ATHENA-F

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

Study protocol

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STUDY INFORMATION

Title	Assessment of The High risk and unmEt Need in patients with coronary artery disease and type 2 diabetes in France (ATHENA-F)
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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 CAD-T2DM population without prior MI or stroke, and THEMIS-like population: - To describe patient characteristics and comorbid conditions; - To describe treatment patterns (cardiovascular and antidiabetic drugs) and persistence for two years; - To describe cardiovascular (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 for two years; - To estimate the crude incidence rate and the cumulative incidence of bleeding events: major organ specific bleedings, intracranial haemorrhages, and fatal bleedings for

	two years.
Country of study	France
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2 LIST OF ABBREVIATIONS

ACEI	Angiotensin-Converting-Enzyme Inhibitor
ADP	Adenosine Diphosphate
APA	Antiplatelet Agent
ARAII	Angiotensin II Receptor Antagonist
ASA	AcetylSalicylic Acid
ATC	Anatomical Therapeutic Chemical
CABG	Coronary Artery Bypass Graft
CAD	Coronary Arterial Disease
CCAM	*Classification Commune des Actes Médicaux*
CI	Confidence Interval
CMU-c	*Couverture Mutuelle Universelle-complémentaire* (100% coverage for socially deprived people)
CNAM-TS	French national health insurance fund for salaried worker (*Caisse Nationale d'Assurance Maladie des Travailleurs Salariés*)
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French data protection commission)
CV	CardioVascular
DM	Diabetes Mellitus
EGB	*Echantillon Généraliste de Bénéficiaires*
GI	Gastro-Intestinal
ICD-10	International Classification of Disease, 10th revision
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)
MI	Myocardial Infarction
MPR	Medication Possession Ratio
NIAD	Non Insulin Antidiabetic Drug
PCI	Percutaneous Coronary Intervention
PMSI	*Programme de Médicalisation des Systèmes d'information*
SAP	Statistical Analysis Plan
SNIIRAM	*Système National d'Information Inter-régimes de l'Assurance Maladie*
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

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4 ABSTRACT

TITLE

Assessment of The High risk and unmEt Need in patients with coronary artery disease and type 2 diabetes in France (ATHENA-F)

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 II 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 1 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 in 2019, this project is 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

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 CAD-T2DM population without prior MI or stroke, and THEMIS-like population:

- 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 cardiovascular (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 for two years;
- To estimate the crude incidence rate and the cumulative incidence of bleeding events: major organ specific bleedings, intracranial haemorrhages, and fatal bleedings for two years.

STUDY DESIGN

Cohort study in the SNDS, the French 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 will be extracted from 1st January 2008 to 31st December 2016:

- The index date will be for prevalent patients (both T2DM and CAD diagnoses) the 1st January 2013, and 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 will start on the study index date and will end two years later, or until the date of death.

	All patients will have a 5-year history period prior the index date in the database.
POPULATION	**CAD-T2DM population**: all patients with T2DM diagnosis between 2013 and 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 or 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 MI or 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 agents or anticoagulant treatments at index date.
VARIABLES	**T2DM diagnosis**: ≥ 3 NIAD dispensed during 1 year; or T2DM diagnosis between 2013 and 2014 from LTD registration or hospitalisation; or ICD-10 code E10 with only longer-acting insulin for T2DM patients misclassified as type I because of insulin therapy; **Outcomes: MI, ischemic or unknown stroke, CV death (or all-cause death), heart failure, major organ specific bleeding** as intracranial haemorrhage, other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular), other bleeding (GI bleeding, urogenital and other bleeding), fatal bleeding. **Exposure: Antidiabetic drugs**, **ASA**, **Antiplatelet agents (APA)** (clopidogrel, prasugrel, ticlopidine, ticagrelor, dipyrimadole), **Anticoagulant treatment** (vitamin K antagonist, direct oral anticoagulant, low molecular weight heparin, fondaparinux), **cardiovascular drugs** (calcium beta-blockers, angiotensin-converting-enzyme inhibitor [ACEI] or angiotensin II receptor blocker [ARB], lipid modifying agents, statins), and diuretics. **Healthcare resources:** Hospitalisation for an outcome and duration, hospitalisation for coronary revascularisation (PCI/CABG) and duration, hospitalisation for another cause and duration, in- and outpatient medical visits (general practitioner, specialists), medication related to CV treatment (antidiabetic, CV, APA treatments), other medications overall (non CV treatment), all in- and outpatient reimbursed healthcare expenditures (medical procedures, lab tests, and medical devices, etc.), total registered healthcare costs.
DATA SOURCE	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 66.6 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires; the main healthcare insurance scheme representing about 85% of French population.
STUDY SIZE	Prevalence of treated diabetes was estimated to 2.6% of the French population in 2000 with a constant increase to reach 4.4% in 2009 using the nationwide claims

database, and can be estimated around 5% 4 years later, at the time of start of inclusion in the study. The 2007 ENTRED cohort (*Echantillon national témoin représentatif des personnes diabétiques*) estimated that 16.7% of diabetes had CAD history and 13.9% history of coronary revascularisation.

The number of T2DM patients with CAD or coronary revascularisation is estimated to approximately 6,500 in the EGB and 550,000 in the SNDS for main scheme. At this time, the number of CAD-T2DM patients without prior MI or stroke, as well as THEMIS-like population is unknown and its assessment is the main objective of this study. If the size of the EGB is enough to estimate CAD-T2DM patients without prior MI or stroke, and THEMIS-like populations, it is too limited to estimate CV and bleeding events in these populations.

In the PEGASUS-TIMI 54 randomized placebo-controlled clinical trial for patients with at least 1-year event-free survival after MI, the rates of MI, stroke and major bleeding were about 5%, 2% and 2% at 3 years, respectively. The SNDS will allow to have precise estimation of CV and bleeding events for CAD-T2DM patients, as well as for CAD-T2DM patients without prior MI or stroke or THEMIS-like subpopulation which could represents only 5% or 10% of the CAD-T2DM population (27,000 or 55,000 patients, respectively).

