses, but are beneficial at low doses to control heart failure.[22] Ginsenosides exert cardioprotective functions through anti-oxidative activity, inhibiting platelet adhesion, promoting vasoconstriction, improving lipid profile, and regulating ion channels.[23] Cinnamic acid is known for the management of diabetes and its complications[24] while borneol is known for its anti-ischemia effects.[25] Therefore, taken together, the combination of different compounds in MUSKARDIA might be beneficial for

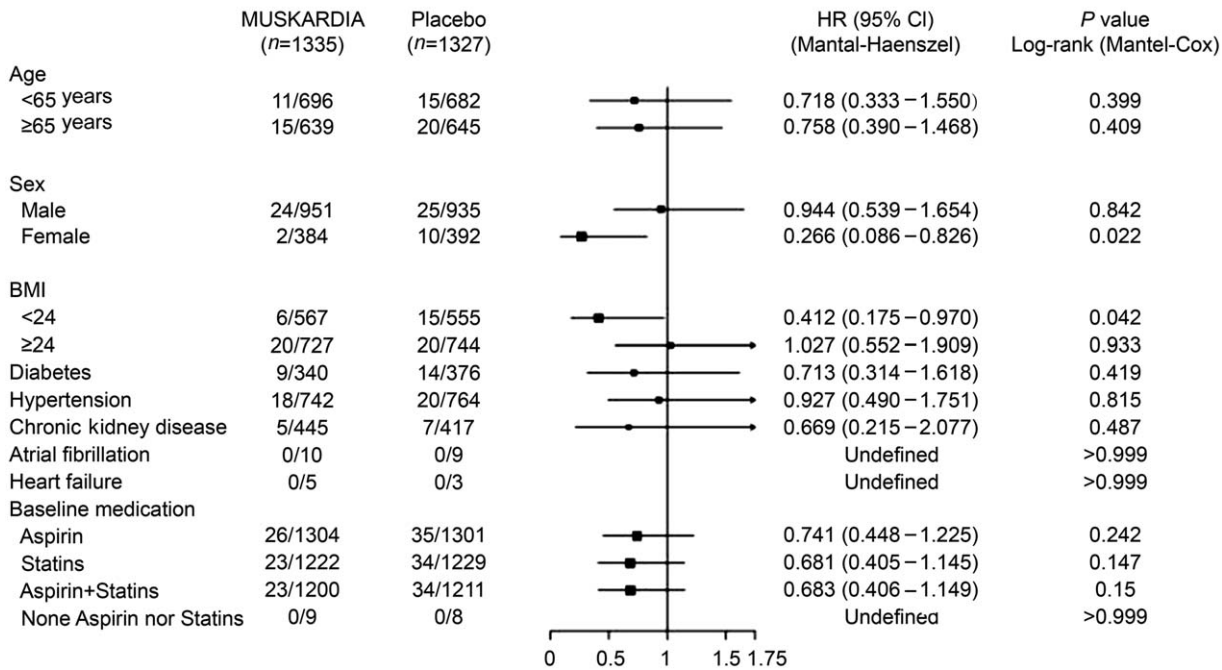

Figure 2: Subgroup analysis indicated benefits of Shexiang Baoxin Pill in females and patients with BMI < 24 kg/m^2.

