SIFNOS study: Retrospective study in patients with atrial fibrillation (AF) exposed and unexposed to an oral anticoagulant therapy between 2016-2020 in France

Pfizer and BMS

Statistical Analysis Plan

Version 2.0, 2023 August 04

Customer study code: [code]

IQVIA study code: 2694548

Pfizer/BMS

Study: SIFNOS study: Retrospective study in patients with atrial fibrillation (AF) exposed and unexposed to an oral anticoagulant therapy between 2016-2020 in France

Prepared for:

PPD, Pfizer, PPD
PPD, Pfizer, PPD
PPD **Pfizer,** PPD
PPD BMS, PPD
PPD, BMS, PPD

Prepared by:

PPD

IQVIA Operations France
Tour D2, 17 bis place des Reflets
TSA 64567, 92099 La Défense Cedex
France

The present statistical analysis plan (SAP) has been developed based on the study protocol version 4.0 dated 06 December 2021.

SAP Approval and Sign-off

I confirm that I have read the contents of this SAP and its attachments. I approve the SAP in its current form.

Pfizer			
	Print name here	Signature	Date
BMS			
	Print name here	Signature	Date
IQVIA Principal	PPD		
	Print name here	Signature	Date
***Reviewer*, Epidemiologist**	PPD		
	Print name here	Signature	Date
***Reviewer*, Epidemiologist**	PPD		
	Print name here	Signature	Date
***Author*, Senior Statistician**	PPD		
	Print name here	Signature	Date

List of Tables

List of Figures

1 Table of contents

2 List of Abbreviations

Abbreviation	Definition
ACCI	Age adjusted Charlson Cormordity Index
ACS	Complementary health care
AD	Associated Diagnosis
AF	Atrial fibrillation
ANSM	National Agency for Medicines and Health Products Safety
ATC	Anatomical Therapeutic Chemical
CAD	Coronary arterial disease
CCAM	*Classification Commune des Actes Médicaux*
CESREES	*Comité éthique et scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé*
CFI	Claims-based frailty index
CI	Confidence Interval
CIP	*Code d'Identification de la Présentation*
CMU-C	*Couverture Médicale Universelle Complémentaire*
CNAM	*Caisse Nationale d'Assurance Maladie*
CNIL	*Commission Nationale de l'Informatique et des Libertés*
COPD	Chronic obstructive pulmonary disease
CSR	*Clinical Study report*
DCIR	*Données de Consommation Inter-Régime*
DOAC	Direct oral anticoagulant
DRG	Diagnosis-related group
DVT	Deep Venous Thrombosis
ICD-10	International Classification of Diseases, 10th revision
INR	International Normalized Ratio
LAA	Left atrial appendage
LTD	Long-Term Disease
NABM	*Nomenclature des Actes de Biologie Médicale*
NGAP	*Nomenclature Générale des Actes Professionnels*

NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non Valvular Atrial Fibrillation
LPPR	*Liste des produits et prestations remboursables*
OAC	Oral anticoagulant
PAD	Peripheral artery disease
PD	Principal Diagnosis
PE	Pulmonary Embolism
PMSI	*Programme de Médicalisation des Systèmes d'Information*
PPPM	Per Patients Per Month
RD	Related Diagnosis
SAP	Statistical Analysis Plan
SE	Systemic embolism
SNDS	*Système National des Données de Santé*
SSRIs	Selective serotonin reuptake inhibitor antidepressants
TE	Thromboembolism
TIA	Transient Ischemic Attack
UCD	*Unité Commune de Dispensation*
VKA	Antivitamins K

3 Responsible Parties

Pfizer

Person	Position	E-mail address
PPD		

BMS

Person	Position	E-mail address
PPD		

IQVIA

Person	Position	E-Mail address
PPD		

Scientific Committee

Person	Position	E-Mail address
Pr PPD	PPD Dijon, Regional University Hospital	PPD
PPD	PPD Marseille, assistance publique-hôpitaux de Marseille (AP-HM)	

Pr PPD PPD	PPD Tours, Regional University Hospital	PPD
Pr PPD PPD	PPD Paris, Broca Hospital, assistance publique-hôpitaux de Paris (APHP)	
Pr PPD PPD	PPD , University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK	

4 Abstract

Section	Description
Background	Atrial fibrillation (AF) is the most common heart rhythm disorder in France. It is a risk factor for thromboembolic complications, in particular stroke, for which it increases the risk fivefold. A previous study by Santé Publique France on data from the National Health Data System (SNDS), estimated in 2018 an annual standardized incidence rate of 410 per 100 000 population in adult patients newly exposed to oral anticoagulants (OACs) for AF. Nevertheless, to our knowledge, the epidemiology of AF in patients not exposed to OACs is very poorly documented in the literature. A French NACORA study conducted from SNDS data compared the occurrence of stroke and major bleeding in patients with nonvalvular atrial fibrillation (AF) over the 2011 and 2012 exposure period to dabigatran, rivaroxaban, and antivitamin K (VKA). The BMS-Pfizer alliance conducted the NAXOS study, following the methodology of the NACORA study with the addition of apixaban, over the 2014-2016 exposure period.
Rationale	Due to the lack of safety data in the population of AF patients unexposed to OAC over a recent period: 2016-2020 and the need to update data on AF exposed to OAC (no new results have been published since 2016), BMS-Pfizer wish to conduct a population-based cohort study in AF patients, that is, the SIFNOS study. This study will also serve as an opportunity to focus on subpopulations most at risk of negative outcomes. From a public health perspective, this study will allow to describe the changes in AF management following the recommendations issued by the HAS in 2018, and thus will provide additional data to optimize the management of patients in routine practice.
Objectives	*Primary objective:* 1. To estimate the incidence rate of stroke (ischemic or hemorrhagic), major bleeding and death in both non-valvular AF patients exposed to OAC (VKA or DOAC) and unexposed to OAC, overall and in subgroups of interest: elderly (≥80 years old); patients with CAD; frail patients, patients reported with active cancer, patients reported with previous stroke. *Secondary objectives:*

	2. To describe the characteristics of non-valvular AF patients exposed and unexposed to OAC; 3. To compare the incidence rate of stroke, major bleeding, and death between those two populations; 4. To estimate the annual incidence and prevalence of patients with non-valvular atrial fibrillation (AF), exposed and unexposed to OAC; 5. To describe the use of oral anticoagulants (OACs) in non-valvular AF patients initiating treatment (AF patients exposed to OAC therapy); 6. To compare Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OAC; 7. To describe the therapeutic management before/after the first stroke occurring after initiation of OAC exposure. *Exploratory objectives:* - To identify subgroups among AF patients with similar profile
Study Design	Observational retrospective cohort study using French national health insurance claims database (SNDS) of non-valvular AF patients (exposed or unexposed to OAC therapy) from 2016 to 2020.
Study Population	Adult patients with non-valvular atrial fibrillation between 2016 and 2020 (inclusion period), with a 2-year historical period before index date (i.e. AF diagnosis date). *Inclusion criteria* Patients are included in the study if they meet all the following criteria: - Age ≥18 years old at index date AND - Have at least one hospital stay with a principal (PD), related (RD) or associated (AD) diagnosis (in PMSI-MSO) of code I48 (Atrial fibrillation of the International Classification of Disease 10th version, ICD-10) OR - Have an active Long-Term Disease (LTD) with ICD-10 code I48 OR

	- Have initiated an OAC (i.e. new users of OAC) for the AF treatment with or without AF diagnosis (PMSI-MSO or LTD), identifying with a validated and published algorithm with a high specificity (c-index 0,93), using a predictive model developed by Billonnet et al. (16). *Exclusion criteria* Patients will be excluded from the study if they meet any exclusion criteria: - Patients with a valve disease or valve surgery; - Standard SNDS exclusion criteria (e.g. unicity of identifier not guaranteed, twins, aberrant demographic data, beneficiaries from Mayotte overseas French territory).
Variables	Variables of interest to meet study objectives are: Primary objectives: - Clinical events of interest: Stroke (ischemic/ hemorrhagic), major bleeding and death; - Drug exposure: Incident AF patients exposed to VKA, apixaban, rivaroxaban, dabigatran / incident AF patients unexposed to OAC therapy. Secondary objectives: - Sociodemographic characteristics: age, sex, complementary universal health care (CMU-c), aid for complementary health care (ACS) for elderly patients, region of patient's residence; - Medical history and comorbidities (identified algorithmically with hospital diagnoses, active long-term disease, drugs and medical procedures): coronary arterial diseases (CAD), dementia, ischemic or hemorrhagic stroke, congestive Heart failure, peripheral arterial disease, other vascular diseases, sleep disorders, active cancer (within 6 months in the historical period), age adjusted Charlson Cormordity Index (ACCI) adapted to the SNDS data, frail patient identified by Claims-Based Fragility Index (CFI) adapted to the SNDS data, malnutrition, morbid Obesity, anemia, COPD, history of diabetes, patients at risk of falls identified by an algorithm adapted to SNDS data, patients poly-medicated, patient with at least one nursing home entry available;

	- Modified risk scores in AF: 1) thromboembolic risk: modified CHA2DS2VASC identified by an algorithm adapted to SNDS data; 2) hemorrhagic risk scores: modified HAS-BLED identified by an algorithm adapted to SNDS data; - Concomitant treatments: beta-blockers, antihypertensives, antiplatelet drugs, other anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticoids, proton pump inhibitors, Selective serotonin reuptake inhibitor antidepressants (SSRIs), systemic azole antifungals, medical procedure of cardioversion, CYP P450 inhibitors, protease inhibitors, antiarrhythmics, glucose-lowering drugs, lipid-lowering drugs, digitalis glycosides, nitrates derivatives. - Annual standardized incidence rate and prevalence of AF, in exposed and unexposed to OAC, every year (2016-2020); - OAC treatment patterns: Line of treatment / regimen, number of lines of treatment (LOT), duration of treatment, time to next treatment; - Healthcare Resource use (HCRU) and associated costs: ambulatory care, hospital care (MCO), rehabilitation care facilities (SSR), Medications.
Data Analysis	*Primary objective* In longitudinal analyses, for each AF population (exposed or unexposed to OAC) and subpopulations of interest: The annual incidence rate will be estimated from the occurrence of each of the events of interest, stroke, major bleeding, and death, during patient follow-up. Annual incidence will be defined as the number of events occurring during the follow-up period divided by the number of person-years of follow-up. *Secondary objective 2:* Patient sociodemographic and clinical characteristics will be analysed through standard descriptive statistics among incident and prevalent AF patients, according to drug exposure (exposed to OAC or unexposed) between 2016 and 2020. *Secondary objective 3:* In longitudinal analysis, comparison of incidence rate of stroke, major bleeding and death, in AF patients exposed and unexposed to OAC therapy, will be performed using a Cox

	regression model adjusted for covariates and with OAC exposure considered as time-dependent variable. *Secondary objective 4:* In cross sectional analyses per calendar year to 2016 to 2020: - Annual age-standardized incidence rate will be estimated as ratio of number of newly diagnosed non valvular AF patients to the number of individuals at risk in the French population (based on INSEE data) per calendar year (N per 100,000 inhabitants). - Annual prevalence as ratio of number of diagnosed non valvular AF patients to the number of individuals in the French population (based on INSEE data) per calendar year. *Secondary objective 5:* In longitudinal analysis during the study period, OAC treatment patterns will be described using a treatment sequence analysis, to define lines of treatment (LOT), switches of OAC, concomitant treatments and temporary or permanent discontinuation. A Sunburst for the visualization will be also performed. Persistence rate at 6 and 12 months after initiation of each OAC and any OAC will be estimate with Kaplan-Meier curves. *Secondary objective 6:* In cross-sectional analyses, HCRU (number and rate of patients using each resource by year of follow up) and associated costs (rate per patient per month (PPPM) in Euros) will be compared between AF patients exposed to OAC and unexposed to OAC every year of follow up. Cost analysis will be performed from the health insurance perspective (reimbursed costs).
Milestones	Start of the study: July 2021 Data access: Third trimester 2023 Study report: April 2024

5 Amendments

Version Number and Date	Section of the SAP	Amendment	Reason
None	None	None	None

6 Milestones

Milestone	Date
Scientific committee meeting	July 2021
Review of protocol by SC members	July-August 2021
Regulatory submission of the project to HDH	September 22, 2021
CESREES opinion about the project	December 2021
CNIL approval	March 18, 2022
Review of study statistical analysis plan by SC members	July-August, 2022
CNAM – IQVIA- Pfizer/BMS agreement Signature	Second trimester 2023
Data access by CNAM	Third trimester 2023
Data management by IQVIA	July 2023 – August 2023
Analysis by IQVIA	September 2023 – December 2023
Validation of the results and study report redaction	January 2024 – March 2024
Study report delivery and Review of the report by SC members	April2024

7 Rationale and Background

7.1 Background

Atrial fibrillation (AF) is a heart rhythm disorder caused by abnormal electrical signals from the atria and is characterized by ineffective atrial contraction and irregular heartbeats. AF can occur in three forms: paroxysmal (episodes lasting less than 7 days), persistent or permanent (lasting more than 7 days) and irreversible (1).

Among patients with AF, more than one-third have associated valve disease, characterized by mitral stenosis or valve prosthesis (1). In this case, AF is called “valvular” (2). Conversely, in patients without associated valvular pathology, AF is said to be “non-valvular”.

In France, two-thirds of AF patients are 75 years of age and older. The prevalence of AF is about 1% of the general population and increases with age to reach 10% of the population aged 80 years and over. The male/female sex ratio of prevalent cases is 3:2 (3). The absolute number of cases is equivalent between men and women because of the higher life expectancy in women (4).

Several pathophysiological mechanisms, including blood flow stasis, prothrombotic state, and hypercoagulability induced by AF, can lead to stroke (5). Clinical signs may include shortness of breath at rest, fatigue, palpitations, or chest pain. AF accounts for approximately 15% of all strokes (6).

The therapeutic management aims to prevent thromboembolic complications (risk multiplied by 5), in particular the occurrence of ischemic stroke, to reduce symptoms, to prevent recurrence of AF using antiarrhythmic treatment and to improve the quality of life of patients (4). The 2014 Guidelines of the French National Authority for Health recommend initiating an oral anticoagulant (OAC) in AF patients to prevent the risk of stroke in the event of a high thromboembolic risk identified by a CHA2DS2-VASC score greater than or equal to 2. If the score is equal to 1, the initiation is to be discussed according to risk factors. Among the OACs, the antivitamins K (VKA) (warfarin, acenocoumarol – and fluindione until 2017) were considered as the reference drugs until 2017; the direct oral anticoagulant (DOAC) including direct factor Xa inhibitors (rivaroxaban and apixaban) and direct thrombin inhibitor (dabigatran) could be prescribed as an alternative (4). Recommendations concerning the good use of OACs has been updated in 2018 (5)**. Since then, DOAC can also be prescribed as a first-line treatment** in non-valvular AF (NVAF) patients**.**

The main risk associated with the use of OACs is the occurrence of serious bleeding events requiring careful use and regular treatment reevaluation. Among patients with AF, some populations have this risk of bleeding potentially increased, especially the elderly and frail (8,9), or those having dementia (10). The risk is also increased in patients with coronary arterial disease (CAD) due to antithrombotic therapy with dual antiplatelet and OAC (4). In case of contraindication to oral anticoagulation, in particular because of major risk of bleeding, a left atrial appendage (LAA) occlusion may be considered to prevent the risk of thromboembolism (11,12)

In France, two previous studies published by Santé Publique France described the annual rate of adult patients newly treated with OAC for AF using data from the National Health Data System (SNDS), of which the most recent published in 2021 estimates in 2018 a standardized rate of 410/100,000 inhabitants (6,7). To our knowledge, no such recent French epidemiological data specific to AF unexposed to OAC is available.

The use of OACs and the associated risks were evaluated in the NACORA study conducted in 2014 by the National Health Insurance (CNAM) in collaboration with the National Agency for Medicines and Health Products Safety (ANSM), using data from the SNDS. This study assessed in France, the hemorrhagic and thromboembolic risks in AF patients exposed to VKA and DOAC (rivaroxaban and dabigatran only), over a short exposure periods of 6 months and a study period from 2011 to 2012 (13,14).

Pfizer and BMS laboratories conducted the NAXOS study, following the methodology of the NACORA study, published in 2020, for the reassessment of the reimbursement of apixaban on the data from the SNDS. The NAXOS study compared the 1-year risk of occurrence of stroke and systemic embolism (SE) and major bleeding in patients initiating OACs (apixaban, rivaroxaban, dabigatran, and VKAs) between 2014 and 2016 with AF (15).

By contrast, there is no such data in AF patients unexposed to OAC in France.

7.2 Rationale of the Study

This study aims to address the lack of safety data in the population of AF patients unexposed to OAC over a recent period: 2016-2020. It will also serve as an opportunity to update data in the population of exposed patients since no new results have been published since 2016 and to focus on subpopulations most at risk. Furthermore, the study will allow to describe the changes in AF management following the recommendations issued by the HAS in 2018.

7.3 Rationale of the Public Interest

Pfizer and BMS need for scientific research purposes, to use the National Health Data System (SNDS) databases in order to have more recent data and to consider any changes in the management of AF patients during the 2016-2020 period and wish to update the NAXOS study (finalized in 2016 and submitted to the authorities in 2020). Unlike the previous NAXOS study, the SIFNOS study will extend the epidemiological data to all patients having NVAF (exposed or unexposed to OAC). It will provide data of AF patients, on their socio-demographic characteristics, care pathways and healthcare resource utilization and incidence rate of clinical outcomes. The incidence rate of clinical outcomes, stroke, major bleeding and mortality will also be studied in AF subpopulations of interest. This knowledge is intended to provide additional data to optimize the management of patients in routine practice.

8 Objectives

8.1 Primary Objective

1. To estimate the incidence rate of stroke (ischemic or hemorrhagic), major bleeding and death in both non-valvular AF patients exposed to OAC (VKA or DOAC) and unexposed to OAC, overall and in the following subgroups of interest:
    - Elderly (≥80 years old)
    - Patients with CAD
    - Frail patients
    - Patients reported with active cancer
    - Patients reported with previous stroke

8.2 Secondary Objectives

2. To describe the characteristics of non-valvular AF patients exposed and unexposed to OAC
3. To compare the incidence rate of stroke, major bleeding, and death between those two populations
4. To estimate the annual incidence and prevalence of patients with non-valvular AF, exposed and unexposed to OAC
5. To describe the use of oral anticoagulants (OACs) in non-valvular AF patients initiating treatment (AF patients exposed to OAC therapy)
6. To compare Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OACs
7. To describe the therapeutic management before/after the first stroke occurring after initiation of OAC exposure

8.3 Exploratory Objectives

8. To identify subgroups among non-valvular AF patients with similar profile

Note: Throughout the SAP, the term "AF" will be used to refer to the "Non-valvular AF" population.

9 Research Methods

9.1 Study Design

SIFNOS study is an observational retrospective cohort study using French national health insurance claims database (SNDS). A unique extraction of AF patients (exposed or unexposed to OAC therapy) in SNDS data will be used to conduct the study from 2016 to 2020.

9.2 Setting

The study setting is described in the subsections below.

9.2.1 Study Time Periods

The study time period from January 1st, 2014 to December 31st, 2020 represents the entirety of the dataset (i.e. the extraction period).

It includes the following sub-study periods defined below.

9.2.1.1 Inclusion period

Within the extraction period, the inclusion period is from January 1st, 2016 to December 31st, 2019 and to December 31st, 2020 for sensitivity analyses.

9.2.1.2 Index Date

Depending on the date of first evidence of AF over the study period, AF patients will be included at the following dates:

- On 1st January 2016 for **prevalent AF patients** (i.e., patients diagnosed AF during the historical period);
- On the first date of evidence of AF (first date of diagnosis of AF identified either by a LTD or the start date of a hospitalization, or the first date of OAC dispensation) for **incident AF patients**.

A patient will be considered exposed to OAC at the time of his/her inclusion if at least one dispensation of OAC is issued within 30 days after inclusion (including date of inclusion). In such a case, the index date will be the date of the first dispensation of OAC (cf. Appendix 1).

Otherwise, if no dispensation of OAC will be identified within 30 days from inclusion, the index date will be the date of inclusion.

9.2.1.3 Historical period

The historical period is a period of 2 years before the index date in order to distinguish incident and prevalent AF-patients, describe patient's comorbidities, medical history and history of treatments. Consequently, this historical period starts from January 1st, 2014.

9.2.1.4 Follow-up and Censoring

The Follow-up period starts at index date and ends on the date of occurrence of one of the following events:

- Death;
- End date of the study fixed to December 31st, 2019 or to December 31st, 2020 for sensitivity analyses;

- Date of the last reimbursement of care recorded in the SNDS (patients with no consumption or reimbursement of care in the 12 months following the date of last consumption).

