

China Coronary Secondary Prevention Study (CCSPS) - Lipid-regulating therapy with Xuezhikang for Secondary Prevention of Coronary Heart Disease

China Coronary Secondary Prevention Study Group

[Abstract]

Objective To determine whether lipid-regulating therapy with Xuezhikang reduces the risk of coronary events and offers an impact on all-cause mortality in Chinese patients with coronary heart disease (CHD) with relatively low cholesterol levels compared with that of western population. **Methods** This study was a multicentre, randomized, double-blind, placebo-controlled, long term follow-up clinical trial designed to compare the effect of Xuezhikang capsule and placebo and conducted at 65 centers in 19 *provinces* in China. A total of 4870 CHD patients aged 18 to 75 years with definite myocardial infarction history who had baseline cholesterol levels between 4.40 and 6.47mmol/L(170-250mg/dl) were recruited between May 1996 and December 2003. Patients were randomly assigned to receive treatment with Xuezhikang capsule, 0.6g Bid or matching placebo and follow-up period was mean 4 years. The primary endpoint were coronary events, including nonfatal myocardial infarction and CHD death. *The secondary endpoint, analysed by the time of first events, was total mortality. Other events, also analysed by the time of first events, includ tumour, stroke, and the need for intervention procedure of percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG).* **Results** During 4-years follow-up period, Xuezhikang significantly reduced the risk of the primary endpoint by 45.1% ($P<0.0001$) compared with placebo group(5.72% vs 10.41%) because the relative risk reduction of CHD death and nonfatal myocardial infarction was 31.0% ($P=0.0048$) (3.79% vs 5.49%) and 60.8% ($P<0.0001$) (1.93% vs.4.92%) respectively in patients who received Xuezhikang compared with those who received placebo. *Of the secondary end-point, There was a 33.0%($P=0.0003$) risk reduction of all-cause mortality in treatment group than in placebo group(5.19% vs. 7.74%), in which 54.7% ($P=0.0138$) risk reduction for tumor death. The incidence of stroke, tumour, and the need for PCI/CABG) were also decreased by 31.1% ($P=0.0004$) with Xuezhikang than with placebo (6.92% vs 10.04%). Xuezhikang reduced the need for PCI/CABG by 33.3% ($P=0.0097$) compared with placebo group(3.01% vs 4.51%) .* Adverse effects and abnormal laboratory parameters did not differ significantly between the two groups. **Conclusion** Compared with placebo, Xuezhikang can significantly decrease the incidence of nonfatal myocardial infarction and CHD death, as well as the need for PCI/CABG , tumor death and all-cause mortality in Chinese CHD patients. The study indicate that lipid-regulating therapy with Xuezhikang in Chinese CHD patients offers great benefits.

[Key Words] Xuezhikang capsule; blood lipid; coronary heart disease; secondary prevention

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The close relationship between the risk of coronary heart disease (CHD) and the total serum cholesterol level (TC) and low-density lipoprotein cholesterol level (LDL-C) has already been revealed by epidemiologic studies. Several international large scale clinical trials had demonstrated that decreases in the serum concentration of TC and LDL-C in western patients with coronary heart disease can reduce the recurrent coronary events^[1-3]. But no such studies had been conducted in Chinese or even oriental population. Oriental population, especially Chinese, has a lower TC and LDL-C level, but a higher TG and HDL-C level compared with western population. Moreover, Chinese diet, life style and genetics-inherited differ significantly from western people. Saturated fat acid and cholesterol in Chinese food is relatively less, also rates of CHD mortality and morbidity in Chinese people are lower. But It is generally believed that Chinese people have higher rates of hypertension and stroke than western population. In previous several large-scale trials concerned, investigators used statins-agents, in this study we use Xuezhikang capsule^[4], a traditional Chinese medicine which contains extracts from red koji. To evaluate the effect of Chinese lipid-regulating drug on the secondary prevention of CHD is of great significance in China and abroad. CCSPS was a coronary secondary prevention Study in Chinese CHD patients. Patients were eligible for enrollment in the study if they had a TC level of 4.40~6.47mmol/L (170-250mg/dl) lower than that of patients in previous trials, covering lipid profile of most Chinese patients. Therefore, this study is able to demonstrate the efficiency of lipid regulation on the prevention of CHD events in this particular population.

Materials and methods

Study Design.

The study was a multicentre, randomized, double-blind and placebo-controlled clinical trial.

