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Epidemiology, treatment patterns and outcomes in patients with coronary or lower extremity artery disease in France

Abbreviated title: Epidemiology, treatment and outcomes of CAD or LEAD

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Summary

Background. – There is a dearth of updated epidemiological data on the prevalence and annual incidence of coronary artery disease (CAD) and lower extremity artery disease (LEAD) in Western countries.

Aims. – To describe the incidence and prevalence of CAD and LEAD, associated medication patterns and long-term outcomes in France.

Methods. – This was a retrospective cohort study using French claims data from a representative sample of the French general population. Any hospitalization or long-term disease status for CAD or LEAD between January 2010 and December 2016 was collected to identify incident cases.

Results. – Of the 763,338 patients screened in the study period, 8559 incident cases of CAD and 4399 of LEAD were identified, with an overall mean follow-up of 2.9 ± 2.0 years. The incidence of CAD, LEAD and CAD or LEAD remained stable over the years, and in 2016 were at 33.5 per 10,000 person-years, 15.1 per 10,000 person-years and 42.5 per 10,000 person-years, respectively. The prevalence of CAD increased from 3.1% in 2010 to 4.2% in 2016, and LEAD from 1.6% to 2.4%. Most patients received guideline-recommended medication with antithrombotic drugs and lipid-lowering drugs following the index event. However, most of the medications initiated were subsequently discontinued during follow-up. Incident CAD or LEAD was associated with considerable morbidity – particularly an incidence of all-cause hospitalization of 7976.9 per 10,000 person-years – and all-cause mortality, with an incidence of 542.8 per 10,000 person-years.

Conclusion. – In recent years, the prevalence of CAD or LEAD has increased progressively, resulting in considerable morbidity and mortality.

Résumé

Contexte. – Il existe un manque de données épidémiologiques récentes concernant la prévalence et l'incidence des cardiopathies ischémiques (CPI) et artériopathies oblitérantes des membres inférieurs (AOMI) dans les pays occidentaux.

Objectif. – Décrire l'incidence et la prévalence des CPI et AOMI, les médications et le devenir clinique associés au long cours.

Méthodes. – Il s'agit d'une étude rétrospective sur une cohorte représentative de la population française. Toutes les hospitalisations et demandes de statut d'affection de longue durée pour CPI ou AOMI entre janvier 2010 et décembre 2016 ont été collectées pour identifier les cas incidents.
Résultats. – Sur les 763,338 patients évalués, un total de 8559 et 4399 cas incidents de CPI et AOMI ont été identifiés, respectivement, avec un suivi moyen de 2,9 ± 2,0 années. Les incidences de CPI, AOMI et CPI ou AOMI sont restés stables au cours du temps et se situaient en 2016 à 33,5 pour 10,000 patients-années, 15,1 pour 10,000 patients-années et 42,5 pour 10,000 patients-années, respectivement. Les prévalences des CPI et AOMI ont augmenté de 3,1 % et 1,6 % en 2010 à 4,2 % et 2,4 % en 2016, respectivement. La plupart des patients étaient traités selon les recommandations, après l'évènement index, par des agents antiplaquettaires et hypolipémiants. Cependant, la plupart des traitements initiés étaient interrompus durant le suivi. Le diagnostic de CPI ou d'AOMI était associé à une morbi-mortalité considérable, avec une incidence d'hospitalisation à 7976,9 pour 10,000 patients-années et de décès à 542,8 pour 10,000 patients-années
Conclusion. – La prévalence des CPI et AOMI a augmenté ces dernières années en France, à l'origine d'une morbi-mortalité significative.

KEYWORDS

Coronary artery disease;

Ischaemic heart disease;

Lower extremity artery disease;

Epidemiology;

Guidelines-recommended treatment

MOTS CLÉS

Coronaropathie ;

Cardiopathie ischémique ;

Artériopathie oblitérante des membres inférieurs ;

Épidémiologie ;

Médications recommandées par les recommandations

Abbreviations: HR, hazard ratio; CAD, coronary artery disease; CI, confidence interval; EGB, Echantillon Généraliste de Bénéficiaires (Permanent Sample of Health Insurance Beneficiaries); ICD-10, International Classification of Diseases, tenth revision; LEAD, lower extremity artery disease; LTD, long-term disease; REACH, Reduction of Atherothrombosis for Continued Health.

Background

Atherosclerosis, with its two main clinical manifestations, coronary artery disease (CAD) and lower extremity artery disease (LEAD), may affect as many as 400 million individuals worldwide [1]. Despite considerable improvement in its management in recent decades, atheroslerosis remains a leading cause of death, and it was estimated that nearly 18 million people died from cardiovascular diseases in 2015 [1]. As both CAD and LEAD are multifaceted conditions, their prevalence and incidence have been difficult to assess, resulting in discrepancies according to the definition used [2, 3]. Thus in Western countries, and particularly in Europe, there is a dearth of updated epidemiological data on the prevalence and annual incidence of CAD and LEAD, as well as on treatment patterns and long-term outcomes [2]. Such information may be of importance to evaluate everyday clinical practices and the implementation of guidelines from the scientific societies, and to identify gaps in management. In fact, over a decade ago, the Reduction of Atherothrombosis for Continued Health (REACH) international registry reported an overall undertreatment of atherothrombotic patients regarding evidence-based risk reduction therapies, such as statins and antiplatelet drugs [4]. We therefore aimed to provide an updated description of the incidence, prevalence, treatment patterns and long-term outcomes of CAD and LEAD, using a large French health insurance claims database, representative of the general French population.

