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Functional status measured by walking impairment questionnaire and cardiovascular risk prediction in peripheral arterial disease: results of the Peripheral Arteriopathy and Cardiovascular Events (PACE) study

Vittorio Schiano, Gregorio Brevetti, Giusy Sirico, Antonio Silvestro, Giuseppe Giugliano and Massimo Chiariello

Abstract: The prognostic impact of the functional status of patients with intermittent claudication is still obscure. From the lists of seven general practitioners, we identified all subjects aged 40–80 years ($n = 4352$). Of those reporting leg symptoms while walking on the Rose questionnaire ($n = 760$), 60 had a qualifying diagnosis of peripheral arterial disease (PAD). All of them received the Walking Impairment Questionnaire (WIQ). For each patient affected by PAD, three sex- and age-matched controls were selected randomly. After a 24-month follow-up, survival curves showed that PAD patients with WIQ scores $>$ median had a higher cardiovascular risk than controls, and patients with WIQ scores $<$ median had an even poorer prognosis ($p < 0.001$ for all WIQ domains). In PAD, after adjustment for age, sex, ankle–brachial index and comorbidity, two WIQ domains (ie walking speed and stair-climbing) were associated with cardiovascular events. The cardiovascular risk of claudicants who had a score $>$ median for at least three WIQ domains was intermediate versus the risk of controls and PAD patients with a WIQ score $<$ median, also when adjusted for the covariates indicated above (RR = 3.26, $p = 0.019$). In intermittent claudication, a worse functional status entails a greater risk of ischemic events versus low functional impairment.

Key words: cardiovascular risk; functional status; intermittent claudication; peripheral arterial disease; walking impairment questionnaire

Introduction

Peripheral arterial disease (PAD) is an important manifestation of atherosclerosis affecting a relatively large proportion of the adult population.^{1–5} Its most common symptomatic form (ie intermittent claudication) places a great burden on healthcare systems and on society as a whole. Actually, it represents an important cause of disability,^{6,7} and, even more importantly, is associated with an elevated risk of myocardial infarction and stroke.^{8–11} This increased risk is widely recognized to be strongly related to the severity of

PAD measured as ankle–brachial index (ABI).^{10–12} Conversely, the prognostic impact of the impaired functional status in patients with intermittent claudication is still obscure. This is particularly unfortunate, because claudicants may be severely limited in their occupational and leisure-time physical activity,^{6,7} and a sedentary lifestyle is a risk factor for adverse cardiovascular events.^{13–15}

In the Peripheral Arteriopathy and Cardiovascular Events (PACE) study,¹⁶ the first survey in Italy to assess the prevalence and the natural history of symptomatic PAD in the general population, we evaluated the degree of disability of claudicant patients at baseline, using the Walking Impairment Questionnaire (WIQ),¹⁷ a validated, disease-specific instrument, widely used in claudication trials.^{18–20} The objective was to ascertain whether functional status is an independent predictor of future cardiovascular events in intermittent claudication. In this regard, we paid special attention to the confounding effect of ABI, the most powerful prognostic indicator in PAD.^{10–12}

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Methods

Participant identification

The details of the PACE study, conducted in five villages of a well-defined area of the Campania region in southern Italy, are reported elsewhere.¹⁶ Briefly, from the lists of seven general practitioners (GPs), we identified all subjects aged 40–80 years ($n = 4352$). GPs excluded 200 patients for the reasons reported in Figure 1. The Rose questionnaire that identifies leg symptoms that occur during walking was mailed to each subject with an explanatory letter. Of these, 287 did not answer. Of the remaining 3865 subjects, those included in the definition of 'possible' symptomatic PAD were patients reporting pain in the calf that began while walking and did not disappear while continuing to walk, and those with other complaints of the calf, foot, thigh or buttock (not of the knee) showing the ischemic pattern described above, regardless of whether the remaining Rose criteria for claudication were met ($n = 760$). To confirm the PAD diagnosis, 'possible' symptomatic PAD cases underwent Doppler examination with assessment of the ABI and flow velocity in the femoral and posterior tibial arteries, which were measured by trained physicians as previously described.¹⁶

