ATHENA-F

Assessment of The High risk and unmEt Need in patients with Coronary Artery Disease and type 2 diabetes in France

Report

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PASS / General information

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RESEARCH QUESTION AND OBJECTIVES	**Research question:** To assess the prevalence and burden of disease in France for CAD-T2DM population (type 2 diabetes mellitus [T2DM] patients with history of coronary arterial disease [CAD]) without prior myocardial infarction (MI) or stroke, as well as for the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population). **Main objective:** To estimate the prevalence of CAD-T2DM without prior MI or stroke in France, as well as of the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population). **Secondary objectives:** For both populations (CAD-T2DM without prior MI or stroke population and THEMIS-like population) are to: - Describe patient characteristics and comorbid conditions; - Describe treatment patterns (cardiovascular and antidiabetic drugs) and persistence for two years; - Describe cardiovascular (CV) and non-CV related healthcare resources use for two years and to estimate mean healthcare cost per year; - Estimate the crude incidence rate, the cumulative incidence, and the predictors of composite CV events: MI, stroke (ischemic, haemorrhagic and unknown) and CV death (or all-cause death otherwise) for two years; - Estimate the crude incidence rate and the cumulative incidence of hospitalisation for heart failure for two years; - Estimate the crude incidence rate and the cumulative incidence of bleeding events: major organ specific bleedings, intracranial bleeding, haemorrhagic stroke, other critical organ or site bleeding, other bleeding with transfusion, and fatal bleedings for two years.

COUNTRY OF STUDY	France
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2. ABSTRACT

TITLE	Assessment of The High risk and unmEt Need in patients with coronary artery disease and type 2 diabetes in France (ATHENA-F)
KEYWORDS	Type 2 diabetes mellitus, coronary arterial disease, myocardial infraction, stroke, cardiovascular events, bleeding events, cardiovascular and antidiabetic drugs, risk assessment, death, claims and hospitalisation database
RATIONALE AND BACKGROUND	AstraZeneca is working on an indication extension of ticagrelor for the prevention of cardiovascular (CV) death, myocardial infraction (MI) or stroke in patients with coronary arterial disease (CAD), but without medical history of previous MI or stroke at high risk of atherothrombotic events due to type 2 diabetes mellitus (T2DM). Inclusion criteria in the THEMIS pivotal randomized clinical trial were CAD-T2DM patient ≥ 50 years old with T2DM since at least 6 months and history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) or angiographic evidence of ≥ 50% lumen stenosis of at least one coronary artery, without MI or stroke history. In the context of the indication extension of ticagrelor that will be evaluated by the European Medicines Agency, this project was designed to assess the burden of illness in different healthcare setting as population size, patient characteristics and comorbidities, treatments patterns, healthcare resources use, as well as risk of CV events for CAD-T2DM patients similar to THEMIS inclusion criteria, using registries or databases. The French part of the study will be performed using the *Système National des Données de santé* (SNDS) nationwide claims database.
RESEARCH QUESTION AND OBJECTIVES	The research question was to assess the prevalence and burden of disease in France for the coronary arterial disease due to type 2 diabetes mellitus (CAD-T2DM) population without prior MI or stroke, as well as for the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population). The main objective was to estimate the prevalence of CAD-T2DM without prior MI or stroke in France, as well as of the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population). The secondary objectives were: i) to describe patient characteristics and comorbidity conditions; ii) to describe treatment patterns (CV and antidiabetic drugs) and persistence for two years; iii) to describe CV and non-CV related healthcare resources use for two years and to estimate mean healthcare cost per year; iv) to estimate the crude incidence rate, the cumulative incidence, and the predictors of composite CV events (MI, stroke (ischemic, haemorrhagic and unknown) and CV death or all-cause death otherwise) for two years; v) to estimate the crude incidence rate and the cumulative incidence of hospitalisation for heart failure, major organ specific bleedings (intracranial bleeding, haemorrhagic stroke, other critical organ or site bleeding, other bleeding with transfusion, and fatal bleeding) for two years.
STUDY DESIGN	Cohort study in the French nationwide healthcare claims and hospitalisation database (*Système National des Données de Santé* - SNDS) including all T2DM patients with CAD history (5-year history or Long-Term Disease [LTD]) on the 1st January 2014 (index date) and followed until 31st December 2015 or date of death.

SETTING	This is a cohort study of all T2DM and CAD patients without MI or stroke history, identified and followed in the SNDS nationwide claims database.
SUBJECTS AND STUDY SIZE, INCLUDING DROPOUTS	Three populations were defined: - **CAD-T2DM population** with all patients with T2DM diagnosis on 01/01/2014 plus CAD history and affiliated to the main healthcare insurance scheme (CNAMTS), because of incomplete history for other schemes included after 2011; - **CAD-T2DM population without prior MI-stroke** included patients of CAD-T2DM population without diagnosis of MI or stroke during the history period; - **THEMIS-like population** included patients of the CAD-T2DM population without prior MI or stroke fulfilling specific criteria (aged ≥ 50 years at the index date, without intracranial bleeding before index date, neither gastro-intestinal (GI) bleeding within 6 months before index date, or renal failure requiring dialysis, or cirrhosis of liver or liver cancer before index date, or antiplatelet agent (APA) or anticoagulant treatments within 2 months before and after index date)**.**
VARIABLES AND DATA SOURCES	The index date was the 1st January 2014 for all patients with T2DM plus CAD without MI or stroke history. Prevalence proportion of CAD-T2DM patients with age and gender standardisation according to national or European statistics was estimated on 01/01/2014. Clinical outcomes studied during the 2-year follow-up period were stroke (ischemic or undefined), MI, CV death or all-cause death otherwise, heart failure, major organ specific bleeding (intracranial blleding, haemorrhagic stroke, other critical organ or site bleeding, other bleeding, fata bleeding), and a composite event (first event among MI, all strokes and death). The SNDS database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry. It currently includes 99% of the French population of 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. It contains individual pseudonymised information on general characteristics: gender, year of birth, area of residence, date of death, LTD with full insurance coverage, outpatient reimbursed healthcare expenditures (visits, medical procedures, nursing acts, …), and hospital discharge summaries for all private and public medical, obstetric and surgery hospitalisations.
RESULTS	On the 1st January 2014, 328 622 were included in the CAD-T2DM population with 258 260 (78.6%) CAD-T2DM patients without prior MI-stroke and 64 334 (19.6%) THEMIS-like patients. The 2014 prevalence rate in France of CAD-T2DM without prior MI-stroke and THEMIS-like populations was estimated at 6.17 and 1.53 per 1 000 adults, corresponding to about 317 000 and 79 000 patients. The prevalence was higher for men and increased with age in both populations. THEMIS-like population represented a quarter of all CAD-T2DM patients without prior MI-stroke, as well as, according to gender and age classes. The prevalence rate with sex-age standardization for the European population was estimated at 6.04 and 1.50 per 1 000 adults, respectively. Patient profil was close for the CAD-T2DM without prior MI-stroke and the THEMIS-like populations with respectively a mean age of 72 years, 68% and

66% of men, 26% and 25% with more than 4-year history of CAD and T2DM, 79% and 76% with hypertension history. However, CAD-T2DM patients without prior MI-stroke presented more revascularisation procedures history than THEMIS-like patients (28% and 19%), were more affected by atrial fibrillation (21% and 10%), renal impairement (20% and 5%), heart failure (16% and 9%), PAD (19% and 11%), and diabetic complications (39% and 32%), and more frequently treated with APA and anticoagulant within the history period (69% *vs.* 43% and 51% *vs.* 33%) as well as over the 2-year follow-up (36% *vs.* 9% and 31% *vs.* 16%).

The 2-year cumulative incidence of main ouctomes for all patients and according to age was little higher for the CAD-T2DM population without prior MI-stroke than for the THEMIS-like population for ischemic or unknown stroke (1.7% *vs.* 1.5%) and MI (1.7% *vs.* 1.3%), and clearly higher for heart failure (9.5% *vs. 5*.3%), major organ specific bleeding (4.9% *vs.* 3.2%), all-cause death (13.6% *vs*. 9.7%) and the composite event (16.2% *vs.* 12.0%). For major bleeding categories details, the 2-year cumulative incidence was also higher for other bleeding with transfusion (3.4% *vs.* 2.0%), for fatal bleeding (1.2% *vs.* 0.7%), for other critical organ or site bleeding (0,7% *vs.* 0.5%), for haemorrhagic stroke (0.5% *vs.* 0.4%), and for intracranial bleeding (0.2% *vs.* 0.1%). For each outcome, the incident rate increased with age in both populations.

The risk of composite of MI, stroke and all-cause death increased according to age with a continuous gradient for both populations, and was also 24% and 30% higher for the men of CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively. Independent prognosis factors of the composite event were heart failure, cancer and PAD history in both populations, with a HR between 1.56 and 1.80, and also neurotic and mood disorders history with a HR between 1.30 and 1.34. Liver diseases (excluding chronic viral hepatitis and cystic fibrosis) was a prognosis factor (HR 1.81) for CAD-T2DM patients without prior MI-stroke but was not significant for the THEMIS-like population. Diuretics used during the follow-up was associated with higher risk of the composite event in both populations (HR between 1.49 and 1.44), as well as APA for the THEMIS-like population (HR 1.26) but not for CAD-T2DM patients without prior MI-stroke. Compared to antidiabetic monotherapy used, no treatment, bitherapy and tritherapy or more were associated with a 30% lower risk, while insulin used to an increased risk (HR 1.27 and 1.20, respectively). However, this statistical analysis did not allow to differentiate drug effect and drug as a marker of disease severity.

For the national health insurance perspective, the mean medical total cost per patient over the 2-year follow-up was €25 025 for CAD-T2DM patients without prior MI-stroke and €17 899 for the THEMIS-like population, while mean total allowances cost was similar in both populations (€1 483 and €1 424€, respectively).

DISCUSSION

Analysis of care reimbursements from the general scheme between 2009 and 2013, extrapolated to the French population on 1st January 2014, allowed to assess for the first time the prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like patients in France. According to this study, the prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like patients was 6.17 (i.e. 316 824 patients throughout France) and 1.53 per 1 000 persons (78 597 patients throughout France) with a higher prevalence for men than women and increasing with age. Taking into account the latest estimate of diabetes prevalence in France in 2015, CAD-T2DM patients without prior MI-stroke would represent approximatively 11% of type 2 diabetic patients and THEMIS-like patients around 3%.

	Our results based on the SNDS showed that the THEMIS-like population had same age as CAD-T2DM patients without prior MI-stroke with some differences for comorbidities, as some cardiovascular diseases (atrial fibrillation, heart failure, PAD), renal impairement, diabetic complications, and exposure to APA or anticoagulant, and represented about a quarter of all CAD-T2DM patients without prior MI-stroke, as well as for men, women and according to age-classes. The 2-year cumulative incidence was lower for the THEMIS-like population than for the CAD-T2DM patients without prior MI-stroke for all events studied, ischemic stroke (-12%), MI (-24%), heart failure (-44%), major organ specific bleeding (-35%), all-cause death (-29%) and composite of MI, stroke and all-cause death (-26%). The THEMIS-like patients of this real-world study were 6 years older in average than those of the placebo arm of the THEMIS randomized trial (i.e. 72 and 66 years old, respectively), with a lower risk of MI (i.e. 1.3% *vs.* 2.2%, assuming 2/3 of the 3-year incidence with constant risk across time for the THEMIS placebo arm), but little higher for ischemic stroke (1.5% *vs.* 1.2%), about the double for the composite event (12.0% *vs.* 6.2%), triple for deaths (9.7% *vs.* 3.2%), and quadruple for major bleedings (1.67% *vs.* 0.38 per 100 PY).
MARKETING AUTHORISATION HOLDER	AstraZeneca
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3. LIST OF ABBREVIATIONS

ACEI	Angiotensin-Converting-Enzyme Inhibitor
ADP	Adenosine Diphosphate
APA	Antiplatelet Agent
ASA	Acetylsalicylic Acid
ATC	Anatomical Therapeutic Chemical
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
CABG	Coronary Artery Bypass Graft
CAD	Coronary Arterial Disease
CCAM	*Classification Commune des Actes Médicaux*
CI	Confidence Interval
CIF	Cumulative Incidence Function
CNAM	*Caisse Nationale d'Assurance Maladie* (French national health insurance fund)
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French data protection commission)
CV	CardioVascular
DM	Diabetes Mellitus
GI	Gastro-Intestinal
ICD-10	International Classification of Diseases, 10th revision
ICU	Intensive Care Unit
CCU	Critical Care Unit
INDS	*Institut National des Données de Santé* (National Institute of Health Data)
LTD	Long-Term Disease (French list of major chronic diseases with full insurance cover of all claims related to disease)
LPP	*Liste des Produits et Prestations* (List of refundable products and services)
MCO	*Médecine, Chirurgie et Obstétrique* (Medicine, Surgery, Obstetrics)
MI	Myocardial Infarction
MPR	Medication Possession Ratio
NABM	*Nomenclature des Actes de Biologie Médicale*
NIAD	Non Insulin Antidiabetic Drug
OSAS	Obstructive Sleep Apnoea Syndrome
PAD	Peripheral Arterial Disease

PCI	Percutaneous Coronary Intervention
PMSI	*Programme de Médicalisation des Systèmes d'information*
PY	Person-Years
SAP	Statistical Analysis Plan
SNDS	*Système National des Données de Santé* (French National healthcare insurance system database)
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist

4. INVESTIGATORS

Not applicable.

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6. MILESTONES

MILESTONES	PLANNED DATE	ACTUAL DATE	COMMENTS
Study Protocol	2018, June	2018, July	
Regulatory aspects and data extraction follow-up with CNAM (SNDS)	2018, June – December	2018, July – 2019, June	SNDS data extracted on June 2019
Statistical Analysis Plan	2018, June – December	2018, June – 2020, January	
Data management and statistical analysis*	2019, January – April	2019, July – 2020 January	Extended by Amendment
Final report*	2019, May	2020, March	Extended by Amendment

** Conditioned by the date of the SNDS data extraction by the CNAM*

7. AMENDMENTS AND UPDATES OF THE STUDY PROTOCOL

The study protocol was updated before the SNDS data reception. These updates were summarized in the table below, and the last version of the study protocol is presented in Annex 1-1.

NUMBER	DATE	SECTION OF STUDY PROTOCOL	AMENDMENT OR UPDATE	REASON
1	25 July 2018	9.1, 9.2, 9.3.1, 9.5, 9.9, 13	Update	Update following the positive opinion with recommendations delivered by the CEREES (*Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé)* on the 18th July 2018.

8. RATIONALE AND BACKGROUND

Coronary arterial diseases (CAD) remain the leading cause of mortality with more than 11 million in Europe as a whole, every year, and a major cause of morbidity in Europe (European Cardiovascular Disease Statistics 2017). With almost 49 million people living with the disease in the European Union (EU), the cost to the EU economies is high at €210 billion a year (European Cardiovascular Disease Statistics 2017).

Epidemiologic studies have outlined a strong association between diabetes mellitus (DM) and CAD with a high risk to develop myocardial infarction (MI) and stroke (Beckmann *et al.*, 2013; Ryden *et al.*, 2013). The REACH registry showed an overall risk of cardiovascular (CV) death, non-fatal MI, or non-fatal stroke greater for patients with diabetes compared to patients without diabetes (16.5% versus 13.1%, p<0.001) over four years, and 14.8% for patients with prior revascularisation but not prior MI (Cavender et *al.*, 2015). Furthermore, epidemiologic studies from the United States have shown clinical outcomes in patients with DM have improved over time. However, the absolute rate of complications from DM increased due to an increasing of DM prevalence (Gregg *et al.*, 2014; Selvin *et al*., 2010). Global estimates of diabetes in adults predict an increase from 8.8% in 2015 to 10.4% in 2045 which confirms the global impact of diabetes, especially in developing countries and imposes a large economic burden on health care systems across the world (Ogurtsova *et al*., 2017). In France, prevalence of treated diabetes was estimated at 2.6% in 2000 with a constant increase to 4.4% in 2009 and 5% in 2015, using the nationwide claims database (Ricci *et al.*, 2010; Mandereau-Bruno *et al.*, 2017).

Evidence of the benefit of acetylsalicylic acid (ASA) use in prevention of CV events in patients with T2DM without prior MI is disputed as reflected by differences in recommendations given by treatment guidelines and current position papers (Ryden *et al.*, 2013). Ticagrelor is an orally active antiplatelet agent. It is a reversible inhibitor of the platelet P2Y12 adenosine diphosphate (ADP)-receptor that prevents the activation of platelet aggregation by ADP, indicated with ASA for the prevention of athero-thrombotic events in adult patients with acute coronary syndrome or history of MI.

AstraZeneca is working on an indication extension of ticagrelor for the prevention of CV death, MI or stroke in patients with CAD, but without medical history of previous MI or stroke at high risk of atherothrombotic events due to T2DM. Inclusion criteria in the THEMIS pivotal randomized clinical trial were CAD-T2DM patient ≥ 50 years old with T2DM since at least 6 months and history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) or angiographic evidence of ≥ 50% lumen stenosis of at least one coronary artery, without MI or stroke history. Recent results of the THEMIS trial on the benefit-risk of ticagrelor plus aspirin versus placebo plus aspirin showed a lower incidence of ischemic cardiovascular events in ticagrelor group than placebo group (7.7% versus 8.5%, p=0.04), whereas the incidence of major bleeding as defined by the Thrombolysis in Myocardial Infarction TIMI criteria was higher (2.2% versus 1.0%, p<0.001) (Steg *et al.,* 2019). Furthermore, in a subpopulation with percutaneaous coronary intervention (PCI) history (58% of the THEMIS trial patients), ticagrelor plus aspirin reduced also the risk of ischemic events (7.3% versus 8.6%, p=0.013), but not for patients without prior PCI (Bhatt *et al.*, 2019).

In the context of the indication extension of ticagrelor that will be evaluated by the European Medicines Agency, this project was designed to assess the burden of illness in different healthcare settings as population size, patient characteristics and comorbidities, treatments patterns, healthcare resources use, as well as risk of cardiovascular events for T2DM patients similar to THEMIS inclusion criteria, using registries or databases. The study was performed using the SNDS, the French nationwide claims database.

9. RESEARCH QUESTION AND OBJECTIVES

The research question was to assess the prevalence and burden of disease in France for the CAD-T2DM population without prior MI or stroke, as well as for the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population).

The main objective was to estimate the prevalence of CAD-T2DM without prior MI or stroke in France, as well as of the population with inclusion and exclusion criteria of the THEMIS randomized controlled trial (THEMIS-like population).

