Mortality in Peripheral Arterial Disease: A Comparison of Patients Managed by Vascular Specialists and General Practitioners

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BACKGROUND: Peripheral arterial disease (PAD) is undertreated by general practitioners (GPs). However, the impact of the suboptimal clinical management is unknown.

OBJECTIVE: To assess the mortality rate of PAD patients in relation to the type of physician who provides their care (GP or vascular specialist).

DESIGN: Prospective study.

SETTING: Primary care practice and academic vascular laboratory.

PARTICIPANTS: GP patients ($n = 60$) were those of the Peripheral Arteriopathy and Cardiovascular Events study (PACE). Patients managed by specialists ($n = 82$) were consecutive subjects with established PAD who were referred to our vascular laboratory during the enrolment period of the PACE study.

MEASUREMENTS: All-cause and cardiovascular mortality.

RESULTS: After 32 months of follow-up, specialist management was associated with a lower rate of all-cause mortality (RR=0.04; 95% CI 0.01–0.34; $p = .003$) and cardiovascular mortality (RR=0.07; 95% CI 0.01–0.65; $p = .020$), after adjustment for patients' characteristics. Specialists were more likely to use antiplatelet agents (93% vs 73%, $p < .001$), statins (62% vs 25%, $p < .001$) and beta blockers (28% vs 3%, $p < .001$). Survival differences between specialists and GPs disappeared once the use of pharmacotherapies was added to the proportional hazard model. The fully adjusted model showed that the use of statins was significantly associated with a reduced risk of all-cause mortality (RR= 0.02; 95% CI 0.01–0.73, $p = .034$) and cardiovascular mortality (RR=0.02; 95% CI 0.01–0.71, $p = .033$).

CONCLUSIONS: Specialist management of patients with symptomatic PAD resulted in better survival than generalist management. This effect appears to be mainly caused by the more frequent use of effective medicines by specialists.

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INTRODUCTION

Evidence suggests that specialists and generalist physicians have different approaches to cardiovascular patients.[1–3] General practitioners (GPs) provide care that is less resource-intensive and, thus, potentially less expensive, but may be less aware of key diagnostic and therapeutic advances. This may lead to worse outcomes.[1–3]

General practitioners are the physicians primarily and largely responsible for the diagnosis and treatment of patients with symptomatic peripheral arterial disease (PAD), a condition associated with high rates of ischemic events and increased mortality.[4–6] However, there are indications that the awareness and management of symptomatic PAD is unsatisfactory in general practice. Indeed, although leg pain during walking can be so troublesome as to adversely affect quality of life,[7,8] about half the cases remain unrecognized.[9–11] Furthermore, in community-based office practice, PAD is undertreated in terms of cardiovascular risk prevention.[10–12] It is worth noting that the rate of aspirin therapy in patients with a cardiologist or generalist as their main physician was 93% and 52%, respectively.[12] Unless referring to a cardiologist or a vascular specialist, these undertreated patients will presumably remain at high risk. Surprisingly, nothing is known about the outcome of PAD patients managed by GPs versus the outcome of patients managed by vascular specialists. This is particularly unfortunate because such information would help health care authorities develop strategies to reduce morbidity and mortality in a high-risk population.

To examine the mortality of patients with symptomatic PAD in relation to the type of physician who provides their care (GPs or vascular specialists), we compared the data of patients of the Peripheral Arteriopathy and Cardiovascular Events study (PACE),[10] who were managed by their GPs (GP-PAD), with those of patients who were regularly monitored by specialists at our vascular laboratory (S-PAD). We also determined whether differences in outcome were caused by PAD severity, prevalence of risk factors and other comorbid illnesses, or to the use of drugs known to reduce cardiovascular risk.

METHODS

We monitored 60 PAD patients managed by GPs, and 82 by vascular specialists for a median of 32.0 (23.7–40.0) months. Patients of both groups were enrolled in the study from February 2002 to January 2003, and were at stage II of Fontaines' classification (i.e., intermittent claudication). No patient of either group was in the terminal phases of severe medical disorders. All 142 patients gave their informed consent to the study, which was approved by the Ethics Committee of our Institution.

