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ORIGINAL ARTICLE

Impact of Xuezhikang on coronary events in hypertensive patients with previous myocardial infarction from the China Coronary Secondary Prevention Study (CCSPS)

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Abstract

Background. The lowering of cholesterol concentrations in individuals at high risk for cardiovascular disease improves clinical outcome. Xuezhikang has a marked impact on lipids.

Methods. In this randomized, double-blinded, placebo-controlled, parallel-group clinical trial, a total of 2704 hypertensive patients with previous myocardial infarction (MI) were assigned either to placebo ($n = 1341$) or to Xuezhikang (0.6 g twice daily, $n = 1363$) for an average of 4.5 years. The primary end-point was recurrent coronary events; the secondary end-point was all-cause mortality and other clinical events, including adverse effects.

Results. There were no differences between the Xuezhikang and placebo group in base-line characteristics. However, Xuezhikang treatment reduced the incidence of coronary events by 43.0% ($P = 0.02$), deaths from coronary heart disease (CHD) by 30.0% ($P < 0.01$), and all-cause mortality by 35.8% ($P = 0.001$).

Conclusions. This study, for the first time, demonstrated that long-term Xuezhikang therapy resulted in significant reduction in cardiovascular events and death in Chinese hypertensive patients with previous MI in a safe manner.

Key words: *Hypertension, myocardial infarction, statin, Xuezhikang*

Introduction

Cardiovascular diseases are the major cause of mortality in the Western world, and it is expected that this will remain so during the foreseeable future. Recent guidelines have recommended an integrated approach to decrease cardiovascular risk by treating hypertension, dyslipidemia, and other cardiovascular risk factors (1). Until recently, a few studies have assessed the effects of statins specifically in hypertensive patients (2,3). However, the results of these studies were conflicting. More recently, a meta-analysis has addressed the impact of systemic hypertension on the cardiovascular benefits of statin therapy and suggested that statin therapy effectively decreased cardiovascular morbidity and mortality to the same extent in hypertensive and non-hypertensive patients (4). More importantly, all previous studies regarding effects of statins on hypertensive patients were from Western populations, and there are no data available from Chinese populations. Furthermore, information on whether statin therapy can confer a greater benefit on hypertensive patients with previous myocardial infarction (MI) has been limited.

Extracts of red yeast rice have been widely used for therapy of patients with cardiovascular disorders in China for centuries. Xuezhikang, an extract of red yeast Chinese rice with multiple components,

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Key messages

- The lowering of cholesterol concentrations in individuals at high risk for cardiovascular disease improves clinical outcome.
- A few previous studies have suggested a benefit impact of statin on hypertensive patients in Western populations.
- The present subgroup analysis demonstrated a favorable effect of Xuezhikang therapy on recurrent of coronary events and mortalities in Chinese hypertens ive patients with previous myocardial infarction.

is a traditional Chinese medication with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibiting activity and contains a family of naturally occurring statins (monacolins), one of which is lovastatin (5). Recent studies including our data have demonstrated that Xuezhikang could effectively modify not only lipid profile but also inflammatory markers (6,7). The China Coronary Secondary Prevention Study (CCSPS) was a large randomized, double-blind, placebo-controlled, parallel-group, multiple-center clinical trial designed to compare the impacts of Xuezhikang and placebo on reducing cardiovascular events in 4870 patients who had a history of MI (8). The primary aim of this study was to perform a detailed *post hoc* subgroup analysis of the 2704 hypertensive patients from the CCSPS.

Methods

Subjects

This study was carried out in 4870 patients with a documented previous MI in 65 Chinese hospitals in 19 provinces across China, and eligible subjects were men and women aged 18 to 75. During the prior 60 months, all eligible patients had to have incurred an MI that met appropriate diagnostic criteria, including increased serum creatine kinase (8). The inclusion and exclusion criteria of subjects have previously been published (8–10). Blood pressure was measured after at least 10 min of rest in a sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the means of two measurements by well trained doctors. The hypertension in the study was defined as SBP $\geq$140 mmHg, DBP $\geq$90 mmHg, or the current use of antihypertensive medication. Finally, 4870 patients participated in the CCSPS, of whom 2704 were identified with hypertension. And then, those hypertensive patients with previous MI were randomly assigned at 1:1 ratio into either placebo (n = 1341) or Xuezhikang 0.6 g twice daily (n = 1363) for an average of 4.5 years.