The secondary objectives for both populations (CAD-T2DM without prior MI or stroke population and THEMIS-like population) were:

- To describe patient characteristics and comorbidity conditions;
- To describe treatment patterns (CV and antidiabetic drugs) and persistence for two years;
- To describe CV and non-CV related healthcare resources use for two years and to estimate mean healthcare cost per year;
- To estimate the crude incidence rate, the cumulative incidence, and the predictors of composite CV events: MI, stroke (ischemic, haemorrhagic and unknown), and CV death or all-cause death otherwise for two years;
- To estimate the crude incidence rate and the cumulative incidence of hospitalisation for heart failure, major organ specific bleedings (intracranial bleeding, haemorrhagic stroke, other critical organ or site bleeding, other bleeding with transfusion, and fatal bleedings) for two years.

10. RESEARCH METHODS

10.1. Study design

The initial design was a cohort study in the SNDS nationwide claims database including all T2DM patients between 2013 and 2014 with CAD history (5-year history or Long-Term Disease [LTD]) with a follow-up of 2 years per patient. Data were extracted from 1st January 2008 to 31st December 2016. The index date was:

- for prevalent patients (both T2DM and CAD diagnoses): the 1st January 2013,
- for incident patients: the first date of T2DM diagnosis for CAD prevalent patients, or the first date of CAD diagnosis for T2DM prevalent patients.

The study follow-up period started on the study index date and ended two years later, or until date of death. Each patient had a 5-year history period in the database before index date.

In view of the low number of incident CAD-T2DM patients without prior MI or stroke during the 2013-2014 period, the study design was modified and approved by the Scientific Committee. According to the new study design, all patients with T2DM and CAD diagnoses on the 1st January 2014 (index date) were included in the CAD-T2DM without prior MI or stroke population. The study period remained unchanged with 5-year history and 2-year follow-up until 31st December 2015 or date of death. The overall design of the study is presented in the Figure 1.

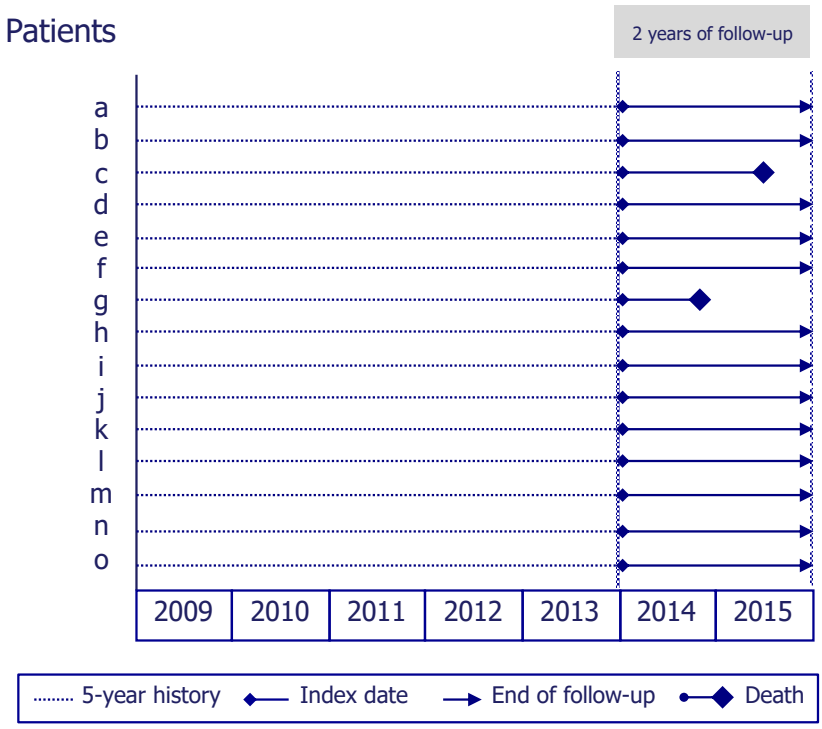

Figure 1. Study design

10.2. Setting

This was a cohort study of all T2DM and CAD patients without MI or stroke history, identified and followed in the SNDS nationwide claims database.

10.3. Subjects

10.3.1. Extracted population

Data were extracted from 1 January 2008 to 31 December 2016 for the main and secondary objectives in June 2019.

All T2DM patients with a 5-year CAD history and a follow-up of 2 years on the 1st January 2014 were extracted from the database.

10.3.2. Study population

Three populations were defined:

- **CAD-T2DM population**: all patients with T2DM diagnosis on 01/01/2014 plus CAD history and affiliated to the main healthcare insurance scheme (CNAMTS), because of incomplete history for other schemes included after 2011;
- **CAD-T2DM population without prior MI-stroke**: patients of the CAD-T2DM population without diagnosis of MI or stroke during the history period;
- **THEMIS-like population**: patients of the CAD-T2DM population without prior MI-stroke fulfilling the following criteria:
  - Aged ≥ 50 years at index date;
  - Without intracranial bleeding before index date;
  - Without gastro-intestinal (GI) bleeding within 6 months before index date;

- Without renal failure requiring dialysis;
- Without cirrhosis of liver or liver cancer before index date;
- Without antiplatelet agent (APA) or anticoagulant treatments within 2 months before and after index date.

Exclusion criteria:
All subjects from all populations with the following criteria were excluded:

- Patients < 18 years at index date;
- Patients dead at index date;
- Patients not affiliated to the general scheme (*Régime Général*) between 2008 and 2016;
- Patients with less than 5 years of history period or incomplete follow-up (without death).

10.4. Variables

10.4.1. Index date

The index date was defined as the 1st January 2014 for all patients.

10.4.2. Disease

Disease definitions were based on the International Classification of Diseases 10th revision (ICD-10) or LTD registration:

- **T2DM diagnosis**: ≥ 3 non-insulin antidiabetic drugs (NIAD, see ATC codes in Annex 1-2, SAP, Appendix 9) dispensed during 1 year between 01/01/2013 and 01/01/2014; or T2DM diagnosis (see ICD-10 codes in Annex 1-2, SAP, Appendix 4) ongoing or occurring between 01/01/2012 and 01/01/2014 from LTD registration or hospitalisation.
- **CAD**: see ICD-10 codes (LTD registration or hospitalisation) and CCAM codes (cardiac revascularisation procedures - PCI/CABG) in Annex 1-2, SAP, Appendix 6 between 01/01/2009 and 01/01/2014;
- **MI**: see ICD-10 codes in Annex 1-2, SAP, Appendix 4 (LTD registration or hospitalisation with an indication of Intensive Care Unit or Critical Care Unit (ICU/CCU);
- **Ischemic or unknown stroke** (excluding transient ischemic attack, TIA): see ICD-10 codes in Annex 1-2, SAP, Appendix 4 (LTD registration or hospitalisation);
- **Intracranial bleeding**: see ICD-10 codes in Annex 1-2, SAP, Appendix 4 (LTD registration or hospitalisation);
- **Haemorrhagic stroke**: see IC-10 codes in Annex 1-2, SAP, Appendix 4 (LTD registration or hospitalisation;
- **GI bleeding**: see ICD-10 codes in Annex 1-2, SAP, Appendix 1 (primary, related or associated diagnosis of hospitalisation);
- **Cirrhosis of liver**: see ICD-10 codes in Annex 1-2, SAP, Appendix 2 (LTD registration or hospitalisation);
- **Liver cancer**: see ICD-10 codes in Annex 1-2, SAP, Appendix 2 (LTD registration or hospitalisation);
- **Renal failure requiring dialysis**: see ICD-10 codes in Annex 1-2, SAP, Appendix 3 (LTD registration or hospitalisation);

10.4.3. Exposure

Exposure definitions were defined using following variables (see ATC codes in Annex 1-2, SAP, Appendix 9):

- **Antidiabetic drugs**;
- **Acetylsalicylic acid (ASA)**;
- **Antiplatelet agents (APA)**: including clopidogrel, prasugrel, ticlopidine, ticagrelor, or dipyrimadole;
- **Anticoagulant treatments**: including vitamin K antagonists, direct oral anticoagulants, low molecular weight heparins, or fondaparinux;
- **Cardiovascular drugs**: including calcium beta-blockers, angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), lipid modifying agents, statins, or diuretics;
- **Follow-up period** defined as the period from the study index date to two years later, or until the date of death with a right censoring on the 31 December 2015;
- **Treatment patterns** during the 2-year follow-up period:
  - Frequency of dispensing;
  - Duration;
  - Persistence defined as medication possession ratio (MPR) of each treatment between first and last dispensing (e.g. percentage of treatment coverage within treatment period, defined as the number of defined daily dose dispensed, divided by the number of days of the treatment period).

10.4.4. Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics were described at index date and during the 5-year history period, using the following variables:

- Gender, age and area of residence (at index date);
- History of T2DM;
- History of CAD;
- Major comorbidities and history including:
  - Heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease (PAD), hypertension, dyslipidemia;
  - Renal impairment;
  - Chronic obstructive pulmonary disease;
  - Cancer;
- Diabetes complications defined as hospitalisation with primary or associated diagnosis ICD-10 codes (see Annex 1-2, SAP, Appendix 5) for diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, diabetic foot ulcer;
- Cardiovascular and antidiabetic treatments (see ATC codes in Annex 1-2, SAP, Appendix 9);
- Other treatments (ATC codes);
- Obstructive Sleep Apnoea Syndrome, OSAS (see ICD-10 codes, LPP codes and CCAM codes in Annex 1-2, SAP, Appendix 5).

10.4.5. Healthcare resources use and costs

Healthcare resources use and costs defined as CV related and non-CV related costs were described during the 2-year follow-up period, using the following variables:

- Hospitalisations for outcome and duration;
- Hospitalisations for coronary revascularisation (PCI/CABG) and duration;

- Hospitalisations for another cause and duration;
- In- and outpatient medical visits (general practitioner, specialists);
- Medication related to CV treatments (antidiabetic, CV, APA treatments);
- Other medications overall (none CV treatment);
- All in- and outpatient reimbursed healthcare expenditures: medical procedures, lab tests, and medical devices, etc.;
- Total registered healthcare costs.

10.4.6. Outcomes

CV events of interest (primary diagnosis ICD-10 codes) occurring during the follow-up period were the followings:

- **Ischemic or unknown stroke** defined above;
- **MI** defined above;
- **CV death**;
- **Composite CV event** of MI, stroke (ischemic, haemorrhagic or unknown stroke) and CV death or all-cause death otherwise;
- **All-cause death**;
- **Heart failure** (see primary diagnosis ICD-10 code in Annex 1-2, SAP, Appendix 4)
- **Major organ specific bleedings** defined as following hospitalisation with primary or associated diagnosis ICD-10 codes (see Annex 1-2, SAP, Appendix 1):
  - Intracranial bleeding;
  - Haemorrhagic stroke;
  - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular);
  - Other bleeding (GI, urogenital and other bleeding) with transfusion during hospital stay;
  - Fatal bleeding defined as death during hospitalisation with primary or associated bleeding (including haemorrhagic stroke) diagnosis ICD-10 codes.

10.5. Data sources

The SNDS database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The SNDS contains individual pseudonymised information on (Moulis 2015, Tuppin 2010, Bezin 2017):

- General characteristics: gender, year of birth, affiliation scheme, area of residence;
- Date of death for those concerned, and cause of death (with a lag of 2-3 years for the cause);
- LTD ("*Affection de longue durée*" in French) and associated ICD-10 codes with starting and ending date. LTD mainly concern costly chronic diseases. LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical imageries, lab tests, drugs, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensing), and codes (but not the medical indication nor result);

- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary and associated diagnosis) for all private and public medical, obstetric and surgery hospitalisations, with the date and duration of hospitalisation, medical procedures, and cost coding system, as well as most of very costly drugs. The hospital discharge summary includes the medical unit summaries when the patient is hospitalised successively in several medical units. Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalised successively in several medical units, the primary diagnosis of the hospitalisation, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure. As primary diagnosis, is taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

Non-hospital data are updated every month and hospital-discharge summaries yearly at end of Q3 for the previous year.

The access to SNDS is regulated and needs approval from the National Institute of Health Data (*Institut National des Données de Santé* - INDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL). The ATHENA-F study received the INDS approval on the 18th July 2018 and the CNIL authorization on the 17th September 2018. Data were received on the 19th June 2019 for the study period.

10.6. Bias

The SNDS is a national healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It provides a unique opportunity to identify all CAD-T2DM patients, with exhaustive information about reimbursed treatments out of hospital and use of reimbursed healthcare resources, as well as all hospitalisations. Furthermore, the SNDS has the advantage of any study that uses patient records from an existing database that is not impacted by the study. The main limitation of this claims and hospitalisation database is that it was built for administrative and reimbursement purposes with little clinical data and no biological results, including severity or stage of the disease or some risk factors such as diet, environmental exposures, obesity, alcohol, family history, smoking status, and no information about drug adherence.

10.6.1. Selection bias

Since all patients identified will be extracted from a national database, there is no study selection bias, nor attrition bias, expecting very rare withdrawals from one of the healthcare insurance system including and covering 98.8% of the French population.

10.6.2. Information bias

Since deaths are recorded in the database using the national death registry, there is no information bias for this outcome. Another limitation is that the diagnosis codes recorded may not be accurate. Certain misclassification bias is so possible, especially in claims databases. To prevent from wrong or inexact recording of individual factors, either risk factors or the disease being studied, validated code lists of diagnosis mapped on ICD-10 international classification will be used. Nevertheless, the PMSI coding is fully independent from the study and there is no reason that a potential miscoding will be different between drugs, excluding an information bias.

Some T2DM patients could be misclassified as type 1 because of insulin therapy. To prevent this classification bias, a 5-year history period will be defined to investigate prior treatment sequences with sufficient delay to select appropriate T2DM patients.

In France, the database does not collect the entire hospital activities: if there is no procedure, then consultations and emergency department stays lasting less than 24 hours are not recorded. During hospital stays, only data regarding the dispensed costly drugs are available that could represent a potential risk of exposure underestimation. However, it should concern few patients for a very short period of time, and the impact over 7-year study period should be negligible.

10.7. Study size

From hypothesis of the protocol (Appendix 1-1, Study protocol, section 9.5), a study size of 550 000 CAD-T2DM patients was estimated in the SNDS database for main scheme.

The number of CAD-T2DM patients without prior MI-stroke, as well as the number of the patients for the THEMIS-like population are a main result of this study.

10.8. Data transformation

Database extraction criteria were described in a data extraction plan (DEP) approved prior to initiating extraction. Extraction of SNDS data was provided by CNAMTS, in charge of SNDS organisation and management.

Data transformation, including decision rules, diseases definitions, exposure definitions, outcomes, risk factors, healthcare resources, and calculated variables are detailed in statistical analysis plan (Annex 1-2, SAP, sections 2.2.4, 3.2 and 3.3).
Data were stored in a secured IT framework compliant with the French data protection commission requirements.

10.9. Statistical methods

Statistical analysis was conducted by the Bordeaux PharmacoEpi using SAS® software (SAS Institute, latest current version, North Carolina, USA). Results are detailed in a Statistical Analysis Report – SAR) in Annex 1-3.
As planned in the protocol, the main analysis was performed in the CAD-T2DM population without prior MI-stroke and in the THEMIS-like population.

10.9.1. Main summary measures

A flow-chart depicting the number of CAD-T2DM patients on 01/01/2014, the number of CAD-T2DM patients without prior MI or stroke, and the number of THEMIS-like patients were presented (see Annex 1-3, SAR, Figure 1).

Following analyses were performed for the CAD-T2DM population without prior MI-stroke and for the THEMIS-like population:

- Estimation of the prevalence proportion of each considered population on 01/01/2014 among French and European adult population on the 01/01/2014 overall and according to age and gender;
- Description of the baseline patient characteristics and history of clinical characteristics;
- Description of patient characteristics during the 2-year follow-up;
- Description of healthcare resource use and their related costs during the 2-year follow-up;
- Estimation of the incidence of outcomes (clinical events) during the 2-year follow-up period;
- Assessment of the predictors of the composite CV event (all strokes, MI or CV death or all-cause death otherwise).

10.9.2. Main statistical methods

Descriptive statistics used classic presentation, frequency and proportion of each modality for qualitative and ordinal variables, denominator, arithmetic mean, standard deviation, median, first and third quartiles, and extreme values for quantitative variables.

Outcome analysis

For each outcome, the following rates were estimated overall and according to 3 age-classes (<65, [65-75], >75 years):

- Crude incidence rate per 1 000 person-years (1 000 PY);
- Kaplan-Meier estimate for probability of first occurrence of each outcome during the 2-year follow-up;
- Cumulative incidence function (CIF) for cumulative incidence of single outcomes (expect death and composite CV event) to take into account death as a competing risk;
- Multivariable Cox proportional hazards regression model for predictor assessment of composite CV event.
  Known risk factors and confounders for the outcome were forced into the model and additional baseline covariates were explored as gender, age, major comorbidities before index date (heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease, hypertension, dyslipidemia, chronic renal disease, renal impairment, chronic obstructive pulmonary disease, cancer), SNDS pathology indicators on 31/12/2013, antidiabetic and CV drugs dispensed during the 2-year follow-up period (time-dependant covariates).

Analysis prognostic for predictors of composite event

Cox proportional hazards model have been used to assess the prognosis factors of the risk of the composite of MI, stroke and all-cause death during the 2-year follow-up period. The candidate independent covariates have been selected among: gender (variable forced in the model), age at index date (variable forced in the model), major comorbidities before index date (heart failure, atrial fibrillation, cerebrovascular disease, PAD), hypertension, dyslipidemia, chronic renal disease, renal impairment, chronic obstructive pulmonary disease, cancer), 56 SNDS pathology indicators on 31/12/2013, antidiabetic and CV drugs exposure during the 2-year follow-up period as time-dependent covariates (considering that a treatment covers a 30-day period at each dispensing).

The following modeling strategy has been used on both populations:

- Non conservation of binary candidate covariates with less than 1% of patients in one of its 2 modalities;
- Collinearity and association between candidate predictors have been assessed independently of the outcome variable using a logistic regression model. In case of significant association between 2 variables (i.e. OR ≥ 2), the variable most associated with the outcome or with better clinical relevance have been retained (see collinearity and association assessment in Annex 1-3, SAR, Appendix 1);
- All covariates with HR ≥ 1.10 (or ≤ 0.9) observed with univariable Cox regression model have been selected and included in a multivariable Cox regression model using a stepwise selection. Significant variables ($p \leq 0.05$) with HR threshold ≥ 1.20 or ≤ 0.80 were retained in the final multivariable model. A threshold of HR ≥ 1.10 (or ≤ 0.90) has been used in a sensitivity analysis;
- The covariates non selected with univariable Cox regression model have been tested in the final multivariable regression model in order to verify the persistence of non-significance;
- To allow more comparability between models, all covariates kept in any of the final multivariable regression models have been forced in final models of both populations.

Healthcare resource use and costs

Healtcare resource use and costs were analysed during the 2-year follow-up period for each area of expenditure according to the collective and the National health insurance perspectives.

10.9.3. Missing values

SNDS database records all reimbursed claims and hospitalisations without missing values. Except for the imputation (see Annex 1-3, SAR), no other imputation of missing data was carried out in these analyses.

10.9.4. Sensitivity analyses

Not applicable.