Of the 760 subjects positive to the Rose questionnaire, 12 died before the vascular examination, 65

moved and 89 did not keep their appointments. Age, sex, risk factors, and prevalence of concomitant cardiovascular disease did not differ between these 166 individuals and those who underwent the vascular examination. Symptomatic PAD defined by an ABI <0.90 or reduced flow velocity in at least one leg²¹ was present in 1.6% (60/3699 subjects) of the whole population.¹⁶ The vascular examination included the administration of the WIQ to assess a patient's perceived ability to walk defined distances and speeds, ability to climb stairs, and degree of walking impairment due to severity of claudication pain.^{17,22} Each domain has a score ranging from 0% (unable to perform the task) to 100% (no limitation). For each patient affected by PAD, three controls negative to the Rose questionnaire, and matched for sex and age (± 2 years) were selected randomly from the alphabetical listing of each GP. These subjects underwent the same investigations as the PAD patients. Baseline characteristics were obtained from the subjects' electronic medical records. The software system, used by approximately 8000 Italian GPs, encodes all diagnostics 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 was diagnosed if systolic arterial pressure exceeded 140 mmHg or diastolic arterial

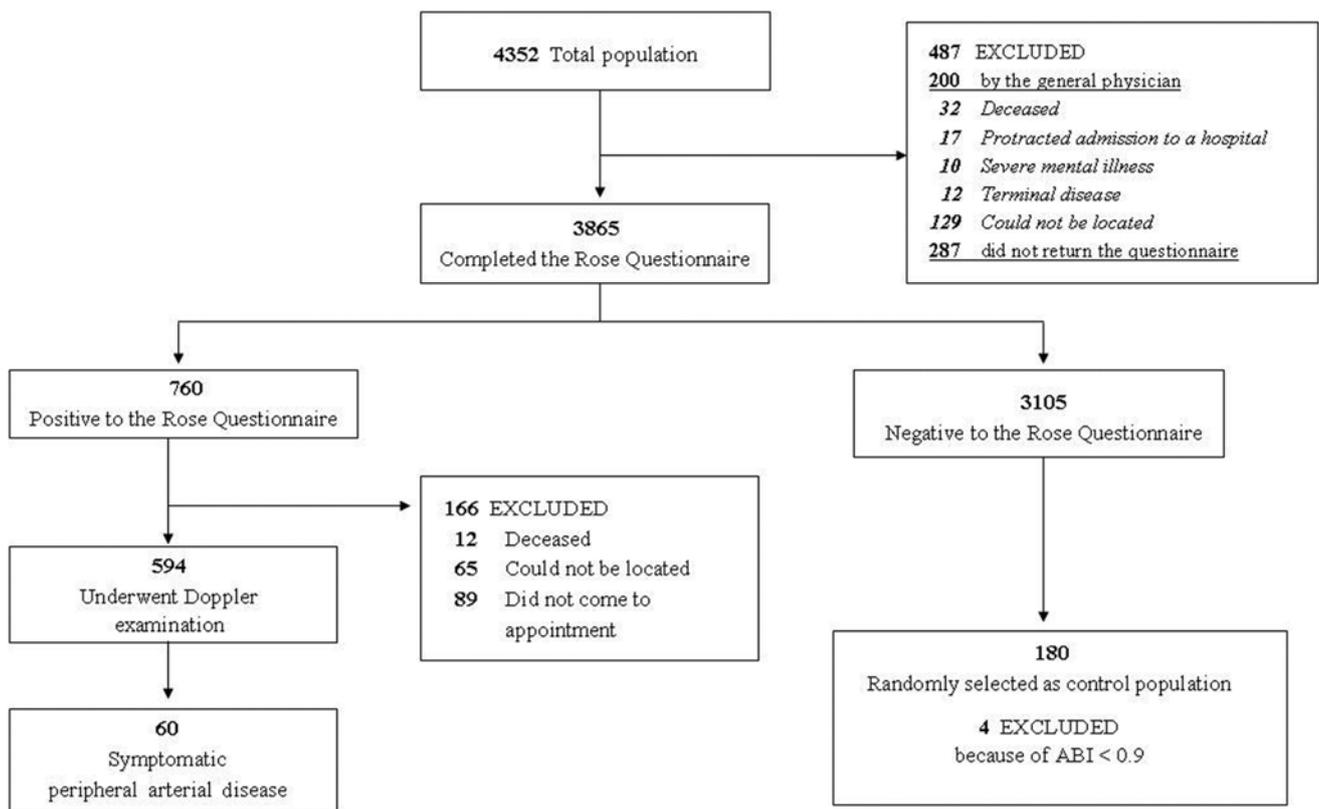


Figure 1 Flow diagram of the PACE study. Reasons for non-participation and exclusion.