9.2.2 Study population

Patients with a AF diagnosis will be identified based on a hospitalization with a diagnosis of AF (discharge diagnosis ICD-10 code I48) or with an active Long-Term Disease (LTD) with ICD-10 code I48 during the study (historical or inclusion) period and on an algorithm developed by Billonnet et al. (16) to identify AF outpatients from new users of OACs (VKA, apixaban, rivaroxaban or dabigatran), from January 1st, 2014 to December 31st ,2019, and to December 31st, 2020 for sensitivity analyses (Figure 1).

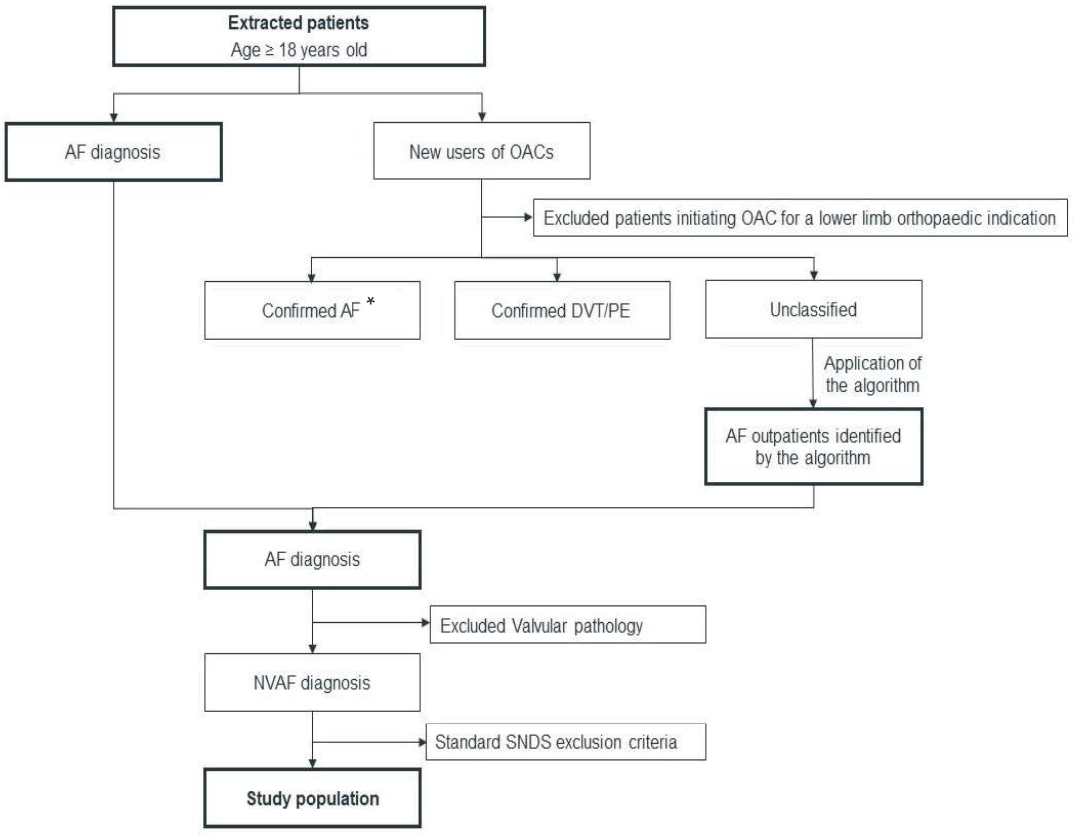


Figure 1. Algorithm for the selection of the study population

9.2.3 Patient Selection

9.2.3.1 Inclusion Criteria

Patients will be included in the study if they meet the following inclusion criteria:

– Age ≥18 years old at index date

AND

(

– Patients with at least one hospital stay with a principal (PD), related (RD) or associated (AD) diagnosis (in PMSI-MSO) of code I48 (Atrial fibrillation of the International Classification of Disease 10th version, ICD-10) or with an active Long-Term Disease (LTD) with ICD-10 code I48 during the study (historical or inclusion) period

AND/OR

– Patients who are new users of OACs for the AF treatment with or without AF diagnosis (PMSI-MSO or LTD), identifying with a validated and published algorithm with a high specificity (c-index 0,93), using a predictive model developed by Billonnet et al. (16).

)

Description of the algorithm:

The algorithm for identifying patients exposed to OAC indicated for AF will be based on the patients who receive at least one reimbursement of an OAC (VKA, apixaban, rivaroxaban or dabigatran) during the inclusion period, without use of any OAC in the 24 months prior to the first reimbursement date.

Patients reported with at least one orthopedic procedure (osteoarticular or muscular) of the lower limb (including hip/knee replacement) as corresponding to the indication of primary prevention of venous thromboembolic events, during a 6-week period before the first date of OAC delivery will be excluded.

Then, three groups of patients will be identified:

- Confirmed AF are defined as patients with at least one hospital stay with a PD, RD or AD of code I48 or with an active LTD with ICD-10 code I48 or with an electrical cardioversion procedure or radiofrequency ablation before the first date of OAC delivery during the historical period;
- Confirmed DVT/PE are defined as patients hospitalized with a diagnosis of PE (code I26 in any position) or DVT (codes I80 except I80.0, I81, I82 in any position) or with a doppler ultrasound examinations, CT venography, MR venography or pulmonary scintigraphy during a 6-week period before the first date of OAC delivery;
- Unclassified patients in other cases.

Patients with both confirmed AF and DVT/PE will be excluded.

Then, a logistic model included 14 independent covariables will be applied on unclassified patients to identify AF outpatients. The model will include following covariables: age, gender, use of treatments as use of beta-blockers, antiarrhythmics, antihypertensive drug, holter/echocardiography procedures, cardiologist prescriber, D-dimer blood test reimbursement and presence of hospitalization for arterial thromboembolic event.

Finally, for each unclassified patient, those with a predicted probability above the cut-off value providing specificity of 95% (sensitivity: 63%), will be assumed to be AF outpatients.

9.2.3.2 Exclusion Criteria

Patients will be excluded from the study if they meet any exclusion criteria:

– Patients with at least one hospital stays with an ICD-10 code in PD, RD or AD for associated valve disease, ICD-10 codes I05 to I09, I34 and I39, or valve surgery;

– Standard SNDS exclusion criteria (e.g. unicity of identifier not guaranteed, twins, aberrant demographic data, beneficiaries from Mayotte overseas French territory).

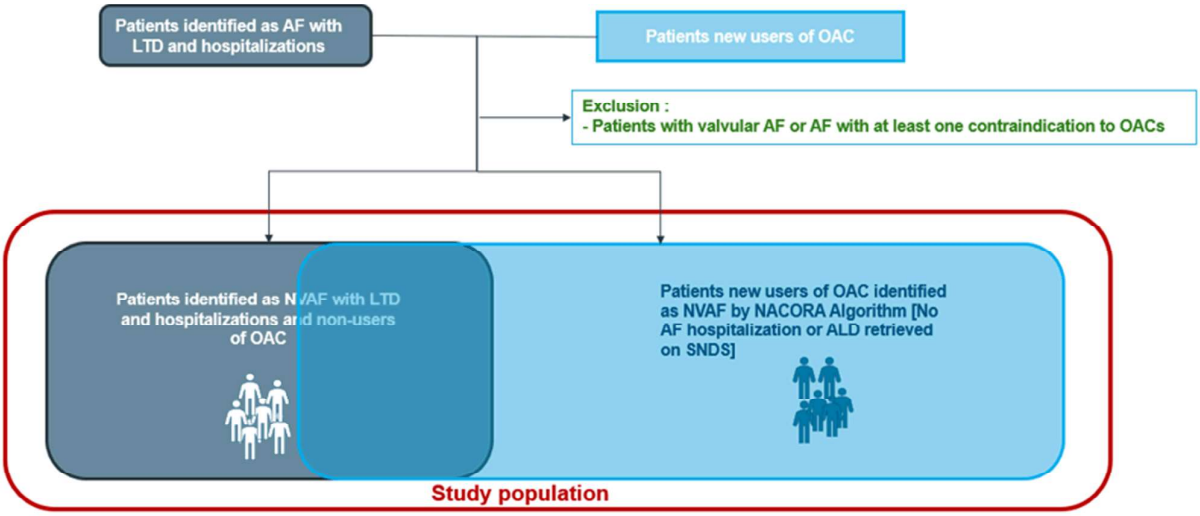


Figure 2. AF study population according to inclusion and non-inclusion criteria

9.2.3.3 Populations

Two populations of AF patients will be considered for analyses according to study objectives:

9.2.3.3.1 Prevalent AF population

Prevalent AF patients will be defined as patients diagnosed with AF during the historical period.

Prevalent AF population will be considered for the following analysis:

- To estimate the annual prevalence of patients with non-valvular AF, exposed and unexposed to OAC (objective 4).

9.2.3.3.2 Incident AF population

Incident AF patients will be defined as patients newly diagnosed with AF (i.e. no AF diagnostic during the historical period) from January 1st, 2016 to December 31st, 2019 (inclusion period), and to December 31st (2020 for sensitivity analyses).

For incident AF population, two datasets of incident AF patients will be considered for the following analyses:

- For longitudinal analyses: objectives 1, 2, 3 and 7 (*cf. 8. Objectives*)

  Inclusion of patients with:

  - An AF newly diagnosed during inclusion period

    AND

- No reported events of interest (stroke, major bleeding, and death) within 30 days before index date (i.e. for patients for whom the date of inclusion is not the date of the first dispensation of OA) (cf. 9.2.3.1. Inclusion Criteria)

- For cross-sectional analyses (objectives 2, 4, 5 and 6) and analysis for exploratory objective (objective 8):

  Inclusion of patients with:

  - An AF newly diagnosed during inclusion period.

9.2.3.4 Sub-Populations

Five subpopulations will be considered in order to meet the objectives of the study:

- Elderly NVAF patients stratified on age-group (≥ 80 years old);
- NVAF patients having a history of coronary arterial disease (CAD);
- NVAF frail patients;
- NVAF patients having an active cancer;
- NVAF patients reported with previous stroke.

9.2.3.5 Stratification groups

Stratification groups will be considered:

- Age groups (<80, 80-90, >90 years old);
- Modified $CHAD_2DS_2VASC$ score strata (Low risk / Moderate risk/ High risk);
- Patients having a history of stroke (Ischemic / Hemorrhagic);
- Patients having a malnutrition (Yes / No);
- Patients at risk of falls identified by an algorithm adapted to SNDS data (Yes / No);
- Frail patients identified by Claims based Frailty Index (CFI) adapted to SNDS data (Yes / No);
- NVAF patients with one or more comorbidities identified by age adjusted Charlson comorbidity index (ACCI) adapted to SNDS data (Yes / No);
- Patients having a morbid obesity (Yes / No);
- Patients with a history of major bleeding;
- Patient with at least one visit to a nursing home;
- Patients with a history of dementia.

9.3 Data Sources

9.3.1 SNDS

9.3.1.1 Presentation of the databases

The French National Health Data System (*Système National des Données de Santé*, SNDS) is the largest and most comprehensive healthcare dataset available in Europe with a 10-year longitudinal follow up for more than 50 million patients. SNDS includes anonymized administrative and healthcare claims data from the French national health care insurance system databases. In particular data from SNIIRAM (*Système National d'Information Inter-Régimes de l'Assurance Maladie*) which consist of hospital-discharge summaries (*Programme de Médicalisation des Systèmes d'Information*, PMSI), all outpatients reimbursed health expenditures (*Données de Consommation Inter-Régime*, DCIR) and national death registry including cause of death (CépiDC). SNDS data consist of anonymized data of reimbursed claims for all patients affiliated with of compulsory health insurance providers (the general scheme covers about 86% of France residents, and 14 other schemes cover the rest) and cover about 99% of French residents.

Data from DCIR and data from PMSI have been linked for each patient to allow for follow-up across different settings of care including outpatient practice and hospital admissions related to medicine, surgery and obstetrics. At this time, date of death from the national death registry is linked to the other data for all the periods. Causes of death are progressively integrated (only available for 2013, 2014 et 2015). Healthcare use of the patient can then be tracked for since birth/first residence in France for 10 years even if a subject is not working, changes occupation or retires and irrespective of socioeconomic status. There is no loss to follow up except for emigration.

SNDS contains information on beneficiaries age, sex, region of residence, death date, complementary universal health coverage status, and all outpatient healthcare consumption including all reimbursed prescription drugs identified by their ATC code, the date of delivery, quantity, and brand name. Medical procedures performed on an outpatient basis or in a healthcare institution are identified by the *classification commune des actes médicaux* (CCAM, or common classification of medical procedures), laboratory procedures are identified by the *nomenclature des actes de biologie médicale* (NABM, clinical pathology test nomenclature) and paramedical or medical visits are identified by the *nomenclature 27nite27le des actes professionnels* (NGAP, General nomenclature of professional procedures).

SNDS informs about the presence of long-term chronic disease (LTD) status, eligible for 100% reimbursement of healthcare expenditure; the date of the LTD diagnosis; and its nature, coded according to the ICD-10. Registration for LTD is requested by the patient's general practitioner, and diagnoses are approved by the health insurance medical consultant. Registration is not mandatory. It may be missing, for instance, if the medical expenses are already covered by another chronic disease or the treatment is not expensive.

Through the PMSI, the SNDS also includes medical summaries of all hospitalizations from all private or public hospitals, including the date of stay, medical procedures and costly innovative drugs Non-English text or implantable devices during the hospital stay, the primary diagnosis (main reason for admission), related diagnoses (specifies the disease context of the primary diagnosis), and diagnoses related to other comorbidities, all encoded according to the ICD-10. Information on occupational diseases, sick leaves are also available.

9.3.1.2 *Main data available*

The data available in DCIR and PMSI databases that are of importance for this study are as follows:

- Administrative data used for sociodemographic, including:
  - Date of birth (month and year);
  - Date of death;
  - Sex;
  - City, department and region of residence;
  - CMU-C;
  - Aid for complementary health care (ACS) for elderly patients.
- Outpatient care data, including:
  - Health professionals visited, medical specialty for physicians, dates of visits;
  - Dates of dispensation, dates of reimbursement, type and number of services carried out by the health professional, reimbursed costs and costs paid by the patients for the associate cares:
  - Drugs coded according to ATC and CIP classifications;
  - Medical and technical acts coded according to CCAM;
  - Biological acts coded according to NABM;
  - Medical devices coded according to LPPR;
  - Medical transportations;
  - Sick leaves;
- Inpatient care data, including;
  - Type of stay coded according to DRG;
  - Localization, type and identifier of hospitals;
  - Dates and reasons for admissions and discharges;
  - Main, related and significant associated diagnoses of admissions coded according to ICD-10;
  - Drugs dispensed at hospital and costly innovative drugs administered during admissions, both coded according to ATC and the common unit of dispensation (28nite commune de dispensation, UCD) classification;
  - Medical and biological acts performed during admissions and coded according to CCAM and NABM, respectively;
  - Other information such as stays in resuscitation units or intensive cares.
- Medical data, including:
  - Presence of a LTD status, start and end dates of LTD coverage and nature of LTDs coded according to ICD-10.

9.4 Derived Variables

9.4.1 Derived Variables for the Selection of the Study Populations

First, all the variables representing the inclusion criteria will be derived for each patient (Table I).

Table I. Derived variables for the selection of the population – Inclusion criteria

Variable	Definition
Atrial fibrillation diagnosis	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e., principal, related or associated diagnosis in PMSI-MSO) of atrial fibrillation during the study (historical or inclusion) period *ICD-10 codes: I48* OR – Is covered by the LTD status for atrial fibrillation at least one day during the study (historical or inclusion) period *ICD-10 codes: I48* Equals to "No" in other cases
Age ≥18 years	Binary variable (Yes / No) Derived based on the date of birth attributed to the patient after cleaning the data extraction Equals to "Yes" if the absolute difference between the year of index date and the year of birth is upper than or equal to 18 years *See also Data Management Plan in section* ***Error! Reference source not found.*** Equals to "No" in other cases

Second, a validated and published algorithm using a predictive model developed by Billonnet et al. (16) will be applied for the identification of AF indications in outpatients initiating OAC (Table II).

Table II. Derived variables for the selection of the population – Identification of AF outpatients initiating OAC

Variable	Definition
New users of OACs (for AF outpatients)	Binary variable (Yes/No) Equals to "Yes" if the patient receives at least one reimbursement of an OAC (VKA, apixaban, rivaroxaban or dabigatran) during the inclusion period, without use of any OAC in the 24 months prior the first date of OAC delivery

Variable	Definition
	ATC codes: B01AA, B01AF02, B01AF01, B01AE07 Equals to "No" in other cases
Patients initiating OAC for a lower limb orthopaedic indication	Binary variable (Yes/No) Equals to "Yes" if the patient receives at least one reimbursement of orthopedic procedure (osteoarticular or muscular) of the lower limb (including hip/knee replacement) as corresponding to the indication of primary prevention of venous thromboembolic events, during a 6-week period before the first date of OAC delivery *DRG code: D02* Equals to "No" in other cases
Confirmed AF	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e. principal, related or associated diagnosis in PMSI-MSO) of atrial fibrillation before the first date of OAC delivery during historical period *ICD-10 codes: I48* OR – Is covered by an ongoing LTD status for atrial fibrillation before the first date of OAC delivery during historical period *ICD-10 codes: I48* OR – Had an electrical cardioversion procedure or radiofrequency ablation before the first date of OAC delivery during historical period *CCAM codes: DERP003, DEPF004, DEPF005* Equals to "No" in other cases
Confirmed DVT/PE	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e. principal, related or associated diagnosis in PMSI-MSO) of PE or DVT during a 6-week period before the first date of OAC delivery *ICD-10 codes: I26.x, I80.1, I80.2, I80.3, I80.8, I80.9, I81.x, I82.x* OR

Variable	Definition
	– Had a doppler ultrasound examinations, CT venography, MR venography or pulmonary scintigraphy during a 6-week period before the first date of OAC delivery *CCAM codes: GFQL007, GFQL006, GFQL005, GFQL002, GLQL002, GFQL001, GFQL004 (pulmonary scintigraphy); EJQM003, DHQM002, EJQM004, EJQM001 (doppler ultrasound examinations); EFQH001, EFQH003, EFQH004, EFQH005, EFQH006, DHQH003 (CT venography); EAQJ001, EBQJ00, EBQJ001, ECQJ001, ELQJ001, EKQJ001, EMQJ001, ELQJ003 (MR venography).* Equals to "No" in other cases
Unclassified patients	Binary variable (Yes/No) Equals to "Yes" if **Confirmed AF** = "No" and **Confirmed DVT/PE** = "No" The algorithm will be applied on the unclassified patients. Patients with both confirmed AF and DVT/PE will be excluded. Equals to "No" in other cases

Then, a logistic model included 14 independent covariables will be applied on unclassified patients to identify AF outpatients initiating OAC (Table III).

Table III. Derived variable for the selection of the population – Covariables included in the logistic model

Variable	Definition
Age	Categorical variable (<65 years old / 65-74 / 75-79 / ≥80 years old) Derived based on the date of birth attributed to the patient after cleaning the data extraction Equals to: 9. "<65 years old" if the absolute difference between the year of index date and the year of birth is strictly lower than 65 years old 10. "65-74" if the absolute difference between the year of index date and the year of birth is between 65 and 74 years old 11. "75-79" if the absolute difference between the year of index date and the year of birth is between 75 and 79 years old 12. "≥80 years old" if the absolute difference between the year of index date and the year of birth is upper than 80 years old *See also Data Management Plan in section **Error! Reference source not found.***

Gender	Binary variable (Female / Male) Equals to the value attributed to the patient after cleaning the data extraction *See Data Management Plan in section* ***Error! Reference source not found.***
Cardiologist prescriber	Binary variable (Yes / No) Equals to "Yes" if the prescriber of the initiation of the OAC is a cardiologist *Code CNAM repository (variable PSE_SPE_COD): 03* Equals to "No" in other cases
Initiation of beta-blockers	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any beta-blockers during the 6 weeks preceding the first date of OAC delivery and with no filled prescription for the medication during the previous 180 days *ATC codes: C07xxxx* Equals to "No" in other cases
Use of beta-blockers	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any beta-blockers during the 6 weeks preceding the first date of OAC delivery *ATC codes: C07xxxx* Equals to "No" in other cases
Initiation of antiarrhythmics	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antiarrhythmics during the 6 weeks preceding the first date of OAC delivery and with no filled prescription for the medication during the previous 180 days *ATC codes: C01Bxxx* Equals to "No" in other cases
Use of antiarrhythmics	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antiarrhythmics during the 6 weeks preceding the first date of OAC delivery *ATC codes: C01Bxxx* Equals to "No" in other cases

Initiation of antihypertensive drugs	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antihypertensive drug during the 6 weeks preceding the first date of OAC delivery and with no filled prescription for the medication during the previous 180 days *ATC codes: C02xxxx, C03xxxx, C08xxxx, C09xxxx (excluding C03BA08 and C03CA01)* Equals to "No" in other cases
Use of antihypertensive drugs	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antihypertensive drug during the 6 weeks preceding the first date of OAC delivery *ATC codes: C02xxxx, C03xxxx, C08xxxx, C09xxxx (excluding C03BA08 and C03CA01)* Equals to "No" in other cases
Holter procedure	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one Holter procedure during the 6 weeks preceding the first date of OAC delivery *CCAM codes: DEQA001, DEQP001, DEQP002, DEQP003, DEQP005, DEQP006* Equals to "No" in other cases
Echocardiography procedure	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one echocardiography procedure during the 6 weeks preceding the first date of OAC delivery *CCAM codes: DZQJ001, DZQJ006, DZQJ009, DZQJ010, DZQJ011, DZQM006.* Equals to "No" in other cases
Thyroid function test	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one thyroid function test during the 6 weeks preceding the first date of OAC delivery *NABM Codes: 1206-1212, 1803.* Equals to "No" in other cases
D-dimer blood test	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one D-dimer blood test during the 6 weeks preceding the first date of OAC delivery

	NABM codes:1021, 1022. Equals to "No" in other cases
Hospitalization for arterial thromboembolic event	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized at least once with any discharge diagnosis (i.e., principal, related or associated diagnosis) of arterial thromboembolic event (ischemic stroke or transient ischemic attack or systemic arterial embolism) during the 6 weeks preceding the first date of OAC delivery *ICD-10 codes: I63 (ischemic stroke) except I63.6 (cerebral infarction due to cerebral venous thrombosis, non-pyogenic), G45 (transient ischemic attack), I74, N28, D73.5, K76.3 (systemic arterial embolism).* Equals to "No" in other cases

Then, all the variables representing the exclusion criteria will be derived for each AF patients included after the inclusion criteria and the application of the algorithm (Table IV).

