Vascular Disease

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-

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.

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

Abbreviations and Acronyms

CVD = cardiovascular disease

DSA = digital subtraction angiography

PAD = peripheral arterial disease

Figure 1   Distribution of Arterial Lesions in the Study Population
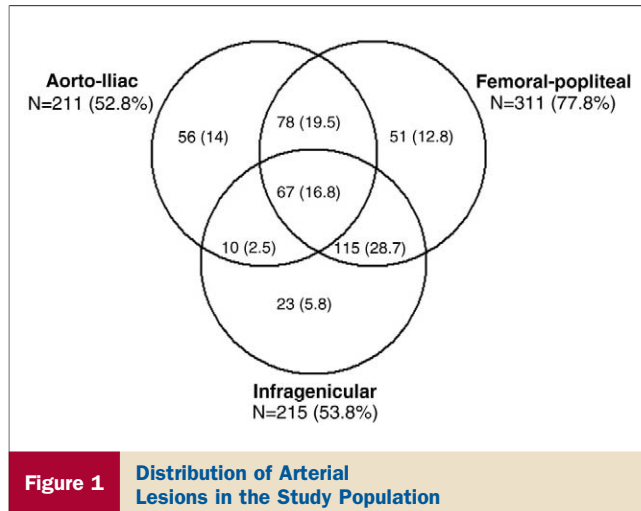
critical ischemia (model 1), then CVD risk factors (model 2), then comorbidities (model 3), and finally treatments (model 4). A p value <0.05 was considered statistically significant. The software used for statistical analysis was Statview version 5.0 for Windows (SAS Institute, Cary, North Carolina).

Results

During the study period, 843 DSA studies of lower limbs were performed on 681 patients. Among them, 400 had their first angiography, no acute ischemia at presentation, and no history of peripheral revascularization. All had at least 1 arterial stenosis ≥50% due to atherosclerotic lesions. We obtained baseline and follow-up data for all patients. Most patients had several lesions distributed in different anatomical levels. Approximately one-third of patients (n = 130) had single-level PAD, affecting

exclusively 1 of the 3 anatomical levels (Fig. 1). The general data for our study population are presented in Table 1 as well as comparisons according the presence/absence of PAD in the 3 anatomical levels. Patients' profiles for aortoiliac PAD differed from those who had either femoral/popliteal or infragenicular lesions. Patients with aortoiliac lesions were overall younger, with higher proportions of male patients and smokers. Conversely, in patients with more distal lesions, higher rates of diabetes, hypertension, and renal and heart failure were observed. As expected, critical ischemia and amputations were more frequent in more distal PAD.

Because a majority of patients had several anatomical levels involved in their disease, 3 separate sets of survival analyses were performed, each time according to the presence or absence of PAD at 1 of the 3 pre-defined levels (Fig. 2). Patients with PAD at the aortoiliac level had more CVD events (p = 0.01) during follow-up than patients without aortoiliac disease, whereas similar comparisons for the other 2 groups did not show significant differences. Additional analyses on the subset of patients who had only 1 anatomical level involved showed similarly poorer prognosis for those with aortoiliac PAD (p = 0.04) compared with either of the other 2 groups, which did not differ significantly from each other (Fig. 3). Overall, it appeared that patients with aortoiliac disease had a poorer outcome than other PAD patients. Therefore, in Figure 4, femoral/popliteal and infragenicular lesions have been combined as the distal PAD group and compared with the proximal aortoiliac lesions. For both overall mortality and cardiovascular events, a poorer prognosis was noted in cases of proximal PAD. We subsequently assessed the association between PAD localization and prognosis in several multivariate models to

Table 1   Study Population and Comparisons According to the Presence of PAD at Each Anatomic Level