pressure exceeded 90 mmHg, or if the patient used antihypertensive drugs. Hyperlipidemia was diagnosed in case of plasma total cholesterol >200 mg/dl, plasma triglycerides >200 mg/dl or HDL-cholesterol <35 mg/dl, or if the patient used lipid-lowering drugs. Diabetes mellitus was diagnosed if plasma fasting glucose exceeded 126 mg/dl, or if the patient used hypoglycemic drugs. Smokers were defined 'former' and 'current' smokers. Furthermore, the GP completed the cumulative illness rating scale (CIRS), which explores the presence and severity of 14 diseases of major organ groups.²³ Each disease group is rated as follows: 1 = no, 2 = mild, 3 = moderate, 4 = severe, 5 = life-threatening. The overall illness severity was represented by the mean of the 13 CIRS items (CIRS-IS). Furthermore, a comorbidity index (CIRS-CI) was computed by counting the number of items for which moderate to severe pathology was reported (scores 3, 4, or 5). All participants gave their written informed consent to the study, which was approved by our institutional ethics committee.

Prospective follow-up

GPs were contacted to determine the occurrence of events at 6-month intervals. The occurrence of cardiac (fatal and non-fatal myocardial infarction, unstable angina, and coronary revascularization procedures), cerebrovascular (fatal and non-fatal stroke, transitory ischemic attack, and carotid surgery), and peripheral (critical limb ischemia and revascularization procedures of the lower limbs) events were prospectively assessed. Peripheral revascularization was defined as the need for surgical or percutaneous transluminal intervention for symptomatic deterioration occurring at least 1 year after the study entry. Information about these events was extracted from the patients' electronic medical records which are updated by the GP on the basis of hospital records and death certificates. Two cardiologists at our department performed a blinded review of the events to confirm the agreement between the diagnosis obtained from the hospital record and death certificate and the ICD code. For patients experiencing more than one event, only the first was considered in the analysis.

Statistical analysis

To evaluate the impact of functional status on cardiovascular risk in PAD, each domain of the WIQ was divided into scores below and above the median. The incidence of cumulative cardiovascular events in the two groups divided according to WIQ score was estimated by survival curves, and probability values were calculated by the Wilcoxon test. Cox proportional hazard regression models were then used to control for confounders identified by univariate analysis (inclusion criteria $p < 0.1$).²⁴ Survival curves were also constructed for PAD patients with a score < the median

for at least three of the four WIQ domains, and in those with less impaired global functional status. Cox proportional hazard regression models were then used to control for age, sex, ABI and CIRS-IS (ie confounders identified at the univariate analysis). Values are expressed as median and interquartile range. Baseline characteristics were compared with the Mann-Whitney U test, or the χ^2 test, as appropriate.

Results

Figure 1 shows the flow diagram of the study and the reasons why some subjects were excluded. The baseline characteristics of the study population are detailed elsewhere.¹⁶ Briefly, compared with controls, the PAD group included a significantly higher number of smokers (44% vs 65%, $p = 0.029$), hypertensives (61% vs 80%, $p = 0.007$) and diabetics (22% vs 47%, $p = 0.001$). No group difference was observed for age, sex distribution, hyperlipidemia and both CIRS-CI (median [interquartile range]) (2.0 [1.0; 3.0] in controls, 2.0 [1.0; 4.0] in PAD patients; $p = 0.123$) and CIRS-IS (1.6 [1.4; 1.9] in controls, 1.7 [1.4; 2.0] in PAD patients; $p = 0.307$). Follow-up data were obtained for all intermittent claudication patients. Conversely, nine controls could not be contacted after the baseline examination. Compared with the other controls, these individuals did not differ appreciably for age, sex, risk factors and cardiovascular comorbidity. As Table 1 shows, after a median period of 24 months, a cardiovascular event was experienced by 18 (10.8%) controls (in three it was fatal) and 20 (33.3%) PAD patients (in five it was fatal). After adjustment for smoking, hypertension, diabetes mellitus, previous myocardial infarction, and previous stroke (confounders identified by univariate analysis), independent predictors of a cardiovascular event were symptomatic PAD (relative risk (RR) 2.65; 95% confidence interval (CI) 1.24–5.69; $p = 0.012$), and previous myocardial infarction (RR 4.00; 95% CI 1.34–11.91; $p = 0.013$). Figure 2 shows event-free survival curves for control subjects, PAD patients with a score > median for each of the four WIQ domains, and patients with a more compromised functional status (WIQ scores < median). In PAD patients, WIQ scores > median were associated with a higher incidence of cardiovascular events compared with controls, and WIQ scores < median with an even poorer prognosis. Group differences were significant for all the four WIQ domains.