Table IV. Derived variable for the selection of the population – Exclusion criteria

Variable	Definition
Valvular pathology	Binary variable (Yes/No) Equals to "Yes" if the patient is hospitalized at least once with any discharge diagnosis (i.e., principal, related or associated diagnosis) of valve disease or valve surgery, during historical or inclusion period *ICD-10 codes: I05.x, I06.x, I07.x, I08.x, I09.x, I34.x, I39.x* *CCAM codes (valve surgery): DBAF003, DBAF002, DBAF005, DBAF004, DBAF001, DBPA002, DBPA004, DBPA005, DBPA006, DBPA007, DBMA008, DBMA012, DBMA003, DBMA002, DBMA011, DBKA004, DBKA008, DBKA007, DBKA012, DBKA010, DBKA005, DBKA002, DBKA006, DBKA003, DBKA001, DBKA011, DBKA009, DBMA007, DBMA013, DBMA005, DBMA009, DBMA010, DBMA006, DBMA001, DBMA015, DBMA004, DBLF009, DBLF001, DBLA004, DBBF198, DBSF001, DBEA001.* Equals to "No" in other cases
Standard SNDS exclusion criteria	Binary variable (Yes / No) *See Data Management Plan in section* ***Error! Reference source not found.***

Moreover, all the variables used to define the sub-populations will be derived for each patient selected in the study population (Table V).

Table V. Derived variables for the selection of the populations – Sub-populations

Variable	Definition
Age ≥80 years old	Binary variable (<80 years old / ≥80 years old) Derived based on the date of birth attributed to the patient after cleaning the data extraction Equals to: 13. "<80 years old" if the absolute difference between the year of index date and the year of birth is strictly lower than 80 years old 14. "≥80 years old" if the absolute difference between the year of index date and the year of birth is upper than 80 years old *See also Data Management Plan in section* ***Error! Reference source not found.***
History of coronary arterial disease (CAD)	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: *15.* Is hospitalized with any diagnosis (i.e., main, related or associated diagnosis) of coronary arterial disease *ICD-10 codes: I21.x, I22.x, I24.x, I25.x* OR – Is covered by the LTD status for coronary arterial disease at least one day *ICD-10 codes: I21.x, I22.x, I24.x, I25.x* Equals to "No" in other cases
Claims-based Frailty Index (CFI) (for frail patients' derivation)	Continuous variable (between 0 and 1) Claims-based frailty index (CFI) estimates a deficit-accumulation frailty index from a clinical assessment using International Classification of Diseases (ICD) diagnosis codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes in the prior 2 years in administrative claims data. *See more details on calculation of CFI in Appendix 22*
Frail patients	Binary variable (Yes / No) Equals to "Yes" if the Claims based Frailty Index (CFI) is upper or equal to 0.20 *See Table Ivariable* ***Claims based Frailty Index (CFI)***
Active cancer	Binary variable (Yes / No)

	Equals to "Yes" if the patient meets any criterion below in the 2 years before index date: 16. Is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of active cancer *ICD-10 codes: C00.x to C80.x, D00.x to D09.x, D37.x to D48.x, Z51.0, Z51.1* OR – Is covered by the LTD status for active cancer at least one day *ICD-10 codes: C00.x to C80.x, D00.x to D09.x, D37.x to D48.x, Z51.0, Z51.1* Equals to "No" in other cases
Previous stroke	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: 17. Is hospitalized at least once with any discharge diagnosis (i.e., main, related or associated diagnosis) of stroke (ischemic or haemorrhagic) *ICD-10 codes: I60.x, I61.x, I62.9, I63.x, I64.x, G45.x, G46.x, G81.x, S06.4, S06.5, S06.6* OR – Is covered by the LTD status for stroke (ischemic or haemorrhagic) at least one day *ICD-10 codes: I60.x, I61.x, I62.9, I63.x, I64.x, G45.x, G46.x, G81.x, S06.4, S06.5, S06.6* Equals to "No" in other cases

Moreover, all the variables used to define stratification groups will be derived for each patient selected in the study population (Table VII).

Table VI. Derived variables for the selection of the population – Stratifications

Variable	Definition
Age groups	Categorical variable (<80, 80-90, >90 years old) *See Table III*
Heart failure history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Derived based on (24)

	Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of cardiac failure *ICD-10 codes: I50.x, I11.0, I13.0, I13.2, I13.9* OR – Is covered by the LTD status for cardiac failure at least one day *ICD-10 codes: I50.x, I11.0, I13.0, I13.2, I13.9* Equals to "No" in other cases
Hypertension history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Derived based on (24) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the specified date: – Is hospitalized with any diagnosis (i.e., main, related or associated diagnosis) of hypertension *ICD-10 codes: I10.x, I11.x, I12.x, I13.x, I15.x, I67.4* OR – Is covered by the LTD status hypertension at least one day *ICD-10 codes: I10.x, I11.x, I12.x, I13.x, I15.x, I67.4* OR – Has reimbursements for at least 3 dispensations at pharmacy of any antihypertensive drug *ATC codes: C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA02, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, ,C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DA02, C03DA04, C03DB01, C03EA, C03EA01, C03EA04, C03EB01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07AG02, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA06, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08EA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15,*

	C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03 OR – Has reimbursements for 2 dispensations at pharmacy of any antihypertensive drug, of which at least one in a package containing >80 pills *ATC codes: C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA02, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, ,C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DA02, C03DA04, C03DB01, C03EA, C03EA01, C03EA04, C03EB01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07AG02, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA06, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08EA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03*</td></tr>
Age groups (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Categorical variable (<65, 65-74, ≥75 years old) *See Table III*
Diabetes history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Derived based on (24) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date:

	– Is hospitalized with a main or related diagnosis of diabetes *ICD-10 codes : E10.x, E11.x, E12.x, E13.x, E14.x* OR – Is hospitalized with the two criteria: o A main or related diagnosis of complication of diabetes *ICD-10 codes: G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3* AND o A significant associated diagnosis of diabetes *ICD-10 codes : E10.x, E11.x, E12.x, E13.x, E14.x* OR – Is covered by the LTD status for diabetes at least one day *ICD-10 codes : E10.x, E11.x, E12.x, E13.x, E14.x* OR – Has reimbursements for at least 3 dispensations at pharmacy of any glucose-lowering drug *ATC codes: A10Axx, A10Bxx excepted for A10BX06* OR – Has reimbursements for 2 dispensations at pharmacy of any glucose-lowering drug, of which at least one in a package containing >80 pills *ATC codes: A10Axx, A10Bxx excepted A10BX06* Equals to "No" in other cases
Previous Stroke (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) *See Table V*
Previous Transient Ischemic Attack (TIA) (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized at least once with any discharge diagnosis (i.e., main, related or associated diagnosis) of TIA, on or in the 2 years prior to the index date *ICD-10 codes:* G45 Equals to "No" in other cases
Previous systemic arterial embolism (TE)	Binary variable (Yes / No)

(for Modified $CHAD_2DS_2VASC$ score strata derivation)	Equals to "Yes" if the patient is hospitalized at least once with any discharge diagnosis (i.e., main, related or associated diagnosis) of TE, on or in the 2 years prior to the index date *ICD-10 codes: I74, N28, D73.5, K76.3*
Previous Stroke, TIA, or TE (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Equals to "Yes" if the variable **Previous stroke** = "Yes" *(see Table V)* or the variable **Previous Transient Ischemic Attack (TIA)** = "Yes" or the variable **Previous Thromboembolism (TE)** = "Yes" Equals to "No" in other cases
Myocardial infarction history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of myocardial infarction *ICD-10 codes: I21.x, I22.x, I25.2, I25.5* OR – Is covered by the LTD status for myocardial infarction history at least one day *ICD-10 codes: I21.x, I22.x, I23.x* Equals to "No" in other cases.
Peripheral artery disease (PAD) history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of peripheral artery disease on or in the 2 years prior to the index date *ICD-10 codes: I70-I74, I771* Equals to "No" in other cases
Vascular disease history (for Modified $CHAD_2DS_2VASC$ score strata derivation)	Binary variable (Yes / No) Equals to "Yes" if the variable **Myocardial infarction** = "Yes" or the variable **Peripheral artery disease** = "Yes" Equals to "No" in other cases
$CHAD_2DS_2VASC$ score	Continuous variable (between 1 and 9) Derived based on (18) Equals to sum of: ○ 1 point if the variable **Heart failure history** equals to "Yes"

	○ 1 point if the variable **Hypertension history** equals to "Yes" ○ 1 point if the variable **Age** equals to "65-74" and 2 points if the variable **Age** equals to "≥75 years old" ○ 1 point if the variable **Diabetes history** equals to "Yes" ○ 2 points if the variable **Previous Stroke, TIA, or TE** equals to "Yes" ○ 1 point if the variable **Vascular disease history** equals to "Yes" ○ 1 point if the variable **Gender** equals to "Female" (*See Table III*)
Modified $CHAD_2DS_2VASC$ score strata	Categorical variable (Low / Moderate / High) For **Gender** = "Male" (*see Table III*), equals to: – "Low" if **Modified $CHAD_2DS_2VASC$ score**=0 – "Moderate" if **Modified $CHAD_2DS_2VASC$ score**=1 – "High" if **Modified $CHAD_2DS_2VASC$ score**≥2 For **Gender** = "Female" (*see Table III*), equals to: – "Low" if **Modified $CHAD_2DS_2VASC$ score**=1 – "Moderate" if **Modified $CHAD_2DS_2VASC$ score**=2 – "High" if **Modified $CHAD_2DS_2VASC$ score**≥3
History of ischemic / haemorrhagic stroke	Binary variable (Ischemic / Haemorrhagic) Derived if **Previous stroke** = "Yes" (see *Table V*) Equals to "Ischemic" if **Previous stroke** = "Yes" with ICD-10 codes below: *I63.x (except I63.6 – cerebral infarction due to cerebral venous thrombosis, non-pyogenic), I64.x, G45.x, G46.x, G81.x* Equals to "Haemorrhagic" if **Previous stroke** = "Yes" with ICD-10 codes below: *I60.x, I61.x, I62.9, S06.4, S06.5, S06.6*
Malnutrition	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main or related diagnosis) of malnutrition on or in the 2 years prior to the index date *ICD-10 codes : E43, E44.0, E44.1, E46* Equals to "No" in other cases
Risk of falls	Binary variable (Yes / No) Patients at risk of falls identified by an algorithm adapted to SNDS data (22) *ICD-10 codes:* • Fractures: S12xxx, S22xxx, S32xxx, S42xxx, S52xxx, S62xxx, S72xxx, S82xxx, T02xx, T08xx, T12xx, T13xx (including open

	and closed fractures, 5th digit = 0 : closed fracture, 5th digit = 1 : open fracture) • Parkinson disease, and other extrapyramidal and movement disorders: G20-G26 (G22*, G26* excluded) • Demyelinating diseases of the central nervous system, ataxias: G35-G37, G11, R26, R27 *ATC codes:* C02A (Centrally acting antihypertensives), N05A (N05AN excluded) (antipsychotics), N05B (anxiolytics), N06AX21, N06AA09, N06AA12, N06AX03, N06AX11, N06AA05 (sedative antidepressants), R06AD01, R06AB01, R06AB51, R06AA08, R06AB02, R06AB52, R06AA09, R06AA59, N05BB01, N05BB51, R06AX17, R06AE05, R06AD07, R06AX25, R06AE06, R06AD08, R06AD02, R06AD52, R06AX28 (sedative antihistamines), N05CD (benzodiazepines), N05CF (Z-drugs)
Frail patients	Binary variable (Yes / No) *See Table VTable I*
Morbid obesity	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main or related diagnosis) of obesity on or in the 2 years prior to the index date *ICD-10 codes: E66.x* Equals to "No" in other cases
History of major bleeding	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main or related diagnosis) of major bleeding on or in the 2 years prior to the index date *ICD-10 codes: I60.x, I61.x, I62.9, S06.4, S06.5, S06.6, I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2, D62, H35.6, H43.1 H45.0, H92.2, I31.2, J94.2, R04.x, K66.1, M25.0, N02, N93.8, N93.9, N95.0, R31, R58, T79.2* Equals to "No" in other cases
At least one visit to a nursing home	Binary variable (Yes / No) Equals to "Yes" if the patient has at least one reimbursement corresponding to a nursing home on or in the 2 years prior to the index date
History of dementia	Binary variable (Yes / No)

	Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized with a main or related diagnosis of dementia *ICD-10 codes: F00.x, F01.x, F02.x, F03.x, F05.1, G30.x, G31.1* OR – Is covered by the LTD status for dementia at least one day *ICD-10 codes: F00.x, F01.x, F02.x, F03.x, F05.1, G30.x, G31.1* OR – Has reimbursements for at least 3 dispensations at pharmacy of any anti-Alzheimer drugs *ATC codes : N06DA01, N06DA02, N06DA03, N06DA04, N06DX01* Equals to “No” in other cases
History of diabetes	Binary variable (Yes / No) See the variable **Diabetes history** (for Modified $CHAD_2DS_2VASC$ score strata derivation)
History of diabetes with complications	Binary variable (Yes / No) Derived only if the variable **History of diabetes** equals to “Yes” Equals to “Yes” if the patient is hospitalized with the two criteria: – A main or related diagnosis of complication of diabetes *ICD-10 codes: G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3* AND – A significant associated diagnosis of diabetes *ICD-10 codes : E10.x, E11.x, E12.x, E13.x, E14.x* Equals to “No” in other cases
History of myocardial infarction	Binary variable (Yes / No) Derived based on (20,23) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of moderate-to-severe liver failure *ICD-10 codes: I21;I22;I252;I255*

	OR – Is covered by the LTD status for myocardial infarction at least one day *ICD-10 codes: I21;I22;I252;I255* Equals to "No" in other cases
Congestive heart failure (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of congestive heart failure *ICD-10 codes: I110;I130;I132;I50* OR – Is covered by the LTD status for congestive heart failure at least one day *ICD-10 codes: I110;I130;I132;I50* Equals to "No" in other cases
Peripheral vascular disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of peripheral vascular disease *ICD-10 codes: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9* OR – Is covered by the LTD status for peripheral vascular disease at least one day *ICD-10 codes: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9* Equals to "No" in other cases
Cerebrovascular disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date:

	– Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of cerebrovascular disease *ICD-10 codes: G45.x, G46.x, H34.0, I60.x, I61.x, I62.x, I63.x, I64.x, I65.x, I66.x, I67.x, I68.x, I69.x* OR – Is covered by the LTD status for cerebrovascular disease at least one day *ICD-10 codes: G45.x, G46.x, H34.0, I60.x, I61.x, I62.x, I63.x, I64.x, I65.x, I66.x, I67.x, I68.x, I69.x* Equals to "No" in other cases
Moderate-to-severe renal disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of moderate-to-severe renal disease *ICD-10 codes: I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18.x, N19.x, N25.0, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2* OR – Is covered by the LTD status for moderate-to-severe renal disease at least one day *ICD-10 codes: I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18.x, N19.x, N25.0* OR – Has at one reimbursement for a dialysis session performed at hospital or in outpatient settings *ICD-10 codes: Z94.1, Z94.2* *CCAM codes: JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008, YYYY007* *PRS codes: 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2142, 2143, 2144, 2145, 2146, 2147, 2334* *GHM codes: 28Z01Z, 28Z02Z, 28Z03Z, 28Z04Z, 11K021, 11K022, 11K023, 11K024, 11K02J*

	Equals to “No” in other cases
Mild liver disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of mild liver failure *ICD-10 codes: B18.x, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73.x, K74.x, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4* OR – Is covered by the LTD status for mild liver disease at least one day *ICD-10 codes: B18.x, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73.x, K74.x, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9* Equals to “No” in other cases
Moderate-to-severe liver disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of moderate-to-severe liver failure *ICD-10 codes: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7* OR – Is covered by the LTD status for moderate-to-severe liver disease at least one day *ICD-10 codes: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7* Equals to “No” in other cases
Chronic pulmonary disease (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date:

	– Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of chronic pulmonary disease *ICD-10 codes: I27.8, I27.9, J40.x, J41.x, J42.x, J43.x, J44.x, J45.x, J46.x, J47.x, J60.x, J61.x, J62.x, J63.x, J64.x, J65.x, J66.x, J67.x, J68.4, J70.1, J70.3* OR – Is covered by the LTD status for chronic pulmonary disease at least one day *ICD-10 codes: I27.8, I27.9, J40.x, J41.x, J42.x, J43.x, J44.x, J45.x, J46.x, J47.x, J60.x, J61.x, J62.x, J63.x, J64.x, J65.x, J66.x, J67.x, J68.4, J70.1, J70.3* OR – Has reimbursements for at least 3 dispensations at pharmacy of any antibronchodilator drugs *ATC codes: R03AB03, R03AC02, R03AC03, R03AC04, R03AC08, R03AC12, R03AC13, R03AC18, R03AK03, R03AK04, R03AK06, R03AK07, R03BA01, R03BA02, R03BA03, R03BA05, R03BB01, R03BB02, R03BB04, R03BC01, R03BC03, R03CC02, R03CC03, R03CC12, R03DA04, R03DA05, R03DA08, R03DC03, R03DX03, R03DX05* Equals to “No” in other cases
Dementia (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized with a main or related diagnosis of dementia *ICD-10 codes: F00.x, F01.x, F02.x, F03.x, F05.1, G30.x, G31.1* OR – Is covered by the LTD status for dementia at least one day *ICD-10 codes: F00.x, F01.x, F02.x, F03.x, F05.1, G30.x, G31.1* OR – Has reimbursements for at least 3 dispensations at pharmacy of any anti-Alzheimer drugs *ATC codes: N06DA01, N06DA02, N06DA03, N06DA04, N06DX01* Equals to “No” in other cases

Connective tissue disease	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of connective tissue disease *ICD-10 codes: M05.x, M06.x, M31.5, M32.x, M33.x, M34.x, M35.1, M35.3, M36.0* OR – Is covered by the LTD status for connective tissue disease at least one day *ICD-10 codes: M05.x, M06.x, M31.5, M32.x, M33.x, M34.x, M35.1, M35.3, M36.0* Equals to "No" in other cases.
Ulcer disease	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of ulcer disease *ICD-10 codes: K25.x, K26.x, K27.x, K28.x* OR – Is covered by the LTD status for ulcer disease at least one day *ICD-10 codes: K25.x, K26.x, K27.x, K28.x* Equals to "No" in other cases
Hemiplegia (for ACCI derivation)	Binary variable (Yes / No) Derived based on (20,23) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of hemiplegia *ICD-10 codes: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9* OR – Is covered by the LTD status for hemiplegia at least one day

	ICD-10 codes: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9 Equals to "No" in other cases
HIV-AIDS (for ACCI derivation)	Binary variable (Yes / No) Derived based on (24) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of HIV-AIDS *ICD-10 codes : B20.x, B21.x, B22.x, B24.x, F02.4, Z21.x* OR – Is covered by the LTD status for HIV-AIDS at least one day *ICD-10 codes : B20.x, B21.x, B22.x, B24.x, F02.4* OR – Has reimbursements for at least 3 dispensations at pharmacy of any anti-retroviral drugs specific to the treatment of HIV-AIDS *ATC codes: 05AF01, J05AF02, J05AF03, J05AF04, J05AF06, J05AF13, J05AG01, J05AG03, J05AG04, J05AG05, J05AR01, J05AR02, J05AR04, J05AE01, J05AE02, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AR10, J05AR06, J05AR08, J05AR09, J05AR13, J05AR18, J05AR19, J05AX07, J05AX08, J05AX09, J05AX12* OR – Has at least one reimbursement for a biological test specific to the treatment of HIV-AIDS *NABM codes: 0805, 0806, 1691, 4117, 4122* Equals to "No" in other cases
Any tumor (including lymphoma and leukemia except for malignant neoplasm of skin) (for ACCI derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any discharge diagnosis (i.e., main, related or associated diagnosis) of any tumor (including lymphoma and leukemia except for malignant neoplasm of skin) *ICD-10 codes :* C00-C26 ;C30-C34 ;C37-C41 ;C43 ; C45-C58 ; C60-C76 ;C81-C85 ;C88 ; C90-C97 OR