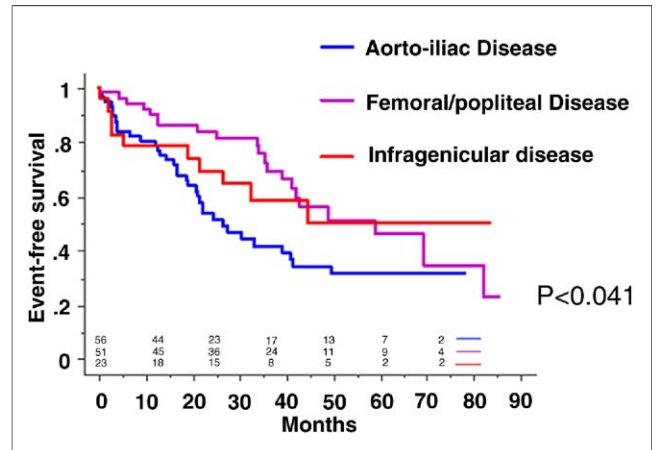|	Overall (n = 400)	Aortoiliac Disease		Femoral/Popliteal Disease		Infragenicular Disease	
		Yes (n = 211)	No (n = 189)	Yes (n = 311)	No (n = 89)	Yes (n = 215)	No (n = 185)
Age	68.3 (12.3)	64.7 (12.3)*	72.3 (11.1)	70.0 (11.5)*	62.4 (13.5)	73.1 (10.1)*	62.9 (12.6)
Male sex	310 (77.5)	184 (87.2)*	126 (66.7)	232 (74.6)†	78 (87.6)	150 (69.7)†	151 (81.6)
Smoking	252 (63.0)	165 (78.2)*	87 (46.0)	187 (60.1)‡	65 (73.0)	104 (48.4)*	142 (76.8)
Diabetes	162 (40.5)	66 (31.3)*	96 (50.8)	132 (42.4)	30 (33.7)	101 (47.0)†	58 (31.4)
Dyslipidemia	173 (43.3)	100 (47.4)	73 (38.6)	126 (40.5)	47 (52.8)	80 (37.2)*	89 (50.6)
Hypertension	258 (64.5)	115 (54.5)*	143 (75.7)	213 (68.5)§	45 (50.6)	153 (71.2)*	99 (53.5)
Renal failure	95 (24.0)	36 (17.1)†	59 (31.7)	76 (24.8)	19 (21.4)	68 (31.9)*	24 (13.0)
Critical ischemia	264 (66)	121 (57.3)*	143 (75.7)	215 (69.1)‡	49 (55.1)	159 (74.0)†	101 (54.6)
CAD or CBVD	171 (42.8)	94 (44.6)	77 (40.7)	141 (45.3)	30 (33.7)	92 (42.8)	76 (41.1)
COPD	73 (18.3)	41 (19.4)	32 (16.9)	57 (18.3)	16 (18.0)	38 (17.7)	34 (18.4)
Heart failure	71 (17.8)	33 (15.6)	38 (20.1)	55 (17.7)	16 (18.0)	46 (21.4)‡	24 (13.0)
Beta-blockers	122 (30.5)	57 (27.0)	65 (34.4)	106 (34.1)§	16 (18.0)	69 (32.1)	52 (28.1)
ACEI/AA2	187 (46.8)	94 (44.6)	93 (49.2)	155 (49.8)‡	32 (36.0)	133 (52.6)‡	70 (37.8)
Statins	188 (47.0)	109 (51.7)	79 (41.8)	149 (47.9)	39 (43.8)	89 (41.4)‡	95 (51.4)
Amputation	95 (23.8)	30 (16.6)†	60 (31.8)	79 (25.4)	16 (18.0)	69 (32.1)*	25 (13.5)

*p < 0.0001. †p < 0.001. ‡p < 0.05. §p < 0.01.