Identification of Patients Managed by GPs. Algorithm of the study is shown in Figure 1. In the PACE study, all subjects aged 40–80 years, included in the lists of 7 GPs from 5 villages of the Campania Region of Southern Italy, received a Rose questionnaire.[10] To avoid that the different ways primary care physicians diagnose and treat PAD patients could affect the results, the 7 GPs who participated in the PACE study were randomly selected from a group of 21. Symptomatic PAD was suspected in subjects who at the questionnaire referred pain in the calf, foot, thigh, or buttock (not in the knee) that began while walking and did not disappear when they continued walking, regardless of whether the remaining Rose criteria for claudication were met. To confirm PAD diagnosis, "suspected" symptomatic PAD cases underwent Doppler examination with assessment of the ankle/brachial index (ABI) and flow velocity in the femoral and posterior tibial arteries.[10] Symptomatic PAD, defined by an ABI <0.90 or reduced flow velocity in at least 1 leg,[13] was diagnosed in 60 subjects.[10] Baseline characteristics were obtained from the subjects' electronic medical records. The software system, used by approximately 8,000 Italian GPs, encodes all diagnostic records according to the ninth edition of the International Classification of Disease (ICD-9), and prescription records according to the Anatomical Therapeutical Chemical Classification system. Hypertension, hypercholesterolemia, and diabetes mellitus were diagnosed with the criteria used in the PACE study. After Doppler examination, all patients were managed by their GPs. The diagnostic and therapeutic strategies used by the GPs were not influenced by vascular specialists. Prescription of cardiovascular therapies was checked at the first visit and 6 months later.

Identification of Patients Managed by Vascular Specialists. To identify patients undergoing specialist care, we evaluated all consecutive subjects aged 40–80 years with suspected or known PAD who were referred to our vascular laboratory. Those with ABI <0.90 or reduced flow velocity in at least 1 leg (i.e., the same criteria used in the PACE study) were enrolled in the present study (n =82; Fig. 1). We obtained information about cardiovascular risk factors and comorbidities from hospital records and personal interviews during the first visit.