In the PAD patient group, no significant differences in age, sex distribution and prevalence of both classic risk factors and previous cardiovascular events were observed between those with and without events at follow-up (Table 2). Similarly no group differences were observed with respect to the use of antiplatelets, statins, ACE inhibitors and other cardiovascular drugs.

Table 1 Cardiovascular mortality and cardiac, cerebrovascular and peripheral events observed during follow-up.

	PAD (n = 60)	Controls (n = 167)	Adjusted RR (95% CI)	p
Cardiovascular mortality	5 (8.3%)	3 (1.8%)	7.77 (1.51–40.16)	0.014
Cardiac events	11 (18.3%)	6 (3.6%)	4.33 (1.46–12.82)	0.008
Sudden death	2 (3.3%)	1 (0.6%)		
Myocardial infarction	2 (3.3%)	1 (0.6%)		
Fatal	1 (1.6%)	0 (0%)		
Coronary revascularization	2 (3.3%)	1 (0.6%)		
Angina	5 (8.3%)	3 (1.8%)		
Cerebrovascular events	5 (8.3%)	11 (6.6%)	1.13 (0.32–4.01)	0.844
Stroke	3 (5.0%)	3 (4.8%)		
Fatal	2 (3.3%)	2 (1.2%)		
TIA	2 (3.3%)	8 (4.8%)		
Carotid revascularization	0 (0%)	0 (0%)		
Peripheral events	4 (6.6%)	1 (0.6%)	9.51 (1.01–91.49)	0.043
Peripheral revascularization	4 (6.6%)	0 (0%)		
Critical limb ischemia	0 (0%)	1 (0.6%)		
Amputation	0 (0%)	0 (0%)		

PAD, peripheral arterial disease; RR, relative risk; CI, confidence interval; TIA, transient ischemic attack.