DATA ANALYSIS

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and will be validated before the analysis.

Qualitative and ordinal variables will be summarized by frequencies and proportions of each modality, taking into account missingness as a modality. Continuous variables will be summarized by size, number of patients with missing data, arithmetic mean, standard deviation, median, interquartile ranges and extreme values.

Cumulative incidence rates of outcomes will be estimated using Kaplan-Meier estimator (for composite CV event) and Cumulative Incidence Function (CIF) to take into account death as a competing risk (for bleedings and hospitalisation for cardiac failure outcomes), overall and according to for 3 age-classes (<65, 65-75, >75).

A multivariable Cox proportional hazards regression model will be used to assess predictors of the composite CV events. Baseline demographic and clinical characteristics, including known risk factors will be selected using a stepwise procedure (significance: $p \leq 0.05$).

MILESTONES

Study Protocol	2018, June
Regulatory aspects and data extraction follow-up with CNAMTS (SNDS)	2018, June-December
Statistical Analysis Plan	2018, June-December
Data management and statistical analysis	2019, January-April
Final report	2019, May

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	25/07/2018	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 18 July 2018.

6 MILESTONES

Milestones	Planned Date
Study Protocol	2018, June
Regulatory aspects and data extraction follow-up with CNAMTS (SNDS)	2018, June-December
Statistical Analysis Plan	2018, June-December
Data management and statistical analysis	2019, January-April
Final report	2019, May

7 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). Furthermore, no other antiplatelet agent (APA) has confirmed benefits in high-risk patients with T2DM. 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 1 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 in 2019, this project is 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 will be performed using the SNDS, the French nationwide claims database.

8 RESEARCH QUESTION AND OBJECTIVES

The research question is 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 primary objective will be 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) will be to:

- Describe patient characteristics and comorbidity conditions;
- Describe treatment patterns (CV and antidiabetic drugs) and persistence for two years;
- Describe 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 haemorrhages, and fatal bleedings for two years.

9 RESEARCH METHODS

9.1 STUDY DESIGN

The design is 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) with a follow-up of 2 years per patient. The overall design of the study is presented in the Figure 1.

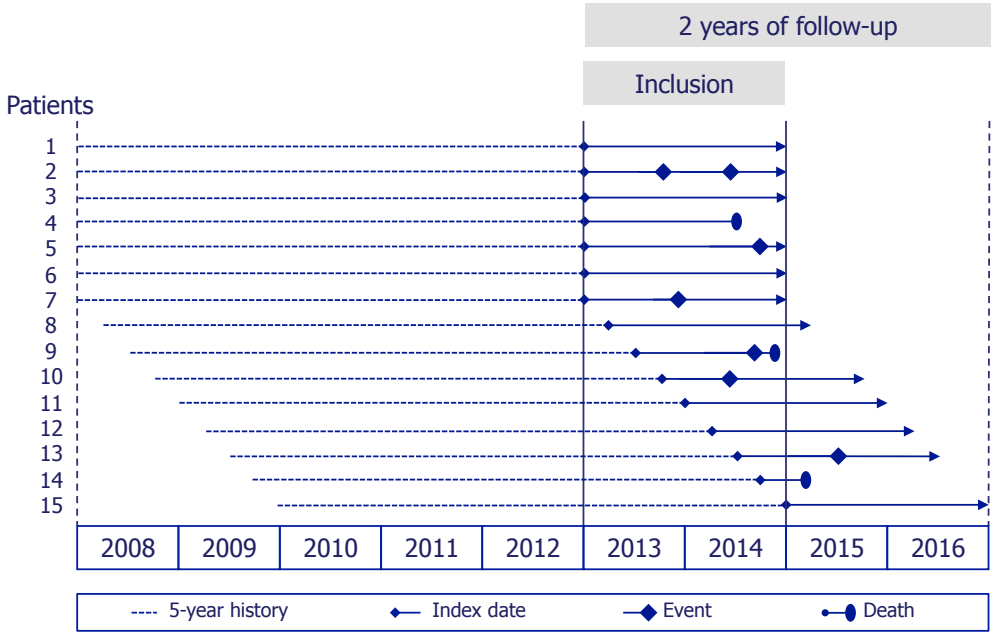

Figure 1. Study design

Data will be extracted from 1st January 2008 to 31st December 2016. The index date will be:

- 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 will start on the study index date and will end two years later, or until date of death. Each patient will have a 5-year history period in the database before index date.

9.2 SETTINGS

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

CAD-T2DM population: all patients with T2DM diagnosis between 2013 and 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 or stroke will be defined as:

- Patients of the CAD-T2DM population without diagnosis of MI or stroke during the history period.

THEMIS-like population will be defined as:

- Patients of the CAD-T2DM population without MI or 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 APA or anticoagulant treatments at index date.

9.3 VARIABLES

9.3.1 Diseases definition

Diseases definition will be based on the International Classification of Disease 10th revision (ICD-10) or Long-Term Disease (LTD) registration and will be finalised in the Statistical Analysis Plan (SAP):

- **Index date** defined as the 1st January 2013 for prevalent patients, and for incident patients the first date of the second diagnosis between T2DM and CAD;
- **T2DM** diagnosis: ≥ 3 NIAD (ATC codes A10B, A10X) dispensed during 1 year; or T2DM diagnosis (ICD-10 code E11) between 2013 and 2014 from LTD registration or hospitalisation; or ICD-10 code E10 with only longer-acting insulin (Anatomical therapeutic chemical (ATC) code A10A) for T2DM patients misclassified as type I because of insulin therapy;
- **CAD**: ICD-10 codes I20-I25 from LTD registration or hospitalisation or PCI/CABG between 2008 and 2014;