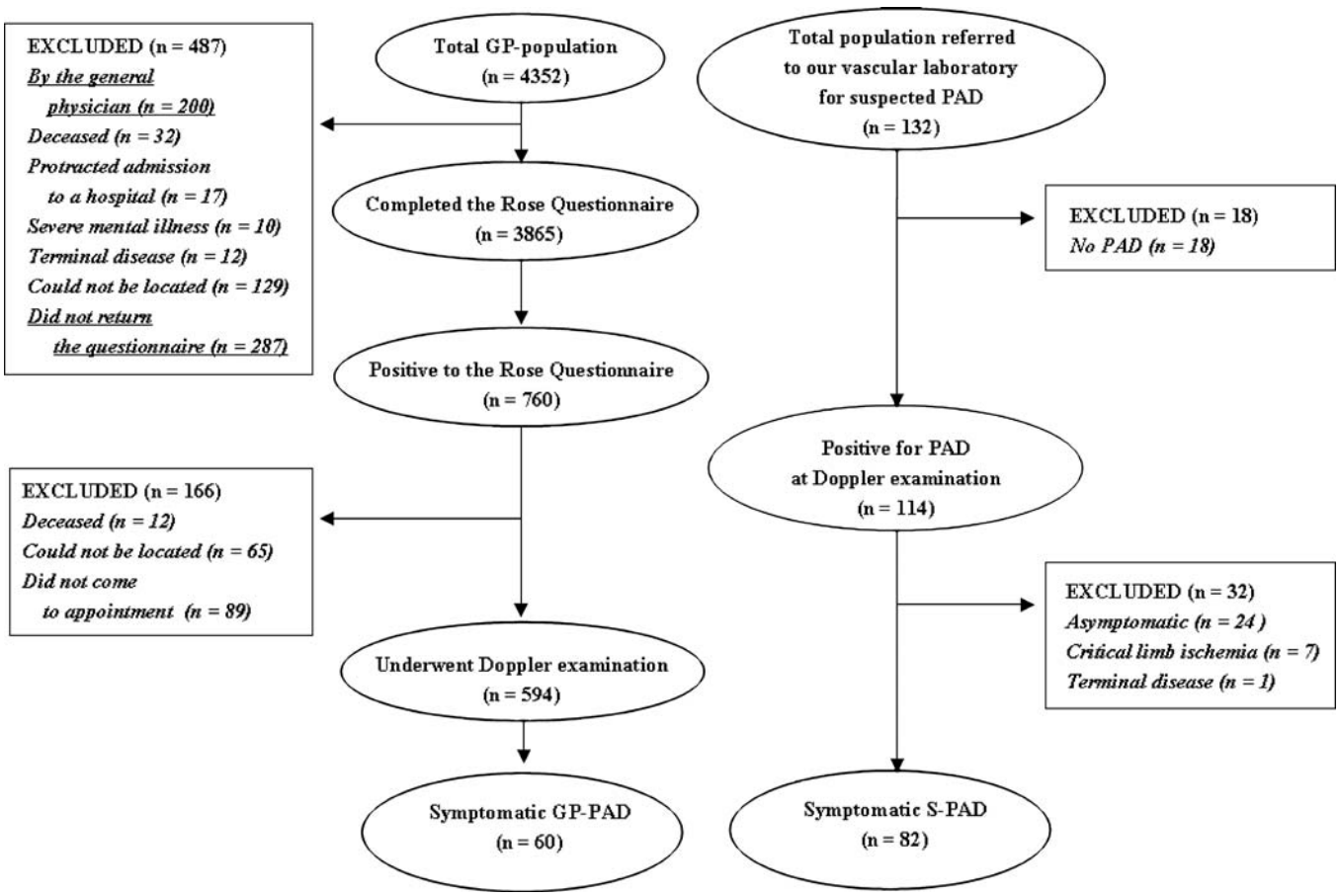

Figure 1. Algorithm of the study population.

We applied the criteria used in the PACE study to diagnose hypertension, hypercholesterolemia, and diabetes mellitus. All S-PAD patients then underwent echo color Doppler scanning of the abdominal aorta and the carotid arteries, according to our routine protocol. S-PAD patients without symptoms or a history of coronary artery disease (CAD) underwent dipyridamole myocardial perfusion imaging (MPI) to verify the presence or the absence of ischemic heart disease. After the screening visits, cardiovascular medicines were prescribed and compliance to treatment was checked at each follow-up visit.

C-Reactive Protein Measurement. High-sensitivity C-reactive protein (hs-CRP) plasma levels were measured by ELISA (Dade Behring Diagnostics, Marburg, Germany).

Prospective Follow-up. We assessed all-cause mortality and cardiovascular mortality, namely, death from myocardial infarction, sudden death, or stroke. To obtain information about deaths in the PACE cohort, every 6 months we reviewed the patients' electronic medical records, which were updated by the GPs on the basis of hospital records and death certificates. S-PAD patients were contacted for follow-up examination every 3 months. Mortality was documented by death certificates or hospital records, which were reviewed by 2 cardiologists at our department who were unaware of the aims of the study.

Statistical Analysis. Mortality rates were estimated by life table curves, and differences in survival between GP-PAD and S-PAD patients were calculated by the Wilcoxon test. Univariate and age- and sex-adjusted Cox proportional hazard analyses were used to evaluate the effect of being managed by a specialist on survival. Cox analyses were also used to investigate whether differences in survival between the GP-PAD and S-PAD groups were affected by ABI, cardiovascular risk factors, previous myocardial infarction, and previous stroke. We included cardiovascular drugs in the proportional hazard models to evaluate whether differences in drug use affected survival in GP-PAD and S-PAD patients. To control for possible systematic differences in the kinds of patients managed by specialists and generalists, which would bias the comparison of mortality rates, we first developed a logistic regression model with specialist status of the attending physician as the dependent variable.[14] This "propensity" model[15] included all the patient-specific demographic and clinical data detailed above. The propensity model was developed using the entire population, and yielded for each patient the estimated probability of being cared for by a specialist, expressed as a continuous variable between 0 and 1. It can be shown that patients with the same propensity score have the same distribution of the patient-specific variables, regardless of whether they are managed by a specialist or a generalist[15,16] (i.e., the propensity score is a balancing score that controls for referral bias owing to the observed variables). This score was then included in the mortality models as an additional independent variable to explicitly adjust for referral bias. Continuous variables are expressed as mean±SD (normally distributed) or median and 25th and 75th percentile (nonnormally distributed). We used the χ^2 test, the t test for unpaired samples, or the Mann–Whitney test as appropriate.