	– Is covered by the LTD status for any tumor (including lymphoma and leukemia except for malignant neoplasm of skin) at least one day *ICD-10 codes :* C00-C26 ; C30-C34 ; C37-C41 ; C43 ; C45-C58 ; C60-C76 ; C81-C85 ; C88 ; C90-C97 Equals to "No" in other cases
Solid metastatic tumor (for ACCI derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any discharge diagnosis (i.e., main, related or associated diagnosis) of metastatic tumor *ICD-10 codes : C77.x, C78.x, C79.x, C80* OR – Is covered by the LTD status for metastatic tumor at least one day *ICD-10 codes : C77.x, C78.x, C79.x, C80* Equals to "No" in other cases
Age adjusted Charlson Cormordity Index (ACCI) adapted to the SNDS data	Continuous variable (point) Derived based on (20,23) Equals to the sum of: ○ 0 point if the variable **History of diabetes** equals to "Yes" ○ 0 point if the variable **History of diabetes with complications** equals to "Yes" ○ 0 point if the variable **History of myocardial infarction** equals to "Yes" ○ 2 points if the variable **Heart failure** equals to "Yes" ○ 1 point if the variable **Peripheral vascular disease** equals to "Yes" ○ 1 point if the variable **Cerebrovascular disease** equals to "Yes" ○ 1 point if the variable **Moderate-to-severe renal disease** equals to "Yes" ○ 2 points if the variable **Mild liver disease** equals to "Yes" ○ 3 points if the variable **Moderate-to-severe liver disease** equals to "Yes" ○ 1 point if the variable **Chronic pulmonary disease** equals to "Yes" ○ 2 points if the variable **Dementia** equals to "Yes"

	○ 0 point if the variable **Connective tissue disease** equals to "Yes" ○ 0 point if the variable **Ulcer disease** equals to "Yes" ○ 2 points if the variable **Hemiplegia** equals to "Yes" ○ 1 point if the variable **HIV-AIDS** equals to "Yes" ○ 2 points if the variable **Any tumor (including lymphoma and leukemia)** equals to "Yes" ○ 11 points if the variable **Solid metastatic tumor** equals to "Yes" ○ 1, 2, 3, 4, 5 or 6 points if the variable **Age** is greater or equal than 50, 60, 70, 80 90 or 100 years old, respectively
ACCI group	Categorical variable (0, 1-2pts / 3-4pts / ≥5 pts) Derived based on ACCI define above Equals to: "0" if ACCI is equal to 0 (the patient has no comorbidities) "1-2pts" if ACCI is greater than 0 and less or equal to 2 "3-4pts" if ACCI is greater than 2 and less or equal to 4 "≥5pts" if ACCI is greater or equal than 10

9.4.2 Derived Variables for the Primary Objective

The incidence rate for each event of interest (stroke, major bleeding and death) in AF incidents patients between 2016 and 2019 will be derived by treatment exposure sequence and by unexposed sequence, for overall and by sub-populations (see section 9.2.3.4).

First the treatment exposure sequences will be derived (Table VII). A patient could have several lines i.e., one line by patient by treatment sequence.

Table VII. Derived variables for identification of treatment exposure or unexposed sequences

Variable	Definition
Start date of treatment sequence	Date variable Equals to the date of the first delivery of each specific treatment (VKA, Apixaban, Rivaroxaban or Dabigatran) of the sequence *ATC codes: B01AA, B01AF02, B01AF01, B01AE07 (respectively)*
End date of treatment sequence	Date variable The end date of treatment sequence is defined as: – The day before the date of first delivery of another OAC if the patient switches to another OAC OR

	– Date of the last delivery of treatment sequence supplemented by 30 days (treatment duration), at the condition that there is no other OAC reimbursement in the next 60 days *ATC codes: B01AA, B01AF02, B01AF01, B01AE07* For sensitivity analyses: duration of 30 days and 90 days of maximal number of days allowed for being refilled will be considered.
Treatment sequence	Category variable (VKA / Apixaban / Rivaroxaban / Dabigatran) Equals to "VKA / Apixaban / Rivaroxaban / Dabigatran" if the patient has a reimbursement of VKA, Apixaban, Rivaroxaban or Dabigatran during the treatment sequence *ATC codes: B01AA, B01AF02, B01AF01, B01AE07(respectively)*
Start date of unexposed sequence	Date variable The start date of unexposed sequence is defined as: – The index date for AF patients without an OAC reimbursement in 30 days after the index date *(for sensitivity analyses, the inclusion date will be the index date for all incident patients, whether or not patients received OAC therapy within 30 days of the inclusion date)* OR – The day after the **End date of treatment sequence** if the patient has stopped an OAC (at the condition that there is no other OAC reimbursement in the next 60 days, period defined as "the grace period")
End date of unexposed sequence	Date variable The end date of unexposed sequence is defined as: – The day before the **Start date of treatment sequence** if the patient starts an OAC OR – End of follow-up period in other cases

Second, each event of interest with the occurred dates available in the data extraction for the AF patients in France during their follow-up will be derived by treatment exposure sequence as indicated in Table VIII.

Table VIII. Derived variables for identifying events of interest

Variable	Definition
Stroke (ischemic or hemorrhagic)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of stroke (ischemic or haemorrhagic)

	ICD-10 codes: I60.x, I61.x, I62.9, I63.x, I64.x, G45.x, G46.x, G81.x, S06.4, S06.5, S06.6 Equals to "No" in other cases
Major bleeding	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of major bleeding *ICD-10 codes: I60.x, I61.x, I62.9, S06.4, S06.5, S06.6, I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2, D62, H35.6, H43.1 H45.0, H92.2, I31.2, J94.2, R04.x, K66.1, M25.0, N02, N93.8, N93.9, N95.0, R31, R58, T79.2* Equals to "No" in other cases
Death	Binary variable (Yes / No) Equals to "Yes" if the date of death is reported in DCIR Equals to "No" in other cases
Date of occurrence	Date variable Equals to the value of date when occurred the event

In the case of a patient presents an event of interest during the grace period, which ends after the end of the study, the event will be considered neither in an exposed nor in an unexposed period, and the patient will be censured at the end of the study period.

Then, the variable presented in Table IXTable X will be derived for the analyses of incidence, for each patient, for each event of interest and for each exposure treatment sequence.

Table IX. Derived variables for the analyses of incidence rate on events of interest

Variable	Definition
Number of occurrences	Continuous variable Equals to the number of occurrences where the two criteria are met: – The variable of the specified event of interest (**Stroke**, **Major bleeding** or **Death**) equals "Yes" – The value of the variable **Date of occurrence** falls in the specific OAC treatment sequence period for exposed patient and during unexposed sequence period for unexposed patient In

And finally, the following variables in Table X will be derived for all patients selected in the study population.

Table X. Derived variables for study population

Variable	Definition
Incident AF patient	Binary variable (Yes / No) Equals to "Yes" if: – The patient is newly diagnosed AF during the inclusion period (i.e. no AF diagnostic during the historical period) AND – No reported events of interest (stroke, major bleeding, and death) between the inclusion date and the first date of OAC delivery among AF patients with at least one dispensation of OAC identified within 30 days from inclusion date (cf. 9.2.3.1. Inclusion Criteria) Equals to "No" in other cases *Sensitivity analyses on incidence rate of stoke, major bleeding and death, and comparison of these events in regression analyzes will be performed on all newly diagnosed AF during the inclusion period (i.e. no exclusion of patients with reported events of interest between inclusion date and index date among those with at least one dispensation of OAC identified within 30 days from inclusion date).*
Gender	Binary variable (Female / Male) *See Table III* ***Error! Reference source not found.***
Age	Categorical variable (<65 years old / 65-74 / 75-79 / ≥80 years old) *See Table III*
Death	Binary variable (Yes / No) *See Table III*
Lost to follow-up	Binary variable (Yes / No) Equal to "Yes" if the patient has no consumption or reimbursement of care in the 12 months following the date of last consumption Equals to "No" in other cases

9.4.3 Derived Variables for the Secondary Objectives

9.4.3.1 To describe the characteristics of AF patients exposed and unexposed to OAC

The sociodemographic characteristics, comorbidities, medical history of interest and concomitant treatments (respectively Table XII, Table XIII and Table XIV) will be derived at start follow-up date for AF incident patients exposed and unexposed to OAC (Table XI).

Table XI. Derived variables for exposition to OAC

Variable	Definition
Exposed to OAC at index date	Binary variable (Exposed to OAC/Unexposed to OAC) Equals to 'Exposed to OAC' if the patient has at least one delivery of AOC (VKA, Apixaban, Dabigatran or Rivaroxaban) at index date (defined in 9.2.1.4) *ATC codes: B01AA, B01AF02, B01AF01, B01AE07* Equals to 'Unexposed to OAC' if the patient has no reimbursement for AOC at index date (defined in 9.2.1.4)Table III
Treatment at index date	Categorical variable (VKA/Apixaban/Dabigatran/Rivaroxaban/Unexposed) Equals to "VKA" if the patient has one reimbursement of VKA at -index date Equals to "Apixaban" if the patient has one reimbursement of Apixaban at index date Equals to "Dabigatran" if the patient has one reimbursement of Dabigatran at index date Equals to "Rivaroxaban" if the patient has one reimbursement of Rivaroxaban at index date Equals to "Unexposed" if the patient has any reimbursement of OAC at index date

Table XII. Derived variables for the sociodemographic characteristics

Variable	Definition
Age	Continuous variable (year) *See Table III*
Sex	Binary variable (Female / Male) *See Table III*
Complimentary universal health care (CMU-c)	Binary variable (Yes / No) Equals to "Yes" if the patient benefits from an exemption from care on the grounds of CMU-c for care received on the index date Equals to "No" in other cases
Aid for complementary health care (ACS) for elderly patients	Binary variable (Yes / No) Equals to "Yes" if the patient benefits from an aid for complementary health care on the index date Equals to "No" in other cases

Region of residence	Categorical variable (*Ile de France, Centre-Val de Loire, Corse, etc.*) Derived based on the code of the department of residence recorded with health cares carried out on index date
Frail patient	Binary variable (Yes / No) *See Table VI*
Modified $CHAD_2DS_2VASC$ score strata	Categorical variable (Low / Moderate / High) *See Table VI*
Hypertension (for HAS-BLED score derivation)	Binary variable (Yes / No) *See Table VI*
Abnormal renal (for HAS-BLED score derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main,related or associated diagnosis) of renal failure on or in the 2 years prior to the index date: *ICD-10 codes: N17-N19* *OR* Equals to "Yes" if the patient is covered by the LTD status for renal failure at least one day *ICD-10 codes: N17- N19* *OR* Equals to "Yes" if the patient has received dialysis sessions *CCAM codes: JVJF004, JVJF008, JVRP004, JVJB001, JVRP007, JVRP008, YYYY007* *PRS codes : 2121, 2122, 2123, 2126, 2129, 2131, 2132, 2134, 2135, 2136, 2139, 2147, 2334, 2124, 2125, 2127, 2128, 2137, 2138, 2140, 2142, 2143, 2144, 2145, 2146* *GHM codes : 11K021, 11K022, 11K023, 11K024, 11K02J, 28Z03Z, 28Z04Z, 28Z01Z, 28Z02Z* Equals to "No" in other cases
Liver function (for HAS-BLED score derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of chronic hepatic disease on or in the 2 years prior to the index date: *ICD-10 codes:* K70-K77 *OR*

	Is covered by the LTD status for chronic hepatic disease at least one day *ICD-10 codes:* K70- K77 Equals to "No" in other cases
Previous Stroke (for HAS-BLED score derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of ischemic/undefined stroke or transient ischemic attack (TIA) on or in the 2 years prior to the index date: *ICD-10 codes: I63, I64, G45, G46, G81* *OR* Is covered by the LTD status for stroke at least one day *ICD-10 codes: I63, I64, G45, G46, G81* Equals to "No" in other cases
Bleeding history or predisposition (for HAS-BLED score derivation)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with hospital-discharge summary with primary diagnosis of bleeding on or in the 2 years prior to the index date: *ICD-10 codes: D62, D683, D698, D699, H113, H313, H356, H431, H450, H922, I230, I312, I600-I616, I618-I621, I629, I850, I983, J942, K250, K252, K254, K256, K262, K264, K270, K272, K274, K276, K280, K282, K284, K286, K661, K920, K921, K922, M250, N020-N029, N421, N920, N921, N923, N924, N938, N939, N950, R040, R041, R042, R048, R049, R31, R58, S064, S065, S066, S260, S271, T792* Equals to "No" in other cases
Labile international normalized ratio (INR) (for HAS-BLED score derivation)	Binary variable (Yes / No) Not applicable to SNDS data (INR results are not captured in SNDS databases).
Elderly (for HAS-BLED score derivation)	Binary variable (≤65 years old / >65 years old)
Drugs predisposing to bleeding or alcohol concomitantly (for HAS-BLED score derivation)	Binary variable (Yes / No) Variable **Drugs** equals to "Yes" if the patient has at least one drug dispensation for antiplatelet agents (acetylsalicylic acid: B01AC06 ATC code, clopidogrel: B01AC04 ATC code) or NSAIDs (M01A ATC code) in the 4 months before the index date. OR

	Variable **Alcohol** equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of all causes related to alcohol on or in the 2 years prior to the index date: *ICD-10 codes : E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, R780, T51, X45, X65, Y15, Y90, Y91, Y573, Z502, Z714, Z721.* Equals to "No" in other cases
HAS-BLED score	Continuous variable (between 1 and 9) Derived based on (19) Equals to sum of: ○ 1 point if the variable **Hypertension** equals to "Yes" ○ 1 or 2 points if the variable **Abnormal renal and liver function** equals to "Yes" (1 point each) ○ 1 point if the variable **Stroke** equals to "Yes" ○ 1 point if the variable **Bleeding** equals to "Yes" ○ 1 point if the variable **Labile INRs** equals to "Yes" ○ 1 point if the variable **Elderly** equals to ">65 years old" ○ 1 or 2 points if the variable **Drugs or alcohol** equals to "Yes" (1 point each)
Contraindications to OAC	Binary variable (Yes/No) Equals to "Yes" if the patient presents at least one contraindication to OAC among the followings: • End-stage renal disease on dialysis • Diseases of the blood and blood-forming organs • Certain disorders involving the immune mechanism • Recent history of acute bleeding gastric or duodenal ulcer • Hepatic cirrhosis or fibrosis or liver failure Equals to "No" in other cases.
Chronic renal disease (for contraindications to OAC)	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – A main or related discharge diagnosis of renal transplantation *ICD-10 code: Z94.0* OR

	– A renal transplantation surgery *CCAM: JAEA003, HNEA002* OR – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of chronic renal disease *ICD-10 codes: N18.x* OR – Is covered by the LTD status for chronic renal disease at least one day *ICD-10 codes: N18.x* OR – Has received ≥19 hemodialysis sessions in inpatient or outpatient settings *CCAM codes : JVJF004, JVJF008, JVRP004* *PRS codes : 2121, 2122, 2123, 2126, 2129, 2131, 2132, 2134, 2135, 2136, 2139, 2147, 2334* *GHM codes : 11K021, 11K022, 11K023, 11K024, 11K02J, 28Z03Z, 28Z04Z* OR – Has received ≥1 peritoneal dialysis session in inpatient or outpatient settings *CCAM codes: JVJB001, JVRP007, JVRP008, YYYY007* *PRS codes : 2124, 2125, 2127, 2128, 2137, 2138, 2140, 2142, 2143, 2144, 2145, 2146* *GHM codes : 28Z01Z, 28Z02Z* Equals to “No” in other cases.
Chronic renal disease requiring dialysis (for contraindications to OAC)	Binary variable (Yes / No) Equals to “Yes” if the patient meets any criterion below on or in the 2 years prior to the index date: – Has the value “Yes” for the variable **Chronic renal disease** AND – Has at one reimbursement for a dialysis session performed at hospital or in outpatient settings *CCAM codes: JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008, YYYY007*

	PRS codes : 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2142, 2143, 2144, 2145, 2146, 2147, 2334 *GHM codes : 28Z01Z, 28Z02Z, 28Z03Z, 28Z04Z, 11K021, 11K022, 11K023, 11K024, 11K02J* Equals to "No" in other cases
Diseases of the blood and blood-forming organs (for contraindications to OAC)	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e. principal, related or associated diagnosis in PMSI-MSO) of disease of the blood and blood forming organs during historical period *ICD-10 codes: D55-D77* OR – Is covered by the LTD status for of disease of the blood and blood forming organs ongoing at the index date *ICD-10 codes: D55-D77* Equals to "No" in other cases
Diseases related to immune disorders (for contraindications to OAC)	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e. principal, related or associated diagnosis in PMSI-MSO) of diseases related to immune disorders during historical period *ICD-10 codes: D80-D89* OR – Is covered by the LTD status for diseases related to immune disorders ongoing at the index date *ICD-10 codes: D80-D89* Equals to "No" in other cases
Recent history of acute bleeding gastric or duodenal ulcer (for contraindications to OAC)	Binary variable (Yes/No) Equals to "Yes" if the patient meets any criterion below: – Is hospitalized at least once with any discharge diagnosis (i.e. principal, related or associated diagnosis in PMSI-MSO) of acute bleeding gastric or duodenal ulcer in the 6 months before the index date *ICD-10 codes : K274, K254 ; K284, K264*

	OR – Is covered by the LTD status for acute bleeding gastric or duodenal ulcer ongoing at the 6 months before the index date *ICD-10 codes : K274, K254 ; K284, K264* Equals to "No" in other cases
Hepatic cirrhosis/fibrosis, liver failure (for contraindications to OAC)	Binary variable (Yes / No) Equals to "Yes" if the patient meets any criterion below on or in the 2 years prior to the index date: – Is hospitalized at least once with any diagnosis (i.e., main, related or associated diagnosis) of hepatic impairment *ICD-10 codes: K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7* OR – Is covered by the LTD status for hepatic impairment at least one day *ICD-10 codes: K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7* Equals to "No" in other cases

Table XIII. Derived variables for the medical history and comorbidities

Variable	Definition
Cerebrovascular diseases (CBVD)	Binary variable (Yes / No) *See Table VI*
Coronary arterial diseases (CAD)	Binary variable (Yes / No) *See Table V*
Dementia	Binary variable (Yes / No) *See Table VI*
Congestive Heart failure	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of congestive heart failure, on or in the 2 years prior to the index date OR Is covered by the LTD status for congestive heart failure at least one day *ICD-10 codes: I50.2, I50.3, I50.4* Equals to "No" in other cases

Peripheral arterial disease	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of peripheral arterial disease, on or in the 2 years prior to the index date OR Is covered by the LTD status for peripheral arterial disease at least one day *ICD-10 codes: I70.0-I74, I771* Equals to "No" in other cases
Other vascular diseases	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of peripheral arterial disease or is covered by the LTD status for peripheral arterial disease at least one day, in the 2 years prior to the index date OR Is covered by the LTD status for other vascular diseases at least one day *ICD-10 codes: I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9.* Equals to "No" in other cases,
Sleep disorders	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of sleep disorders, on or in the 2 years prior to the index date *ICD-10 codes: G47.x* Equals to "No" in other cases
Active cancer	Binary variable (Yes / No) *See Table V*
Age adjusted Charlson Comorbidity Index (ACCI) adapted to SNDS data	Continuous variable (point) *See Table V*
Malnutrition	Binary variable (Yes / No) *See Table V*
Morbid Obesity	Binary variable (Yes / No) *See Table V*
Anemia	Binary variable (Yes / No)

	Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of anemia, on or in the 2 years prior to the index date OR Is covered by the LTD status for anemia at least one day *ICD-10 codes : D50.x, D53.x* Equals to "No" in other cases
Chronic obstructive pulmonary disease (COPD)	Binary variable (Yes / No) Equals to "Yes" if the patient is hospitalized with any discharge diagnosis (i.e., main, related or associated diagnosis) of chronic obstructive pulmonary disease, on or in the 2 years prior to the index date OR Is covered by the LTD status for COPD at least one day *ICD-10 codes: J44.9* Equals to "No" in other cases
History of Diabetes	Binary variable (Yes / No) *See Table V*
Risk of falls	Binary variable (Yes / No) *See Table V*
Poly-medicated	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for >= 5 different medications (different ATC5) in the year before the index date. Equals to "No" in other cases (i.e., patient with reimbursement for < 5 different medications in the year before the index date).
At least one visit to a nursing home	Binary variable (Yes / No) *See Table V*
History of major bleeding	Binary variable (Yes / No) *See Table VI*
One or more comorbidities	Binary variable (Yes / No) *See Table VI*

