Peripheral arterial disease versus other localizations of vascular disease: The ATTEST study

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Objective: **Despite the increased cardiovascular morbidity and mortality risk of patients with peripheral arterial disease, previous worldwide studies have documented undertreatment of cardiovascular risk factors in such patients.**
Method: **The ATTEST study was an observational cross-sectional epidemiologic study. Patients (n = 8475) were selected by 3020 general practitioners in France who were asked to include the first three patients with at least one site of proven atherothrombotic disease (peripheral arterial disease of the lower limbs for two patients and coronary artery disease or ischemic stroke for the third patient). We designed the ATTEST study to compare medical management of patients with peripheral arterial disease, including pharmacologic treatment, cardiovascular tests, and physician's assessment of future cardiovascular and amputation risks, with patients with coronary artery disease or ischemic stroke.**
Results: **Only 13% of the patients with peripheral arterial disease (n = 3811) received angiotensin converting enzyme inhibitors, statins, and antiplatelet agents vs 30% of the patients with coronary artery disease or ischemic stroke (n = 4664). This undertreatment of the population with peripheral arterial disease was associated with a too-optimistic physician's assessment of future cardiovascular risk: only 27% of the general practitioners predicted a 5-year cardiovascular risk >20%. Conversely, amputation risk prediction was greatly overestimated: only 44% of the practitioners predicted a 5-year amputation risk <5%.**
Conclusions: **Patients with atherothrombotic disease recruited from primary care practices were not adequately tested and treated, especially the patients with peripheral arterial disease. To improve the medical management of patients with peripheral arterial disease, there is a need for epidemiologic and clinical education of physicians. (J Vasc Surg 2006;44: 314-8.)**

Epidemiologic and natural history studies have determined that peripheral arterial disease (PAD) is highly prevalent and confers a high risk of fatal and nonfatal cardiovascular and cerebrovascular events.[1-4] The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program has included 6979 patients aged ≥70 years or 50 to 69 years with a history of smoking or diabetes mellitus in which PAD was detected by measurement of the ankle-brachial index (ABI). The usual definition of ABI <0.9 was used to assess PAD in 1865 of these patients (29%).[1]

Furthermore, in a longitudinal study, Criqui et al[4] demonstrated that after a 5-year follow-up of 100 patients with PAD, 16 cardiovascular deaths, 4 cerebrovascular deaths, 3 other vascular deaths, and 7 nonvascular deaths will occur (30% mortality at 5 years); during the same period, two patients will undergo an amputation. Despite this high prevalence of PAD in elderly patients and the increased cardiovascular morbidity and mortality risk associated with PAD, several studies have documented undertreatment of cardiovascular risk factors in patients with PAD.[1,3,5,6]

Again, in the PARTNERS program, participants with PAD were treated less intensively with antihypertensives, antiplatelet therapy, and cholesterol-lowering therapy than those with coronary artery disease (CAD).[1] Reasons for the undertreatment of cardiovascular risk factors in patients with PAD are not well understood. However, a national survey study from the United States documented deficiencies in physician knowledge and attitudes regarding the importance of treatment of atherosclerotic risk factors for patients with PAD.[5,6]

The objectives of the ATTEST (prise en charge de l'ArTériopaThie oblitErante des membreS inférieurs chez les paTients en médecine générale) study were to compare pharmacologic treatment (primary objective) and medical management, including cardiovascular tests, and physician's assessment of future cardiovascular and amputation risks (secondary objectives) of patients with proven PAD with patients with other vascular site(s) involved in atherothrombosis.

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Competition of interest: Marie-Annick Herrmann and Pascal Michon are employees of Bristol-Myers Squibb and Sanofi Aventis France, respectively. The other authors have received honoraria from Bristol-Myers Squibb for their participation on the scientific committee of the ATTEST study.

This work has been made possible by Bristol-Myers Squibb and Sanofi Aventis France.

