Effect of Statins and Calcium Channel Blockers on All-Cause Mortality and Cardiovascular and Cerebrovascular Disease Mortality in 958 Chinese Hospitalized Patients with Peripheral Arterial Disease after 13 Months of Follow-up

Xiankai Li,[a] Jue Li,[a] Thach Nguyen,[b] Mingzhong Zhao,[a] Liqiang Zheng,[a] Buaijiaer Hasimu,[a] Jinming Yu,[a] Yingyi Luo,[a] and Dayi Hu*,[a]

[a]*Heart, Lung and Blood Vessel Center, Tongji University, 1239 Siping Road, Shanghai, 200092, China and* [b]*St. Mary Medical Center, Hobart, IN 46410, U.S.A.*

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Many clinical trials showed that antiatherosclerotic drugs could significantly reduce the mortality in patients with peripheral arterial disease (PAD). The aim of this study was to evaluate the effect of statins, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), antiplatelet drugs, beta-blockers, diuretics, and hypoglycemic drugs in hospitalized Chinese patients with PAD. Nine hundred fifty-eight hospitalized patients (mean age 72.35 ± 9.39 years, 472 male) with PAD were continuously enrolled in a cohort study from June to December 2004 and followed up for 13.31 ± 0.11 months. Cox's proportional hazards model analysis of mortality adjusted for other risk factors in relation to diuretics, statins, CCBs, and risk factors showed that diuretic use [relative risk (RR) 1.682, 95% confidence interval (CI) 1.184–2.389] was independently associated with an increased all-cause mortality rate, but statins (RR 0.457, 95% CI: 0.306–0.681) and CCBs (RR 0.677, 95% CI: 0.469–0.978) were independently associated with a decreased all-cause mortality rate during 13 months of follow-up. Statins (RR 0.459, 95% CI: 0.257–0.820) and CCBs (RR 0.443, 95% CI: 0.243–0.810) were significantly associated with a decreased cardiovascular and cerebrovascular mortality rate during 13 months of follow-up. Statins and CCBs were independent protective factors against all-cause mortality and cardiovascular and cerebrovascular disease mortality, while diuretic use was an independent risk factor for all-cause mortality in patients with PAD during the 13 months of follow-up.

*To whom correspondence should be addressed: Heart, Lung and Blood Vessel Center, Tongji University, 1239 Siping Road, Shanghai, 200092, China. Tel. & Fax: +86-21-6598-3185; E-mail: jueli59jp@yahoo.co.jp

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INTRODUCTION

Peripheral arterial disease (PAD), which is caused by atherosclerotic occlusion in the arteries of the legs, is an important manifestation of systemic atherosclerosis. PAD is associated with considerable general and cardiovascular morbidity and mortality. The age-adjusted prevalence of PAD is approximately 12%.[1)] One US study estimated a prevalence of more than 5 million adults.[2)] The risk of death is high whether or not PAD is symptomatic. Patients with critical PAD face an annual mortality rate of 25%, which is overwhelmingly due to myocardial infarction and ischemic stroke.[3)] The ankle-brachial index (ABI), a ratio of ankle systolic blood pressure to brachial systolic pressure, is widely used in clinical practice to assess the potency of the lower arterial system and to screen for PAD. Recently, many clinical trials have shown that drugs, especially those that are either antiatherosclerotic or statins, could significantly reduce the mortality rate in patients with PAD. Other drugs used to control risk factors for cardiovascular and cerebrovascular disease could also reduce mortality. The purpose of this study was to evaluate whether or not those drugs could reduce the mortality rate in Chinese patients with PAD.

MATERIALS AND METHODS

Patients —— This cohort study was designed to investigate the relationship between drug therapy for PAD and all-cause mortality and cardiovascular and cerebrovascular disease mortality. Our cohort study population consisted of 958 men and women aged from 36 to 95 years, who had PAD and were hospitalized in 29 hospitals, such as Tongji Hospital affiliated with Tongji University of Shanghai, and Beijing Tongren Hospital affiliated with Capital Medical University of Beijing. They were continuously enrolled from June to December 2004. They were inpatients from the cardiology, cardiac care unit (CCU), intensive care unit (ICU), endocrinology, nephrology, vascular disease departments, *etc.*, and were hospitalized because of hypertension, dyslipidemia, diabetes mellitus (DM), acute coronary syndrome, or renal disease. Those who had renal failure or ketoacidosis were excluded. The patients with PAD used statins, or calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), antiplatelet drugs, beta-blockers, diuretics, or hypoglycemic drugs to treat dyslipidemia, hypertension, and DM, *etc*. The doses of all drugs were conventional. Drugs such as simvastatin or lovastatin and other statin drugs were registered as statins. This study was approved by the Ethics Committee of Tongji University and informed consent was obtained from the participants.