RESULTS

Baseline Characteristics. As Table 1 shows, patients managed by specialists were younger and included a higher percent of males. There were no statistical differences in classic risk factors, plasma levels of hs-CRP and ABI between the 2 groups. S-PAD patients had a significantly higher prevalence of CAD and previous myocardial infarction than GP-PAD patients. Conversely, the prevalence of cerebrovascular disease and previous stroke tended to be lower in S-PAD.

Medications and Cardiovascular Procedures. There were pronounced differences in treatment between the 2 groups. In fact, the rate of cardiovascular drug use was higher in S-PAD patients. As Table 2 shows, the use of antiplatelet agents and statins in S-PAD was about double that in GP-PAD (p <.001 for both drugs). Beta blockers were used in a few patients in both cohorts, but significantly less often by GPs (3% vs 29 %, p <.001). Undertreatment of PAD by GPs is confirmed by the finding that among hypertensives, 10 of 47 (21.3%) were untreated versus 4 of 66 (6.0%, p =.057) in S-PAD. Among hypercholesterolemic subjects, 28 of 43 (65.1%) patients in the GP-PAD group were untreated versus 14 of 57 (24.6%, p <.001) in the S-PAD group. To evaluate whether the low rate of cardiovascular drug use in the GP-PAD group was because GPs were unaware of the presence of PAD, we checked cardiovascular drug prescriptions 6 months after the first visit (i.e., when PAD had been identified in cases previously unknown to the GPs). The cardiovascular therapies remained substantially unchanged (Table 2).

Interventional therapies did not differ between the 2 groups. The myocardial revascularization rate by cardiac artery by-pass graft or percutaneous coronary intervention was 4% in S-PAD patients and 5% in GP-PAD patients (p =.695). The corresponding values for carotid surgery were 4% and 0% (p =.134).

With respect to diagnostic procedures, 29 S-PAD patients with no symptoms or history of CAD underwent dipyridamole MPI. Abnormal dipyridamole MPI was found in 4 (13.8%) patients who

Table 1. Baseline Characteristics of the Study Population

	S-patients (n =82)	GP-patients (n =60)	P
ABI	0.65±0.16	0.63±0.15	.371
Risk factors			
Age (yr)	64.8±10	69.0±8	.007
Males (%)	70 (85)	43 (72)	.045
Ex-smokers (%)	42 (51)	22 (37)	.101
Actual smokers (%)	33 (40)	15 (25)	.067
Hypercholesterolemia (%)	57 (70)	43 (72)	.786
Diabetes mellitus (%)	38 (46)	30 (50)	.666
Hypertension (%)	66 (80)	47 (78)	.753
Hs-CRP (mg/L)	2.8 (1.7–6.0)	3.4 (1.3–7.5)	.550
Comorbidities			
CAD (%)	48 (58)	20 (33)	< .001
Previous MI (%)	34 (41)	7 (12)	< .001
CVD (%)	12 (15)	16 (27)	.067
Previous stroke (%)	2 (2)	3 (5)	.402

S=specialist; GP=general practice; ABI=ankle/brachial index; hs-CRP=high sensitivity C reactive protein; CAD=coronary artery disease; MI=myocardial infarction; CVD=cerebrovascular disease

Table 2. Use of Cardiovascular Drugs in the Study Population

	S-patients (n =82)		GP-patients (n =60)		
	At the study entry	At 6 month follow-up	At the study entry	At 6 month follow-up	P*
Beta blockers (%)	24 (29)	23 (28)	2 (3)	2 (3)	<.001
ACE inhibitors (%)	41 (50)	43 (52)	26 (43)	26 (43)	.432
Calcium antagonists (%)	38 (46)	38 (46)	33 (55)	33 (55)	.308
Antiplatelets (%)	76 (93)	76 (93)	35 (58)	37 (61)	<.001
Statins (%)	49 (60)	51 (62)	12 (20)	15 (25)	<.001

S=specialist; GP=general practice; p refers to comparison between S- and GP-patients at 6 month follow-up; ACE=angiotensin converting enzyme.*

were classified as having coexistent CAD. A review of the electronic medical records at the first visit and during follow-up showed that no GP-PAD patient underwent dipyridamole MPI. All S-PAD patients underwent echo color Doppler scanning of the carotid arteries and abdominal aorta. These 2 examinations were performed in only 19 (31.7%) and 1 (1.7%) GP-PAD patients, respectively.