Study design

The protocol of the study was approved by the data and safety monitoring and regional ethics committees of each study site, and informed consent forms were signed by all enrolled patients before study initiation, and this has previously been reported elsewhere (8–10). In brief, the CCSPS study was a randomized, double-blinded, placebo-controlled, parallel-group clinical trial. Randomization was done according to the number allocated to each hospital by the study data center. Adherent individuals who did not have major clinical events or other serious medical conditions during the run-in were randomly assigned to receive a Xuezhikang capsule, 0.6 g twice daily (Beijing WBL Peking University Biotech Co. Ltd, Beijing, China), or a matching placebo twice daily. (Xuezhikang 0.6 g twice daily comes from the habit of Chinese traditional drugs.) Xuezhikang is an extract of cholestin from *Monascus purpureus* (red yeast rice or Hongqu). Each capsule of Xuezhikang contains the combination of lovastatin, also termed monacolin K (2.5–3.2 mg/capsule), unsaturated fatty acids, essential amino acids, and a small quantity of lovastatin hydroxyl acid, as well as ergosterol and some other components (8,9). Previous medical treatments for hypertension, coronary heart disease (CHD), or complications of CHD were continued, but all medications known to influence blood lipid levels were prohibited.

Study end-point and follow-up

The primary study end-point was to assess the efficacy of Xuezhikang on reducing coronary events including non-fatal or fatal MI, sudden death, and deaths from coronary heart disease. The secondary study end-point was mortality due to all causes. Other registered events were the occurrence of stroke and other cerebrovascular events, and requirement for percutaneous coronary intervention (PCI), coronary artery by-pass graft (CABG), cancer, suicide, all-cause death, and drug-related adverse events, including symptoms and abnormal laboratory findings.

All patients maintained a stable diet and life-style during follow-up. Routine visits were scheduled 6–8 weeks later after randomization and every 6 months thereafter to monitor clinical events until the final follow-up visit. The detailed protocol of follow-up has previously been reported (8–10).

Data evaluation

An independent data and safety monitoring committee reviewed the safety and efficacy data, and the events were coded according to pre-specified criteria. Analyses were based on confirmed reports. Confirmation of

MI required evidence of typical symptoms, diagnostic electrocardiographic changes, and diagnostic elevation of cardiac enzyme concentration. Deaths attributed to MI, other coronary diseases (such as heart failure due to CHD), and sudden or unexpected deaths without post-mortem evidence of another cause were classified as coronary death. Stroke was defined as the rapid onset of focal or global neurological deficits lasting more than 24 hours or leading to death, with clinical evidence supplemented by neurological imaging. Cancers were classified according to their primary anatomical site.

Statistical analysis

Data were analyzed using SPSS statistical software, version 11.5 (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviations (SD). The results are presented as percentages for discrete variables and as mean ± SD for continuous variables unless otherwise indicated. The differences between demographic variables of the groups were assessed using the Student *t* test for continuous data and chi-square test for categorical data. The base-line and post-treatment lipid components were analyzed with ANOVA, and other biochemical variables were compared between the two groups with the Student *t* tests. Cox proportional hazards regression models were applied to estimate relative risk and confidence intervals. The Kaplan-Meier method was used to construct the time-to-event curves (Figure 1). Results were reported as the number of participants and events for each treatment group. A *P*-value <0.05 was considered statistically significant.