Measurement of Baseline Characteristics —— Smoking habits were recorded, and were considered positive in those who smoked at least on cigarette per day for at least 1 year. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), serum creatinine (Scr), uric acid (UA), and blood glucose (BG) levels were measured using standard laboratory techniques. Dyslipidemia was defined as TC $>$ 5.7 mmol/l, TG $>$ 1.7 mmol/l, LDL-C $>$ 3.6 mmol/l or HDL-C $<$ 0.9 mmol/l, or treatment with antihyperdyslipidemic agents. Type 2 DM was defined as: a fasting plasma glucose concentration of $>$ 7.0 mmol/l in the absence of treatment; a fasting plasma glucose concentration of $\geq$ 11.0 mmol/l, 2 hr after a 75 g oral glucose load; and current treatment with hypoglycemic drugs. All selected patients had no history of ketoacidosis. The presence of underlying coronary heart disease (CHD) was defined as a history of confirmed myocardial infarction, evidence of prior myocardial infarction by electrocardiogram, or a history of a prior coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting). Hypertension was defined as systolic blood pressure of $\geq$ 140 mmHg and/or diastolic blood pressure of $\geq$ 90 mmHg. Blood pressure was measured on 2 different days without any drugs or current use of antihypertensive drugs to control hypertension.

Measurement of ABI —— All participants underwent duplicate resting measurements of the blood pressure to calculate the ABI. The ABI is the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure. The ABI used here was the minimum of the two values, and was measured by trained technicians according to a standard protocol. Briefly, the participant was asked to lie flat on an examination table, and after 5 min of rest, standard brachial blood pressure cuffs were applied to each upper arm and each ankle. After palpation of the brachial and posterior tibial arteries, ultrasound gel was applied, and a standard Doppler stethoscope (5 MHz; Nicolet Vascular, Elite 100R, St. Nicolet Vascular, Madison, WI, U.S.A.) and standard mercury manometer were used to assess systolic blood pressure in each brachial artery and in each posterior or anterial tibial artery in rapid succession. These measurements have been shown to be reliable between observers, stable over time, and highly correlated between the left and right legs. In the case of a missing ABI value in one leg, the value from the other was used, and a missing brachial artery pressure value in one arm was addressed in the same manner. Accordingly, in the case of a missing artery pressure value (posterior or anterial tibial artery) above the ankle in one leg, the other was used for calculation of the side-specific ABI. Patients with ABI $<$ 0.9 were defined as having PAD.

Diagnosis of PAD —— The diagnosis of PAD was assessed by clinical evaluation and ABI measurements (ABI $<$ 0.9), and was confirmed by lower-limb angiography. All patients in the study had confirmed PAD. Severe PAD was defined as those with ABI $\leq$ 0.4, and mild to moderate PAD was defined as those with 0.4 $<$ ABI $\leq$ 0.9.

Identification of All-cause and Cardiovascular and Cerebrovascular Disease Deaths —— Deaths were identified through the records of the 29 hospitals or by contact with participants and their families. Causes of death were investigated using medical records and informant interviews. All materials were reviewed independently by physicians of

the ABI cohort study to confirm the cause of death. Cardiovascular and cerebrovascular disease mortality was defined as any patients who died of coronary heart disease, ischemic stroke, or hemorrhagic stroke.

Statistical Analysis —— The baseline examination of patients with PAD was performed during the period from June to December 2004. Then the patients were followed up until an end-point was reached or until December 2005. Mean follow-up time was 13.31 ± 0.11 months. Continuous variables, such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, HDL-C, LDL-C, BUN, Scr, UA, BG, and ABI, are expressed as mean ± S.D. Categorical variables are expressed as percentages. Each drug was classified into the use group and nonuse group. The relationship between each group of drug therapy to patients with PAD and mortality was calculated using χ^2 tests. Cox proportional hazards regression modeling was used to estimate the independent association (independent protective factor or risk factor) between drugs and all-cause mortality, and cardiovascular and cerebrovascular disease mortality after adjusting for gender, age, smoking history, ACEIs, ARBs, antiplatelet drugs, beta-blockers, hypoglycemic drugs, DM, stroke, dyslipidemia, and hypertension. A p value of < 0.05 was considered significant. All analyses were performed with the Statistics Package for Social Science, version 13.0.