66 centers (65 medical center and 1 quality control center) in 19 cities and provinces all over China participated in this study. The primary main objective was to investigate whether cholesterol lowering with Xuezhikang capsule would reduce recurrent nonfatal myocardial infarction (MI) and fatal CHD events. Fatal CHD events included fatal MI, sudden death and other coronary death. The secondary end point included *all-cause mortality. Other events, included tumour, stroke, need for intervention procedure of percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), and all-cause hospitalization, was also analysed by the time of first events. The study also evaluated the* treatment effects on measured lipid level throughout the trial, as well as the long term effect and safety of Xuezhikang.

Patients who were eligible for this study were randomly assigned to receive either Xuezhikang capsule, 0.6g twice per day (Beijing WBL Peking University Biotech Co., Ltd) or matching placebo. During the study, it was forbidden to take other medications which were to influence the blood lipid level, but previous treatment drug against CHD, hypertension or other complications were continued. The dietary and lifestyle adjustments was kept same throughout the study. Patients were followed up and registered at 6-8 weeks after randomization and every 6 month thereafter. At each visit, the procedures include comprehensive counselling and determination of serum lipid level and safety parameters. During the follow-up, all coronary events including non-fatal MI, fatal MI, CHD sudden death and other CHD death were registered in time. *Other events including stroke or other cardiocerebral vascular events, the need for PCI and/or CABG, cancer, accidental death, suicide, other cause death and all-cause hospitalization.* Patients were to continue study medications and follow up if adverse events

happened were generally endurable. Fill out adverse events forms including symptoms of adverse events or lab abnormalities and keep observing until normal. Due to adverse events of study medications, patients were to discontinue treatment at the discretion of the leader of the research center and these were to be reported to the leading medical center of the trial. Severe or fatal adverse events must be reported within 24 hours. An evaluation board of clinical end-point events or an evaluation board of adverse events monitoring board blinded to the assignment of the patients reviewed all cardiovascular events and adverse events.

Inclusion criteria

We recruited men or women with previous history of acute MI during 28 days to 5 years before enrollment. According to the time of outbreak of MI, patients were classified into two groups. Patients experiencing MI previously between 3 months to 5 years before randomization was assigned to A group, between 28 days to 3 months to B group. Exclusion criteria included: age over 75 years or younger than 18 years; sustained systolic blood pressure (SBP) of more than 180 mmHg or diastolic blood pressure (DBP) of more than 110 mmHg despite medical therapy; NYHA cardiac function grade of more than II; consistently elevated fasting blood glucose level ≥ 11.1 mmol/L (200mg/dl) despite drug therapy; Severe arrhythmia, eg high grade atrioventricular block, paroxysmal ventricular tachycardia or sick sinus syndrome; Evident hepatic or renal dysfunction or recent hepatitis history; comorbidities that may impact lipid metabolism, such as malignancy, thyroid disorders, tuberculosis or hormone therapy; psychiatric disorders, such as depression, mania and other psychiatric disorders that might cause patients' noncooperation; patients who can not consistently collaborate with the investigators; Elective CABG or PCI (patients with previous history of CABG or PCI were enrolled);

significant enlargement of heart; Premenopause women except sterilization; Severe unstable angina; severe valve heart disease which impact hemodynamics; history of stroke; Alcoholic or drugger; Tendon xanthoma patients.

Blood lipid (first test) of MI survivors were assessed at a referral laboratory. Patients who had a TC level between 4.40 mmol/L and 6.47 mmol/L (170-250mg/dl) and TG level ≤ 4.52 mmol/L (400mg/dl) were given a bottle of placebo (35 capsules) for wash-out, one capsule after each dinner for 28 days, meanwhile other lipid lowering therapies were forbidden. Patients handed in the original bottle when follow-up visits 28 days later. Their physicians were to check residuary capsules and calculate compliance using the formula below:

$$\text{Compliance} = \frac{35 - \text{residual capsules}}{\text{Days of treatment}} \times 100\%$$

The second measures of serum lipid levels were assessed in patients with a compliance between 80%-120%. The average value (X) of the first and second results was calculated. Patient whose second lipid levels was in the range of $X \pm 12\%X$ was enrolled and the second result was taken as the baseline level. If not, a third test was performed, and the average of the three results was taken as the baseline data. Patients with isolated hypertriglyceridemia were excluded. Patients with high TG level of below 4.52 mmol/L (400mg/dl) were enrolled.

