NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	*Atrial Fibrillation In Real practice on Management of oral Anticoagulation– AFIRMA 4.0*
Protocol number	*B0661131*
Version identifier of the final study report	*1.0*
Date	*15 March 2023*
EU Post Authorization Study (PAS) register number	EUPAS36330
Active substance	*Oral anticoagulants (OACs)*
Medicinal product	*Apixaban, rivaroxaban, edoxaban, dabigatran, warfarin, and acenocoumarol.*
Product reference	*Apixaban*
Procedure number	*Not applicable*
Marketing Authorization Holder (MAH)	*Pfizer SLU Spain*
Joint PASS	*No*
Research question and objectives	*PRIMARY: To describe the demographic and clinical characteristics, including comorbidities, for patients with non-valvular atrial fibrillation (NVAF) who were prescribed OAC, both NOAC (apixaban, dabigatran, rivaroxaban, edoxaban) and VKA (acenocoumarol or warfarin).* *SECONDARY:* • *SO-1: To describe treatment pathways, including initial treatment, switching treatment, and treatment after switch.*

	• *SO-2: To describe annual incidence rates of effectivity and safety-related outcomes (stroke, SE, major and minor bleedings).* • *SO-3: To compare the rates of effectivity and safety-related outcomes (stroke, SE, major and minor bleedings) between AVK and NOAC.*
Country(-ies) of study	*Spain.*
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1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Atrial Fibrillation In Real practice on Management of oral Anticoagulation– AFIRMA 4.0.

Date: 10 March 2023.

Name and affiliation of the main author: Susana Fernández de Cabo (Sr Medical Advisor, Pfizer Spain); Daniel Arumí (Medical Director CV, Pfizer Spain), Juan Cosín (Cardiologist, H. Arnau de Valencia).

Keywords: Oral anticoagulants, novel oral anticoagulants, non-valvular atrial fibrillation, stroke, systemic embolism, bleeding, electronic health records, real-world evidence, natural language processing, machine learning.

Rationale and background: Options for oral anticoagulation (OAC) have been expanding in the last decade. In addition to the standard treatment with vitamin K antagonists or VKA (warfarin and acenocoumarol), novel oral anticoagulants (NOACs) directly target the activity of thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), revolutionizing management and thromboprophylaxis for stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF). Understanding treatment patterns and clinical outcomes (effectivity and safety) of patients with NVAF underwent OAC is critical to develop effective strategies to reduce the overall disease burden. There is still a need to obtain real-world evidence (RWE) of OAC therapy in NVAF patients in Spain. Because of that, we performed a study based on the reuse of data from electronic health records (EHRs), using EHRead® technology, a data-driven system based on natural language processing (NLP) and machine learning (ML) techniques in this population.

Research question and objectives: To describe demographic, clinical characteristics and treatment pathways in patients with NVAF receiving OACs. To compare effectivity (rates of stroke or SE) and safety data (major and minor bleeding) related to OAC in these patients.

Study design: Observational retrospective cohort study based on RWE.

Setting: The study was conducted in 15 hospitals within the Spanish healthcare system from January 2014 to December 2020.

Subjects and study size, including dropouts: Patients aged ≥18 years diagnosed with NVAF and receiving OACs (NOACs as apixaban, rivaroxaban, dabigatran, and edoxaban or VKA as acenocoumarol or warfarin) during the study period were eligible for the study. Patients with rheumatic mitral valvular heart disease, mitral valve stenosis, venous thromboembolism (VTE), or pregnant were excluded. Finally, we included 62,163 patients with NVAF and treated with OACs. Among them, 12,766 (20.5%) received NOACs and 49,397 (79.4%) received VKAs. To describe and compare effectivity and safety data we selected partial sets

of patients including 45,349 and 47,525 patients respectively after applying adequate criteria selection.

Variables and data sources: Characteristics as age, gender, weight, CHA_2DS_2-VASc score, comorbidities, toxic habits, and OAC therapy were included at baseline. OAC switches were also included as well as clinical events and effectivity and safety related outcomes such as stroke, SE, and major and minor bleeding events during the follow-up. All data were collected from EHRs, including all available information from inpatient, outpatient, and emergency room in each participating site. Descriptive analyses and an effectivity and safety analysis using Kaplan Meier and comparative analysis by Cox in previously matched patients were performed.

Results: The most used OAC in patients with NVAF were VKA, particularly acenocoumarol. VKA patients tended to be older, with more cardiovascular comorbidities and higher CHA2DS2-VASc scores than NOAC patients. The incidence of overall stroke and ischemic stroke, as well as of major and minor bleeding, was lower in NOAC patients. NOAC group also had a lower risk of stroke and minor bleeding, without differences in major bleeding compared to VKA.