RESULTS

Table 1 shows the baseline characteristics of 958 Chinese patients with PAD. The average age of the patients was 72.35 ± 9.39 years. The average ABI of all patients with PAD was 0.68 ± 0.20. The mean values of SBP, TC, LDL-C, and BG were higher than the normal values. Thus the patients with PAD also had other diseases, such as hypertension, dyslipidemia, or DM.

Four hundred seven patients used CCBs, 376 used statins, 512 used ACEIs, 92 used ARBs, 666 used antiplatelet drugs, 389 used beta-blockers, 351 used diuretics, and 397 used hypoglycemic drugs. Table 2 lists the stage of PAD and drug used by patients. Most of the patients (54.75%) had mild-to-moderate PAD and use no less than three drugs for treatment.

During a median follow-up period of 13 months, 129 patients died. Of these, 43 patients died of coronary heart disease, 9 of ischemic stroke, and 6 of hemorrhagic stroke, while the remainder died of noncardiovascular and noncerebrovascular causes. In the 13 month follow-up, the incidence of all-cause mortality among those who used statins was significantly lower than among those who did not in unadjusted analyses. The result was similar in the CCB group. However, the incidence of all-cause mortality among those who used diuretics was significantly higher than among those who did not (Fig. 1). The difference in the incidence of car-

Table 1. Baseline Characteristics of 958 Chinese Patients with PAD

Baseline characteristics	Patients with PAD
Age (years)	72.35 ± 9.39
Gender: male (n, %)	472, 49.30
Smoking habit (%)	42.6
SBP (mmHg)	143.15 ± 25.42
DBP (mmHg)	80.60 ± 13.27
TC (mmol/l)	4.69 ± 1.20
TG (mmol/l)	1.74 ± 1.39
HDL-C (mmol/l)	1.18 ± 0.40
LDL-C (mmol/l)	2.76 ± 0.89
BUN (mmol/l)	7.26 ± 4.51
Scr (umol/l)	106.79 ± 74.92
UA (mmol/l)	340.63 ± 127.24
BG (mmol/l)	6.71 ± 2.94
ABI	0.68 ± 0.20

Mean ± S.D. SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, BUN: blood urea nitrogen, Scr: serum creatinine, UA: uric acid, BG: blood glucose, ABI: ankle-brachial index.

Table 2. Stage of PAD and Drug Therapy

	Only PAD			PAD and DM/PAD and CHD/PAD and stroke		
	one drug	two drugs	≥ three drugs	one drug	two drugs	≥ three drugs
≤0.4, n (%)	3 (0.33)	1 (0.11)	4 (0.44)	3 (0.33)	11 (1.21)	60 (6.59)
0.41–0.90, n (%)	24 (2.63)	26 (2.85)	90 (9.87)	69 (7.57)	142 (15.57)	499 (54.70)
total, n (%)	27 (2.96)	27 (2.96)	94 (10.31)	72 (7.90)	153 (16.78)	559 (61.29)

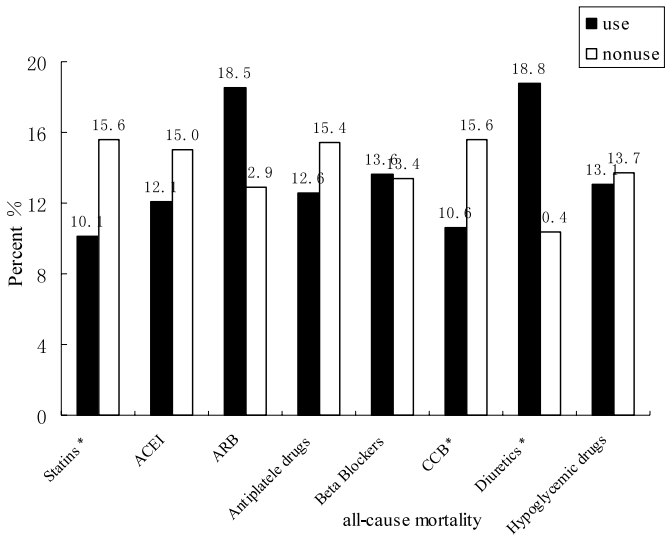

Fig. 1. Rate of All-cause Mortality in 958 Chinese PAD Patients with Drug Therapy in 13 Months of Follow-up (129 Patients Died)

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker. $^{*}p < 0.05$.