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0741-5214/$32.00

doi:10.1016/j.jvs.2006.04.002

Table I. Cardiovascular risk factors of patients included in the ATTEST study according to localization of vascular disease

Parameters	*Isolated PAD n = 3811*	*PAD and (CAD or CVD) n = 2416*	*CAD and/or CVD (without PAD) n = 2248*	P*
Cardiovascular risk factors				
Age (years)	66 ± 12	69 ± 10	66 ± 12	<.001
Gender (% male)	80	83	76	<.001
Body mass index (kg/m^2)	25.6 ± 3.8	26.3 ± 3.9	26.6 ± 3.9	<.001
Hypertension (%)	58	72	61	<.001
Dyslipidemia (%)	62	73	70	<.001
Diabetes mellitus (%)	22	32	22	<.001
Current smoker (%)	44	32	23	<.001
SBP (mm Hg)	138 ± 13	138 ± 14	135 ± 14	<.001
DBP (mm Hg)	79 ± 8	79 ± 9	78 ± 8	<.001
LDL cholesterol (mmol/l)	3.36 ± 0.78	3.21 ± 1.03	3.10 ± 0.78	<.001

PAD, Peripheral arterial disease; *CAD,* coronary artery disease; *CVD,* cerebrovascular disease; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *LDL,* low-density lipoprotein.
*Analysis of variance.

METHODS

Population. The design of the ATTEST study has been reported elsewhere.[7] Briefly, it was an observational, cross-sectional epidemiologic study that took place in France between April and November 2003. Patients were selected by a geographically representative panel of 3020 general practitioners who agreed to participate in the study. Each physician was asked to include the first three patients identified from his or her practice to fulfill the inclusion criteria. The inclusion criteria were patients (1) >18 years old, (2) with at least one site of proven atherothrombotic disease (PAD of the lower limbs for two patients and proven CAD or ischemic stroke for the third patient), and who were (3) willing to participate in the study and give consent after receiving written and oral information. A total of 8475 patients were included (all data completed) and analyzed. The protocol was approved by the institutional review committees Conseil National de l'Ordre des Médecins, Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le domaine de la Santé, Commission Nationale Informatique et Liberté.

Atherothrombotic diseases were defined using the International Classification of Diseases (10th edition). PAD disease was defined as typical symptoms of and/or severe (>70%) stenosis at arterial duplex or arteriography (99% of patients had arterial duplex examinations), and/or a history of surgical or percutaneous transluminal treatment for lower limb arterial disease (excluding the renal and splanchnic circulation and abdominal aortic aneurysm). Coronary heart disease was defined as any history of angina pectoris (chest pain precipitated by exertion and relieved by rest or nitrates) confirmed by coronary angiography, myocardial infarction, typical sequelae on electrocardiography, coronary percutaneous transluminal angioplasty, or coronary artery bypass surgery or a combination. Cerebrovascular disease was defined as a history of ischemic stroke confirmed by computed tomography or magnetic resonance imaging.

A physician-completed inclusion questionnaire contained the following data: gender, age, weight, height, personal history of diabetes mellitus, dyslipidemia, or hypertension, current and previous smoking habit, cardiovascular tests previously performed, and current use of antiplatelet, cardiovascular, lipid-lowering, and antidiabetic drugs. These medical data were not obtained from a formal testing protocol, and the ATTEST study was not planned to add any tests to the management of the patients. Rather, physicians were asked to give the most recent information present in their medical files. Finally, the physicians were asked to estimate future cardiovascular and amputation risks, choosing for each of their 3 patients included for both risks: <5%, 5% to <10%, 10% to <20%, 20% to <50%, and ≥50%.

Statistical analysis. The population was divided into three groups: (1) patients with isolated PAD (n = 3811), (2) patients with PAD associated with atherosclerosis in at least one other location, CAD or cerebrovascular disease (n = 2416), and (3) patients with CAD or cerebrovascular disease, or both, but without PAD (n = 2248). Quantitative parameters were described by using means and standard deviations, and qualitative parameters by number and percent. Qualitative parameter distributions within the three groups were analyzed using the χ^2 test. Analysis of variance (ANOVA) was used for quantitative parameter comparisons among the three groups; no post hoc test was performed. $P < .05$ was considered significant. All analyses were performed using SAS 8.1 software (SAS Institute, Cary, NC).