- **MI**: ICD-10 codes I21-I24 from LTD registration or hospitalisation history;
- **Ischemic or unknown stroke** (excluding TIA): ICD-10 codes I63 and I64 from LTD registration or hospitalisation;
- **Intracranial haemorrhage**: ICD-10 codes I610 to I619 and I629 from LTD registration or hospitalisation (see Appendix 1);
- **GI bleeding**: hospitalisation with primary or associated diagnosis ICD-10 codes I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922 (see Appendix 1);
- **Cirrhosis of liver**: ICD-10 codes K701, K702, K703, K704, K709, K740, K743, K744, K745, K746, K761 from LTD registration or hospitalisation (see Appendix 2);
- **Liver cancer**: ICD-10 codes C220 to C224, C227 to C229, C787, C7B02, D015, D376 from LTD registration or hospitalisation (see Appendix 2);
- **Renal failure requiring dialysis**: ICD-10 codes I120, I131, I132, N170, N171, N172, N178, N179, N184, N185, N189, Z490, Z491, Z940, Z992 (see Appendix 3).

9.3.2 Exposure

Exposure definitions will use the following variables:

- **Antidiabetic drugs** defined as A10 ATC code;
- **ASA** defined as B01AC06, C10BX01, C10BX02, C10BX04, C10BX05, or B01AC30 ATC codes;
- **Antiplatelet agents (APA)** defined as clopidogrel (B01AC04 or B01AC30 ATC codes), prasugrel (B01AC22 ATC code), ticlopidine (B01AC05 ATC code), ticagrelor (B01AC24 ATC code), or dipyrimadole (B01AC07 ATC code);
- **Anticoagulant treatment** defined as vitamin K antagonist (B01AA ATC codes), direct oral anticoagulant (B01AF01, B01AF02, B01AE07 ATC codes), low molecular weight heparin (B01AB04, B01AB05, B01AB06, B01AB10 ATC codes), fondaparinux (B01AX05 ATC code);
- **Cardiovascular drugs** defined as calcium beta-blockers (C08 ATC code), angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) (C09 ATC code), lipid modifying agents (C10 ATC code), statins (C10AA, C10BA ATC codes), and diuretics (C03 ATC code);
- **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 31th December 2016;
- **Treatment patterns of treatments** during the 2-year follow-up period:
    - Frequency of dispensing;
    - Duration;
    - Persistence defined as medication possession rate (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).

9.3.3 Outcomes

CV events of interest occurring during the follow-up period will be the followings:

- **Stroke** defined above;

- **MI** defined above;
- **CV death (or all-cause death)** (if cause of death available in the database at the time of analysis);
- **Composite criterion** of MI, stroke (all strokes) and CV death (or all-cause death otherwise);
- **Heart failure** defined as hospitalisation with primary diagnosis ICD-10 codes I50, I11.0, I13.0, or I13.2;
- **Major organ specific bleedings** defined as following hospitalisation with primary or associated diagnosis ICD-10 codes:
  - Intracranial haemorrhage (see Appendix 1);
  - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular) (see Appendix 1);
  - Other bleeding (GI, urogenital and other bleeding) with transfusion during hospital stay (see Appendix 1);
  - Fatal bleeding defined as death during hospitalisation with primary or associated bleeding diagnosis ICD-10 codes (see Appendix 1).

9.3.4 Other variables

9.3.4.1 *Baseline demographic and clinical characteristics*

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

- Gender, age and area of residence (at the index date);
- Duration of T2DM;
- History of CAD using LTD, hospitalisation diagnosis, and cardiac revascularisation procedure (PCI/CABG) with time for the most recent (<1, [1-3], >3 years);
- Major comorbidities (ICD-10 codes will be specified in the SAP) and duration including:
  - heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease, hypertension, dyslipidemia;
  - Chronic renal disease, renal impairment
  - Chronic obstructive pulmonary disease;
  - Cancer;
- Diabetes complications defined as hospitalisation with primary or associated diagnosis ICD-10 codes for diabetic nephropathy (E11.21, E11.22), diabetic retinopathy (E11.31-34, E11.35, E11.37), diabetic neuropathy (E11.40-43), diabetic foot ulcer (E11.621);
- Cardiovascular and antidiabetic treatment (ATC code);
- Other treatment (ATC code);
- Obstructive Sleep Apnoea Syndrome.

9.3.4.2 *Healthcare resources use and costs*

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

- Hospitalisation for outcome and duration;
- Hospitalisation 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 treatment (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.

9.4 DATA SOURCE

The SNDS (*Système National des Données de Santé*) 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 66.6 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires; the main healthcare insurance scheme representing about 85% of French population. The SNDS contains individual pseudonymised information on (Tuppin *et al.*, 2010, Bezin *et al.*, 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;
- Long-term disease (LTD, or ALD in French, and associated ICD-10 codes) with starting and ending date. LTD mainly concerned 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. 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 EGB (*Echantillon Généraliste de Bénéficiaires*) is a permanent 1/97th random sample of the SNDS. EGB currently includes more than 800,000 persons from the three main healthcare insurance systems (*Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAMTS) including recently civil servants and students, *Mutualité Sociale Agricole* and *Régime Social des Indépendants*), which represent 85% of the French population. The EGB is fully representative of the French population in terms of gender, age and mean expenditure reimbursed by individual.

9.5 STUDY SIZE

Prevalence of treated diabetes was estimated to 2.6% of the French population in 2000 with a constant increase to reach 4.4% in 2009 using the nationwide claims database (Ricci *et al.*, 2010), and can be estimated around 5% 4 years later, at the time of start of inclusion in the study. The 2007 ENTRED cohort (*Echantillon national témoin représentatif des personnes diabétiques*) (Fagot-Campagna *et al.*, 2009) estimated that 16.7% of diabetes had CAD history and 13.9% history of coronary revascularisation.