Outcome. Follow-up data were obtained for all 142 patients. As Table 3 shows, there were 18 deaths: 4 (4.9%) in the S-PAD group and 14 (23.3%) in the GP-PAD group. The corresponding values for cardiovascular deaths were 2 (2.4%) and 10 (16.7%). All-cause mortality and cardiovascular mortality were significantly lower in S-PAD than in GP-PAD (p <.001 for both endpoints) (Fig. 2). Crude and age- and sex-adjusted analyses revealed that clinical outcome was significantly better in S-PAD than in GP-PAD patients (Table 4). The survival of patients managed by specialists was even better when the statistical models were adjusted for ABI, risk factors, cardiovascular comorbidities, and propensity scores (Table 4, model 1).

Differences in treatment between specialists and GPs influenced outcome. In fact, survival differences between S-PAD and GP-PAD patients were no longer significant when the use of statins, beta blockers, and antiplatelet agents was added to the proportional hazard model (Table 4, model 2). However, results changed when medication variables were added to the models one at a time. The better survival in S-PAD versus GP-PAD patients remained significant when either antiplatelet agents or beta blockers were included in the analysis (results not shown). Conversely, survival differences disappeared with the addition of statins to the model. In fact, statins were associated with a reduced risk of all-cause mortality (RR=0.02; 95% CI 0.01–0.73, p =.034) and cardiovascular mortality (RR= 0.02; 95% CI 0.01–0.71, p =.033).

DISCUSSION

We found that patients with symptomatic PAD treated by vascular specialists had better outcomes than patients treated by GPs. After adjusting for ABI, risk factors, and cardiovascular comorbidity (i.e., factors that can confound the association between type of physician and survival, or known to be associated with survival), GP-PAD patients continued to have a greater incidence of both all-cause and cardiovascular death than S-PAD patients.

Theoretically, our findings may be explained by at least 3 factors. The first is that differences in classical risk factors and in plasma levels of hs-CRP, which is a marker of cardiovascular risk in PAD,[17,18] led to lower mortality among patients managed by specialists. However, adjustment for these confounders did not account for the differences in survival. Secondly, differences in mortality between S- and GP-PAD patients might be caused by differences in PAD severity and in the prevalence of coexisting cardiovascular disease. However, ABI, which is a sensitive index of the severity of peripheral arterial insufficiency and a strong predictor of cardiovascular risk,[6,19] was similar in the 2 cohorts. Moreover, the prevalence of previous myocardial infarction was over 3 times greater in S-PAD patients than in GP-PAD patients. Even so, the incidence of death was about 4 times greater for GP-PAD patients. In any case, the better survival associated with specialist management remained after adjustment for previous myocardial infarction and previous stroke. The greater prevalence of previous myocardial infarction in the S-PAD cohort is consistent with a report comparing patients from a vascular laboratory with those from a general medicine practice.[20] This difference may be because PAD patients with coexisting CAD are more likely to be referred to specialists.

The third possibility is that specific aspects of care by specialists were responsible for the better outcomes. Cardiologists and vascular specialists have more experience with patients affected by cardiovascular disease, and more time to devote to continuing education relevant to the treatment of this condition. Consequently, they would be expected to be more familiar than GPs with the diagnosis and management of PAD and associated comorbidities such as coronary and carotid artery disease. Indeed, PAD is a marker of generalized atherosclerosis,[21] and coronary and carotid arterial disease have been documented also in PAD patients asymptomatic for coronary and cerebrovascular disease. This is why PAD patients referring to our vascular laboratory without a history of CAD at the study entry undergo dipyridamole MPI, which detects abnormal perfusion patterns in a high percentage of PAD patients without a history or symptoms of CAD.[22] This diagnostic approach was not used by GPs in their PAD patients, as shown by a review of the electronic medical records at the time of the first visit and during follow-up. Similarly, all patients managed at our vascular laboratory underwent echo color Doppler scanning of the carotid arteries