RESULTS

Table I shows the cardiovascular risk factors of the study population according to the site of atherothrombosis. All ANOVA comparisons are statistically significant because of the large numbers. The most relevant differences showed that patients with isolated PAD were more fre-

Table II. Pharmacologic treatment and medical management of patients included in the ATTEST study according to localization of vascular disease

Parameters	*Isolated PAD n=3811 (%)*	*PAD and (CAD or CVD) n=2416 (%)*	*CAD and/or CVD (without PAD) n=2248 (%)*	P*
Pharmacologic treatment				
Aspirin	32	39	54	<.001
Clopidogrel/ticlopidine	66	64	57	<.001
No antiplatelet drug	8	8	6	<.001
β-blockers	12	40	57	<.001
ACE inhibitors	23	46	41	<.001
Angiotensin II RA	17	18	14	<.001
Calcium-channel antagonist	25	42	31	<.001
Diuretic	23	37	27	<.001
Statin	53	71	74	<.001
Other hypocholesterolemic	10	11	9	.003
Antidiabetic agent	18	29	18	<.001
Vasoactive agent	63	60	18	<.001
Antiplatelet + ACEI. + statin	13	31	30	<.001
Medical management				
Medical cost full reimbursement	76	87	83	<.001
ABI measurement	34	31	9	<.001
Peripheral ADP	99	97	41	<.001
Cervical ADP	68	71	61	<.001
Abdominal ADP	59	57	31	<.001
Electrocardiogram	81	94	93	<.001
Stress test	40	66	67	<.001
Myocardial scintigraphy	6	35	36	<.001
Coronarography	5	60	67	<.001

PAD, peripheral arterial disease; *CAD,* coronary artery disease; *CVD,* cerebrovascular disease; *ACEI,* angiotensin-converting enzyme inhibitor; *RA, r*eceptor antagonist; *ABI,* ankle-brachial index; *ADP,* arterial duplex.
*Analysis of variance

quently current smokers and had higher low-density lipoprotein cholesterol levels.

Characteristics of the patients concerning pharmacologic treatment and medical management are given in Table II. Patients with isolated PAD were less likely to be treated with cardiovascular and lipid-lowering drugs. The use of antiplatelet drugs, particularly aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium-channel antagonists, diuretics, and statins, as well as the combination of antiplatelet agents, ACE inhibitors, and statins were all lower in the PAD group compared with the other groups. In France, the right to full cost reimbursement is provided for artery diseases, regardless of location. However, practitioners tend to propose to their patients such a full reimbursement less often in PAD than in the other groups.

In addition, measurement of ABI was performed in only a third of the patients with PAD. Cardiac tests were also less likely to be performed in patients with PAD than in the two other groups: electrocardiogram, 81% vs 94% and 93%; stress test, 40% vs 66% and 67%; myocardial scintigraphy, 6% vs 35% and 36%; and coronary angiography, 5% vs 60% and 67%.

Table III shows cardiovascular and amputation risk predictions of the study population according to the site of atherothrombosis. Patients with PAD were predicted to have a more favorable risk profile than patients in the two other groups ($P < .001$). Physician assessment of 5-year cardiovascular death risk was ≥20% in 27% patients with PAD vs 48% and 29% in the two other groups. Conversely, amputation risk prediction was greatly overestimated: only 44% of the practitioners predicted a 5-year amputation risk >5% in the PAD group, which corresponds to published data on its incidence of 2% risk at 5 years.[4]

DISCUSSION

The major findings of the ATTEST study are that (1) this atherothrombotic population recruited from primary care practices in France was not adequately tested and treated as a whole, (2) the underuse of medical therapy was especially true for patients with PAD, and (3) cardiovascular death risk was underestimated and amputation risk was overestimated in patients with PAD.

In the ATTEST study, ABI was performed in only a third of the patients with PAD. This result is not surprising, because general practitioners in France rarely perform ABI. However, several epidemiologic studies, such as the PARTNERS program, have demonstrated that although more than half of the patients with PAD have leg symptoms, relatively few reported classic Rose claudication.[1] In addition, PAD patients with atypical or no symptoms were more likely to have their PAD diagnosis established only by ABI measurement. Such data suggest that clinicians who use a classic history of claudication alone to detect PAD (ie,

Table III. General practitioner predictions of cardiovascular and amputation risks of patients included in the ATTEST study according to localization of vascular disease

*5-year prediction**	*Isolated PAD n = 3811 (%)*	*PAD and (CAD or CVD) n = 2416 (%)*	*CAD and/or CVD (without PAD) n=2248 (%)*	P†
Cardiovascular death risk				<.001
<5%	21	7	19	
5% to <10%	25	17	26	
10% to <20%	27	28	26	
20% to <50%	20	33	21	
≥50%	7	15	8	
Amputation risk				<.001
<5%	44	38	88	
5% to <10%	27	28	7	
10% to <20%	15	18	2	
20% to <50%	10	11	1	
≥50%	4	5	2	

