NON-INTERVENTIONAL STUDY PROTOCOL
STUDY INFORMATION

Title	Patient characteristics, treatment patterns and incidence of events (discontinuation, persistence, key primary clinical outcomes) in NVAF patients initiating OAC therapy in Colombia
Protocol number	B0661148
Protocol version identifier	1.0
Date of last version of protocol	10 October 2019
Active substance	Apixaban
Medicinal product	Eliquis
Research question and objectives	***Primary Objectives*** • To assess demographic and clinical characteristics of NVAF patients treated with Oral Anticoagulants (OACs) in Colombia. • To describe treatment patterns (eg OAC usage, dose, concomitant medications, persistence) ***Exploratory Objectives*** • To descriptively assess the time to clinical events (Effectiveness and Safety Outcomes) among patients persistent on OAC therapy *Effectiveness outcomes*: First stroke/ Systemic Embolism; CCI *Safety outcomes:* Major bleeding, CCI
Author	PPD

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ARB	Angiotensin II receptor blockers
ACE	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
AEM	Adverse event monitoring
AIDS	Acquired Immune Deficiency Syndrome
AF	Atrial fibrillation
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
CHA_2DS_2-VASc	C: Congestive heart failure
	H: Hypertension
	A: Age ≥75 years
	D: Diabetes mellitus
	S_2: Prior Stroke or transient ischemic attack or Thromboembolism
	V: Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque)
	A: Age 65–74 years
	Sc: Sex category (female sex)
$CHADS_2$	C: Congestive heart failure
	H: Hypertension
	A: Age ≥75 years
	D: Diabetes mellitus
	S_2: Prior Stroke or transient ischemic attack or Thromboembolism
COPD	Chronic obstructive pulmonary disease
ECR	Electronic Case Report
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HAS-BLED	H: Hypertension
	A: Abnormal renal and liver function
	S: Stroke
	B: Bleeding
	L: Labile INR
	E: Elderly
	D: Drugs or alcohol
HMO	Health Maintenance Organizations
ICD-10	10th revision of the International classification of diseases
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MANOVA	Multivariate analysis of variance
NI	Non- interventional
NIS	Non-interventional study
NOAC	New oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation

Abbreviation	Definition
OAC	Oral anticoagulant
SAMe-TT_2R_2	S: Sex (female)
	A: Age (<60 years)
	Me: Medical history
	T: Treatment
	T: Tobacco use (within 2 years)
	R: Race (non-Caucasian)
SPSS	Statistical Package for the Social Sciences
TIA	Transient ischaemic attack
VKA	Vitamin K Antagonist
VTE	Venous thromboembolism

1. RESPONSIBLE PARTIES

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Principal Investigator of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD MD	MD, MSc	PPD	PPD

Country Coordinating Investigators

Name, degree(s)	Job Title	Affiliation	Address
PPD PPD MD, MSc	MD, MSc	PPD	PPD PPD
PPD	MD, MSc	PPD	PPD PPD
PPD	Pharmacist, MSc	PPD	PPD PPD
PPD	Economist	PPD	PPD PPD

2. ABSTRACT

Study title: Patient characteristics, treatment patterns and incidence of events (discontinuation, persistence, key primary clinical outcomes) in NVAF patients initiating OAC therapy in Colombia					
Protocol number	B0661148	**Phase**	4	**Type**	Observational
Condition/Disease	Non-valvular atrial fibrillation (NVAF)				
Number of patients	The total population of patients treated with OAC between January 1, 2013 and June 30, 2018 was analyzed in the claim dabtabase. For the purpose of the study, it contains the information of 7,500 patients, once they were verified that they met the inclusion criteria of the study.		**Duration of the patients in the study**	Follow-up will be performed until the patient presents a switch, discontinuation, death, event of stroke / systemic embolism or major bleeding, or until June 30, 2019.	
Country participants	Colombia		**Duration of the study**	8 months	

Rational and background:

Non-valvular atrial fibrillation (NVAF) is an acute or chronic heart disorder that is associated with an increase in the mortality rate, strokes and other thromboembolic events (1). This is further increased by individual conditions of patients, such as hypertension, abnormal renal or hepatic function, stroke, history of or predisposition to bleeding, people over 65, among others. (2)

One of the standard treatments for management of these patients is usually vitamin K antagonists (VKA, for example, warfarin); in the analysis of net clinical benefits of this therapy it is suggested that the effect of VKA is even more positive in patients with a high score on the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly, drugs/alcohol concomitantly) scale. (3) Another therapeutic alternative is the new oral anticoagulants (NOACs) ─ dabigatran, rivaroxaban and apixaban ─, which according to evidence have advantages in efficacy and safety compared to warfarin (4) and even when the risk of bleeding and stroke are high, the net clinical benefit appears to be greater when compared to warfarin. (5) Likewise, there is a lower prevalence of intracranial hemorrhage and its different subtypes of patients being treated with new oral anticoagulants when compared to warfarin. (6)

While it is true there are several studies that seek to understand the characteristics of patients who were diagnosed with NVAF under different treatment options, and even subpopulation analyses, the evidence at the national level is limited, both in demographic and clinical characteristics and in treatment patterns of this population. In a retrospective descriptive study of an emergency department in a third level care center in the city of Bogota, it was observed that the main comorbidities of patients with atrial fibrillation (AF) were arterial hypertension and heart failure where most patients do not receive anticoagulation. (7) In turn, for the overall population it is estimated that the prevalence of AF in Colombia (4.8%) seems to be higher than that reported in developed countries (0.03% to 1.25%) (8), according to a study conducted in a university hospital in the country (9).

Taking into account the limited knowledge on the use of oral anticoagulants in patients diagnosed with NVAF in the country and, even more in the differences in the response to these therapies in different patient subpopulations. The purpose of this study is to assess the demographic and clinical charateristics, treatment patterns and incidence of events (discontinuation, persistence, key primary clinical outcomes) in NVAF patients that initiated OACs in study period.

Primary Objectives

- To assess demographic and clinical characteristics of NVAF patients treated with oral anticoagulants (OACs) in Colombia.
- To describe treatment patterns (eg OAC usage,dose, concomitant medications, persistence)

Exploratory Objectives

- To descriptively assess the time to clinical events (Effectiveness and Safety Outcomes) among patients persistent on OAC therapy

Effectiveness outcomes: First Stroke/ Systemic Embolism; CCI [redacted]
Safety outcomes: Major bleeding CCI [redacted]

Design:
Observational, descriptive study of a retrospective cohort of adult patients diagnosed with NVAF in selected Health Maintenance Organizations (HMO) of Colombia. These patients will be identified from the drug claim database, whose index date of the study will be the first prescription with any of the oral anticoagulants, that is, they are patients with NVAF for the first time starting a therapy with any of the NOACs between January 1, 2013 and June 30, 2018 and follow up period will be among January 2013 to July 2019, to ensure that the last patients can provide follow-up for one year. Patients will be required to have an NVAF diagnosis before or on the index date and health plan for 6 months pre-index date (baseline period).

Population:
The total population of patients treated with any oral anticoagulant between January 1, 2013 and June 30, 2018 will be analyzed in the claim database. This means that patients who start warfarin and NOACs would be included within this period. Patients who initiate NOACs within the established period and who have been exposed to warfarin before 2013 will also be included.

Inclusion criteria:
Patients must meet the following inclusion criteria in order to be able to take part in the study:

a) Patients with a diagnosis of AF considered according to the following diagnoses as per the 10th revision of the International classification of diseases (ICD-10) I48 codes at some point before or on the index date, without recorded valvular disease;

b) Patients who have started treatment with apixaban, dabigatran, rivaroxaban and warfarin for the first time during the identification period, understanding as start of drug delivery by insurer, and after the diagnosis of AF between January 1, 2013 to June 30, 2018;

c) Patients starting apixaban, dabigatran, rivaroxaban from January 1, 2013 to June 30, 2018 in patients previously exposed to warfarin;

d) Patient had continuous health plan enrolment for 6 months pre-index date (baseline period);

e) Patients older than 18 years old on the index date;

f) NVAF diagnosis before or on the index date.

Exclusion criteria:
Patients who meet any of the following criteria will not be included in the study:

a) Patients with any of the following diagnoses prior to the use of the treatments of interest or index date:
   - Valvular heart disease or valve replacement – ICD-10 codes: I05, I06, I07, I08, I09, I21, I22, I34, I35, I36, I37, I38, I39, I700, I702-I709; Q22, Q23, Q25, T82, Z95
   - Pregnancy during the study period. ICD-10 O00-O9A
   - Diagnosis of venous thromboembolism (VTE) – ICD-10 codes: I26, I80 - I82;

b) Individuals with a transitory diagnosis of NVAF prior to the use of the treatments of interest or index date;
c) Exposure to more than one OAC on or after the index date, during the follow-up period;
d) NOAC doses different from those recommended by the manufacturing laboratories.

Data Collection:

The information will be analyzed in two moments: (i) the period of the index date, where the baseline information of patients will be collected; (ii) and the follow-up period, during this period the clinical results will be evaluated as well as the continuation of the treatment in the study population and for specific subpopulations.

