Outcomes and management costs of peripheral artery disease in France

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ABSTRACT

Background: Little is known about the characteristics and prognosis of patients with peripheral arterial disease (PAD) and related real-life health costs in France.

Methods: A cohort of patients diagnosed with PAD between 2007 and 2011 was extracted from the French *Echantillon Généraliste des Bénéficiaires* (EGB) claims database. The patients were followed up from the date of PAD diagnosis. Their characteristics, incidence of death and other events, treatments, and costs were analyzed by comparison with age- and gender-matched PAD-free controls.

Results: There were 5889 patients with PAD identified. Mean age was 70.8 years, and 68.1% of patients were male. Diabetes was present in 28.9% of patients (13.2% of controls), hypercholesterolemia in 52.9% (28.7%), and hypertension in 46.6% (12.3%); 4.9% of patients had a history of unstable angina or myocardial infarction (0.5%), and 6.0% had a history of stroke or transient ischemic attack (1.4%). At inclusion, 69.3% of patients were receiving antiplatelet drugs (17.3%), 52.3% statins (21.9%), 26.7% angiotensin-converting enzyme inhibitors (13.7%), and 24.2% angiotensin receptor blockers (16.6%). Cumulative mortality rates were 13.2% at 1 year and 19.4% at 2 years (3.2% and 6.5% in controls). Cumulative incidence rates of death and major cardiovascular events (myocardial infarction and ischemic stroke) were 15.7% (95% confidence interval [CI], 14.8%-16.6%) at 1 year and 22.9% (95% CI, 21.9%-24.0%) at 2 years vs 3.9% (95% CI, 3.4%-4.4%) and 7.8% (95% CI, 7.1%-8.5%) in controls. All differences were statistically significant ($P < .05$). Total annual management costs were €14,949 in the PAD group and €3812 in the control group.

Conclusions: Mortality is elevated and cardiovascular events are frequent among French PAD patients. PAD drug treatment guidelines are not fully implemented in France. (J Vasc Surg 2017;■:1-10.)

Lower extremity peripheral arterial disease (PAD) is the third most common cause of atherosclerotic cardiovascular morbidity after coronary artery disease and stroke. PAD affects about 200 million people globally.[1] The estimated prevalence of PAD in the United States and Europe is 3% to 10% overall and 15% to 20% among persons older than 70 years.[2] In France in 2014, about 500,000 patients had 100% health care coverage for PAD, which means that 100% of their reimbursable health care consumption was covered by the national health insurance system.[3]

The management of PAD risk factors, such as hypercholesterolemia, diabetes, smoking, and hypertension, is an important public health priority, with the aim of preventing other cardiovascular events, such as myocardial infarction (MI) and stroke, and cardiovascular mortality. Secondary preventive measures have been implemented in guidelines to help physicians in their daily practice.[4-7]

It is important to monitor the implementation and impact of practice guidelines in everyday clinical practice. In France, two recent observational studies[8,9] indicated that the proportion of patients who received recommended prescriptions for PAD was lower than expected. These studies also estimated the frequency of cardiovascular events in patients with PAD. However, observational studies have several drawbacks in assessing standards of care, for example, participation bias as these studies are voluntary, incomplete or missing information on health care consumption, and the risk of modifying the physicians' practices because of their participation in the study (observation bias).

It has recently become possible to access data from nationwide claims and hospitalization databases in France, enabling the collection of data that may provide a more accurate representation of real-world practice than that available in patient registries.[10] The *Echantillon Généraliste des Bénéficiaires* (EGB) database provides representative information on medical conditions and

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everyday clinical practice in France.[11] The database includes information on all reimbursed health care resources in France. To update and complete the results of observational studies, we conducted a cohort study focusing on the management, outcomes, and health care costs of PAD in France based on the representative sample of the EGB.

METHODS

In France, the national health insurance scheme, composed of several specific regimes, covers the whole of the population. The general regime, the Health Insurance Fund for Salaried Workers and their relatives, covers approximately 77% of the population residing in France.[10] In the mandatory French national health care system, the majority of prescribed medications, for any indication and any duration, are reimbursed by the national health care insurance with variable copayment schemes.[12] This information is captured automatically at the time of drug dispensing by the pharmacy or, when a medical or other procedure is done, at the end of the consultation. In the French health care system, 30 major chronic diseases, including diabetes, cancer, and PAD, have been designated by the health care insurance *affection de longue durée* (ALD), that is, chronic disease, and result in full insurance coverage for all related medical, pharmaceutical, and transport expenses. The recorded information includes the chronic disease code, the associated *International Classification of Diseases, Tenth Revision* (ICD-10) codes, and the date of first registration of the ALD. There is no diagnostic information on non-ALD acute disorders, but all medical interventions and prescribed medicines are included in the database, whatever the indication, allowing proxy assessment of such conditions.