The number of T2DM patients with CAD or coronary revascularisation is estimated to approximately 6,500 in the EGB and 550,000 in the SNDS for main scheme. At this time, the number of CAD-T2DM patients without prior MI or stroke, as well as THEMIS-like population is unknown and its assessment is the main objective of this study. If the size of the EGB is enough to estimate CAD-T2DM patients without prior MI or stroke, and THEMIS-like populations, it is too limited to estimate CV and bleeding events in these populations.

In the PEGASUS-TIMI 54 randomized placebo-controlled clinical trial for patients with at least 1-year event-free survival after MI, the rates of MI, stroke and major bleeding were about 5%, 2% and 2% at 3 years, respectively (Bonaca MP *et al., 2015*). Table 1 and 2 show that the SNDS will allow to have precise estimation of CV and bleeding events for CAD-T2DM patients, as well as for CAD-T2DM patients without prior MI or stroke or THEMIS-like subpopulation which could represents only 5% or 10% of the CAD-T2DM population (27,000 or 55,000 patients, respectively, tables 1 and 2).

Table 1. CI for rate, Normal approximation, with 2-year follow-up

	True rate		
Sample size	0.5/100 py	1/100 py	2/100 py
2000	(0.28;0.72)	(0.69;1.31)	(1.56;2.44)
5000	(0.36;0.64)	(0.8;1.2)	(1.72;2.28)
10000	(0.4;0.6)	(0.86;1.14)	(1.8;2.2)
15000	(0.42;0.58)	(0.89;1.11)	(1.84;2.16)
20000	(0.43;0.57)	(0.9;1.1)	(1.86;2.14)
25000	(0.44;0.56)	(0.91;1.09)	(1.88;2.12)
30000	(0.44;0.56)	(0.92;1.08)	(1.89;2.11)
35000	(0.45;0.55)	(0.93;1.07)	(1.9;2.1)
40000	(0.45;0.55)	(0.93;1.07)	(1.9;2.1)

Table 2. CI for risk, Wilson method, with 2-year follow-up

Risk at 2 years	1%	1.98%	3.92%
	True rate		
Sample size	0.5/100 py	1/100 py	2/100 py
2000	(0.64;1.53)	(1.46;2.69)	(3.15;4.86)
5000	(0.76;1.31)	(1.63;2.4)	(3.42;4.5)
10000	(0.82;1.21)	(1.72;2.27)	(3.56;4.32)
15000	(0.85;1.17)	(1.77;2.22)	(3.62;4.24)
20000	(0.87;1.14)	(1.8;2.18)	(3.66;4.2)
25000	(0.88;1.13)	(1.81;2.16)	(3.69;4.17)
30000	(0.89;1.11)	(1.83;2.14)	(3.71;4.15)
35000	(0.9;1.1)	(1.84;2.13)	(3.72;4.13)
40000	(0.9;1.1)	(1.85;2.12)	(3.74;4.12)

9.6 DATA MANAGEMENT

Database extraction criteria will be described in a Data Extraction Plan (DEP) approved prior to the initiating extraction. Extraction of SNDS data will be done by the CNAMTS.

Data transformation, including decision rules, diseases definitions, exposure definitions, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a statistical analysis plan (SAP).

9.7 DATA ANALYSIS

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and will be validated before analyses. The following analyses will be performed:

- A flow chart depicting the number of patients identified in the database for the CAD-T2DM population, and those satisfying the two cohort criteria: CAD-T2DM population without prior MI or stroke, and THEMIS-like population;
- Estimation of the prevalence of CAD-T2DM population, CAD-T2DM population without prior MI or stroke, and THEMIS-like population;
- For CAD-T2DM population without prior MI or stroke, and THEMIS-like population, a description of:
  - patient characteristics and comorbidity conditions at index date;
  - treatment patterns at index date and persistence for two years;
  - healthcare resources use and costs for two years according to the national health insurance perspective and the collective perspective;

- crude incidence rate and cumulative incidence of outcomes (composite CV events, hospitalisation for heart failure, bleedings) for two years. Factors associated with the composite CV events will also be assessed.

Qualitative and ordinal variables will be summarized by frequencies and proportions of each modality, taking into account missingness as a modality. Continuous variables will be summarized by size, number of patients with missing data, arithmetic mean, standard deviation, median, interquartile ranges and extreme values.

The outcomes incidence rates will be estimated using total number of person-years that patients at risk contribute during each time period of interest as a denominator, and the number of first events occurring during each time period of interest as a numerator. In case outcomes are not rare, 95% confidence interval (95%CI) of incidence rates will be calculated using Normal approximation. Otherwise, it will be calculated using the Wilson score interval, which is recommended as the most robust for rare events (*Brown et al.*, 2001).

Cumulative incidence rates of outcomes will be estimated using Kaplan-Meier estimator (for composite CV event) and Cumulative Incidence Function (CIF) to take into account death as a competing risk (for bleedings and hospitalisation for cardiac failure outcomes), overall and according to 3 age classes (<65, 65-75, >75).

A multivariable Cox proportional hazards regression model will be used to assess predictors of the composite CV events.
Prior to modelling, all candidate covariates will be assessed through:

- eliminating candidate covariates whose distributions are very narrow;
- association of candidate predictors without using the outcome variable will be assessed and factors can be grouped according to subject matter, and it can be determined if the group can be summarized into a single factor or if the most accurately measured factor within the group can replace the group.

Known risk factors and confounders for the outcome will be forced into the model and additional baseline covariates will be explored. As a rule of thumb for model robustness, candidate covariate with at least 10-15 events in the data *(Harrell 2015; Schumacher 2012*) will be simultaneously included in the Cox regression using a stepwise selection method (level of significance: $p \leq 0.05$). Time-dependent covariates of interest will also be considered (drug exposure…). Time proportional hazard assumption will be checked for each covariate included in the model. Estimated Hazard ratios (HR) with 95%CI and Wald test p-value will be presented. Confounding, collinearity and interaction between covariates will be also investigated.