Results

Base-line clinical characteristics

All the 2704 patients with hypertension were randomly assigned to the Xuezhikang group ($n = 1363$) and the placebo group ($n = 1341$). Because the second interim analysis showed $P<0.05$ for the primary end-point, the study was discontinued in June 2003. The average follow-up period was 4.5 years. Base-line clinical characteristics of patients with either placebo or Xuezhikang are illustrated in Table I. There were no significant differences of base-line clinical variables between the placebo group and the Xuezhikang group. The average follow-up period for enrolled patients was 4.5 years (range 0.5–7 years). A total of 25 patients (0.92%) were lost to follow-up because of adverse effects, of whom 15 were in the Xuezhikang group (first year $n = 7$; second year $n = 4$; third year $n = 3$; fourth year $n = 1$, respectively), and 10 patients were in the placebo group (first year $n = 5$; second year $n = 2$; third year $n = 3$; fourth year $n = 0$, respectively).

Changes in lipid profiles and blood pressure

As shown in Table II, there were no differences in lipid profiles between the groups at base-line. However, over an average of 4.5 years, therapy with 1.2 g Xuezhikang per day induced significant reductions in total cholesterol (TC)(10.9%), and low-density lipoprotein cholesterol (LDL-C) (16.9%), compared with corresponding reductions of 2.4% and 3.3% in the placebo group, respectively ($P < 0.0001$). Triglyceride (TG) levels fell 11.5% in the Xuezhikang group, compared with 5.5% in the placebo group ($P = 0.0007$). Additionally, Xuezhikang therapy resulted in elevation of high-density lipoprotein cholesterol (HDL-C) by 4.6% compared to base-line ($P = 0.0002$), while there were no such changes in the placebo group ($P = 0.07$).

The reduction of blood pressure was expected because of continued medical treatments for hypertension during the follow-up. As presented in Table II, although there was no significant difference in changes of blood pressure including systolic as well as diastolic blood pressure between the Xuezhikang group and the placebo group at base-line and the end-point of follow-up, the blood pressure was significantly decreased after 4.5-year therapy with Xuezhikang as well as placebo compared with base-line data due to continued medical treatments for hypertension during the follow-up.

Modification in cardiovascular events

There were significant differences in incidence of coronary events between the two groups during the follow-up as summarized in Table III. During the average 4.5-year follow-up, 225 cases of coronary events occurred in all the 2704 patients, among which there were 91 cases (6.7%) in the Xuezhikang group and 160 cases (11.9%) in the placebo group ($P = 0.0214$). Risk reduction for coronary events was 43.0% by Xuezhikang therapy (Table III). Xuezhikang also decreased risk of non-fatal MI by 59.6% ($P < 0.0001$) and risk of death due to coronary disease by 30% ($P = 0.0059$). The calculated number needed to treat (NNT) to prevent one coronary event during the average 4.5-year follow-up was 19/4.5 years (Table IV).

The beneficial effects of Xuezhikang on mortality could be also observed after the 4.5-year treatment. During the period of follow-up, 205 cases died from various causes, among which there were 81 patients in the Xuezhikang group and 124 cases in the placebo group. The risk for all-cause death was 35.8% lower