Discussion Our study showed that NOACs have a better safety and effectivity profile than traditional anticoagulants. However, in Spain VKA were the most used OAC treatment in patients with NVAF, maybe related with the restricted use of NOACs in this country during the study period due to economic reasons rather than issues related to their effectivity or safety. Moreover, since the data was exclusively obtained from hospitals, the demographic characteristics, comorbidities, and complications may not be representative of the entire population of NVAF patients receiving anticoagulant treatment or those reported in previous studies. Nevertheless, the large sample size of patients included in this study and the rigorous statistical analysis conducted on outcomes such as stroke, SE, major bleeding, and minor bleeding, provide reliable and valuable information to enhance our understanding of the use of these drugs in real-world settings.

Marketing Authorization Holder(s): Pfizer SLU (Avda. Europa 20B, 28108 Alcobendas (Madrid) Spain).

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial fibrillation
AI	Artificial intelligence
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
her	Electronic health records
FAS	Full analysis set
HR	Hazard ratio
IAA	Inter-annotator agreement
INR	International normalized ratio
K-M	Kaplan-Meier
LMWH	Low Molecular Weight Heparin
ML	Machine learning
MD	Medsavana Medical Doctor
NED	Name Entity Disambiguation
NER	Name Entity Recognition
NLP	Natural language processing
NOAC	Novel oral anticoagulants
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulants
PO	Primary objective
PSM	Propensity score matching
SAP	Statistical analysis plan
SE	Systemic embolism
SO	Secondary objective
SD	Standard deviation
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
VKA	Vitamin K antagonists
VTE	Venous thromboembolism

TP	True positive

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Susana Fernández. de Cabo	Sr Medical Advisor	Pfizer Spain
Daniel Arumí	Medical Director CV	Pfizer Spain
Miren Taberna	Chief Scientific Officer (CSO)	Savana Research S.L.
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Carlos Arias	Medical expert	Savana Research S.L.
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Eduard Sarró	Medical Documentation Expert	Savana Research S.L.

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Daniel Arumí	Medical Director CV	Pfizer Spain
Juan Cosín	Cardiologist	H. Arnau de Valencia

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Manuel Anguita – Cardiologist H.Reina Sofía (Córdoba)	Scientific Committee member
Carmen Suárez – Internal Medicine H. La Princesa (Madrid)	Scientific Committee member
SAVANA Research	Data Collection and Analysis

5. MILESTONES

Milestone	Planned date	Actual date	Comments
<Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol>	31 October 2019	31 October 2019	
Start of data collection	January 2014	January 2014	
End of data collection	December 2020	December 2020	
<Registration in the EU PAS register>	July 2020 EUPAS36330	July 2020	
Final report of study results	October 2023	October 2023	

6. RATIONALE AND BACKGROUND

Options for oral anticoagulation have been expanding steadily over the past few decades, providing a greater number of oral anticoagulant (OAC) agents for prevention and management of thromboembolic disease. In addition to the standard treatment with vitamin K antagonists (VKA as warfarin and acenocoumarol), novel oral anticoagulants (NOACs) that directly target the activity of thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have recently revolutionized thromboprophylaxis for stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF) (1). Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits. Thus, advantages and disadvantages of each agent must be individualized to the patient and clinical setting (2).

Atrial fibrillation (AF) remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world (3). Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. Because of that, among clinical indications for NOACs, NVAF has been the most studied disease unlike the rest of indications (4-7). NOACs are an alternative for VKA for most patients with NVAF, in whom oral anticoagulant therapy is chosen, and are the preferred choice in those AF populations with increased risks of both thromboembolic and bleeding events (8). Its indications include the prevention of stroke and SE in adult patients with one or more risk factors, such as prior stroke or transient ischemic attack (TIA), age $\geq$ 75 years, or presenting one of the following: hypertension, diabetes mellitus, or symptomatic heart failure (NYHA Class $\geq$ II). These agents have an improved effectivity/safety ratio, a predictable anticoagulant effect without need for routine monitoring, and fewer food and drug interactions compared with VKAs (9-13). However, the proper use of this treatment requires a careful approach to many practical aspects, including to obtain the safety profile of patients underwent NOACs. Understanding treatment patterns and clinical outcomes (regarding effectivity and safety) of NVAF treatment is critical to develop effective strategies to reduce the overall disease burden (14).