To facilitate the creation of patient cohorts for the most common diseases, a sample of 1/97th of the national health care insurance database has been established. This sample is named the permanent beneficiaries sample (EGB).[10,13,14] The EGB has been described in previous publications.[10,12-14] This 1/97th random sample of the French hospital and claims database, which at the time of the study concerned about 600,000 salaried workers and their relatives (77% of French citizens), was fully representative of the French population in terms of gender, age, and mean health care expenditures reimbursed to individual patients.[10] The EGB database contains individual, pseudoanonymized information on the following: gender, age, area of residence, and date of death (but not the cause of the death); full health care coverage for chronic illness (ALD); health care delivered and reimbursed in private and public establishments, with the drug and devices delivery dates, biologic and radiologic tests, and consultations; and hospital discharge summaries for all stays in public and private establishments, with the corresponding ICD-10 diagnosis and diagnosis-related group.[10]

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective case-control study using data of a prospectively maintained national claims-based registry
- **Take Home Message:** There were 5889 patients with peripheral arterial disease (PAD) identified from a national claims-based registry in France, with 69.3% taking antiplatelet agents and 52.3% taking statins. The 1-year mortality rate was 13.2%, and death and major cardiovascular event incidence was 15.7%, significantly higher than for matched cohorts without PAD (3.9%; $P < .05$)
- **Recommendation:** This paper suggests that PAD patients in France have a significant risk of death and adverse events and are undertreated with respect to medical therapy.

This was a cohort study of patients who were hospitalized for PAD between 2007 and 2011 and who had full health care coverage for PAD during the same period, identified and followed up for 2 years in the EGB database. All outcomes were compared with those of an age- and gender-matched control group of PAD-free subjects.

Inclusion criteria

We restricted the populations to subjects for whom a 1-year retrospective period and a 2-year follow-up period were available.

PAD patients. We studied adults for whom the ICD-10 codes I70.0 (atherosclerosis of aorta), I70.2 (atherosclerosis of arteries of extremities), and I70.9 (generalized and unspecified atherosclerosis) were documented in the EGB database between January 1, 2007, and December 31, 2011. The first occurrence of one of these codes represented the index date.

Control group. The patients with PAD were matched with a control group of patients who were never diagnosed with PAD in the database between 2006 and 2013. The matching was performed with two variables: age (in years) and gender. Each PAD patient has been matched with a control subject who had the same age (in years) and the same gender.

Data collection

For each included patient, the characteristics were extracted from the database on demographics (gender and age), reimbursed medications, comorbidities, events, and death. The reimbursed medications of interest were limited to oral anticoagulants (B01AE, B01AA), antiplatelet drugs (B01AC), lipid-lowering agents (Anatomical Therapeutic Chemical Classification System code C10), antidiabetic drugs (A10), and other cardiovascular medicines (C).

The studied comorbidities and risk factors were acute coronary syndrome, stroke or transient ischemic attack

(TIA), hypercholesterolemia, diabetes, and hypertension. They were identified from three sources: relevant ICD-10 codes reported as a main or secondary diagnosis during a hospital admission; reimbursements for drugs specific to a given condition, such as antidiabetic drugs for diabetes and cholesterol-lowering drugs for hypercholesterolemia; and eligibility for full reimbursement of health care costs because of long-term disability status, as identified through the relevant ICD-10 code.

Post-index date events of interest (MI/unstable angina, stroke, TIA, amputations of lower extremities, and deaths) were issued from hospitalizations subsequent to the index event with the related ICD-10 codes. Specific arterial procedures were also retrieved, such as percutaneous revascularization, surgical revascularization, fibrinolysis, and carotid and coronary revascularization.

All expenses related to hospital stays were extracted directly from the database. Nonhospital expenditures were grouped into the following categories: consultations, drugs, laboratory tests, nursing and other paramedical activities, medical transport, and other expenses.

Statistical analysis

The data presentation is mainly descriptive. Continuous data are reported as means ± standard deviation, median, and range. Categorical data are reported as frequency counts and percentages. Time to events of interest was evaluated by actuarial survival analysis. These analyses used the Kaplan-Meier method. The proportion of patients who received the different classes of medication was compared between the 3 months preceding and the 3 months following the index PAD diagnosis, using the χ^2 test. Demographic features and comorbidities were compared between subjects who experienced a cardiovascular event after PAD and those who did not, using Student *t*-test for age and the χ^2 test for other variables. A bilateral probability threshold of .05 was used to determine statistical significance. All statistical analyses used SAS software version 9.3 (SAS Institute, Cary, NC). Costs were compared using the Wilcoxon nonparametric test.

Based on epidemiologic estimates, it was expected that about 4000 subjects would be available in the database for this analysis and that this number would yield sufficiently precise estimates of the cumulative incidences of events. Therefore, the database was considered large enough for the objectives of the analyses.

Ethical considerations

As this was a study of an anonymized database and had no influence on patient care, ethics committee approval and patients' informed consent were not required.

RESULTS

Patients. Between 2007 and 2011, there were 7266 patients who had a diagnosis of PAD (Fig 1). Of these, 1162 patients were excluded because a 1-year retrospective period was not available, and a further 215 patients were excluded because their follow-up was <2 years. The remaining 5889 patients composed the study population. These subjects were followed up for 2 years.

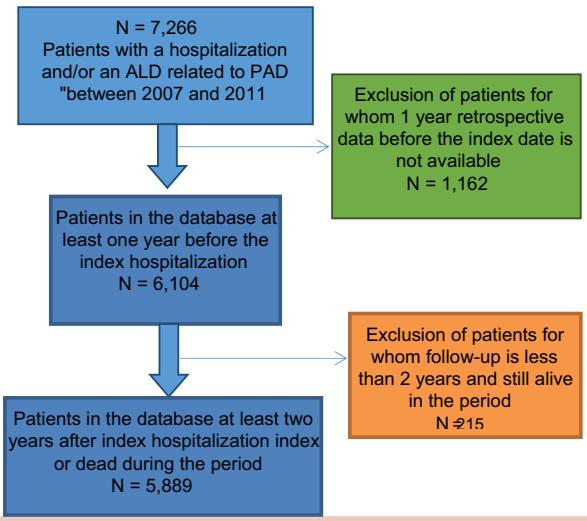

Fig 1. Patient distribution and study populations. *ALD, Affection de longue durée* (chronic disease); *PAD,* peripheral arterial disease.