10.9.5. Amendments to the statistical analysis plan

Not applicable.

10.10. Quality control

The Bordeaux PharmacoEpi, INSERM CIC1401, has implemented a quality management system for all its activities and is certified ISO 9001:v2015 for its activities in pharmaco-epidemiology research. An independent double programming was performed for main criteria analyses, and the results compared for validation. All statistical logs are kept and can be provided. All results (Annex 1-3) are included in this study report.

11. RESULTS

11.1. Population

11.1.1. Identification of study populations

On the 1st January 2014, 359 595 CAD-T2DM patients have been identified in the nationwide SNDS database (Figure 2). Among them, 328 622 (91.4%) were included in the CAD-T2DM population, with 258 260 (71.8%) eligible patients for the CAD-T2DM population without prior MI-stroke and 64 334 (17.9%) for the THEMIS-like population (Figure 2; Annex 1-3, SAR, Figure 1).

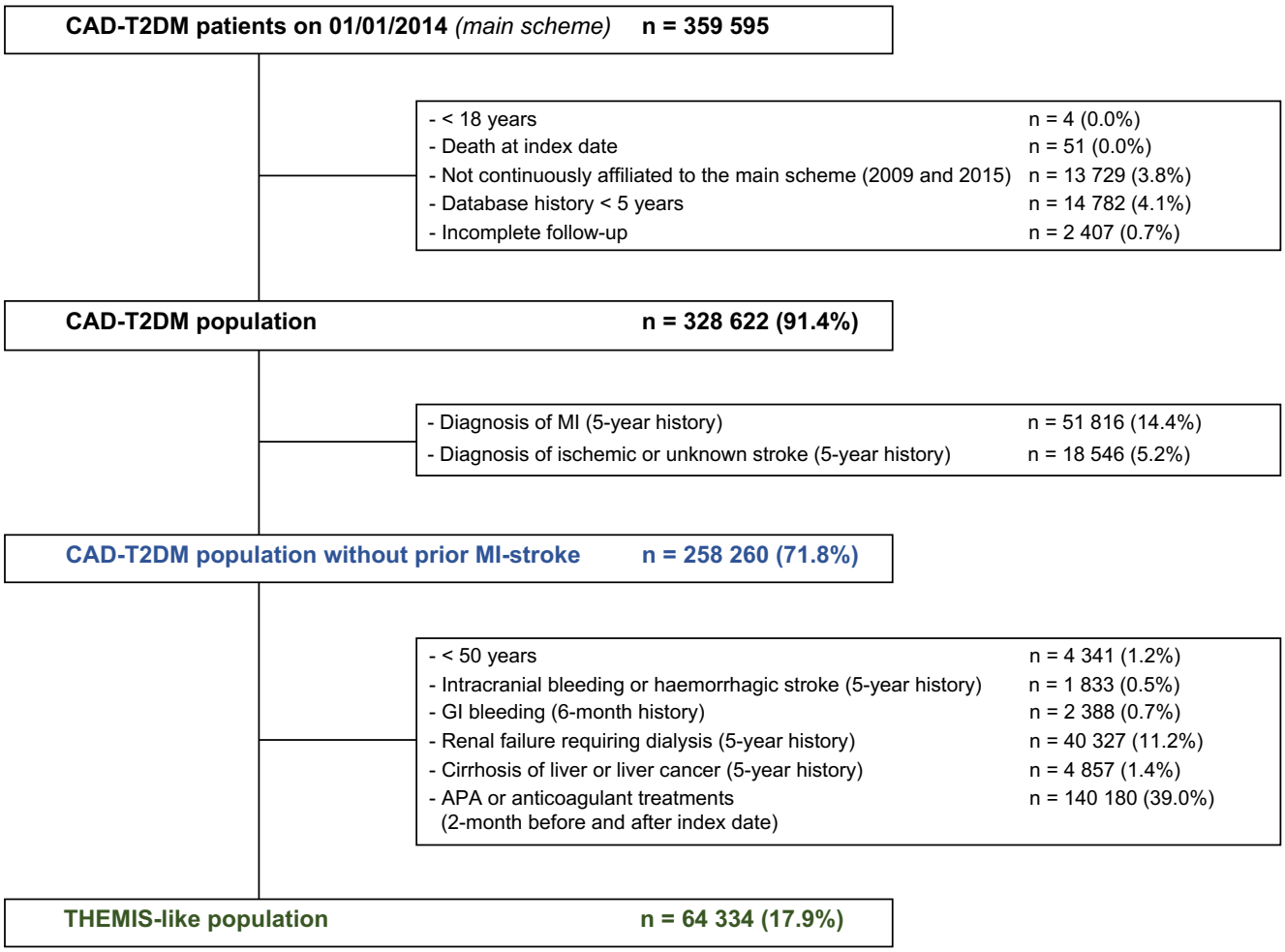

Figure 2. Identification and selection of study populations

The exclusion criteria for the different populations are detailed in Table I (Annex 1-3, SAR, Table 1). Within 61-day preceding or following the index date, 68.6% of patients in the CAD-T2DM population without prior MI-stroke had a dispensing of APA or anticoagulant. Furthermore, among patients with an anticoagulant dispensing (29.9% of patients), 3.0% had an atrial fibrillation history within 5-year or 2-month following the index date and 5.7% an orthopaedic procedure history within 1-year preceding or 2-month following the index date.

Table I. Description of exclusion criteria for the study populations

	CAD-T2DM population n = 328 622	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population n = 64 334
At index date, n (%)			
< 50 years	6 680 (2.0)	4 341 (1.7)	-
Within 5-year history, n (%)			
MI (LTD/Hospitalisation with ICU/CCU stay)	51 816 (15.8)	-	-
Ischemic/unknown stroke (excluding TIA)	21 888 (6.7)	-	-
MI or ischemic/unknown stroke (excl. TIA)	70 362 (21.4)	-	-
Intracranial haemorrhage	3 737 (1.1)	1 855 (0.7)	-
Cirrhosis of liver	7 457 (2.3)	6 066 (2.3)	-
Liver cancer	2 544 (0.8)	2 075 (0.8)	-
Renal failure requiring dialysis	55 874 (17.0)	42 307 (16.4)	-
Within 6-month history, n (%)			
GI bleeding	3 235 (1.0)	2 445 (0.9)	-
Within 61-day preceding/following index date, n (%)			
Dispensing of APA/Anticoagulant	229 466 (69.8)	177 173 (68.6)	-
APA alone	-	*99 977 (38.7)*	-
Anticoagulant alone	-	*47 559 (18.4)*	-
APA + anticoagulant	-	*29 637 (11.5)*	-
Dispensing of anticoagulant	-	77 196 (29.9)	-
Atrial fibrillation [-5 yrs; +2 mths]***	-	*1 416 (3.0)*	-
Orthopaedic procedure [-1 yr; +2 mths]****	-	*2 707 (5.7)*	-
Orthopaedic procedure [-61 d; + 61 d]*****	-	*1 033 (2.2)*	-
Within 31-day preceding/following index date, n (%)			
Dispensing of APA/Anticoagulant	121 094 (36.8)	94 643 (36.6)	-

* among patients concerned; ** within 5 years preceding or 2 months following the index date; *** within 1 year preceding or 2 months following the index; **** within 61 days preceding or following the index date

11.1.2. Prevalence proportion of CAD-T2DM without prior MI-stroke and THEMIS-like patients

The 2014 prevalence rate in France of CAD-T2DM without prior MI-stroke and THEMIS-like populations was estimated at 6.17 and 1.53 per 1 000 French adults, corresponding to about 317 000 and 79 000 patients, respectively (Table II; Annex 1-3, SAR, Table 2). The prevalence was higher for men than women in both populations (8.96 and 2.14 per 1 000 adult men, respectively, versus 3.63 and 0.98 per 1 000 adult women, respectively), and increased with age (1.78 and 0.47 per 1 000 for 18-64 years old, 16.73 and 4.34 per 1 000 for 65-75 years old, 25.45 and 5.86 per 1 000 for > 75 years old, respectively). For all patients, as well as according gender and age classes, THEMIS-like population represented a quarter of all CAD-T2DM patients without prior MI-stroke.

The prevalence rates estimated with sex-age standardization for the European adult population was 6.04 and 1.50 per 1 000 adults, respectively, close to that of the French population (Table III; Annex 1-3, SAR, Table 2).

Table II. 2014 Prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like populations for French adult population (stratified by age and gender)

	French adult (≥ 18 years) population from INSEE	CAD-T2DM population without prior MI-stroke		THEMIS-like population	
		Estimated number of patients	Prevalence rate / 1 000	Estimated number of patients	Prevalence Rate / 1 000
Total	**51 341 304**	**316 824**	**(6.17)**	**78 597**	**(1.53)**
Male	24 468 453	219 319	(8.96)	52 371	(2.14)
Female	26 872 851	97 505	(3.63)	26 226	(0.98)
[18-65 years[	**39 478 257**	**70 169**	**(1.78)**	**18 681**	**(0.47)**
Male	19 448 237	54 633	(2.81)	14 082	(0.72)
Female	20 030 020	15 536	(0.78)	4 599	(0.23)
[65-75 years]	**6 341 554**	**106 122**	**(16.73)**	**27 552**	**(4.34)**
Male	2 964 622	81 218	(27.40)	20 397	(6.88)
Female	3 376 932	24 904	(7.37)	7 155	(2.12)
> 75 years	**5 521 493**	**140 533**	**(25.45)**	**32 364**	**(5.86)**
Male	2 055 594	83 468	(40.61)	17 892	(8.70)
Female	3 465 899	57 065	(16.46)	14 472	(4.18)

Table III. 2014 Prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like populations for European adult population (stratified by age and gender)

	European adult (≥ 18 years) population from Eurostat	CAD-T2DM population without prior MI-stroke		THEMIS-like population	
		Estimated number of patients	Prevalence rate / 1 000	Estimated number of patients	Prevalence Rate / 1 000
Total	**411 670 644**	**2 484 478**	**(6.04)**	**617 215**	**(1.50)**
Male	198 490 922	1 735 311	(8.74)	415 164	(2.09)
Female	213 179 722	749 167	(3.51)	202 051	(0.95)
[18-65 years[	**317 653 393**	**58 870**	**(1.73)**	**145 927**	**(0.46)**
Male	158 513 473	44 884	(2.71)	110 216	(0.70)
Female	159 139 920	13 986	(0.76)	35 711	(0.22)
[65-75 years]	**53 161 006**	**897 267**	**(16.88)**	**232 529**	**(4.37)**
Male	24 570 561	681 573	(27.74)	170 793	(6.95)
Female	28 590 445	215 694	(7.54)	61 736	(2.16)
> 75 years	**40 856 245**	**1 037 002**	**(25.38)**	**238 759**	**(5.84)**
Male	15 406 888	624 650	(40.54)	134 155	(8.71)
Female	25 449 357	412 352	(16.20)	104 604	(4.11)

11.2. Descriptive data

11.2.1. Baseline characteristics: demographic data, history of T2DM and CAD

About two thirds of CAD-T2DM patients without prior MI-stroke were men with a mean age of 72.7 (± 10.6) years, including 42.6% of elderly patients (> 75 years). The THEMIS-like population had a similar profil with 65.7% men, mean age of 72.3 (±10.2) and 39.5% of elderly (Table IV; Annex 1-3, SAR, Table 3).

Table IV. Demographic characteristics of patients at index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
Gender, n (%)				
Male	176 407	(68.3)	42 238	(65.7)
Age (in years)				
Mean (± SD)	72.7	(10.6)	72.3	(10.2)
Median	73.0		72.0	
[p25% - p75%]	[65.0;81.0]		[65.0;80.0]	
[Min - Max]	[20.0;108.0]		[50.0;105.0]	
Age (in years), n (%)				
< 65	58 870	(22.8)	15 695	(24.4)
[65-75]	89 345	(34.6)	23 232	(36.1)
> 75	110 045	(42.6)	25 407	(39.5)

Table V. History of T2DM and CAD diagnoses at index date and revascularisation procedures before the index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
History of T2DM diagnosis in years, n (%)				
≤ 1	58 771	(22.8)	14 675	(22.8)
]1-2]	34 512	(13.4)	7 980	(12.4)
]2-3]	11 474	(4.4)	3 114	(4.8)
]3-4]	10 941	(4.2)	3 133	(4.9)
>4	142 562	(55.2)	35 432	(55.1)
History of CAD diagnosis in years, n (%)				
≤ 1	33 280	(12.9)	7 460	(11.6)
]1-2]	32 788	(12.7)	8 677	(13.5)
]2-3]	33 295	(12.9)	9 021	(14.0)
]3-4]	37 258	(14.4)	9 614	(14.9)
>4	121 639	(47.1)	29 562	(46.0)
History of CAD/T2DM diagnosis in years, n (%)				
≤ 1	82 493	(31.9)	20 001	(31.1)
]1-2]	51 733	(20.0)	12 703	(19.7)
]2-3]	28 676	(11.1)	7 816	(12.1)
]3-4]	28 318	(11.0)	7 468	(11.6)
>4	67 040	(26.0)	16 346	(25.4)
Revascularisation procedures within 5-year history, n (%)				
≥ 1 PCI	71 576	(27.7)	11 657	(18.1)
≥ 1 CABG	1 860	(0.7)	335	(0.5)
≥ 1 PCI/CABG	73 101	(28.3)	11 957	(18.6)
Revascularisation procedures within 1-year history, n (%)				
≥ 1 PCI	24 009	(9.3)	1 337	(2.1)
≥ 1 CABG	440	(0.2)	95	(0.1)
≥ 1 PCI/CABG	24 413	(9.5)	1 429	(2.2)

In the CAD-T2DM population without prior MI-stroke, 55.2% of patients were diagnosed with T2DM more than 4 years before the index date and 47.1% with CAD. The concomitance of both diagnoses was found for around half of patients within the 2 years before the index date and for around a quarter of patients more than 4 years before the index date. The THEMIS-like population had a similar profil (Table V; Annex 1-3, SAR, Table 4). At least one revascularisation procedure within the 5-year history was found for 28.3% of CAD-T2DM patients without prior MI-stroke and 18.6% for THEMIS-like patients, including 9.5% and 2.2% within the year before the index date,

respectively. The main revascularistaion procedure was PCI in both populations (Table V; Annex 1-3, SAR, Tables 9 and10).

11.2.2. History of clinical characteristics

Long-term diseases

Almost all CAD-T2DM patients without prior MI-stroke (95.3%) had at least one long-term disease (LTD) within the 5-year history as well as the 1-year. The five most frequent LTD (≥ 10% of patients) were: diabetes, coronary heart disease, severe arterial hypertension, malignant tumours, malignant lymphatic or haematopoietic tissue, and severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy. The THEMIS-like population had a similar profil, except little less severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy with a frequency around 7% (Table VI; Annex 1-3, SAR, Tables 5 and 6).

Table VI. History of LTD declared or ongoing before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 LTD declared or ongoing within 5-year history, n (%)	**246 179**	**(95.3)**	**61 001**	**(94.8)**
Type of LTD (several diseases possible, frequency ≥ 10%)				
Diabetes type 1, diabetes type 2	199 425	(77.2)	50 060	(77.8)
Coronary heart disease	111 419	(43.1)	28 144	(43.7)
Severe arterial hypertension*	46 377	(18.0)	10 997	(17.1)
Malignant tumours, malignant lymphatic or haematopoietic tissue	34 583	(13.4)	8 452	(13.1)
Severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy	27 759	(10.7)	4 633	(7.2)
≥ 1 LTD declared or ongoing within 1-year history, n (%)	**244 156**	**(94.5)**	**610 447**	**(94.0)**
Type of LTD (several diseases possible, frequency ≥ 10%)				
Diabetes type 1, diabetes type 2	196 198	(76.0)	49 262	(76.6)
Coronary heart disease	108 332	(41.9)	27 384	(42.6)
Severe arterial hypertension*	39 542	(15.3)	9 387	(14.6)
Malignant tumours, malignant lymphatic or haematopoietic tissue	31 178	(12.1)	7 643	(11.9)
Severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy	26 625	(10.3)	4 422	(6.9)

* Not considered as LTD since 2011

Hospitalisations and major comorbidities

Almost all patients of the CAD-T2DM without prior MI-stroke and THEMIS-like populations have been hospitalised within the 5-year history, 97.2% and 96.3%, respectively, with a median of 4 and 3 hospitalisations per patient, respectively. For each diagnosis, the frequency of hospitalisations was close for both populations. The main hospitalisation diagnoses were for: diseases of circulatory system, followed by endocrine nutrional and metabolic diseases, digestive system diseases, and various diagnosis linked with abnormal clinical and laboratory findings or specific care (Table VII; Annex 1-3, SAR, Tables 7, 8). At least one hospitalisation within the year before index date was observed for 54.7% and 47.0% of the CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively, (Table VII; Annex 1-3, SAR, Tables 7, 8).

Table VII. History of hospitalisations before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 hospitalisation within 5-year history, n (%)	**250 908**	**(97.2)**	**61 980**	**(96.3)**
Number of hospitalisations per patient*				
Mean (± SD)	7.3 (29.5)		4.3 (4.5)	
Median	4.0		3.0	
[p25% - p75%]	[2.0;6.0]		[2.0;5.0]	
≥ 1 of the following diagnosis within 5-year history (the 5 most frequent), n (%)**				
Diseases of the circulatory system	244 283	(94.6)	59 853	(93.0)
Endocrine, nutritional and metabolic diseases	230 036	(89.1)	55 552	(86.3)
Factors influencing health status and contact with health services	196 398	(76.0)	44 588	(69.3)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	134 035	(51.9)	29 621	(46.0)
Diseases of the digestive system	98 981	(38.3)	22 363	(34.8)
≥ 1 hospitalisation within 1-year history, n (%)	**141 149**	**(54.7)**	**30 215**	**(47.0)**

* Among concerned patients; ** Main, related or associated diagnosis (ICD-10 code classification – Main chapter)

The most frequent comorbidity within the 5-year history was hypertension with around three-quarters of patients concerned in both populations. Differences were found regarding atrial fibrillation affecting 21.4% of CAD-T2DM patients without prior MI-stroke and 10.3% of the THEMIS-like population, and also for renal impairment (20.0% and 4.6%, respectively), heart failure (16.2% and 9.0%, respectively), and PAD (19.2% and 11.4%, respectively) (Table VIII; Annex 1-3, SAR, Table 11).