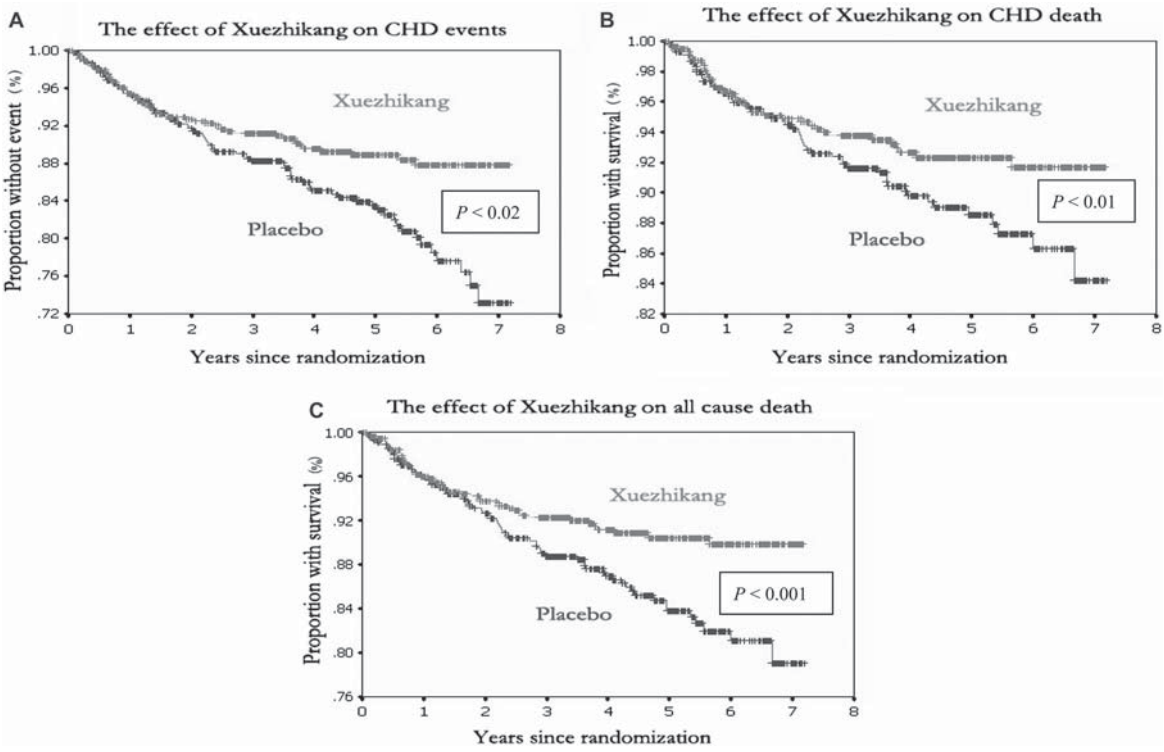

Figure 1. Kaplan-Meier analysis of time to primary and secondary end-points in hypertensive patients. A: Total coronary events, including recurrent non-fatal myocardial infarction (MI), fatal MI, sudden death and other coronary death; B: coronary heart disease death; and C: all-cause death.

in the Xuezhikang group than in the placebo group ($P = 0.012$). The NNT to prevent one death within the average 4.5-year follow-up was 30/4.5 years (Table IV). In addition to coronary death, two patients in the Xuezhikang group and one patient in the placebo group died from other cardiovascular disease (Table III).

Comparison of treatment effect between hypertensive and non-hypertensive patients

Hypertension was found to be a significant risk factor for coronary events, death from coronary events, and mortality from all causes in the placebo-treated patients ($P < 0.01$ for all end-points, Tables III and IV). More

Table I. Base-line clinical characteristics ($n = 2704$).

Variables	Placebo ($n = 1341$)	Xuezhikang ($n = 1363$)	*P*-value
Male/female	1054/287	1093/270	0.31
Age, mean ± SD			
Male	59.2 ± 9.5	59.4 ± 9.2	0.29
Female	63.2 ± 7.1	63.0 ± 6.6	0.28
Body mass index (kg/m^2), mean ± SD	25.1 ± 2.8	25.2 ± 3.0	0.26
Heart rate (beats per minute)	74.9 ± 9.1	74.7 ± 9.7	0.12
Medical History, *n* (%)			
Smoking	442 (33.0)	434 (31.8)	0.53
Alcohol consumption	202 (15.1)	184 (13.5)	0.25
Diabetes	186 (11.0)	209 (15.3)	0.38
Medication, *n* (%)			
Aspirin	1264 (94.3)	1277 (93.7)	0.54
β-Blocker	747 (55.7)	791 (58.0)	0.22
ACEI	725 (54.1)	710 (52.1)	0.30
Calcium channel blocker	578 (43.1)	598 (43.9)	0.69
Nitrate	1223 (91.2)	1281 (89.4)	0.11

ACEI = angiotensin-converting enzyme inhibitor.

Table II. Changes of lipid profiles (mg/dL) and blood pressure (mmHg) after Xuezhikang therapy.