Table XIV. Derived variables for concomitant treatments

Variable	Definition

Beta-blockers	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any beta-blockers, on or in the 4 months prior to the index date *ATC codes: C07xxxx* Equals to "No" in other casesTable V
Antihypertensives	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antihypertensive drug, on or in the 4 months prior to the index date *ATC codes: C02xxxx, C03xxxx, C08xxxx, C09xxxx (excluding C03BA08 and C03CA01)* Equals to "No" in other cases
Antiplatelet drugs	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antiplatelet drug, on or in the 4 months prior to the index date *ATC codes: B01ACxx* Equals to "No" in other cases
Other anticoagulants	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any other anticoagulant, on or in the 4 months prior to the index date *ATC codes: B01ABxx, B01AExx (except B01AE07), B01AFxx (except B01AF01 and B01AF02), B01AXxx* Equals to "No" in other cases
Non-steroidal anti-inflammatory drugs (NSAIDs)	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any NSAID, on or in the 4 months prior to the index date *ATC codes: M01Axxx* Equals to "No" in other cases
Oral corticoids	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any oral corticoid, on or in the 4 months prior to the index date

	ATC codes: H02AB Equals to "No" in other cases
Proton pump inhibitors	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any proton pump inhibitor, on or in the 4 months prior to the index date *ATC codes: A02BC* Equals to "No" in other cases
Selective serotonin reuptake inhibitor antidepressants (SSRIs)	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any SSRI, on or in the 4 months prior to the index date *ATC codes: N06AB* Equals to "No" in other cases
Systemic azole antifungals	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any systemic azole antifungal, on or in the 4 months prior to the index date *ATC codes: J02AB, J02AC* Equals to "No" in other cases
Medical procedure of cardioversion	Binary variable (Yes / No) Equals to "Yes" if the patient has at least one medical procedure of cardioversion, on or in the 4 months prior to the index date *Codes: DERP004, DERP003* Equals to "No" in other cases
CYP P450 inhibitors	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any CYP P450 inhibitors, on or in the 4 months prior to the index date *ATC codes: B01AC24, C05AE03, C09BB10, C01BD01, J01FAxx excepted J01FA02* Equals to "No" in other cases
Protease inhibitors	Binary variable (Yes / No)

	Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any CYP P450 inhibitors, on or in the 4 months prior to the index date *ATC codes: J05AE* Equals to "No" in other cases
Antiarrhythmics	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any antiarythmics, on or in the 4 months prior to the index date *ATC codes: C01BA, C01BB, C01BC, C01BD, C01BG* Equals to "No" in other cases
Glucose-lowering drugs	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any glucose-lowering drugs, on or in the 4 months prior to the index date *ATC codes:* C10AA, C10BA, C10BX; C10AB; C10AX06; C10AX13, C10AX14 Equals to "No" in other cases
Lipid-lowering drugs	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least 3 dispensations at pharmacy of any glucose-lowering drug, on or in the 4 months prior to the index date: *ATC codes: A10Axx, A10Bxx excepted for A10BX06* OR Has reimbursements for 2 dispensations at pharmacy of any glucose-lowering drug, of which at least one in a package containing >80 pills, on or in the 4 months prior to the index date: *ATC codes: A10Axx, A10Bxx excepted A10BX06* Equals to "No" in other cases
Digitalis glycosides	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any digitalis glycosides, on or in the 4 months prior to the index date *ATC codes: C01AA* Equals to "No" in other cases

Nitrate derivatives	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of any nitrates derivatives on or in the 4 months prior to the index date *ATC codes: C01DA* Equals to "No" in other cases

9.4.3.2 *Comparison of the incidence of stroke, major bleeding, death*

The incidence rate ratio for each event of interest (stroke, major bleeding and death; see Table VIII for derivation of events of interest) will be compared using a Cox regression model with OAC exposure (see Table VII for derivation of exposure sequences) considered as time-dependent variable adjusted for covariates. Covariates will be derived at index date as indicated in Table XV.

Table XV. Derived variables for confounders

Variable	Definition
Age	Categorical variable (<80 years old / 80-90 / >90 years old) *See Table III*
Sex	Binary variable (Female / Male) *See Table III*
Prescriber's specialty at initiation of OAC	Categorical variable (Hospital-based physician/ City cardiologist/ Generalist practitioners/Other) *See Table III*
Having Malnutrition	Binary variable (Yes / No) *See Table III*
Risk of falls	Binary variable (Yes / No) *See Table III*
Frail patients	Binary variable (Yes / No) *See Table V*
Morbid obesity	Binary variable (Yes / No) *See Table VI*
At least one visit to a nursing home	Binary variable (Yes / No) *See Table VI*
Concomitant treatments	Binary variable (Yes / No) for each concomitant treatment listed in Table XIV

	For example, for antiplatelet drugs, equals to "Yes" if the patient has at least one reimbursement for an antiplatelet drug in the 4 months before the index date
HAS-BLED score	Categorical variable (0, 1, 2, 3, ≥4) *See Table VI*
$CHAD_2DS_2VASC$ score	Categorical variable (0, 1, 2, 3, 4, ≥5) *See Table VI*
Age adjusted Charlson Cormordity Index (ACCI) adapted to SNDS data	Categorical variable (0, 1-2, 3-4, ≥5) *See Table VI XII*

9.4.3.3 Estimation of the AF annual standardized incidence rate and prevalence

All the variables in Table XVI will be derived for all AF patients in France in 2016, 2017, 2018 and 2019.

Table XVI. Derived variables for incidence and prevalence

Variable	Definition
Incident AF patient	Binary variable (Yes / No) *See Table X*
Prevalent AF patient	Binary variable (Yes / No) Equals to "Yes" if the patient is diagnosed AF during the historical period Patients belonging to the study population

9.4.3.4 To describe the use of oral anticoagulants (OACs) in AF patients initiating treatment (AF patients exposed to OAC therapy)

Table XVII. Derived variables for OAC treatment pattern

Variable	Definition
New user of OAC (for all incident AF patients)	Binary variable (Yes/No) Equals to "Yes" if the patient receives at least one reimbursement of an OAC (VKA, apixaban, rivaroxaban or dabigatran) during the follow-up period, without use of any OAC in the 24 months prior to the first date of OAC delivery *ATC codes: B01AA, B01AF02, B01AF01, B01AE07* Equals to "No" in other cases

VKA	Binary variable (Yes / No) Equals Yes if at least one reimbursement associated to VKA is identified during the follow-up period Equals to "No" in other cases. *Same methodology for Apixaban, Rivaroxaban, Dabigatran*
Number of sequence treatment	Categorical variable (1/2/3/4/5+) Equals to "1", "2", "3", "4" and "5+" if one only, two, three, four and five or more different OAC respectively, are identified in a discontinuous sequence during the follow-up period
Duration of each OAC	Continuous variable Equals to the sum of prescription duration for each OAC during the follow-up period (for duration calculation refer to table VII for start and end date of each OAC)
Switch of OAC treatment	Binary variable (Yes/no) Equal to 'Yes' if the patient has at least one reimbursement of a OAC different from the first OAC delivered Equal to 'No' if the patient has no reimbursement of a OAC different from the first OAC delivered or have permanent discontinuation of treatment
Temporary or permanent discontinuation	Binary variable (Yes/no) Equal to 'Yes' if the patient has at least 60 days without reimbursement of an OAC after the date of the first OAC delivery Equal to 'No' in the other case
Concomitant treatments	Binary variable (Yes/no) Equal to 'Yes' if the patient has at least one reimbursement of beta-blockers, antihypertensives, antiplatelet drugs, other anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticoids, proton pump inhibitors, selective serotonin reuptake inhibitor antidepressants (SSRIs), systemic azole antifungals, CYP P450 inhibitors, protease inhibitors, lipid-lowering drugs, glucose-lowering drugs, antiarrhythmics during the follow-up period Equal to 'No' in other case
Type of delivery	Categorical variable (Hospital/Private medical practice) Equal to 'Hospital' if the variable PSE_STJ_COD (mode of practice) = 61, 62 Equal to 'Private medical practice' if the variable PSE_STJ_COD = 51, 55, 63, 64, 69.

Prescriber's specialty	Categorical variable (Hospital-based physician/ City cardiologist/ Generalist practitioners/Other) Equal to 'Hospital-based physician' if PSE_STJ_COD = 61, 62 Equal to 'City cardiologist' if the variable PSE_SPE_COD (medical specialty of the prescriber) = 3 and PSE_STJ_COD = 51, 55, 63, 64, 69. Equal to 'Generalist practitioners' if the variable PSE_SPE_COD = 1 and PSE_STJ_COD = 51, 55, 63, 64, 69. Equal to 'Other' if the variable PSE_SPE_COD not in 3 or 1.

9.4.3.5 Comparison of HCRU and associated costs

Table XVIII. Derived variables for HCRU and associated cost

Variable	Definition
HCRU	Categorical variable (hospital admission/hospital at home/palliative care/emergency visit/outpatient physician's visits (private practice, home or outpatient)/outpatient paramedic visits/ rehabilitation care facilities/dispensing of observable drugs (AF drugs and other) /medication related to AF/Lab tests/Medical procedures/Medical devices (LPP)/sickness benefits/reimbursed transports) Equal to: - "hospital admission" if the reimbursement corresponds to any hospital admission - "hospital at home" if the reimbursement corresponds to any home hospitalization stay - "palliative care" if the reimbursement corresponds to any palliative care stay - "emergency visit" if the reimbursement corresponds to any emergency visit - "outpatient physician's visits" if the reimbursement corresponds to any private practice, home or outpatient visit - "outpatient paramedic visit" if the reimbursement corresponds to any outpatient paramedic visit - "rehabilitation care facilities" if the reimbursement corresponds to any SSR stays - "dispensing of observable drugs" if the reimbursement corresponds to any observable drugs (AF drugs and other)

	- “medication related to AF” if the reimbursement corresponds to any anticoagulants, antiplatelets, antihypertensive drugs glucose-lowering drugs, lipid-lowering drugs, antiarrhythmics or beta-blockers - “Lab tests” if the reimbursement corresponds to any lab tests - “Medical procedures” if the reimbursement corresponds to any Medical procedures - “Medical devices (LPP)” if the reimbursement corresponds to any Medical devices (LPP) - “sickness benefits” if the reimbursement corresponds to any sickness benefits - “reimbursed transports” if the reimbursement corresponds to any reimbursed transports
Date of care	Date variable Equals to the value of date of care indicated in the data extraction and associated with the reimbursement
Cost	Continuous variable (euros) Equals to the value of cost (i.e. including reimbursed and non-reimbursed amounts) indicated in the data extraction and associated with the reimbursement
Number of occurrences	Continuous variable Equals to the number of occurrences where the two criteria are met: – The variable **HCRU** equals to the specified HCRU – The value of the variable Date of care falls in the specified time period
Rate of occurrences per patient-month	Continuous variable (occurrence in month) Equals to the value of the variable **Number of occurrences** divided by the duration of follow-up in month of the specified time period
Total cost HCRU	Continuous variable (euros) Equals to the sum of the values of the variable Cost where the two criteria are met: – The variable HCRU equals to the specified HCRU – The value of the variable Date of care falls in the specified time period

9.4.3.6 Description of the therapeutic management before/after the first stroke occurring after initiation of OAC therapy

Table XIX. Derived variables for the description of therapeutic management at 6 and 12 months before / after the first stroke occurring after initiation of AOC therapy

Variable	Definition
HCRU after first stroke	Categorical variable (Ambulatory care/hospital care/rehabilitation care facilities/medications related to AF) Equal to: - "Ambulatory care" if the reimbursement corresponds to any outpatient physician's visits (private practice, home or outpatient) or outpatient paramedic visits or dispensing of observable drugs (AF drugs and other) - "Hospital care" if the reimbursement corresponds to any Hospital admission or Hospital at home or Palliative care or Emergency visit - "Rehabilitation care facilities" if the reimbursement corresponds to any SSR stays - "Medication related to AF" if the reimbursement corresponds to any anticoagulants, antiplatelets, antihypertensive drugs glucose-lowering drugs, lipid-lowering drugs, antiarrhythmics or beta-blockers
Date of care	Date variable Equals to the value of date of care indicated in the data extraction and associated with the reimbursement
Time period	Categorical variable ("From 12 to 6 months before 1st stroke date"/ "From 6 months to the 1st stroke date" / "From 1st the stroke date to 6 months after" / "From 6 to 12 months after the 1st stroke date") Equals to "From 12 to 6 months before 1st stroke date" if date of care indicated in the data extraction and associated with the reimbursement is between 12 months and 6 months before 1st stroke Equals to "From 6 months to the 1st stroke date" if date of care indicated in the data extraction and associated with the reimbursement is between 6 months and 1st stroke Equals to "From 1st the stroke date to 6 months after" if date of care indicated in the data extraction and associated with the reimbursement is between 1st stroke and 6 months after 1st stroke Equals to "From 6 to 12 months after the 1st stroke date" if date of care indicated in the data extraction and associated with the reimbursement is between 6 months and 12 months after 1st stroke

Number of occurrences	Continuous variable Equals to the number of occurrences where the two criteria are met: – The variable **HCRU** after first stroke equals to the specified HCRU after first stroke – The value of the variable Date of care falls in the specified time period

9.4.4 Exploratory Outcomes

Table XX. Variables to identify subgroups among AF patients with similar profile

Variable	Definition
Sociodemographic characteristics	Age/Sex/CMU-c/ACS/Region of residence/Frail patient/Modified $CHAD_2DS_2VASC$ score/HAS-BLED score *See Table VXII*
Medical history and comorbidities	Ischemic or hemorrhagic stroke/CAD/Dementia/ Congestive Heart failure/ Peripheral arterial disease/ Other vascular diseases/ Sleep disorders/ Active cancer/Charlson score/ Malnutrition/ Morbid Obesity/ Anemia/ COPD/ Diabetes history/ Risk of falls/ Poly-medicated/ At least one visit to a nursing home/ History of major bleeding/ One or more comorbidities *See Table VXII*
Concomitant treatments	Binary variable (Yes / No) Equals to "Yes" if the patient has reimbursements for at least one dispensation at pharmacy of Beta-blockers/ Antihypertensives/ Antiplatelet drugs/ Other anticoagulants/ Non-steroidal anti-inflammatory drugs (NSAIDs)/ Oral corticoids/ Proton pump inhibitors/ Selective serotonin reuptake inhibitor antidepressants (SSRIs)/ Systemic azole antifungals/ Medical procedure of cardioversion/ CYP P450 inhibitors/ Protease inhibitors/ Antiarrhythmics/ Glucose-lowering drugs/ Lipid-lowering drugs/ Digitalis glycosides/ Nitrate derivatives during the follow-up period Equals to "No" in the other case
Event of interest	Stroke (ischemic or hemorrhagic)/ Major bleeding/ Death *See Table VVIII*
Event of interest: Number of occurrences	Number of occurrences *See Table VIXI*
OAC at start follow-up date	Categorical variable (VKA / Apixaban / Dabigatran / Rivaroxaban / Unexposed)

	See Table VXII
OAC treatment pattern	New user of OAC/VKA/Apixaban/Rivaroxaban/Dabigatran/ Number of sequence treatment/ Duration of each OAC/ Switch of OAC treatment/ Temporary or permanent discontinuation/ Concomitant treatments/ Type of delivery/ Prescriber's specialty *See Table VXVII*
HCRU	Number of occurrences/ Total cost HCRU *See Table VXVIII*

9.5 Study Size

All analyses (except the estimation of the prevalence of NVAF) will be conducted in patients newly diagnosed with FA. In 2018, a study conducted by Santé Publique France, showed that 225,747 NVAF patients were OAC new users (6). If the number of new patients remains constant during the study period of 5 years from 2016 to 2020, we expect that approximately 1.3 million patients will be exposed to OAC in the SIFNOS study.

9.6 Data Management Plan

Data management for this study will be conducted using standard IQVIA processes. Further details on the data handling procedures are provided below. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

Data transfers

Trained IQVIA personnel involved in the study and specified in the contract with CNAM will get access to the SNDS secure web portal where the extracted data will be made available. They will receive an email containing their login dedicated to this study and a mail, delivered by a carrier against signature, containing a token dedicated to this study too. The token will first be activated via the IQVIA internal activation code provided by CNAM to IQVIA for all the studies conducted on SNDS. Then, the owner will define his/her own activation code to be able to generate a random 8-digit password valid for one minute and allowing the connection to the secure SNDS web portal.

Trained IQVIA personnel involved in the study will access the data via secure IQVIA computers and internet connections and will perform the data management and the analysis through the secure SNDS web portal. As specified in the contract with CNAM, they are banned from downloading individual patient data from this portal to a local computer (i.e., no transfer of data will take place from CNAM to IQVIA) as well as displaying or reproducing these data in any format (e.g., Excel®, screen shot) and for any purpose (e.g., data review). No technical solutions are implemented for ensuring these requirements. Trained IQVIA personnel involved in the study are personally accountable to the French law to comply with these conditions.

Data storage and backup

Extracted data will be stored on CNAM's servers in a dedicated data folder accessible only to trained IQVIA personnel involved in the study. Each CNAM's server systematically contains a copy of the study data folder with all extracted and derived data tables as a backup copy.

Data cleaning and preparation

Extracted data are made available in the form of several hundreds of tables and several thousands of variables. The overall aim of data cleaning and preparation is to clean and to gather the data within a reduced work-frame.

Details of the process is available upon request.

Data analysis and results generation

The same trained IQVIA statistician will create the derived variables and will perform data analysis following the instructions provided in the signed-off statistical analysis plan. It will also develop dedicated macros to report the results within the format specified in the table shells in the signed-off statistical analysis plan automatically in a Microsoft Word® document.

Data archival/destruction for project close

The study data folder including all extracted and derived data tables will be destroyed from all the CNAM's servers at the end of the official communication of the results of this study, as clarified in the submitted ethics dossier. No archive of the study data folder can be requested.

Quality control (QC) processes

At the end of each of the following key stages – data management of the extracted data, derived variables creation, data analysis and results reporting – the Statistical Analysis Software (SAS) programs used will be inspected and quality checked by a second trained IQVIA statistician involved in the study and different from the one who will perform the stages. Validation of the SAS programs and successful execution of QC after each stage will be necessary in order to proceed to the following stage.

Data management risks

As data will not be transferred to IQVIA and only trained personnel will be able to access it for the purpose of analysis and results generation, there is no foreseeable risk that is expected to affect data integrity or data protection.

9.7 Data Analysis

9.7.1 General Considerations

Individual patient data will be analysed through the SNDS secure web portal using SAS Enterprise Guide® version 7.1. Aggregated data will be exported to an IQVIA secure server to generate figures of results using R version 3.6 or higher, or SAS® version 9.4 (SAS Institute North Carolina, USA).

Results will be reported only if they represent at least 10 patients to comply with French individual data protection policy. In the event of subgroups include strictly less than 10 patients, the analysis will not be performed, or the subgroups will be re-defined to extend the populations to be included. Decision will be taken on a case-by-case basis in agreement with PFIZER/BMS, IQVIA and/or the experts of the scientific committee.

Presence of missing data is not expected in SNDS because of its completeness. Therefore, results will not report missing data and no imputation of missing data will be done.

Descriptive analysis will be conducted depending on the nature of the variable:

- For qualitative variables, this includes the number of observed (and missing if relevant) values, and the number and percentage of patients per class. Percentages will be calculated in the population without missing data.
- For quantitative variables, this includes number of observed (and missing if relevant) values, mean, standard-deviation, median, first and third quartiles, and minimum and maximum.

An overview of the planned analysis for the primary, secondary and exploratory objectives is presented in **Error! Reference source not found.**.