Variables:

- Clinical and demographic characteristics
- Treatment patterns (OAC usage, dose, concomitant medications, persistence)

Effectiveness outcomes:

- First [redacted] switch of treatment, first event of stroke/ systemic embolism

Safety outcomes:

- Major bleeding
- [redacted]

Data sources:

The information will be used in the study comes exclusively form secondary sources.

- Claim database:
  - The persistence on therapy and treatment patterns (duration of treatment, changes, persistence), pharmacy claim information, demographic information, diagnosis and insurance data.
- Medical records
  - Baseline demographic and clinical characteristics and the information related to the outcomes of interest (stroke/systematic embolism, bleeding events and death)

Statistic analysis

This type of analysis is descriptive and explanatory, as it depends largely on the sample size. Continuous variables will be presented as means, standard deviation or other measures of central tendency or position, while categorical variables will be presented as frequencies and percentages.

Regarding bivariate analyses of continuous variables with normal behavior, the Student's t test will be performed. In case of presenting non-normal behavior, the Mann-Withney test will be used. For variables that are continuous with several categories, analysis of variance (ANOVA) will be assessed. In the event of presenting a non-normal behavior, the multivariate analysis of variance (MANOVA) test will be carried out. For categorical variables, the X^2 test will be used.

The cumulative incidence of clinical outcomes (stroke/ systemic embolism and major bleeding) will be calculated throughout the study period, from which the incidence or survival curves will be derived using the Kaplan Meier method. Incidence of events will be explored in clinically relevan subgroups based on sample size.

A similar analysis will be performed for the group of patients who have not presented stroke/ systemic embolism or major bleeding events to estimate the time for discontinuation events and change of treatment.

In the independent variables, the significance will be analyzed, as a level of statistical significance $p < 0.05$.

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Milestone	Planned Data
Start of data collection	November 15, 2019
End of data collection	March 31 , 2020
Data analysis	CCI [redacted]
Preliminary report	CCI [redacted]
Final study report	CCI [redacted]

5. RATIONALE AND BACKGROUND

Non-valvular atrial fibrillation (NVAF) is an acute or chronic heart disorder that is associated with an increase in the mortality rate, strokes and other thromboembolic events (1). This is further increased by individual conditions of patients, such as hypertension, abnormal renal or hepatic function, stroke, history of or predisposition to bleeding, people over 65, among others. (2)

One of the standard treatments for management of these patients is usually vitamin K antagonists (VKA, for example, warfarin); in the analysis of net clinical benefits of this therapy it is suggested that the effect of VKA is even more positive in patients with a high score on the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly, drugs/alcohol concomitantly) scale. (3) Another therapeutic alternative is the new oral anticoagulants (NOAC) ─ dabigatran, rivaroxaban and apixaban ─, which according to evidence have advantages in efficacy and safety compared to warfarin (4) and even when the risk of bleeding and stroke are high, the net clinical benefit appears to be greater when compared to warfarin. (5) Likewise, there is a lower prevalence of intracranial hemorrhage and its different subtypes of patients being treated with new oral anticoagulants when compared to warfarin. (6)

While it is true there are several studies that seek to understand the characteristics of patients who were diagnosed with NVAF under different treatment options, and even subpopulation analyses, the evidence at the national level is limited, both in demographic and clinical characteristics and in treatment patterns of this population. In a retrospective descriptive study of an emergency department in a third level care center in the city of Bogota, it was observed that the main comorbidities of patients with atrial fibrillation (AF) were arterial hypertension and heart failure where most patients do not receive anticoagulation. (7) In turn, for the overall population it is estimated that the prevalence of AF in Colombia (4.8%) seems to be higher than that reported in developed countries (0.03% to 1.25%) (8), according to a study conducted in a university hospital in the country (9).

Taking into account the limited knowledge on the use of oral anticoagulants in patients diagnosed with NVAF in the country and, even more in the differences in the response to these therapies in different patient subpopulations. The purpose of this study is to assess the demographic and clinical charateristics, treatment patterns and incidence of events (discontinuation, persistence, key primary clinical outcomes) in NVAF patients that initiated OACs in study period.

6. RESEARCH QUESTION AND OBJECTIVES

Primary Objectives

- To assess demographic and clinical characteristics of NVAF patients treated with oral anticoagulants (OACs) in Colombia.
- To describe treatment patterns (eg. OAC usage, dose, concomitant medications, persistence)

Exploratory Objectives

- To descriptively assess the time to clinical events (Effectiveness and Safety Outcomes) among patients persistent on OAC therapy.

Effectiveness outcomes: First Stroke/ Systemic Embolism; CCI [redacted]
Safety outcomes: Major bleeding, CCI [redacted]

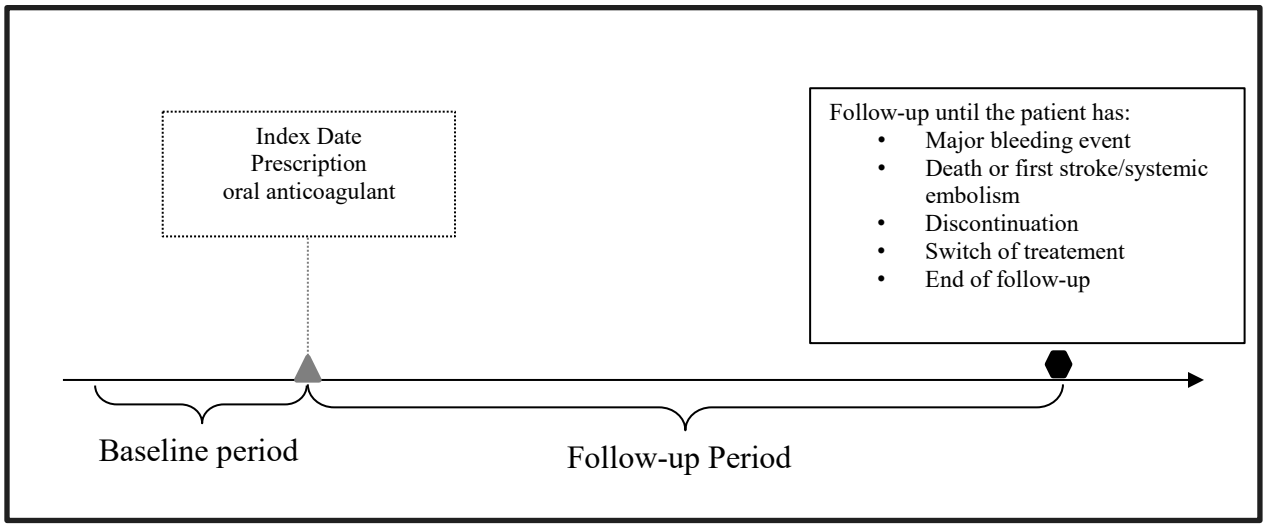
7. RESEARCH METHODS

7.1. Study Design

Observational, descriptive study of a retrospective cohort of adult patients diagnosed with NVAF in selected Health Maintenance Organization (HMO) of Colombia. These patients will be identified from the drug claim database, whose index date of the study will be the first prescription with any of the oral anticoagulants, that is, they are patients with NVAF for the first time starting a therapy with any of the NOACs between January 1, 2013 and June 30, 2018 and follow up period will be among January 2013 to July 2019, to ensure that the last patients can provide follow-up for one year. Patients will be required to have an NVAF diagnosis before or on the index date and health plan for 6 months pre-index date (baseline period).

Following, it will be verified that the patients meet the inclusion and exclusion criteria of the study. Once patients are selected and with the index date of each patient, they will be followed-up until discontinuation, switch of treatment, death or first event of stroke/ systemic embolism, major bleeding event, death or end of follow-up. Patients who are lost to follow-up, change of HMO and do not have access to the medical record will be considered as missing (Figure 1).

Figure 1. Study Design



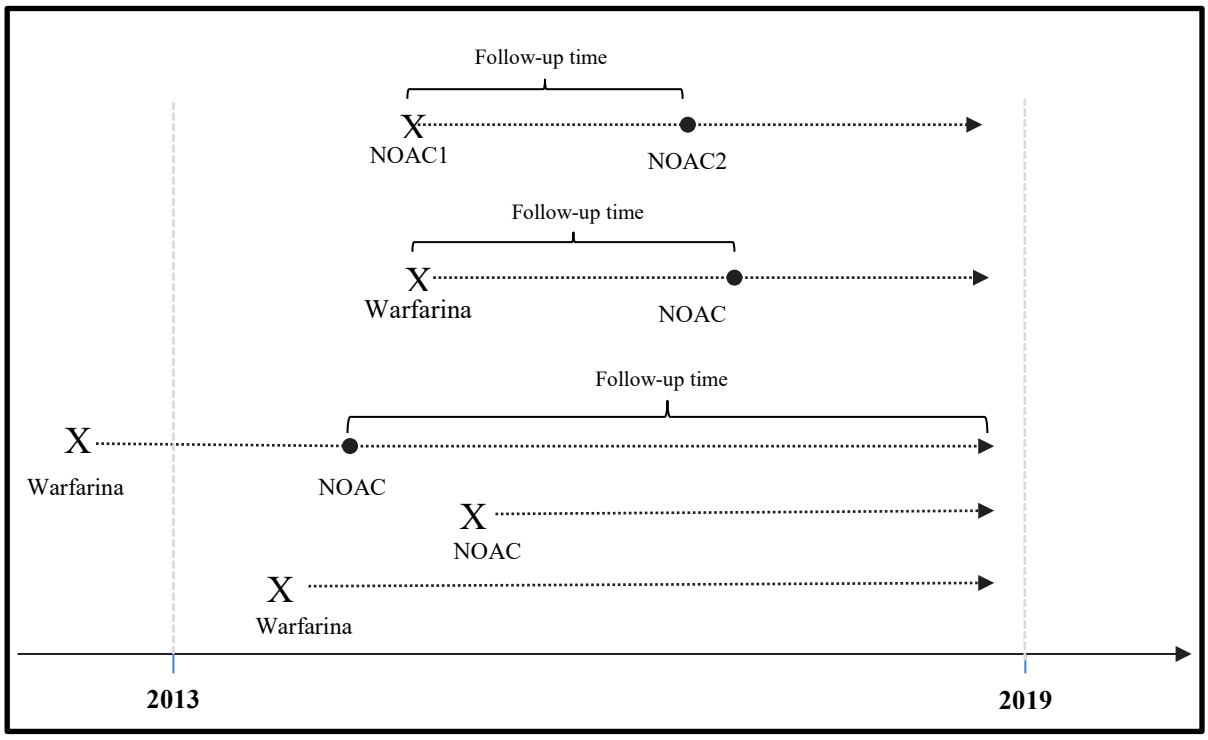
The information will be analyzed in two moments: (i) the period of the index date, where the baseline information of patients will be collected; (ii) and the follow-up period, during this period the clinical results will be evaluated as well as the continuation of the treatment in the study population and for specific subpopulations.

