Effect of Xuezhikang, an Extract From Red Yeast Chinese Rice, on Coronary Events in a Chinese Population With Previous Myocardial Infarction

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Results of well-controlled prospective clinical trials showed the efficacy of lipid-lowering therapies in the reduction of cardiovascular (CV) events in western populations, but they were not reported with a Chinese population. This multicenter study was conducted to determine the effects of Xuezhikang (XZK), a partially purified extract of red yeast rice, on lipoprotein and CV end points in Chinese patients who experienced a previous myocardial infarction. Nearly 5,000 of these patients with average low-density lipoprotein cholesterol levels at baseline were randomly assigned either to placebo or to XZK daily for an average of 4.5 years. The primary end point was a major coronary event that included nonfatal myocardial infarction and death from coronary heart disease. Frequencies of the primary end point were 10.4% in the placebo group and 5.7% in the XZK-treated group, with absolute and relative decreases of 4.7% and 45%, respectively. Treatment with XZK also significantly decreased CV and total mortality by 30% and 33%, the need for coronary revascularization by 1/3, and lowered total and low-density lipoprotein cholesterol and triglycerides, but raised high-density lipoprotein cholesterol levels.

In conclusion, long-term therapy with XZK significantly decreased the recurrence of coronary events and the occurrence of new CV events and deaths, improved lipoprotein regulation, and was safe and well tolerated. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:1689–1693)

Extracts of red yeast rice have been widely used for therapy of patients with circulatory disorders in China for centuries. These extracts can decrease plasma lipids in animal models and have been used in several countries, including the United States. Lovastatin, the first statin drug approved by regulatory authorities, was extracted from yeast rice. Xuezhikang (XZK), produced by the Beijing WBL Peking University Biotech Co. Ltd (WPU) (Beijing, Peoples Republic of China), is a partially purified extract of red yeast Chinese rice with multiple components. Results of smaller clinical trials indicated that red yeast rice preparation can alter plasma lipoproteins effectively.\textsuperscript{1–7} The primary aim of this study was to evaluate the long-term efficacy of XZK in the reduction of recurrent cardiovascular (CV) events in a multicenter study of Chinese patients with average levels of low-density lipoprotein (LDL) cholesterol.

Study medication, design, and patients:

The study medication consisted of 300-mg capsules of XZK, each containing the combination of lovastatin, also termed monocholin K (2.5 to 3.2 mg/capsule); a small quantity of lovastatin hydroxyl acid; as well as ergosterol and some other components.

The study protocol 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. This randomized, double-blind, placebo-controlled, parallel-group study was carried out with 4,870 patients (age 18 to 70 years) each with a documented previous myocardial infarction (MI) in 65 Chinese hospitals. During the prior 60 months, all eligible patients had to have incurred an MI that met appropriate diagnostic criteria, including increased serum creatine kinase. Other entry criteria were total cholesterol 170 to 250 mg/dl and triglycerides ≤400 mg/dl. Patients with LDL cholesterol levels >180 mg/dl at screening could be restaged after 4 weeks of dietary therapy. Patients who met entry criteria at screening underwent a 4-week diet control period during which all lipid-lowering agents were discontinued. Patients taking other necessary medications unlikely to alter plasma lipoproteins at stable doses for 4 prior weeks were

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Clinical visits were set at 6- to 8-week intervals after ran- 

placebo, administered orally for an average of 4.5 years. 

were excluded from this study. 

potential; or history of alcohol or narcotic substance abuse 

study participation; premenopausal women of childbearing 

considered to pose an undue risk or contraindication to 

trolled clinical condition that may alter plasma lipids or be 

excluding nonmelanoma skin cancer; any other uncon- 

significant renal or hepatic diseases; active malignancy, 

litus with fasting plasma glucose 

ure; history of completed stroke; uncontrolled diabetes mel-

Heart Association class III or worse congestive heart fail-

or diastolic blood pressures 

planned interventions, systolic blood pressure 

4-week dietary period were used as baseline. 