Table 3. All Cause Mortality and Cardiovascular Mortality

	S-patients (n =82)	GP-patients (n =60)
All-cause mortality (%)	4 (4.9)	14 (23.3)
Cardiovascular mortality (%)	2 (2.4)	10 (16.7)
Sudden death (%)	0 (0)	2 (3.3)
Myocardial infarction (%)	1 (1.2)	4 (6.7)
Stroke (%)	0 (0)	4 (6.7)
Rupture of AAA (%)	1 (1.2)	0 (0)

S=specialist; GP=general practice; AAA=aneurysm of abdominal aorta.

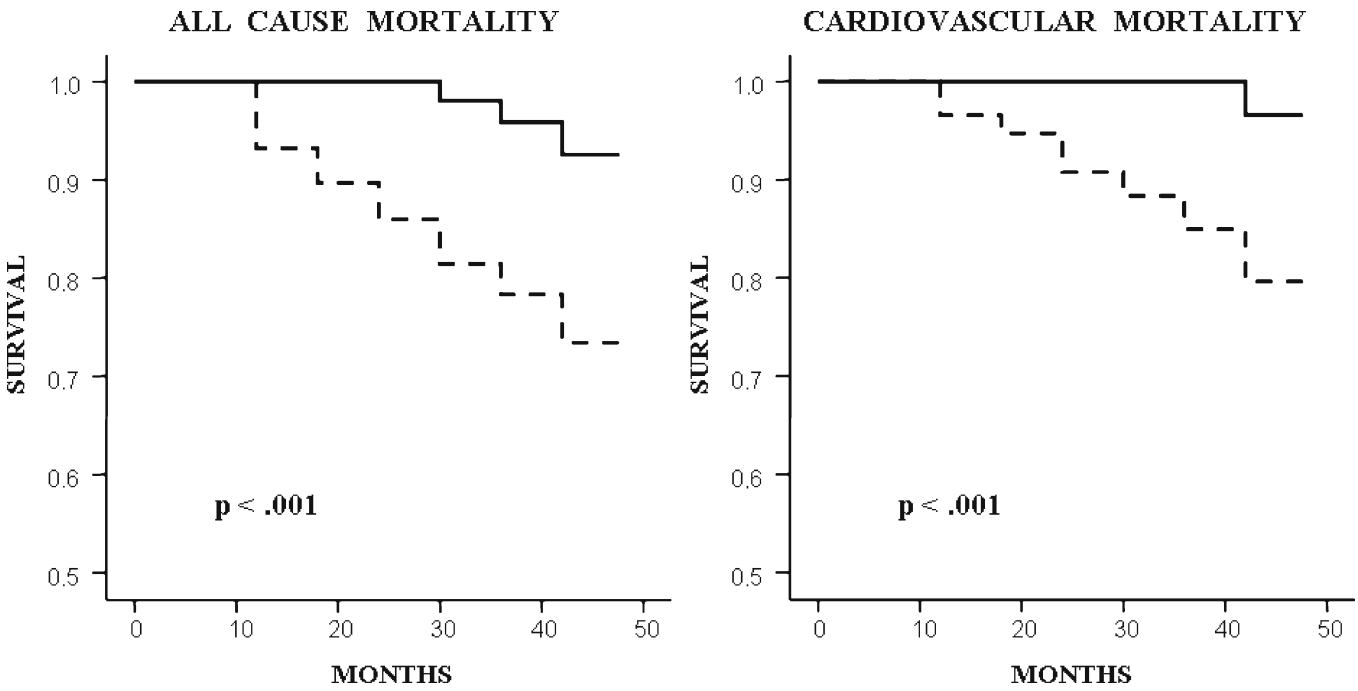

Figure 2. Survival curves in PAD patients managed by specialists (S-PAD, continuous line) and PAD patients managed by general practitioners (GP-PAD, broken line). Left panel: all-cause mortality; right panel: cardiovascular mortality.