AA2 = angiotensin II antagonist; ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; CBVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; PAD = peripheral arterial disease.
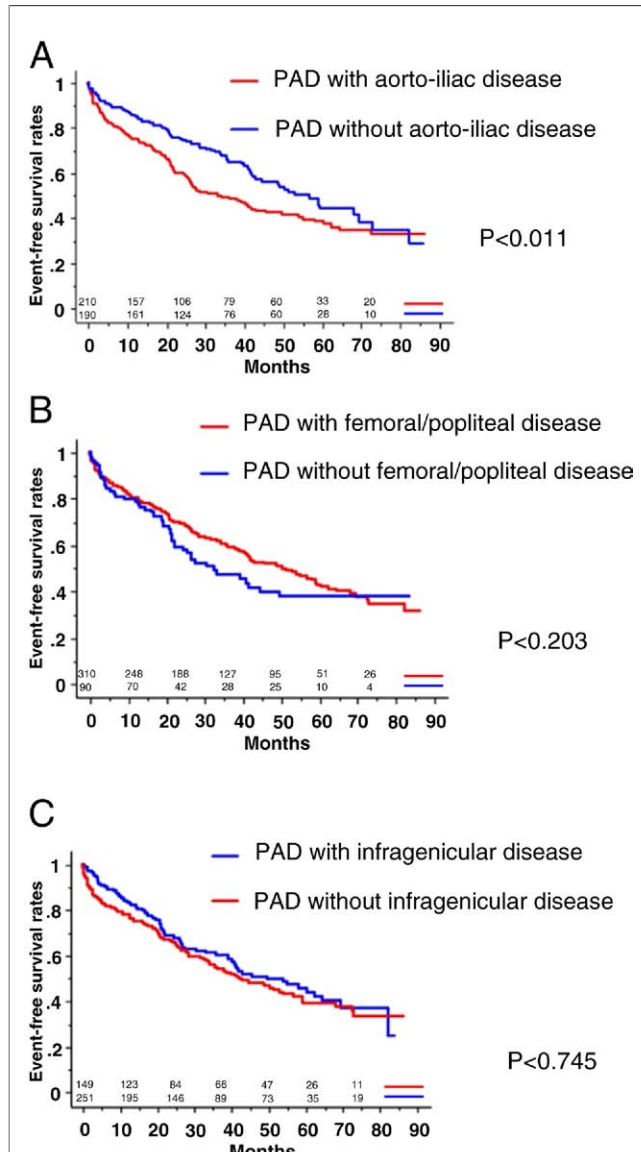
Figure 2 Comparison of Event-Free
Survival Curves Among PAD Patients

Comparison of event-free survival curves among peripheral arterial disease
(PAD) patients according to the presence/absence of aortoiliac **(A)**, femoral/
popliteal **(B)**, and infragenicular **(C)** lesions.

Figure 3 Event-Free Survival According to the PAD
Localization in Patients With Single-Level Disease

PAD = peripheral arterial disease.

Discussion

In this longitudinal retrospective study, our data confirmed
our hypothesis that the general prognosis of PAD patients
varies according to the disease localization. Several risk
factors and comorbidities were differentially associated with
proximal and distal PAD, with male sex and smokers more
frequent in proximal PAD patients and aging, diabetes,
hypertension, and renal and heart failure more frequent in
distal PAD patients. Among these PAD patients, proximal
PAD was found to be independently associated with poorer
survival and CVD prognosis, even after adjustments for
these potential confounders.

Several studies have already reported different risk factors
associated with PAD according to proximal/distal or large/
small vessel PAD, although we reached no consensus on
these topographic definitions (1). In the angiographic stud-
ies, proximal arteries usually referred to aortoiliac arteries

Figure 4 Event-Free Survival According to PAD Distribution

PAD = peripheral arterial disease.