Those patients who initiated treatment with any oral anticoagulant between January 2013 and June 30, 2018 will be included. This means that patients who start warfarin and NOACs would

be included within this period. Patients who initiate NOACs within the established period and who have been exposed to warfarin before 2013 will also be included.

Only the exposure period will be considered with the initial treatment, even in those patients who were on warfarin treatment before 2013, in the latter, the follow-up will be the treatment initiation with a NOAC in case of change after 2013. Follow-up will be carried out until the patient has a switch of treatment, discontinuation, death, first stroke/ systemic embolism, or major bleeding, or until end of follow-up, June 30, 2019 (Figure 2).

Figure 2. Inclusion of Patients



7.2. Setting

The study will be conducted with the Audifarma patient cohort that meets the inclusion and exclusion criteria between the periods from January 2013 to June 30, 2018. The follow up period will be among January 2013 to July 2019, to ensure that the last patients can provide follow-up for one year.

This study will include the entire population in which medical records can be accessed. This will depend on the authorization of the HMOs for review of medical records. Participating patients will be followed-up until the patient has a stroke/systemic embolism, major bleeding, discontinuation, change of treatment or until the data collection period is completed.

7.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

a) Patients with a diagnosis of AF considered according to the following diagnoses as per the ICD I48 codes at some point before or on the index date, without recorded valvular disease;

b) Patients who have started treatment with apixaban, dabigatran, rivaroxaban and warfarin for the first time during the identification period, understanding as start of drug delivery by insurer, and after the diagnosis of AF between January 1, 2013 to June 30, 2018;

c) Patients starting apixaban, dabigatran, rivaroxaban from January 1, 2013 to June 30, 2018 in patients previously exposed to warfarin;

d) Patient had continuous health plan for 6 months pre-index date (baseline period);

e) Patients older than 18 years old on the index date;

f) NVAF diagnosis before or on the index date

7.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

e) Patients with any of the following diagnoses prior to the use of the treatments of interest or index date:

- Valvular heart disease or valve replacement – ICD-10 codes: I05, I06, I07, I08, I09, I22, I34, I35, I36, I37, I38, I39, I700, I702-I709; Q22, Q23, Q25, T82,Z95.
- Pregnancy during the study period. ICD-10 O00-O9A
- Diagnosis of venous thromboembolism (VTE) – ICD-10 codes: I26, I80 - I82;

f) Individuals with a transitory diagnosis of NVAF prior to the use of the treatments of interest or index date;

g) Exposure to more than one OAC on or after the index date, during the follow-up period.

h) NOAC doses different from those recommended by the manufacturing laboratories.

7.2.3. Cohorts

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following four cohorts based on the OAC received on the index date.

1. Apixaban

2. Dabigatran
3. Rivaroxaban
4. Warfarin

Depending on the dosage of the NOAC prescribed on the index date, and in comparison to the standard conventions of total daily doses, patients may be classified into 3 different groups:

- **High doses:** apixaban 10 mg/day - rivaroxaban: 20 mg/day - dabigatran: 300 mg/day;
- **Low doses:** apixaban 5 mg/day - rivaroxaban: 15 mg/day - dabigatran: 220 mg/day
- **Other doses:** to be excluded, doses not recommended by the manufacturing laboratories.

7.3. Variables

The described variables are classified into two variable groups according to the role, the clinical outcome and baseline (demographic, clinical, treatment variables). The latter include the possible subgroups to consider. These analyses are initially exploratory to the extent that the specific analyses may be performed according to the sample collected.

Table 1. Table of Variables

Variable	Role	Data source (s)	Operational definition
Age	Demographic characteristic	Medical record	Birthday
Gender	Demographic characteristic	Medical record	Male, female, other
Race	Demographic characteristic	Medical record	White, half-breed, indigenous, black, others
Weight	Demographic characteristic	Medical record	Kg
Height	Demographic characteristic	Medical record	Mt (meters)
Body mass index	Demographic characteristic	Medical record	Kg/mt2
City of residence	Demographic characteristic	Medical record	Cities of Colombia
Time to diagnosis to NVAF	Clinical characteristic	Medical record	Date (dd/mm/yy)
High alcohol intake at OAC prescription date	Clinical characteristic	Medical record	Yes, No

Variable	Role	Data source (s)	Operational definition
Diabetes	Clinical characteristic	Medical record	No, without chronic complication, with end-organ damage
Liver disease	Clinical characteristic	Medical record	No, mild, moderade, severe
Hypertension	Clinical characteristic	Medical record	Diagnosis of hypertension (Yes, No)
Uncontrolled hypertension at OAC prescription date	Clinical characteristic	Medical record	Yes, No
Rheumatic disease	Clinical characteristic	Medical record	Yes, No
Acquired Immune Deficiency Syndrome (AIDS)	Clinical characteristic	Medical record	Yes, No
Severe renal disease (dialysis, organ transplant)	Clinical characteristic	Medical record	Yes, No
Moderade renal disease (creatinine > 3 mg/dL)	Clinical characteristic	Medical record	Yes, No
Chronic heart failure	Clinical characteristic	Medical record	Yes, No
Myocardial infarction	Clinical characteristic	Medical record	Yes, No
Chronic obstructive pulmonary disease (COPD)	Clinical characteristic	Medical record	Yes, No
Peripheral vascular disease	Clinical characteristic	Medical record	Yes, No
Stroke or transient ischemic attack (TIA)	Clinical characteristic	Medical record	Yes, No
Dementia	Clinical characteristic	Medical record	Yes, No
Hemiplegia	Clinical characteristic	Medical record	Yes, No
Connective tissue disease	Clinical characteristic	Medical record	Yes, No
Leukemia	Clinical characteristic	Medical record	Yes, No

Variable	Role	Data source (s)	Operational definition
Malignant lymphoma	Clinical characteristic	Medical record	Yes, No
Peptic ulcer disease	Clinical characteristic	Medical record	Yes, No
Metastatic solid tumor	Clinical characteristic	Medical record	Yes, No
History of ischemic or hemorrhagic stroke	Clinical characteristic	Medical record	Yes, No
History of TIA	Clinical characteristic	Medical record	Yes, No
History of de tromboembolismo	Clinical characteristic	Medical record	Yes, No
Enfermedad coronaria	Clinical characteristic	Medical record	Yes, No
History of de hemorragia gastrointestinal	Clinical characteristic	Medical record	Yes, No
History of Intracranial bleeding	Clinical characteristic	Medical record	Yes, No
History of Other bleeding	Clinical characteristic	Medical record	Yes, No
Bleeding history or predisposition at start OAC treatment	Clinical characteristic	Medical record	Yes, No
INR > 60% at start OAC treatment	Clinical characteristic	Medical record	Yes, No
Use of aspirin at start OAC treatment	Clinical characteristic	Medical record	Yes, No
Use of clopidogrel at start OAC treatment	Clinical characteristic	Medical record	Yes, No
Use of NSAIDs at start OAC treatment	Clinical characteristic	Medical record	Yes, No
HASBLED at start OAC treatment	Clinical characteristic	Medical record	Score – number higher than 0
CHA2DS2-VASc at start OAC treatment	Clinical characteristic	Medical record	Score – number higher than 0
Anaemia at start OAC treatment	Clinical characteristic	Medical record	Yes, No
Stroke	Clinical outcome	Medical record	Yes, No
Time to stroke	Clinical outcome	Medical record	Date of event dd/mm/yy