XZK and placebo groups. Lipid levels measured after the 

ages. Patients were randomly assigned at a 1:1 ratio into the 

permitted to continue those medications at the same dos- 

ges. Patients were randomly assigned at a 1:1 ratio into the 

XZK and placebo groups. Lipid levels measured after the 

4-week dietary period were used as baseline. 

Table 1 
Baseline characteristics of patients in the placebo and Xuezhikang 
(XZK) groups 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 2,441)</th>
<th>XZK (n = 2,429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>58.0 ± 9.7</td>
<td>58.1 ± 9.9</td>
</tr>
<tr>
<td>Women</td>
<td>62.6 ± 7.4</td>
<td>62.9 ± 6.7</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>β Blocker</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>37%</td>
<td>36%</td>
</tr>
<tr>
<td>Converting enzyme inhibitor</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Nitrate</td>
<td>92%</td>
<td>91%</td>
</tr>
<tr>
<td>Plasma lipid levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/l (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.38 ± 0.83 (208 ± 25)</td>
<td>5.35 ± 0.67 (207 ± 26)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.34 ± 0.78 (129 ± 29)</td>
<td>3.34 ± 0.65 (129 ± 28)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.19 ± 0.36 (46 ± 15)</td>
<td>1.19 ± 0.39 (46 ± 15)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.85 ± 0.83 (164 ± 74)</td>
<td>1.85 ± 0.86 (164 ± 77)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or percent. 

HDL = high-density lipoprotein.

permitted to continue those medications at the same dos- 

ges. Patients were randomly assigned at a 1:1 ratio into the 

XZK and placebo groups. Lipid levels measured after the 

4-week dietary period were used as baseline. 

Patients with any of the following concomitant conditions 

at the screening visit of significant CV disorders, including clinically uncontrolled arrhythmias, cardiac val- 

cular disease, unstable angina, congestive heart failure, 

planned interventions, systolic blood pressure >180 mm Hg 

or diastolic blood pressures >110 mm Hg, and New York 

Heart Association class III or worse congestive heart fail- 

ure; history of completed stroke; uncontrolled diabetes mel- 

litus with fasting plasma glucose >200 mg/dl; clinically 

significant renal or hepatic diseases; active malignancy, 

excluding nonmelanoma skin cancer; any other uncon- 

controlled clinical condition that may alter plasma lipids or be 

considered to pose an undue risk or contraindication to 

study participation; premenopausal women of childbearing 

potential; or history of alcohol or narcotic substance abuse 

were excluded from this study. 

Eligible patients were randomly assigned into 1 of the 2 

groups for twice-daily treatment with XZK 600 mg or 

placebo, administered orally for an average of 4.5 years. 

Clinical visits were set at 6- to 8-week intervals after ran- 

domization and biannually thereafter. The primary study 

dend point was the occurrence of a major coronary event that 

consisted of nonfatal MI or death from coronary or cardiac 

causes. Secondary end points included total CV mortality, 

total all-cause mortality, need for coronary revasculariza-

and change in lipoprotein lipids. Plasma samples were 

drawn from properly fasted study subjects and obtained at 

baseline, 6 to 8 weeks after randomization, and at 6-month 

intervals.

Statistical analysis: Treatment effects of XZK were an-

alyzed using the prespecified primary end point of major 

coronary events. Based on published data,8 about 2,350 

intention-to-treat patients per group was sufficient to have 

90% power to detect a mean 20% decrease in coronary 

events in the treatment group compared with the placebo 

group after 5 years at p <0.05 (2 tailed) with a 15% dropout 

data. Data for baseline patient characteristics and efficacy 

and safety were summarized using descriptive statistics and 

analyzed using the chi-square test. Numerical data were 

presented as mean ± SD and 95% confidence interval and 

analyzed using the t test. Clinical end points of the trial were 

analyzed using the Kaplan-Meier method for 

the major end points in both study groups. SPSS 11.5 

software (SPSS Institute, Chicago, Illinois) was used for 

statistical analysis.