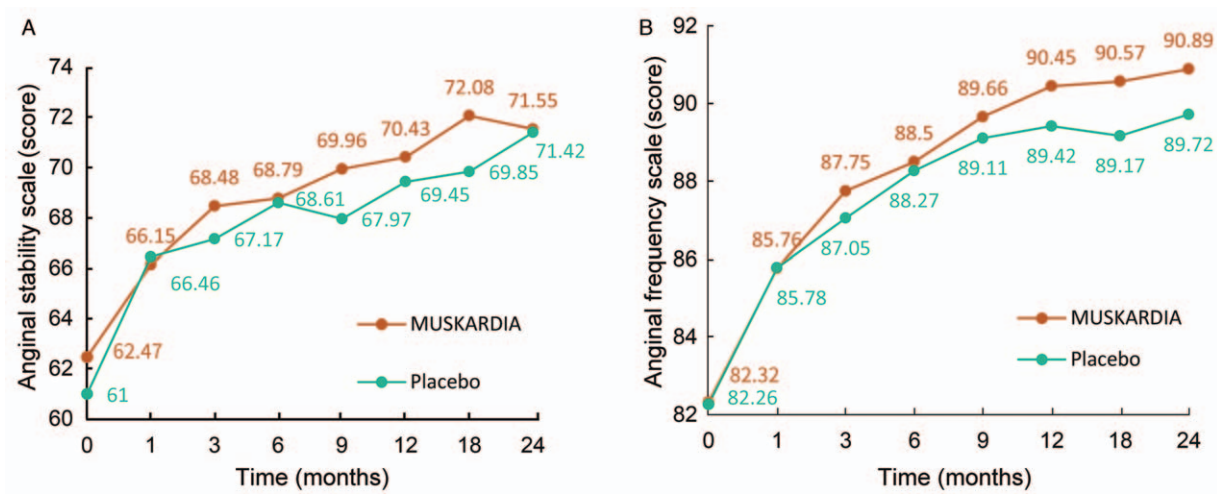

Figure 3: Angina assessed by the Seattle angina questionnaire. Shexiang Baoxin Pill improved angina stability (A) and frequency (B) in patients with stable coronary artery disease at 18 months.

patients with CAD, as supported by data from preliminary studies.[13,17,18]

Despite OMT, CAD patients might still face residual cardiovascular risk.[5-7] Indeed, Bhatt *et al*[5] showed that among 45,227 patients with stable CAD, the risk of MACE was about 12%. The ACTION trial reported the occurrences of 1.53 to 1.64 per 100 person-years for death and 4.60 to 4.75 per 100 person-years for the primary endpoint, which was the combination of death, acute MI, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularization.[19] In the recently published Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial the occurrence of MACE was 4% to 6% after 1.95 years.[26]

The combined use of aspirin and statin is a standard approach to reduce the risk of cardiovascular events in patients with stable CAD in a secondary prevention context.[1-4] Several studies showed that the long-term use of statin decreased the residual risk of MACE in CAD patients.[27-32] In a study on 7657 CAD patients, the use of both aspirin and statin reduced the risk of MACE over 10 years.[32] The confirm registry showed that statin but not

Table 2: Adverse events of patients with coronary artery disease undergoing different treatment.

Variables	Placebo ($n = 1327$)	MUSKARDIA ($n = 1335$)
Had ≥1 AE	231 (17.4)	236 (17.7)
Had ≥1 SAE	41 (3.1)	47 (3.5)
Cardiovascular events		
Unstable angina	11 (0.8)	7 (0.5)
Atrial fibrillation	1 (0.1)	3 (0.2)
Acute MI	4 (0.3)	3 (0.2)
Stable angina	21 (1.6)	16 (1.2)
Old MI	2 (0.2)	0
Hepatobiliary disease		
Liver dysfunction	3 (0.2)	2 (0.1)
Liver discomfort	0	1 (0.1)
Gamma glutamyl transferase	5 (0.4)	3 (0.2)
Elevated alanine aminotransferase	3 (0.2)	4 (0.3)
Elevated aspartate aminotransferase	3 (0.2)	2 (0.1)
Elevated blood cholesterol	7 (0.5)	4 (0.3)
Elevated blood triglycerides	18 (1.4)	15 (1.1)
Elevated transaminase	2 (0.2)	1 (0.1)
Renal and urinary system diseases		
Chronic kidney failure	1 (0.1)	0
Urinary incontinence	1 (0.1)	0
Renal failure	0	1 (0.1)
Renal pain	1 (0.1)	0
Acute kidney injury	0	1 (0.1)
Hematuria	3 (0.2)	1 (0.1)
Elevated serum creatinine	5 (0.4)	5 (0.4)
Proteinuria	9 (0.7)	9 (0.7)
Elevated uric acid	14 (1.1)	14 (1.0)
Metabolic and nutritional diseases		
New onset type 2 diabetes	1 (0.1)	3 (0.2)
Hypoglycemia	0	1 (0.1)
Hypercholesterolemia	1 (0.1)	0
Hypertriglyceridemia	2 (0.2)	2 (0.1)
Hyperuricemia	6 (0.5)	3 (0.2)
Hyperglycemia	0	1 (0.1)
Hyperlipidemia	12 (0.9)	10 (0.7)
Loss of appetite	1 (0.1)	0
Diabetes	1 (0.1)	2 (0.1)
Peripheral edema	1 (0.1)	0
Dyslipidemia	1 (0.1)	0