In this regard, the growing need for real-world evidence (RWE) is motivated to complement data from clinical trials and has increasingly been used in the process of decision-making. Despite previous observational studies have already been performed in different populations with NVAF treated with NOACs (15, 16), there is still a need to obtain local RWE including the treatment with acenocoumarol, the most used VKA in Spain. In this study we conducted a RWE retrospective study on the characteristics, effectivity and safety profile of patients with NVAF treated with OACs based on readily available information in the Electronic Health Records (EHRs) of patients from participating sites, analyzed using Natural Language Processing (NLP) and machine learning (ML) to provide more accurate real-life data.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The study objectives are mentioned below:

7.1. Primary Objective (PO)

- To describe the demographic and clinical characteristics, including comorbidities, for patients with non-valvular atrial fibrillation (NVAF) who were prescribed OAC, both NOAC (apixaban, dabigatran, rivaroxaban, edoxaban) and VKA (acenocoumarol or warfarin).

7.2. Secondary Objectives (SO)

- SO-1: To describe treatment pathways, including initial treatment, switching treatment, and treatment after switch.
- SO-2: To describe annual incidence rates of effectivity and safety-related outcomes (stroke, SE, major and minor bleedings).
- SO-3: To compare the rates of effectivity and safety-related outcomes (stroke, SE, major and minor bleedings).

The study occurred over three phases:

- Phase I, describing patient characteristics and treatment pathways (PO and SO-1).
- Phase II, describing incidence of Stroke/SE, and major and minor bleeding events (SO-2).
- Phase III, including a comparative analysis for Stroke/SE, and major and minor bleeding (SO-3).

The study period end in Phase I was December 2020 as the most recent data available. From Phase II, where outcomes were studied, the study period end was fixed on 29th February 2020 to avoid the period with COVID-19 pandemic.

The power and estimated sample size was verified before conducting any comparative analysis between treatments.

8. RESEARCH METHODS

8.1. Study design

This was a multicenter, retrospective, and observational, cohort study based on RWE by reusing clinical information captured in the EHRs of patients from participating centers.

8.2. Setting

The study was conducted in 15 participating hospital sites (**Table 1**) from the Spanish National Healthcare Network from January 2014 to December 2020. All patients with NVAF and treatment with OAC during the study period were selected from all the participating centers. Patients were included when both conditions were met (index date). Clinical data was extracted at baseline and during a follow up. Each patient was followed until the end of the study or until most recent data available to avoid losing valuable information.

Table 1. List of participating hospital sites in the study

Participating site	Location
Hospital Regional Universitario Carlos Haya	Andalucía
Hospital de la Santa Creu i Sant Pau	Cataluña
Hospital Universitario Vall d´Hebron	Cataluña
Hospital de León	Castilla y León
Hospital del Río Hortega	Castilla y León
Hospital Universitario de La Princesa	Comunidad de Madrid
Hospital Universitario de Fuenlabrada	Comunidad de Madrid
Hospital Universitario Infanta Leonor	Comunidad de Madrid
Hospital Universitario Infanta Sofía	Comunidad de Madrid
Hospital Universitario Puerta de Hierro	Comunidad de Madrid
Hospital General Universitario de Castellón	Comunidad Valenciana
Hospital Clínico Universitario de Valencia	Comunidad Valenciana
Hospital Universitario y Politécnico La Fe	Comunidad Valenciana
Hospital Universitario Son Espases	Islas Baleares
Clínica Universitaria de Navarra	Navarra

8.3. Subjects

Among selected patients, only those who met all the following inclusion criteria and none of the exclusion criteria were finally included in the Full Analysis Set (FAS):

8.3.1. *Inclusion criteria*

- Patients with diagnosis of NVAF and taking NOACs (apixaban, rivaroxaban, dabigatran and edoxaban), or VKA (acenocumarol, warfarin) during the study period.
- Aged ⩾18 years at the index date.

8.3.2. *Exclusion criteria*

- Rheumatic mitral valvular heart disease and mitral valve stenosis.
- Venous thromboembolism (VTE).
- Pregnancy.

8.3.3. *Analysis populations, subgroups, and subpopulations*

Patients from the FAS were further stratified regarding the first type of OAC received as VKA or NOAC.

- VKA group: included patients treated with acenocoumarol or warfarin.
- NOAC group: included patients treated with apixaban, dabigatran, rivaroxaban or edoxaban.

For the SO-2 and SO-3 objectives two partial analysis sets (pAS) were used as following:

- pAS-1: patients with Stroke/SE events after inclusion.
- pAS-2: patients with major and minor bleeding events after inclusion.