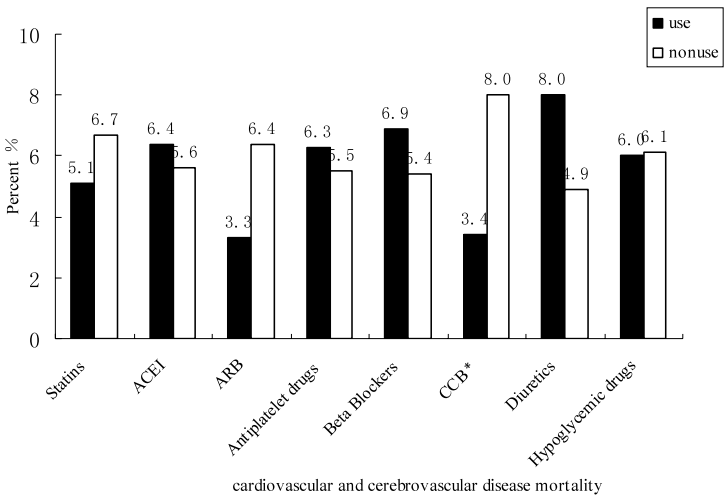

Fig. 2. Cardiovascular and Cerebrovascular Disease Mortality Rate in Each Group of Drug Therapy in 13 Months of Follow-up (58 Patients Died from Cardiovascular and Cerebrovascular Causes)

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker. $^{*}p < 0.05$.

diovascular and cerebrovascular mortality between those who used and did not use CCBs was also statistically significant (Fig. 2).

Cox's proportional hazards model analysis of mortality adjusted for gender, age, smoking history, ACEIs, ARBs, antiplatelet drugs, beta-blockers, hypoglycemic drugs, DM, stroke, dyslipidemia and hypertension in relation to diuretics, statins, CCBs, and risk factors showed that diuretics [relative risk (RR) 1.682, 95% confidence interval (CI): 1.184–2.389] were independently associated with an increased all-cause mortality rate, while statins (RR 0.457, 95% CI: 0.306–0.681), and CCBs (RR 0.677, 95% CI: 0.469–0.978) were independently associated with a decreased all-cause mortality during 13 months of follow-up (Fig. 3A). Figure 3B demonstrates that statins (RR 0.459, 95% CI: 0.257–0.820) and CCBs (RR 0.443, 95% CI: 0.243–0.810) were significantly associated with a decreased cardiovascular and cerebrovascular mortality rate during 13 months of follow-up.

DISCUSSION

Atherosclerotic vascular disease is the leading cause of death in adults worldwide. Atherosclerosis is a systemic process with variable expression in

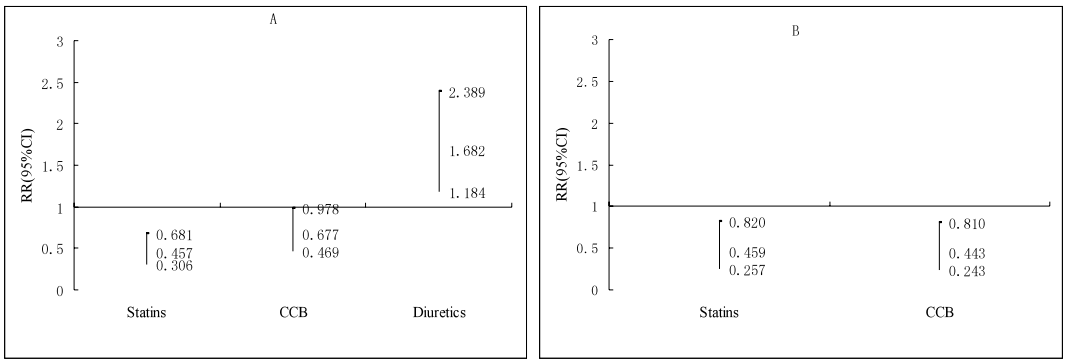

Fig. 3. Relative risks of all-cause mortality, and cardiovascular and cerebrovascular disease mortality after adjusting for gender, age, smoking history, ACEI, ARB, antiplatelet drugs, beta blockers, hypoglycemic drugs, diabetes mellitus, stroke, dyslipidemia and hypertension. A. Relative risks of all-cause mortality. B. Relative risks of cardiovascular and cerebrovascular disease mortality. (CCB, calcium channel blocker)