Randomization and statistical analysis

The study was designed as a randomized, double-blind, controlled trial. Sample size was calculated using rate comparative single-side test method to provide the study with 90% power for a single-side, α -level of 0.05, assuming a 16% accumulative rate of primary end-point events, predicted events reduction of 20% and follow-up rate of 85% at 5 years in placebo group. It is estimated that a total sample of 4700 patients should be recruited to the study. The baseline data was monitored and managed using

Powerbuilder software during the study. Data of enrollments, follow-up, termination or clinical events were reported so that corresponding measures of quality control could be taken in time.

Quality control of serum lipid measurement.

The serum lipid was measured using the method recommended by the Chinese Society of Laboratory Medical. Standard sample was provided by the central lab of the study whose quality control has been conducted by American CDC since 1982. Each associated lab accepted inter-laboratory assessments by central lab regularly. Associated labs can use their own intralaboratory quality control serum and assessed 20 times repeatedly before formal determination to evaluate precision and determine quality control border. Intralaboratory coefficient of variation (CV) standard was: TC:CV \leq 5%, TG: CV \leq 5%~8%, HDL-C: CV \leq 5%~8%. Only labs meeting this criteria can participate in the study. Labs were assessed every half year, criteria of accuracy (CV%), TC \leq 5%, TG \leq 5%~8%, HDL-C \leq 5%~8%; precision (bias%), TC \leq \pm 5%, TG \leq \pm 5% ~ 8%, HDL-C \leq \pm 10% was required. All measurements staff were trained using a uniform manipulation manual to ensure an standard operation procedure [6].

Organization.

The principal investigator was responsible for all work of the study. A special organization of project team was set up. The study steering committee reviewed study protocol and supervised the progress of the study; ethical committee was responsible for protecting the interests of participants; the project executive committee handled daily study work. The executive committee subdivided into double-blind randomization and data collection group, clinical quality control and end-point assessment group, data safety monitoring group, lipid measurement quality control group and secretary group. Execution and monitor team consisted of project executive committee and

secretary group was responsible for daily work.

Result

Baseline characteristics and follow-up

Between November 1996 and December 2000, a total of 4870 patients were recruited and were randomized assigned to receive either Xuezhikang (n=2429) or placebo (n=2441). The two groups were well balanced with regard to baseline characteristics, concurrent medication and baseline lipid level (Table 1,2). The average follow-up period was 4 years with a longest period of 7 years and 2 months at the termination of the study on December 31,2003. Totally 93 patients were lost to follow, of which 46 were in treatment group, 47 in control group, thus the lost to follow rate was 1.99%. *Confirmation of whether the patients were alive or dead was obtained in other cases at the end of the study.*

Change of Serum Lipid

The patients involved in CCSPS had a relatively low TC and LDL-C level, high TG and HDL-C level, which reflected the characteristic of Chinese population. The baseline TC level in Xuezhikang group was 5.36mmol/L (207.2mg/dl) and decreased significantly after 6-8 weeks of treatment and then stabilized. TC level in Xuezhikang group by average 3.5 years was 13.2% lower compared with control group (2.9%) with a baseline TC level of 5.37mmol/L (207.6mg/dl). The baseline LDL-C level in Xuezhikang group was 3.34mmol/L (129.1mg/dl) and reduced 20.2% after average 3.5 years of treatment, while this number in control group was 3.5%. Xuezhikang group had baseline TG level of 1.85mmol/L (164.2mg/dl) and reduced 15.0% after average 3.5 years of treatment while this number in control group was 5.3%. The baseline HDL-C level of Xuezhikang group was 1.19mmol/L (45.9mg/dl) and increased 4.9% after 3.5 years while this number in control group was 0.7%. Xuezhikang capsule was significantly more efficient in decreasing TC, LDL-C and TG (P<0.001), as well as increasing

HDL-C ($P=0.006$) compared with placebo.