Table XXI. Overview of the data analysis by objective

Type of Objective	Primary	Secondary						Exploratory
Name of the analysis	To estimate the incidence rate of stroke (ischemic or hemorrhagic), major bleeding and death in both AF patients (exposed and unexposed to OAC)	To describe the characteristics of AF patients exposed and unexposed to OAC	To compare the incidence rate of stroke, major bleeding, and death between those two populations	To estimate the annual incidence and prevalence of patients with AF, exposed and unexposed to OAC	To describe the use of oral anticoagulants (OACs) in AF patients initiating treatment (AF patients exposed to OAC therapy)	To compare the Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OACs	To describe the therapeutic management before/after the first stroke occurring after initiation of OAC exposure	To identify subgroups among AF patients with similar profile
Outcomes	Estimation of the incidence rate of stroke, major bleeding, and death. Incidence rate in unexposed patients will be standardized on age using the exposed to OAC group as population of reference.	Description of sociodemographic characteristics, comorbidities, medical history of interest and concomitant treatments	Comparison of incidence rate in longitudinal analysis for each event of interest (stroke, major bleeding, and death)	Estimation of the annual incidence and prevalence of patients with AF. Annual incidence will be standardized on age using INSEE data (French population) as population of reference	Description of the use of oral anticoagulants (OACs) in AF patients initiating treatment (AF patients exposed to OAC therapy)	Comparison of the Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OACs	Description of the therapeutic management before/after the first stroke occurring after initiation of OAC exposure	Identification of subgroup of AF patients with similar profile

Periods	2016 - 2019	2016-2019 (per calendar year)	2016 - 2019	2014 – 2019 (per calendar year)	2016 - 2019	2016 - 2019	2016 - 2019	2016 - 2019
Populations	Incident AF patients	Incident AF patients	Incident AF patient	All AF patients (prevalent & incident)	Incident AF patients exposed to OAC	Incident AF patients exposed and unexposed to OAC	Incident AF patients exposed to OAC	Incident AF patients exposed and unexposed to OAC
Subgroups	Elderly patients (≥ 80 years old) Patients with CAD Frail patients Patients having an active cancer Patients reported with previous stroke		-Patients with high thromboembolic risk	Elderly patients (≥ 80 years old) Patients with CAD Frail patients Patients having an active cancer Patients reported with previous stroke				
Stratification	-Modified $CHAD_2DS_2VASC$ score strata (Low risk / Moderate risk/ High risk) **- For stroke event** type of stroke (ischemic or hemorrhagic)							

Type of analysis	Longitudinal	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Analysis methods	Descriptive	Descriptive	Cox regression model with OAC exposure considered as time-dependent variable (Crude and variable described in table XV)	Descriptive	Descriptive	Descriptive + ANOVA or Welch test or Kruskal-Wallis *(according to the verification of the hypothesis)* + post-hoc test *(if previous global test significant)*		Clustering models (TAK, K-Means, Random-Forest, Ascending hierarchical clustering) with a data visualization
Sensitivity analyses	-Integration of 2020 data -30 and 90 days of maximal number of days allowed for being refilled -Integration of all incident AF patients (i.e. inclusion of patients with an event of interest between inclusion date and index date)	-Integration of 2020 data	-Integration of 2020 data -30 and 90 days of maximal number of days allowed for being refilled - Integration of all incident AF patients (i.e. inclusion of patients with an event of interest between inclusion date and index date)	-Integration of 2020 data -Integration of all incident AF patients (i.e. inclusion of patients with an event of interest between inclusion date and index date) - On AF patients identified only by LTD or hospitalization (new OAC users identified				

				by algorithm of Billionnet et al. not included)				

9.7.2 Planned Analysis for the Selection of the Study Population

The selection of the study population will be described as counts of patients included or excluded after each inclusion or exclusion criterion and after the algorithm and summarized through a flow diagram.

Description of the duration of the follow-up in years and the reason for end of follow-up (death, lost to follow-up or end of the study period) will also be provided for AF patients exposed and unexposed to OAC and overall.

9.7.3 Planned Analysis for the Primary Objective

9.7.3.1 To estimate the incidence rate of stroke (ischemic or hemorrhagic), major bleeding and death in AF patients exposed to OAC (VKA or DOAC) and unexposed to OAC

The analysis of incidence rate for the first occurrence of each event of interest (stroke, major bleeding and death) will be conducted in the population of AF incident patients excluding those with a reported outcomes of interest up to 30 days prior index date.

As a reminder, incident AF patients will be the patients newly diagnosed AF during the inclusion period i.e., with a date of first diagnosis of AF, identified by the date of the start of LTD or of the index hospital stay during inclusion period, or the date of initiation of the OAC.

Event rates will be estimated over the 4-year period 2016-2019, in the overall population and according to the treatment exposure.

The incidence rate for each event of interest (stroke, major bleeding and death) will be defined as the number of events occurring during the follow-up period divided by the number of person-years of follow-up (sum of durations of follow-up period for incident patients).

Incidence rates in unexposed patients will be standardized by age using exposed patients as the population of reference.

Analyses will be descriptive in nature (proportion and 95% confidence interval).

Event rates will also be displayed by sub-populations (see section 9.2.3.4).

9.7.4 Planned Analysis for the Secondary Objectives

9.7.4.1 To describe the characteristics of AF patients exposed and unexposed to OAC

The sociodemographic characteristics, comorbidities, medical history of interest and concomitant treatments will be described at index date in terms of:

- Mean, SD, median, Q1, Q3, min and max for every continuous variable.
- Counts and percentages of patients per category for every binary and categorical variable.

The analysis will be performed in AF incident patients, overall and according to the exposition status at index date (exposed or unexposed to OAC). Patient characteristics will be displayed by calendar year from 2016 to 2019 and over the 4-year period 2016-2019.

In addition, patient characteristics will be also described, overall and according to the exposition status at index date (exposed or unexposed to OAC), **for the population of AF incident patients excluding those with a reported outcomes of interest up to 30 days prior index date** (i.e. population studied in incidence rates for

each event of interest (stroke, major bleeding and death) and in Cox model analysis) for the 4-year period 2016-2019.

9.7.4.2 Comparison of the incidence of stroke, major bleeding, death

Analyses will be performed independently for each event of interest stroke, major bleeding and death.

Survival analysis will be performed to compare incidence rate (stroke, major bleeding or death) in AF incident patients exposed and unexposed to OAC therapy **excluding those with a reported outcomes of interest up to 30 days prior index date**, using a Cox regression model. The Cox regressions models will consider the first event of interest occuring in AF incident patients exposed and unexposed to OAC. OAC exposure will be considered as time-dependent variable and the models will be adjusted for covariates defined below. By applying the OAC exposure variable as a time dependent variable, estimates of Hazard Ratio will account for switches and discontinuations. Time-dependent exposure Cox proportional hazards models will be used to estimate:

- The Crude hazard ratio (i.e. the incidence rate ratio), and therefore the risk of each outcome at any point during the follow-up since index date
- The adjusted hazard ratio on potential confounders including patient:
    - Time-fixed confounders: sex, age (<80, 80-90, >90 years old), prescriber's specialty at initiation of OAC, having malnutrition (yes/no), risk of falls (yes/no), morbid obesity (yes/no), history of stroke (yes/no), history of major bleeding (yes/no), at least one visit to a nursing home (yes/no), history of dementia (yes/no), concomitant treatments (e.g. receiving at least one antiplatelet drugs (yes/no), other anticoagulant drugs (yes/no), *etc.- cf. Table XV for all confounders*)
    - Time-dependent confounders: AOC treatment exposure

In a first model, patient exposure will be modelled according to five categories: exposure to apixaban, dabigatran or rivaroxaban, exposure to VKA or unexposed patients. In a second model, exposure to DOACs will be integrated instead of exposure to apixaban, dabigatran or rivaroxaban. For both models, the reference for comparison will be VKA exposure.

Same models will be performed on AF incident patients with a high thromboembolic risk (if modified $CHAD_2DS_2VASC$ score is ≥2 for males and ≥3 females). Patient exposure will be modelled according to three categories: exposure to DOAC (Apixaban, Dabigatran or Rivaroxaban), exposure to VKA or unexposed patients. The reference for comparison will also be VKA exposure.

Censor is defined as patient's last health record, or date of end of follow-up. Hazard ratios and associated 95% CI will be reported. Models will be considered valid if they meet the proportional hazards assumption as assessed by examination of Schoenfeld residuals and log-log plots. In case of the proportionality assumption is violated, the nonparametric additive hazard model (Aalen-model) with OAC exposure considered as time-dependent variable will be applied.

9.7.4.3 Estimation of the annual standardized incidence rate and prevalence

The analysis of annual standardized incidence rate and prevalence of diagnosed AF patients in France in 2016, 2017, 2018 and 2019 will be descriptive in nature and will be performed for each calendar year, from 2016 to 2020.

Prevalent and incident patients with an AF diagnosis will be the patients with a diagnosed NVAF during the historical period and the patients newly diagnosed AF during the inclusion period. The estimations of the prevalence and incidence of AF will be based on the count of patients living in France as denominator (based on socio-demographic data published by the National Institute for Statistics and Economic Studies (INSEE) and will be expressed per 100,000 inhabitants.

The analysis will include the following measures for summarizing the information on the prevalence and incidence of diagnosed AF patients, for each calendar year between 2016 and 2019 in France:

- Overall count of prevalent and incident of diagnosed AF patients in year Y, separately
- Overall crude prevalence and cumulative incidence of diagnosed AF patients in year Y, separately; computed as:

$$\mathrm{CP}_Y = \frac{\text{count of prevalent diagnosed NVAF patients in year Y}}{\text{count of French adult residents from census data in year Y}} \times 100{,}000$$

  - CP_Y represents the crude prevalence of diagnosed AF patients in the year Y
  - *Y* represents the year of interest

$$\mathrm{CI}_Y = \frac{\text{count of incident diagnosed NVAF patients in year Y}}{\text{count of patients at risk in year Y}} \times 100{,}000$$

  - CI_Y represents the cumulative incidence of diagnosed NVAF patients in the year Y
  - *Y* represents the year of interest
  - *Count of patients at risk* represents French adult residents from census data in year Y minus count of prevalent diagnosed NVAF patients in year Y

- Overall age-standardized cumulative incidence of diagnosed AF patients in year Y computed as:

$$age - SCI_Y = \frac{\sum_i CI_{i,Y} \times N_{i,Y}}{\sum_i N_{i,Y}} \times 100{,}000$$

  - *age-SCI*$_Y$ represents the age-standardized cumulative incidence of diagnosed AF patients in year Y
  - *i* represents the age group (<65 years old / 65-74 / 75-79 / ≥ 80 years)
  - *Y* represents the year of interest
  - $CI_{i,Y}$ represents the crude cumulative incidence of diagnosed AF patients in the age group *i* in the year *Y*
  - $N_{i,Y}$ represents the counts of patients at risk (French adult residents from census data in year Y minus count of prevalent diagnosed AF patients in year Y) in the age group *i* in the year *Y*

The estimations of the annual standardized incidence and annual prevalence of AF will be also performed according to exposure status (exposed to OAC or unexposed), every year. A patient will be considered exposed to OAC in a given year if the patient presents at least one sequence treatment for an OAC in the corresponding year.

9.7.4.4 *Description of the use of oral anticoagulants (OACs) in AF incident patients initiating treatment (AF patients exposed to OAC therapy)*

The analysis of the OAC treatment patterns will be descriptive and exploratory in nature.

The date of first reimbursement of any drugs of interest (VKA, apixaban, rivaroxaban, and dabigatran) will be considered as the regimen initiation date and mark the beginning of the identification of the treatment sequence (cf. table VII).

The duration of a prescription will be of 30 days for any drugs of interest. The grace period considered for any drugs of interest considered will be 60 days (30 days and 90 days will be considered for sensitivity analyses).

A treatment sequence will continue until one of the following occurs:

- A regimen switch, defined as the reimbursement of another OAC. The end date of the first treatment sequence is the day before the date of first reimbursement of another OAC.
- Discontinuation of drugs in the treatment sequence: if a period between two consecutive claims is superior to the duration of the treatment of the last claim, plus a permissible gap of at least 60 days (30 and 90 days for sensitivity analyses) then the medication is considered as stopped within the treatment sequence. The date of discontinuation (end date of the treatment sequence) will be fixed at the date of the last claim, plus the treatment duration of this last claim.
- End of follow-up.

The treatment pattern analysis will be providing the following information:

- Number and percentage of patients receiving each of OAC treatment during the follow-up
- Number and percentage of patients who received 1, 2, 3, 4 and 5+ sequence treatment during the follow-up
- Number and percentage of patients who have switched from an OAC to another during the follow-up
- Number and percentage of patients who have concomitant treatments during the follow-up (cf. Table XIV. Derived variables for concomitant treatments).
- Number and percentage of patients who have a temporary or permanent discontinuation during the follow-up
- Number and percentage of the type of structure (hospital or private medical practice) and type of prescriber's specialty (generalist, city cardiologist or other) for each OAC and for each treatment exposure sequence (1/2/3/4/5+)
- Analyses of duration of treatment for each OAC (only median (Q1/Q3) and min/max will be presented).
- Time to next treatment (TTNT) changed for each OAC

Sunbursts (example in fig. A2) will be used to illustrate treatment pattern sequence.

Persistence rate at 6 and 12 months after initiation of each OAC and any OAC will be estimate with Kaplan-Meier curves (example in fig. A3). Persistence rate will be defined as no interruption of treatment sequences during follow-up (at 6 and 12 months) from the date of first OAC delivery. Patients will be considered non-persistent at the occurrence of the first treatment sequence end during follow-up.

- For persistence rate of overall OAC, switching from one DOAC therapy to VKA therapy will not be considered as a treatment discontinuation.
- For persistence rate of each OAC, switching from one OAC therapy to another OAC will not be considered as a treatment discontinuation.
- In the case of persistence rate for DOAC overall or VKA overall, switching from one DOAC therapy to VKA will be considered as a treatment discontinuation, and inversely.

Similarly, to sequence treatments, sensitivity analysis will be performed to test the impact of different gaps on the measurement of persistence rate using a 30- and 90-day gap (i.e. grace period).

9.7.4.5 Comparison of Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OACs

HCRU and associated costs including event-related costs (i.e. stroke related and/or bleed related), will be described overall and for each resource (ambulatory care, hospital care, rehabilitation care facilities and medications) at every calendar year of follow-up for AF incident patients exposed to apixaban, rivaroxaban, dabigatran, VKA and unexposed to OAC from index date to end of follow-up, including number and rate of patients using each resource by year of follow up in term of :

- Counts and percentages of patients with at least 1 reimbursement of specific OAC or no reimbursement for patients unexposed to OAC.
- Mean, SD, median, Q1, Q3, min and max of the rate of reimbursements per patient per month of follow-up in patients with at least 1 reimbursement of specific OAC or no reimbursement for patients unexposed to OAC.

All costs will be provided in Euros, annualized based on 2019 prices and presented per patients per month (PPPM) to consider differences in follow-up duration. Cost analysis will be performed from the health insurance perspective (reimbursed costs).

For the comparison of average of the overall PPPM costs (e.g. during all the follow-up) between AF incident patients exposed to apixaban, rivaroxaban, dabigatran vs NVAF patients exposed to VKA, significant differences between groups will be detected with an ANOVA for global equality of means. In case of the global test is significant, Tukey post-hoc test will be calculated to evaluate pair comparison. Normality will be tested before processing the analyses by the evaluation of the residuals (QQ plot and Shapiro-Wilk test) and homogeneity of variance with the Levene test and the plot of residuals versus fits. If normality not verified, Kruskal-Wallis test will be used. If homogeneity not verified, the Welch ANOVA will be used and Games-Howell for post-hoc test. The tests will be two-sided with a significance level of 5%.

9.7.4.6 Description of the therapeutic management before/after the first stroke occurring after initiation of OAC therapy

HCRU overall and for each resource (ambulatory care, hospital care, rehabilitation care facilities and medications) will be described at 6 and 12 months before and after the first stroke occurring after initiation of OAC therapy for patients exposed to apixaban, rivaroxaban, dabigatran and VKA in term of :

- Counts and percentages of patients with at least 1 reimbursement HCRU.

- Mean, SD, median, Q1, Q3, min and max of the rate of reimbursements per patient per month of follow-up in patients with at least 1 reimbursement of HCRU.

9.7.5 Planned Analysis for the Exploratory Objective

9.7.5.1 Identification of subgroups among patients with similar profile with clustering models

The identification of subgroups among patients with similar profile will be descriptive and exploratory in nature with the variables listed in the table XX. The analysis will be run following the clustering models like K-Means, Random-Forest or Ascending hierarchical clustering. Data visualization will be also presented.

9.7.6 Sensitivity analyses

We will perform the following sensitivity analyses:

1. Analyses on the evaluation of the incidence rate and comparison of the events of interest (stroke, major bleeding, and death) will be performed from the inclusion date for all incident AF patients (i.e. the inclusion date will be the index date for all incident patients, whether or not patients received OAC therapy within 30 days of the inclusion date).

2. Analyses including the 2020 data (given the uncertainty of the impact of the Covid 19 health crisis on the management of NVAF incident patients) will be conducted on:
   - Description of the follow-up of the study population (Table A1);
   - Sociodemographic characteristics (Tables A4 and A7), medical history and comorbidities (Table A5 and A8); concomitant treatments (Tables A6 and A9);
   - Estimation and comparisons of the incidence of interest-events in AF exposed and unexposed to OAC (primary objective - Table A2, secondary objective - Table A10);
   - Estimation of the annual incidence rate and the prevalence of AF patients (Tables A12 and A13 respectively).

3. Analyses on AF patients without the second inclusion criteria (new OAC users identified by the algorithm of *Billionnet et al*. not included) will be performed for the estimation of the annual standardized incidence and prevalence (Tables A12 and A13 respectively).

4. Analyses will be considered to test the impact of different grace periods (duration of 30 days and 90 days) in the calculation of treatment sequences for the following objectives:
   - Estimation and comparisons of the incidence of interest-events in AF exposed and unexposed to OAC (primary objective - Table A2, secondary objectives - Table A10)
5. If more than 10% of each event of interest occur during the 60 days grace period, analyses will be performed considering this event of interest in an unexposed period for the following objectives:

- Estimation and comparisons of the incidence of interest-events in AF exposed and unexposed to OAC (primary objective - Table A2, secondary objectives - Table A10)

9.8 Quality Control

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA Quality Management System and in accordance to the following policies and procedures:

- RWI_OP_RWW0009 “Retrospective Database Studies”
- RWI_OP_BIOS0003 “Statistical Analysis Plan for retrospective database studies”
- RWI_WI_EPI0005 “Real-World Protocol development”
- RWI_OP_PM0020 “Real World Records Management”

According to the policies and procedures above, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies
- The Principal-in-Charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal-in-Charge of the study

Also, the Principal-in-Charge of the study will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure RWI_WI_PM0035 “Real-World Project Specific Training and Staff Transition.

9.9 Limitations of the study

Limitations of this study include those inherent to the use of retrospective administrative claims data and limitations associated with missing data. Several limits related to the use of SNDS data have been identified in this study, no biological and clinical information were available for this study. The drug intake of patients is not measurable. Health insurance scheme: the dates of death and information on long term disease (LTD) for the self-employed and agricultural schemes (MSA/RSI) as well as for SLMs (government employees and student schemes) are partially available in the DCIR.

10 Protection of Human Subjects

The ethics approval process is complex, requiring approval from several committees although it has been simplified in February 2020.

The Health Data Hub (HDH), responsible for facilitating access to healthcare data. HDH checks the completeness of the ethics application submitted and transfers it to the two following committees:

- *Comité Éthique et Scientifique pour les Recherches, les Études et les Évaluations dans le domaine de la santé* (CESREES);
- *Commission Nationale de l'Informatique et des Libertés* (CNIL).

CESREES is the expert committee for research, studies and evaluations in the field of health. It advises on the methodology adopted on the need for the use of personal data, their relevance, the scientific quality and the public interest of the project. It is composed of 21 members from the public and private sectors, representing various skill sets: epidemiology, sociology, philosophy, ethics, law, health economics, medicine, pharmacy, health democracy, hospital administration, industry (digital and health products), innovation and participatory open science.

The CNIL is the national commission for information technology and freedom, who regulates personal data, assisting professionals in their compliance and helps individuals to control their personal data and exercise their rights.

11 Management and Reporting of Adverse Events/ Adverse Reactions

Pursuant to the European Medicines Agency requirements for reporting of adverse events for secondary data (Good Pharmacovigilance Practices module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

12 Plans for Disseminating and Communicating Study Results

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at Pfizer/BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (i.e., ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

- Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (e.g., evaluable subjects with quality data or data generation), analysis, or interpretation of data for the work (e.g., problem solving, advice, evaluation, insights and conclusion);
- Drafting the work or revising it critically for important intellectual content;
- Final approval of the version to be published;
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered for authorship of the publication.

13 References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Feb 1;42(5):373–498.

2. Fauchier L, Philippart R, Clementy N, Bourguignon T, Angoulvant D, Ivanes F, et al. How to define valvular atrial fibrillation? Arch Cardiovasc Dis. 2015 Oct 1;108(10):530–9.

3. Charlemagne A, Blacher J, Cohen A, Collet J-P, Diévart F, de Groote P, et al. Epidemiology of atrial fibrillation in France: extrapolation of international epidemiological data to France and analysis of French hospitalization data. Arch Cardiovasc Dis. 2011 Feb;104(2):115–24.

4. HAS. Guide parcours de soins Fibrillation atriale. 2014.

5. HAS. Fiche bon usage du médicament : Fibrillation auriculaire non valvulaire. Quelle place pour les anticoagulants oraux ? [Internet]. 2018 [cited 2020 Nov 23]. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2018-05/fiche_bon_usage_anticoagulants_oraux.pdf

6. Santé Publique France. Bulletin épidémiologique hebdomadaire- Épidémiologie de la fibrillation atriale en France. Incidence des patients nouvellement traités par un anticoagulant oral, évolutions temporelles et disparités territoriales [Internet]. 2021 [cited 2021 May 25]. Available from: http://beh.santepubliquefrance.fr/beh/2021/5/2021_5_1.html

7. Gabet A, Chatignoux E, Billionnet C, Maura G, Giroud M, Béjot Y, et al. Annual rate of newly treated atrial fibrillation by age and gender in France, 2010-2016. Eur J Epidemiol. 2020 Dec;35(12):1139–47.