Around two-thirds of the PAD patients were men (n = 4010; 68.1%). Mean age was 70.8 years. As the control population was matched for age and sex, the controls had the same age and gender distribution (Table I).

Hypertension and hypercholesterolemia were the most frequent comorbidities in the study population. Respectively, 4.9% and 6.0% of PAD patients experienced an acute coronary syndrome or stroke/TIA in the year before the index date. The proportions of patients with these comorbidities and risk factors were between 2 and 10 times higher in the PAD group than in the control group, and all the differences were statistically significant. Cancers occurred in 16.4% of PAD patients and 11.4% of controls ($P < .0001$). The following cancer sites were statistically significantly more frequent in the PAD patients than in the controls: lip, oral cavity, and pharynx (1.2% vs 0.4%; $P < .0001$); digestive organs (3.3% vs 2.0%; $P < .0001$); respiratory tract and intrathoracic organs (2.9% vs 0.9%; $P < .0001$); urinary tract (2.6% vs 1.2%; $P < .0001$), and malignant neoplasms of ill-defined, secondary, and unspecified sites (1.9% vs 0.5%; $P < .0001$).

Medications. An antiplatelet agent or an anticoagulant was dispensed to 76.2% of PAD patients (antiplatelet monotherapy, 59.4%; dual antiplatelet therapy, 9.9%; and an anticoagulant, 11.6%; Table II). The antiplatelet drugs consisted mainly of acetylsalicylic acid and clopidogrel. About one-quarter (23.8%) of PAD patients were treated for diabetes (11.3% of controls), and 56.6% received a lipid-lowering drug (28.1% of controls). Other frequent drug classes were calcium channel blockers

Table I. Characteristics of the patients

	PAD population (n = 5889)	Control population (n = 5889)	*P* value
Age at the index date, years			
Mean (standard deviation)	70.8 (12.7)	70.8 (12.7)	1.0000[a]
Median, minimum, maximum	72.0, 22.0, 107.0	72.0, 22.0, 107.0	
Gender			
Men	4010 (68.1)	4010 (68.1)	1.0000[b]
Women	1879 (31.9)	1879 (31.9)	
Hypertension	2742 (46.6)	727 (12.3)	<.0001[b]
Hypercholesterolemia	3113 (52.9)	1689 (28.7)	<.0001[b]
Diabetes	1700 (28.9)	776 (13.2)	<.0001[b]
Unstable angina or MI	291 (4.9)	28 (0.5)	<.0001[b]
Stroke or TIA	356 (6.0)	84 (1.4)	<.0001[b]
Heart failure	680 (11.5)	143 (2.4)	<.0001[b]
Neoplasia	965 (16.4)	673 (11.4)	<.0001[b]

MI, Myocardial infarction; *PAD,* peripheral arterial disease; *TIA,* transient ischemic attack.
Categorical variables are presented as number (%).
[a]Student *t*-test.
[b]χ^2 test.

(29.9%), beta blockers (29.9%), angiotensin-converting enzyme (ACE) inhibitors (26.7%), angiotensin II receptor blockers (24.2%), and diuretics. All these drugs were significantly more frequently dispensed to PAD patients than to controls ($P < .0001$). Statins plus an antiplatelet drug or anticoagulant were dispensed to 48.9% of PAD patients, and statins plus an antiplatelet drug or anticoagulant plus an ACE inhibitor or angiotensin II receptor antagonist were dispensed to 31.6% of PAD patients.

Events. Death, MI, and stroke/TIA were issued in the period after the index date. Accrual of these events over time is shown in Fig 2. Death was the most frequent event among both PAD patients and controls. Death was relatively frequent among PAD patients during the 2 months after the index date and then stabilized. In the PAD group, the cumulative mortality incidences were 13.2% (95% confidence interval [CI], 12.3%-14.0%) at 1 year and 19.4% at 2 years (95% CI, 18.4%-20.5) vs 3.2% (95% CI, 2.7%-3.6%) and 6.5% (95% CI, 5.9%-7.1%) in the control group. The cumulative proportions of PAD patients who were hospitalized for MI were 1.5% (95% CI, 1.2%-1.9%) at 1 year and 2.6% at 2 years (95% CI, 2.2%-3.1%) vs 0.2% (95% CI, 0.1%-0.3%) and 0.4% (95% CI, 0.2%-0.6%) in the control group. The cumulative proportions of PAD patients who were hospitalized for stroke/TIA were 2.4% (95% CI, 2.0%-2.8%) at 1 year and 3.5% at 2 years (95% CI, 3.0%-4.0%) vs 0.7% (95% CI, 0.5%-1.0%) and 1.3% (95% CI, 1.0%-1.6%) in the control group. In the PAD group, the cumulative proportions of patients with a composite event were 15.7% (95% CI, 14.8%-16.6%) at 1 year and 22.9% at 2 years (95% CI, 21.9%-24.0) vs 3.9% (95% CI, 3.4%-4.4%) and 7.8% (95% CI, 7.1%-8.5%) in the control group.