versus only 32% of GP-PAD patients. Therefore, it is conceivable that asymptomatic coronary or carotid artery disease went undiagnosed, and thus untreated in some GP-PAD patients. Furthermore, specialists were more likely than GPs to treat PAD patients with antiplatelet agents, beta blockers, and statins, which reduce the cardiovascular risk in PAD.[23–26] We treated our PAD patients according to TransAtlantic Inter-Society Consensus (TASC) recommendations,[27] which may not be familiar to GPs. This may be caused by several factors. First, the expanding body of research makes it difficult for a generalist to be aware of every applicable guideline. Furthermore, physicians may not be able to overcome the inertia of previous practice. Third, GPs are under great pressure from health authorities to reduce costs, and this may lead to a shortfall in the translation of knowledge to action. Indeed, undertreatment of PAD by GPs is well recognized.[10–12] Therefore, our finding of a better outcome associated with specialists, and worse outcome associated with GPs, may be related to the use, or lack of use, of appropriate cardiovascular therapies. Indeed, when the multivariate model was adjusted for these therapies, the differences in mortality disappeared and statins were significantly associated with better survival. This result, coupled with that of a recent study on the effectiveness of cardiac medications in PAD,[26] indicates that greater use of guideline-supported therapies can lead to lower mortality in these patients.

Table 4. Relative Risk (95% Confidence Interval) for All-cause and Cardiovascular Mortality (Specialists Versus General Practitioners)

	All-cause mortality	*P*	Cardiovascular mortality	*P*
Univariate analysis	0.17 (0.06–0.52)	.002	0.11 (0.02–0.52)	.005
Age–gender adjusted	0.09 (0.02–0.41)	.002	0.13 (0.03–0.62)	.010
Multivariate adjusted Analysis (model 1)	0.02 (0.01–0.28)	.004	0.04 (0.01–0.60)	.020
Multivariate adjusted Analysis (model 2)	0.02 (0.01–1.53)	.076	0.03 (0.01–5.62)	.190

Model 1: adjusted for age, sex, ABI, smoking, diabetes mellitus, hypercholesterolemia, hypertension, hs-CRP, previous myocardial infarction, previous stroke, and propensity scores.
Model 2: use of antiplatelet agents, beta blockers, and statins was added to the covariates of model 1.

Study Limitations and Strengths. A major limitation of this study is that patients were not assigned randomly to specialist or generalist management. However, we used propensity analysis and adjusted for known and possible confounding factors in multivariate analysis. This procedure adjusts for selection bias.[15] Moreover, ABI, the most sensitive prognostic indicator in PAD, was similar in the 2 cohorts, and the 2 groups came from the same geographic area, which rules out genetic, ethnic, and lifestyle differences. Therefore, not surprisingly, the prevalence of cardiovascular risk factors in S-PAD cohort was similar to that in the GP-PAD cohort. The 2 populations differed with respect to cardiac comorbidity. However, mortality was greater among GP-PAD patients, although they had a significantly lower prevalence of coexisting CAD and previous myocardial infarction. Secondly, our results may not apply to patients with asymptomatic PAD, who constitutes the majority of PAD population. Furthermore, future studies are needed to determine the generalizability of our findings to other countries. Lastly, because patients receiving specialist care still have a primary care provider, we cannot exclude that our results could have been affected by an increased level of care ("additive effect").

The strengths of our study are the objective determination of PAD in both cohorts, and follow-up information available for all 142 patients. Furthermore, the 7 GPs who participated in the PACE study were randomly selected from a group of 21. Thus, the different ways that primary care physicians diagnose and treat patients with symptomatic PAD were well represented.

Conclusions. We found, in our study, that patients with symptomatic PAD who were managed by vascular specialists had a better survival rate than those managed by GPs. Based on our data, it is conceivable that a greater use of pharmacotherapies by specialists could contribute to survival advantage. Care by specialists was also associated with the use of more cardiovascular diagnostic procedures. In fact, it is well documented that PAD is largely underdiagnosed and undertreated in GP.[10–12] Our data indicate that this suboptimal clinical pattern may result in increased mortality. Although the results of this study alone do not justify a policy requiring that all patients with symptomatic PAD be cared for by vascular specialists, they indicate a critical need for an educational initiative directed at GPs to increase the awareness of PAD, its consequences, and treatments effective in improving survival of affected individuals.

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Conflict of Interest: *None disclosed.*

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