different vascular beds.[4] PAD is a common manifestation of the severe atherosclerosis process and is defined as abnormal arterial flow to the lower extremities. An ABI of < 0.90 has been used in clinical practice and epidemiologic studies as an indicator of PAD.[5–9] Compared with those without PAD, both symptomatic and asymptomatic patients with PAD have an increased mortality rate.[10] The excess mortality attributable to PAD appears to be related in large part to the increased risk of death from cardiovascular disease. For example, compared with patients without a history of PAD, the 10 year mortality rate for cardiovascular events increased 3- to 6-fold in patients with PAD.[5] The severity of PAD is closely associated with the risk of myocardial infarction, ischemic stroke, and death from vascular causes. ABI, as a marker of PAD, has been associated with total mortality, cardiovascular morbidity and mortality, heart failure, and peripheral vascular disease.[9,11–16] The lower the ABI, the greater the risk of cardiovascular events.[17] Thus it is necessary to control the risk factors for PAD. Treatment guidelines recommend aggressive management of risk factors and lifestyle modifications in patients with abnormal ABI or with confirmed PAD.[18]

This is the first cohort study on Chinese patients with PAD revealing the protective or detrimental drug effects on all-cause mortality and cardiovascular and cerebrovascular mortality. In our study, we focused on statins, ACEIs, ARBs, antiplatelet drugs, beta-blockers, CCBs, diuretics, and hypoglycemic drugs used to control risk factors for PAD, such as hypercholesterolemia, hypertension, and diabetes. The incidence of all-cause mortality in patients with PAD was significantly lower in patients taking statins or CCBs. The opposite was seen in patients taking diuretics. Patients taking CCBs had markedly lower cardiovascular and cerebrovascular mortality rate than those not taking CCBs. After adjusting for gender, age, smoking history, ACEIs, ARBs, antiplatelet drugs, beta-blockers, hypoglycemic drugs, DM, stroke, dyslipidemia, and hypertension, statins and CCB were independent protective factors against all-cause mortality, while diuretics were independent risk factors for all-cause mortality. Statins and CCBs were also independent protective factors against cardiovascular and cerebrovascular mortality during the 13 months of follow-up.

The LDL-C level is the most important risk factor for atherosclerosis. Several large clinical trials have determined the benefits of lowering cholesterol concentrations in patients with coronary artery disease, especially LDL-C levels.[19–23] Many studies have confirmed that statins have cholesterol-lowering activity, stabilize atherosclerotic plaque, have beneficial activity in atherosclerosis and improve vascular function. Statins increase the production of nitric oxide in the endothelium, which has local vasodilatory properties in addition to antithrombogenic, antiproliferative, and leukocyte-adhesion inhibiting effects, as well as intense inflammatory activity.[24–26] Other mechanisms by which statins favorably influence atherosclerosis include enhancement of endothelium-dependent relaxation, inhibition of platelet function,[27] and inhibition of endothelin-1, a potent vasoconstrictor and mitogen.[28]

Some studies have also shown that statins can improve the leg function of patients with

PAD.[29, 30] Other research has indicated that statin therapy is associated with a substantially improved intermediate-term survival of patients with severePAD.[31] Statins used to control dyslipidemia also benefit patients with PAD. We have obtained the same results in relation to statins.

Some reports have suggested that calcium channel antagonists may be associated with an increase in the risk of myocardial infarction and mortality in patients with hypertension or coronary artery disease. However, several trials have also indicated that CCBs did not increase the risk of death.[32–35] In our study, we found that CCBs can reduce the all-cause mortality and cardiovascular and cerebrovascular mortality rate in patients with PAD. Hypertension is the major risk factor for PAD, and control of the blood pressure is an important step in prevention. However, there were very few data that demonstrated the impact of antihypertensive therapy on PAD outcomes. The effect of CCBs in decreasing mortality was thought to be due to its antihypertensive activity.

Although diuretics contribute to lowering hypertension, they have other adverse effects, especially metabolic changes, such as increases in BG, TG, LDL-C, and UA. All these changes could accelerate the atherosclerotic process. This is why diuretics are independent risk factors for all-cause mortality. The most common diuretics used by Chinese patients are thiazide diuretic use. In our study, there was no statistical difference between diuretics and cardiovascular and cerebrovascular disease mortality. Therefore diuretics can be used in patients with cardiovascular and cerebrovascular risk factors, especially thiazide diuretics.

Hypoglycemic drugs and antiplatelet drugs are also an effective treatment for PAD, but there was no statistically significant difference between patients who used them and those who did not in our study.

There are several limitations to our study. First, the number of patients was only 958. Second, the time of follow-up was 13 months; the results may be different after longer follow-up. Third, we obtained a positive relation between statins and CCBs, but we did not determine the optimal dose and duration of treatment of those drugs. Fourth, our study was only a longitudinal observational study, not a randomized, controlled trial.

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