Variable	Role	Data source (s)	Operational definition
Type of stroke	Clinical outcome	Medical record	Ischemic stroke, Haemorrhagic or not specified
Pulmonary embolism	Clinical outcome	Medical record	Yes, No
Time to pulmonary embolism	Clinical outcome	Medical record	Date of event dd/mm/yy
Gastrointestinal bleeding	Clinical outcome	Medical record	Yes, No
Time to gastrointestinal bleeding	Clinical outcome	Medical record	Date of event dd/mm/yy
Intracranial bleeding	Clinical outcome	Medical record	Yes, No
Time to Intracranial bleeding	Clinical outcome	Medical record	Date of event dd/mm/yy
Other major bleeding	Clinical outcome	Medical record	Yes, No
Time to other major bleeding	Clinical outcome	Medical record	Date of event dd/mm/yy
CCI [redacted]			
Persistence	Clinical outcome	Claim databases	Yes, No
OAC treatment	Treatment	Claim databases	Warfarin, apixaban, rivaroxaban, dabigatran
Diagnosis at index date	Treatment	Claim databases	Diagnosis AF based on ICD-10
Date of OAC prescription	Treatment	Claim databases	Date reported dd/mm/yy
Dosage of the initial OAC treatment	Treatment	Claim databases	Mg per dose
Initial frequency of OAC treatment	Treatment	Claim databases	Number of doses at initial OAC treatment
OAC escalation	Treatment	Claim databases	Yes, No
Type of OAC escalation	Treatment	Claim databases	Dose increase or dose decrease
Time to OAC escalation	Treatment	Claim databases	Date reported dd/mm/yy
CCI [redacted]			

Variable	Role	Data source (s)	Operational definition
CCI			
INR testing monthly in patients with warfarin	Treatment	Medical record	INR reported in the medical record per month
Switch to another OAC treatment:	Treatment	Claim databases	Yes, No
Time to Switch to another OAC treatment	Treatment	Claim databases	Date reported dd/mm/yy
Causa de cambio	Treatment	Medical record	Adverse events, effectiveness, adherence, patient preference, administrative problems, not reported, others
Concomitant therapies by OAC prescription	Treatment	Medical record	NSAIDs, Angiotensin-converting-enzyme (ACE) inhibitors, Amiodarone, Beta-blockers, Angiotensin II receptor blockers (ARBs), Aspirin, Clopidogrel, Digoxin, Diuretics, calcium blockers, statins, proton pump inhibitor, selective H2 antagonists, antidiabetics, insulin, serotonin reuptake inhibitors
Previously exposed to warfarin	Treatment	Claim databases	Yes, No

7.3.1. Definition of outcome variables

- **OAC escalation**: The dose escalation of the OAC dose will be considered as a dose frequency according to the index dose, as well as the follow-up doses. The proportion of patients experiencing "dose increase", "dose decrease" or "no change" during follow-up with respect to the index dose will be measured, and the time to dose increase or decrease will be calculated.

[redacted]

[redacted]

- **Switch of treatment:** A switch among anticoagulants will be defined as a prescription filled for non-index anticoagulants within +/- 30 days after the date of discontinuation.
- **Persistence:** Persistence will be defined as the time under OAC therapy, calculated as the time in days from the index date to the date of discontinuation or change to treatment. As previously stated, discontinuation will be defined as a change of treatment, that is, to another OAC, or when there is no evidence of a prescription for 60 days from the last supply delivered, whichever comes first.

  Therefore, if a patient does not receive his next prescription for the OAC therapy within 60 days after the end of the previous prescription, it will be considered that he discontinued therapy, and the date of the last prescription will be considered as the final date of persistence.

  Persistence with OAC therapy will be considered during the period of individual patient follow-up. Patients will be censored at the end of their follow-up period.
- **Major bleeding:** Patients presenting any of the following diagnoses during the follow-up period:

ICD-10	Description
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage
I692	Sequelae of other nontraumatic intracranial haemorrhage
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage
I850	Oesophageal varices with bleeding
K250	Acute with haemorrhage

ICD-10	Description
K252	Acute with both haemorrhage and perforation
K254	Chronic or unspecified with haemorrhage
K256	Chronic or unspecified with both haemorrhage and perforation
K260	Acute with haemorrhage
K262	Acute with both haemorrhage and perforation
K264	Chronic or unspecified with haemorrhage
K266	Chronic or unspecified with both haemorrhage and perforation
K270	Acute with haemorrhage
K272	Acute with both haemorrhage and perforation
K274	Chronic or unspecified with haemorrhage
K276	Chronic or unspecified with both haemorrhage and perforation
K280	Acute with haemorrhage
K282	Acute with both haemorrhage and perforation
K284	Chronic or unspecified with haemorrhage
K286	Chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K625	Haemorrhage of anus and rectum
K920	Haematemesis
K921	Melaena
K922	Gastro-intestinal haemorrhage, unspecified
D62	Acute posthaemorrhagic anaemia
H356	Retinal haemorrhage
H431	Vitreous haemorrhage
H450	Vitreous haemorrhage in diseases classified elsewhere
H922	Otorrhagia
I312	Haemopericardium, not elsewhere classified
J942	Haemothorax
R04	Haemorrhage from respiratory passages
K661	Haemoperitoneum
M250	Haemarthrosis
N02	Recurrent and persistent haematuria
N938	Other specified abnormal uterine and vaginal bleeding
N939	Abnormal uterine and vaginal bleeding, unspecified
N950	Postmenopausal bleeding
R31	Unspecified haematuria
R58	Haemorrhage, not elsewhere classified
T792	Traumatic secondary and recurrent haemorrhage

- **Ischemic stroke:** Patients who report the following diagnoses in the medical history during the follow-up period:

ICD-10	Description
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

Except I63.6 Cerebral infarction due to thrombosis of cerebral veins, non-pyogenic

- **Hemorrhagic stroke:** Patients presenting the following diagnosis in the medical record:

ICD-10	Description
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage

- **Systemic embolism:** Patients who report any of the following diagnoses:

ICD-10	Description
I74	Arterial embolism and thrombosis

Definition of covariates

- **Age:** Categorical variable, continues in years. It will be defined from the index date and will be used to assign patients to the following age categories:

18 - 49
50 - 59
60 - 69
70 - 79
≥ 80 years old.

- **Charlson Index**: Charlson comorbidity index will be created during the reference period taking into account the following score:

1 point each:

- *Myocardial infarction*

ICD-10	Description
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I252	Old myocardial infarction

- *Congestive heart failure*

ICD-10	Description
I110	Hypertensive heart disease with (congestive) heart failure
I130	Hypertensive heart and renal disease with (congestive) heart failure
I132	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I110	Hypertensive heart disease with (congestive) heart failure

- *Peripheral vascular disease*

ICD-10	Description
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I731	Thromboangiitis obliterans [Buerger]
I738	Other specified peripheral vascular diseases
I739	Peripheral vascular disease, unspecified

ICD-10	Description
I771	Stricture of artery
I790	Aneurysm of aorta in diseases classified elsewhere
I792	Peripheral angiopathy in diseases classified elsewhere
K551	Chronic vascular disorders of intestine
K558	Other vascular disorders of intestine
K559	Vascular disorder of intestine, unspecified
Z958	Presence of other cardiac and vascular implants and grafts
Z959	Presence of cardiac and vascular implant and graft, unspecified

- *Dementia*

ICD-10	Description
F00	Dementia in Alzheimer's disease
F01	Vascular dementia
F02	Dementia in other diseases classified elsewhere
F03	Unspecified dementia
G30	Alzheimer's disease
F051	Delirium superimposed on dementia
G311	Senile degeneration of brain, not elsewhere classified

- *Cerebrovascular disease*

ICD-10	Description
G45	Transient cerebral ischaemic attacks and related syndromes
G46	Vascular syndromes of brain in cerebrovascular diseases
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
H340	Transient retinal artery occlusion

- *Chronic pulmonary disease*

ICD-10	Description
J40	Bronchitis, not specified as acute or chronic
J41	Simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	Other chronic obstructive pulmonary disease
J45	Asthma
J46	Status asthmaticus
J47	Bronchiectasis
J60	Coalworker's pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibres
J62	Pneumoconiosis due to dust containing silica

ICD-10	Description
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J65	Pneumoconiosis associated with tuberculosis
J66	Airway disease due to specific organic dust
J67	Hypersensitivity pneumonitis due to organic dust
I278	Other specified pulmonary heart diseases
I279	Pulmonary heart disease, unspecified
J684	Chronic respiratory conditions due to chemicals, gases, fumes and vapours
J701	Chronic and other pulmonary manifestations due to radiation
J703	Chronic drug-induced interstitial lung disorders

- *Connective tissue disease*

ICD-10	Description
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M315	Giant cell arteritis with polymyalgia rheumatica
M351	Other overlap syndromes
M353	Polymyalgia rheumatica
M360	Dermato(poly)myositis in neoplastic disease

- *Ulcer disease*

ICD-10	Description
K25	Gastric ulcer
K26	Duodenal ulcer
K27	Peptic ulcer, site unspecified
K28	Gastrojejunal ulcer