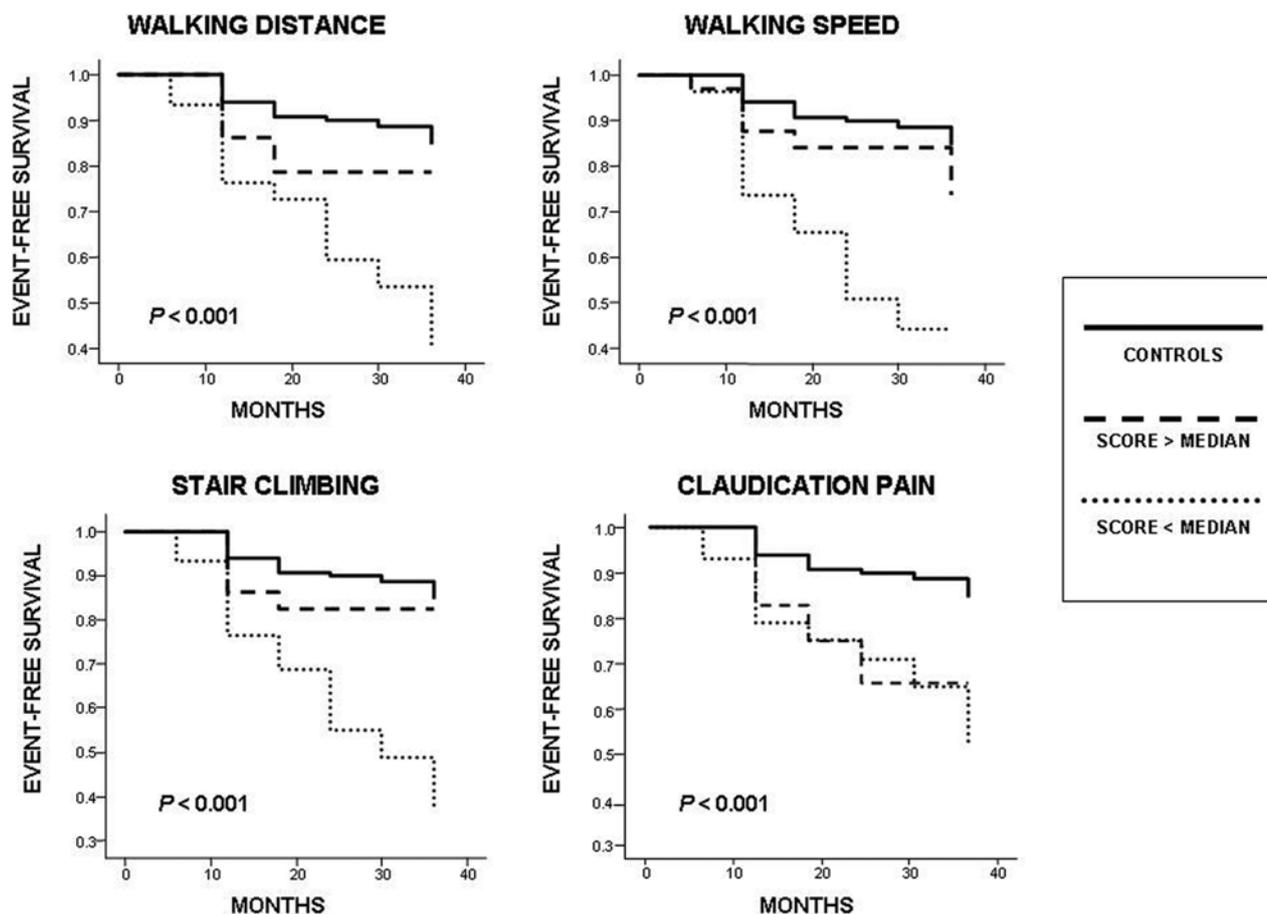


Figure 2 Cardiovascular event (fatal plus non-fatal)-free survival curves refer to control subjects and to PAD patients with scores above and below the median for each of the four walking impairment questionnaire (WIQ) domains.

Conversely, a significant difference was observed for ABI, which was 0.44 (0.60; 0.67) in patients with, and 0.70 (0.62; 0.78) ($p = 0.007$) in those without events. As reported in Table 2, group difference in CIRS-IS approached the statistical significance, while CIRS-CI

was similar in the two groups. In the 60 PAD patients, after adjustment for age and sex, the ABI and three WIQ domains (ie walking distance, walking speed and stair-climbing) were significantly associated with cardiovascular events (Table 3). Of note, both walking

Table 2 Baseline characteristics of symptomatic PAD patients with and without a cardiovascular event at follow-up.

	Cardiovascular events		<i>p</i>
	With (<i>n</i> = 20)	Without (<i>n</i> = 40)	
Clinical characteristics			
Age (years)	67.0 (61.0; 76.0)	70.0 (63.5; 77.5)	0.410
Men, <i>n</i> (%)	15 (75)	26 (65)	0.432
Smokers, <i>n</i> (%)	12 (60)	25 (63)	0.961
Hypertension, <i>n</i> (%)	15 (75)	32 (80)	0.658
Diabetes mellitus, <i>n</i> (%)	10 (50)	20 (50)	1.000
Hyperlipidemia, <i>n</i> (%)	11 (55)	27 (68)	0.220
Previous MI, <i>n</i> (%)	4 (20)	3 (8)	0.155
Previous stroke, <i>n</i> (%)	2 (10)	1 (3)	0.218
CIRS-CI	3.0 (1.0; 5.0)	2.0 (1.0; 4.0)	0.375
CIRS-IS	1.9 (1.5; 2.2)	1.7 (1.4; 1.5)	0.082
ABI	0.44 (0.60; 0.67)	0.70 (0.62; 0.78)	0.007
Treatments			
β-blockers (%)	0 (0)	2 (5)	0.223
ACE inhibitors (%)	11 (55)	16 (40)	0.271
Antiplatelets (%)	13 (65)	22 (55)	0.459
Lipid-lowering drugs (%)	5 (25)	7 (18)	0.494
WIQ domains			
Claudication pain	50.0 (25.0; 75.0)	75.0 (50.0; 75.0)	0.370
Walking distance	9.0 (2.0; 46.0)	34.0 (12.0; 75.0)	0.022
Walking speed	6.0 (3.0; 20.0)	22.0 (7.0; 36.0)	0.046
Stair climbing	12.0 (0.0; 42.0)	54.0 (19.0; 75.0)	0.012

MI, myocardial infarction; CIRS-CI, cumulative illness rating scale – comorbidity index; CIRS-IS, cumulative illness rating scale – illness severity; ABI, ankle-brachial index; ACE, angiotensin converting enzyme; WIQ, walking impairment questionnaire. Data presented as median (interquartile range).