Clinical Events

The primary end-point of CCSPS was CHD events, including nonfatal and fatal acute MI, sudden CHD death and other CHD death. The result of the study showed Xuezhikang decreased the risk of CHD events by 45.1% (**$RR:0.537$, $95\%CI:0.437-0.660$, $P<0.0001$** , table 3) compared with placebo. The benefit was observed after half year of treatment (figure 1-3) and keep increasing along with extension of follow-up period. There were 47(1.93%) cases of non-fatal acute MI in Xuezhikang group, and 120(4.92%) cases in control group, risk reduction was **60.8% ($RR:0.382$, $95\%CI:0.272-0.535$, $P<0.0001$)**; 19(0.78%) patients in Xuezhikang group and 28(1.15%) in control group died from fatal acute MI, risk reduction was **32.2% ($RR:0.671$, $95\%CI:0.373-1.202$, $P=0.1928$)**; 51(2.10%) patients in Xuezhikang group and 67(2.74%) in control group had CHD sudden death, risk reduction was **23.4% ($RR:0.749$, $95\%CI:0.520-1.078$, $P=0.1432$)**; 22 (0.91%) cases of other CHD death were observed in Xuezhikang group, and 39(1.60%) cases in control group, risk was reduced by 43.1% (**$RR:0.557$, $95\%CI:0.330-0.940$, $P=0.0299$**); 92(3.79%) patients in Xuezhikang group compared with 134 (5.49%) in control group underwent other cause CHD deaths, Xuezhikang reduced the risk of total CHD deaths by 31.0% (**$RR:0.677$, $95\%CI:0.519-0.883$, $P=0.0048$**).

The secondary endpoint was all-cause mortality, 126(5.19%)patients in Xuezhikang group and 189(7.74%) in control group died from all causes, the risk was 33.0% lower ($RR:0.656$, $95\%CI:0.523-0.822$, $P=0.0003$) in Xuezhikang group than in placebo controls. The beneficial effect of Xuezhikang in reducing death events can be observed after a half year of treatment (figure 4), and show a increasing significance along with follow-up period.

63 (2.59%) patients in Xuezhikang group

and 85 (3.48%) placebo controls underwent stroke, resulting in 25.6% reduction in risk of stroke for Xuezhikang compared with placebo ($P=0.1023$); 32(1.32%) patients in Xuezhikang group and 50(2.05%)placebo control had a tumor, risk reduction of tumor was 35.6% ($P=0.0501$), in which 13 (0.54%) patients in Xuezhikang group and 29 (1.19%)placebo controls had fatal tumor, resulting in a statistically significantly reduction of 54.6% in risk of fatal tumor for Xuezhikang (**$RR:0.437$, $95\%CI:0.227-0.841$, $P=0.0138$**); and 73(3.01%) patients in Xuezhikang group compared with 110 (4.51%) placebo controls underwent PCI or CABG with risk reduction of 33.3% ($P=0.0097$) in Xuezhikang group. Total 168 (6.92%) patients in Xuezhikang group and 245 (10.04%)in control group had above three events, total risk reduction was 31.1% ($P=0.0004$). 126(5.19%) patients in Xuezhikang group and 189(7.74%) in control group died from all causes, the risk was 33.0% lower ($P=0.0003$) in Xuezhikang group than in placebo controls. The beneficial effect of Xuezhikang in reducing death events can be observed after a half year of treatment (figure 4), and show a increasing significance along with follow-up period.

Safety

There were 43 (1.77%) reported adverse events in Xuezhikang group and 39(1.60%) in control group, there was no significant difference ($P=0.6842$). Common adverse events in both groups included gastrointestinal disorders, allergic reaction, mental-neurological symptoms, myoparesis and myodynia. 5(0.2%) cases of male sexual disorders were reported in control group while none in Xuezhikang group ($P=0.0253$). 37 (1.52%) patients in Xuezhikang group withdrew treatment due to adverse events compared with 28(1.15%) in control group, there was no significant difference between two groups. In laboratory measures, 15(0.62%) patients in Xuezhikang group and 22 (0.90%)

in control group had elevations in alanine aminotransferase (ALT) level of 3 times the upper limit of normal (ULN). There were no elevations in creatine kinase level of 5 times and 10 times ULN in the Xuezhikang group, and there were 2 (0.08%) and 1 (0.04%) reported cases in control group respectively. 124(5.10%) patients in Xuezhikang group had elevations in blood urea nitrogen (BUN) level of more than ULN compared with 131 (5.37%) cases in control group, but no reported cases had elevations to more than 2 times the ULN; 104(4.28%) patients in Xuezhikang group and 89 (3.65%) in control group had elevations in creatinin (Cr) level of ULN, but no elevations to more than 2 times the ULN. Laboratory abnormalities in Xuezhikang group did not differ significantly from that of placebo.

