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Progression of Peripheral Arterial Disease Predicts Cardiovascular Disease Morbidity and Mortality

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Objectives The purpose of this study was to examine the association of progressive versus stable peripheral arterial disease (PAD) with the risk of future cardiovascular disease (CVD) events.

Background An independent association between PAD, defined by low values of the ankle-brachial index (ABI), and future CVD risk has been demonstrated. However, the prognostic significance of declining versus stable ABI has not been studied.

Methods We recruited 508 subjects (59 women, 449 men) from 2 hospital vascular laboratories in San Diego, California. ABI and CVD risk factors were measured at Visit 2 (1990 to 1994). ABI values from each subject's earliest vascular laboratory examination (Visit 1) were abstracted from medical records. Mortality and morbidity were tracked for 6 years after Visit 2 using vital statistics and hospitalization data.

Results In multivariate models adjusted for CVD risk factors, very low (<0.70) and, in some cases, low ($0.70 \leq$ ABI <0.90) Visit 2 ABIs were associated with significantly elevated all-cause mortality, CVD mortality, and combined CVD morbidity/mortality at 3 and 6 years. Decreases in ABI of more than 0.15 between Visit 1 and Visit 2 were significantly associated with an increased risk of all-cause mortality (risk ratio [RR]: 2.4) and CVD mortality (RR: 2.8) at 3 years, and CVD morbidity/mortality (RR: 1.9) at 6 years, independent of Visit 2 ABI and other risk factors.

Conclusions Progressive PAD (ABI decline >0.15) was significantly and independently associated with increased CVD risk. Patients with decreasing ABI may be candidates for more intensive cardiovascular risk factor management. (J Am Coll Cardiol 2008;52:1736–42) © 2008 by the American College of Cardiology Foundation

The association of peripheral arterial disease (PAD) with future cardiovascular disease (CVD) events and CVD and total mortality has been demonstrated in multiple studies. More recent studies using the ankle-brachial index (ABI), the ratio of the ankle to the arm blood pressure, and other noninvasive tests have shown the mortality association to be based largely on increased CVD, and independent of traditional CVD risk factors (1–15).

Most studies have used a dichotomous definition of PAD based on an ABI cut point of 0.90. Although some studies stratified ABI into additional categories for survival curve analysis, only a few have used additional ABI categories in full multivariate analysis. Many studies excluded patients with unusually high ABIs (e.g., ≥1.40), because such ABIs may reflect medial arterial calcification (MAC), which precludes accurate ABI assessment.

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Previous studies of the association of PAD with other CVD outcomes used ABI at baseline, and did not address the potential additional significance of changes in ABI over time. The progression of PAD itself has received relatively little attention (16–19). The prognostic significance of PAD progression for incident CVD events is unknown.

In the present study, the association between PAD, as measured by the ABI, with CVD morbidity and mortality was assessed in a group of vascular laboratory patients. The association of Visit 2 ABI with incident CVD morbidity and mortality was first examined, and the additional prognostic significance of changes in ABI between Visits 1 and 2 was then explored.

Methods

Subjects were recruited for Visit 2 in 1990 to 1994 from patients who had been seen in the previous 10 years for

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noninvasive lower extremity arterial testing at the vascular laboratories of the San Diego Veterans Administration Medical Center (SDVAMC) or the University of California San Diego Medical Center (UCSDMC). Each patient's first vascular laboratory examination constituted Visit 1 for that patient. Of 2,265 patients having such visits, 481 were deceased and another 1,272 could not be located or declined to participate. Informed consent was obtained from the remaining 512 patients, who were examined for this study (Visit 2). A previous analysis of this cohort found that participants had slightly less advanced PAD than did surviving nonparticipants and included a higher percentage of women (13% vs. 8%), but were similar with respect to age (17).