PAD, Peripheral arterial disease; *CAD,* coronary artery disease; *CVD,* cerebrovascular disease.
*Different choices for risk prediction were, <5%, 5% to <10%, 10% to <20%, 20% to <50% and ≥50%.
†Analysis of variance.

most of the general practitioners recruited in the ATTEST study) are likely to miss 85% to 90% of the patients with PAD.[1] Because atherosclerosis risk factor treatment is clearly associated with better prognosis in patients with PAD,[3,8-10] we believe that late diagnosis (ie, absence of ABI measurements) could be considered as the loss of a chance for an improved outcome in these patients. In this respect, some experts have proposed the creation of a national PAD public awareness program.[11]

PAD confers a high cardiovascular risk,[3] and the risks of future cardiovascular events in patients with PAD are comparable with those in patients with CAD.[8] In recent therapeutic trials that included heterogeneous populations at increased cardiovascular risk, such as the Heart Protection Study (HPS)[9] and Heart Outcome Prevention Evaluation (HOPE)[10] trials, patients with PAD were at even greater risk for cardiovascular events than patients with previous myocardial infarction or patients with diabetes mellitus. Despite these facts, in the ATTEST study, patients with PAD were undertreated and cardiovascular tests were underperformed.

Three classes of drugs—ACE inhibitors, statins, and antiplatelet agents—have clearly demonstrated benefit in patients with PAD with a high level of evidence.[3,8-10] In the present study, however, only 13% of the patients with PAD received the combination of these drugs vs 30% of the patients in the other groups. In contrast, a class of drugs that was most frequently prescribed in the present study was vasoactive agents, which have never been proven to decrease cardiovascular morbid events. The same was true concerning cardiovascular tests: only 40% of the patients with PAD had had a stress test, although fatal myocardial infarction is the leading cause of death in this population.

Previous reports worldwide are in accordance with these findings.[1,5,6,12] Part of the observed undermanagement and undertreatment in the present population with PAD was probably related to a too-optimistic cardiovascular risk prediction: only 27% of the practitioners predicted a 5-year cardiovascular risk >20%. On the contrary, amputation risk prediction was greatly overestimated: only 44% of the practitioners predicted a 5-year amputation risk <5%.

Several limitations of the ATTEST study deserve mention. First, because blood tests and cardiovascular tests were not systematically performed, previous cardiovascular events and prevalence of cardiovascular risk factors were probably underestimated. Second, neither diagnostic nor therapeutic recommendations were given to the investigators; priority was given to "real life" evaluation to be close to everyday medical practice in its heterogeneity. This last point is probably not true for antiplatelet agents, however. In fact, the setup of the ATTEST study was performed in association with a sensitization program concerning the benefits of prescribing antiplatelet agents in patients with atherothrombosis. So, the 13% of the patients receiving ACE inhibitors, statins, and antiplatelet agents is probably overestimated compared with the national prescription of the combination of these drugs.

CONCLUSIONS

The increased cardiovascular morbidity and mortality risk in patients with PAD could presumably be reduced by appropriate lifestyle and pharmacologic interventions within a primary care setting.[3,8-10] Such interventions should preferably be initiated by each patient's general practitioner, who has the best ability to establish the PAD diagnosis and to maintain a long-term therapeutic relationship with the patient. Furthermore, it is well known that patients' requests for treatment and attitudes about the importance of treatment are major determinants of a physician's behavior toward the use of preventive interventions.[13] Compared with patients with CAD without peripheral arterial disease, the high risk of cardiovascular events associated with PAD and the benefits of cholesterol-

lowering therapy were underestimated.[6] Such findings may help explain the low rates of cardiovascular risk factor control previously reported in patients with PAD.[6]

Finally, because patients with PAD or CAD have the same magnitude of cardiovascular risk,[8-10] we believe that improvement of PAD management needs epidemiologic and medical education of the physicians, and measurement of ABI should be systematic in the primary care in the elderly or after the age of 50 in smokers or in patients with diabetes.[1]

Members of the ATTEST Scientific Committee would like to acknowledge the contribution of each general practitioner.

AUTHOR CONTRIBUTIONS

Conception and design: JB, PC, FL, JJM, HL, JB, PM, MAH, PP
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Submitted Nov 25, 2005; accepted Apr 3, 2006.