Other events that occurred during the 2 years of follow-up are reported in Table III. The most frequent event during follow-up was peripheral percutaneous revascularization, which occurred in 9.5% of PAD patients vs 0.1% of the controls. Other procedures that were more frequent in the PAD population were lower extremity amputation (3.7% vs 0.1% in the control group), lower limb surgical revascularization (7.9% of PAD patients vs 0.1% in the control group), and percutaneous coronary revascularization (3.2% vs 0.8% in the control group). Other procedures were less frequently performed and are reported in Table III.

Bleeding was also frequent. During the 2 years of follow-up, a major bleed occurred in 8.0% of the PAD population (3.1% in the control group). The bleed involved the gastrointestinal tract in 2.0% of PAD patients (1.0% in the control group), the brain in 1.0% (0.5%), and other locations in 5.6% (1.7%). Major bleeds occurred more frequently in patients who received dual antiplatelet therapy and an anticoagulant (20.7% during the 2 years of follow-up) than in patients treated with an anticoagulant alone (9.6%) or an antiplatelet drug alone (7.2%) or without anticoagulant or antiplatelet drugs (7.3%).

Costs. The total annual societal cost of care for PAD patients in the year after the index date was €14,949 (€3812 in the control group; Fig 3). From a societal perspective, the cost of ambulatory care was €5903 (€2409 in the control group), and hospital costs were €9046 (€1403 in the control group). From a third-party payer perspective, the cost of ambulatory care was €5233 (€1792 in the control group), and hospital costs were the same as the societal cost because they are fully reimbursed by the public health insurance system.

Table II. Medications dispensed in the 3 months after the index date

	PAD population (n = 5889)	Control population (n = 5889)	*P* value
Antiplatelet agents and oral anticoagulants			
Antiplatelet agents and oral anticoagulants	4488 (76.2)	1330 (22.6)	<.0001[a]
Oral anticoagulants	686 (11.6)	349 (5.9)	<.0001[a]
Antiplatelet agents	4082 (69.3)	1016 (17.3)	<.0001[a]
Antiplatelet monotherapy	3498 (59.4)	958 (16.3)	<.0001[a]
Acetylsalicylic acid	1635 (46.7)	745 (77.8)	<.0001[a]
Clopidogrel	1848 (52.8)	209 (21.8)	<.0001[a]
Other (dipyrimidine, ticlopidine)	15 (0.4)	4 (0.4)	.6[b]
Dual antiplatelet therapy	583 (9.9)	58 (1.0)	<.0001[a]
Acetylsalicylic acid and clopidogrel	568 (97.4)	58 (100.0)	
Other combinations	15 (2.6)	0	
Drugs used in diabetes	1401 (23.8)	667 (11.3)	<.0001[a]
Insulin and analogues	657 (11.2)	121 (2.1)	<.0001[a]
Glucose-lowering drugs, excluding insulin	1008 (17.1)	601 (10.2)	<.0001[a]
Lipid-lowering agents	3334 (56.6)	1657 (28.1)	<.0001[a]
Statins	3081 (52.3)	1289 (21.9)	<.0001[a]
Fibrates	249 (4.2)	357 (6.1)	<.0001[a]
Ezetimibe	242 (4.1)	95 (1.6)	<.0001[a]
Other lipid-lowering agents[c]	56 (1.0)	24 (0.4)	.0003[a]
Diuretics			
Thiazide diuretics	860 (14.6)	682 (11.6)	<.0001[a]
Diuretics excluding thiazides	1509 (25.6)	809 (13.7)	<.0001[a]
Cardiac glycosides	152 (2.6)	123 (2.1)	.08[a]
Vasodilators			
Calcium channel blockers	1762 (29.9)	913 (15.5)	<.0001[a]
Nitrates	502 (8.5)	175 (3.0)	<.0001[a]
Other vasodilators	712 (12.1)	258 (4.4)	<.0001[a]
Antiarrhythmics			
Class I antiarrhythmics	101 (1.7)	115 (2.0)	.3363[a]
Class III antiarrhythmics	324 (5.5)	151 (2.6)	<.0001[a]
Drugs acting on the RAS			
ACE inhibitors	1572 (26.7)	805 (13.7)	<.0001[a]
Angiotensin II receptor blockers	1427 (24.2)	978 (16.6)	<.0001[a]
Beta blockers	1758 (29.9)	1028 (17.5)	<.0001[a]
Combinations of recommended therapies in PAD			
Statin and antiplatelet or anticoagulant	2880 (48.9)	641 (10.9)	<.0001[a]
Statin and antiplatelet or anticoagulant and ACE inhibitor or angiotensin II receptor blocker	1862 (31.6)	393 (6.7)	<.0001[a]

ACE, Angiotensin-converting enzyme; *PAD*, peripheral arterial disease; *RAS*, renin-angiotensin system.
As a given subject could be prescribed more than one medication, these variables are not mutually exclusive.
Values are reported as number (%).
[a] χ^2 test.
[b] Fisher exact test.
[c] Including omega-3 fatty acids, cholestyramine, nicotinic acid, tiadenol.

Among the costs of ambulatory care from a societal perspective, the costs in the PAD population were €1903 for pharmacy consumption (€880 in the control group), €1138 for physician visits (€486 for the control group), €1032 for medical auxiliaries (€376 for the control group), €718 for medical devices (vs €293), €699 for transport (vs €107), and €285 for laboratory tests (vs €117).