8.4. Variables

The study variables were collected from the information registered and available in the EHRs. Therefore, it is possible that some of the variables specified to be extracted in the protocol were not finally included in the analysis if they were not contained in the EHRs. Clinical information was extracted from all available inpatient, outpatient, and emergency notes records. A complete and detailed guidance on the evaluation of each variable and outcomes was presented in the statistical analysis plan (SAP). Following variables were finally included in the study:

8.4.1. ***Baseline or follow up characteristics***

- Age.
- Gender: (male/female).
- Height, weight, and body mass index (BMI).
- Alcohol/smoking habit.
- CHA_2DS_2-VASc score.
- Comorbidities: hypertension, heart failure, diabetes mellitus, coronary artery disease, myocardial infarction, peripheral vascular disease, TIA, renal disease, hemodialysis, chronic pulmonary disease, sleep apnea syndrome, thrombocytopenia, dyspepsia.
- Concomitant medication: low molecular weight heparin (LMWH), antiplatelets, insulin and analogues, oral hypoglycemic drugs, diuretics, beta blockers, ACE inhibitors, Angiotensin II antagonists, statins, fibrates, non-steroidal anti-inflammatory drugs (NSAIDs) and others.
- Laboratory values.
- Vital signs.
- Acute and chronic clinical events.
- OAC therapy:
    - Type.
    - Treatment switch.
    - Treatment after switch.
    - Time to switch.

- Time of follow-up.

8.4.2. ***Effectivity variables***

Stroke or SE were identified in the EHR. The stroke/SE set included the following 3 categories: ischemic stroke, hemorrhagic stroke, and SE.

8.4.3. ***Safety variables***

Major and minor bleeding were identified in the EHR. Definitions used for major and minor bleeding are described below.

8.4.3.1. Major Bleeding

Major bleeding was considered when following variables were identified in the free text of the EHRs: critical bleeding, primary hemorrhagic stroke, intracranial hemorrhage, pericardial bleeding, retroperitoneal bleeding, intraocular bleeding, intraspinal bleeding and gastrointestinal bleeding.

Moreover, following previous recommendations for major bleeding definition in anticoagulated patients (17), in this study major bleedings were also described as below:

- Fatal bleeding or bleeding and death of the patient during episode (at same hospital admission).
- Bleeding and hemoglobin fall in more than 2 g/dl in 48 h.
- Bleeding and transfusion of at least two units of whole blood or red cells, with temporal association within 48 h to the bleeding.
- In surgical patients, bleeding with surgical site bleeding and new surgery during admission.

In surgical patients, these data should have been detected from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).

8.4.3.2. Minor Bleeding

All non-major bleedings were considered as minor bleedings in this study.

8.4.4. ***Other variables***

Variables related with time to events and treatment switch as described before, were also extracted from EHR. Switch among OAC was defined as a prescription filled for non-index

OAC (any OAC prescribed different than the one detected on index date) within ±30 days after the date of discontinuation.

8.5. Data sources and measurement

The source of information was free text, i.e., unstructured information (and structured, when available), including outpatient clinic reports, discharge reports, emergency reports, prescriptions, and other medical reports. Images, such as hand-drawn pictures and scanned images, were not extracted. No data entry by physicians or their delegates into the hospital data platform were performed a posteriori specifically for this study. No Clinical Research Documents (CRDs) were collected for this study.

Medsavana received pseudonymized EHRs from heterogeneous sources, as every site may had different Information Systems, and then uploaded information to a secure file transfer protocol (SFTP) utility exclusively available for each site.

8.6. Study Size

Given the descriptive nature of this study, no hypothesis testing was performed and determination of a minimum sample size was not required. Nevertheless, in order to provide reliable results that could give value to the analysis, a recommended sample size was calculated.

The calculation took into account that some of the descriptive analyses were going to be performed by sub-groups (e.g. OAC treatment). Assuming a 5% as the minimum percentage of patients, the sample size of a sub-group was calculated as:

$$n = \frac{P \cdot (1 - P) \cdot Z^2_{1-\alpha/2}}{d^2}$$

where,

P is the proportion of the class (10%),

Z is the inverse of the standard normal distribution,

α significance level of 5%,

d is the desired precision, representing half of the desired confidence interval width.

For the description of demographic and clinical characteristics (PO) it was recommended to count with at least 384 patients with an OAC prescription within each sub-group, assuming a maximum percentage of patients in a class of 50% (most conservative value) and a precision *d* of 5% (pp). This made a total of 7,683 patients with OAC prescription (384/0.05).

In the case of annual incidence rates (SO-2, Stroke/SE, Major and Minor Bleedings), and considering the scenarios described in **Table 2**, we needed at least 1,825 patients with an OAC prescription within each sub-group, and a total of 36,494 patients with OAC prescription (1,825/0.05).

In order to achieve comparative analysis planned in the SO-3, the rate of the different events of interest in each cohort was evaluated with Cox proportional hazard models, assuming a power of 80% and a significance level of 5%.