Lipid profile (mg/dL) and blood pressure (mmHg)		Placebo (n = 1341)	Xuezhikang (n = 1363)	P-value
Total cholesterol	Base-line	208.1 ± 25.8	207.6 ± 26.1	0.59
	After therapy	203.1 ± 37.2[a]	185.0 ± 34.1[a]	<0.001
Triglyceride	Base-line	166.0 ± 75.7	164.8 ± 76.1	0.68
	After therapy	156.8 ± 82.9 [b]	146.0 ± 76.6[a]	0.00
High-density lipoprotein cholesterol	Base-line	45.9 ± 14.4	45.9 ± 14.5	0.89
	After therapy	47.0 ± 12.8	48.0 ± 13.0[a]	0.06
Low-density lipoprotein cholesterol	Base-line	129.4 ± 28.9	129.2 ± 28.2	0.89
	After therapy	125.1 ± 35.9 [b]	107.4 ± 32.2[a]	<0.001
Blood pressure Systolic				
	Base-line	137.7 ± 16.8	137.7 ± 16.5	0.94
	After therapy	132.9 ± 14.5[a]	132.2 ± 14.3[a]	0.18
Diastolic	Base-line	84.4 ± 10.1	84.7 ± 10.3	0.46
	After therapy	80.7 ± 9.5[a]	80.4 ± 8.7[a]	0.34

[a]$P < 0.05$ compared with base-line.
[b]$P < 0.05$ compared with base-line.

importantly, a similar reduction in risk for all of the aforementioned specified events with Xuezhikang treatment was observed in hypertensive patients (Table IV). When treating with Xuezhikang, the NNT to prevent one coronary event was estimated at 19/4.5 years, one coronary death at 50/4.5 years, and all-cause mortality at 30/4.5 years in hypertensive patients, respectively, while the NNT to prevent one coronary event, one coronary death, and one mortality due to all causes in non-hypertensive patients were 25/4.5 years, 71/4.5 years, and 59/4.5 years, respectively. These findings suggested that hypertensive patients could gain the same or even more benefit than non-hypertensive patients from Xuezhikang treatment with respect to coronary events and total mortality.

Results in other common events

Other clinical events that were monitored were cancer, stroke, and the requirement for PCI or CABG procedures. During the 4.5-year follow-up, 263 cases of other common events occurred in all 2704 patients. In the Xuezhikang group 108 (7.9%) patients suffered from other common clinical events, while 155 (11.6%) patients did in the placebo group (P = 0.0046). The risk was thus 31.5% lower in the Xuezhikang group compared with the placebo group (Table III). Specifically, the incidence of cancer was 44.2% lower, and the need for PCI or CABG procedures was 24% lower with Xuezhikang therapy. The risk for stroke was 32.0% lower in the Xuezhikang group compared with the placebo group. However, those events mentioned

Table III. Comparison of various events between Xuezhikang and placebo group.

Clinical events	Placebo (n = 1341)	Xuezhikang (n = 1363)	Intergroup difference (%)	P-value
CHD events				
Non-fatal MI	73 (5.4)	30 (2.2)	−59.6	<0.001
Fatal MI	18 (1.3)	13 (1.0)	−29.2	0.34
Sudden death	45 (3.4)	32 (2.4)	−30.1	0.12
Other CHD death	24 (1.8)	16 (1.2)	−34.6	0.19
Total CHD death	87 (6.5)	61 (4.5)	−30.0	0.001
Total CHD events	160 (11.9)	91 (6.7)	−43.0	0.02
Common events				
Stroke survival	58 (4.3)	39 (2.9)	−34.0	0.07
Stroke death	10 (0.8)	8 (0.6)	−21.3	0.61
Total stroke	68 (5.1)	47 (3.5)	−32.0	0.06
Cancer survival	9 (0.7)	10 (0.7)	9.0	0.85
Cancer death	21 (1.6)	7 (0.5)	−65.5	0.001
Total cancer	30 (2.2)	17 (1.3)	−44.2	0.06
PCI/CABG	57 (4.3)	44 (3.2)	−24.0	0.19
Total common events	155 (11.6)	108 (7.9)	−31.5	0.00
Other cardiovascular death	2 (0.2)	1 (0.1)	−53.3	0.63
Total death	124 (9.3)	81 (5.9)	−35.8	0.001

CHD = coronary heart disease; MI = myocardial infarction; PCI/CABG = percutaneous coronary intervention/coronary artery by-pass graft; Intergroup difference = percentage difference of events between the placebo and Xuezhikang.