- *Mild liver disease*

ICD-10	Description
B18	Chronic viral hepatitis
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K700	Alcoholic fatty liver
K701	Alcoholic hepatitis
K702	Alcoholic fibrosis and sclerosis of liver
K703	Alcoholic cirrhosis of liver
K709	Alcoholic liver disease, unspecified
K717	Toxic liver disease with fibrosis and cirrhosis of liver
K713	Toxic liver disease with chronic persistent hepatitis
K714	Toxic liver disease with chronic lobular hepatitis
K715	Toxic liver disease with chronic active hepatitis
K760	Fatty (change of) liver, not elsewhere classified
K762	Central haemorrhagic necrosis of liver
K763	Infarction of liver
K764	Peliosis hepatis
K768	Other specified diseases of liver
K769	Liver disease, unspecified
Z944	Liver transplant status
B18	Chronic viral hepatitis
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K700	Alcoholic fatty liver
K701	Alcoholic hepatitis
K702	Alcoholic fibrosis and sclerosis of liver
K703	Alcoholic cirrhosis of liver
K709	Alcoholic liver disease, unspecified
K717	Toxic liver disease with fibrosis and cirrhosis of liver
K713	Toxic liver disease with chronic persistent hepatitis
K714	Toxic liver disease with chronic lobular hepatitis

ICD-10	Description
K715	Toxic liver disease with chronic active hepatitis
K760	Fatty (change of) liver, not elsewhere classified
K762	Central haemorrhagic necrosis of liver
K763	Infarction of liver
K764	Peliosis hepatis
K768	Other specified diseases of liver
K769	Liver disease, unspecified
Z944	Liver transplant status

- *Diabetes without chronic complication*

ICD-10	Description
E100	Insulin-dependent diabetes mellitus with coma
E101	Insulin-dependent diabetes mellitus with ketoacidosis
E106	Insulin-dependent diabetes mellitus with other specified complications
E108	Insulin-dependent diabetes mellitus with unspecified complications
E109	Insulin-dependent diabetes mellitus without complications
E110	Non-insulin-dependent diabetes mellitus with coma
E111	Non-insulin-dependent diabetes mellitus with ketoacidosis
E116	Non-insulin-dependent diabetes mellitus with other specified complications
E118	Non-insulin-dependent diabetes mellitus with unspecified complications
E119	Non-insulin-dependent diabetes mellitus without complications
E120	Malnutrition-related diabetes mellitus with coma
E121	Malnutrition-related diabetes mellitus with ketoacidosis
E126	Malnutrition-related diabetes mellitus with other specified complications
E128	Malnutrition-related diabetes mellitus with unspecified complications
E129	Malnutrition-related diabetes mellitus without complications
E130	Other specified diabetes mellitus with coma
E131	Other specified diabetes mellitus with ketoacidosis
E136	Other specified diabetes mellitus with other specified complications
E138	Other specified diabetes mellitus with unspecified complications
E139	Other specified diabetes mellitus without complications
E140	Unspecified diabetes mellitus with coma
E141	Unspecified diabetes mellitus with ketoacidosis
E146	Unspecified diabetes mellitus with other specified complications
E148	Unspecified diabetes mellitus with unspecified complications
E149	Unspecified diabetes mellitus without complications
E100	Insulin-dependent diabetes mellitus with coma
E101	Insulin-dependent diabetes mellitus with ketoacidosis
E106	Insulin-dependent diabetes mellitus with other specified complications
E108	Insulin-dependent diabetes mellitus with unspecified complications
E109	Insulin-dependent diabetes mellitus without complications
E110	Non-insulin-dependent diabetes mellitus with coma
E111	Non-insulin-dependent diabetes mellitus with ketoacidosis
E116	Non-insulin-dependent diabetes mellitus with other specified complications
E118	Non-insulin-dependent diabetes mellitus with unspecified complications
E119	Non-insulin-dependent diabetes mellitus without complications
E120	Malnutrition-related diabetes mellitus with coma
E121	Malnutrition-related diabetes mellitus with ketoacidosis
E126	Malnutrition-related diabetes mellitus with other specified complications
E128	Malnutrition-related diabetes mellitus with unspecified complications
E129	Malnutrition-related diabetes mellitus without complications

ICD-10	Description
E130	Other specified diabetes mellitus with coma
E131	Other specified diabetes mellitus with ketoacidosis
E136	Other specified diabetes mellitus with other specified complications
E138	Other specified diabetes mellitus with unspecified complications
E139	Other specified diabetes mellitus without complications
E140	Unspecified diabetes mellitus with coma
E141	Unspecified diabetes mellitus with ketoacidosis
E146	Unspecified diabetes mellitus with other specified complications
E148	Unspecified diabetes mellitus with unspecified complications
E149	Unspecified diabetes mellitus without complications

2 point each:

- *Hemiplegia or paraplegia*

ICD-10	Description
G81	Hemiplegia
G82	Paraplegia and tetraplegia
G041	Tropical spastic paraplegia
G114	Hereditary spastic paraplegia
G801	Spastic diplegia
G802	Infantile hemiplegia
G830	Diplegia of upper limbs
G831	Monoplegia of lower limb
G832	Monoplegia of upper limb
G833	Monoplegia, unspecified
G834	Cauda equina syndrome
G839	Paralytic syndrome, unspecified
G81	Hemiplegia
G82	Paraplegia and tetraplegia
G041	Tropical spastic paraplegia
G114	Hereditary spastic paraplegia
G801	Spastic diplegia
G802	Infantile hemiplegia
G830	Diplegia of upper limbs
G831	Monoplegia of lower limb
G832	Monoplegia of upper limb
G833	Monoplegia, unspecified
G834	Cauda equina syndrome
G839	Paralytic syndrome, unspecified

- *Moderate or severe renal disease*

ICD-10	Description
N18	Chronic renal failure
N19	Unspecified renal failure
N052	Diffuse membranous glomerulonephritis
N053	Diffuse mesangial proliferative glomerulonephritis
N054	Diffuse endocapillary proliferative glomerulonephritis
N055	Diffuse mesangiocapillary glomerulonephritis
N056	Dense deposit disease
N057	Diffuse crescentic glomerulonephritis

ICD-10	Description
N250	Renal osteodystrophy
I120	Hypertensive renal disease with renal failure
I131	Hypertensive heart and renal disease with renal failure
N032	Diffuse membranous glomerulonephritis
N033	Diffuse mesangial proliferative glomerulonephritis
N034	Diffuse endocapillary proliferative glomerulonephritis
N035	Diffuse mesangiocapillary glomerulonephritis
N036	Dense deposit disease
N037	Diffuse crescentic glomerulonephritis
Z490	Preparatory care for dialysis
Z491	Extracorporeal dialysis
Z492	Other dialysis
Z940	Kidney transplant status
Z992	Dependence on renal dialysis

- *Diabetes with end-organ damage*

ICD-10	Description
E102	Insulin-dependent diabetes mellitus with renal complications
E103	Insulin-dependent diabetes mellitus with ophthalmic complications
E104	Insulin-dependent diabetes mellitus with neurological complications
E105	Insulin-dependent diabetes mellitus with peripheral circulatory complications
E107	Insulin-dependent diabetes mellitus with multiple complications
E112	Non-insulin-dependent diabetes mellitus with renal complications
E113	Non-insulin-dependent diabetes mellitus with ophthalmic complications
E114	Non-insulin-dependent diabetes mellitus with neurological complications
E115	Non-insulin-dependent diabetes mellitus with peripheral circulatory complications
E117	Non-insulin-dependent diabetes mellitus with multiple complications
E122	Malnutrition-related diabetes mellitus with renal complications
E123	Malnutrition-related diabetes mellitus with ophthalmic complications
E124	Malnutrition-related diabetes mellitus with neurological complications
E125	Malnutrition-related diabetes mellitus with peripheral circulatory complications
E127	Malnutrition-related diabetes mellitus with multiple complications
E132	Other specified diabetes mellitus with renal complications
E133	Other specified diabetes mellitus with ophthalmic complications
E134	Other specified diabetes mellitus with neurological complications
E135	Other specified diabetes mellitus with peripheral circulatory complications
E137	Other specified diabetes mellitus with multiple complications
E142	Unspecified diabetes mellitus with renal complications
E143	Unspecified diabetes mellitus with ophthalmic complications
E144	Unspecified diabetes mellitus with neurological complications
E145	Unspecified diabetes mellitus with peripheral circulatory complications
E147	Unspecified diabetes mellitus with multiple complications
E102	Insulin-dependent diabetes mellitus with renal complications
E103	Insulin-dependent diabetes mellitus with ophthalmic complications
E104	Insulin-dependent diabetes mellitus with neurological complications
E105	Insulin-dependent diabetes mellitus with peripheral circulatory complications
E107	Insulin-dependent diabetes mellitus with multiple complications
E112	Non-insulin-dependent diabetes mellitus with renal complications
E113	Non-insulin-dependent diabetes mellitus with ophthalmic complications
E114	Non-insulin-dependent diabetes mellitus with neurological complications
E115	Non-insulin-dependent diabetes mellitus with peripheral circulatory complications

ICD-10	Description
E117	Non-insulin-dependent diabetes mellitus with multiple complications
E122	Malnutrition-related diabetes mellitus with renal complications
E123	Malnutrition-related diabetes mellitus with ophthalmic complications
E124	Malnutrition-related diabetes mellitus with neurological complications
E125	Malnutrition-related diabetes mellitus with peripheral circulatory complications
E127	Malnutrition-related diabetes mellitus with multiple complications
E132	Other specified diabetes mellitus with renal complications
E133	Other specified diabetes mellitus with ophthalmic complications
E134	Other specified diabetes mellitus with neurological complications
E135	Other specified diabetes mellitus with peripheral circulatory complications
E137	Other specified diabetes mellitus with multiple complications
E142	Unspecified diabetes mellitus with renal complications
E143	Unspecified diabetes mellitus with ophthalmic complications
E144	Unspecified diabetes mellitus with neurological complications
E145	Unspecified diabetes mellitus with peripheral circulatory complications
E147	Unspecified diabetes mellitus with multiple complications