Methods

Study population and data source

This was an observational retrospective cohort study, using French claims data obtained from the Permanent Sample of Health Insurance Beneficiaries (Echantillon Généraliste de Bénéficiaires [EGB]), an anonymous representative national sample that lists all outpatient and inpatient healthcare consumption by the French population that is covered by the general insurance scheme. The inclusion period extended from 1 January 2010 to 31 December 2016, but all data from 1 July 2008 were also collected to ensure an 18-month prestudy period (Fig. A.1).

Among the population recorded in the EGB database, three groups of incident adult patients were identified: patients with incident CAD (i.e. patients newly diagnosed with CAD in the studied period); patients with incident LEAD (i.e. patients newly diagnosed with LEAD in the studied period); patients with incident CAD or LEAD (i.e. patients newly diagnosed with CAD and/or LEAD in the studied

period). Incident CAD or LEAD was defined as the presence of a hospital admission and/or at least one reimbursement linked to a long-term disease (LTD) status for CAD or LEAD in the study period, and the absence of such criteria in the 18-month period before the index event. LTD status registration is obtained for serious and/or chronic diseases requiring prolonged and costly therapy, at the request of the patient's treating physician, and is validated by the French health insurance system physician. This status provides full insurance coverage for healthcare related to a list of 30 LTDs, among which LEAD and CAD are included.

Baseline clinical characteristics were identified according to the International Classification of Diseases, tenth revision (ICD-10) codes for hospital admission (Table A.1) or LTD status. Treatment patterns were described for drug class of interest using the Anatomical Therapeutic Chemical (ATC) classification (Table A.2). Medication discontinuation was defined as the absence of dispensation for at least 60 days during follow-up. Patients were followed from index date to the end of follow-up: the last patient's health record recorded in the database before a period of 6 months without any reimbursed care; the death of the patient; or the end of study period. Adverse events were defined using the ICD-10 codes for hospital admission and the Classification of Medical Procedures (Classification Commune des Actes Médicaux [CCAM]), as detailed in Table A.3.

Statistical analysis

Descriptive statistics are reported as means ± standard deviations or numbers and percentages. Prevalences and incidences of CAD and/or LEAD were determined overall and yearly between 2010 and 2016. The prevalence was determined within the entire adult population recorded in the EGB database overall or in each calendar year. Prevalent cases consisted of both incident cases at the time of interest and patients with previous evidence of the condition (in the prestudy period). Incidence was reported per 10,000 person-years over the at-risk population (not including patients with previous hospitalization or LTD status in the 18-month prestudy period). Outcomes were assessed using the Kaplan-Meier method. A multivariable Cox regression model was used to assess the adjusted risk of all-cause death in the CAD cohort. Covariates included in the model were: myocardial infarction as an index event of CAD; the presence of stage 3–5 chronic kidney disease; concomitant presence of LEAD or heart failure within the 18-month period before the CAD diagnosis; age; sex; social deprivation; Charlson score; HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke,

Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol) score; history of bleeding; polyvascular disease; cancer; atrial fibrillation; venous thromboembolism; and amputation of lower limb. A two-tailed probability value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Epidemiology of CAD and LEAD

Among the 763,338 patients recorded in the EGB database during the study period and screened for inclusion, incident CAD, LEAD and CAD or LEAD were diagnosed in 8559 (1.1%), 4399 (0.6%) and 12,408 (1.6%) patients, respectively (Fig. 1). A total of 556 (0.07%) patients were diagnosed with concomitant incident CAD and LEAD. Overall incidences of CAD, LEAD and CAD or LEAD in the study period were 32.3 per 10,000 person-years, 16.3 per 10,000 person-years and 43.1 per 10,000 person-years, respectively, and 7.0 per 10,000 person-years for CAD and LEAD. Yearly incidences remained stable over the years, as detailed in Fig. 2A. Yearly prevalences of CAD, LEAD and CAD or LEAD are detailed in Fig. 2B. Baseline characteristics are detailed in Table 1. Patients with incident CAD and LEAD were mostly male. More than one-quarter of patients with incident LEAD and one-fifth of patients with incident CAD were aged > 80 years. Systemic hypertension and diabetes mellitus were the most frequent co-morbidities, affecting 69.5% and 23.0% of the population, respectively.

Dispensed medications

Medications dispensed before the index event (i.e. during the prestudy period) are described in Table 2. Approximately half of the patients with incident CAD or LEAD were already being treated with antiplatelet drugs, renin-angiotensin system modulators or lipid-lowering drugs at baseline. One-third of the patients were already being treated with beta-blockers. Following the index event, antiplatelet therapy, lipid-lowering drugs, renin-angiotensin system modulators and beta-blockers were initiated in most of the remaining patients. However, the majority of the medications initiated following the index event were subsequently discontinued during follow-up (Table 2).

Adverse outcomes during long-term follow-up

Mean follow-up was 2.9 ± 2.0 years for patients with incident CAD or LEAD, 3.0 ± 2.0 years for incident CAD and 2.9 ± 2.1 years for incident LEAD. Rates of adverse events are detailed in Table 3, Table A.4 and Fig. 3. Among patients diagnosed with CAD or LEAD, the incidence of all-cause death was 542.8 per 10,000 person-years. The most frequent adverse events were all-cause hospitalization and cardiovascular hospitalization, with incidences of 7976.9 and 2966.4 per 10,000 person-years, respectively, followed by percutaneous coronary intervention, with an incidence of 1317.1 per 10,000 person-years. Of note, recurrences of complications were frequent, concerning 73.0% of the 9178 patients hospitalized during follow-up, and 30.2% of the 2256 patients who presented a myocardial infarction during follow-up.