Table 2 Incidence and precision scenarios

	Annual Incidence Rate		
Precision	**1%**	**5%**	**10%**
0.5%	1,521		
1%		1,825	
2%			864

8.7. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), was documented in the statistical analysis plan (SAP), which was dated, filed and maintained by the sponsor (Appendix 4).

8.8. Statistical methods

The complete Statistical Analysis Plan can be found in section 16.4.

8.8.1. *Main summary measures*

Frequency tables were performed for categorical variables, whereas continuous variables were described by means of summary tables that include the mean, standard deviation, median and quartiles of each variable. The number of non-evaluable outcomes and of missing data are also provided. Transformations were considered where appropriate.

Data such as medical history, life-style conditions, comorbidities, signs and symptoms, general findings, evaluation findings and surgical interventions were coded according to the Medsavana terminology (SNOMED CT based). Medications and substances used were coded according to the Anatomical Therapeutic Chemical (ATC) classification system and were tabulated by ATC levels 1 and 5 (18).

Due to the non-randomized nature of the study, the propensity score matching (PSM) technique was used to control confounders when comparing the cohorts in SO-3.

8.8.2. *Main statistical methods*

8.8.2.1. Brief Methodological Explanation

Incidence rates per 100 patients-year were calculated as the number of patients with an event (considering only first events) during follow-up, divided by the sum of follow-up time (in years) per each patient included in the group and multiplied per 100. Patients with either a treatment switch or death reported prior the appearance of any event were censored. In the absence of events or censors, end of follow-up was the timepoint of the last EHR available within each participating hospital site (**Table 3)**.

Table 3. Date of last available EHR within study period and per each participating site.

Participating site	Date of the last available EHR (dd/mm/yyyy)
1	27/02/2018
2	01/04/2018
3	28/12/2018
4	28/12/2018
5	31/12/2018
6	31/12/2018
7	02/01/2019
8	14/03/2019
9	15/03/2019
10	3/11/2019
11	11/01/2020
12	14/08/2020
13	17/08/2020
14	31/12/2020
15	31/12/2020

EHR: Electronic Health Record.

8.8.2.2. Events Definition

Stroke and SE events were only considered when appeared in at least two different reports from hospitalizations reports, emergency notes, or discharge reports. In addition, regarding incidence rate calculation, patients with any stroke or SE event between one-month prior index date and index date were excluded from the study.

Major and minor bleeding events occurring in a time window of 8 days after the mention of LMWH were not considered, since they could be secondary to heparin and not to OAC.

8.8.2.3. Group comparison

For group comparison (SO-3), first PSM was calculated matching patients one-to-one based on the scores generated by logistic regression using the following confounders, according to Lip et al. (19): year of index date, bleeding history*, hypertension*, diabetes mellitus*, renal disease*, sex, transient ischemic cirrhosis*, anemia, stroke*, thrombocytopenia, age, peripheral vascular disease*, myocardial infarction*, coronary disease*, cirrhosis*, drinking habit, heart failure*, dyspepsia, multicomorbidity index and the following concomitant medication: antiplatelet treatments, insulin and analogs, angiotensin-converting enzyme or angiotensin II receptor blockers inhibitors, oral hypoglycemic drugs, lipid lowering treatments, beta blockers, nonsteroidal anti-inflammatory drugs. Nearest neighbor matching method without replacement with a caliper of 0.2 standard deviation (20), was used. The balance of covariates was checked using love plots based on observed standardized mean differences with a threshold of 10%.

**Note: For multicomorbidity index, comorbidities marked with * were included as +1 each, two groups considered index <3 and index >=3.*

For each outcome (effectivity and safety) Kaplan-Meier (K-M) curves for matched patients were done and are presented for direct comparison between the groups of treatments (VKA and NOAC). In the curves, p-value for the log-rank test is indicated. K-M curves with a scale break are also shown for the better visualization of the differences between groups. In addition, univariate Cox regression with matched patients was used to compare the survival curves among different anticoagulant treatments (VKA, and NOAC). Analysis was performed using VKA as the reference group (HR=1). For each event, the HR (95% confidence interval (CI)) of the NOAC group is indicated and the p-value is used to assess statistical significance. To note, the p-value of the univariate Cox regression corresponds to the p-value of the log-rank test. Differences were considered statistically significant when the 95% CI of the NOAC group did not contain the value 1, and thus the p-value was <0.05.

8.8.3. ***Missing values***

Due to the nature of data source (unstructured free-text of the EHR generated during routine clinical practice), missing data elements in EHRs had to be differentiated between "true zero", or null. Bearing in mind that physicians tend to write down relevant data, in terms of data

calculations, these patients must be included in the percentage calculations unless otherwise specified. The number of patients with missing data is shown in the analysis for discrete and continuous variables.