adjust it to potential confounding variables, such as CVD
risk factors and comorbidities, that were distributed
differently in PAD patients according to arteries involved
(Table 2). In all models, proximal PAD was significantly
and substantially associated with mortality as well as with
the occurrence of death or nonfatal CVD events. Regard-
ing distal PAD, we found no significant prognostic
differences when femoral/popliteal and infragenicular
lesions were studied separately. The multivariate association
between single-level PAD and CVD events is displayed in
Table 3 and shows the increased risk in the aortoiliac group
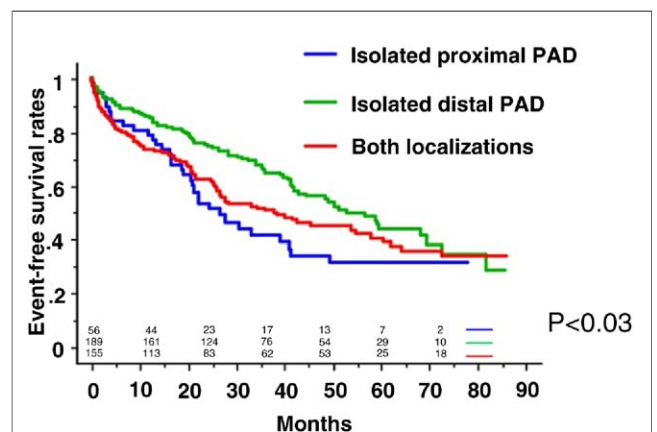and no differences between the other 2 groups.

Table 2	**Association Between Proximal Peripheral Arterial Disease and Prognosis**			
Event	**Model 1**	**Model 2**	**Model 3**	**Model 4**
All	3.44 (2.10–5.63)*	3.51 (2.11–5.84)*	3.60 (2.16–6.02)*	3.28 (1.87–5.75)*
Death	2.65 (1.45–4.83)†	2.87 (1.52–5.42)†	2.91 (1.53–5.53)†	3.18 (1.57–6.46)†

Values are hazard ratio (95% confidence interval). In all models, distal peripheral arterial disease is used as reference. Model 1 = age, sex, and critical ischemia; Model 2 = Model 1 + smoking, dyslipidemia, diabetes, hypertension, and renal failure; Model 3 = Model 2 + cardiovascular disease history, chronic obstructive pulmonary disease, and heart failure; Model 4 = Model 3 + angiotensin II antagonists/angiotensin-converting enzyme inhibitors, beta-blockers, statins, and amputations. *p < 0.0001. †p < 0.002.

(8–11) or above-knee arteries (12,13). For this reason, we first divided pragmatically the anatomical levels into 3 territories and ultimately decided to fix the lower limit of proximal PAD at the common femoral artery origin because the cross-sectional and longitudinal analyses both favored a similar pattern for femoral/popliteal and infragenicular lesions. Other studies using noninvasive methods to detect PAD defined distal PAD as below-knee (14) arteries and even small-vessel PAD as foot arteries (2,15).

Our cross-sectional data regarding the association between risk factors and PAD localization are consistent with the earlier reports (2,8–18) Accordingly, several studies reported more distal PAD in elderly patients (8,10,17,18). Among traditional risk factors, diabetes has been consistently associated with more distal PAD in several series (8–10,12,13,17), whereas smoking was predominantly associated with proximal PAD (8–10,13,15,17,18). These observations were confirmed by a longitudinal study in which smoking was associated with PAD progression in large vessels only, whereas diabetes was associated with disease progression in small vessels only (2). Our data regarding higher rates of hypertension in distal PAD confirm earlier data reported in another angiographic series (10).

To our knowledge, this is the first study reporting different general prognosis in PAD patients according to their disease topography, determined by DSA. Using noninvasive methods, 2 earlier studies provided prognostic data in line with our current findings (15,17). In a population study (15), a significant association between mortality and large-vessel PAD was reported as opposed to no similar association in isolated small-vessel (foot arteries) disease. In that study, large-vessel PAD involved all arteries above the ankle. In a vascular clinical study including patients with and without PAD, Vogt et al. (17) reported a higher risk of

mortality in patients with aortoiliac and/or femoral/popliteal disease than in those with infragenicular disease, adjusted for CVD risk factors and comorbidities. The current study permits refining these earlier results and determining a significant prognostic difference in patients with aortoiliac disease versus those affected by a more distal pattern of PAD. Additionally, the Vogt et al. study (17) used segmental blood pressure gradients to determine disease location. This approach raises the question of an accurate assessment of a limb segment distal to a diseased one. In our study, the use of DSA, still considered the gold standard for PAD assessment, bypassed this issue. In addition, our study is the first to assess not only mortality, but also nonfatal CVD events. Nonetheless, all 3 studies are concordant for a worse general prognosis in (more) proximal PAD.