8. Martinez BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Versus Warfarin in Frail Patients With Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2018 Apr 13;7(8).

9. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. Age Ageing. 2019 Mar;48(2):196–203.

10. Chen N, Lutsey PL, MacLehose RF, Claxton JS, Norby FL, Chamberlain AM, et al. Association of Oral Anticoagulant Type With Risk of Dementia Among Patients With Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2018 Nov 6;7(21):e009561.

11. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. The Lancet. 2009 Aug 15;374(9689):534–42.

12. Haute Autorité de santé. Evaluation de l'occlusion de l'appendice auriculaire gauche par voie transcutanée. 2014;113.

13. ANSM, CNAMTS. Etudes NACORA-BR et NACORA-Switch [Internet]. 2014. Available from: http://ansm.sante.fr/Dossiers/Les-anticoagulants/Quelles-sont-les-informations-publiees-sur-les-NACO-depuis-leur-mise-a-disposition-en-France/(offset)/2

14. Bouillon K, Bertrand M, Maura G, Blotière P-O, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or

switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. Lancet Haematol. 2015 Apr;2(4):e150-159.

15. Van Ganse E, Danchin N, Mahé I, Hanon O, Jacoud F, Nolin M, et al. Comparative Safety and Effectiveness of Oral Anticoagulants in Nonvalvular Atrial Fibrillation: The NAXOS Study. Stroke. 2020 Jul;51(7):2066–75.

16. Billionnet C, Alla F, Bérigaud É, Pariente A, Maura G. Identifying atrial fibrillation in outpatients initiating oral anticoagulants based on medico-administrative data: results from the French national healthcare databases. Pharmacoepidemiol Drug Saf. 2017 May;26(5):535–43.

17. Caisse Nationale d'Assurance Maladie. Nouveaux anti-coagulants oraux : une étude de l'Assurance Maladie souligne la dynamique forte de ces nouveaux médicaments et la nécessité d'une vigilance accrue dans leur utilisation. 2013 Nov.

18. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263–72.

19. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093–100.

20. Bannay A, Chaignot C, Blotière P-O, Basson M, Weill A, Ricordeau P, et al. The Best Use of the Charlson Comorbidity Index With Electronic Health Care Database to Predict Mortality. Med Care. 2016 Feb;54(2):188–94.

21. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. J Gerontol A Biol Sci Med Sci. 2018 Jun 14;73(7):980–7.

22. Beziz D, Colas S, Collin C, Dray-Spira R, Zureik M. Association between Exposure to Benzodiazepines and Related Drugs and Survivorship of Total Hip Replacement in Arthritis: A Population-Based Cohort Study of 246,940 Patients. PloS One. 2016;11(5):e0155783.

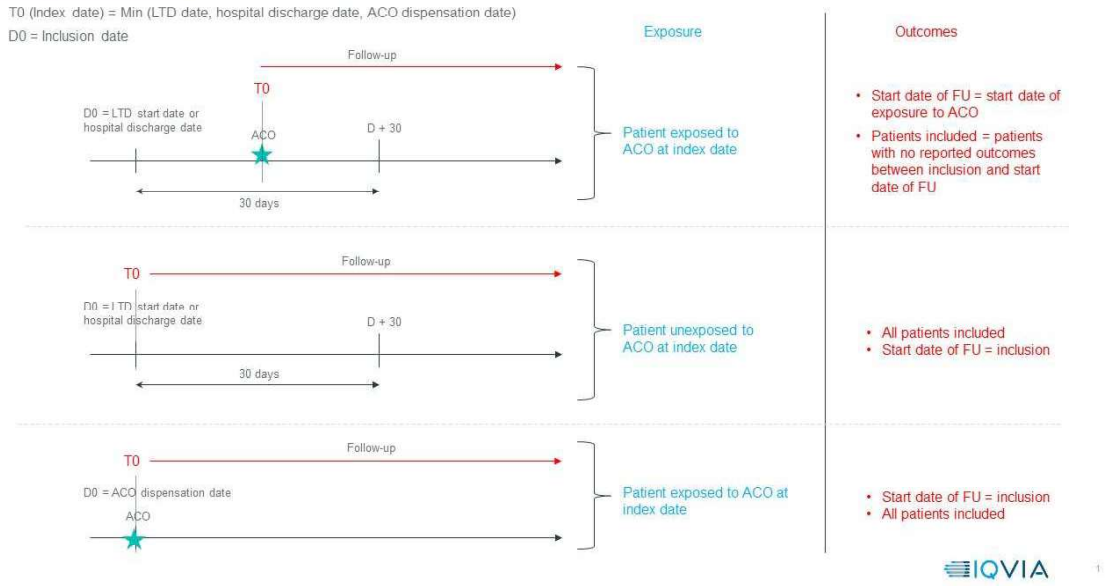
23. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of Clinical Epidemiology. 1994 Nov;47(11):1245–51.

24. Caisse Nationale d'Assurance Maladie (CNAM). Méthodologie médicale de la cartographie des pathologies et des dépenses, version G6 (années 2012 à 2017) [Internet]. 2019 [cité 10 févr 2020]. Disponible sur: https://www.ameli.fr/fileadmin/user_upload/documents/Methodologie_medicale_cartographie.pdf

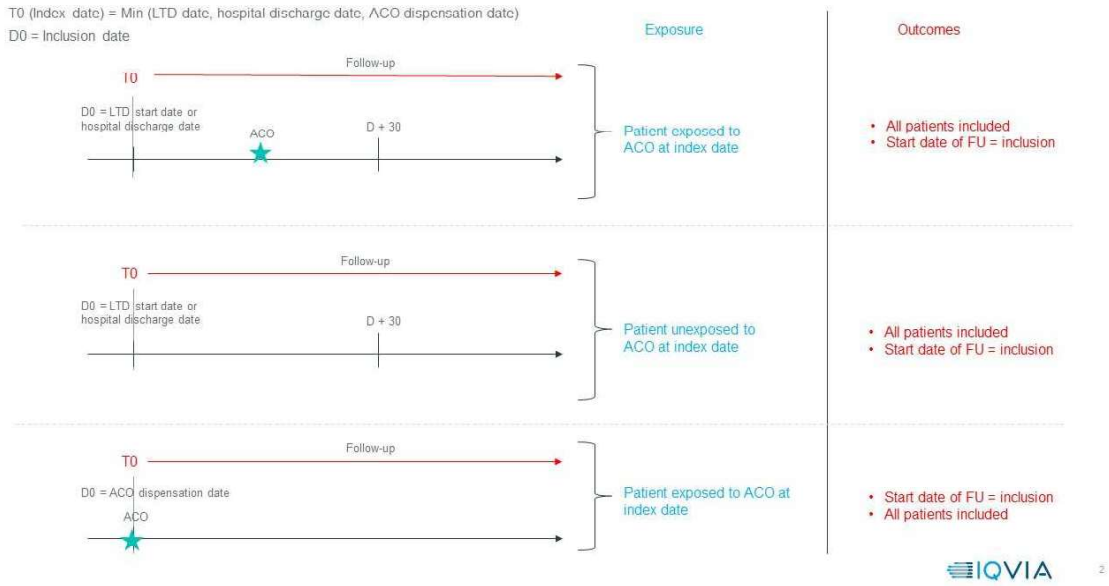
25. https://documentation-snds.health-data-hub.fr/files/presentations/meetup-snds3/2019.09.19_Heva_Boite-a-outil-data-scientist_MPL-2.0.pptx

Appendix 1 - Design for analyses performed on incident AF patients (objectives 1, 2, 3 and 7)

Principal analysis



Sensitivity analysis



Appendix 2 Calculation of Claims-based Frailty Index (CFI)

Claims-based frailty index (CFI) estimates a deficit-accumulation frailty index from a clinical assessment using International Classification of Diseases (ICD) diagnosis codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes in the prior 2 years in administrative claims data.

Interpretation: Analogous to a deficit-accumulation frailty index, the CFI gives a score ranging from 0 to 1 with a submaximal limit around 0.6-0.7. In the analysis, it can be used as a continuous variable or as a categorical variable with the following suggested cut-points: non-frail <0.10, prefrail 0.10-0.19, mildly frail 0.20-0.29, moderately frail 0.30-0.39, and severely frail ≥0.40. The latter three categories could be combined as frail (≥0.20).

Validation: Performance of CFI against clinical assessments of frailty and functional status:

- Frailty phenotype: C-statistic 0.78
- Deficit-accumulation frailty index: Spearman correlation 0.59
- ADL dependency: C-statistic 0.81
- ≥2 ADL dependency (severe disability): C-statistic 0.84

Program Download: https://dataverse.harvard.edu/dataverse/cfi/

Appendix 3 Shell Tables and Examples of Figures

1. Shell Tables and Figures of Results of the Selection of the Study Population

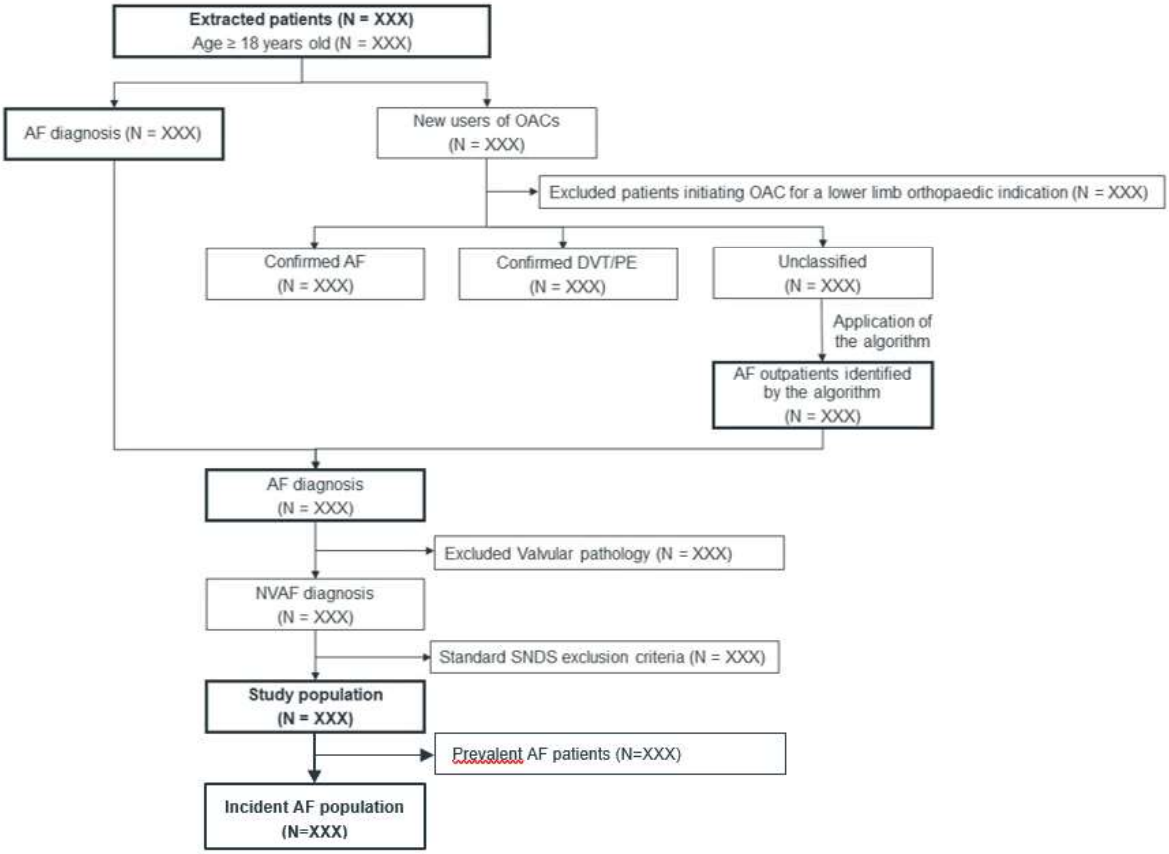


Figure A1. Flow chart of the selection of the study population

Table A1. Description of the follow-up of the AF incident population

	Exposed to OAC (N=XXX)	Unexposed to OAC (N=XXX)	Overall (N=XXX)
Reason for censoring the follow-up: n (%)			
Death	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Lost to follow-up	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
End of study period	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Duration of the follow-up in years			
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Duration group of the follow-up in years: n (%)			
[0-1[	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
[1-2[	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
[2-3[	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
[3-4[	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
[4-5[*	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

*This category will be display only for the sensitivity analysis (up to 2020)

2. Shell Tables and Figures of Results of the Planned Analysis for the Primary Objective

Table A2. Incidence rate for stroke, major bleeding and death in AF incidents patients between 2016 and 2019 in France – <POPULATION>

	Stroke				Major bleeding				Death			
	n	N	Crude	Standardized **	n	N	Crude	Standardized %**	n	N	Crude	Standardized **
<POPULATION>												
Overall	**x**	**x**	**x,x**	**NA**	**x**	**x**	**x,x**	**NA**	**x**	**x**	**x,x**	**NA**
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
Unexposed to OAC*	**x**	**x**	**x,x**	**x,x**	**x**	**x**	**x,x**	**x,x**	**x**	**x**	**x,x**	**x,x**
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
Exposed to OAC	**x**	**x**	**x,x**	**NA**	**x**	**x**	**x,x**	**NA**	**x**	**x**	**x,x**	**NA**
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
VKAs	x	x	x,x	NA	x	x	x,x	NA	x	x	x,x	NA
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
DOACs	x	x	x,x	NA	x	x	x,x	NA	x	x	x,x	NA
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
Apixaban	x	x	x,x	NA	x	x	x,x	NA	x	x	x,x	NA
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
Dabigatran	x	x	x,x	NA	x	x	x,x	NA	x	x	x,x	NA
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA
Rivaroxaban	x	x	x,x	NA	x	x	x,x	NA	x	x	x,x	NA
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA			[x.x;x.x]	NA

OAC: Oral anticoagulant; DOACs: Direct oral anticoagulants; VKAs: Antivitamins K; NA, not applicable.
n: number of events of interest; N: number of person-years of follow-up
**Unexposed and exposed to OAC correspond to the period of time where the patients are not exposed to OAC and exposed to OAC, respectively*
%: Incidence of the event of interest; CI 95%: 95% confidence interval
***: Standardized on age group (<65 years old; 65-74 years old; 75-79 years old; ≥80 years old) using the exposed population as reference*
< POPULATION >: Incidence rate of events will be stratified in the following sub-groups:
Incident elderly AF patient (≥80 years old)
Incident AF patient having a history of coronary arterial disease (CAD)
Incident AF frail patient
Incident AF patient having an active cancer
Incident AF patient reported with previous stroke
Modified CHAD2DS2VASC score groups (Low risk / Moderate risk/ High

This table will be presented for sensitivity analyses:
- with integration of 2020 data;
- with a grace period of 30 days and 90 days;
- with integration of all incident AF patients (i.e. inclusion of patients with an event of interest between inclusion date and index date).

Table A3. Incidence rate for ischemic and hemorrhagic stroke in AF incidents patients between 2016 and 2019 in France

	Stroke							
	Ischemic				Hemorrhagic			
	n	N	Crude	Standardized **	n	N	Crude	Standardized **
<POPULATION>								
Overall	**x**	**x**	**x,x**	**NA**	**x**	**x**	**x,x**	**NA**
CI 95%			[x.x;x.x]	NA			[x.x;x.x]	NA
Unexposed to OAC*	**x**	**x**	**x,x**	**x,x**	**x**	**x**	**x,x**	**x,x**
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
Exposed to OAC*	**x**	**x**	**x,x**	**x,x**	**x**	**x**	**x,x**	**x,x**
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
VKAs	x	x	x,x	x,x	x	x	x,x	x,x
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
DOACs	x	x	x,x	x,x	x	x	x,x	x,x
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
Apixaban	x	x	x,x	x,x	x	x	x,x	x,x
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
Dabigatran	x	x	x,x	x,x	x	x	x,x	x,x
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]
Rivaroxaban	x	x	x,x	x,x	x	x	x,x	x,x
CI 95%			[x.x;x.x]	[x.x;x.x]			[x.x;x.x]	[x.x;x.x]

OAC: Oral anticoagulant; DOACs: Direct oral anticoagulants; VKAs: Antivitamins K; NA, not applicable.
n: number of events of interest; N: number of person-years of follow-up
**Unexposed to OAC and exposed to OAC correspond to the period of time where the patients are not exposed to OAC and exposed to OAC respectively*
*** Standardized on age group (<65 years old; 65-74 years old; 75-79 years old; ≥80 years old) using the exposed population as reference.*

3. Shell Tables and Figures of Results of the Planned Analysis for the Secondary Objectives

3.1. To describe the characteristics of AF incidents patients at index date, per year

Table A4. Description of sociodemographic characteristics in AF incident patients at index date, per year

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed To OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Age in years										
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Age group: n (%)										
<80 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
80-90 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
>90 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Sex: n (%)										
Female	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed To OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Male	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Exposed to DOACs, at index date: n (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Apixaban	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dabigatran	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Rivaroxaban	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Exposed to VKA, at index date: n (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Contraindications to OAC, at index date: n (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x) xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Complimentary universal health care (CMU-c): n (%)										
Yes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed To OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
No	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Aid for complementary health care (ACS) for elderly patients: n (%)										
	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Yes	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
No	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Area of residence: n (%)										
Ile de France	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Centre-Val de	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Loire	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Bourgogne-	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Franche-Comté	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Normandie	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			
Hauts-de-France	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x)	xx.x	xx.x	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	(xx.x)	(xx.x)	(xx.x)	(xx.x)		(xx.x)	(xx.x)			

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed To OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Grand-Est	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pays de la Loire	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Bretagne	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Nouvelle Aquitaine	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Occitanie	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Auvergne-Rhône-Alpes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Provence-Alpes-Côte d'Azur	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Corse	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Overseas districts and territories	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Frail patient: n (%)										
Yes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed To OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
No	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Modified $CHAD_2DS_2VASC$ score strata: n (%)										
Low	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
High										
HAS-BLED score: n (%)										
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

Sociodemographic characteristics with integration of 2020 data will be presented for sensitivity analyses

Table A5. Description of medical history and comorbidities in AF incident patients at index date, per year

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed to OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Stroke: n (%)										
Ischemic	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hemorrhagic	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Comorbidities: n (%)										
CAD	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dementia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Myocardial infarction	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Congestive Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Peripheral arterial disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Other vascular diseases	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Sleep disorders	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed to OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Active cancer	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Malnutrition	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Morbid Obesity	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Anemia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
COPD	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diabetes with complications	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Connective tissue disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ulcer disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Risk of falls	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Polymedicated	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed to OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
At least one visit to a nursing home	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Major bleeding	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Charlson Index' comorbidity (CCI): n (%)										
Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Peripheral vascular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Cerebrovascular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate-to-severe renal disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mild liver disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate-to-severe liver disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Chronic pulmonary disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed to OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Dementia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hemiplegia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
HIV-AIDS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Solid metastatic tumor	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Any tumor (including leukemia and lymphoma)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
ACCI										
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
ACCI (categorical): n (%)										

	Exposed to OAC				Total exposed to OAC	Unexposed to OAC				Total unexposed to OAC
	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
0 pt	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
1-2pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
3-4pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
≥5pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

OAC: Oral anticoagulant; CAD: Coronary arterial disease; COPD: Chronic obstructive pulmonary disease; ACCI: Age/Sex adjusted Charlson Cormordity Index
Medical history and comorbidities with integration of 2020 data will be presented for sensitivity analyses

Table A6. Description of concomitant treatments in AF incident patients at index date, per year

	Exposed to OAC	Total exposed to OAC	Unexposed to OAC	T T c o t t a a l l e u x n p e c x s p e o d s t e c d C t A o C C A C

N, %	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)	2016 (N=XXX)	2017 (N=XXX)	2018 (N=XXX)	2019 (N=XXX)	2016-2019 (N=XXX)
Beta-blockers	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Antihypertensives	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x ((x x x x . . x x))
Antiplatelet drugs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x ((x x x x . . x x))
Other anticoagulants	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x ((x x x x . . x x))

									x x)) x x x x . . x x ((x x x x . . x x))
NSAIDs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Oral corticoids	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Proton pump inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x

SSRIs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x.x (x.x, x.x)
Systemic azole antifungals	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x.x (x.x, x.x)
Medical procedure of cardioversion	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x.x (x.x, x.x)

									x x . . x x))
CYP P450 inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Protease inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Antiarrhythmics	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((

									x x x x . . x x))
Glucose-lowering drugs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Digitalis glycosides	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x ((x x x x . . x x))
Nitrate derivatives	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	x x x x . . x x