Table IV. Comparison of effects of Xuezhikang treatment on clinical events between hypertensive (n = 2704) and non-hypertensive patients (n = 2166) with previous myocardial infarction.

	Events in groups (%)				
Events and groups	Placebo	Xuezhikang	Relative risk (95% CI)	*P*-value	NNT
CHD events					
Hypertensive	11.9	6.7	0.68 (0.48–0.97)	<0.01	19
Non-hypertensive	8.5	4.5	0.48 (0.37–0.65)	<0.01	25
CHD death					
Hypertensive	6.5	4.5	0.61 (0.41–0.80)	<0.01	50
Non-hypertensive	4.3	2.9	0.66 (0.40–0.91)	<0.05	71
All-cause death					
Hypertensive	9.3	5.9	0.65 (0.42–0.77)	<0.01	30
Non-hypertensive	5.9	4.2	0.62 (0.39–0.95)	<0.05	59

CHD = coronary heart disease; CI = confidence interval; NNT = number needed to treat.

above did not reach statistically significant differences (P = 0.0545 for cancer; P = 0.1905 for PCI/CABG; P = 0.0626 for stroke, respectively).

Clinical and laboratory adverse events

Clinical adverse effects were rare and comparable in the Xuezhikang group and the placebo group (1.6% versus 1.0%, $P > 0.05$). There were 13 reported adverse events in the placebo group including 3 patients with gastrointestinal discomfort, 2 patients with allergic reactions, 2 patients with myalgias and psychoneurological symptoms, 3 patients with erectile dysfunction, and 3 patients with other adverse events. In the Xuezhikang group 22 patients had adverse effects (gastrointestinal discomfort in 10 patients, allergic reactions in 3 patients, myalgias in 5 patients, edema in 2 patients, and other adverse events in 2 patients).

In the present study, 7 (0.5%) patients in the Xuezhikang group and 13 (1.0%) patients in the placebo group experienced significant (three times upper limit of normal) elevation of serum glutamic-pyruvic transaminase (GPT). Similarly, 74 (5.4%) patients in the Xuezhikang group and 80 (5.9%) in the placebo group had elevated blood urea nitrogen (BUN) beyond the upper limit of normal. The two laboratory abnormalities mentioned above did not reach statistically significant differences between the two groups. Serum creatinine increased the upper limit of normal in 60 (4.4%) patients treated with Xuezhikang and 57 (4.3%) patients treated with placebo, which showed no significant difference between the two groups ($P > 0.05$). No patient experienced significant elevation (five times the upper limit of normal) of serum creatine phosphokinase or elevation (two times the upper limit of normal) of BUN or serum creatinine.

Discussion

A few previous studies have suggested a benefit impact of statin on hypertensive patients in Western populations. The present *post hoc* subgroup analysis demonstrated a favorable effect of Xuezhikang therapy on recurrence of coronary events and on mortalities in Chinese hypertensive patients with previous MI. Our data indicated that Xuezhikang therapy could reduce the relative risk for major coronary events by 44%, coronary death by 30%, and all-cause mortality by 35.8% during an average 4.5-year follow-up period and was well tolerated.

It is well known that hypertension and dyslipidemia are highly prevalent, independent, modifiable risk factors for cardiovascular disease (10,11), which are interrelated metabolically, epidemiologically, and clinically (12,13). The association of hypertension and dyslipidemia confers a greater increase in CHD than would be expected with either risk alone (13,14). Observational studies have suggested that the coexistence of hypertension and dyslipidemia exerts a greater than additive effects on the risk of developing CHD (13). Intervention data also showed that a major benefit in terms of CHD risk reduction could be achieved through the combined control of both blood pressure and cholesterol levels (15,16). As shown in Table IV, our present data indicated hypertensive patients with MI had more frequent recurrent cardiovascular events but could achieve more benefits from Xuezhikang therapy than non-hypertensive patients with MI (Table IV), suggesting that an integrated strategy should be recommended for high-risk hypertensive patients with MI including statin therapy.