COMMENT

CCSPS study demonstrated lipid-lowering therapy with Xuezhikang in Chinese CHD can reduce significantly the risk of coronary events. The results of the study suggest that treating 1000 Chinese CHD patients with Xuezhikang for 4 years would reduce 47 CHD events, including 17 CHD deaths, 30 non-fatal acute MI, 15 PCI or CABG and 9 strokes. In addition, the benefits associated with Xuezhikang on non-cardiovascular events were demonstrated that Xuezhikang would reduce 25.6 cases of all-cause death per 1000 patients. Meanwhile, No more clinical adverse events and laboratory abnormalities occurred in Xuezhikang group compared with that of placebo.

Previous study indicated pravastatin therapy in elder patients was associated with an increased risk of gastrointestinal tumors, the rate of newly diagnosed tumor raised 25%^[5]. But meta-analysis on the rate of tumor in Previous CHD prevention studies with statins showed there were no elevations in the risk of tumor in all cases with statins, and no evidence showing increase of non-heterogenic risk in any clinical

trial with statins. But these trials did not mention that statins could reduce the risk of tumour death. Tumour deaths were reported in 42 patients during CCSPS study: 29 in control group and 13 in Xuezhikang group. The risk of tumour death were lowered by 55% in Xuezhikang group compared with placebo ($P=0.00138$). Tumor were totally reported in 82 patients during the study: 32 cases in Xuezhikang group and 50 cases in control group, risk reduction was 36% ($P=0.0501$). Although some basic research had demonstrated that lipid-regulating agents may depress some kinds of tumor cells, but this is the first time to be revealed in large scale clinical trial.

Although CCSPS study showed Chinese CHD patients with a lower lipid level than western population had a lower risk of various clinical events compared with western population, still could lipid lowering with Xuezhikang provide great clinical benefit in Chinese CHD patients. Moreover, CCSPS study indicated that the benefit was more significant than that in western CHD patients with statins. The mean baseline TC and LDL-C level in CCSPS is in the lowest range of those classic international secondary prevention trials with statins and HDL-C level in the highest. Xuezhikang treatment using conventional recommended dosage can offer satisfactory lipid regulatory effect. Compared with 4S, CARE and LIPID study, CCSPS had a less reduction in TC and LDL-C but a greater reduction in all-cause mortality, CHD events and the need for PCI/CABG. A significant risk reduction of Xuezhikang in end-point events compared with that of pravastatin, 40mg/d, in CARE and LIPID study suggests that it is not sufficient to assess clinical effects just according to LDL-C lowering.

The U.S. National Cholesterol Education Program (NCEP) Adults Treatment Plan III (ATPIII) had brought forward a series of recommendations on the goal of dyslipidemia treatment^[6], but all based on chemical statins.

The ultimate goal of lipid lowering treatment is to reduce the risk of clinical events. Only 10mg of Lovastatin contained in daily dosage of Xuezhikang could not explain its clinical benefit. Xuezhikang, a modern Chinese traditional medicine preparation, also contains many other substances good to human body which may play a great synergistic role in reducing clinical adverse events in CHD patients. Previous studies had shown that Xuezhikang could provide other effects with regard to prevention and treatment of CHD events beyond lipid lowering^[7]. CCSPS study also demonstrated that it is not appropriate to evaluate clinical benefits associated with Xuezhikang just by the extent of lipid lowering.

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Table 1. Baseline characteristics, history and medication of patients involved*

	Control group(n=2441)	Treatment group(n=2429)
Basic characteristics (n)		
Gender male	1990	1996
female	451	433
age(y)		
male	58.0±9.7	58.1±9.9
female	62.6±7.4	62.9±6.7
BMI	24.7±2.8(2430)	24.8±2.9(2412)
Blood pressur (mmHg)		
SBP	128.6±17.6(2441)	129.0±17.4(2427)
DBP	79.9±10.1(2441)	80.1±10.4(2427)
Heart rate	74.3±9.0(2438)	74.5±9.3(2427)
History and medication n (%)		
Smoke	865(35.44)	824(33.92)
Alcoholic	356(14.58)	344(14.16)
Type 2 diabetes	285(11.68)	306(12.60)
Hypertension	1341(54.94)	1363(56.11)
Aspirin	2307(94.51)	2301(94.73)
β blocker	1348(55.22)	1377(56.69)
ACEI	1211(49.61)	1182(48.66)
nitrate	2241(91.81)	2211(91.03)
Calcium blocker	905(37.07)	886(36.48)

*Data are expressed as mean ± SD unless otherwise specified.