Data are shown as *n* (%). AE: Adverse event; MI: Myocardial infarction; MUSKARDIA: Shexiang Baoxin Pill; SAE: Serious adverse event.

aspirin reduced the risk of MACE in CAD patients.[33] A previous study reported that statins and aspirin improved the long-term clinical outcomes after PCI.[34] In a recent Chinese study the incidence of MACE was 1.8% in CAD patients treated with statin.[35] In the present study the 24-month MACE rate for the overall study population was 2.3% for the MUSKARDIA group and 3.1% for the placebo group. These rates of occurrence were lower than those observed in other populations,[5,19,26] but similar to that found in a recent Chinese study.[35] The relatively low MACE rate might have several explanations. Notably, the proportion of patients on optimal therapy at baseline was high in the present study, with 99.7% on aspirin and 93.0% on statin, these values were much higher than those reported in previous studies.[27-32] Moreover, the compliance with medication was high during the 24-month study period (good compliance for more than 80% of the study patients), which was also considerably higher than previous findings.[27-32] Second, the patients enrolled in this trial had a relatively low risk of recurrent CVD. The inclusion criterion for coronary stenosis was ≥50% in one or more coronary arteries compared with ≥50% in two or more coronary arteries in the COMPASS trial.[26] Other trials, such as the Intravascular Cooling in the Treatment of Stroke trial, reported MACE rates of > 20%, but they enrolled patients who were at higher risks.[36] Nevertheless, the unexpectedly low MACE rate might underpower the results of the present study given the sample size. The Kaplan-Meier curves showed a separation after 18 months of treatment, indicating that MUSKARDIA had a trend towards a superior effect compared with the placebo. This delay in curve separation was in accordance with the characteristic slow action of TCM.[37] In other words, an underpowered sample size and a relatively short treatment

period might be the main causes of the borderline neutral results on the occurrence of MACE, despite a numerical reduction of 26.9%. On the contrary, the subgroup analyses revealed statistically significant results in females and patients with BMI $< 24\ kg/m^2$. This result might provide a hint of treatment option for Asian females who generally have a lower BMI and higher gastric intolerance to aspirin.

Nevertheless, the present trial confirmed the relative long-term safety of MUSKARDIA. For this 2-year TCM add-on treatment, the levels of creatinine clearance, serum alanine aminotransferase, and serum aspartate aminotransferase were similar between the two groups throughout the trial under strict monitoring. Safety, particularly long-term safety, is a major concern for the use of TCM. The present study addressed this concern, at least regarding MUSKARDIA, with the help of a large-scale RCT in CAD for a 2-year period. Nevertheless, additional studies are required to examine the adverse effects of TCM over a longer period.

Angina stability and angina frequency scores were significantly reduced at 18 months in the MUSKARDIA group compared with the placebo group. This time point was in accordance with the separation of the Kaplan-Meier curves for MACE. These results might suggest that the chronic administration of MUSKARDIA ≥18 months might be essential to induce better coronary circulation and thus result in lower angina frequency.

The present trial has several limitations. First, the trial was registered after the enrollment of the first study patient. For historical reasons, China had not adopted the tradition of trial registration at the time of trial preparation in 2011. Still, there was no exposure of preliminary results or bias induced from the delay of registration. Between the randomization of the first patient (07/2011) and trial registration (04/2012), no change in the trial protocol or statistical analysis plan was made and no unblinding was undertaken. Second, the 2-year treatment might just allow the starting action of MUSKARDIA, but not reveal its maximal beneficial effects. The follow-up after 2 years was not conducted, leading to loss of precious information beyond the trial. The underestimation of the occurrence of the primary endpoint resulted in a relatively small sample size and the underpowered sample size probably contributed to the negative results for the primary endpoint. Finally, several important variables were not examined (*eg,* inflammatory markers and oxidative stress status).

In conclusion, as an add-on therapy to aspirin and statin, the 24-month use of MUSKARDIA is safe and reduced angina frequency in patients with CAD. Moreover, a 26.9% reduction in MACE was found in the MUSKARDIA group compared with the placebo group; however, this reduction did not reach statistical significance.`

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Conflicts of interest

None.

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