After adjustment, in the CAD cohort, the presence of a myocardial infarction as index event was a risk factor for all-cause death: adjusted hazard ratio (HR) 1.45, 95% confidence interval (CI) 1.28–1.64 ($P < 0.001$) in the absence of concomitant chronic kidney disease; and adjusted HR 2.57 95% CI 1.71–3.87 ($P < 0.001$) with concomitant chronic kidney disease. A history of heart failure in the 18 months before the index event was also a risk factor for all-cause death (adjusted HR 1.26, 95% CI 1.03–1.54; $P = 0.024$). However, the diagnosis of concomitant incident CAD and LEAD was not significantly associated with all-cause death (adjusted HR 0.92, 95% CI 0.68–1.25; $P = 0.60$).

Discussion

The main results of this study are: (1) that the yearly incidence of newly diagnosed CAD or LEAD has remained constant in recent years, resulting in a progressive increase in the respective prevalence from 4.2% in 2010 to 5.7% in 2016 (Fig. 2B); (2) that guideline-recommended therapy, including antithrombotic drugs, lipid-lowering drugs, beta-blockers and renin-angiotensin system modulators were initiated or already dispensed at baseline in the majority of patients with incident CAD or LEAD, but most of the medications initiated following the index event were subsequently interrupted during follow-up; (3) that incident CAD or LEAD was associated with significant morbidity, particularly all-cause and cardiovascular hospitalizations, and mortality; and (4) that myocardial infarction as an index event for the diagnosis of incident CAD and the presence of heart failure before the diagnosis of CAD were independently associated with an increased risk of all-cause mortality.

Epidemiology of CAD and LEAD

The reported prevalence of CAD in this large French cohort is consistent with results from other Western countries. Between 2011 and 2014, the American Heart Association estimated the total prevalence of CAD to be 6.3% in adults aged > 20 years [5]. There have been repeated reports of a progressive decrease in the incidence of CAD in recent decades [5]. Using data from two prospective cohorts from the USA – the Atherosclerosis Risk in Communities (ARIC) study for the early period of 1987–1996 and the Reasons for Geographic And Racial Difference in Stroke (REGARDS) study for the late period of 2003–2009 – Carson et al. reported a decrease in CAD incidence from 39 per 10,000 person-years in the early period to 22 per 10,000 person-years in the late period [6]. Conversely, in the present study, the yearly incidence of newly diagnosed CAD remained stable: 33.2 per 10,000 person-years in 2010 and 33.5 per 10,000 person-years in 2016.

The reported prevalence of LEAD may vary considerably, depending on whether the presence of clinical symptoms is noted. Indeed, in a large Danish study, LEAD was diagnosed in 10.9% of the patients; however, only one-third of them reported clinical manifestation [7]. Similarly, we reported a 2.4% prevalence of LEAD in 2016. As the definition of incident LEAD in our study included the presence of a hospital admission and/or an LTD status for LEAD, it is likely that only the most severe and symptomatic patients were accounted for.

The baseline characteristics of the incident CAD and LEAD population in our study are consistent with the population of the REACH registry, over a decade ago, where the mean age was 68.5 ± 10.1 years, and 63.7% of patients were men [4]. Similar findings were also described more recently [8, 9]. Overall, this indicates that the profile of patients with a clinical manifestation of atherosclerosis has remained consistent over the years.

Medication patterns

Although medications at discharge are frequently reported in large observational registries, there is a dearth of data regarding the actual long-term dispensation following the diagnosis of CAD or LEAD. In the present study, we found that many patients with incident CAD or LEAD were already being treated with antiplatelet drugs, lipid-lowering drugs, beta-blockers or renin-angiotensin system modulators. Such medications were probably prescribed in a primary prevention care setting, considering the large prevalence of cardiovascular risk factors in our population. An important finding of this study is that, for the majority of the cases, guideline-recommended medications initiated after the first hospitalization or

LTD status for incident CAD or LEAD were subsequently discontinued during follow-up. Medication-related complications and side effects or a strategy of prescription simplification in stable patients may explain these results. Of note, the rate of antiplatelet interruption is consistent with the patterns of non-adherence to antiplatelet regimens in stented patients in the PARIS registry [10]. However, although the long-term benefit of dual antiplatelet therapy has been debated, and may be limited to patients with high ischaemic risk and low bleeding risk, the long-term prescription of at least one antiplatelet drug is recommended in the setting of both CAD and LEAD, with a strong level of evidence [2, 3, 11-14]. A high rate of long-term non-observance to beta-blocker therapy was reported in 2002 by Butler et al., with a no-refill rate of 39% at 1 year after myocardial infarction [15]. The benefit of the long-term pursuit of beta-blockers in stable patients after an uncomplicated myocardial infarction in the era of percutaneous reperfusion has been debated recently, and is currently being investigated in large randomized controlled trials, such as the Assessment of Beta blocker interruption after uncomplicated mYocardial infarction on Safety and Symptomatic cardiac events requiring hospitalization (AβYSS) trial (ClinicalTrials.gov Identifier: NCT03498066) [16, 17]. The long-term benefit of lipid-lowering drugs, statins in particular, however, has been demonstrated by numerous randomized controlled trials in both CAD and LEAD settings, particularly when an objective of low-density lipoprotein cholesterol < 70 mg/dL is reached [4, 18-25]. As such, a premature interruption of these medications during follow-up may result in undertreatment of these patients, which has been associated with an increased risk of adverse events, including death [26, 27]. Further studies exploring the causes of these premature interruptions are warranted.