Table 3 Predictive value of ABI and WIQ domains in PAD patients.

	Cox proportional hazard models					
	Adjusted for age and sex			Adjusted for age, sex, ABI and CIRS-IS		
	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>
ABI < median	3.57	1.26–10.13	0.017			
WIQ domains						
Claudication pain < median	1.10	0.43–2.86	0.840	0.92	0.36–2.35	0.861
Walking distance < median	2.84	1.07–7.49	0.035	2.30	0.84–6.33	0.105
Walking speed < median	3.92	1.46–10.03	0.007	3.73	1.33–10.42	0.012
Stair-climbing < median	3.61	1.30–10.03	0.014	2.94	1.04–8.35	0.043

ABI, ankle-brachial index; WIQ, walking impairment questionnaire; PAD, peripheral arterial disease; CIRS-IS, cumulative illness rating scale – illness severity; RR, relative risk; CI, confidence intervals.

speed score and stair-climbing score < median, maintained their predictive value also after adjustment for ABI and CIRS-IS (ie the variables showing significant differences at the univariate analysis) (Table 3).

Figure 3 shows event-free survival curves for control subjects and PAD patients categorized as being above or below the median value for at least three WIQ domains. The cardiovascular risk of PAD patients who had a score > median for at least three WIQ domains was intermediate versus the response of controls and patients with a more impaired functional status (ie WIQ score < median) (*p* < 0.001), also when peripheral events were excluded (*p* < 0.001).

Cox analysis showed that a more impaired functional status remained significantly associated with an increased cardiovascular risk, also when adjusted for age, sex, ABI and CIRS-IS (RR = 3.26, 95% CI 1.22–4.74; *p* = 0.019).

Discussion

As a result of a large number of observational epidemiologic studies, physical inactivity and a sedentary lifestyle have been recognized as risk factors for the development or progression of coronary artery disease

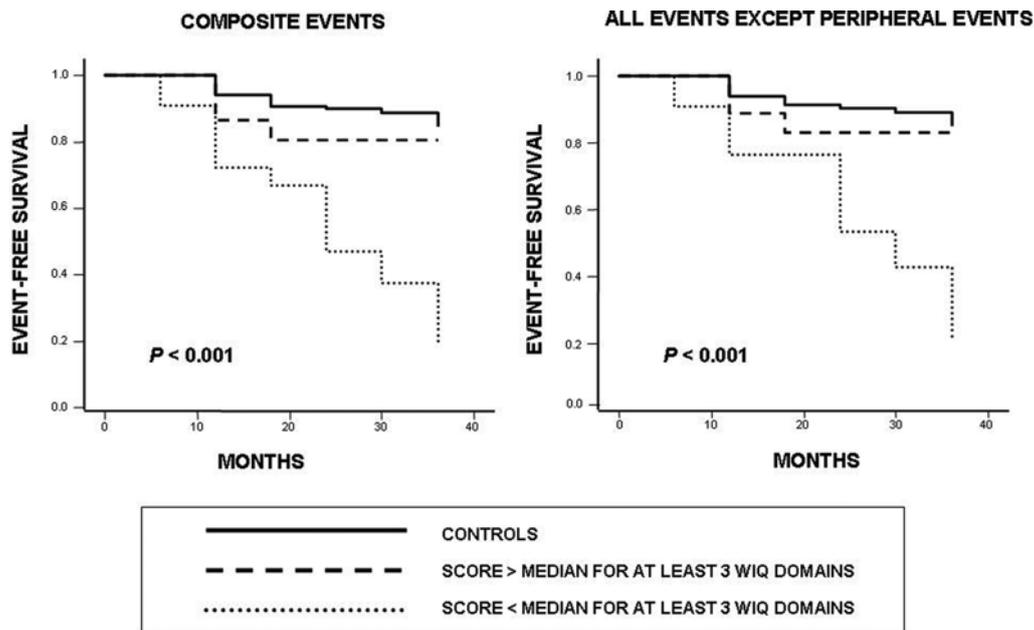


Figure 3 Cardiovascular event (fatal plus non-fatal)-free survival curves refer to control subjects and to PAD patients who had a score $>$ the median for at least three walking impairment questionnaire (WIQ) domains and patients with greater functional impairment. Left panel: all cardiovascular events; right panel: all events except peripheral events.