Table VIII. Major comorbidities before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
Major comorbidities within 5-year history, n (%)				
Hypertension	204 943	(79.4)	48 554	(75.5)
Atrial fibrillation	55 155	(21.4)	6 647	(10.3)
Renal impairment	51 647	(20.0)	2 943	(4.6)
PAD	49 703	(19.2)	7 326	(11.4)
Dyslipidemia	49 406	(19.1)	10 673	(16.6)
Cancer	47 066	(18.2)	10 958	(17.0)
Heart failure	41 744	(16.2)	5 821	(9.0)
COPD	35 558	(13.8)	7 137	(11.1)
Cerebrovascular disease	27 821	(10.8)	4 676	(7.3)

Diabetic complications

Diabetic complications affected 39.3% and 31.6% of CAD-T2DM without prior MI-stroke and THEMIS-like patients, respectively, withing the 5-year history. The main complication was diabetic foot ulcer, in the same range for both populations (67.2% and 66.5%, respectively), as well as diabetic retinopathy and diabetic neuropathy which affected about one quarter of patients in both populations. While diabetic nephrophaty was more frequent in the CAD-T2DM population without prior MI-stroke than in the THEMIS-like population (32.7% and 21.2%, respectively) (Table IX; Annex 1-3, SAR, Table 13).

Table IX. History of diabetic complications within 5-year before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 diabetic complication, n (%)	**101 419**	**(39.3)**	**20 301**	**(31.6)**
Diabetic complications (several answers possible)*, n (%)				
Diabetic foot ulcer	68 149	(67.2)	13 506	(66.5)
Diabetic nephropathy	33 126	(32.7)	4 299	(21.2)
Diabetic retinopathy	27 715	(27.3)	5 400	(26.6)
Diabetic neuropathy	25 891	(25.5)	4 874	(24.0)
Obstructive Sleep Apnoea Syndrome, n (%)	**58 497**	**(22.7)**	**13 090**	**(20.3)**

* Among concerned patients;

History of drugs dispensing

All patients in both populations had at least one drug dispensed within the 5-year history, mainly for alimentary tract and metabolism, cardiovascular system, nervous system, general anti-infectives for systemic use, and blood and blood forming organs (for more than 95% of patients). The frequency of dispensing for all drug classes were close for both populations (Table X; Annex 1-3, SAR, Table 22).

Results within the year before the index date were lower and remained close for each drug class in both populations, except for blood and blood forming organs more dispensed in the CAD-T2DM population without prior MI-stroke than in the THEMIS-like population (87.9% and 77.9%, respectively) (Table X; Annex 1-3, SAR, Table 23).

Table X. Drugs dispensing before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 drug dispensed (5-year history), n (%)	**258 247**	**(100.0)**	**64 327**	**(100.0)**
Drugs according to ATC classification (several answers possible, frequency ≥ 20%), n (%)				
A - Alimentary tract and metabolism	258 199	(100.0)	64 303	(100.0)
C - Cardiovascular system	258 109	(99.9)	64 261	(99.9)
N - Nervous system	257 315	(99.6)	64 001	(99.5)
J - General anti-infectives for systemic use	256 587	(99.4)	63 735	(99.1)
B - Blood and blood forming organs	256 132	(99.2)	62 937	(97.8)
D - Dermatologicals	244 868	(94.8)	60 185	(93.6)
M - Musculo-skeletal system	243 136	(94.1)	60 593	(94.2)
R - Respiratory system	239 316	(92.7)	58 865	(91.5)
S - Sensory organs	199 413	(77.2)	48 907	(76.0)
H - Systemic hormonal prep, excl. sex hormones	180 161	(69.8)	44 056	(68.6)
V - Various	138 936	(53.8)	31 757	(49.4)
G - Genito urinary system/Sex hormones	122 255	(47.3)	30 243	(47.0)
≥ 1 drug dispensed (1-year history), n (%)	**249 442**	**(96.6)**	**60 517**	**(94.1)**
Drugs according to ATC classification (several answers possible, frequence ≥ 20%), n (%)				
A - Alimentary tract and metabolism	244 616	(94.7)	58 999	(91.7)
C - Cardiovascular system	243 328	(94.2)	58 142	(90.4)
B - Blood and blood forming organs	226 952	(87.9)	50 106	(77.9)
N - Nervous system	219 212	(84.9)	52 531	(81.7)
J - General anti-infectives for systemic use	202 623	(78.5)	47 559	(73.9)
D - Dermatologicals	148 384	(57.5)	34 352	(53.4)
M - Musculo-skeletal system	141 855	(54.9)	34 574	(53.7)
R - Respiratory system	139 880	(54.2)	32 746	(50.9)
S - Sensory organs	94 862	(36.7)	22 665	(35.2)
H - Systemic hormonal prep, excl. sex hormones	82 652	(32.0)	19 552	(30.4)
G - Genito urinary system/Sex hormones	58 453	(22.6)	13 806	(21.5)

For specific treatments, almost all patients (more than 99%) had at least one dispensing of antidiabetic and CV drugs in both populations within the 5-year history. In the CAD-T2DM population without prior MI-stroke, the most CV drugs dispensed were statins (96.5%), ACEI or ARB (96.3%), ASA (90.7%) and betablocking agents (89.6%). More than two thirds of patients (68.8%) had a dispensing of APA, mainly clopidogrel, and 51.1% of patients a dispensing of anticoagulants, mainly vitamin K antagonist and low molecular weight heparin. Moreover, diuretics and calcium beta-blockers were also widely dispensed with 68.6% and 67.0% of patients concerned, respectively. In the THEMIS-like population, results were close, except for APA, anticoagulants and vitamin K antagonists less dispensed (42.6%, 33.0% and 11.8% of patients, respectively) (Table XI; Annex 1-3, SAR, Table 24).

Patients in both populations remained widely treated with antidiabetic (> 85%) and CV drugs (> 91%) within the year before the index date (Annex 1-3, SAR, Table 25).

Table XI. Specific drugs dispensing within 5-year before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 antidiabetic drug*, n (%)	**256 640**	**(99.4)**	**63 781**	**(99.1)**
≥ 1 CV drug, n (%)**	**258 157**	**(100.0)**	**64 283**	**(99.9)**
≥ 1 ASA, n (%)	**234 222**	**(90.7)**	**60 725**	**(94.4)**
ASA dispensed (several answers possible), n (%)				
Acetylsalicylic acid	231 883	(89.8)	60 101	(93.4)
Pravastatin and acetylsalicylic acid	15 992	(6.2)	4 892	(7.6)
≥ 1 APA, n (%)	**177 581**	**(68.8)**	**27 432**	**(42.6)**
APA dispensed (several answers possible), n (%)				
Clopidogrel	171 775	(66.5)	26 204	(40.7)
Prasugrel	11 148	(4.3)	1 951	(3.0)
Ticagrelor	4 115	(1.6)	266	(0.4)
Ticlopidine	640	(0.2)	110	(0.2)
≥ 1 anticoagulant treatment, n (%)	**131 936**	**(51.1)**	**21 233**	**(33.0)**
Anticoagulants (several answers possible), n (%)				
Vitamin K antagonist	82 020	(31.8)	7 591	(11.8)
Low molecular weight heparin	78 321	(30.3)	14 904	(23.2)
Direct oral anticoagulant	15 436	(6.0)	1 383	(2.1)
Fondaparinux	13 317	(5.2)	2 620	(4.1)
≥ 1 other CV drug, n (%)	**258 073**	**(99.9)**	**64 243**	**(99.9)**
Other CV drugs (several answers possible), n (%)				
Statins	249 188	(96.5)	61 313	(95.3)
ACEI or ARB	248 778	(96.3)	60 902	(94.7)
Betablocking agents	231 421	(89.6)	55 329	(86.0)
Diuretics	177 263	(68.6)	37 844	(58.8)
Calcium beta-blockers	173 137	(67.0)	40 200	(62.5)
Organic nitrates	138 055	(53.5)	31 841	(49.5)
Other lipid modifying agents than statins	80 472	(31.2)	19 394	(30.1)
Other vasodilatators used in cardiac diseases	61 078	(23.6)	13 290	(20.7)
≥ 1 other treatment*, n (%)**	**258 241**	**(100.0)**	**64 323**	**(100.0)**

* antidiabetics: A10 ATC code except benfluorex (A10BX06); ** CV drugs: C, B01A ; *** other than antidiabetics (A10 ATC code except A10BX06) and CV drugs (C, B01A)

History of medical visits and lab tests

All patients had physician visit reimbursements within the 5-year history, with a median of 68 visits in the CAD-T2DM population without prior MI-stroke and 63 in the THEMIS-like population (Table XII; Annex 1-3, SAR, Table 16). The median number of visits was about 9 per year for both populations with general practitioners (GP), about one per year with cardiologists, and about 3 per year with other specialists (Table XII; Annex 1-3, SAR, Table 18). Lab tests were largely dispensed for all patients within the 5-year history (Table XII), and the detail by type of lab test (NABM codes) is presented in Annex 1-3, SAR, Tables 20 and 21.

Table XII. Medical visits and lab tests within 5-year before index date in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population n = 64 334
≥ 1 medical visit*, n (%)	**258 257 (100.0)**	**64 333 (100.0)**
Number per patient, mean (± SD)**	74.9 (38.0)	69.0 (34.3)
Median	68.0	63.0
[p25% - p75%]	[51.0;90.0]	[47.0;83.0]
≥ 1 general practitioner visit, n (%)	**258 119 (99.9)**	**64 273 (99.9)**
Number per patient, mean (± SD)**	49.9 (26.2)	46.8 (24.2)
Median	45.0	42.0
[p25% - p75%]	[33.0;62.0]	[31.0;58.0]
≥ 1 cardiologist visit, n (%)	**227 556 (88.1)**	**55 361 (86.1)**
Number per patient, mean (± SD)**	5.7 (5.7)	4.9 (4.7)
Median	4.0	4.0
[p25% - p75%]	[2.0;7.0]	[2.0;6.0]
≥ 1 other specialist visit, n (%)	**256 447 (99.3)**	**63 779 (99.1)**
Number per patient, mean (± SD)**	20.2 (23.3)	18.1 (19.6)
Median	15.0	14.0
[p25% - p75%]	[8.0;25.0]	[8.0;23.0]
≥ 1 lab test, n (%)	**258 213 (100.0)**	**64 310 (100.0)**
≥ 1 HbA1c test, n (%)	**257 147 (99.6)**	**63 988 (99.5)**
≥ 1 creatinine test, n (%)	**258 025 (99.9)**	**64 236 (99.8)**

* including medical visits with unknown specialty and visits from inpatient care (hospitalisation data from obstetric and surgery) and from outpatient care; ** among concerned patients

11.2.3. Healthcare resource use during the 2-year follow-up period

Follow-up period duration

The median follow-up duration was 24 months for both populations (Table XIII; Annex 1-3, SAR,Table 26), because patients remain in the database from birth to death, except because of immigration for some subjects.

Table XIII. Duration of the follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population n = 64 334
Follow-up duration per patient (in months)		
Mean (± SD)	22.3 (4.9)	22.8 (4.2)
Median	24.0	24.0
[p25% - p75%]	[24.0;24.0]	[24.0;24.0]
[Min - Max]	[0.0;24.0]	[0.0;24.0]
Follow-up duration per patient (in months) (in categories), n (%)		
<6	9 148 (3.5)	1 597 (2.5)
[6-12[	8 535 (3.3)	1 488 (2.3)
[12-18[	9 423 (3.6)	1 697 (2.6)
[18-24[	7 941 (3.1)	1 429 (2.2)
24	223 213 (86.4)	58 123 (90.3)

Hospitalisations, medical visits and lab tests

At least one hospitalisation was found for 69.2% of CAD-T2DM patients without prior MI-stroke and 63.0% for the THEMIS-like population during the 2-year follow-up, with five hospitalisations or more for 20.1% and 14.4% of patients, respectively. The most frequent primary diagnosis was diseases of the circulatory system (30.1% and 21.9%, respectively), followed by various disease health care management and the follow-up (ICD-10 Z codes) as factors influencing health status and contact with health services (23.9% and 19.4%, respectively) or symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (15.3% and 12.3%, respectively) (Table XIV; Annex 1-3, SAR,Table 27).

Almost all patients for both populations had physician visit reimbursements during the 2-year follow-up, with a median of 25 visits in the CAD-T2DM population without prior MI-stroke and 24 visits in the THEMIS-like population. For both populations, the median number of visits per year was 8 with GP, one with a cardiologist, and 3 with other specialists (Table XIV; Annex 1-3, SAR, Tables 39 and 40). Lab tests were also widely used and concerned around 97% of patients in both study populations (Table XIV). The detail by type of lab test (NABM codes) is presented in Annex 1-3, SAR, Table 41.

Table XIV. Hospitalisations, medical visits and lab tests during the 2-year follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 hospitalisation, n (%)	**178681**	**(69.2)**	**40540**	**(63.0)**
≥ 1 of the following main diagnosis* (≥ 10%), n (%)				
Diseases of the circulatory system	77774	(30.1)	14087	(21.9)
Factors influencing health status, contact with health services	61709	(23.9)	12494	(19.4)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified**	39565	(15.3)	7896	(12.3)
Endocrine, nutritional and metabolic diseases	32527	(12.6)	7358	(11.4)
Diseases of the digestive system	31836	(12.3)	7125	(11.1)
≥ 1 medical visit*, n (%)**	**256491**	**(99.3)**	**63925**	**(99.4)**
Number per patient, mean (± SD)***	29.8	(21.9)	27.4	(18.8)
Median	25.0		24.0	
[p25% - p75%]	[17.0;37.0]		[16.0;34.0]	
≥ 1 general practitioner visit, n (%)	**252185**	**(97.6)**	**62782**	**(97.6)**
Number per patient, mean (± SD)****	19.3	(13.4)	18.5	(12.5)
Median	16.0		16.0	
[p25% - p75%]	[11.0;25.0]		[11.0;24.0]	
≥ 1 cardiologist visit, n (%)	**147662**	**(57.2)**	**35193**	**(54.7)**
Number per patient, mean (± SD)****	3.1	(3.8)	2.7	(3.3)
Median	2.0		2.0	
[p25% - p75%]	[1.0;4.0]		[1.0;3.0]	
≥ 1 other specialist visit, n (%)	**228894**	**(88.6)**	**56501**	**(87.8)**
Number per patient, mean (± SD)****	10.1	(15.7)	8.7	(11.7)
Median	6.0		6.0	
[p25% - p75%]	[3.0;12.0]		[3.0;11.0]	
≥ 1 lab test, n (%)	**251622**	**(97.4)**	**62523**	**(97.2)**
≥ 1 HbA1c, n (%)	**239788**	**(92.8)**	**60211**	**(93.6)**
≥ 1 creatinine test, n (%)	**247844**	**(96.0)**	**61621**	**(95.8)**

* ICD-10 codes (main or related diagnoses); ** various disease health care management and the follow-up (ICD-10 Z codes); *** including medical visit with unknown specialty and visits from inpatient care (hospitalisation data from obstetric and surgery) and from outpatient care; **** among concerned patients

Drugs dispensing

Almost all patients of the CAD-T2DM population without prior MI-stroke (98.6%) and the THEMIS-like population (98.2%) have at least one drug dispensing during the 2-year follow-up. The five most frequent drugs dispensed (first level of the ATC classification) for both populations were for: alimentary tract and metabolism, cardiovascular system, blood and blood forming organs, nervous system, and general anti-infectives for system use (Table XV; Annex 1-3, SAR, Table 42).

Table XV. Drugs dispensing during the 2-year follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 drug dispensed, n (%)	**254 607**	**(98.6)**	**63 155**	**(98.2)**
Drugs according to ATC classification (several answers possible, frequency ≥ 20%), n (%)				
A - Alimentary tract and metabolism	252 501	(97.8)	62 570	(97.3)
C - Cardiovascular system	250 956	(97.2)	61 960	(96.3)
B - Blood and blood forming organs	241 501	(93.5)	57 135	(88.8)
N - Nervous system	238 251	(92.3)	58 685	(91.2)
J - General anti-infectives for systemic use	229 210	(88.8)	56 537	(87.9)
D - Dermatologicals	191 178	(74.0)	46 251	(71.9)
R - Respiratory system	172 091	(66.6)	41 958	(65.2)
M - Musculo-skeletal system	169 958	(65.8)	43 229	(67.2)
S - Sensory organs	126 869	(49.1)	31 265	(48.6)
H - Systemic hormonal prep, excl. sex hormones	111 343	(43.1)	26 851	(41.7)
V - Various	80 650	(31.2)	17 935	(27.9)
G - Genito urinary system/Sex hormones	71 236	(27.6)	17 691	(27.5)

In the CAD-T2DM population without prior MI-stroke, antidabetic and CV drugs were dispensed for 92.3% and 97.6% of patients, respectively, with for antidiabetics a medication possession ratio (MPR) ≥ 80% for almost 70% of patients. ASA dispensing were found for 67.8% of patients with a MPR ≥ 80% for 63% of patients, while ASA and anticoagulants were two times less dispensed with a MPR ≥ 80% for 63% and 41% of patients, respectively. Furthermore, the most frequent CV drugs dispensed were statins (79.3%) with a MPR ≥ 80% for 77.7% of patients, ACEI or ARB (77.9%) with a MPR ≥ 80% for 80.0% of patients, betablocking agents (68.7%) with a MPR ≥ 80% for 75.9% of patients, diuretics (47.4%) with a MPR ≥ 80% for 66.4% of patients, and calcium beta-blockers (39.5%) with a MPR ≥ 80% for 70.2% of patients. For the THEMIS-like population, similar results were found, except for ASA more dispensed (around 82%), while APA and anticoagulants were less dispensed (9.4% and 16.0% of patients), and a MPR ≥ 80% less frequent with 55.3% and 29.6% of patients concerned, respectively (Table XVI; Annex 1-3, SAR, Table 43).

The results of specific drugs dispensing restricted to the first year of follow-up remained broadly unchanged (Annex 1-3, SAR, Table 43).