Adverse outcomes associated with CAD or LEAD

The burden of all-cause and cardiovascular hospitalizations in patients with incident CAD or LEAD was substantial in our study, and even greater than previous findings. In a large retrospective cohort study of Medicare beneficiaries hospitalized for myocardial infarction during 2000–2010 in the USA, 20.6% of the overall population underwent at least one subsequent readmission for cardiovascular cause, among whom 35.9% presented several consecutive hospitalizations [28]. In the present study, we also reported a significant incidence of all-cause readmissions, which further emphasizes the overall frailty of these patients. Finally, the presence of an myocardial infarction as the index event for incident CAD or heart failure before the index event were correlated with an increased risk of all-cause

mortality, consistent with previous findings, highlighting the need for thorough monitoring and aggressive medication of these high-risk patients [29, 30].

Study limitations

We acknowledge several limitations. The study was based on administrative claims and not on clinical evaluation. However, EGB data quality is ensured, monitored and audited internally by the French health system, while the reliability and accuracy of collected medical information are verified in each hospital by appointed physicians. The diagnosis of incident CAD and LEAD, based on hospitalization or LTD status, may have led to overestimation of the severity of these conditions, as the patients with the most severe conditions were more likely included. However, it also ensured a specificity of the diagnosis compared with a primary care setting. We cannot exclude that some atherosclerotic stable patients, without recent hospitalization or LTD status, were incorrectly identified as being newly diagnosed with CAD or LEAD, leading to a potential overestimation of incident cases. However, as an LTD status provides a complete coverage of the healthcare cost related to the disease, it is unlikely that patients with CAD or LEAD and their physician would not request such a status. Relevant variables, such as smoking status, body mass index and biological measurements, were not collected in the EGB database, and therefore are not included in the analyses. Medication dispensation was based on reimbursement claims, but true observance could not be assessed. The use of ICD-10 codes may be limited for some conditions, such as limb ischaemia or transient ischaemic attack, leading to a potential underestimation of their true incidence. Similarly, heart failure is not well recorded in the EGB database, and thus is not well captured in this study. Only a few patients had concomitant cases of incident CAD and LEAD, leading to an underpowered analysis of the respective clinical impact. Despite these limitations, this study is, to the knowledge of the authors, the largest to date on the trends in incidence and prevalence of CAD and LEAD in the French population.

Conclusions

In recent years, the incidence of CAD or LEAD has remained constant, leading to a progressive increase in their prevalence in the French population. Although guideline-recommended medications were largely prescribed following the diagnosis of such conditions, they were frequently discontinued during follow-up, resulting in undertreatment of these patients. Better long-term implementation of

guideline-recommended medical treatment for CAD or LEAD could help to reduce the considerable morbidity and mortality associated with these conditions.

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Figure legends

Figure 1. Study flow chart. CAD: coronary artery disease; EGB: Echantillon Généraliste de Bénéficiaires (Permanent Sample of Health Insurance Beneficiaries); LEAD: lower extremity artery disease; LTD: long-term disease status.

Figure 2. A. Yearly incidence of coronary artery disease (CAD) or lower extremity artery disease (LEAD). B. Yearly prevalence of CAD or LEAD.

Figure 3. Kaplan-Meier curves of event-free survival. CAD: coronary artery disease; CAD/LEAD: coronary artery disease or lower extremity artery disease; LEAD: lower extremity artery disease.

Table 1 Baseline characteristics

	Incident CAD (*n* = 8559)	Incident LEAD (*n* = 4399)	Incident CAD or LEAD (*n* = 12,408)
Male sex	5489 (64.1)	2753 (62.6)	7853 (63.3)
Age at index event (years)	67.3 ± 13.3	68.8 ± 14.2	67.8 ± 13.8
Age category (years)			
18–49	872 (10.2)	431 (9.8)	1268 (10.2)
50–59	1547 (18.1)	678 (15.4)	2133 (17.2)
60–69	2346 (27.4)	1117 (25.4)	3301 (26.6)
70–79	2030 (23.7)	1015 (23.1)	2885 (23.3)
≥ 80	1764 (20.6)	1158 (26.3)	2821 (22.7)
Social deprivation	487 (5.7)	247 (5.6)	704 (5.7)
Cardiovascular risk factors			
Diabetes mellitus	2048 (23.9)	937 (21.3)	2850 (23.0)
Systemic hypertension	5837 (68.2)	3172 (72.1)	8626 (69.5)
Hyperlipidaemia	197 (2.3)	85 (1.9)	276 (2.2)
Medical history			
Atrial fibrillation	456 (5.3)	329 (7.5)	755 (6.1)
Heart failure	377 (4.4)	269 (6.1)	623 (5.0)
Cancer (malignant)	971 (11.3)	579 (13.2)	1,481 (11.9)
Chronic kidney disease (stage 3–5)	113 (1.3)	179 (4.1)	278 (2.2)
Chronic obstructive pulmonary disease	247 (2.9)	156 (3.5)	384 (3.1)
Gastritis or duodenitis	157 (1.8)	93 (2.1)	239 (1.9)
Haemorrhagic stroke	20 (0.2)	19 (0.4)	39 (0.3)
Ischaemic stroke	218 (2.5)	160 (3.6)	367 (3.0)
Transient cerebral ischaemic attack	35 (0.4)	27 (0.6)	58 (0.5)
Leg ulceration	37 (0.4)	43 (1.0)	77 (0.6)
Major bleeding events	192 (2.2)	152 (3.5)	336 (2.7)
Myocardial infarction	0 (0.0)	324 (7.4)	324 (2.6)

Other vascular diseases (aneurysm, vasculitis)	1 (0.0)	19 (0.4)	19 (0.2)
Venous thromboembolism	54 (0.6)	56 (1.3)	106 (0.9)

Data are expressed as number (%) or mean ± standard deviation. CAD: coronary artery disease; LEAD: lower extremity artery disease.