Results

This trial was carried out from May 1996 to December 2003 

in 65 hospitals in China, led by the Cardiovascular Institute 

and Fuwai Hospital at the Chinese Academy of Medical 

Sciences. Patients (3,986 men, 884 women) were randomly 

assigned at a ratio of 1:1 into the XZK (n = 2,429) and 

placebo (n = 2,441) groups. The study plan was to enroll 

4,700 patients with 2 interim analyses as prespecified and to 

discontinue the study upon detection of a significant differ-
ference for the primary end point between the drug-treated and placebo groups. Because the second interim analysis showed \( p < 0.05 \) for the primary end point, the study was discontinued in June 2003. Mean duration of treatment was 4.5 years.

The XZK and placebo treatment groups were well matched at baseline for plasma lipids, concomitant medications, CV risk factors, and other baseline characteristics (Table 1). Mean LDL cholesterol was 129 mg/dl in both groups at baseline, and 98% of patients completed the study.

Patients treated with XZK showed a highly significant (\( p < 0.001 \)) decrease in frequency of major coronary events, with 10.4% in the placebo group compared with 5.7% in the XZK-treated group. Thus, treatment with XZK produced striking relative and absolute decreases of, respectively, 45% and 4.7% in major coronary events compared with placebo. These improved outcomes in XZK-treated patients increased progressively during the course of the trial (Figure 1). Treatment with XZK during a 4-year period appeared to have prevented 47 major (17 fatal, 30 nonfatal) coronary events. Moreover, the XZK-treated group experienced highly significant relative decreases of 62% in the occurrence of nonfatal MI and 32% in fatal coronary events (Table 2). These patients also experienced a highly significant decrease of about \( \frac{1}{3} \) in both CV and total mortality compared with those treated with placebo. Patients treated with XZK also experienced a \( \frac{1}{2} \) decrease in the need for coronary revascularization, which was 2.8% compared with 4.2% in placebo-treated patients. No significant differences were observed for other measures, except for deaths caused by cancer (Table 2); 29 patients experienced cancer-related death in the placebo group compared with 13 in the XZK-treated group.

XZK produced significant decreases in levels of total and LDL cholesterol and triglycerides and increases in high-density lipoprotein cholesterol compared with placebo (Table 3). These differences were significant (\( p < 0.05 \)) by 6 to 8 weeks after randomization, and were maintained over the study duration. Treatment with XZK also produced a significant (\( p < 0.001 \)) decline in plasma total cholesterol of 13% from baseline compared with only a 2% decrease in the placebo group. LDL cholesterol was diminished significantly by 20% in the XZK-treated group compared with 3.5% in placebo-treated patients. A significant (\( p < 0.01 \)) 4.2% increase in high-density lipoprotein cholesterol was observed in the XZK group, with no change in the placebo group. No treatment-related serious adverse events or deaths were reported during the study period, and XZK appeared to be well tolerated by patients. Total adverse experiences and discontinued participation because of these or all causes were similar in both groups. Mild transient gastrointestinal side effects were reported similarly in both groups. Changes in laboratory findings did not differ between the 2 treatment groups. Minor occasional and transient increases in serum transaminase and creatine kinase were observed in both groups.

Discussion

Most large clinical trials with statin therapy examined the impact of about a 25% to 40% fall in LDL cholesterol on the occurrence of CV events and mortality. This relation appears to be greater in patients with rather high levels of LDL cholesterol. The first placebo-controlled multicenter trial with a statin showed a significant decrease in both all-cause mortality and CV events in simvastatin-treated patients with increased serum cholesterol.10,11 However, because patients with coronary atherosclerosis commonly have rather modest increases in LDL cholesterol,12,13 more information is needed to develop strategies to identify and treat these patients effectively.