One might suggest that the differences regarding CVD events might be related to acute events during the perioperative period because revascularization is more often feasible in cases of proximal PAD. However, the survival and event-free curves continue to diverge even several months after hospitalization. In contrast, it could be supposed that higher rates of chronic limb ischemia and amputation might be associated with a poorer general prognosis in distal PAD. Our findings do not support this hypothesis. In addition, in the multivariate models, the association between mortality or CVD events and proximal PAD persisted even after adjustments to the clinical status, comorbidities, and the use of major cardiovascular drugs as well as the need for amputation at baseline.

Looking for any rationale to explain our findings is challenging. We did not find any difference regarding the association between proximal/distal PAD and clinical coronary or cerebrovascular disease. Further, multiple adjustments to control confounders exclude a priori that prognos-

Table 3	**Association of Peripheral Arterial Disease Localization and Fatal and Nonfatal Cardiovascular Events in Patients With a Single-Level Disease (n = 130)**			
Peripheral Arterial Disease Location	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 HR (95% CI)**
Aortoiliac	3.83 (1.73–8.50)*	3.74 (1.57–8.91)†	3.67 (1.55–8.70)*	4.70 (1.65–13.31)*
Femoral/popliteal	1.18 (0.45–2.57)	1.10 (0.48–2.50)	1.01 (0.43–2.35)	1.31 (0.52–3.31)
Infragenicular	Reference	Reference	Reference	Reference

Values are hazard ratio (95% confidence interval). Model 1 = age, sex, and critical ischemia; Model 2 = Model 1 + smoking, dyslipidemia, diabetes, hypertension, and renal failure; Model 3 = Model 2 + cardiovascular disease history, chronic obstructive pulmonary disease, and heart failure; Model 4 = Model 3 + angiotensin II antagonists/angiotensin-converting enzyme inhibitors; beta-blockers, statins, and amputations. *p < 0.001. †p < 0.005.

tic differences might be related to different patient risk profiles. One hypothesis is that proximal PAD could be more strongly associated with central arterial stiffness than distal PAD. Central arterial stiffness is shown to be a strong predictor of further coronary events (19). The major limitation of our study is that our patients were at an advanced stage of their disease. Currently, DSA is limited to severe PAD cases requiring revascularization. Noninvasive tests are used before DSA is indicated. The latter is performed only for considering revascularization strategies in the most severe cases. This explains why all our patients had at least 1 arterial stenosis >50%. Consequently, we are unable to generalize our findings to patients with less-severe PAD. Due to its invasive characteristics, DSA can only be performed in patients with PAD. It is important to point out that our study does not suggest a benign prognosis for distal PAD. In fact, the CVD event rate was high in distal PAD, although significantly lower than proximal PAD.

Additional clinical and large-scale epidemiologic studies are necessary to validate our findings. Nearly all population studies to date have used the ankle-brachial index alone to define PAD and thus have been unable to define the levels of diseased arteries. Ultrasonography can now be used as an imaging modality in population studies, although at considerable expense. If our findings were confirmed, this could result in additional risk stratification of PAD patients depending on which lower extremity arteries are affected.

Conclusions

Among PAD patients, those with proximal lesions have a 2.5- to 3.5-fold risk of mortality and CVD events compared with those with distal PAD. This association is independent of several risk factors and comorbidities, which are differentially associated with these 2 localizations of PAD. Our results contrast with the poorer limb prognosis in cases of distal PAD. Our finding is limited to hospitalized PAD patients and needs further confirmation in prospective population studies.

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