Table 2 Dispensed medication.

	Incident CAD (*n* = 8559)	Incident LEAD (*n* = 4399)	Incident CAD or LEAD (*n* = 12,408)
Medication before index event			
Antithrombotic drugs			
Antiplatelet therapy	3644 (42.6)	2349 (53.4)	5700 (45.9)
Vitamin K antagonists	612 (7.2)	503 (11.4)	1080 (8.7)
Direct thrombin inhibitors	59 (0.7)	21 (0.5)	78 (0.6)
Direct factor Xa inhibitors	135 (1.6)	64 (1.5)	194 (1.6)
Beta-blockers	2896 (33.8)	1452 (33.0)	4169 (33.6)
Renin-angiotensin system drugs	4145 (48.4)	2376 (54.0)	6242 (50.3)
Calcium channel blockers	2047 (23.9)	1180 (26.8)	3069 (24.7)
Diuretics	1779 (20.8)	1163 (26.4)	2817 (22.7)
Lipid-lowering drugs	4028 (47.1)	2256 (51.3)	5989 (48.3)
Glucose-lowering drugs[a]	1788 (20.9)	740 (16.8)	2411 (19.4)
Insulin and analogues	581 (6.8)	317 (7.2)	858 (6.9)
Class I or III antiarrhythmic drugs	516 (6.0)	290 (6.6)	778 (6.3)
Proton pump inhibitors	4386 (51.2)	2217 (50.4)	6336 (51.1)
Medication initiated after the index event			
Antithrombotic drugs			
Antiplatelet therapy	3774 (44.1)	1215 (27.6)	4760 (38.4)
Vitamin K antagonists	623 (7.3)	414 (9.4)	952 (7.7)
Direct thrombin inhibitors	111 (1.3)	44 (1.0)	145 (1.2)
Direct factor Xa inhibitors	430 (5.0)	175 (4.0)	568 (4.6)
Beta-blockers	3541 (41.4)	538 (12.2)	3847 (31.0)
Renin-angiotensin system drugs	2302 (26.9)	556 (12.6)	2693 (21.7)
Calcium channel blockers	1205 (14.1)	627 (14.3)	1709 (13.8)
Diuretics	1628 (19.0)	603 (13.7)	2083 (16.8)
Lipid-lowering drugs	3087 (36.1)	815 (18.5)	3704 (29.9)

Glucose-lowering drugs[a]	383 (4.5)	164 (3.7)	517 (4.2)
Insulin and analogues	292 (3.4)	144 (3.3)	403 (3.2)
Class I or III antiarrhythmic drugs	657 (7.7)	238 (5.4)	832 (6.7)
Proton pump inhibitors	2636 (30.8)	1090 (24.8)	3522 (28.4)
Discontinuation during follow-up of medication initiated after the index event[b]			
Antithrombotic drugs			
Antiplatelet therapy	1972 (52.3)	788 (64.9)	2624 (55.1)
Vitamin K antagonists	492 (79.0)	317 (76.6)	742 (77.9)
Direct thrombin inhibitors	84 (75.7)	30 (68.2)	106 (73.1)
Direct factor Xa inhibitors	209 (48.6)	88 (50.3)	275 (48.4)
Beta-blockers	2301 (65.0)	372 (69.1)	2523 (65.6)
Renin-angiotensin system drugs	1763 (76.6)	450 (80.9)	2084 (77.4)
Calcium channel blockers	982 (81.5)	514 (82.0)	1390 (81.3)
Diuretics	1165 (71.6)	450 (74.6)	1499 (72.0)
Lipid-lowering drugs	2433 (78.8)	681 (83.6)	2947 (79.6)
Glucose-lowering drugs[a]	268 (70.0)	115 (70.1)	360 (69.6)
Insulin and analogues	249 (85.3)	123 (85.4)	345 (85.6)
Class I or III antiarrhythmic drugs	503 (76.6)	164 (68.9)	619 (74.4)
Proton pump inhibitors	1922 (72.9)	872 (80.0)	2637 (74.9)

Data are expressed as number (%). CAD: coronary artery disease; LEAD: lower extremity artery disease.

[a] Except insulin.

[b] Percentages are described according to medication initiated after the index event.