8.8.4. ***Sensitivity analyses***

None.

8.8.5. ***Amendments to the statistical analysis plan***

The study period end in Phase I was December 2020 as the most recent data available. From Phase II, where outcomes were studied, the study period end was fixed at 29th February 2020 to avoid the period with COVID-19 pandemic.

The secondary objective "*To describe bleeding and stroke-related health care resource utilization in the study populations*" was not developed. Also, the comparative analysis between NOAC types and VKA types individually was not delivered (just by group comparison) and incidences were calculated excluding warfarin and edoxaban anticoagulants due to sample size.

Regarding Study Phases explained in SAP: "*The study will occur over three phases: an initial one describing patient characteristics and treatment pathways; the second one with a description of the minor bleeding events and comparative analysis between treatments; and a third one describing stroke/SE and major bleedings and a comparative analysis between treatments*". Phase I was as stated but for better results delivery Phase II included descriptive incidence analysis of minor bleeding, major bleeding and Stroke/SE while Phase III included comparative analysis for minor bleeding, major bleeding and Stroke/SE.

The definition of major and minor bleeding was slightly changed according to the data. See section 8.4.3 from this clinical study report (CSR).

Regarding study populations, it was stated "Analysis of the secondary endpoints will be performed in the Full analysis set population as well as each data set based on the propensity scores generated", for the secondary endpoints a partial analysis set was used due to processing improvements. Then, as accorded with sponsor, non OAC non-experienced patients (naïve) were considered for analysis.

8.9. Quality control

8.9.1. ***Data Integration Process***

The target for each stage of the data integration process was to refine the received information from data sources until it was integrated safely into the Medsavana ecosystem. At each stage, we had intermediate information that allowed the system to determine data status, getting metrics on quality and completeness.

We considered the following stages:

1. Data Gathering: The data was moved to the Medsavana environment. This step did not involve processing of the data but involved analysis and checking the shared information.

2. Data Admission: In this step we built the dataset with which we worked in the following steps. Trying to minimize the manipulation of the data, we mapped the data to the Medsavana glossary of terms.

3. Data Integration: Upload of hospital data into the Medsavana ecosystem. This step included processing, correction and discarding information.

4. Data Incorporation: After data was integrated to an adequate level of quality, it was incorporated into Medsavana's internal ecosystem.

Knowing how data was performed at each stage let us decide if we could work with this information during early stages, obtaining reports which supported decisions regarding records or even to reject certain documents.

8.9.2. ***Data Quality Assessment***

To assess the quality of the information gathered from EHRs, the total number of screened records and patients were analyzed per site, according to the main data sources (admission, consultation, or emergency notes) and hospital department or services (cardiology, neurology, emergency department, and others). Sites remained anonymous and undisclosed in this section.

8.9.3. ***NLP Data Processing to Generate Study Database***

Medsavana developed the *EHRead*® technology (21-25), which uses NLP, ML and deep learning techniques for extracting free text from de-identified and processed EHRs and translates it into a synthetic database.

EHRead® technology is a powerful engine of multi-lingual free text (natural language) analysis, which is capable of meaningfully interpreting the content included in clinical records regardless of the EHR system on which it operates. The program can capture numerical values and physician's notes and translate these into usable variables, enabling reuse of information included in large-scale collections of clinical records. Using the information obtained from this processing (study database), a statistical model was generated to describe the population with NVAF, both from a clinical and a demographic perspective.

Information was analyzed and expressed by means of concepts that contain the most significant information in the text. The terminology considered by Medsavana is based on SNOMED CT (25). This terminology includes codes, concepts, synonyms, and definitions used in clinical documentation and is considered the most comprehensive terminology in the world (18). It also includes symptoms, diagnoses, body structures, and substances. Only patients who

fulfilled all inclusion and no exclusion criteria were included in the study database. This approach allowed to respect the data minimization principle.

Free-text information translated into concepts using specific terminology was converted into a database using NLP and ML techniques. The general NLP pipeline was made up of several modules. A first pre-processing step was necessary to "clean" the raw text into an input for NLP models. A Name Entity Recognition (NER) Section detection module and Temporality NER followed, independently of each other. Name Entity Disambiguation (NED) was then performed after the NER module, as well as various attribute modules that added information to the NER entities, and Negation/Speculation modules. Finally, a relationship module linked the Temporality entities to the main NER entities. All these various steps guarantee the uniqueness of the detected entities (made of all the different qualifiers).

The study database was pseudonymized in a structured format and contained no personal information from any patient. Likewise, personal information was not accessed during either the application of automated and algorithmic methods (i.e., NLP) or during the conversion of unstructured data into the study database by *EHRead*®. The results obtained from this study database were delivered such that patient's personal information could not be accessed by any party.