Among the costs of ambulatory care from the third-party payer perspective, the costs in the PAD population were €1707 for pharmacy consumption (€698 in the

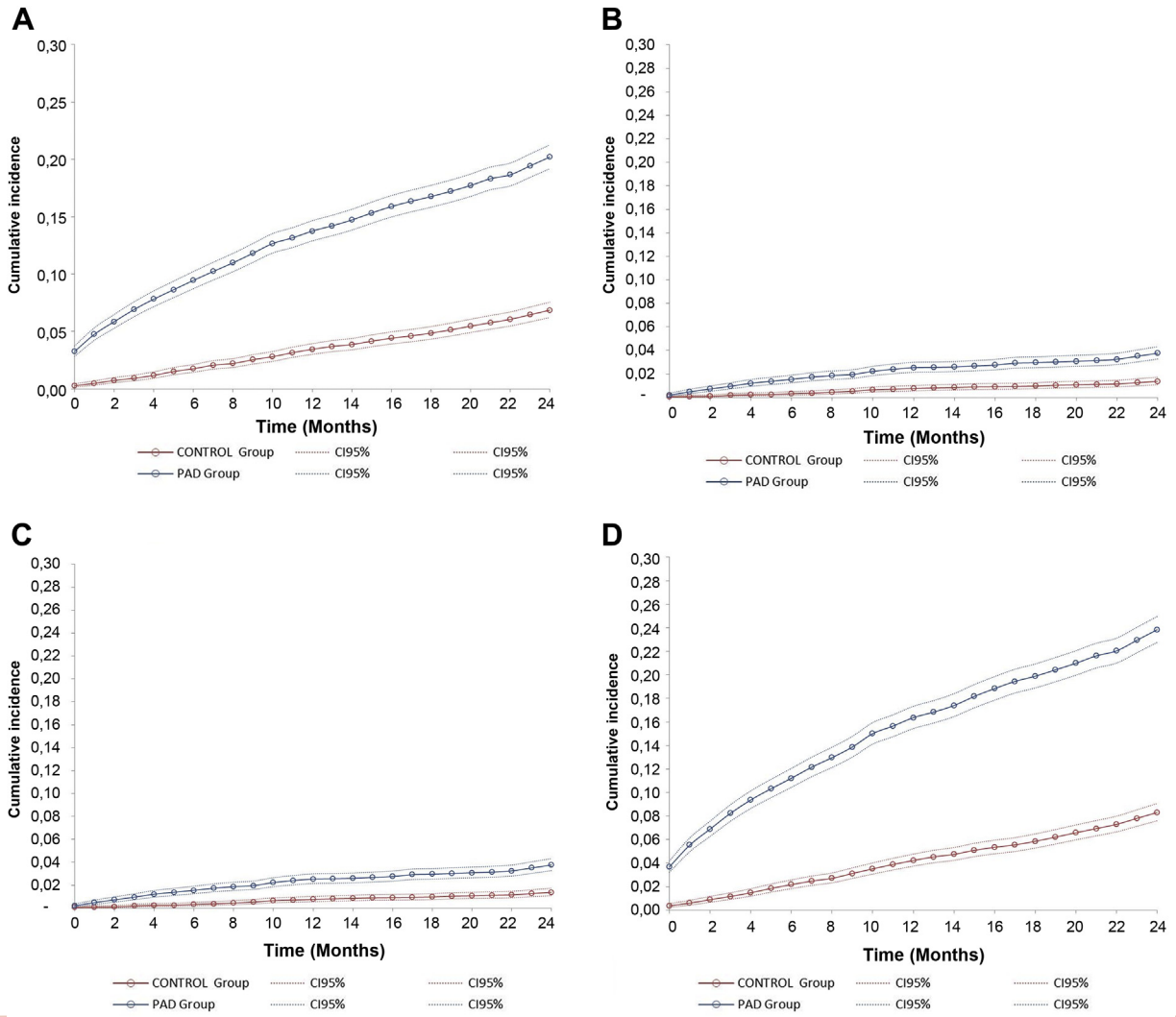

Fig 2. Time-to-event analysis of the time to death **(A)**, myocardial infarction (MI; **B**), stroke or transient ischemic attack (TIA; **C**), and the triple composite outcome **(D)**. The *dashed lines* represent the confidence intervals (*CIs*). *PAD,* Peripheral arterial disease.

control group), €1006 for physician visits (€371 in the control group), €981 for medical auxiliaries (€334 for the control group), €677 for medical devices (vs €98), €561 for transport (vs €153), and €257 for laboratory tests (vs €90).

DISCUSSION

We describe the characteristics, management, and burden of illness of patients with lower limb PAD by comparison with an age- and gender-matched PAD-free control group. The study was based on a claims database (EGB) providing a representative sample of the French population. The database contains exhaustive information on treatments and consumption of reimbursed health care resources. It therefore avoids the selection and information biases of observational studies. Moreover, the risk of attrition can be considered insignificant as there were few reasons for an individual to leave one of the three main health care insurance systems (move to another French health care insurance system or expatriation).