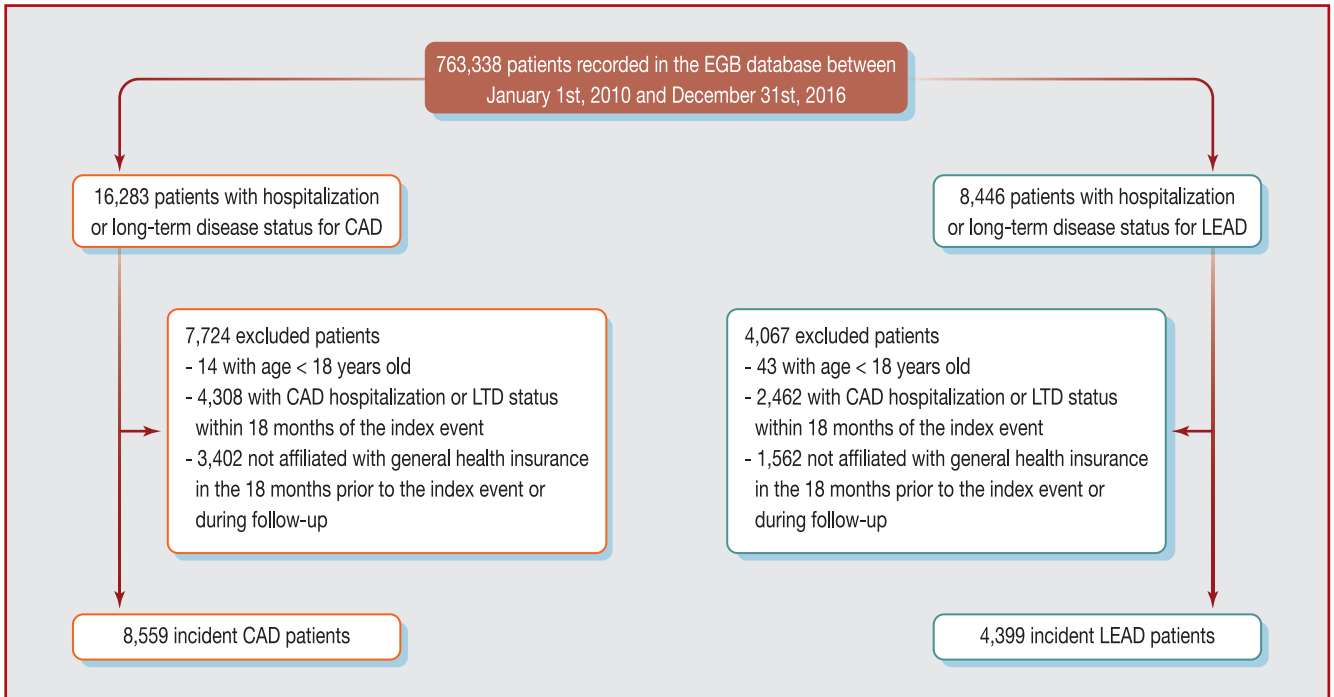
Table 3 Adverse outcomes and their recurrences during follow-up.

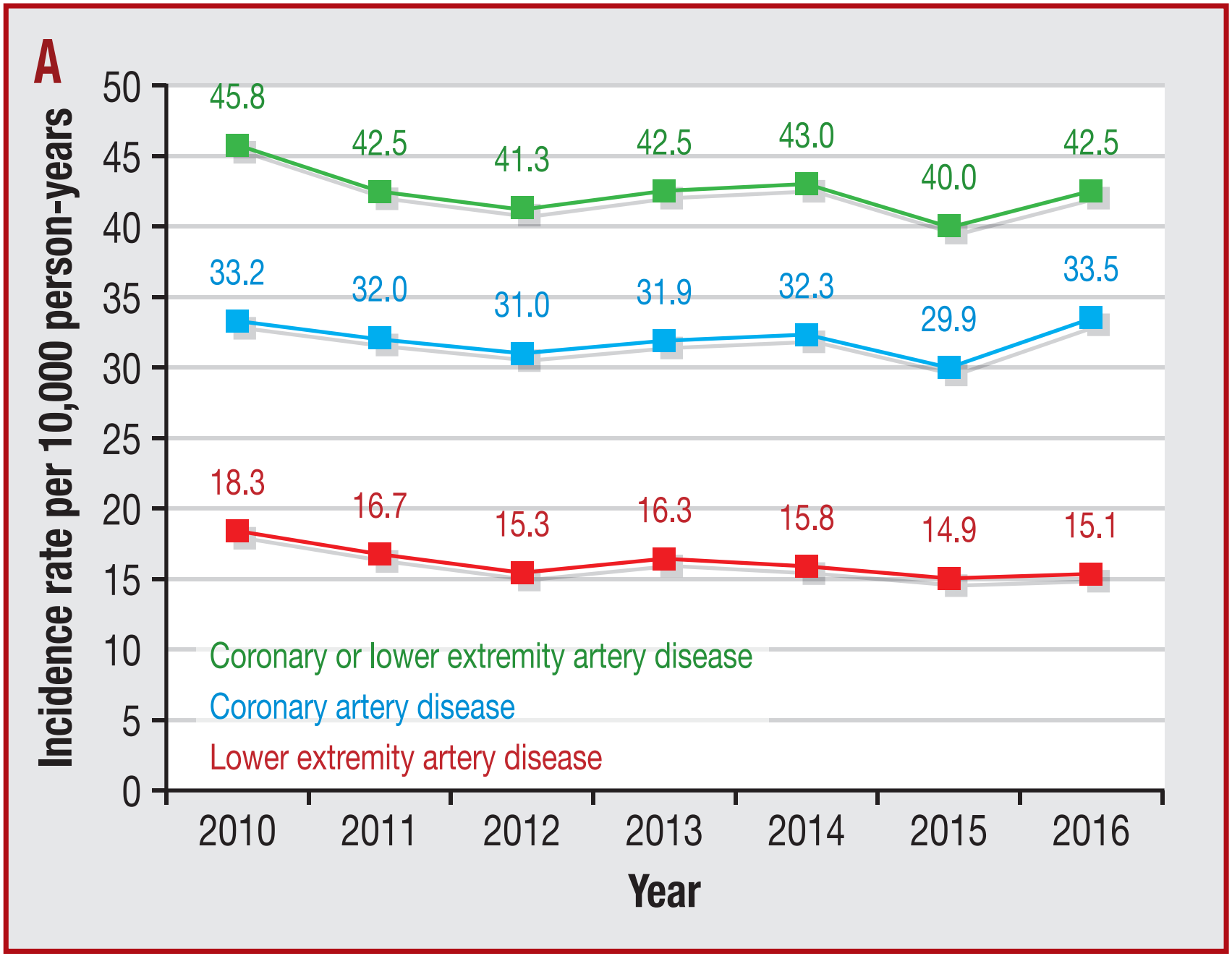
Complications	Incident CAD or LEAD			
	Incidence (per 10,000 person-years)	Number (%) of patients with a recurrence	Time between first event and first recurrence (days)[a]	Number (%) of patients with more than one recurrence
All-cause death	542.8	-	-	-
Cardiovascular death	97.8	-	-	-
All-cause hospitalization	7976.9	6700 (73.0)	83.0 (21.0–334.5)	4854 (72.4)
Cardiovascular hospitalization	2966.4	2856 (48.1)	239.5 (40.0–748.0)	1333 (46.7)
Myocardial infarction	770.2	682 (30.2)	36.0 (7.0–299.0)	193 (28.3)
Ischaemic stroke	73.9	32 (12.3)	36.5 (3.5–200.0)	8 (25.0)
Transient ischaemic attack	31.9	7 (6.2)	260.0 (2.0–336.0)	2 (28.6)
Heart failure	258.5	333 (37.7)	91.0 (33.0–315.0)	157 (47.1)
Major bleeding event	165.5	90 (15.7)	59.0 (9.0–339.0)	22 (24.4)
Haemorrhagic stroke	21.1	8 (10.7)	37.0 (3.5–239.5)	2 (25.0)
PCI	1317.1	941 (27.5)	99.0 (16.0–393.0)	260 (27.6)
CABG	290.7	123 (12.9)	83.0 (3.0–464.0)	29 (23.6)
Limb ischaemia	178.3	194 (31.8)	71.0 (23.0–297.0)	71 (36.6)
Amputation of lower limb	60.1	64 (30.2)	85.5 (22.5–255.0)	27 (42.2)