The last phase of this process consisted of an internal medical validation step performed by Medsavana Medical Doctor (MD) staff.

8.9.4. ***External Validation of EHRead® performance***

The objective of this phase was to detect whether there were medical terms that were not correctly detected or, conversely, to detect any incorrect terms (false positives) that required adjustment and re-processing, as compared to external physician's annotations from the participating sites.

Due to the novel methodological approach that we performed, we complemented our clinical findings with an evaluation of the performance of Medsavana by external investigators participating in the research study (a comprehensive description of this methodology can be found in (26). This evaluation aimed to verify the system's accuracy when identifying records that contained mentions of NVAF and its related variables (27). The subset of patients identified with registered or available data regarding NVAF were assumed to be representative of the disease, and no corrections were applied to the population sample. This evaluation was performed in each participating site of the study.

The workflow was as follows:

- Two designated physicians (hereinafter referred to as "the annotators") at each hospital participating in the study annotated a set of randomly selected records from their site. They annotated clinical entities relevant to the study. The annotators were not allowed

to communicate with each other, as far as the annotation was concerned, but they could turn to the medical team of Medsavana when needed.

- When the annotations were finalized, a third physician from the same hospital assessed them, reviewing the annotations made by the two annotators and resolving differences, yielding the standard corpus to evaluate Medsavana's performance (**Figure 1**).

Figure 1. Evaluation Process.

A set of EHRs (1) collected via EHRead® (2) was annotated by physicians to generate the gold standard (3a) and compare it to the study results (3b), obtaining precision, recall and F-scores to evaluate the quality of Savana's output (4).

The aim of this annotation process was to measure inter-annotator agreement (IAA) and to ensure the consistency of the guidelines and the reliability of the annotated parameters (28). The results of the annotations were used to generate the standard. This resource was used to calculate EHRead® performance compared with designated physicians' annotations. The performance of the system was calculated in terms of the standard metrics of Precision (P), Recall, and their harmonic mean, or "F1-score" (29).

Precision = $\frac{tp}{tp+fp}$ Indicates the accuracy of the information the system retrieves.

Recall = $\frac{tp}{tp+fn}$ Indicates the amount of information the system retrieves.

F1-Score = $\frac{2\times Precision\times Recall}{Precision+Recall}$ Overall performance indicator of information retrieval.

In all cases, *tp* is the number of true positives, *fn* is the number of false negatives (i.e., records incorrectly not retrieved), and *fp* is the number of false positives (i.e., records incorrectly retrieved).

These metrics were obtained in the final analysis, as an average of the metrics for each hospital. The results of the external validation of EHRead® for key variables analyzed in this study are summarized in the Results section.

8.9.5. *Overview of Savana Methodology*

A summary of the methodological steps described in this section are shown in **Figure 2**.

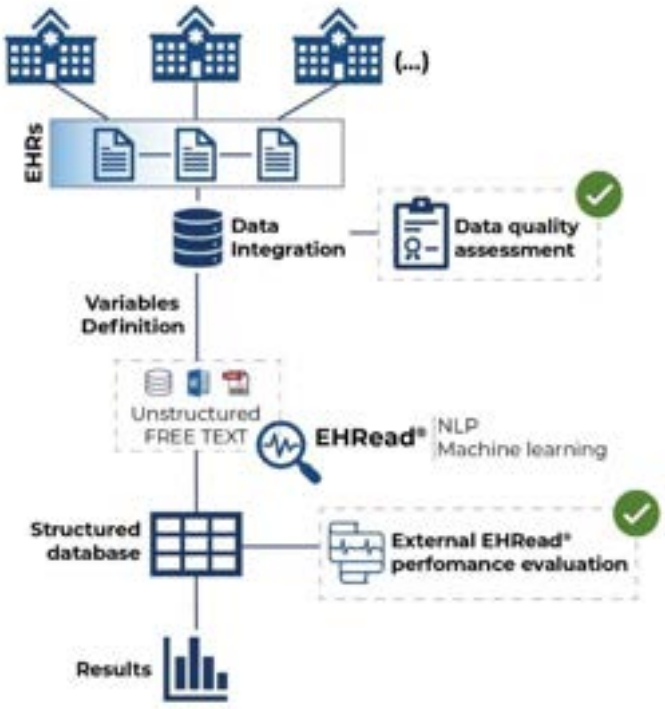


Figure 2. Overall summary of Savana methodology.

EHR data from participating hospitals was integrated by Medsavana and assessed for data quality. Following the definition of the study variables, the unstructured free text from EHRs was extracted using Savana's EHRead® technology. The resulting study database was used to analyze the data and generate the study results. The external performance evaluation of EHRead® output was performed considering a subset of records as described in Figure 1.