9.8 QUALITY CONTROL

The BPE, INSERM CIC1401, has implemented a quality management system for all its activities. CNAMTS extraction of SNDS data will be validated using the expected population size estimated using the EGB. An independent double programming will be performed for main criteria and analysis, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analysis, the database for the interim analysis is locked and kept for ulterior validation if needed. The Statistical Analysis Report (SAR) will be included in the final study report.

9.9 LIMITATIONS OF THE RESEARCH METHODS

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 use patient records from an existing database that are 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.

Selection bias

Since all patients identified will be extracted from a national database, there is no study selection bias, nor attrition bias, expect very rare withdrawals from one of the healthcare insurance system including and covering more than 95% of the French population.

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 4-year study period should be negligible.

9.10 OTHER ASPECTS

None.

10 PROTECTION OF HUMAN SUBJECTS

This project is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNDS is regulated and needs approval from National Institute of Health Data (INDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This project is a database analysis using anonymous 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 PLANS FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

This database analysis will be performed by the BPE, INSERM CIC1401, an Academic Research Organization (ARO), for which scientific communication and publication is a major component of its activities. Study methods and results will be submitted to scientific meetings and for publication in international scientific journals.

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14 APPENDICES

Appendix 1. List of ICD-10 codes for bleeding
Appendix 2. List of ICD-10 codes for cirrhosis of liver and liver cancer
Appendix 3. List of ICD-10 codes for renal failure requiring dialysis

Appendix 1. List of ICD-10 codes for bleeding

All ICD codes with the following label were selected: “hémorragie (hemorrhage), hémorragique (hemorrhagic), saignement (bleeding), épistaxis (epistaxis), otorragie (otorrhagia), hématémèse (hematemesis), rectorragie (proctorrhagia), melena (melena), hematuria (hematuria), hémoptysie (hemoptysis), métrorragies (metrorrhagia), hémopéritoine (hemoperitonea), hémothorax (hemothorax), hémopéricarde (hemopericardia)”.

1) ICD label that do not correspond to a bleeding event were excluded (grey list), such as:
- No bleeding
- Chronic disease with bleeding in the definition
- Infectious diseases with bleeding in the definition
- After effect of cerebral haemorrhage
- Accident during surgical and medical care, including other events than a bleeding.

ICD-10 code	ICD label (French)	ICD label (English)	Class
1. Intracranial haemorrhage			
I610	Hémorragie intracérébrale hémisphérique, sous-corticale	Intracerebral haemorrhage in hemisphere, subcortical	Haemorrhagic Stroke
I611	Hémorragie intracérébrale hémisphérique, corticale	Intracerebral haemorrhage in hemisphere, cortical	Haemorrhagic Stroke
I612	Hémorragie intracérébrale hémisphérique, non précisée	Intracerebral haemorrhage in hemisphere, unspecified	Haemorrhagic Stroke
I613	Hémorragie intracérébrale du tronc cérébral	Intracerebral haemorrhage in brain stem	Haemorrhagic Stroke
I614	Hémorragie intracérébrale cérébelleuse	Intracerebral haemorrhage in cerebellum	Haemorrhagic Stroke
I615	Hémorragie intracérébrale intraventriculaire	Intracerebral haemorrhage, intraventricular	Haemorrhagic Stroke
I616	Hémorragie intracérébrale, localisations multiples	Intracerebral haemorrhage, multiple localized	Haemorrhagic Stroke
I618	Autres hémorragies intracérébrales	Other intracerebral haemorrhage	Haemorrhagic Stroke
I619	Hémorragie intracérébrale, sans précision	Nontraumatic extradural haemorrhage	Haemorrhagic Stroke
I629	Hémorragie intracrânienne (non traumatique), sans précision	Intracranial haemorrhage (nontraumatic), unspecified	Haemorrhagic Stroke
2. Other critical organ or site bleeding			
H313	Hémorragie et rupture de la choroïde	Choroidal haemorrhage and rupture	Other critical organ or site bleeding (Intraocular)
H356	Hémorragie rétinienne	Retinal haemorrhage	Other critical organ or site bleeding (Intraocular)
H431	Hémorragie du corps vitré	Vitreous haemorrhage	Other critical organ or site bleeding (Intraocular)
H450	Hémorragie du corps vitré au cours de maladies classées ailleurs	Vitreous haemorrhage in diseases classified elsewhere	Other critical organ or site bleeding (Intraocular)
I230	Hémopéricarde comme complication récente d'un infarctus aigu du myocarde	Haemopericardium as current complication following acute myocardial infarction	Other critical organ or site bleeding (pericardial)
I312	Hémopéricarde, non classé ailleurs	Haemopericardium, not elsewhere classified	Other critical organ or site bleeding (pericardial)
I600	Hémorragie sous-arachnoïdienne de la bifurcation et du siphon carotidien	Subarachnoid haemorrhage from carotid siphon and bifurcation	Other critical organ or site bleeding (Intraspinal)