However, one limitation regarding the use of a claims database is the lack of precise clinical information, especially clinical and biologic details of the trigger event (eg, PAD, severity) as well as major cardiovascular risk factors, such as smoking, body mass index, blood pressure, and cholesterol values, that could have an impact on the prognosis. A risk of miscoding cannot be excluded but is considered infrequent, with no systematic errors. The bias would rather result in PAD patients being missed, not in PAD-free subjects being considered PAD patients. The database includes only salaried workers and their relatives. It is possible that other categories of citizens may be more or less likely to suffer from PAD and that our results would be biased for the whole French population. However, salaried workers represent 77% of the French population. As a consequence, taking into account the 23% remaining persons would not substantially modify our results.

Table III. Other events in the 2 years after the index date

	PAD population (n = 5889)	Control population (n = 5889)	*P* value
Peripheral percutaneous revascularization	561 (9.5)	4 (0.1)	<.0001[a]
Lower extremity surgical revascularization	465 (7.9)	4 (0.1)	<.0001[a]
Lower extremity amputation	217 (3.7)	5 (0.1)	<.0001[a]
Peripheral fibrinolysis	16 (0.3)	—	<.0001[a]
Carotid surgical or percutaneous revascularization	99 (1.7)	10 (0.2)	<.0001[a]
Coronary surgical revascularization	59 (1.0)	18 (0.3)	<.0001[a]
Percutaneous coronary revascularization	190 (3.2)	50 (0.8)	<.0001[a]
Major intracranial bleed (during the 2-year follow-up period)	61 (1.0)	30 (0.5)	.0011[a]
Major gastrointestinal bleed (during the 2-year follow-up period)	115 (2.0)	60 (1.0)	<.0001[a]
Other major bleed (during the 2-year follow-up period)	330 (5.6)	102 (1.7)	<.0001[a]

PAD, Peripheral arterial disease.
Values are reported as number (%).
[a]χ^2 test.

Inpatients were selected on the basis of hospitalization with a diagnosis of PAD, and outpatients were selected on the basis of full insurance coverage for PAD during the study period. The first occurrence of this diagnosis during the study period represents the first date of follow-up. Generally speaking, as PAD is a chronic disease that progresses gradually from histopathologic changes to serious clinical events, it is difficult to define exactly when the disease begins. For the beginning of follow-up, we have chosen an arbitrary date that was easily defined in the database. It is also difficult to determine the clinical phase at which the patients were selected. They were clearly selected at a clinically significant stage because they were either hospitalized with this diagnosis or fully reimbursed for PAD-related health care consumption. In addition, as the mean age of our population is similar to that of other studies (Table IV), the patients may have been at a clinical stage similar to that of other observational registries.

Two French studies of PAD patients have been reported.[8,9] The prospective REduction of Atherothrombosis for Continued Health (REACH) registry enrolled 4693 patients in France and 5594 patients in Germany in 2003 and 2004.[8] In France, the patients were enrolled in 509 outpatient centers. Patients were eligible for inclusion if they were at least 45 years old and had documented symptomatic PAD (history of current intermittent claudication with an ankle-brachial index [ABI] <0.90; peripheral angioplasty, stenting, or bypass grafting; amputation). The prospective multicenter Cohorte des Patients Artériopathes (COPART) registry recruited consecutive patients from the vascular medicine departments of three university hospitals in southwestern France.[9] Its objective was to assess current "real-world" management of hospitalized patients with lower extremity PAD and to assess 1-year outcomes. To be included, the patients needed to meet two criteria: age >18 years and referral to the hospital specifically for clinical PAD of atherosclerotic origin. The clinical stages were intermittent claudication associated with an abnormal ABI (<0.90 or >1.30) or, in case of a normal resting ABI, a positive treadmill test result (Strandness protocol); arterial stenosis >50% revealed by duplex ultrasound or angiography; ischemic rest pain or ulceration and gangrene; and acute lower limb ischemia related to documented PAD with significant arterial stenosis. A study similar to ours was conducted in Sweden.[15] The Swedish National Registry for Vascular Surgery database was used to identify revascularized PAD patients. Current risks of cardiovascular events and death were analyzed along with drugs prescribed for secondary prevention.

The results of these three studies are reported and compared with ours in Table IV.[8,9,15] The age distribution of the subjects in our study is consistent with that of the two French studies.

The proportions of patients with cardiovascular risk factors were somewhat lower in our study than in the other three studies. These differences may be related to the use of different definitions of comorbidities. In the COPART and REACH studies, they were based on investigator declarations, whereas we used information available in the database (specific treatments, hospitalizations, and full health care coverage for chronic illness). The fact that not all patients may receive treatment for these risk factors might explain some of the differences. Another reason could be the use of different inclusion criteria.

The lower proportions of MI and cerebrovascular disease observed in our study might be due to the short period in which retrospective information is available in our database (from 2006 until the inclusion date).