This trial was designed to test the efficacy and safety of XZK in a Chinese patient population with previous MI and average levels of LDL cholesterol to test the impact of this therapy on recurrent coronary events. Results showed that treatment of this study population with XZK produced profound changes in both lipoprotein lipids and the number of recurrent coronary events. The decrease in these events found in the present study appear to exceed those reported with statin monotherapy in a similar trial of western patients enrolled in the Cholesterol and Recurrent Events14 and other statin trials10–13.
Table 3

Effects of Xuezhikang (XZK) on plasma lipids at baseline and at the end of 3.5 years of treatment (intention-to-treat population)

<table>
<thead>
<tr>
<th>Plasma Lipids, mmol/l (mg/dl)</th>
<th>Placebo</th>
<th>XZK</th>
<th>% Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.38 ± 0.83 (208 ± 31)</td>
<td>5.22 ± 0.89 (202 ± 34)</td>
<td>10.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.34 ± 0.78 (129 ± 25)</td>
<td>3.23 ± 0.83 (125 ± 26)</td>
<td>3.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.19 ± 0.36 (46 ± 15)</td>
<td>1.19 ± 0.36 (46 ± 15)</td>
<td>0%</td>
<td>0.98</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>4.19 ± 0.73 (164 ± 74)</td>
<td>4.03 ± 0.88 (155 ± 78)</td>
<td>4.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.85 ± 0.48 (164 ± 74)</td>
<td>1.75 ± 0.64 (144 ± 63)</td>
<td>5.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.9 ± 1.6</td>
<td>4.6 ± 1.6</td>
<td>6.7%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD unless otherwise specified.

* Differences in mean plasma lipids between XZK- and placebo-treated patients.

Appendix

Investigators: Fuwai Hospital (Y.S. Xu, D.F. Gu, X. Jia, Z. Chen, J.L. Sun, J. Chen); Peking University Shougang Hospital (X.H. Yu, J.H. Wang, N. Wang, R.P. Zheng, S.H. Zhang); Heilongjiang Yichun Forest Industry Central Hospital (C.X. Liu, L.H. Sun, Y.C. Zhao, Y. Lin, J.B. Huang); Capital Medical University Beijing Chaoyang Hospital (D.Y. Hu, X.C. Yang, Y.Z. Liu, M.M. Gao, P. Zhang); LiaoNeing People’s Hospital (C.X. Deng, Y. Liu, Z.Q. Li, Y.Q. Shi, T.S. Hu); Chongqing Medical University First Hospital (Y.Z. Chen, S. Tan, W.R. Zhao, G.L. Deng, W.J. Huang); Hebei Baoding Second Hospital (J.C. Zhang, H. Yu, Q.S. Shi, X.Z. Wang, B. Jiang); Shangdong University Qilu Hospital (X.R. Pan, L. Li, P.L. Pu, M.Q. Shu, Q.L. Xu); Peking University First Hospital (J.H. Zhang, W.H. Ding, L. Li, J.J. Yang, J.L. Su); Anshan Steel Company Tiedong Hospital (W.D. Zhao, X. Liu, L.J. Li, J.F. Yang, Q.S. Wang); Institut of Cardiology, Tianjing Medical University Second Hospital (T.G. Huang, L.F. Li, J.L. Zhou); Peking University Third Hospital (J.X. Guo, W.H. Li, Z.P. Li); Beijing Fangshan First Hospital (X.G. Zhang, X.M. Meng, Y.W. An); Xi’an Jiaotong University First Hospital (J. Shu, L.T. Ma, H. Ge, M.J. Zhang, Z.R. Lv); Beijing Haidian Hospital (J.H. Li, J.W. Yang, L. Zhang); Jiangsu People’s Hospital (Y.L. Cheng, J.G. Chen, C.W. Zhou, H.H. Zhang); Harbing Medical University First Hospital (Y.L. Huang, X.F. Qu, J.J. Li, H. Guo); Shangdong Dezhou Hospital (G.X. Wang, S.Z. Hao, S.J. Li, H.S. Chang); Beijing Military Area General Hospital (S.M. Zhou, H.Q. Liang, S.J. Cao, J.G. Liu); Shanxi Hanzhong People’s Hospital (J. Yang, M.Y. Zhao, Y. Lv, S.L. Xu); Central South University Xiangya Second Hospital (Z.L. Wang, S.P. Zhao, X.P. Li, X.L. Luo); Beijing Jiangong Hospital (Y.P.


Monitoring offices: National Center for Cardiovascular Diseases (NCCD), China.


Associate laboratory and quality control for serum lipid measurement: Ministry of Health Institute of Gerontology.