ICD-10 code	ICD label (French)	ICD label (English)	Class
I601	Hémorragie sous-arachnoïdienne de l'artère cérébrale moyenne	Subarachnoid haemorrhage from middle cerebral artery	Other critical organ or site bleeding (Intraspinal)
I602	Hémorragie sous-arachnoïdienne de l'artère communicante antérieure	Subarachnoid haemorrhage from anterior communicating artery	Other critical organ or site bleeding (Intraspinal)
I603	Hémorragie sous-arachnoïdienne de l'artère communicante postérieure	Subarachnoid haemorrhage from posterior communicating artery	Other critical organ or site bleeding (Intraspinal)
I604	Hémorragie sous-arachnoïdienne de l'artère basilaire	Subarachnoid haemorrhage from basilar artery	Other critical organ or site bleeding (Intraspinal)
I605	Hémorragie sous-arachnoïdienne de l'artère vertébrale	Subarachnoid haemorrhage from vertebral artery	Other critical organ or site bleeding (Intraspinal)
I606	Hémorragie sous-arachnoïdienne d'autres artères intracrâniennes	Subarachnoid haemorrhage from other intracranial arteries	Other critical organ or site bleeding (Intraspinal)
I607	Hémorragie sous-arachnoïdienne d'une artère intracrânienne, sans précision	Subarachnoid haemorrhage from intracranial artery, unspecified	Other critical organ or site bleeding (Intraspinal)
I608	Autres hémorragies sous-arachnoïdiennes	Other subarachnoid haemorrhage	Other critical organ or site bleeding (Intraspinal)
I609	Hémorragie sous-arachnoïdienne, sans précision	Subarachnoid haemorrhage, unspecified	Other critical organ or site bleeding (Intraspinal)
I620	Hémorragie sous-durale (aiguë) (non traumatique)	Subdural haemorrhage (acute)(nontraumatic)	Other critical organ or site bleeding (Intraspinal)
I621	Hémorragie extradurale non traumatique	Nontraumatic extradural haemorrhage	Other critical organ or site bleeding (Intraspinal)
M250	Hémarthrose	Haemarthrosis	Other critical organ or site bleeding (intra-articular)
S064	Hémorragie épidurale	Epidural haemorrhage	Other critical organ or site bleeding (Intraspinal)
S065	Hémorragie sous-durale traumatique	Traumatic subdural haemorrhage	Other critical organ or site bleeding (Intraspinal)
S066	Hémorragie sous-arachnoïdienne traumatique	Traumatic subarachnoid haemorrhage	Other critical organ or site bleeding (Intraspinal)
S260	Lésion traumatique du cœur avec hémopéricarde	Injury of heart with haemopericardium	Other critical organ or site bleeding (pericardial)
3. Gastro-intestinal bleeding			
I850	Varices œsophagiennes hémorragiques	Oesophageal varices with bleeding	Gastro-intestinal bleeding
I983	Varices œsophagiennes hémorragiques au cours de maladies classées ailleurs	Oesophageal varices with bleeding in diseases classified elsewhere	Gastro-intestinal bleeding
K226	Syndrome de dilacération hémorragique gastro-œsophagienne	Gastro-oesophageal laceration-haemorrhage syndrome	Gastro-intestinal bleeding
K250	Ulcère de l'estomac aigu, avec hémorragie	Gastric ulcer: Acute with haemorrhage	Gastro-intestinal bleeding
K252	Ulcère de l'estomac aigu, avec hémorragie et perforation	Gastric ulcer: Acute with both haemorrhage and perforation	Gastro-intestinal bleeding
K254	Ulcère de l'estomac chronique ou non précisé, avec hémorragie	Gastric ulcer: Chronic or unspecified with haemorrhage	Gastro-intestinal bleeding
K256	Ulcère de l'estomac chronique ou non précisé, avec hémorragie et perforation	Gastric ulcer: Chronic or unspecified with both haemorrhage and perforation	Gastro-intestinal bleeding
K260	Ulcère du duodénum aigu, avec hémorragie	Duodenal ulcer: Acute with haemorrhage	Gastro-intestinal bleeding
K262	Ulcère du duodénum aigu, avec hémorragie et perforation	Duodenal ulcer: Acute with both haemorrhage and perforation	Gastro-intestinal bleeding

ICD-10 code	ICD label (French)	ICD label (English)	Class
K264	Ulcère du duodénum chronique ou non précisé, avec hémorragie	Duodenal ulcer: Chronic or unspecified with haemorrhage	Gastro-intestinal bleeding
K266	Ulcère du duodénum chronique ou non précisé, avec hémorragie et perforation	Duodenal ulcer: Chronic or unspecified with both haemorrhage and perforation	Gastro-intestinal bleeding
K270	Ulcère digestif, de siège non précisé, aigu avec hémorragie	Peptic ulcer, site unspecified: Acute with haemorrhage	Gastro-intestinal bleeding
K272	Ulcère digestif, de siège non précisé, aigu avec hémorragie et perforation	Peptic ulcer, site unspecified: Acute with both haemorrhage and perforation	Gastro-intestinal bleeding
K274	Ulcère digestif, de siège non précisé, chronique ou non précisé, avec hémorragie	Peptic ulcer, site unspecified: Chronic or unspecified with haemorrhage	Gastro-intestinal bleeding
K276	Ulcère digestif, de siège non précisé, chronique ou non précisé, avec hémorragie et perforation	Peptic ulcer, site unspecified: Chronic or unspecified with both haemorrhage and perforation	Gastro-intestinal bleeding
K280	Ulcère gastro-jéjunal aigu, avec hémorragie	Gastrojejunal ulcer: Acute with haemorrhage	Gastro-intestinal bleeding
K282	Ulcère gastro-jéjunal aigu, avec hémorragie et perforation	Gastrojejunal ulcer: Acute with both haemorrhage and perforation	Gastro-intestinal bleeding
K284	Ulcère gastro-jéjunal chronique ou non précisé, avec hémorragie	Gastrojejunal ulcer: Chronic or unspecified with haemorrhage	Gastro-intestinal bleeding
K286	Ulcère gastro-jéjunal chronique ou non précisé, avec hémorragie et perforation	Gastrojejunal ulcer: Chronic or unspecified with both haemorrhage and perforation	Gastro-intestinal bleeding
K290	Gastrite hémorragique aiguë	Acute haemorrhagic gastritis	Gastro-intestinal bleeding
K625	Hémorragie de l'anus et du rectum	Haemorrhage of anus and rectum	Gastro-intestinal bleeding
K920	Hématémèse	Haematemesis	Gastro-intestinal bleeding
K921	Mélæna	Melaena	Gastro-intestinal bleeding
K922	Hémorragie gastro-intestinale, sans précision	Gastrointestinal haemorrhage, unspecified	Gastro-intestinal bleeding
4. Urogenital bleeding			
N020	Hématurie récidivante et persistante avec anomalies glomérulaires mineures	Recurrent and persistent haematuria: Minor glomerular abnormality	Urogenital bleeding
N021	Hématurie récidivante et persistante avec lésions glomérulaires segmentaires et focales	Recurrent and persistent haematuria: Focal and segmental glomerular lesions	Urogenital bleeding
N022	Hématurie récidivante et persistante avec glomérulonéphrite membraneuse diffuse	Recurrent and persistent haematuria: Diffuse membranous glomerulonephritis	Urogenital bleeding
N023	Hématurie récidivante et persistante avec glomérulonéphrite proliférative mésangiale diffuse	Recurrent and persistent haematuria: Diffuse mesangial proliferative glomerulonephritis	Urogenital bleeding
N024	Hématurie récidivante et persistante avec glomérulonéphrite proliférative endocapillaire diffuse	Recurrent and persistent haematuria: Diffuse endocapillary proliferative glomerulonephritis	Urogenital bleeding
N025	Hématurie récidivante et persistante avec glomérulonéphrite mésangiocapillaire diffuse	Recurrent and persistent haematuria: Diffuse mesangiocapillary glomerulonephritis	Urogenital bleeding
N026	Hématurie récidivante et persistante avec maladie à dépôt dense	Recurrent and persistent haematuria: Dense deposit disease	Urogenital bleeding
N027	Hématurie récidivante et persistante avec glomérulonéphrite diffuse en croissant	Recurrent and persistent haematuria: Diffuse crescentic glomerulonephritis	Urogenital bleeding