- *Any tumor (including lymphoma and leukemia except malignant neoplasms of skin)*

ICD-10	Description
C00	Malignant neoplasm of lip
C01	Malignant neoplasm of base of tongue
C02	Malignant neoplasm of other and unspecified parts of tongue
C03	Malignant neoplasm of gum
C04	Malignant neoplasm of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of other and unspecified parts of mouth
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of other and unspecified major salivary glands
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of pyriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15	Malignant neoplasm of oesophagus
C16	Malignant neoplasm of stomach
C17	Malignant neoplasm of small intestine
C18	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21	Malignant neoplasm of anus and anal canal
C22	Malignant neoplasm of liver and intrahepatic bile ducts
C23	Malignant neoplasm of gallbladder
C24	Malignant neoplasm of other and unspecified parts of biliary tract
C25	Malignant neoplasm of pancreas
C26	Malignant neoplasm of other and ill-defined digestive organs
C30	Malignant neoplasm of nasal cavity and middle ear
C31	Malignant neoplasm of accessory sinuses
C32	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38	Malignant neoplasm of heart, mediastinum and pleura
C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40	Malignant neoplasm of bone and articular cartilage of limbs
C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43	Malignant melanoma of skin
C45	Mesothelioma
C46	Kaposi's sarcoma
C47	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48	Malignant neoplasm of retroperitoneum and peritoneum
C49	Malignant neoplasm of other connective and soft tissue
C50	Malignant neoplasm of breast
C51	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53	Malignant neoplasm of cervix uteri

ICD-10	Description
C54	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56	Malignant neoplasm of ovary
C57	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C60	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C62	Malignant neoplasm of testis
C63	Malignant neoplasm of other and unspecified male genital organs
C64	Malignant neoplasm of kidney, except renal pelvis
C65	Malignant neoplasm of renal pelvis
C66	Malignant neoplasm of ureter
C67	Malignant neoplasm of bladder
C68	Malignant neoplasm of other and unspecified urinary organs
C69	Malignant neoplasm of eye and adnexa
C70	Malignant neoplasm of meninges
C71	Malignant neoplasm of brain
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73	Malignant neoplasm of thyroid gland
C74	Malignant neoplasm of adrenal gland
C75	Malignant neoplasm of other endocrine glands and related structures
C76	Malignant neoplasm of other and ill-defined sites
C81	Hodgkin's disease
C82	Follicular [nodular] non-Hodgkin's lymphoma
C83	Diffuse non-Hodgkin's lymphoma
C84	Peripheral and cutaneous T-cell lymphomas
C85	Other and unspecified types of non-Hodgkin's lymphoma
C88	Malignant immunoproliferative diseases
C90	Multiple myeloma and malignant plasma cell neoplasms
C91	Lymphoid leukaemia
C92	Myeloid leukaemia
C93	Monocytic leukaemia
C94	Other leukaemias of specified cell type
C95	Leukaemia of unspecified cell type
C96	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue
C97	Malignant neoplasms of independent (primary) multiple sites

3 points each:

- *Moderate or severe liver disease*

ICD-10	Description
K704	Alcoholic hepatic failure
K711	Toxic liver disease with hepatic necrosis
K721	Chronic hepatic failure
K729	Hepatic failure, unspecified
K765	Hepatic veno-occlusive disease
K766	Portal hypertension
K767	Hepatorenal syndrome
I850	Oesophageal varices with bleeding
I859	Oesophageal varices without bleeding
I864	Gastric varices
I982	Oesophageal varices in diseases classified elsewhere

6 points each:

- *Metastatic solid tumor*

ICD-10	Description
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other sites
C80	Malignant neoplasm without specification of site

- *Human immunodeficiency virus (HIV)-AIDS*

ICD-10	Description
B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases
B24	Unspecified human immunodeficiency virus [HIV] disease
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

One point was added to the total score of the Charlson index for each decade after the age of 50 years:

50 to 59: 1 point,

60 to 69: 2 points,

70 to 79: 3 points,

80 to 89: 4 points,

>90: 5 points.

- **CHA_2DS_2-VACs score**: The CHA_2DS_2-VASc score will be used to analyze the effect of stratification of the risk of stroke. CHA_2DS_2-VASc scores range from 0 to 9. ICD-10 diagnostic codes for each component of the index when applicable:
-

C: I11.0, I13.0, I13.2, I50
Score 1 point

ICD-10	Description
I110	Hypertensive heart disease with (congestive) heart failure
I130	Hypertensive heart and renal disease with (congestive) heart failure
I132	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I50	Heart failure

H: I10, I11, I12, I13, I15
Score 1 point

ICD-10	Description
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension

A: Age ≥75 years
Score 2 points

D: E10 a E14
Score 1 point

ICD-10	Description
E10	Insulin-dependent diabetes mellitus
E11	Non-insulin-dependent diabetes mellitus
E12	Malnutrition-related diabetes mellitus
E13	Other specified diabetes mellitus
E14	Unspecified diabetes mellitus

S_2: G45.0, G45.1, G45.2, G45.3, G45.8, G45.9
Score 2 points

ICD-10	Description
G450	Vertebro-basilar artery syndrome
G451	Carotid artery syndrome (hemispheric)
G452	Multiple and bilateral precerebral artery syndromes
G453	Amaurosis fugax
G458	Other transient cerebral ischaemic attacks and related syndromes

V: I26, I82, I21- I25, I65, I70- I72, I73.1, I73.8, I73.9, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Score 1 point

ICD-10	Description
I26	Pulmonary embolism
I82	Other venous embolism and thrombosis
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I72	Other aneurysm
I731	Thromboangiitis obliterans [Buerger]
I738	Other specified peripheral vascular diseases
I739	Peripheral vascular disease, unspecified
I790	Aneurysm of aorta in diseases classified elsewhere
I792	Peripheral angiopathy in diseases classified elsewhere
K551	Chronic vascular disorders of intestine
K558	Other vascular disorders of intestine

A: Age 64-74 years
Score 1 point

Sc: Sex category (female)
Score 1

- **HASBLED score:** The HAS-BLED score will be used to analyze the risk of bleeding. The modified HAS-BLED score ranges from 0 to 8. ICD-10 diagnostic codes for each component of the index when applicable:
-

H: I10, I11, I12, I13, I15
Score 1 point

ICD-10	Description
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension

A: N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N057, N18- N19, N25.0, Z49.0, Z49.2, Z94.0, Z99.2

Score 1 point

ICD-10	Description
N032	Diffuse membranous glomerulonephritis
N033	Diffuse mesangial proliferative glomerulonephritis
N034	Diffuse endocapillary proliferative glomerulonephritis
N035	Diffuse mesangiocapillary glomerulonephritis
N036	Dense deposit disease
N037	Diffuse crescentic glomerulonephritis
N052	Diffuse membranous glomerulonephritis
N053	Diffuse mesangial proliferative glomerulonephritis
N054	Diffuse endocapillary proliferative glomerulonephritis
N055	Diffuse mesangiocapillary glomerulonephritis
N056	Dense deposit disease
N057	Diffuse crescentic glomerulonephritis
N18	Chronic renal failure
N19	Unspecified renal failure
N250	Renal osteodystrophy
Z490	Preparatory care for dialysis
Z492	Other dialysis
Z940	Kidney transplant status
Z992	Dependence on renal dialysis

A: B18, I85, I86.4, I98.2, K70, K71.1,K71.3, K71.4, K71.5, K71.7, K72.1, K72.9, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.5, K76.6, K76.7, K76.8, K76.9, Z94.4

Score 1 point

ICD-10	Description
B18	Chronic viral hepatitis
I85	Oesophageal varices
I864	Gastric varices
I982	Oesophageal varices in diseases classified elsewhere
K70	Alcoholic liver disease
K711	Toxic liver disease with hepatic necrosis
K713	Toxic liver disease with chronic persistent hepatitis
K714	Toxic liver disease with chronic lobular hepatitis
K715	Toxic liver disease with chronic active hepatitis
K717	Toxic liver disease with fibrosis and cirrhosis of liver
K721	Chronic hepatic failure
K729	Hepatic failure, unspecified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K760	Fatty (change of) liver, not elsewhere classified
K762	Central haemorrhagic necrosis of liver
K763	Infarction of liver
K764	Peliosis hepatis
K765	Hepatic veno-occlusive disease
K766	Portal hypertension
Z944	Liver transplant status

S: I64, I69.3, D62, D68.3, D69.8, D69.9, H31.3, H35.6, H43.1, H45.0, H92.2, I23.0, I31.2

Score 1 point

ICD-10	Description
I64	Stroke, not specified as haemorrhage or infarction
I693	Sequelae of cerebral infarction
D62	Acute posthaemorrhagic anaemia
D683	Haemorrhagic disorder due to circulating anticoagulants
D698	Other specified haemorrhagic conditions
D699	Haemorrhagic condition, unspecified
H313	Choroidal haemorrhage and rupture
H356	Retinal haemorrhage
H431	Vitreous haemorrhage
H450	Vitreous haemorrhage in diseases classified elsewhere
H922	Otorrhagia
I230	Haemopericardium as current complication following acute myocardial infarction
I312	Haemopericardium, not elsewhere classified