At Visits 1 and 2, systolic brachial pressure was measured in both arms sphygmomanometrically with detection at the third finger by photoplethysmography, and ankle systolic blood pressure was similarly measured with detection at the toe (20,21). At Visit 2, subjects completed a health history questionnaire and the San Diego Claudication Questionnaire (SDCQ) (22). Basic laboratory, anthropometric, and physiologic measurements were obtained. Information from the earliest prior vascular laboratory visit (Visit 1) was abstracted for all subjects. The ABI at Visit 1 was used to calculate the change in ABI in the period before Visit 2 (mean ± SD: 5.0 ± 2.4 years). Four subjects failed to provide a Social Security number, the primary identifier used for morbidity and mortality follow-up (see the following text); these subjects were excluded from subsequent analysis. This resulted in a final group of 508 subjects.

Mortality in the study cohort after Visit 2 was identified using Social Security Administration data available through the end of 2002. A certified nosologist coded the causes of death based on death certificates. CVD morbidity, defined as inpatient hospitalization, was identified from 2 sources. Electronic hospital admission records for study participants were obtained from the SDVAMC. In addition, hospitalizations were identified from data collected by the California Office of Statewide Health Planning and Development, which include all admissions to all nonfederal hospitals in the state. Hospital discharge codes have been shown to agree well with independent assessment for cardiovascular diagnoses in Medicare patients (23). To protect patient privacy, data processing that involved the Office of Statewide Health Planning and Development data was carried out on remote secure servers by Health Information Solutions of Rocklin, California under contract with the Office of Statewide Health Planning and Development.

Three end points were analyzed: all cause mortality, CVD mortality, and combined CVD morbidity and mortality. Mortality was classified based on listed causes of death on the death certificate. Morbidity was classified based on the principal hospitalization diagnosis. A morbidity/mortality end point was identified as the earliest CVD morbidity or mortality event for a subject. CVD mortality and morbidity were identified by International Classification of Disease-9 (mortality) or International Classification of Disease-9-Clinical Modification (morbidity) codes in the range 401 to 437.9, excluding 412.

Abbreviations and Acronyms

ABI = ankle-brachial index
CHD = coronary heart disease
CVD = cardiovascular disease
MAC = medial arterial calcification
PAD = peripheral arterial disease
RR = risk ratio
SDCQ = San Diego Claudication Questionnaire

The ABI for each leg was computed as the ratio of the ankle pressure for that leg to the higher of the left and right brachial pressures. The higher brachial pressure was used because of the strong correlation between PAD and subclavian stenosis (24). The lower ABI value of the 2 legs was used. The ABI was categorized into five ranges: <0.70, $0.70 \leq \text{ABI} < 0.90$, $0.90 \leq \text{ABI} < 1.00$, $1.00 \leq \text{ABI} < 1.40$, and ≥ 1.40. In addition, the set of models evaluating PAD progression and outcome had the change in ABI from Visit 1, categorized into 3 ranges: < -0.15, -0.15 to $+0.15$, and $> +0.15$. This 0.15 cut point has been used to represent clinically significant ABI change in several studies (16–18). In these latter models, subjects with Visit 1 or 2 ABI values ≥ 1.4 were excluded, since ABI change could be biased by MAC. The Visit 1 ABI value was also the lower of the 2 legs.

The following baseline cardiovascular risk factors were included in the analysis: age, gender, race (non-Hispanic white vs. other), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, (log) triglycerides, self-reported history of coronary heart disease (myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty), and self-reported history of stroke. Diabetes was included as a dichotomous variable based on plasma glucose ≥ 126 mg/dl among subjects reporting having fasted for 8 or more hours before their examination, or self-reported use of insulin or oral hypoglycemics (25). Hypertension was included as a dichotomous variable based on systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of hypertension medication (26). Smoking was included in models as 2 separate variables: pack-years and smoking status (current/former/never). The SDCQ was included as a 5-level categorical variable, based on the most symptomatic leg (22). Models involving the change in ABI were also adjusted for the time elapsed between ABI measurements. At Visit 2, 32.9% of subjects reported earlier revascularization for PAD, which was coded as a dichotomous variable.

Subjects were tabulated by morbidity and mortality status, and age-adjusted mean values of risk factors were calculated within these groups. To test for proportional hazards over follow-up time, initially Cox models for the 3 end points (all-cause mortality, CVD mortality, and combined morbidity and mortality from CVD) were fit for 3- and 6-year durations from the time of Visit 2. The relative hazard for all-cause and CVD mortality decreased over