ICD-10 code	ICD label (French)	ICD label (English)	Class
N028	Hématuries récidivantes et persistantes avec autres lésions morphologiques	Recurrent and persistent haematuria: Other	Urogenital bleeding
N029	Hématurie récidivante et persistante, sans précision	Recurrent and persistent haematuria: Unspecified	Urogenital bleeding
N421	Congestion et hémorragie prostatiques	Congestion and haemorrhage of prostate	Urogenital bleeding
N920	N920 « Menstruation trop abondante et trop fréquente avec cycle menstruel régulier »	Excessive and frequent menstruation with regular cycle	Urogenital bleeding
N921	N921 « Menstruation trop abondante et trop fréquente avec cycle menstruel irrégulier »	Excessive and frequent menstruation with irregular cycle	Urogenital bleeding
N923	Saignements de l'ovulation	Ovulation bleeding	Urogenital bleeding
N924	Saignements abondants de la préménopause	Excessive bleeding in the premenopausal period	Urogenital bleeding
N930	Saignements post-coïtaux et de contact	Postcoital and contact bleeding	Urogenital bleeding
N938	Autres saignements anormaux précisés de l'utérus et du vagin	Other specified abnormal uterine and vaginal bleeding	Urogenital bleeding
N939	Saignement anormal de l'utérus et du vagin, sans précision	Abnormal uterine and vaginal bleeding, unspecified	Urogenital bleeding
N950	Saignements post-ménopausiques	Postmenopausal bleeding	Urogenital bleeding
R31	Hématurie, sans précision	Unspecified haematuria	Urogenital bleeding
5. Other bleeding			
D62	Anémie posthémorragique aiguë	Acute posthaemorrhagic anaemia	Other bleeding **(= with <u>transfusion</u>)**
D683	Troubles hémorragiques dus à des anticoagulants circulants	Haemorrhagic disorder due to circulating anticoagulants	Other bleeding
D698	Autres affections hémorragiques précisées	Other specified haemorrhagic conditions	Other bleeding
D699	Affection hémorragique, sans précision	Haemorrhagic condition, unspecified	Other bleeding
H113	Hémorragie conjonctivale	Conjunctival haemorrhage	Other bleeding
H922	Otorragie	Otorrhagia	Other bleeding
J942	Hémothorax	Haemothorax	Other bleeding
K661	Hémopéritoine	Haemoperitoneum	Other bleeding
K762	Nécrose hémorragique centrale du foie	Central haemorrhagic necrosis of liver	Other bleeding
R040	Épistaxis	Epistaxis	Other bleeding
R041	Hémorragie de la gorge	Haemorrhage from throat	Other bleeding
R042	Hémoptysie	Haemoptysis	Other bleeding
R048	Hémorragie d'autres parties des voies respiratoires	Haemorrhage from other sites in respiratory passages	Other bleeding
R049	Hémorragie des voies respiratoires, sans précision	Haemorrhage from respiratory passages, unspecified	Other bleeding
R58	Hémorragie, non classée ailleurs	Haemorrhage, not elsewhere classified	Other bleeding

ICD-10 code	ICD label (French)	ICD label (English)	Class
S271	Hémothorax traumatique	Traumatic haemothorax	Other bleeding
T792	Hémorragie traumatique secondaire et récidivante	Traumatic secondary and recurrent haemorrhage	Other bleeding

2) All CCAM codes with the following label were selected: “transfusion”, “globules rouges”, “sanguin”.

CCAM code	CCAM label (French)
Selected Codes	
FELF008	Transfusion de concentré de globules rouges, à domicile
FELF011	Transfusion de concentré de globules rouges d'un volume inférieur à une demimasse sanguine
FELF001	Transfusion de concentré de globules rouges d'un volume supérieur à une demimasse sanguine, au cours d'une intervention sous anesthésie générale ou locorégionale
FELF004	Transfusion de concentré de globules rouges d'un volume supérieur à une demi-masse sanguine chez l'adulte ou à 40 millilitres par kilogramme [ml/kg] chez le nouveau-né en moins de 24 heures

3) All ICD-10 codes with the following label were selected: “transfusion”, “globules rouges”. “sanguin”.

