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Cardioprotective Medication Is Associated With Improved Survival in Patients With Peripheral Arterial Disease

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OBJECTIVES We sought to investigate the effect of cardiac medication on long-term mortality in patients with peripheral arterial disease (PAD).

BACKGROUND Peripheral arterial disease is associated with increased cardiovascular morbidity and mortality. Treatment guidelines recommend aggressive management of risk factors and lifestyle modifications. However, the potential benefit of cardiac medication in patients with PAD remains ill defined.

METHODS In this prospective observational cohort study, 2,420 consecutive patients (age, 64 ± 11 years, 72% men) with PAD (ankle-brachial index ≤0.90) were screened for clinical risk factors and cardiac medication. Follow-up end point was death from any cause. Propensity scores for statins, beta-blockers, aspirin, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins, and digoxin were calculated. Cox regression models were used to analyze the relation between cardiac medication and long-term mortality.

RESULTS Medical history included diabetes mellitus in 436 patients (18%), hypercholesterolemia in 581 (24%), smoking in 837 (35%), hypertension in 1,162 (48%), coronary artery disease in 1,065 (44%), and a history of heart failure in 214 (9%). Mean ankle-brachial index was 0.58 (±0.18). During a median follow-up of eight years, 1,067 patients (44%) died. After adjustment for risk factors and propensity scores, statins (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.36 to 0.58), beta-blockers (HR 0.68, 95% CI 0.58 to 0.80), aspirins (HR 0.72, 95% CI 0.61 to 0.84), and ACE inhibitors (HR 0.80, 95% CI 0.69 to 0.94) were significantly associated with a reduced risk of long-term mortality.

CONCLUSIONS On the basis of this observational longitudinal study, statins, beta-blockers, aspirins, and ACE inhibitors are associated with a reduction in long-term mortality in patients with PAD. (J Am Coll Cardiol 2006;47:1182–7) © 2006 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis and carries a poor prognosis as a result of the frequent association with cerebral, renal, and coronary artery disease (1–4). Although patients with PAD may present with symptoms ranging from pain on exertion that is relieved by rest (intermittent claudication) to pain at rest, ulceration, or gangrene (critical limb ischemia), most patients with PAD are asymptomatic (1). The prevalence of PAD ranges from 4% in patients aged 40 years and older to more than 20% in patients aged 70 years and older (5–10).

Peripheral arterial disease remains an underdiagnosed disease in the primary care, and patients with PAD are not treated as aggressively as are patients with other manifestations of atherosclerotic disease (7,11). The treatment of PAD focuses on walking exercise, aggressive management of risk factors, lifestyle modifications, and antiplatelet therapy (12,13). Cardiovascular events are a major cause of morbidity and mortality in patients with PAD. However, the potential benefit of cardiac medication therapy remains ill defined. Beta-adrenergic receptor blockers were considered relatively contraindicated in PAD; however, several studies have revealed that beta-blockers do not adversely affect walking capacity, symptoms of intermittent claudication, and peripheral skin microcirculation (14–16).

In this report, we sought to determine the effect of chronic treatment with cardiac medication, including statins, beta-blockers, aspirins, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins, and digoxin on long-term mortality among patients with PAD. In this observational cohort study, we used propensity analysis to adjust for selection bias in the comparison of treatments.

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Abbreviations and Acronyms

ABI = ankle-brachial index
ACE = angiotensin-converting enzyme
CI = confidence interval
HR = hazard ratio
PAD = peripheral arterial disease

METHODS

Assessment of baseline characteristics. The Erasmus Medical Center serves a population of approximately 3 million people and acts as a tertiary referral center for approximately 30 affiliated hospitals. Patients with suspected or known PAD who were referred to the Erasmus Medical Center, Rotterdam, the Netherlands, between January 1983 and January 2005, for the diagnosis and management of PAD were evaluated. The ankle-brachial index (ABI) at rest was measured in each patient and patients with PAD (ABI ≤0.90) were included in the study.