Table XVI. Specific drugs dispensing during the 2-year follow-up in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260		THEMIS-like population n = 64 334	
≥ 1 antidiabetic drug*, n (%)	**238 363**	**(92.3)**	**59 395**	**(92.3)**
*MPR ≥ 80%**, n (%)*	*162 145*	*(68.0)*	*41 281*	*(69.5)*
≥ 1 CV drugs*, n (%)**	**252 178**	**(97.6)**	**62 309**	**(96.9)**
≥ 1 ASA, n (%)	**174 994**	**(67.8)**	**52 681**	**(81.9)**
*MPR ≥ 80%**, n (%)*	*110 961*	*(63.4)*	*36 810*	*(69.9)*
ASA dispensed (several answers possible), n (%)				
Acetylsalicylic acid	**174 887**	**(67.7)**	**52 657**	**(81.8)**
*MPR ≥ 80%**	*111 077*	*(63.5)*	*36 861*	*(70.0)*
Pravastatin and acetylsalicylic acid	**3 845**	**(1.5)**	**1 423**	**(2.2)**
*MPR ≥ 80%**	*15*	*(0.4)*	*4*	*(0.3)*
≥ 1 APA, n (%)	**92 986**	**(36.0)**	**6 063**	**(9.4)**
MPR ≥ 80%, n (%)*	*58 817*	*(63.3)*	*3 354*	*(55.3)*
APA dispensed (several answers possible), n (%)				
Clopidogrel	87 986	(34.1)	5 355	(8.3)
*MPR ≥ 80%**	*56 059*	*(63.7)*	*2 848*	*(53.2)*
Ticagrelor	4 126	(1.6)	709	(1.1)
*MPR ≥ 80%**	*1 709*	*(41.4)*	*380*	*(53.6)*
Prasugrel	3 406	(1.3)	283	(0.4)
*MPR ≥ 80%**	*1 329*	*(39 0)*	*146*	*(51.6)*
Ticlopidine	130	(0.1)	3	(0.0)
*MPR ≥ 80%**	*68*	*(52.3)*	*2*	*(66.7)*
Dipyrimadole	5	(0.0)	2	(0.0)
*MPR ≥ 80%**	*2*	*(40.0)*	*1*	*(50.0)*
≥ 1 anticoagulant treatment, n (%)	**80 383**	**(31.1)**	**10 266**	**(16.0)**
*MPR ≥ 80%**, n (%)*	*33 231*	*(41.3)*	*3 040*	*(29.6)*
Anticoagulants dispensed (several answers possible), n (%)				
Vitamin K antagonist	48 431	(18.8)	3 339	(5.2)
*MPR ≥ 80%**	*21 482*	*(44.3)*	*1 409*	*(42.2)*
Low molecular weight heparin	34 247	(13.3)	5 986	(9.3)
*MPR ≥ 80%**	*2 439*	*(7.1)*	*445*	*(7.4)*
Direct oral anticoagulant	14 946	(5.8)	2 098	(3.3)
*MPR ≥ 80%**	*9 997*	*(66.9)*	*1 307*	*(62.3)*
Fondaparinux	3 789	(1.5)	783	(1.2)
MPR ≥ 80%**	*235*	*(6.2)*	*53*	*(6.8)*
≥ 1 other CV drug, n (%)	**250 619**	**(97.0)**	**61 872**	**(96.2)**
Other CV drugs (several answers possible), n (%)				
Statins	204 695	(79.3)	50 266	(78.1)
*MPR ≥ 80%**	*158 993*	*(77.7)*	*38 748*	*(77.1)*
ACEI or ARB	201 239	(77.9)	49 610	(77.1)
*MPR ≥ 80%**	*161 131*	*(80.0)*	*40 320*	*(81.3)*
Betablocking agents	177 308	(68.7)	41 764	(64.9)
*MPR ≥ 80%**	*134 647*	*(75.9)*	*31 667*	*(75.8)*
Diuretics	122 524	(47.4)	23 779	(37.0)
*MPR ≥ 80%**	*81 315*	*(66.4)*	*15 067*	*(63.4)*
Calcium beta-blockers	101 991	(39.5)	24 007	(37.3)
*MPR ≥ 80%**	*71 586*	*(70.2)*	*17 285*	*(72.0)*
Organic nitrates	67 656	(26.2)	15 221	(23.7)
*MPR ≥ 80%**	*18 612*	*(27.5)*	*3 907*	*(25.7)*
Lipid modifying agents (excluding statins)	31 850	(12.3)	7 913	(12.3)
*MPR ≥ 80%**	*15 415*	*(48.4)*	*3 958*	*(50.0)*
Other vasodilatators used in cardiac diseases	27 129	(10.5)	5 944	(9.2)
*MPR ≥ 80%**	*18 043*	*(66.5)*	*3 929*	*(66.1)*
≥ 1 other treatments**, n (%)**	**254 130**	**(98.4)**	**63 008**	**(97.9)**

* Antidiabetics: A10 ATC code except benfluorex (A10BX06); ** among concerned patients; *** CV drugs: C, B01A; **** other than antidiabetics (A10 ATC code except A10BX06) and CV drugs (C, B01A)

11.3. Outcome data

The main outcomes (ischemic or unknown stroke, MI, heart failure, major organ specific bleeding, all-cause death, composite event of MI, all stroke, heart failure, death) and details for major organ specific bleeding (intracranial bleeding, haemorrhagic stroke, other critical organ or site bleeding, other bleeding with transfusion, fata bleeding) were described during the follow-up period for all patients and according to age in the two study populations.

11.4. Main results

11.4.1. Incidence rate of outcomes

The overall incidence rates of main outcomes (first event) in the two study populations during the 2-year of follow-up are presented in Table XVII.

For ischemic or unknown stroke, the incidence rate was 9.1 per 1 000 person-years (PY) for the CAD-T2DM population without prior MI-stroke and 8.1 for the THEMIS-like population, 9.1 and 7.0 for MI, 53.2 and 28.6 for heart failure, 27.0 and 16.7 for major bleeds, 73.0 and 50.8 for all-cause death, and 88.4 and 63.9 for the composite event (MI, all stroke, all-cause death), respectively. For each outcome, the incident rate increased with age in the two study populations (Table XVII; Annex 1-3, SAR, Tables 44, 54, 59, 64, 92, 95).

Table XVII. Incidence rate of main outcomes per 1 000 person-years (‰ PY) during the 2-year follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke			THEMIS-like population		
	n event	PY	Incidence ‰ PY	n event	PY	Incidence ‰ PY
Stroke (ischemic or unknown)	**4 358**	**477 432**	**9.1**	**981**	**121 594**	**8.1**
<65 years	548	114 258	4.8	119	30 786	3.9
[65-75] years	1 222	169 743	7.2	267	44 956	5.9
>75 years	2 588	193 431	13.4	595	45 851	13.0
MI	**4 319**	**477 037**	**9.1**	**848**	**121 635**	**7.0**
<65 years	938	113 821	8.2	199	30 697	6.5
[65-75] years	1 447	169 517	8.5	275	44 949	6.1
>75 years	1 934	193 699	10.0	374	45 989	8.1
Heart failure	**24 465**	**459 811**	**53.2**	**3 419**	**119 538**	**28.6**
<65 years	2 524	112 300	22.5	365	30 562	11.9
[65-75] years	6 329	164 866	38.4	836	44 459	18.8
>75 years	15 612	182 645	85.5	2 218	44 517	49.8
Major organ specific bleeding	**12 728**	**471 828**	**27.0**	**2 052**	**120 968**	**16.7**
<65 years	1 732	113 339	15.3	251	30 688	8.2
[65-75] years	3 904	167 888	23.3	590	44 751	13.2
>75 years	7 092	190 600	37.2	1 184	45 529	26.0
All-cause death	**35 083**	**480 779**	**73.0**	**6 217**	**122 362**	**50.8**
<65 years	3 061	114 752	26.7	512	30 895	16.6
[65-75] years	7 949	170 761	46.6	1 318	45 178	29.2
>75 years	24 073	195 266	123.3	4 387	46 289	94.8
Composite event*	**41 827**	**473 152**	**88.4**	**7 722**	**120 757**	**63.9**
<65 years	4 424	113 246	39.1	810	30 577	26.5
[65-75] years	10 212	168 338	60.7	1 821	44 687	40.7
>75 years	27 191	191 568	141.9	5 091	45 493	111.9

* MI, all stroke, and all-cause death

The incidence rate for individual bleeding categories are detailed in Table XVIII. The most frequent was other bleeding with transfusion with 18.8 and 10.6 per 1 000 PY for the CAD-T2DM population without prior MI-stroke and the THEMIS-like population, respectively, then 5.9 and 3.7 for fatal bleeding, 3.6 and 2.7 for other critical organ or site bleeding, 2.6 and 2.0 for haemorrhagic stroke, and 1.1 and 0.8 for intracranial bleeding. For each outcome, incident rate increased also with age for the two study populations (Table XVIII; Annex 1-3, SAR, Tables 69, 74, 79, 84, 89).

Table XVIII. Incidence rate of major organ specific bleeding details per 1 000 person-years (PY) during the 2-year follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke			THEMIS-like population		
	n event	PY	Incidence ‰ PY	n event	PY	Incidence ‰ PY
Intracranial bleeding	**538**	**480489**	**1.1**	**92**	**122 316**	**0.8**
<65 years	66	114 710	0.6	7	30 892	0.2
[65-75] years	142	170 677	0.8	29	45 158	0.6
>75 years	330	195 101	1.7	56	46 266	1.2
Haemorrhagic stroke	**1247**	**480 162**	**2.6**	**243**	**122 234**	**2.0**
<65 years	144	114 656	1.3	23	30 882	0.7
[65-75] years	352	170 570	2.1	72	45 128	1.6
>75 years	751	194 936	3.9	148	46 224	3.2
Other critical organ or site bleeding	**1736**	**479 450**	**3.6**	**331**	**122 088**	**2.7**
<65 years	308	114 479	2.7	58	30 843	1.9
[65-75] years	507	170 347	3.0	92	45 093	2.0
>75 years	921	194 624	4.7	181	46 152	3.9
Other bleeding with transfusion	**8896**	**473 888**	**18.8**	**1285**	**121 413**	**10.6**
<65 years	1209	113 720	10.6	158	30 760	5.1
[65-75] years	2804	168 531	16.6	384	44 895	8.6
>75 years	4883	191 638	25.5	743	45 758	16.2
Fatal bleeding	**2855**	**480 668**	**5.9**	**449**	**122 345**	**3.7**
<65 years	288	114 737	2.5	29	30 893	0.9
[65-75] years	842	170 724	4.9	132	45 173	2.9
>75 years	1725	195 206	8.8	288	46 279	6.2

11.4.2. Cumulative incidence/probability of outcomes

The 2-year cumulative incidence/probability of main outcomes for all patients and according to age was little higher for the CAD-T2DM population without prior MI-stroke than for the THEMIS-like population for ischemic or unknown stroke (1.7% *vs.* 1.5%) and MI (1.7% *vs.* 1.3%), and clearly higher for heart failure (9.5% *vs. 5*.3%), major organ specific bleeding (4.9% *vs.* 3.2%), all-cause death (13.6% *vs*. 9.7%) and the composite event (16.2% *vs.* 12.0%). For each outcome, the incident rate increased with age in the two study populations (Table XIX, Figure 3 to Figure 5; Annex 1-3, SAR, Tables 45 to 48, 55 to 58, 60 to 63, 65 to 68, 93, 94, 96, 97, and Figures 6 to 9, 14 to 25, 44 to 47).

Table XIX. Cumulative incidence/probability of outcomes (Kaplan-Meier or CIF estimate) at 2-year of follow-up for all patients and according to age at index date in the two study populations

	CAD-T2DM population without prior MI-stroke				THEMIS-like population			
	Total	**< 65**	**[65-75]**	**>75**	**Total**	**< 65**	**[65-75]**	**>75**
Ischemic / unknown stroke	**1.7**	0.9	1.4	2.4	**1.5**	0.8	1.2	2.3
MI	**1.7**	1.6	1.6	1.8	**1.3**	1.3	1.2	1.5
Heart failure	**9.5**	4.3	7.1	14.2	**5.3**	2.3	3.6	8.7
Major organ specific bleeding	**4.9**	2.9	4.4	6.4	**3.2**	1.6	2.5	4.7
All-cause death	**13.6**	5.2	8.9	21.9	**9.7**	3.3	5.7	17.3
Composite event	**16.2**	7.5	11.4	24.7	**12.0**	5.2	7.8	20.0

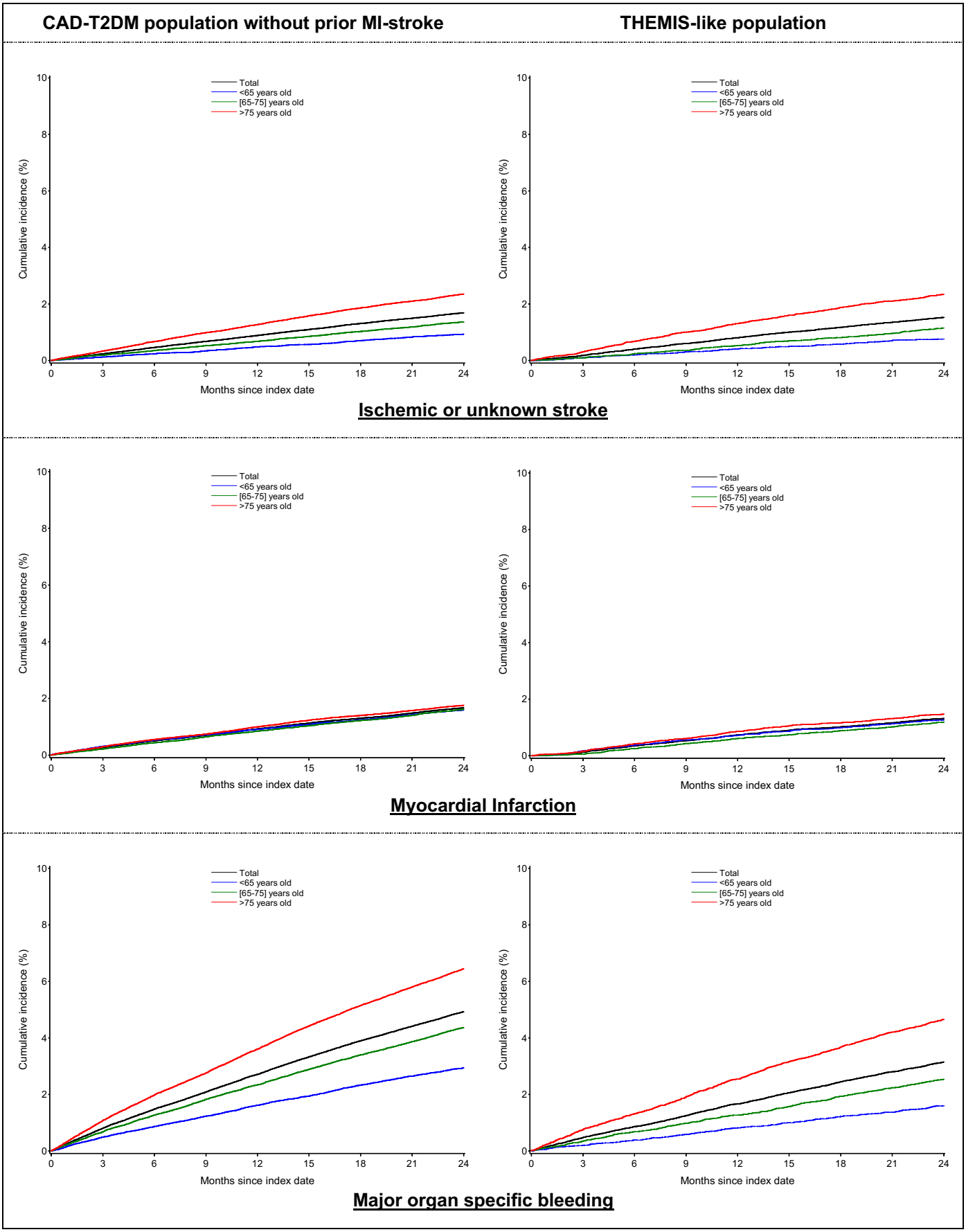

Figure 3. Cumulative incidence/probability of main outcomes (Kaplan-Meier or CIF estimate, scale adjusted according to the number of events) during the 2-year follow-up period according to age at index date in the CAD-T2DM population without prior MI-stroke and the THEMIS-like population

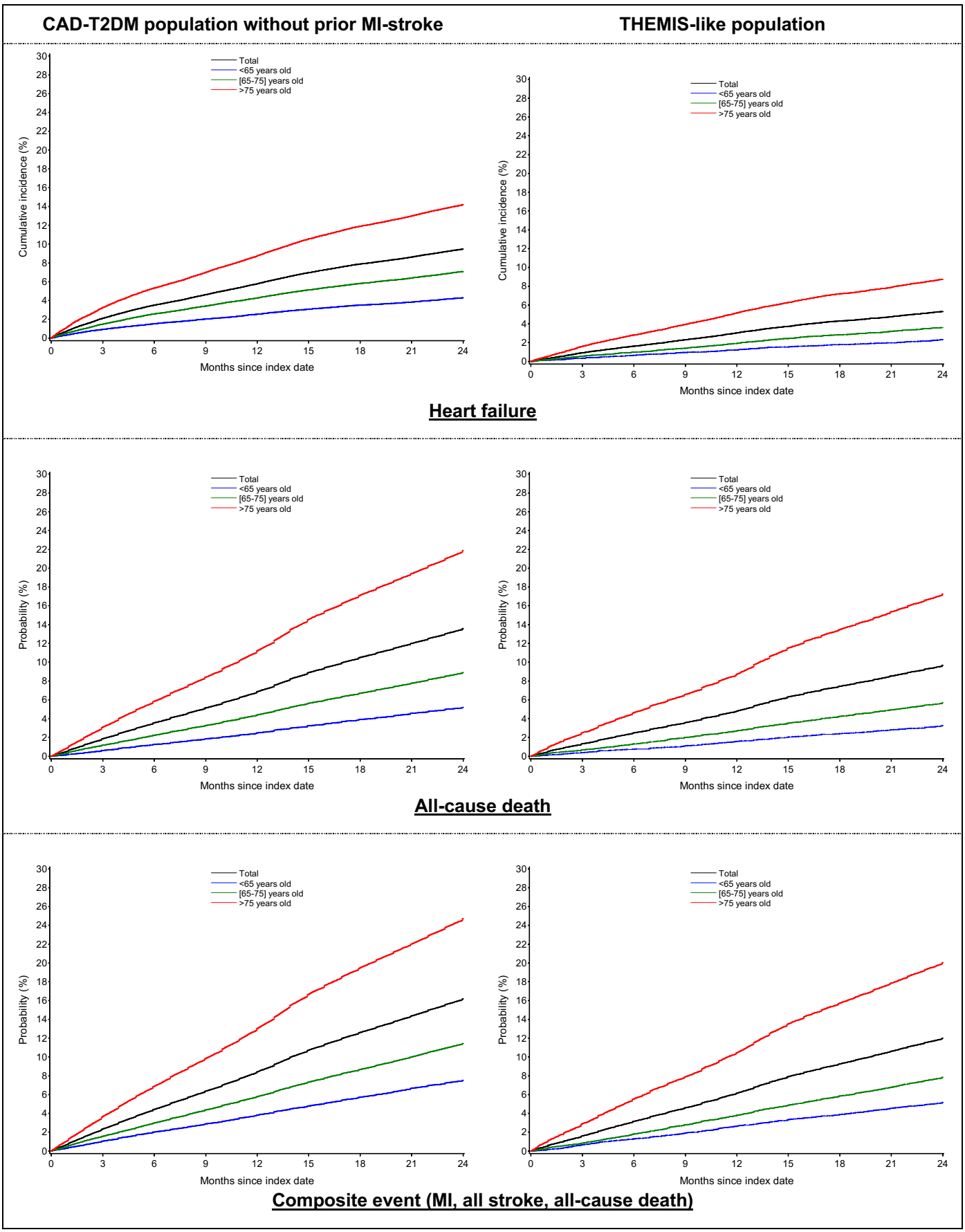

Figure 3. (continued) Cumulative incidence/probability of main outcomes (Kaplan-Meier or CIF estimate, scale adjusted according to the number of events) during the 2-year follow-up period according to age at index date in the CAD-T2DM population without prior MI-stroke and the THEMIS-like population