Besides extending the known benefit of lipid-lowering by statins to an under-studied ethnic group (Chinese), the present observations essentially confirmed findings of previous clinical studies. Recently, there were several large-scale clinical trials to assess the effects of statins on cardiovascular events in hypertensive patients with or without CHD. The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) evaluated the effect of adding a statin to the antihypertensive

treatment regimen in patients with hypertension and no clinically evident CHD, with average TC levels ≤250 mg/dL, and ≥3 cardiovascular disease risk factors in addition to hypertension (2). Statin addition in ASCOT-LLA was associated with a 36% decrease in non-fatal MI and fatal CHD and a 27% decrease in the incidence of fatal and non-fatal stroke compared with placebo. A subgroup analysis of the Heart Protection Study (HPS) also revealed significant benefits from simvastatin 40 mg daily over placebo (17). Additionally, a recently published meta-analysis (only trials that followed ≥1000 patients for ≥2 years were included in this analysis, involving 69,984 patients) evaluated effects of statin on hypertensive patients and showed that patients receiving statins had statistically significantly lower rates of cardiac events compared with patients in the control groups. Hypertensive patients and non-hypertensive patients had similar results regardless of the analytic approach employed (randomized trials, subgroup analyses, or meta-regression) (4). Therefore, our data confirm and extend the data concerning the benefit of statin treatment in hypertensive patients at very high risk of developing cardiovascular events in a Chinese population (18).

Stroke is a common complication in hypertensive patients, especially in the Chinese population. The ASCOT-LLA study showed that atorvastatin treatment had resulted in a highly significant reduction in the primary end-point compared with placebo and a significant reduction in the incidence of stroke (2). Additionally, in the SPARCL study, the data demonstrated the efficacy of high-dose atorvastatin in lowering LDL cholesterol and prevented the occurrence of ischemic stroke/MI but increased the occurrence of hemorrhagic stroke (19). The increase in the incidence of hemorrhagic stroke among patients with cerebrovascular disease treated with simvastatin (40 mg) was also noted in HPS (17). The potential risk of recurrent hemorrhage, therefore, should be considered when one is deciding whether to administer a statin to patients who have had a hemorrhagic stroke (19). Interestingly, the base-line characteristics of study subjects bore close resemblance to those of our study. Specifically, the base-line mean systolic blood pressure of the patients was 138.9 mmHg in SPARCL, diastolic blood pressure was ~82.0 mmHg in SPARCL (137.7 mmHg and 84.4 mmHg in our patients, respectively); mean LDL cholesterol was 132.7 mg/dL in SPARCL (129.4 mg/dL in our patients). In contrast, our study showed that the risk for stroke was 32.0% lower in the Xuezhikang group compared with the placebo group. However, it did not reach statistically significance ($P = 0.0626$). It is unclear why our subgroup analysis did not demonstrate a benefit of statin on the incidence of stroke. The mean TC of base-line in the patients receiving lipid-lowering therapy was also similar in our patients compared with the ASCOT-LLA study (5.4 ± 0.6 mmol/L) (11). Different ethnic backgrounds and different statins used may be underlying causes. In addition, as shown in Table III, there was a big difference in strokes between the two treatment groups although the number of strokes was quite small. Therefore, the most probable reason was the small number of strokes in the present study. In the ASCOT-LLA, patients were not permitted to have had a prior major coronary event (previous clinical MI or currently treated angina pectoris) or a cerebrovascular event within 3 months of study onset, and patients receiving atorvastatin in ASCOT-LLA experienced a significant reduction in TC and LDL-C levels compared to our patients (50 mg/dL versus 22 mg/dL; and 46 mg/dL versus 22 mg/dL), which may also be an explanation for the different results between ASCOT-LLA and our study. Moreover, a recent study showed a significant interaction between statins and race. In white patients, statins were associated with statistically significantly lower odds of poor outcome, but in black patients statins were associated with a non-statistically significant increase in poor outcome (20). These findings indicated the need for further studies, including randomized trials, to examine differential effects of statins on ischemic stroke outcomes among patients with different ethnic backgrounds.