(CAD) and for adverse cardiovascular events and death.^{13–15} The results of the present study confirm the poor overall prognosis for individuals with symptomatic PAD, and first demonstrate an increasingly poor prognosis with increasing impairment in functional status. Actually, PAD patients with a reduced walking speed, a greater limitation in stair-climbing, and a score below the median for at least three WIQ domains showed a nearly threefold increased risk of developing a cardiovascular event, as compared with those with a less compromised functional status. Of note, the predictive value of WIQ was independent of the ABI, the most powerful prognostic indicator in intermittent claudication.^{10–12} Furthermore, the results appeared to be not affected by other factors that may influence the cardiovascular risk. Actually, the incidence of cardiovascular events was independent from traditional risk factors, history of previous myocardial infarction or stroke (the prevalence of these factors was similar in PAD patients with and without events at the follow-up), and from the CIRS-IS, a comorbidity index which explores the presence and severity of 14 diseases of major organ groups.²³ This is in line with previous studies indicating that, in claudicants, cardiovascular risk appears to be independent of risk factors, and is poorly related to the expected association of PAD with coronary and cerebrovascular disease.^{8,10} Moreover, no group differences were observed with respect to the use of antiplatelet therapy and interventions aimed at correcting risk factors.

Previous data of the PACE study¹⁶ showed that the prevalence of PAD in Italy tended to be lower than that in northern American and northern European countries.^{1–5} This might be due to a less aggressive nature of the atherogenic factors and/or to a lower susceptibility to them in the Italian population. However, we found that the cardiovascular risk of our claudicants was similar to that in Anglo-Saxon^{8–11} populations. It is difficult to explain the discrepancy we observed in our population between the low symptomatic PAD prevalence and the elevated cardiovascular risk of the affected individuals. However, it may be hypothesized that, in claudicants, the various atherogenic factors are important in the development of atherosclerotic disease in the lower limbs, but scarcely influence the progression of the atherosclerosis in other vascular districts. In this regard, it is interesting to note that smoking and diabetes mellitus, which are important risk factors for the development of symptomatic PAD,^{11,25} scarcely influence the systemic cardiovascular risk in claudicants, as observed in this and previous studies.^{8,10}

A limitation of the study is that we cannot be sure that all non-fatal events were recorded by the GPs, but given the changes in therapy and requests for laboratory examinations contained in the electronic records, it is likely that non-notified events were negligible. One of the strengths of our study is that all Italians are registered with a GP and so the population of a general practice is a segment of the general population. Other features of our study are the objective determination of

PAD, follow-up examinations every 6 months, and follow-up information available for all the claudicant patients.

Beyond its novelty (to the best of our knowledge, there are no previous reports on the relationship between functional status and cardiovascular risk in PAD), our study may have important implications. First, it indicates that WIQ, which requires only few minutes to administer, could be included among the measures used to gauge cardiovascular risk in claudicants. Second, because ABI determination is more time-consuming than the self-administered questionnaire, and requires training of the observers, the WIQ could prove to be very useful in epidemiologic studies involving GPs. In this context, it should be noted that WIQ is a subjective measure of functioning. However, the repeatability and validity of the questionnaire has been documented.¹⁷

Exercise training improves prognosis in diabetics²⁶ and patients with coronary artery disease,²⁷ who are highly prevalent in the PAD population.^{1,2,16} However, there are no data about the effect of exercise on cardiovascular risk in intermittent claudication. This is particularly unfortunate because in these patients exercise increases the capacity to perform daily physical activities,^{18,19} favorably modifies the cardiovascular risk factors profile,²⁸ and improves endothelial function.²⁹ Thus, there is a need for studies aimed at verifying whether exercise training may reduce cardiovascular risk in patients with symptomatic PAD.

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