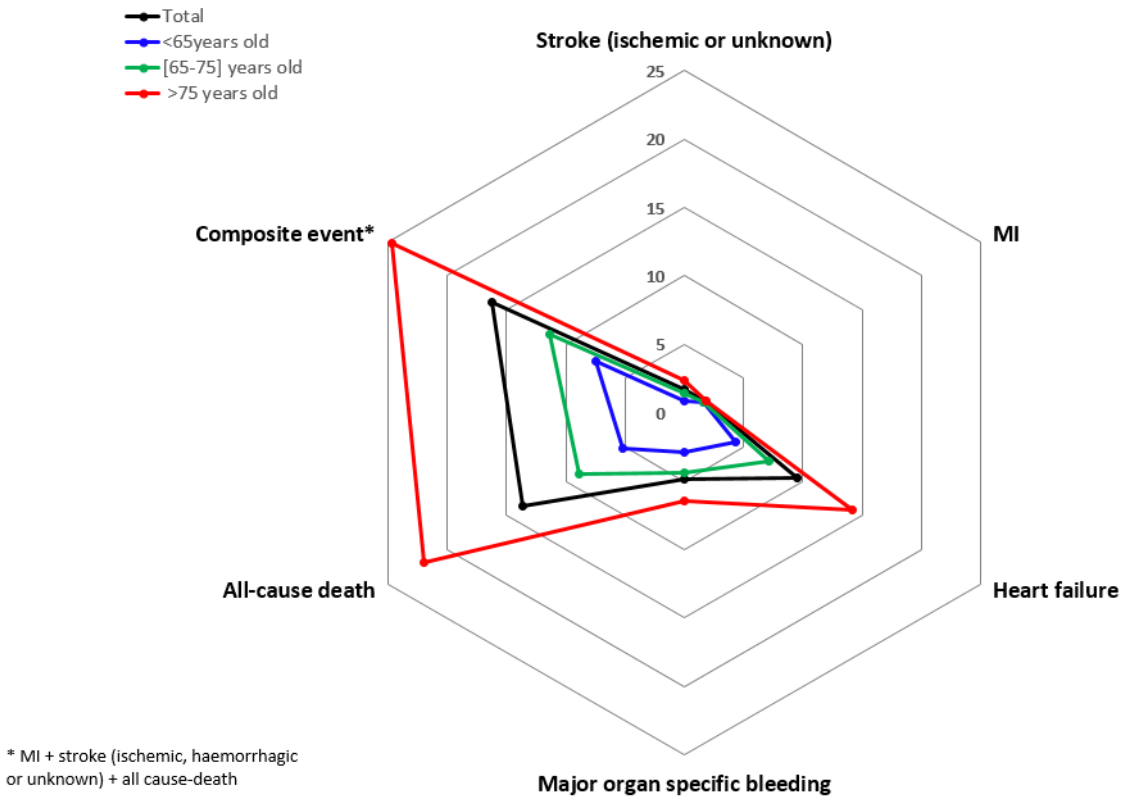

Figure 4. Cumulative incidence/probability of main outcomes (Kaplan-Meier or CIF estimate) at 2-year of follow-up for all patients and according to age at index date in the CAD-T2DM population without prior MI-stroke

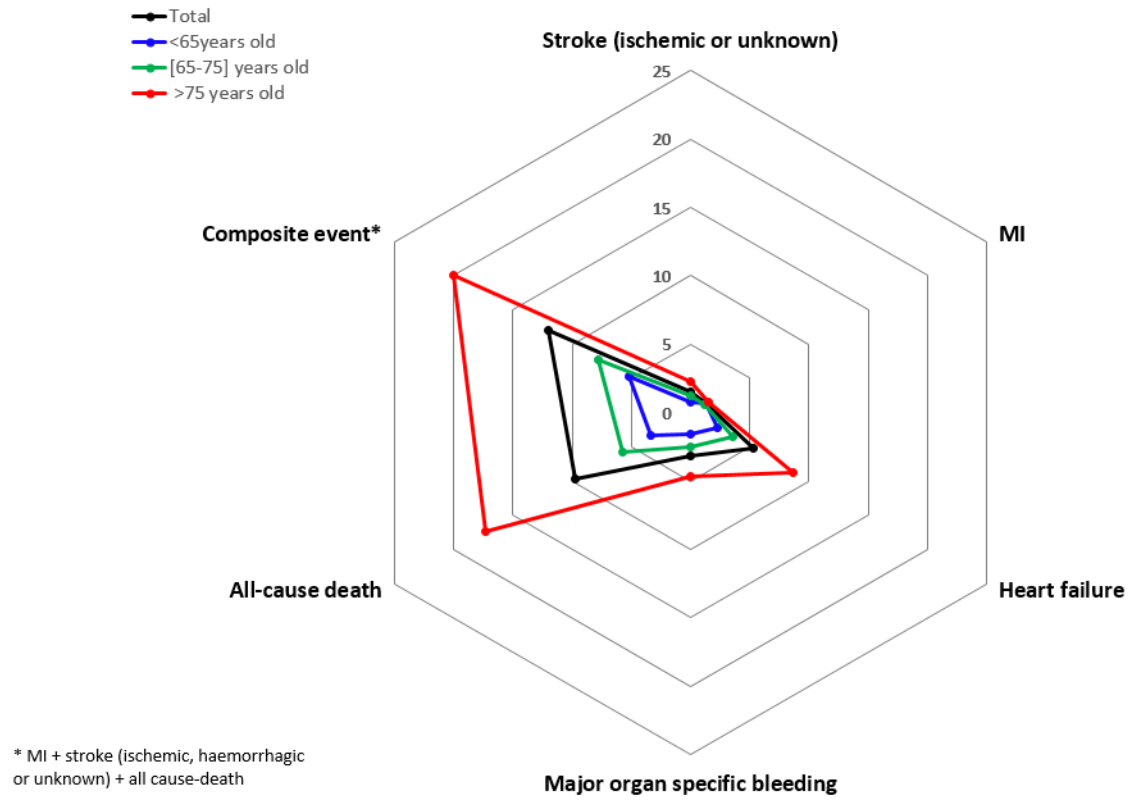

Figure 5. Cumulative incidence/probability of main outcomes (Kaplan-Meier or CIF estimate) at 2-year of follow-up for all patients and according to age at index date in the THEMIS-like population

For major bleeding categories details, the 2-year cumulative incidence/probability was also higher for the CAD-T2DM population without prior MI-stroke than for the THEMIS-like population: 3.4% *vs.* 2.0% for other bleeding with transfusion, 1.2% *vs.* 0.7% for fatal bleeding, 0,7% *vs.* 0.5% for other critical organ or site bleeding, 0.5% *vs.* 0.4% for haemorrhagic stroke and 0.2% *vs.* 0.1% for intracranial bleeding. For each bleeding categories, the incident rate increased with age in the two study populations (Table XX, Figure 6**Erreur ! Source du renvoi introuvable.** to Figure 8; Annex 1-3, SAR, Tables 70 to 73, 75 to 78, 80 to 83, 85 to 88, 90, 91, 93, 94, 96, 97, and Figures 26 to 43).

Table XX. Cumulative incidence/probability of major bleeds details (Kaplan-Meier or CIF estimate) at 2-year of follow-up for all patients and according to age at index date in the two study populations

	CAD-T2DM population without prior MI-stroke				THEMIS-like population			
	Total	**< 65**	**[65-75]**	**>75**	**Total**	**< 65**	**[65-75]**	**>75**
Intracranial bleeding	**0.2**	0.1	0.2	0.3	**0.1**	0.0	0.1	0.2
Haemorrhagic stroke	**0.5**	0.2	0.4	0.7	**0.4**	0.2	0.3	0.6
Other critical organ or site bleeding	**0.7**	0.5	0.6	0.8	**0.5**	0.4	0.4	0.7
Other bleeding with transfusion	**3.4**	2.1	3.1	4.4	**2.0**	1.0	1.7	2.9
Fatal bleeding	**1.2**	0.5	1.0	1.8	**0.7**	0.2	0.6	1.2

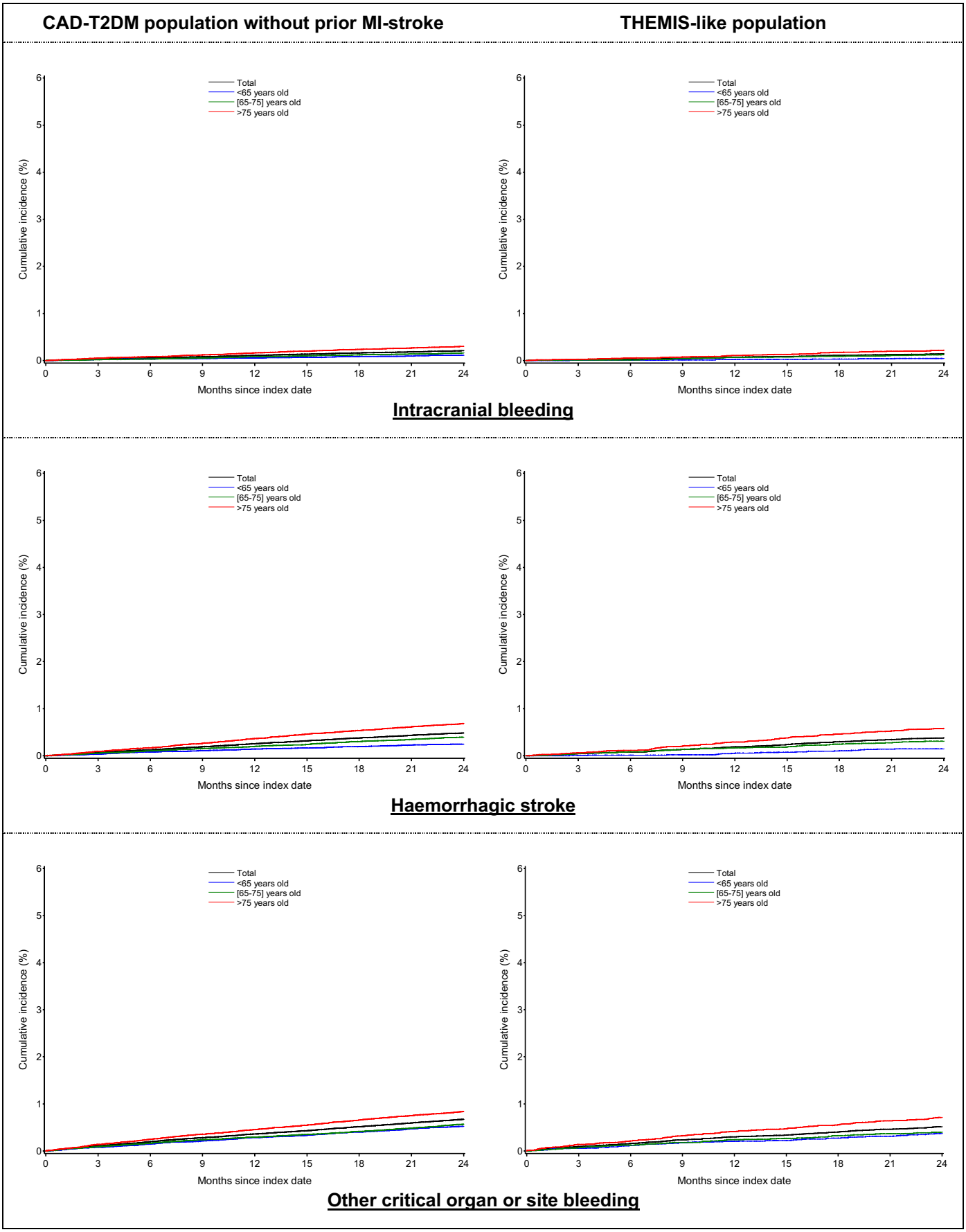

Figure 6. Cumulative incidence/probability of major bleeds details (Kaplan-Meier or CIF estimate, scale adjusted according to the the number of events) during the 2-year follow-up period and according to age at index date in the CAD-T2DM population without prior MI-stroke and the THEMIS-like population

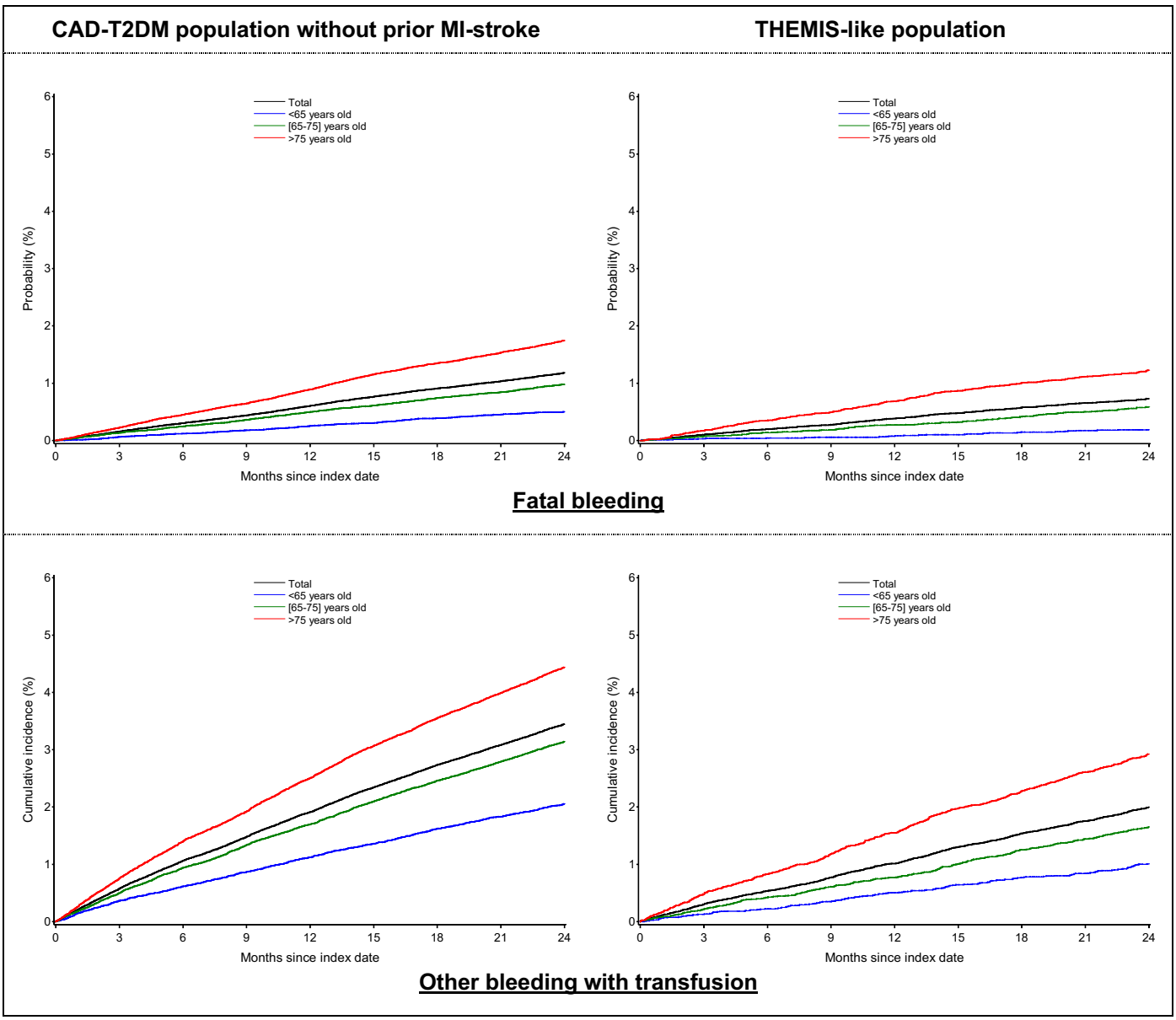

Figure 6. (continued) Cumulative incidence/probability of major bleeds details (Kaplan-Meier or CIF estimate, scale adjusted according to the the number of events) during the 2-year follow-up period and according to age at index date in the CAD-T2DM population without prior MI-stroke and the THEMIS-like population

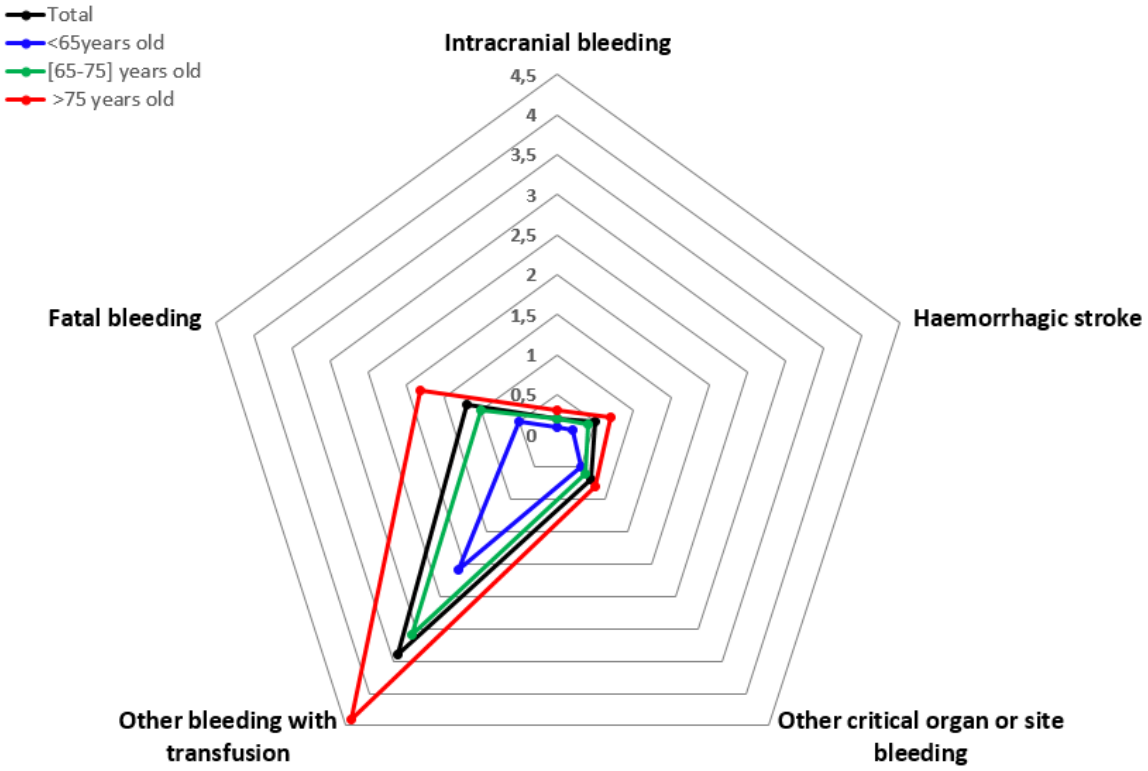

Figure 7. Cumulative incidence/probability of major bleeds details (Kaplan-Meier or CIF estimate) 2-year of follow-up for all patients and according to age at index date in the CAD-T2DM population without prior MI-stroke