B: I60, I61, I62, I85.0, I98.3, J94.2, 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, K66.1, K76.2, K92.0, K92.1, K92.2

Score 1 point

ICD-10	Description
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I850	Oesophageal varices with bleeding
I983	Oesophageal varices with bleeding, , not elsewhere classified
J942	Haemothorax
K226	Gastro-oesophageal laceration-haemorrhage syndrome
K250	Acute with haemorrhage
K252	Acute with both haemorrhage and perforation
K254	Chronic or unspecified with haemorrhage
K256	Chronic or unspecified with both haemorrhage and perforation
K260	Acute with haemorrhage
K262	Acute with both haemorrhage and perforation
K264	Chronic or unspecified with haemorrhage
K266	Chronic or unspecified with both haemorrhage and perforation
K270	Acute with haemorrhage
K272	Acute with both haemorrhage and perforation
K274	Chronic or unspecified with haemorrhage
K276	Chronic or unspecified with both haemorrhage and perforation
K280	Acute with haemorrhage
K282	Acute with both haemorrhage and perforation
K284	Chronic or unspecified with haemorrhage
K286	Chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K625	Haemorrhage of anus and rectum
K661	Haemoperitoneum
K762	Central haemorrhagic necrosis of liver
K920	Haematemesis
K921	Melaena
K922	Gastro-intestinal haemorrhage, unspecified

L: INR
Score 1 point

E: Elderly ≥ 65 years
Score 1 point

D: E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, T51, Y90.4, Y90.5, Y90.6, Y90.7, Y90.8, Y91.2, Y91.3, Z50.2, Z71.4, Z72.1
1 or 2 point each

ICD-10	Description
E244	Alcohol-induced pseudo-Cushing's syndrome
F10	Mental and behavioural disorders due to use of alcohol
G312	Degeneration of nervous system due to alcohol
G621	Alcoholic polyneuropathy
G721	Alcoholic myopathy
I426	Alcoholic cardiomyopathy
K292	Alcoholic gastritis
K852	Alcohol-induced acute pancreatitis
K860	Alcohol-induced chronic pancreatitis
T51	Toxic effect of alcohol
Y904	Blood alcohol level of 80-99 mg/100 ml
Y905	Blood alcohol level of 100-119 mg/100 ml
Y906	Blood alcohol level of 120-199 mg/100 ml
Y907	Blood alcohol level of 200-239 mg/100 ml
Y908	Blood alcohol level of 240 mg/100 ml or more
Y912	Severe alcohol intoxication
Y913	Very severe alcohol intoxication
Z502	Alcohol rehabilitation
Z714	Alcohol abuse counselling and surveillance
Z721	Alcohol use

Codes Anatomical Therapeutic Chemical (ATC): B01AC, M01A

- **SMAe-TT$_2$R2 score:** The estimation of SAMe-TT$_2$R$_2$ will be performed by adding the following variables:

  Sex (female) Score 1 point

  Age (<60 years) Score 1 point

  Medical history (history of more than two of the following: hypertension, diabetes, coronaty artery disease or myocardial infactions, peripheral artery disease, heart failure, stroke; pulmonary, hepatic, or renal disease**)** Score 1 point

  Treatment (interacting medications , amiodarone ATC- C01BD01**)** Score 1 point

  Tobacco use (within 2 years**)** Score 2 points

Race (non-Caucasian**)** Score 2 points

Table 2. Baseline variables or possible confounders

Variable	Operacional definition ICD-10
Diabetes	E10 Insulin-dependent diabetes mellitus E11 Non-insulin-dependent diabetes mellitus E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus
Hypertension	I10 Essential (primary) hypertension I11 Hypertensive heart disease I12 Hypertensive renal disease I13 Hypertensive heart and renal disease I15 Secondary hypertension
Ischaemic stroke	I63 Cerebral infarction *Excepto I636 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic* I64 Stroke, not specified as haemorrhage or infarctionz
Haemorrhagic stroke	I60 Subarachnoid haemorrhage I61 Intracerebral haemorrhage I62 Other nontraumatic intracranial haemorrhage
Bleeding (gastrointestinal intracranial, other)	I60 Subarachnoid haemorrhage I61 Intracerebral haemorrhage I62 Other nontraumatic intracranial haemorrhage S064 Epidural haemorrhage S065 Traumatic subdural haemorrhage S066 Traumatic subarachnoid haemorrhage I850 Oesophageal varices with bleeding K250 Acute with haemorrhage K252 Acute with both haemorrhage and perforation K254 Chronic or unspecified with haemorrhage K256 Chronic or unspecified with both haemorrhage and perforation K260 Acute with haemorrhage K262 Acute with both haemorrhage and perforation K264 Chronic or unspecified with haemorrhage K266 Chronic or unspecified with both haemorrhage and perforation K270 Acute with haemorrhage K272 Acute with both haemorrhage and perforation K274 Chronic or unspecified with haemorrhage K276 Chronic or unspecified with both haemorrhage and perforation K280 Acute with haemorrhage K282 Acute with both haemorrhage and perforation K284 Chronic or unspecified with haemorrhage K286 Chronic or unspecified with both haemorrhage and perforation K290 Acute haemorrhagic gastritis K625 Haemorrhage of anus and rectum K920 Haematemesis K921 Melaena K922 Gastro-intestinal haemorrhage, unspecified D62 Acute posthaemorrhagic anaemia H356 Retinal haemorrhage H431 Vitreous haemorrhage H450 Vitreous haemorrhage in diseases classified elsewhere H922 Otorrhagia

Variable	Operacional definition ICD-10
	I312 Haemopericardium, not elsewhere classified J942 Haemothorax R04 Haemorrhage from respiratory passages K661 Haemoperitoneum M250 Haemarthrosis N02 Recurrent and persistent haematuria N938 Other specified abnormal uterine and vaginal bleeding N939 Abnormal uterine and vaginal bleeding, unspecified N950 Postmenopausal bleeding R31 Unspecified haematuria R58 Haemorrhage, not elsewhere classified T792 Traumatic secondary and recurrent haemorrhage
Systemic embolism	I74 Arterial embolism and thrombosis
Alcohol consumption	E244 Alcohol-induced pseudo-Cushing's syndrome E52 Niacin deficiency [pellagra] G312 Degeneration of nervous system due to alcohol G621 Alcoholic polyneuropathy G721 Alcoholic myopathy I426 Alcoholic cardiomyopathy K292 Alcoholic gastritis K70 Alcoholic liver disease K860 Alcohol-induced chronic pancreatitis O354 Maternal care for (suspected) damage to foetus from alcohol T51 Toxic effect of alcohol Z714 Alcohol abuse counselling and surveillance Z721 Alcohol use
Peripheral artery disease	I702 Atherosclerosis of arteries of the extremities I708 Atherosclerosis of other arteries I709 Generalised and unspecified atherosclerosis
Anaemia	D50 Iron deficiency anaemia D51 Vitamin B12 deficiency anaemia D52 Folate deficiency anaemia D53 Other nutritional anaemias D55 Anaemia due to enzyme disorders D56 Thalassaemia D57 Sickle-cell disorders D58 Other hereditary haemolytic anaemias D59 Acquired haemolytic anaemia
Congestive heart failure	I110 Hypertensive heart disease with (congestive) heart failure I130 Hypertensive heart and renal disease with (congestive) heart failure I132 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
Renal disease	B15 Acute hepatitis A B16 Acute hepatitis B B17 Other acute viral hepatitis B18 Chronic viral hepatitis B19 Unspecified viral hepatitis C22 Malignant neoplasm of liver and intrahepatic bile ducts K70 Alcoholic liver disease K71 Toxic liver disease K72 Hepatic failure, not elsewhere classified K73 Chronic hepatitis, not elsewhere classified K74 Fibrosis and cirrhosis of liver

Variable	Operacional definition ICD-10	
	K75	Other inflammatory liver diseases
	K76	Other diseases of liver
	K77	Liver disorders in diseases classified elsewhere
	Z944	Liver transplant status
Myocardial infarction	I21	Acute myocardial infarction
	I22	Subsequent myocardial infarction
	I252	Old myocardial infarction
Peripheral vascular disease	I70	Atherosclerosis
	I71	Aortic aneurysm and dissection
	I731	Thromboangiitis obliterans [Buerger]
	I738	Other specified peripheral vascular diseases
	I739	Peripheral vascular disease, unspecified
	I771	Stricture of artery
	I790	Aneurysm of aorta in diseases classified elsewhere
	I792	Peripheral angiopathy in diseases classified elsewhere
	K551	Chronic vascular disorders of intestine
	K558	Other vascular disorders of intestine
	K559	Vascular disorder of intestine, unspecified
	Z958	Presence of other cardiac and vascular implants and grafts
	Z959	Presence of cardiac and vascular implant and graft, unspecified
TIA	G450	Vertebro-basilar artery syndrome
	G458	Other transient cerebral ischaemic attacks and related syndromes
	G451	Carotid artery syndrome (hemispheric)
	G459	Transient cerebral ischaemic attack, unspecified
Coronary artery disease	I20	Angina pectoris
	I21	Acute myocardial infarction

7.4. Data Sources

The information that will be used in the study comes exclusively from secondary sources. Two databases will be used to extract the information:

7.4.1. Claim Database

Claim databasee contains all prescriptions of all patients' medications chronologically. From this database, the index date will be established and the diagnosis of NVAF of the patient will be extracted. Similarly, this base will be used to assess the persistence on therapy and treatment patterns (duration of treatment, changes, persistence), pharmacy claim information, demographic information, diagnosis and insurance data.