Venous thromboembolism	20.0	9 (12.7)	92.0 (22.0–273.0)	3 (33.3)

CABG: coronary artery bypass graft; CAD: coronary artery disease; LEAD: lower extremity artery disease; PCI: percutaneous coronary intervention.

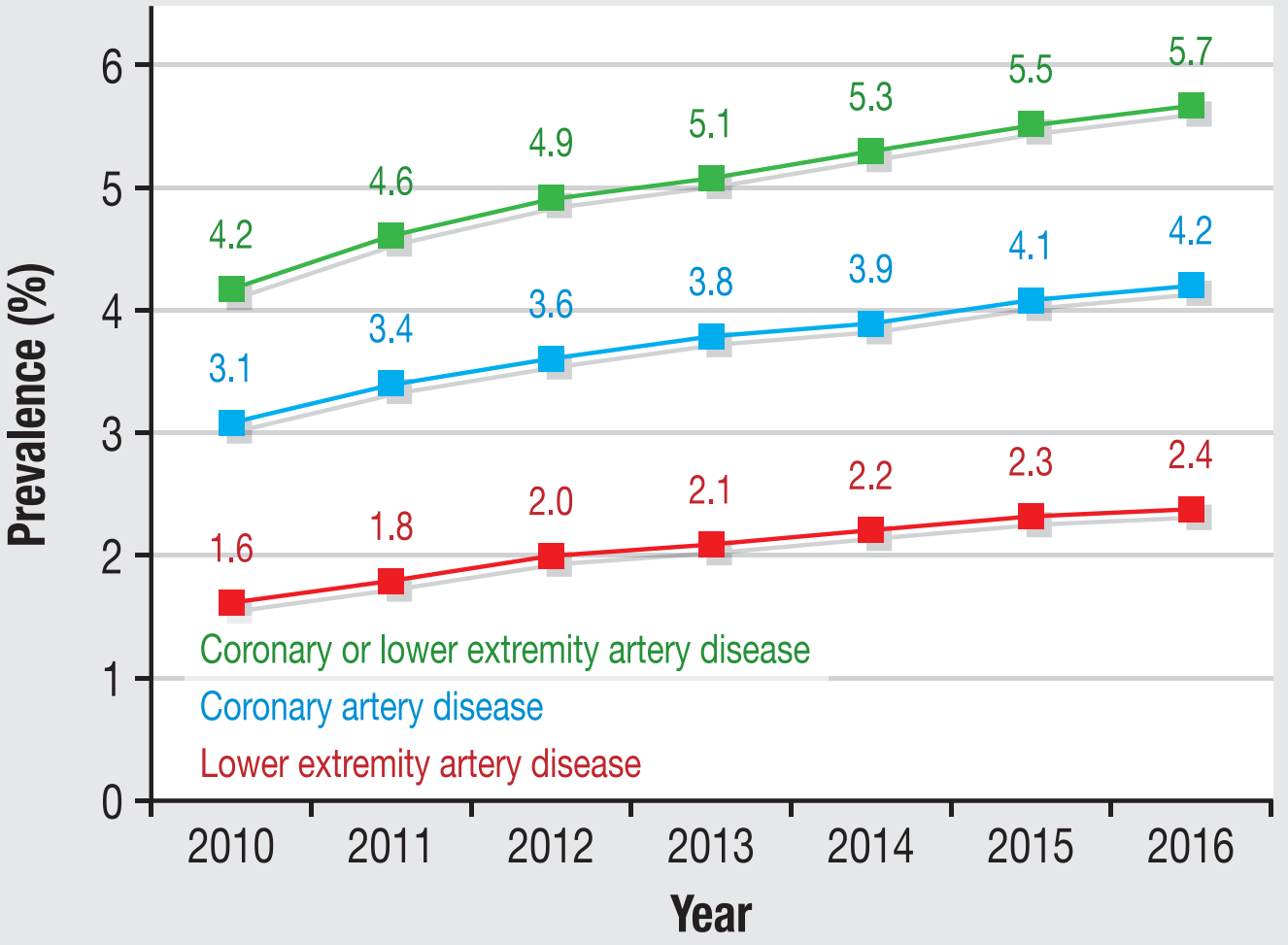
[a] Time between first event and first recurrence is reported as median (interquartile range).