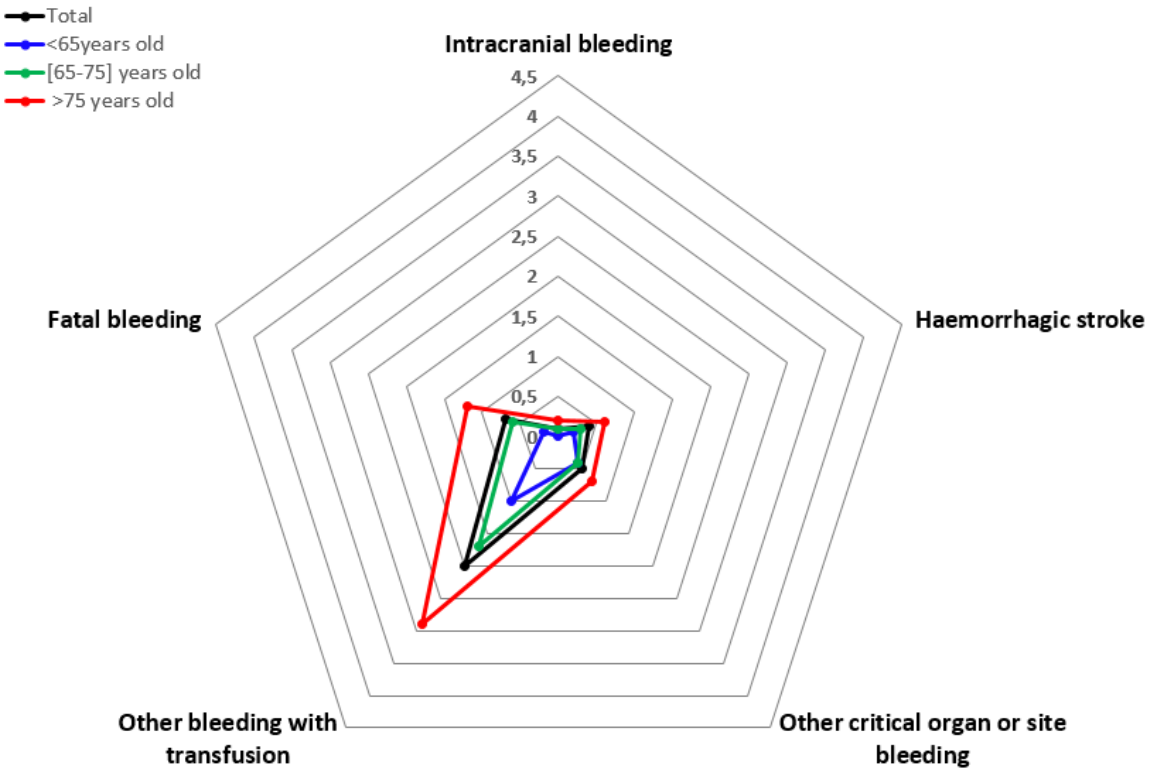

Figure 8. Cumulative incidence/probability of major bleeds details (Kaplan-Meier or CIF estimate) at 2-year of follow-up for all patients and according to age at index date in the THEMIS-like population

11.4.1. Associated risk factors of composite event

Multivariate analysis for the risk of composite of MI, stroke and all-cause death showed a classic gradient according to age for both populations, which increased slowly up to about 2 for the 70-74 years old compared to the youngest (< 55 years), and then faster to reach about 8 for ≥ 90 years old for CAD-T2DM patients without prior MI-stroke and 10 for those of the THEMIS-like population. The risk was also 24% and 30% higher for men of the CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively (Table XXI; Annex 1-3, SAR, Tables 141 and 143).

Independent prognosis factors of the composite event were heart failure, cancer and PAD history in both populations, with a HR between 1.56 and 1.80 (and lower bound of the 95% CI > 1.5), as well as, neurotic and mood disorders history SNDS indicator, with a HR between 1.30 and 1.34. Liver diseases (excluding chronic viral hepatitis and cystic fibrosis) was also a prognosis factor (HR 1.81) for CAD-T2DM patients without prior MI-stroke but was not significant for the THEMIS-like population (Table XXI; Annex 1-3, SAR, Tables 141 and 143).

Table XXI. Associated factors of composite event in the two study populations (multivariate Cox proportional hazards risk model, selection threshold HR ≥ 1.20 or HR ≤ 0.80)

	CAD-T2DM population without prior MI-stroke n = 258 260			THEMIS-like population n = 64 334		
	No	Yes	HR [95% CI]	No	Yes	HR [95% CI]
Male[1]	148 849	27 558	1.24 [1.21 - 1.27]	37 396	4 842	1.30 [1.24 - 1.37]
Age (in years) in categories						
< 55	11 412	712	1	2 334	102	1
[55 - 60[	15 739	1 210	1.18 [1.07 - 1.29]	4 757	225	1.04 [0.82 - 1.31]
[60 - 65[	27 295	2 502	1.37 [1.26 - 1.49]	7 794	483	1.34 [1.08 - 1.66]
[65 - 70[	37 571	4 244	1.64 [1.51 - 1.77]	10 421	758	1.53 [1.24 - 1.88]
[70 - 75[	34 402	4 804	1.95 [1.80 - 2.11]	9 143	857	1.92 [1.56 - 2.36]
[75 - 80[	35 768	6 698	2.49 [2.31 - 2.69]	8 946	1 164	2.56 [2.09 - 3.13]
[80 - 85[	31 106	8 954	3.53 [3.27 - 3.81]	7 438	1 536	3.79 [3.10 - 4.63]
[85 - 90[	16 767	7 687	5.11 [4.73 - 5.53]	4 066	1 453	6.01 [4.91 - 7.36]
≥ 90	6 373	5 016	7.86 [7.26 - 8.51]	1 713	1 144	10.00 [8.15 - 12.26]
Within the 1-year history						
Heart failure[2] [3]	15 240	7 783	1.77 [1.73 - 1.82]	2 278	892	1.80 [1.67 - 1.93]
Cancer[2] [3]	26 547	9 521	1.67 [1.63 - 1.71]	6 777	1 728	1.70 [1.61 - 1.80]
Liver diseases (excl. chronic viral hepatitis/cystic fibrosis)[2] [3]	5 176	1 882	1.81 [1.73 - 1.90]	580	82	1.17 [0.94 - 1.45]
PAD[2] [3]	20 657	6 996	1.56 [1.52 - 1.60]	2 957	799	1.71 [1.58 - 1.84]
Neurotic and mood disorders[2] [3]	11 996	3 377	1.30 [1.26 - 1.35]	3 221	660	1.34 [1.24 - 1.46]
Within the 2-year follow-up						
Diuretics[3] [4]	-	-	1.49 [1.46 - 1.52]	-	-	1.44 [1.37 - 1.51]
APA[3] [4]	-	-	1.01 [0.99 - 1.04]	-	-	1.26 [1.11 - 1.43]
Antidiabetic treatment[4]						
Monotherapy	-			-	-	1
No antidiabetic treatment	-	-	0.71 [0.68 - 0.75]	-	-	0.72 [0.65 - 0.80]
Bitherapy	-	-	0.68 [0.65 - 0.72]	-	-	0.70 [0.62 - 0.79]
Tritherapy or more	-	-	0.65 [0.60 - 0.70]	-	-	0.67 [0.56 - 0.79]
Insulin	-	-	1.27 [1.21 - 1.32]	-	-	1.20 [1.08 - 1.34]

[1]Reference is femal; [2]SNDS pathology indicator; [3]Reference is non-presence of variable; [4]Time dependent variables

Diuretics used during the follow-up was associated with higher risk (HR 1.49 and 1.44 for CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively), as well as APA for the THEMIS-like population (HR 1.26) but not for CAD-T2DM patients without prior MI-stroke (HR 1.01). Compared to antidiabetic monotherapy used, no treatment, bitherapy and tritherapy or more were associated with a 30% lower risk, while insulin used was associated to an increased risk (HR 1.27 and 1.20, CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively) (Table XXI; Annex 1-3, SAR, Tables 141 and 143).

However, this statistical analysis did not allow to differentiate drug effect and drug as a marker of disease severity.

Sensitive analysis (based on HR threshold ≥ 1.10 or ≤ 0.90) found one more prognosis factor: 16% and 7% higher risk with organic nitrates used during the follow-up for the CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively; without any change for the previous prognostics list and corresponding HR (Annex 1-3, SAR, Tables 142 and 144).

11.5. Other analyses: Healthcare resources use and costs during the 2-year follow-up period

11.5.1. Healthcare resources use during the 2-year follow-up period

The healthcare resources use during the 2-year follow-up was similar for CAD-T2DM patients without prior MI-stroke and the THEMIS-like population (Table XXII; Annex 1-3, SAR, Table 98):

- More than 85% of patients had one of the following healthcare: medical visits or technical acts (99% for both populations), medical visits (99% for both populations), non-cardiovascular and non-antidiabetic drug dispensing (98% for both populations), cardiovascular and antidiabetic drug dispensing (98% for both populations), lab tests (96% for both populations), technical acts (90% for both populations), and products and services (90% for the CAD-T2DM patients without prior MI-stroke and 87% for the THEMIS-like population);
- Between 45% and 85% had one of the following healthcare: nursing acts (82% and 79%, respectively), other medical healthcare resources (73% and 74%, respectively), public hospital external consultations or acts (72% and 69%, respectively), MCO cardiovascular hospitalisations (57% and 48%, respectively), and transports (57% and 49%, respectively);
- Between 20% and 45% had one of the following healthcare: physiotherapy acts (39% and 38%, respectively), and MCO non-cardiovascular hospitalisations (37% and 35%, respectively);
- Less than 20% of patients had one of the following healthcare: SSR hospitalisations (15% and 13%, respectively) and HAD hospitalisations (< 1% for both populations);
- Sick leaves or daily allowances concerned 4% of patients in both populations, while assistances, pensions or disability allowances concerned 16% and 15% of patients, respectively.

Table XXII. Healthcare resources use during the 2-year follow-up period in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population n = 64 334
Type of areas of expenditures (several answers possible), n (%)		
Medical area of expenditures		
Medical consultation, visit or technical act	255 969 (99.1)	63 791 (99.2)
Medical consultation, visit	255 347 (98.9)	63 646 (98.9)
Non-cardiovascular/non-antidiabetic drug	254 111 (98.4)	63 007 (97.9)
Cardiovascular/antidiabetic drug	253 227 (98.1)	62 744 (97.5)
Lab test	248 036 (96.0)	61 741 (96.0)
Technical act	232 326 (90.0)	58 059 (90.2)
Product and service	231 321 (89.6)	56 108 (87.2)
Nursing act	210 649 (81.6)	50 629 (78.7)
Other medical healthcare resource	187 834 (72.7)	47 408 (73.7)
Public hospital external consulation or act (MCO[1])	185 141 (71.7)	44 227 (68.7)
MCO[1] cardiovascular hospitalisation	147 029 (56.9)	31 009 (48.2)
Transport	146 175 (56.6)	31 231 (48.5)
Physiotherapy act	101 063 (39.1)	24 241 (37.7)
MCO[1] non-cardiovascular hospitalisation	94 786 (36.7)	22 286 (34.6)
SSR hospitalisation	38 339 (14.8)	8 058 (12.5)
HAD hospitalisation	2 288 (0.9)	387 (0.6)
Allowances		
Assistance, pension or disability allowance	40 400 (15.6)	9 361 (14.6)
Sick leave or daily allowance	9 611 (3.7)	2 664 (4.1)

[1]**MCO**: *Médecine, Chirurgie et Obstétrique* (Medicine, Surgery, Obstetrics); [2]**SSR**: *Soins de Suite et de Réadaptation* (rehabilitation centers); [3]**HAD**: *Hospitalisation A Domicile* (home hospitalisation)

11.5.2. Healthcare resource costs during the 2-year follow-up period

11.5.2.1. National health insurance perspective

The mean total medical cost per patient over the 2-year follow-up, and according to the national health insurance perspective, was €25 025 for CAD-T2DM patients without prior MI-stroke and €17 899 for the THEMIS-like population, while mean total allowances cost was similar in both populations (€1 483 and €1 424€, respectively) (Table XXIII, Figure 9; Annex 1-3, SAR, Tables 99 to 140). The mean cost per patient of each area of expenditure was also higher for CAD-T2DM patients without prior MI-stroke than for the THEMIS-like population:

- Firstly, MCO cardiovascular hospitalisations for both populations, with a mean cost per patient of €7 360 for the CAD-T2DM patients without prior MI-stroke and €4 597 for the THEMIS-like population (29% and 26% of the mean total medical cost of each population, respectively),
- Nursing acts with a mean of €2 622 and €1 895, respectively (10% and 11% of the mean total medical cost, respectively),
- MCO non-cardiovascular hospitalisations with a mean of €2 541 and €1 469, respectively (10% and 8% of the mean total medical cost, respectively),
- Non-cardiovascular and non-antidiabetic drugs with a mean of €2 157 and €1 835, respectively (9% and 10% of the mean total medical cost, respectively),
- Cardiovascular and antidiabetic drugs with a mean of €2 114 and €1 812, respectively (8% and 10% of the mean total medical cost, respectively),
- SSR hospitalisations with a mean of €1 879 and €1 563, respectively (8% and 9% of the mean total medical cost, respectively),
- Medical visits and technical acts with a mean of €1 681 and €1 195, respectively (7% and 7% of the mean total medical cost, respectively),
- Produts and services with a mean of €1 619 and €1 286, respectively (6% and 7% of the mean total medical cost, respectively),
- Transports with a mean of €1 220 and €481, respectively (5% and 3% of the mean total medical cost, respectively),
- Other medical healthcare resources with a mean of €746 and €626, respectively (3% and 3% of the mean total medical cost, respectively),
- Public hospital external consulations and acts with a mean of €415 and €350, respectively (2% and 2% of the mean total medical cost, respectively),
- Physiotherapy acts with a mean of €410 and €356, respectively (2% and 2% of the mean total medical cost, respectively),
- Lab tests with a mean of €405 and €303, respectively (2% and 2% of the mean total medical cost, respectively),
- And HAD hospitalisations with a mean of €229 and €154, respectively (< 1% and < 1% of the mean total medical cost, respectively).

Table XXIII. Healthcare resource costs during the 2-year follow-up period according to the national health insurance perspective in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population N = 64 334
Mean (±SD) total cost (€/patient)	**26 508 (40 864)**	**19 324 (35 946)**
[p25% - p75%]	[6 258;32 025]	[4 844;23 857]
Total medical cost	**25 025 (40 303)**	**17 899 (35 378)**
MCO[1] cardiovascular hospitalisations	7 360 (15 445)	4 597 (9 791)
Nursing acts	2 622 (6 562)	1 895 (5 573)
MCO[1] non-cardiovascular hospitalisations	2 541 (12 046)	1 469 (5 274)
Non-cardiovascular/non-antidiabetic drugs	2 157 (17 549)	1 835 (24 506)
Cardiovascular/antidiabetic drugs	2 114 (2 387)	1 812 (1 494)
SSR[2] hospitalisations	1 879 (8 649)	1 563 (8 076)
Medical consultations, visits and technical acts	1 681 (5 568)	1 195 (1 407)
Technical acts	*1 014 (5 362)*	*576 (1 228)*
Medical consultations, visits	*667 (561)*	*619 (483)*
Products and services	1 619 (3 113)	1 286 (2 651)
Transports	1 220 (5 656)	481 (1 588)
Other medical healthcare resources	746 (4 119)	626 (3 720)
Public hospital external consulations and acts (MCO[1])	415 (2 610)	350 (3 606)
Physiotherapy acts	410 (1 159)	356 (1 066)
Lab tests	405 (453)	303 (277)
HAD[3] hospitalisations	229 (5 458)	154 (3 697)
Total allowances cost	**1 483 (5 412)**	**1 424 (5 286)**
Assistances, pensions and disability allowances	1 281 (4 999)	1 211 (4 850)
Sick leaves and daily allowances	202 (1 775)	213 (1 816)

[1]**MCO**: *Médecine, Chirurgie et Obstétrique* (Medicine, Surgery, Obstetrics); [2]**SSR**: *Soins de Suite et de Réadaptation* (rehabilitation centers); [3]**HAD**: *Hospitalisation A Domicile* (home hospitalisation)

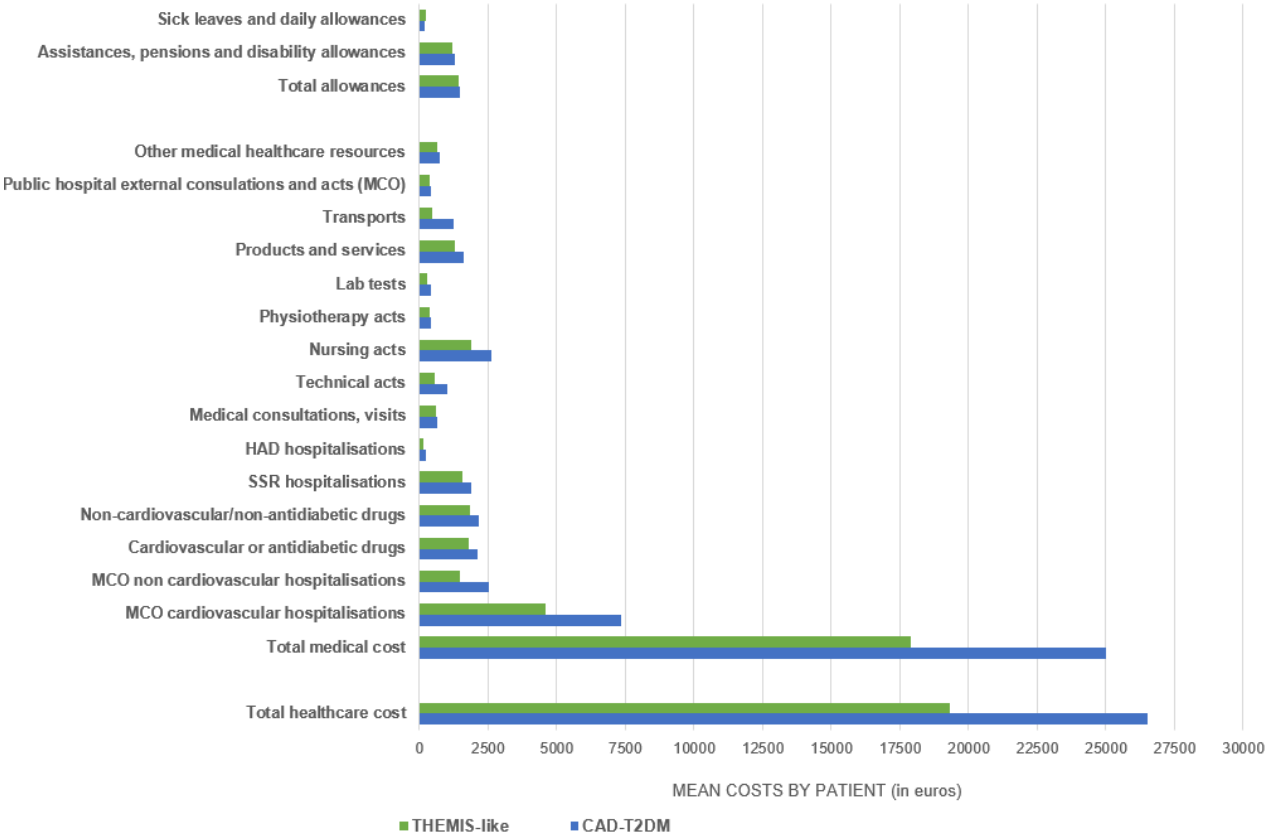

Figure 9. Distribution of the resource costs during the 2-year follow-up period according to the national health insurance perspective in the two study populations