7.4.2. Medical Record

Of the patients identified from the claim database, information will be extracted from the second database, the medical record, it will serve to characterize patients based on their baseline demographic and clinical characteristics, that is, on the index date. In turn, it contains the main control variables and the information related to the outcomes of interest, stroke and bleeding events.

7.5. Study Size

The total population of patients treated with OAC between January 1, 2013 and June 30, 2018 was analyzed in the claim dabtabase. For the purpose of the study, it contains the information of 7,500 patients, once they were verified that they met the inclusion criteria of the study. This means that patients who start warfarin and NOACs would be included within this period. Patients who initiate NOACs within the established period and who have been exposed to warfarin before 2013 will also be included.

7.6. Data Management

The data sources are databases owned by the investigator, he will execute the data management for this study.

7.6.1 Electronic Case Report (ECR)

As used in this protocol, the term ECR should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. ECR is required and should be completed for each included patient. The completed original ECRs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The party performing medical record review shall ensure that the ECRs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The party performing medical records review has ultimate responsibility for the abstraction of all clinical, safety, and laboratory data entered on the ECRs and any other data collection forms (source documents).
In order to ensure the accurate, complete, consistent, timely enduring of the data, Pfizer and the third party will design and validate the ECR from review of 30 medical records to guarantee the operationalization adequate of the variables, idenfifying alternative coding data available (abbreviatures, synonyms, symbols, units, etc) and setting of the variables following this protocol. From the results of the validation and the standard operating procedures of Pfizer, data magement plan, data review plan, ECR completion instruction and data entry guidelines will be builted to ensure the consistency and accurate of data. and distribuited to different physicians who participate in the abstraction of the data.
The personal responsible to abstract the data will be physicians who will be trained in the abstraction process, use of manuals and ECR. These grupo will be blinded of the objective of the study in order to avoid the reviewer bias. The party will responsible to conduct and record this activity.
Likewise, the party execute monitoring of tha data which will be follow the guidelines described in the data review plan and data quality control plan as required by the Pfizer policy.
Finally, the concordance of the abstracters, the intrarater and interrater reliability, will be measure for cohens kappa and interclass correlation, respectively.

7.6.2 Record Retention

To enable evaluations or inspections/audits from regulatory authorities or Pfizer, third party responsible for performing medical record review agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., ECRs and medical records), ECR file, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by third party responsible for performing medical record review according to local regulations or as specified in the vendor contract, whichever is longer. Third party responsible for performing medical record review must ensure that the records continue to be stored securely for so long as they are retained.
If third party responsible for performing medical record review becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless third party responsible for performing medical record review and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.
The third party responsible for performing medical record review obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

7.6.3 Patient Identification

The Investigators will identify patients from the claim database, initially, in this database the type of therapy with any of the OACs will be verified, and then that they meet the inclusion criteria of the study.

7.6.4 Collection of Information

For the analysis of the data, the statistical package Statistical Package for the Social Sciences (SPSS) Statistics, version 26.0 (IBM, US) for Windows will be used.

Data collection will be performed by healthcare providers following a data collection template developed in Microsoft Excel. For the purpose of unifying criteria and concepts, the template will be parametrized according to the possible responses or options for each variable, which will be defined by the medical expertise, information availability and published clinical studies. The template will be then validated according to a pilot testing of 20 randomly selected clinical charts.

Data collection will be performed after verifying the inclusion and exclusion criteria by the investigation staff. Firstly, the data regarding demographic data and delivery of the medications of interest to the patients meeting the criteria will be reviewed and collected. Subsequently, the electronic medical chart will be reviewed for collecting the clinical data will be identified.
In order to ensure protection of the patient's personal data and maintain high confidentiality and protection of the personal data according to the corporative policy 404 on *Protecting the Privacy of Personal Data*, the vendor will not transfer the collected database.

Pfizer will monitor the vendor to ensure the protection of the patient's personal data.

7.6.5 Database Retention

The Principal Investigator will store the database, adverse event reports and relevant correspondence securely to prevent unauthorized personnel from accessing the information.

7.7 Data Analysis

This type of analysis is descriptive and explanatory, as it depends largely on the sample size. Continuous variables will be presented as means, standard deviation or other measures of central tendency or position, while categorical variables will be presented as frequencies and percentages.

Regarding bivariate analyses of continuous variables with normal behavior, the Student's t test will be performed. In case of presenting non-normal behavior, the Mann-Withney test will be used. For variables that are continuous with several categories, analysis of variance (ANOVA) will be assessed. In the event of presenting a non-normal behavior, the multivariate analysis of

variance (MANOVA) test will be carried out. For categorical variables, the X2 test will be used.

Exploratory analyses based on sample size:

The cumulative incidence of clinical outcomes (Stroke/ systemic embolism and major bleeding) will be calculated throughout the study period, from which the incidence or survival curves will be derived using the Kaplan Meier method. Incidence of events will be explored in clinically relevant subgroups based on sample size.

For the execution of the analysis, CCI [redacted] and change of treatment, and missing treatments are considered as censures. Treatment comparison will be not conducted.

A similar analysis will be performed for the group of patients who have not presented stroke/ systemic embolism or major bleeding events to estimate the time for CCI [redacted] CCI change of treatment.

In the independent variables, the significance will be analyzed, as a level of statistical significance $p < 0.05$.

7.7.1 Missing Data Management

There will be no imputation or replacement of missing data. All analyses will be conducted on observed cases.

7.8 Quality Control

The Principal Investigator or his designee will validate the database constructed, based on the information collected, and they will verify the following:

- Review of illogical data or outliers.
- Verification of conflicting data.
- Review of very high response percentages, such as "unknown" or "not available data"
- Verification of the accuracy of the data collected compared to the source documents
- Report of adverse events (AE)

7.9 Limitations of the research methods

This study, as other observational studies, has some limitations; these are the result of the type of study and the source of information used. It is possible that there is some misclassification of the diagnoses of patients with NVAF as in turn in the diagnoses of the outcomes. For example, in the medical record, it is possible for the Investigator to use indirect information or to relate some type of approximation to obtain the variable or information of interest or to perform. Although this is a risk, the presence has been mitigated through a clear definition of the outcomes and with the case report format, which allows the Investigator to extract the relevant information only.

As for the claim database, a limitation is that prescription does not indicate whether the patient actually took the therapy as prescribed in both dosage and frequency.

On the other hand, this study will not obtain information related to hospitalizations of patients during the follow-up period; therefore, in the event of having any during this period it will not be known if the patient continued therapy. It is worth noting that these types of limitations are not differential among the cohorts of therapies to assess.

In spite of the limitations previously described, this information is very valuable, especially because it allows linking the claim information of medications with the medical records of each patient, providing a large sample size with a significant number of variables.

7.10 Other aspects

Not applicable

8 PROTECTION OF STUDY SUBJECTS

8.1 Patient Information

All parties will comply with all applicable laws, including those relating to the implementation of organizational and technical measures to ensure the protection of patients' personal data. Such measures will include the omission of the patient's name, or other directly identifiable data in reports, publications or other means of dissemination, except when required by the current legislation.
Patient personal data will be stored in the third party research location in an encrypted electronic form and will be password protected to ensure that only authorized study personnel have access. Audifarma will implement the appropriate technical and organizational measures to ensure that personal data may be recovered in the event of a disaster. In the event of a possible violation of personal data, Audifarma will be responsible for determining if there has been a violation of personal data and, if so, providing notifications of violation as required by law.

To protect the rights and freedoms of natural persons with respect to the processing of personal data, when the study data is compiled to be transferred to Pfizer and other authorized parties, any patient´s name will be removed and replaced by a unique and specific numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified with this unique and specific patient´s code. In the event of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data in accordance with the applicable Audifarma and privacy laws.

8.2 Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

8.3 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have a prospective approval of the study protocol, the protocol amendments, and other relevant documents (for example, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC must be kept in the Investigator's file. Copies of IRB/IEC approvals must be sent to Pfizer.

The study will be evaluated by the Bioethics Committee of the Technological University of Pereira in the category of risk-free research. The principles of confidentiality of the information established by the Declaration of Helsinki will be followed, in accordance with Resolution No. 8430 of 1993 of the Ministry of Health of Colombia. Once you have the support from the committee, the HMO will give authorization to access the medical records.

8.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The safety reporting language below is applicable to Research staff with oversight of electronic medical records in this study (Human review of unstructured data):
This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AE with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.
The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the ECR and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these adverse events with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.
All research staff members must complete the following Pfizer training requirements:

"*YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

The results will be published in an indexed journal and presented at an international congress according to the availability of the results.

11. REFERENCES

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8. LIST OF TABLES

9. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.