763,338 patients recorded in the EGB database between January 1st, 2010 and December 31st, 2016
16,283 patients with hospitalization or long-term disease status for CAD
8,446 patients with hospitalization or long-term disease status for LEAD
7,724 excluded patients
- 14 with age < 18 years old
- 4,308 with CAD hospitalization or LTD status within 18 months of the index event
- 3,402 not affiliated with general health insurance in the 18 months prior to the index event or during follow-up
4,067 excluded patients
- 43 with age < 18 years old
- 2,462 with CAD hospitalization or LTD status within 18 months of the index event
- 1,562 not affiliated with general health insurance in the 18 months prior to the index event or during follow-up
8,559 incident CAD patients
4,399 incident LEAD patients


A
Incidence rate per 10,000 person-years
50
45
40
35
30
25
20
15
10
5
0
45.8
42.5
41.3
42.5
43.0
40.0
42.5
33.2
32.0
31.0
31.9
32.3
29.9
33.5
18.3
16.7
15.3
16.3
15.8
14.9
15.1
Coronary or lower extremity artery disease
Coronary artery disease
Lower extremity artery disease
2010
2011
2012
2013
2014
2015
2016
Year

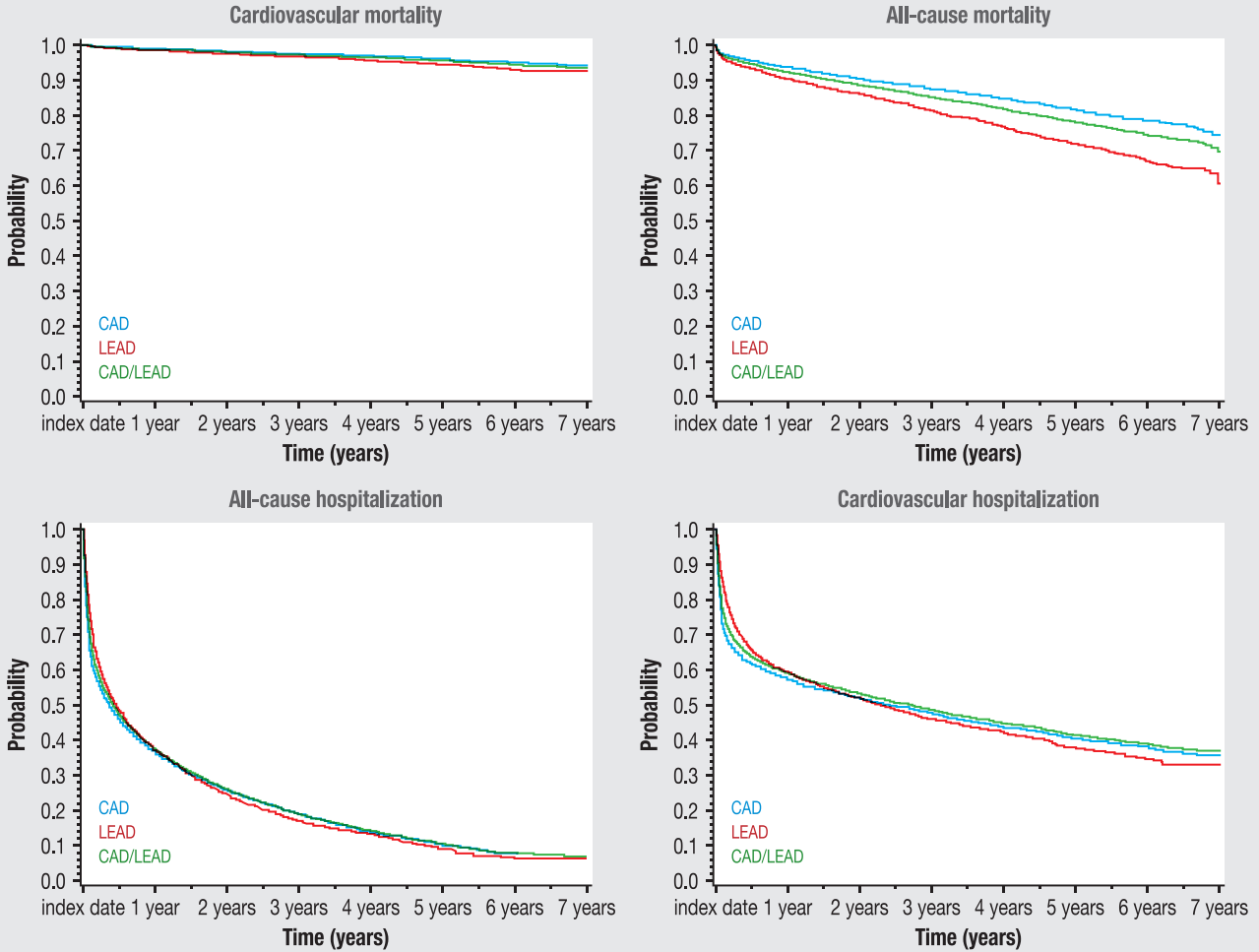
B

Yearly prevalence of coronary and lower extremity artery disease in France



Clinical impact of coronary or peripheral artery disease

	Incidence rates (per 10,000 person-year)
All-cause death	542.8
All-cause hospitalization	7,976.9
Myocardial infarction	770.2


Cardiovascular mortality
All-cause mortality
All-cause hospitalization
Cardiovascular hospitalization
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
CAD
LEAD
CAD/LEAD
index date 1 year
2 years
3 years
4 years
5 years
6 years
7 years
Time (years)