On the basis of hospital records and personal interviews at the time of the visit, a medical history was recorded. Information on the presence of previous myocardial infarction, angina pectoris, previous coronary artery revascularization, congestive heart failure, previous stroke or transient ischemic attack, diabetes mellitus, hypertension, current smoking, hypercholesterolemia, and renal dysfunction were obtained. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/l, or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mm Hg or if patients were medically treated for hypertension. Hypercholesterolemia was recorded when patients presented with the diagnosis, made by the referring physician, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥2.0 mg/dl (177 μmol/l) or in those who required dialysis. A baseline 12-lead electrocardiography was obtained and was considered abnormal in the presence of one or more of the following: Q waves, ST-segment depression or elevation, left ventricular hypertrophy, right or left bundle branch block, and atrial fibrillation.

Use of medication. All prescription and over-the-counter medications were noted at the time of the visit and were classified as follows: statins, beta-blockers, aspirins, ACE inhibitors, calcium channel blockers (dihydropyridines or non-dihydropyridines), diuretics, nitrates, coumarins, and digoxin. To ascertain the long-term use of cardiovascular medication, medication had to be documented at least at two months after the visit.

Follow-up. Patients were followed during a median time of 8 years (interquartile range, 4 to 11 years) for the occurrence of all-cause death. End point was mortality. Information about the patient's vital status was obtained by approaching the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were retrieved and reviewed. For patients who died outside our hospital, general practitioners were approached to ascertain the cause of death.

Statistical analysis. Continuous data with a normal distribution were expressed as mean and compared using the Student *t* test. Categorical data are presented as percent frequencies, and differences between proportions were compared using the chi-square test with Yates' correction. The Kaplan-Meier method with log-rank test was used to compare survival curves in two or more groups. We applied univariate and multivariate Cox proportional hazards regression analyses to study the relation between cardiac medication therapy and long-term survival. Cardiac medication use was not randomly assigned in these patients, and the impact of selection bias may profoundly distort the results of our study.

Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been previously described (17). Therefore, separate propensity scores were calculated and ranged from 0.04 to 0.92 for statins, 0.002 to 0.98 for beta-blockers, 0.05 to 0.92 for aspirin, 0.04 to 0.95 for ACE inhibitors, 0.08 to 0.76 for calcium channel blockers, 0.0001 to 0.87 for diuretics, 0.04 to 0.91 for nitrates, 0.35 to 0.91 for coumarins, and 0.15 to 0.77 for digoxin, which were constructed using multiple logistic regression analysis. Variables (including baseline characteristics as listed in Table 1 and medication use as listed in Table 2) that were independently associated with the decision to prescribe statins, beta-blockers, aspirin, ACE inhibitors, calcium channel blockers, diuretics, ni-

Table 1. Baseline Characteristics of the 2,420 Study Participants

Characteristic	Total Population (n = 2,420)
Demographics	
Age (yrs)	64 ± 11
Male gender	1,748 (72%)
Cardiovascular history	
Angina pectoris	567 (23%)
Previous myocardial infarction	923 (38%)
History of congestive heart failure	214 (9%)
History of cerebrovascular disease	195 (8%)
Previous coronary revascularization	464 (19%)
Clinical risk factors	
Diabetes mellitus	436 (18%)
Hypercholesterolemia	581 (24%)
Hypertension	1,162 (48%)
Current smoking	837 (35%)
Renal failure	127 (5%)
Chronic pulmonary disease	288 (12%)
Ankle brachial index >0.70 and ≤0.90	557 (23%)
Ankle brachial index ≤0.70	1,863 (77%)
Electrocardiography	
Q waves	630 (26%)
ST-segment changes	382 (16%)
Left ventricular hypertrophy	113 (5%)
Left bundle branch block	98 (4%)
Right bundle branch block	56 (2%)
Atrial fibrillation	54 (2%)

Values are expressed as n (%) or mean ± SD.