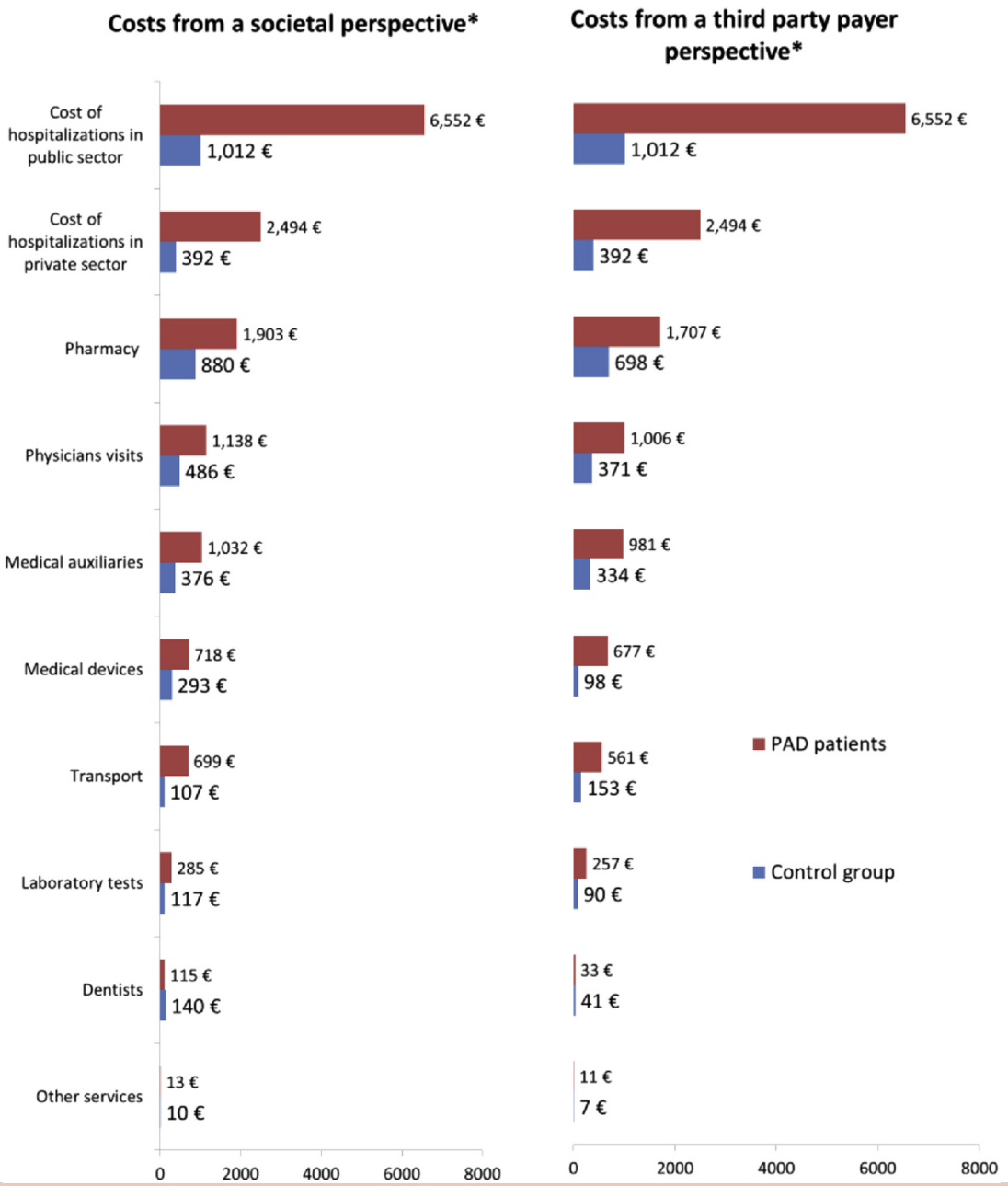

Fig 3. Costs of peripheral arterial disease (*PAD*) patients and matched controls during the first year. Except for "other services," all differences between the groups were statistically significant ($P < .001$). *The third-party payer perspective is restricted to costs reimbursed by public health insurance, whereas the societal perspective adds the part of costs not reimbursed by the health insurer.

Another possible explanation is the inclusion of more severely ill patients in the COPART cohort, as recruitment took place in the vascular medicine departments of university hospitals. The higher proportions of cardiovascular disease observed in the Swedish study may also be explained by the higher risk nature of the population in this study (restricted to revascularized PAD patients). Another explanation is the higher risk of these conditions in northern countries than in France.[16]

The cancers observed more frequently in PAD patients than in controls affected sites (oral cavity, lungs, urinary tract) for which the risk factors are the same as for atherosclerosis (smoking, alcoholism).

International guidelines[4-7] state that PAD patients should be treated with antiplatelet agents, as they lower cardiovascular morbidity and mortality by 25%. Oral anticoagulants are not recommended for these patients, but if they are receiving these drugs for another disorder, there is no need to add an antiplatelet agent, as this would increase the bleeding risk. Statins are recommended for PAD patients because they lower the risk of cardiovascular events and all-cause mortality by about 24%.

Table IV. Comparison of results with other studies

	COPART	REACH	Swedish study	EGB PAD
No.	940	923	18,742	5889
Male gender	68.4	81.4	51.2	68.1
Age, years, mean	70.2	69.3	74.3	70.8
Cardiovascular risk factors				
Dyslipidemia	53.1	69.8		52.9
Hypertension	69.0	73.0	84.1	46.6
Diabetes	43.9	33.8	38.8	28.9
Previous history of cardiovascular events				
MI	20.9		18.1	4.9
Cerebrovascular disease	15.2		18.8	6.0
Heart failure	11.9		22.6	11.5
Previous history of invasive treatment for PAD				
Peripheral angioplasty	18.8			9.2
Peripheral bypass	18.4			4.0
Amputation	16.9			3.0
Treatment				
Antiplatelet agents	81.6	88.1		69.3
Anticoagulant	15.3	15.2		11.6
Statins	70	62.7		52.3
ACE inhibitor	40.4	37.0		26.7
Angiotensin II receptor blocker	18.1	21.1		24.2

ACE, Angiotensin-converting enzyme; *COPART,* Cohorte des Patients Artériopathes; *EGB,* Echantillon Généraliste des Bénéficiaires; *MI,* myocardial infarction; *PAD,* peripheral arterial disease; *REACH,* REduction of Atherothrombosis for Continued Health.
Categorical variables are reported as %.

