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The General Prognosis of Patients With Peripheral Arterial Disease Differs According to the Disease Localization

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Objectives The purpose of this study was to assess the general prognosis of patients with peripheral arterial disease (PAD) according to the disease localization.

Background PAD is associated with poor cardiovascular disease prognosis. However, it is unknown whether the general prognosis could differ according to PAD topography.

Methods Data for all patients who underwent a first digital subtraction angiography of their lower limbs between January 2000 and December 2005 at our hospital were reviewed. Arterial stenoses ≥50% were located by 2 experienced vascular physicians. The following events were collected until April 2007: death, nonfatal myocardial infarction or stroke, and coronary or carotid revascularization. The primary outcome combined all these events.

Results We studied 400 PAD patients (age 68.3 ± 12.3 years, 77.5% men). Aortoiliac disease (proximal PAD) and infrailiac disease (distal PAD) were noted in 211 (52.8%) and 344 (86.0%) cases, respectively. Male sex and smoking were more prevalent in proximal PAD, whereas older age, diabetes, hypertension, and renal failure were more prevalent in distal PAD ($p < 0.05$). During the follow-up period (34 ± 23 months), the event-free survival curves differed according to the PAD localization ($p < 0.03$). Adjusted for age, sex, cardiovascular disease history and cardiovascular disease risk factors, critical leg ischemia status, and treatments, proximal PAD was significantly associated with a worse prognosis (primary outcome hazard ratio: 3.28; death hazard ratio: 3.18, $p < 0.002$ vs. distal PAD).

Conclusions This is the first study to report a poorer general prognosis of patients with proximal (aortoiliac) PAD compared with those with more distal PAD, independent of risk factors and comorbidities. (J Am Coll Cardiol 2010;55: 898–903) © 2010 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) refers to a partial or complete obstruction of lower limb arteries due to the development of atherosclerotic lesions. It includes all localizations, from proximal arteries as large as the terminal abdominal aorta to distal vessels as small as foot arteries. Beyond their sizes, these arteries differ also by their histology, with a predominance of the elastic components in the proximal artery media and a progressive predominance of muscular components of the same layer in more distal arteries. Similarly, the endothelium possesses different properties, in part related to variable shear stress according to its location (1). Beyond these histological differences, several clinical/epidemiological studies have already shown that the levels of sociodemographic and cardiovascular disease (CVD) risk factors associated with PAD differ according to the localization of the disease (1). Similarly, it was recently shown that factors affecting the progression of PAD differ between large and small vessels (2). It is also well-known that distal PAD is associated with more severe limb prognosis, especially because revascularization is more difficult and not always possible, leading to higher rates of amputation (3,4).

Regarding the general cardiovascular prognosis, patients with PAD are overall at higher risk of mortality as well as coronary and cerebral ischemic events (5,6). These findings led to considering PAD as a high CVD risk condition, with the necessity for strict preventive strategies, similar to those proposed for the secondary preven-

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tion (5,6). However, it is unclear whether the general prognosis of PAD patients could differ according to the distribution of PAD lesions.

We hypothesized that the general prognosis of PAD patients may differ according to localization, independent of risk factors and conditions that may be differentially associated with proximal compared with distal PAD.

Methods

Baseline data. We retrospectively reanalyzed all digital subtraction angiography (DSA) studies of lower limb arteries performed between January 1, 2000, and December 31, 2005 in our department for the assessment of PAD. We only considered patients who had their first angiography. Patients with any history of lower limb revascularization and those who had angiography in the past were excluded from the study. We also excluded patients hospitalized for the management of nonatherosclerotic diseases (e.g., aneurysms, inflammatory diseases) and those with acute lower limb ischemia.

All DSA studies were read by 2 senior physicians, and consensus was reached in cases of disagreement. For each limb, these physicians determined the presence/absence of a ≥50% stenosis in any artery, down to the 3 ankle arteries. They were unaware of the patients' prognosis during the DSA interpretation. The stenoses locations were secondarily grouped into 3 anatomical levels: aortoiliac arteries, femoral/popliteal arteries, and infragenicular arteries. Each patient could have 1 or more levels affected, with coexisting lesions in a same leg or in the other leg. No distinction was made regarding the laterality of the lesion (e.g., a patient with both femoral/popliteal and infragenicular lesions might have the former in 1 leg and the latter in the contralateral leg, have both lesions in the same leg, or have both legs affected by both lesions). Similarly, the extent of the lesions (stenoses length, the number of arteries affected at each level) was not considered. After an initial series of analyses on the 3 arterial levels, aortoiliac, femoral/popliteal, and infragenicular arteries, the decision was made to reclassify lesions into 2 patterns due to a similar prognosis in patients with the 2 latter localizations of PAD: the proximal lesions affecting the abdominal aorta bifurcation and the iliac arteries and the distal lesions for any localization from the femoral arteries down to and including the infragenicular arteries.

The risk factors, comorbidities, and treatments at the time of the angiography were collected from the medical charts, with baseline variables defined as follows: patients were considered smokers if they were active smokers ever, at baseline, or in the past. Diabetes was defined by a fasting blood glucose ≥7 mmol/l at admission or the use of any oral antidiabetic agent and/or insulin. Hyperlipidemia was defined according to the documented patient's history and/or a fasting blood cholesterol ≥240 mg/dl at admission. Patients were considered hypertensive if they took any antihypertensive drug for this purpose and/or if their average systolic blood pressure exceeded 140 mm Hg or diastolic blood pressure exceeded 90 mm Hg during the first 2 blood pressure measurements after admission.

Abbreviations and Acronyms

CVD = cardiovascular disease

DSA = digital subtraction angiography

PAD = peripheral arterial disease

At baseline, several comorbidities were also taken into account: coronary artery disease was defined according to any documented ischemic episode reported in the medical chart and/or any history of coronary revascularization. Heart failure was defined according to the documented medical history and/or the presence of New York Heart Association functional class III to IV dyspnea. Cerebrovascular disease was defined by any documented episode of stroke, transient ischemic attack, or carotid revascularization. Other conditions listed were the presence of documented chronic obstructive pulmonary disease and the presence of renal failure. The latter was defined in cases of end-stage renal disease with dialysis or a glomerular filtration rate <60 ml/min/1.73 m^2 calculated according to the MDRD (Modification of Diet in Renal Disease) formula (7). Finally, the PAD clinical status was categorized according to the presence or absence of critical leg ischemia defined according to the TransAtlantic InterSociety Consensus II criteria (5).

Among baseline therapies, the use of beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II antagonists were considered at discharge. We did not consider the use of antiplatelet drugs in our analysis because all patients were so treated at discharge, except for those who were taking anticoagulation medications for various medical reasons (cardiac or vascular diseases) that could interfere with the assessment of prognostic factors. Last, we also included the occurrence of any limb amputation during the index hospitalization in our baseline data list.

We also performed separate analyses in a subset of patients whose lesions were limited to 1 of the arterial levels (i.e., only aortoiliac, femoral/popliteal, or infragenicular lesions).

Follow-up data. Patients' medical charts were systematically reviewed until April 2007, and follow-up was completed by phone contact with family physicians. Events noted during follow-up were death, fatal and nonfatal myocardial infarction or stroke, and coronary or carotid revascularization. The primary outcome combined these adverse events.

Statistical analysis. Data are reported as mean (SD) and number (percentage) for continuous and categorical variables, respectively. The Kaplan-Meier survival method was used for the comparison of survival according to PAD localization, using the log-rank test. Multivariate analysis was performed by using a Cox proportional hazards model. For this purpose, several models were run, by sequentially adding baseline demographic factors and the presence of