Compared with previous studies from Western populations, the current study showed a greater reduction in mortality from all causes and coronary events from Xuezhikang therapy in hypertensive Chinese patients with previous MI. Although the reasons for the expectedly greater reduction in risk in the current study than in other studies are unknown, several possible reasons have been proposed. Firstly, our results were apparently in agreement with a primary prevention study performed in an Asian-ethnic Japanese cohort (21). In their study, 10–20 mg of pravastatin reduced TC and LDL-C by 11.5% and 18.0%, respectively, but the risk of CHD was reduced by 33%. Secondly, a study on rosuvastatin pharmacokinetics demonstrated that the rosuvastatin area under the plasma concentration—time curve was approximately two times as great in Chinese, Malay, and Asian-Indian subjects as in Caucasian subjects living in Singapore (22), suggesting that a difference in statin pharmacokinetics might exist between Chinese and Western populations. Moreover, as a Chinese traditional medicine, Xuezhikang contains lovastatin, as well as other useful substances, and has also shown many pleiotropic effects (6,7,23). Therefore, the clinical benefits in our population might be associated with lipid-dependent and lipid-independent effects of Xuezhikang. Finally, a higher-risk population enrolled in the current study might be another explanation.

Additionally, a recent meta-analysis has indicated a neutral effect on cancer and the risk of cancer death in randomized, controlled trials (24). However, the risk of death from cancer was significantly lower, and the rate of cancer tended to be lower with Xuezhikang than placebo in the present study, although the exact mechanism was unknown. In fact, ankaflavin, a compound from *Monascus*-fermented red rice, is toxic to the human cancer cell lines HepG2 and A549 but not to normal MRC-5 and WI-38 cells, as indicated by a cell-based cytotoxicity assay (25). Extract of red yeast rice is found to inhibit prostate cancer cell line (LNCaP) proliferation and induce apoptosis, which is more obvious for red yeast rice extract than lovastatin in an *in vivo* study (9). It is speculated that, therefore, as a Chinese traditional medicine, the useful substance contained in Xuezhikang may play a synergistic role in the reduction of cancer risk (9). However, further studies are needed to confirm this finding and the possible mechanism.

The mechanisms of the statins in reducing cardiovascular events in hypertensive patients with MI are not fully understood. These mechanisms may include anti-inflammatory, neuroprotective, antithrombotic, direct vascular, and plaque-stabilizing effects. The clinical benefits in our population may be associated with lipid-dependent and lipid-independent effects of Xuezhikang. Xuezhikang, similarly to other statins, is known to improve endothelial function (23), reduce blood thrombogenicity (6), and exert anti-inflammatory actions (7). In addition, the statin-induced inhibition of Rho and its downstream target Rho kinase function may have beneficial effects in hypertensive patients, including angiotensin-II-elicited intracellular signals that could have important clinical consequences (26,27). Finally, hypertensive patients tolerated Xuezhikang well in the present study.

In conclusion, in hypertensive patients with previous MI at high risk of recurrent cardiovascular events, cholesterol-lowering with Xuezhikang 0.6 g twice daily was associated with a highly significant reduction in the primary end-point of incidence of coronary events. Significant reductions in the secondary end-points of cancer death, total coronary death, and all-cause mortality were also observed. These findings suggested that long-term Xuezhikang therapy resulted in significant reduction in cardiovascular events and death in Chinese hypertensive patients with previous MI, in reliable safety.

Limitations

The current study may extend the known benefit of lipid-lowering by statins to an under-studied ethnic group (Chinese hypertensive patients). However, several potential limitations of the present study deserve attention. The *post hoc* subgroup analysis from CCSPS is the first limitation. Apparently, the primary hypothesis and numbers of studies might be relatively limited. More importantly, sex unbalance of enrolled patients (female patients were under-represented) may limit the generalizability of the current study.

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Appendix

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