11.5.2.2. Collective perspective

The mean total medical cost per patient over the 2-year follow-up, and according to the collective perspective, was €27 368 for CAD-T2DM patients without prior MI-stroke and €20 242 for the THEMIS-like population, and mean total allowances cost remained unchanged in both populations (Table XXIV, Figure 10; Annex 1-3, SAR, Tables 99 to 140). The mean cost per patient of each area of expenditure was also higher for CAD-T2DM patients without prior MI-stroke than for the THEMIS-like population:

- Firstly, MCO cardiovascular hospitalisations for both populations, with a mean cost per patient of €7 584 for CAD-T2DM patients without prior MI-stroke and €5 009 for the THEMIS-like population (28% and 25% of the mean total medical cost of each population, respectively),
- SSR hospitalisations with a mean of €2 707 and €1 999, respectively (10% and 10% of the mean total medical cost, respectively),
- Nursing acts with a mean of €2 658 and €1 928, respectively (10% and 10% of the mean total medical cost, respectively),
- MCO non-cardiovascular hospitalisations with a mean of €2 570 and €1 654, respectively (9% and 8% of the mean total medical cost, respectively),
- Non-cardiovascular and non-antidiabetic drugs with a mean of €2 364 and €2 050, respectively (9% and 10% of the mean total medical cost, respectively),
- Cardiovascular and antidiabetic drugs with a mean of €2 148 and €1 846, respectively (8% and 9% of the mean total medical cost, respectively),
- Medical visits and technical acts with a mean of €1 839 and €1 363, respectively (7% and 7% of the mean total medical cost, respectively),
- Produts and services with a mean of €1 818 and €1 478, respectively (7% and 7% of the mean total medical cost, respectively),
- Transports with a mean of €1 246 and €503, respectively (4% and 2% of the mean total medical cost, respectively),
- Other medical healthcare resources with a mean of €1 191 and €1 101, respectively (4% and 5% of the mean total medical cost, respectively),
- Lab tests with a mean of €458 and €352, respectively (2% and 2% of the mean total medical cost, respectively),
- Physiotherapy acts with a mean of €449 and €398, respectively (2% and 2% of the mean total medical cost, respectively),
- Public hospital external consulations and acts with a mean of €447 and €398, respectively (2% and 2% of the mean total medical cost, respectively),
- And HAD hospitalisations with a mean of €230 and €162, respectively (<1% and < 1% of the mean total medical cost, respectively).

Table XXIV. Healthcare resource costs during the 2-year follow-up period according to the collective perspective in the two study populations

	CAD-T2DM population without prior MI-stroke n = 258 260	THEMIS-like population n = 64 334
Mean (±SD) total cost (€/patient)	**28 851 (53 791)**	**21 666 (46 923)**
[p25% - p75%]	[7 609;33 842]	[6 091;25 682]
Total medical cost	**27 368 (53 369)**	**20 242 (46 482)**
MCO[1] cardiovascular hospitalisations	7 584 (13 717)	5 009 (9 943)
SSR[2] hospitalisations	2 707 (36 253)	1 999 (28 829)
Nursing acts	2 658 (6 607)	1 928 (5 618)
MCO[1] non-cardiovascular hospitalisations	2 570 (10 845)	1 654 (5 281)
Non-cardiovascular/non-antidiabetic drugs	2 364 (17 555)	2 050 (24 510)
Cardiovascular/antidiabetic drugs	2 148 (2 392)	1 846 (1 501)
Medical consultations, visits and technical acts	1 839 (5 587)	1 363 (1 496)
Technical acts	*1 089 (5 371)*	*656 (1 273)*
Medical consultations, visits	*750 (609)*	*707 (547)*
Products and services	1 818 (3 259)	1 478 (2 782)
Transports	1 246 (5 672)	503 (1 610)
Other medical healthcare resources	1 191 (4 606)	1 101 (4 823)
Lab tests	458 (475)	352 (301)
Physiotherapy acts	449 (1 199)	398 (1 109)
Public hospital external consulations and acts (MCO[1])	447 (4 190)	398 (7 402)
HAD[3] hospitalisations	230 (5 128)	162 (3 922)
Total allowances cost	**1 483 (5 412)**	**1 424 (5 286)**
Assistances, pensions and disability allowances	1 281 (4 999)	1 211 (4 850)
Sick leaves and daily allowances	202 (1 775)	213 (1 816)

[1]**MCO**: *Médecine, Chirurgie et Obstétrique* (Medicine, Surgery, Obstetrics); [2]**SSR**: *Soins de Suite et de Réadaptation* (rehabilitation centers); [3]**HAD**: *Hospitalisation A Domicile* (home hospitalisation)

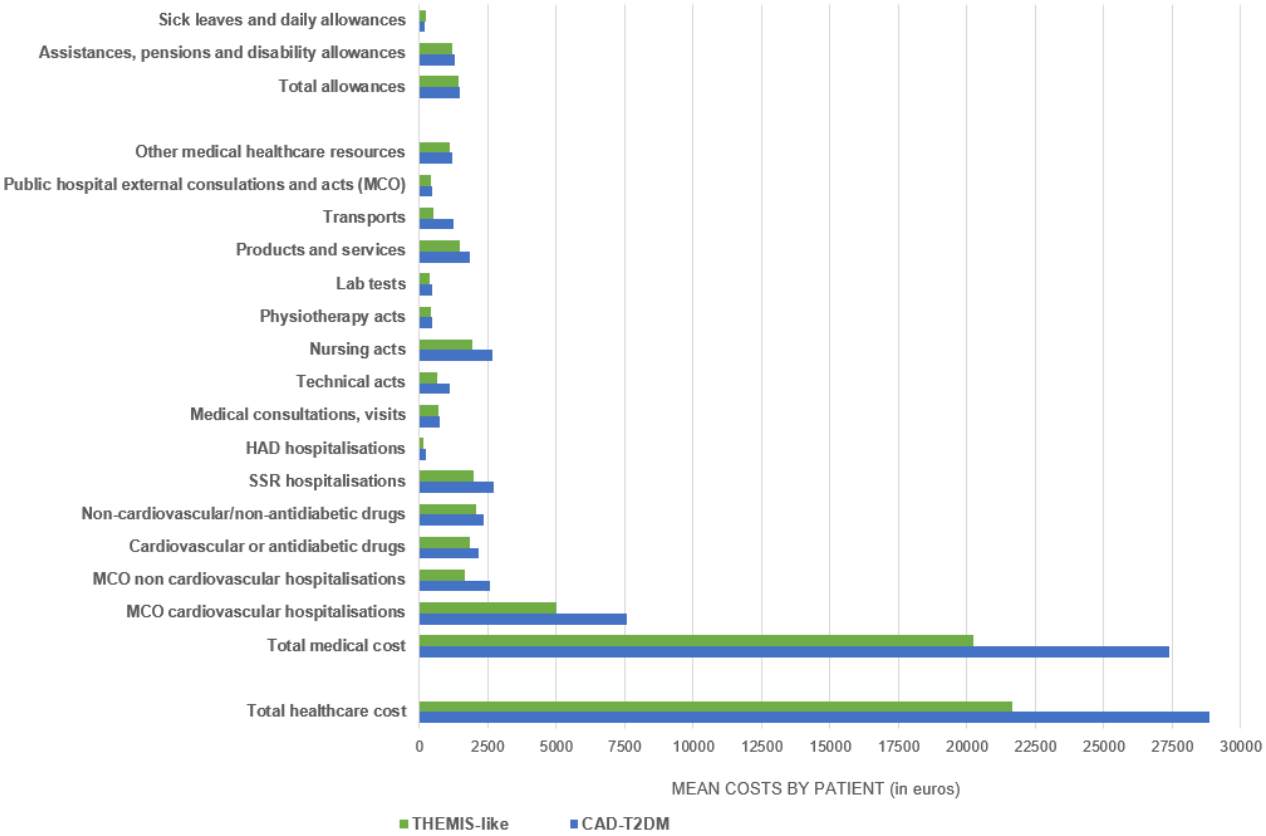

Figure 10. Distribution of the resource costs during the 2-year follow-up period according to the collective perspective in the two study populations

11.6. Adverse events/adverse reactions

This project was a database analysis using secondary pseudonymised individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP VI*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

*The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) from EMA (coming into effect 22 Nov 2017) specifies: For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.2): “The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting due to justification”.

12. DISCUSSION

12.1. Key results

On the 1st January 2014, 328 622 were included in the CAD-T2DM population with 258 260 (78.6%) CAD-T2DM patients without prior MI-stroke and 64 334 (19.6%) THEMIS-like patients. The 2014 prevalence rate in France of CAD-T2DM without prior MI-stroke and THEMIS-like populations was estimated at 6.17 and 1.53 per 1 000 French adults, corresponding to about 317 000 and 79 000 patients. The prevalence was higher for men and increased with age in both populations. THEMIS-like population represented a quarter of all CAD-T2DM patients without prior MI-stroke, as well as, according to gender and age classes. The prevalence rate with sex-age standardization for the European population was estimated at 6.04 and 1.50 per 1 000 adults, respectively.

Patient profil was close for the CAD-T2DM without prior MI-stroke and the THEMIS-like populations with respectively a mean age of 72 years, 68% and 66% of men, 26% and 25% with more than 4-year history of CAD-T2DM, 79% and 76% with hypertension history. However, CAD-T2DM patients without prior MI-stroke presented more revascularisation procedures history thanTHEMIS-like patients (28% and 19%), were also more affected by comorbidities as atrial fibrillation (21% and 10%), renal impairement (20% and 5%), heart failure (16% and 9%), PAD (19% and 11%), and diabetic complications (39% and 32%), and more frequently treated with APA and anticoagulant within the history period (69% *vs.* 43% and 51% *vs.* 33%) as well as over the 2-year follow-up (36% *vs.* 9% and 31% *vs.* 16%).

The 2-year cumulative incidence of main ouctomes for all patients and according to age was little higher for the CAD-T2DM population without prior MI-stroke than for the THEMIS-like population for ischemic or unknown stroke (1.7% *vs.* 1.5%) and MI (1.7% *vs.* 1.3%), and clearly higher for heart failure (9.5% *vs. 5*.3%), major organ specific bleeding (4.9% *vs.* 3.2%), all-cause death (13.6% *vs*. 9.7%) and the composite event (16.2% *vs.* 12.0%). For major bleeding categories details, the 2-year cumulative incidence/probability was also higher for other bleeding with transfusion (3.4% *vs.* 2.0%), for fatal bleeding (1.2% *vs.* 0.7%), for other critical organ or site bleeding (0,7% *vs.* 0.5%), for haemorrhagic stroke (0.5% *vs.* 0.4%), and for intracranial bleeding (0.2% *vs.* 0.1%). For each outcome, the incident rate increased with age in the two study populations.

The risk of composite of MI, stroke and all-cause death increased according to age with a continuous gradient for both populations, and was also 24% and 30% higher for the men of CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively. Independent prognosis factors of the composite event were heart failure, cancer and PAD history in both populations, with a HR between 1.56 and 1.80 (and lower bound of the 95% CI > 1.5), as well as neurotic and mood disorders history, a SNDS indicator, with a HR between 1.30 and 1.34. Liver diseases (excluding chronic viral hepatitis and cystic fibrosis) was also a prognosis factor (HR 1.81) for CAD-T2DM patients without prior MI-stroke but was not significant for the THEMIS-like population. Diuretics used during the follow-up was associated with higher risk of the composite event (HR 1.49 and 1.44 for CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively), as well as APA for the THEMIS-like population (HR 1.26) but not for CAD-T2DM patients without prior MI-stroke (HR 1.01). Compared to antidiabetic monotherapy used, no treatment, bitherapy and tritherapy or more were associated with a 30% lower risk, while insulin used was associated to an increased risk (HR 1.27 and 1.20 for CAD-T2DM without prior MI-stroke and THEMIS-like populations, respectively). However, this statistical analysis did not allow to differentiate drug effect and drug as a marker of disease severity.

For the national health insurance perspective, the mean medical total cost per patient over the 2-year follow-up was €25 025 for CAD-T2DM patients without prior MI-stroke and €17 899 for the THEMIS-like population, while mean total allowances cost was similar in both populations (€1 483 and €1 424€, respectively). The mean cost per patient of each area of expenditure was also higher for CAD-T2DM patients without prior MI-stroke than for the THEMIS-like population

with the highest for MCO cardiovascular hospitalisations (€7 360 and €4 597, i.e. 28% and 25% of the mean total medical cost, respectively).

12.2. Limitations

12.2.1. Selection bias

All subjects were from the main scheme of the SNDS, representing about 86% of the French population. Given the good coverage of the French population, there is neither study selection bias nor attrition bias except regarding some occupational status (*e.g.* farmer are covered by a specific insurance scheme) and few emigrations.

12.2.2. Information bias

The SNDS is a national healthcare claims database linked to the national hospital discharge summaries database and the national death registry. It provided a unique opportunity to identify CAD-T2DM patients in 2014, with exhaustive information about reimbursed outpatient healthcare resources including reimbursed drugs, as well as all public and private hospitalisations. The main limit is that it was built for administrative and reimbursement purposes with a lack of clinical information (obesity, family history, smoking status …) that could impact the patients' prognosis. Some T2DM patients could be misclassified as type 1 because of insulin therapy. To prevent this classification bias, a 5-year history period was defined to investigate prior treatment sequences with sufficient delay to select appropriate T2DM patients.
In France, the database does not collect the entire hospital activities: if there is no procedure, then consultations and emergency department stays lasting less than 24 hours are not recorded. During hospital stays, only data regarding the dispensed costly drugs are available that could represent a potential risk of exposure underestimation. However, it should concern few patients for a very short period of time, and the impact over 7-year study period should be negligible.
Since deaths are recorded in the database using the national death registry, there is no information bias for this outcome. To take into account death as a competing risk of other clinical outcomes, the Fine and Gray model was used (Fine 1999). Clinical outcomes were defined using the ICD-10 primary discharge diagnosis, which is the health problem that motivated the hospital admission. The coding is done by the hospital physician of the patient to determine the cost of the hospitalisation, with a hospital process of coherence and quality information verification. Nevertheless, miscoding cannot be excluded but should be really sparse for the clearly defined events studied (MI, isckemic stroke, major organ specific bleeding).

12.2.3. Confusion bias

This study report provides information about patient characteristics, prevalence and outcome occurence. Since results presented do not involved any direct comparison between treatments, there is no confusion bias.

12.3. Interpretation

Analysis of care reimbursements from the general scheme between 2009 and 2013, extrapolated to the French population on 1st January 2014, allowed to assess for the first time the prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like patients in France. According to this study, the prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like patients was 6.17 (i.e. 316 824 patients throughout France) and 1.53 per 1 000 persons (78 597 patients throughout France) with a higher prevalence for men than women and increasing with age. Taking into account the latest estimate of diabetes prevalence in France in 2015, CAD-T2DM patients without prior MI-stroke would represent approximatively 11% of type 2 diabetic patients and THEMIS-like patients around 3% (Mandereau-Bruno et al., 2017).

Our results based on the SNDS showed that the THEMIS-like population had same age as CAD-T2DM patients without prior MI-stroke with some differences for comorbidities, as some cardiovascular diseases (atrial fibrillation, heart failure PAD), renal impairement, diabetic complications, and exposure to APA or anticoagulant, and represented about a quarter of all CAD-T2DM patients without prior MI-stroke, as well as for men, women and according to age-classes. Furthermore, whatever the study population considered, the annual number of medical visits per patient was double compared to that published by the OECD Health Statistics in 2017 for France from 2015 administrative source (12.5 for the follow-up period vs. 6.3, respectively), probably due to the specific profile of T2DM patients at high risk cardiovascular. The 2-year cumulative incidence was lower for the THEMIS-like population than for the CAD-T2DM patients without prior MI-stroke for all events studied, ischemic stroke (-12%), MI (-24%), heart failure (-44%), major organ specific bleeding
(-35%), all-cause death (-29%) and composite of MI, stroke and all-cause death (-26%). The differences could likely be related to the selection of the THEMIS-like population among CAD-T2DM population without MI-stroke including less severe patients, but also to comorbidities history, especially atrial fibrillation which could have an impact on mortality and heart failure rates, as described in a recent Sweden cohort study (Karayiannides *et al.*, 2018), or nephropathy diabetic and renal impairment also strongly correlated to heart failure. The THEMIS-like patients of this real-world study were 6 years older in average than those of the placebo arm of the THEMIS randomized trial (i.e. 72 and 66 years old, respectively, Steg *et al.*, 2019), with a lower risk of MI (i.e. 1.3% *vs.* 2.2%, assuming 2/3 of the 3-year incidence with constant risk across time for the THEMIS placebo arm), but little higher for ischemic stroke (1.5% *vs.* 1.2%), about the double for the composite event (12.0% *vs.* 6.2%), triple for deaths (9.7% *vs.* 3.2%), and quadruple for major bleedings (1.67 *vs.* 0.38 per 100 PY).

12.4. Generalizability

Results of this study can be extrapolated to the French population because patients were identified from the "*Régime Général*", the main healthcare insurance scheme, which covers 86% of the French population.

13. OTHER INFORMATION

Not applicable

14. CONCLUSION

This study is the first to asses the real-world prevalence of CAD-T2DM without prior MI-stroke and THEMIS-like patients, with an estimation for France of 6.17 and 1.53 per 1 000 in 2014. The THEMIS-like population presented few differences, especially for some comorbidities, than all CAD-T2DM patients without prior MI-stroke. In current practice, the THEMIS-like population was older than those of the placebo arm of the THEMIS trial with about four times more major bleedings, three times more deaths and twice more composite of MI, stroke and all-cause death.

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Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1-1	Version 2.0	25/07/2018	Study Protocol
1-2	Version 2.0	20/03/2020	Statistical Analysis Plan
1-3	Version 1.0	20/03/2020	Statistical Analysis Report
1-4	-	-	Approval pages

Annex 2. Additional information