ICD-10 code	ICD-10 label (French)	ICD label (English)
Selected Codes		
Z513	Transfusion sanguine (sans mention de diagnostic)	Blood transfusion without reported diagnosis
Z5130	Séance de transfusion de produit sanguin labile	Session of transfusion of unstable blood product

Appendix 2. List of ICD-10 codes for cirrhosis of liver and liver cancer

ICD-10 code	ICD label (French)	ICD label (English)	Class
1. Cirrhosis of liver			
K701	Hépatite alcoolique	Alcoholic hepatitis	Cirrhosis liver
K702	Fibrose et sclérose alcooliques du foie	Alcoholic fibrosis and sclerosis of liver	Cirrhosis liver
K703	Cirrhose alcoolique du foie	Alcoholic cirrhosis of liver	Cirrhosis liver
K704	Insuffisance hépatique alcoolique	Alcoholic hepatic failure	Cirrhosis liver
K709	Maladie alcoolique du foie, sans précision	Alcoholic liver disease, unspecified	Cirrhosis liver
K740	Fibrose hépatique	Hepatic fibrosis	Cirrhosis liver
K743	Cirrhose biliaire primitive	Primary biliary cirrhosis	Cirrhosis liver
K744	Cirrhose biliaire secondaire	Secondary biliary cirrhosis	Cirrhosis liver
K745	Cirrhose biliaire, sans précision	Biliary cirrhosis, unspecified	Cirrhosis liver
K746	Cirrhoses du foie, autres et sans précision	Other and unspecified cirrhosis of liver	Cirrhosis liver
2. Liver cancer			
C220	Carcinome hépatocellulaire	Liver cell carcinoma	Cancer liver
C221	Carcinome du canal biliaire intrahépatique	Intrahepatic bile duct carcinoma	Cancer liver
C222	Hépatoblastome	Hepatoblastoma	Cancer liver
C223	Angiosarcome du foie	Angiosarcoma of liver	Cancer liver
C224	Autres sarcomes du foie	Other sarcomas of liver	Cancer liver
C227	Autres carcinomes du foie précisés	Other specified carcinomas of liver	Cancer liver
C228	Tumeur maligne du foie, primaire, type non spécifié	Malignant neoplasm of liver, primary, unspecified as to type	Cancer liver
C229	Foie, sans précision	Liver, unspecified	Cancer liver
C23	Tumeur maligne de la vésicule biliaire	Malignant neoplasm of gallbladder	Cancer liver
C240	Canal biliaire extra-hépatique	Extrahepatic bile duct	Cancer liver
C241	Ampoule de Vater	Ampulla of Vater	Cancer liver
C248	Lésion à localisations contiguës des voies biliaires	Overlapping lesion of biliary tract	Cancer liver
C249	Voies biliaires, sans précision	Biliary tract, unspecified	Cancer liver
C250	Tête du pancréas	Head of pancreas	Cancer liver
C251	Corps du pancréas	Body of pancreas	Cancer liver
C252	Queue du pancréas	Tail of pancreas	Cancer liver
C253	Canal pancréatique	Pancreatic duct	Cancer liver

ICD-10 code	ICD label (French)	ICD label (English)	Class
C254	Pancréas endocrine	Endocrine pancreas	Cancer liver
C257	Autres parties du pancréas	Other parts of pancreas	Cancer liver
C258	Lésion à localisations contiguës du pancréas	Overlapping lesion of pancreas	Cancer liver
C259	Pancréas, sans précision	Pancreas, unspecified	Cancer liver
C787	Tumeur maligne secondaire du foie et des voies biliaires intrahépatiques	Secondary malignant neoplasm of liver and intrahepatic bile duct	Cancer liver
C7B02	Tumeurs carcinoiddes secondaires du foie	Secondary carcinoid tumors of liver	Cancer liver
D015	Foie, vésicule et voies biliaires	Liver, gallbladder and bile ducts	Cancer liver
D376	Foie, vésicule et voies biliaires	Liver, gallbladder and bile ducts	Cancer liver

Appendix 3. List of ICD-10 codes for renal failure requiring dialysis

ICD-10 code	ICD label (French)	ICD label (English)	Class
I120	Néphropathie hypertensive, avec insuffisance rénale	Hypertensive renal disease with renal failure	Renal failure requiring dialysis
I131	Cardionéphropathie hypertensive, avec insuffisance rénal	Hypertensive heart and renal disease with renal failure	Renal failure requiring dialysis
I132	Cardionéphropathie hypertensive, avec insuffisance cardiaque (congestive) et rénale	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	Renal failure requiring dialysis
N170	Insuffisance rénale aiguë avec nécrose tubulaire	Acute renal failure with tubular necrosis	Renal failure requiring dialysis
N171	Insuffisance rénale aiguë avec nécrose corticale aiguë	Acute renal failure with acute cortical necrosis	Renal failure requiring dialysis
N172	Insuffisance rénale aiguë avec nécrose médullaire	Acute renal failure with medullary necrosis	Renal failure requiring dialysis
N178	Autres insuffisances rénales aiguës	Other acute renal failure	Renal failure requiring dialysis
N179	Insuffisance rénale aiguë, sans précision	Acute renal failure, unspecified	Renal failure requiring dialysis
N184	Insuffisance rénale chronique, stade 4	Chronic kidney disease, stage 4	Renal failure requiring dialysis
N185	Insuffisance rénale chronique, stade 5	Chronic kidney disease, stage 5	Renal failure requiring dialysis
N189	Insuffisance rénale chronique, sans précision	Chronic kidney disease, unspecified	Renal failure requiring dialysis
Z490	Soins préparatoires en vue d'une dialyse	Preparatory care for dialysis	Renal failure requiring dialysis
Z491	Dialyse extra-corporelle	Extracorporeal dialysis	Renal failure requiring dialysis
Z940	Greffe de rein	Kidney transplant status	Renal failure requiring dialysis
Z992	Dépendance envers une dialyse rénale	Dependence on renal dialysis	Renal failure requiring dialysis