ACE inhibitors are recommended by international guidelines because they lower the composite risk of cardiovascular death, MI, and stroke.[4-7]

Despite these recommendations, a significant proportion of patients are not appropriately treated: 48.9% of patients in our study were receiving a statin plus an antiplatelet or anticoagulant drug, and this proportion fell to only 31.6% when we added an ACE inhibitor or angiotensin II receptor blocker. The other two observational studies conducted in France also showed low prescriber compliance with recommended medications.[8,9] The proportions of patients treated with these medications were somewhat higher in the Swedish study.[15]

The REACH registry records events and invasive treatments that occur during 2 years of follow-up. Except for stroke and heart failure, which were more frequent in our study, the different outcomes were similarly frequent in the two studies. Although cardiovascular events are much more frequent in PAD patients, their frequency is much lower than the proportion of patients who died: 13.2% after 1 year and 19.4% after 2 years. These cumulative incidences were far higher than those observed in the control group (3.2% after 1 year and 6.5% after 2 years). Deaths and cardiovascular events were similarly frequent in the Swedish study and our study.[15]

The EGB is a representative database of all individuals covered by the largest French public health insurer, which includes all salaried workers and their families. The agricultural workers, students, self-employed, and civil servants were not covered by this scheme at the time of the study. Nonetheless, the use of this database for real-world evidence research does have limitations. Some are inherent in prescription claims databases, like the absence of validated diagnoses, the limited sociodemographic and clinical information, and the risk of incomplete or inaccurate coding of medical events. For example, no information is available on smoking status, which is a major risk factor for PAD.

In the EGB database, diagnoses are documented in only one of three cases: if the patient is hospitalized; if the patient is reimbursed for full coverage of a chronic illness (ALD); and if medication is specific for a unique condition. In our study, comorbidities such as hypertension were identified on the basis of ALD status or as comorbidities if they were hospitalized. It is thus possible that these comorbidities were underestimated. Medication use is documented only when the medication is dispensed, not when it is prescribed. Thus, the suboptimal use of secondary preventive medication observed in our study might reflect poor adherence of the patients rather than the physicians' failure to follow practice guidelines.

The difference between the total annual societal cost of care for PAD patients (€14,949) and the controls (€3812)

suggests that the attributable annual cost of PAD is about €11,137. This is similar to the estimated attributable costs of MI in the following year in France (€12,679).[17] Extrapolating this cost to the approximately 500,000 patients who had full health care coverage for PAD in 2014 in France[3] gives an estimated annual cost of PAD of €5.5 thousand million.

CONCLUSIONS

Our study shows that the risk of death and cardiovascular events is high in patients with PAD in France. This may be explained by the inadequate uptake of recommended secondary preventive medications. Further efforts are therefore required to ensure that all patients at risk receive optimal secondary prevention.

AUTHOR CONTRIBUTIONS

Conception and design: ABR, SB, CL, FTD
Analysis and interpretation: SB, CL, ET
Data collection: ET, JG
Writing the article: ABR, SB, FTD
Critical revision of the article: ABR, SB, CL, ET, JG, FTD
Final approval of the article: ABR, SB, CL, ET, JG, FTD
Statistical analysis: Not applicable
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Overall responsibility: SB

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:1329-40.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1-75.
3. Affection de longue durée (ALD). Prévalence. Available at: http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/prevalence/prevalence-des-ald-en-2014.php. Accessed December 15, 2017.
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease. Int Angiol 2007;26:81-157.
5. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, et al; American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:1555-70.
6. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851-906.
7. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:1465-508.
8. Smolderen KG, Wang K, de Pouvourville G, Brüggenjürgen B, Röther J, Zeymer U, et al; REACH Registry Investigators. Two-year vascular hospitalisation rates and associated costs in patients at risk of atherothrombosis in France and Germany: highest burden for peripheral arterial disease. Eur J Vasc Endovasc Surg 2012;43:198-207.
9. Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: the COPART Registry. Eur J Vasc Endovasc Surg 2010;39:577-85.
10. Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Santé Publique 2010;54:286-90.
11. Blin P, Philippe F, Bouée S, Laurendeau C, Torreton E, Gourmelin J, et al. Outcomes following acute hospitalised myocardial infarction in France: an insurance claims database analysis. Int J Cardiol 2016;219:387-93.
12. Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia 2012;55:644-53.
13. Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: what interest for medical research? Rev Med Interne 2015;36:411-7.
14. De Roquefueil L, Studer A, Neumann A, Merlière Y. L'échantillon généralistedes bénéficiaires: rerpésentativité, portée et limites. Prat Organ Soins 2009;40:213-23.
15. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. J Vasc Surg 2016;64:1009-17.e3.
16. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014;35:2929.
17. Blin P, Philippe F, Laurendeau C, Bouee S, Gourmelen J, Levy Bachelot L, et al. Increased costs due to myocardial infarction (MI) in France: an observational analysis using a claims database. Value Health 2015;18:A386.

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