Table 2 Baseline lipid level of enrolled patients (x ± s, mmol/L)

	Control group	Treatment group
TC	5.37±0.66	5.36±0.68
LDL-C 数)	3.34±0.74	3.33±0.73
TG	1.85±0.81	1.85±0.84
HDL-C	1.19±0.39	1.19±0.37

Table3 Events in different groups

Event	Control group	Treatment group	Intergroups difference (±%)	P value	Relative risk	95%CI
CHD events (%)						
Non-fatal AMI	120(4.92)	47(1.93)	-60.77	<0.0001	0.382	0.272-0.535
Fatal AMI	28(1.15)	19(0.78)	-32.17	0.1928	0.671	0.375-1.202
Sudden death	67(2.74)	51(2.10)	-23.36	0.1432	0.749	0.520-1.078
Other CHD death	39(1.60)	22(0.91)	-43.13	0.0299	0.557	0.330-0.940
Total	254(10.41)	139(5.72)	-45.05	<0.0001	0.537	0.437-0.660
Secondary events (cases/1000patients)						
Survival from stroke	72(29.5)	51(21.0)	-28.81	0.0886		
Death of stroke	13(5.3)	12(4.9)	-7.55	0.8508	0.909	0.415-1.993
Total stroke	85(34.8)	63(25.9)	-25.57	0.1023		
Survival from tumor	21(8.6)	19(7.8)	-9.30	0.7628		
Death of tumor	29(11.9)	13(5.4)	-54.65	0.0138	0.437	0.227-0.841
Total tumor	50(20.5)	32(13.2)	-35.61	0.0501		
PCI/CABG	110(45.1)	73(30.1)	-33.26	0.0097		
Other						
cardiovascular death	2(0.8)	1(0.4)	-50.00	1.0000	0.487	0.044-5.367
Suicide	2(0.8)	0(0.0)	-100.00	0.4999		
Accidental violent death	1(0.4)	1(0.4)	0.00	1.0000	0.975	0.061-15.593
Other death	8(3.3)	7(2.9)	-12.12	0.8033	0.851	0.308-2.347
All-cause death	189(7.74%)	126(5.19)	-32.95	0.0003	0.656	0.523-0.822

Figure 1 CHD events in two groups

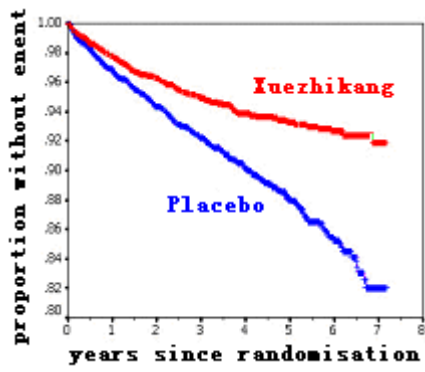


Figure 3 Acute MI events in two groups

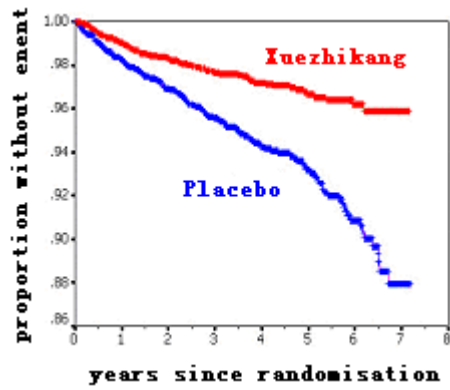


Figure 2 CHD death in two groups

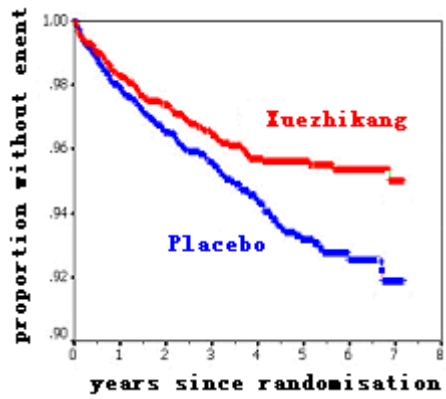


Figure 4 All-cause mortality in two groups