											((x x x x . . x x))
Benzodiazepines	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	

Concomitant treatments with integration of 2020 data will be presented for sensitivity analyses

3.2. *Description of the characteristics of AF incidents patients at index date (without events of interest between the inclusion date and the index date), years 2016-2019 (incidence rate of events, Cox regression analyses, therapeutic management before/after stroke)*

Table A7. Description of sociodemographic characteristics in AF incident patients at index date, years 2016-2019

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Age in years							
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Age group: n (%)							
<80 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
80-90 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
>90 years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Sex: n (%)							
Female	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Male	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Complimentary universal health care (CMU-c): n (%)							
Yes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
No	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Aid for complementary health care (ACS) for elderly patients: n (%)							
Yes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
No	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Area of residence: n (%)							

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Ile de France	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Centre-Val de Loire	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Bourgogne-Franche-Comté	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Normandie	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hauts-de-France	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Grand-Est	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pays de la Loire	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Bretagne	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Nouvelle Aquitaine	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Occitanie	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Auvergne-Rhône-Alpes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Provence-Alpes-Côte d'Azur	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Corse	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Overseas districts and territories	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Frail patient: n (%)							
Yes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
No	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Contraindications to OACs: n (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Modified $CHAD_2DS_2VASC$ score strata: n (%)							
Low	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
High							
HAS-BLED score: n (%)							

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

Sociodemographic characteristics with integration of 2020 data will be presented for sensitivity analyses
**Presented for sensitivity analysis with integration of 2020 data*

Table A8. Description of medical history and comorbidities in AF incident patients at index date, years 2016-2019

		Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)		VKAs (N=XXX)	All exposed to OAC (N=XXX)
		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Stroke: n (%)									
Ischemic		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Hemorrhagic		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Comorbidities: n (%)									
CAD		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Dementia		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Myocardial infarction	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Congestive Heart failure		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Peripheral arterial disease		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Other vascular diseases		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)

			Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)		VKAs (N=XXX)	All exposed to OAC (N=XXX)
Sleep disorders			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Active cancer			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Malnutrition			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Morbid Obesity			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Anemia			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
COPD			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Diabetes with complications	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Connective tissue disease	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Ulcer disease	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Risk of falls			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
Poly-medicated			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)
At least one visit to a nursing home			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x)	xx.x (xx.x)

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Major bleeding	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Charlson Index' comorbidity (CCI): n (%)							
Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Peripheral vascular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Cerebrovascular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate-to-severe renal disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mild liver disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate-to-severe liver disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Chronic pulmonary disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dementia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hemiplegia	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
HIV-AIDS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Solid metastatic tumor	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Any tumor (including leukemia and lymphoma)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
ACCI							
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
ACCI (categorical): n (%)							
0 pt	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
1-2pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
3-4pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
≥5pts	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

DOACs: Direct oral anticoagulant, OAC: Oral anticoagulant; CAD: Coronary arterial disease; COPD: Chronic obstructive pulmonary disease; ACCI: Age/Sex adjusted Charlson Cormordity Index
Medical history and comorbidities with integration of 2020 data will be presented for sensitivity analyses

Table A9. Description of concomitant treatments in AF incident patients at index date, years 2016-2019

N (%)	Unexposed to OAC (N=XXX)	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	Exposed to DOACs (N=XXX)	VKAs (N=XXX)	All exposed to OAC (N=XXX)
Beta-blockers	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Antihypertensives	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Antiplatelet drugs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Other anticoagulants	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
NSAIDs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Oral corticoids	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Proton pump inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
SSRIs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Systemic azole antifungals	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Medical procedure of cardioversion	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
CYP P450 inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Protease inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Antiarrhythmics	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Glucose-lowering drugs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Digitalis glycosides	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Nitrate derivatives	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

n (%); OAC: Oral anticoagulant; DOACs: Direct oral anticoagulant, NSAIDs: Non-steroidal anti-inflammatory drugs; SSRIs: Selective serotonin reuptake inhibitor antidepressants
Concomitant treatments with integration of 2020 data will be presented for sensitivity analyses

3.3. Comparison of the incidence of stroke, major bleeding, death

Table A10. Risk of stroke, major bleeding or death in AF incident patients

	Event		Crude risk[1]		Adjusted risk[2,*]	
	n	%	HR	[95%CI]	HR	[95%CI]
Risk of stroke						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Dabigatran	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Rivaroxaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	
Risk of major bleeding						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Dabigatran	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Rivaroxaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	
Risk of death						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Dabigatran	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Rivaroxaban	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	

AF : Non Valvular Atrial Fibrillation; HR: hazard ratio; 95%CI: 95% confidence interval
Note: For considering DOAC treatment in models, two regressions models will be performed for this table: one model with "Exposure to DOACs" as independent variable; second model with exposure for each molecule within the class of DOAC (Apixaban, Dabigatran, Rivaroxaban).[1]From a time-dependant exposure to OAC Cox proportional hazards model
[2]From a time-dependant exposure to OAC and time-fixed covariates Cox proportional hazards model;
**Adjusted on the following covariates at index date: age (<80, 80-90, >90 years old), sex, having malnutrition, risk of falls, morbid obesity, history of stroke, history of major bleeding, at least one visit to a nursing home, history of dementia, each concomitant treatments*
***Unexposed to OAC correspond to the period where the patients are not exposed to OAC.*

Same table will be presented for sensitivity analyses:
- with integration of 2020 data
- with 30 days and 90 days of maximal number of days allowed for being refilled
- with integration of all incident AF patient (i.e. inclusion of patients with an event of interest between inclusion date and index date)

Table A11. Risk of stroke, major bleeding or death in AF incident patients with a high thromboembolic risk (modified CHA2DS2VASC score is ≥2 for males and ≥3 females)

	Event		Crude risk[1]		Adjusted risk[2,*]	
	n	%	HR	[95%CI]	HR	[95%CI]
Risk of stroke						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban						
Exposure to Dabigatran						
Exposure to Rivaroxaban						
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	
Risk of major bleeding						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban						
Exposure to Dabigatran						
Exposure to Rivaroxaban						
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	
Risk of death						
Exposure to DOACs	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to Apixaban						
Exposure to Dabigatran						
Exposure to Rivaroxaban						
Unexposed to OAC**	xx	(x.x)	x.xx	[x.xx–x.xx]	x.xx	[x.xx–x.xx]
Exposure to VKA	xx	(x.x)	*ref*		*ref*	

AF : Non Valvular Atrial Fibrillation; HR: hazard ratio; 95%CI: 95% confidence interval; DOAC= Direct oral anticoagulant; VKA= Antivitamin K; Note: For considering DOAC treatment in models, two regressions models will be performed for this table: one model with "Exposure to DOACs" as independent variable; second model with exposure for each molecule within the class of DOAC (Apixaban, Dabigatran, Rivaroxaban).

[1]From a time-dependant exposure Cox proportional hazards model

[2]From a time-dependant exposure toOAC and time-fixed covariates Cox proportional hazards model;

**Adjusted on the following covariates at or from index date: age (<80, 80-90, >90 years old), sex, having malnutrition, risk of falls, morbid obesity, history of stroke, history of major bleeding, at least one visit to a nursing home, history of dementia, each concomitant treatments*

***Unexposed to OAC correspond to the period where the patients are not exposed to OAC.*

3.4. *Estimation of the annual standardized incidence rate and prevalence of AF patients*

Table A12. Annual incidence rate of all AF patients between 2016 and 2019 (2020 for sensitivity analyses) in France

	2016			2017			2018			2019			2020*		
	N	Crude[1]	Standardized[1,2]	N	Crude[1]	Standardized[1,2]	N	Crude[1]	Standardized[1,2]	N	Crude[1]	Standardized[1,2]	N	Crude[1]	Standardized[1,2]
Overall	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x
CI 95%		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]
Unexposed to OAC	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x
CI 95%		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]
Exposed to OAC[3]	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x	xxx	x,x	x.x
CI 95%		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]		[x.x;x.x]	[x.x;x.x]

AF : Non Valvular Atrial Fibrillation
[1]Estimation are provided per 100,000 inhabitants
[2]Age-standardized using the French population as reference
Incidence rate will be stratified in the following subgroups: age groups (<80 years, 80-90 years, >90 years), active cancer, CAD, Modified $CHAD_2DS_2VASC$ score strata, Stroke history, Having a malnutrition, Risk of falls, Frail patients, Morbid obesity, History of major bleeding, at least one visit to a nursing home, History of dementia, ACCI (categorical)
[3]Exposed to OAC if at least one treatment sequence for an OAC in a given year.

**For sensitivity analyses*
Same table will be presented for sensitivity analyses:
- with 30 days and 90 days of maximal number of days allowed for being refilled
- with integration of all incident AF patient (i.e. inclusion of patients with an event of interest between inclusion date and index date)
- with AF patients identified only by LTD or hospitalization (new OAC users identified by the algorithm of Billonnet et al. not included)

Table A13. Annual prevalence of all AF patients between 2016 and 2019 (2020 for sensitivity analyses) in France

	2016		2017		2018		2019		2020*	
	N	Crude[1]	N	Crude[1]	N	Crude[1]	N	Crude[1]	N	Crude[1]
Overall	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**
CI 95%		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]
Unexposed to OAC	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**
CI 95%		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]
Exposed to OAC[3]	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**	**xxx**	**x,x**
CI 95%		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]		[x.x;x.x]

AF : Non Valvular Atrial Fibrillation
[1]Estimation are provided per 100,000 inhabitants
Annual prevalence will be stratified in the following subgroups: age groups (<80 years, 80-90 years, >90 years), active cancer, CAD, Modified $CHAD_2DS_2VASC$ score strata, Stroke history, Having a malnutrition, Risk of falls, Frail patients, Morbid obesity, History of major bleeding, At least one visit to a nursing home, History of dementia, ACCI (categorical)
[3]Exposed to OAC if at least one treatment sequence for an OAC in a given year.

**For sensitivity analyses*
Same table will be presented for sensitivity analyses:
- with 30 days and 90 days of maximal number of days allowed for being refilled
- with integration of all incident AF patient (i.e. inclusion of patients with an event of interest between inclusion date and index date)
- with AF patients identified only by LTD or hospitalization (new OAC users identified by the algorithm of Billonnet et al. not included)

3.5. Description of OAC treatment patterns

Table A14. Description of OAC treatment pattern during the follow-up

	VKA		Apixaban		Dabigatran		Rivaroxaban		Overall	
	N	%	N	%	N	%	N	%	N	%
Sequence treatment										
Only 1	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
At least 2	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
At least 3	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
At least 4	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
At least 5	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Patients who switch from an OAC to another	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Treatment duration (months)										
Median	xx.x		xx.x		xx.x		xx.x		xx.x	
Q1 - Q3	xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x	
Min – Max	xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x	
Time to next treatment (months)										
Mean (std)	xx.x (xx.x)		xx.x (xx.x)		xx.x (xx.x)		xx.x (xx.x)		xx.x (xx.x)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x	
Q1 - Q3	xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x	
Min – Max	xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x		xx.x- xx.x	

Patients with temporary or permanent discontinuation	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Type of delivery										
Hospital	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Private medical practice	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Prescriber's specialty										
Hospital-based physicians	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
City cardiologist	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Generalist practitioners	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Other	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
FIRST TREATMENT SEQUENCE										
Patients who switch from an OAC to another	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Patients with temporary or permanent discontinuation	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Patients with concomitant treatments	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Type of delivery										
Hospital	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Private medical practice	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Prescriber's specialty										
Hospital-based physicians	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x

City cardiologist	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Generalist practitioners	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Other	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
SECOND TREATMENT SEQUENCE										
….	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
THIRD TREATMENT SEQUENCE										
….	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x

Same table will be presented for sensitivity analyses with 30 days and 90 days of maximal number of days allowed for being refilled

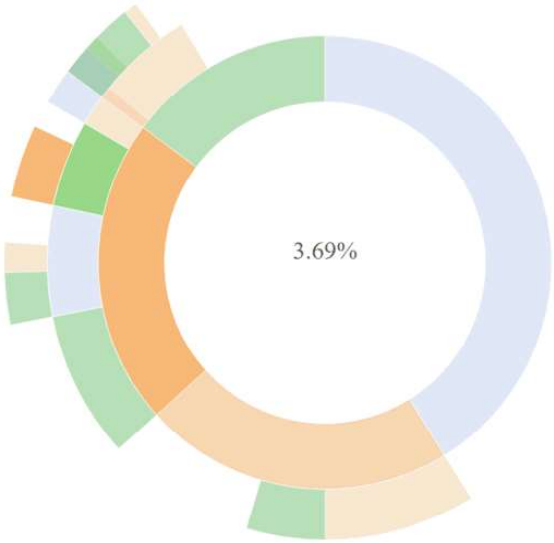


Figure A2. Example of sunburst for describing OAC treatment pattern

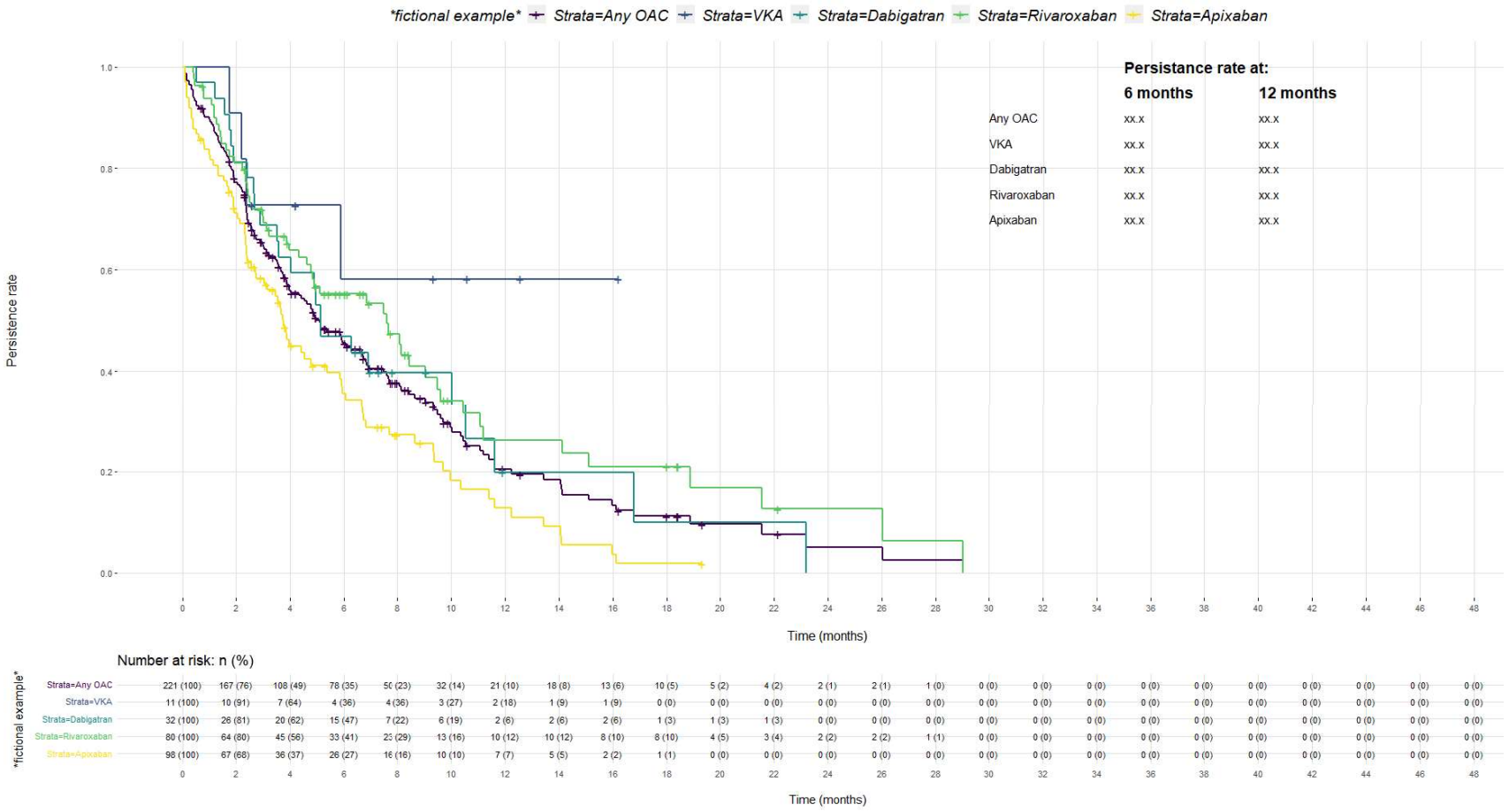


Figure A3. Example of Kaplan Meier curves of persistence rate in months

3.6. HCRU and associated costs

Table A15. Description of HCRU and associated costs (including event related cost): <time period>

	Exposed to OAC					Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
HCRU (2016-2019)						
Total						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Total (PPPM)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Hospital admission						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Hospital admission (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Hospital at home						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

			Exposed to OAC			Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Hospital at home (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Palliative care						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Palliative care (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Emergency visit						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Emergency visit (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Outpatient physician's visits (private practice, home or outpatient)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

			Exposed to OAC			Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Outpatient physician's visits (private practice, home or outpatient) (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Outpatient paramedic visits						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Outpatient paramedic visits (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Rehabilitation care facilities						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Rehabilitation care facilities (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Exposed to OAC					Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Dispensing of observable drugs (AF drugs and other)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Dispensing of observable drugs (AF drugs and other) (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medication related to AF						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medication related to AF (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Lab tests						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

			Exposed to OAC			Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Lab tests (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medical procedures						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medical procedures (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medical devices (LPP)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Medical devices (LPP) (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Sickness benefits						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

			Exposed to OAC			Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Sickness benefits (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Reimbursed transports						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Reimbursed transports (pppm)						
N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Total cost in euros (2016-2019) (pppm)						
Total						
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Hospital admission						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)

	Exposed to OAC					Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Hospital at home						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Palliative care						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Emergency visit						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Outpatient physician's visits (private practice, home or outpatient)						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Outpatient paramedic visits						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

	Exposed to OAC					Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Rehabilitation care facilities						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Dispensing of observable drugs (AF drugs and other)						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Medication related to AF						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Lab tests						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Medical procedures						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

			Exposed to OAC			Unexposed to OAC
	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKAs (N=XXX)	All exposed (N=XXX)	(N=XXX)
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Medical devices (LPP)						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Sickness benefits						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)
Reimbursed transports						
n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
IC 95%	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)	(xx.x – xx.x)

All cost are calculated per patient per month (PPPM)
< Time period >:
6. All: 2016-2019
7. 2016
8. 2017
9. 2017
10. 2018
11. 2019

Table A16. Overall comparison of HCRU and associated cost (during all the follow-up)

	Cost				Anova/Welch test/ Kruskall-Wallis*		Tukey test / Games-Howell test*	
	N (%)	Mean (std)	Median (Q1-Q3)	Min-Max	F	p-value	p-value	Sig**
All cost (2016-2019)								
Total								
Apixaban	xx (x.x)	xx.x (xx.x)	xx.x – xx.x	xx.x – xx.x	x.xx	x.xx	x.xx	ns/*
Dabigatran	xx (x.x)	xx.x (xx.x)	xx.x – xx.x	xx.x – xx.x			x.xx	ns/*
Rivaroxaban	xx (x.x)	xx.x (xx.x)	xx.x – xx.x	xx.x – xx.x			x.xx	ns/*
Unexposed	xx (x.x)	xx.x (xx.x)	xx.x – xx.x	xx.x – xx.x			x.xx	ns/*
VKA *(ref)*	xx (x.x)	xx.x (xx.x)	xx.x – xx.x	xx.x – xx.x				

All cost is calculated per patient per month (PPPM)
**Test considered depend on verification of the hypothesis*
**Post hoc comparisons type of exposure and unexposed vs. VKA (ref) : ***p<0.001, **p<0.01, *p<0.05*

3.7. *Description of the therapeutic management before/after the first stroke occurring after initiation of OAC therapy*

Table A17. Number of occurrences of HCRU 6 and 12 months before and after the first stroke for patients exposed to OAC

	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKA (N=XXX)	All exposed (N=XXX)
HCRU					
From 12 to 6 months before 1st stroke date					
n* (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
From 6 months to the 1st stroke date					
n* (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
From 1st the stroke date to 6 months **after**					
n* (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
From 6 to 12 months after the 1st stroke date					
n* (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Mean (std)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q1 - Q3	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Ambulatory care					
….					
Hospital care					

	Apixaban (N=XXX)	Dabigatran (N=XXX)	Rivaroxaban (N=XXX)	VKA (N=XXX)	All exposed (N=XXX)
….					
Rehabilitation care facilities (SSR)					
….					
Medications related to AF					
….					

N: number of patients with at least one reimbursement of the specific OAC during the follow-up
**n: represent the number of patients with at least 1 HCRU and at least one reimbursement of specific OAC during the time-period considered*

3.8. Sensitivity analyses

All results associated to the sensitivity analyses are notified in the previous tables.