8.10. Protection of human subjects

Subject information and consent

Not Applicable.

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

Before the start of data collection, the study was presented for review or notification to a national or central Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in the designated country, as and if required by local regulations. Additionally, the study was presented or notified to regional and site IEC/IRBs, as and if required by local laws or regulations and/or hospital policies.

All amendments to the protocol were subject to the appropriate review and approval process, in accordance with local regulations. At the end of the study, when required by local regulations, the participating physician or participating site director (or the funding company where necessary) notified the IEC of the completion of the study.

Ethical conduct of the study

The study was conducted in compliance with legal and regulatory requirements and followed generally accepted research practices described in the ICH Guideline for Good Clinical Practice, the Helsinki Declaration in its latest edition, GPP, and applicable local regulations.

Given that this was a retrospective, observational study, the proposed research had no possibility of causing any hazard to the study population. Similarly, this study did not modify in any way the prescription habits of the physicians. The assignment of a patient to a specific therapeutic strategy was not decided in advance by the protocol of the study but was determined by the corresponding physician, team, or hospital. On the other hand, the results and conclusions derived from this study may increase our knowledge of disease and offer novel insights into the medical management of these patients.

9. AMENDMENTS AND UPDATES

None

10. RESULTS

10.1. *EHRead*® performance evaluation

Table 4. Inter-annotator agreement (IAA) in terms of F1 score between the annotators identifying records that contains mentions of the variables of interest.

Variable	F1-score (95% CI)
Atrial fibrillation	0.91 (0.87-0.95)
Hemoglobin	0.87 (0.81-0.92)
Transfusion	0.78 (0.68-0.88)
Intracranial hemorrhage	0.74 (0.59-0.86)
Transient ischemic attack	0.74 (0.59-0.86)
Bleeding	0.64 (0.54-0.73)
Treatments	
Rivaroxaban	0.97 (0.78-1.00)
Dabigatran	0.95 (0.76-0.99)
Apixaban	0.94 (0.77-0.98)
Acenocumarol	0.93 (0.87-0.96)
Edoxaban	0.93 (0.63-1.00)
Warfarin	0.88 (0.58-1.00)

CI: Confidence Interval.

Table 5. EHRead® performance (Precision, Recall, and F1-score) identifying records that contain mentions per variables of interest.

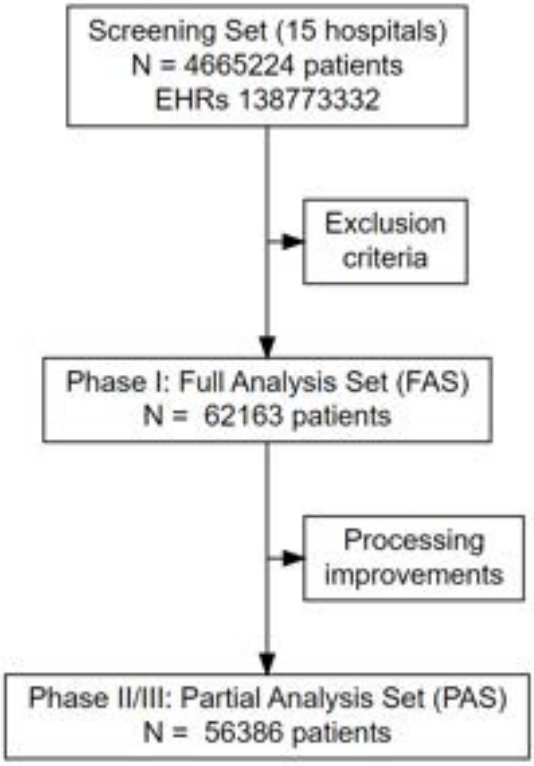
Variable	Precision	Recall	F1-score
Hemoglobin	0.97	0.92	0.94
Atrial fibrillation	0.97	0.83	0.89
Transient ischemic attack	0.91	0.82	0.86
Intracranial hemorrhage	0.87	0.55	0.67
Bleeding	0.74	0.73	0.74
Transfusion	0.73	0.95	0.83
Treatments			
Dabigatran	0.99	0.94	0.96
Edoxaban	0.99	091	0.95

Rivaroxaban	0.99	0.93	0.96
Warfarin	0.99	0.91	0.95
Acenocumarol	0.98	0.90	0.93
Apixaban	0.95	0.96	0.95

10.2. Population processing

As mentioned in the methods section, the study was conducted in three phases, and Figure 3 shows the subjects included in each of these phases:

Figure 3. Patients' flowchart and patients included in each phase.



10.3. Study population included in descriptive analyses (PO and SO-1)

Figure 4. Patient disposition

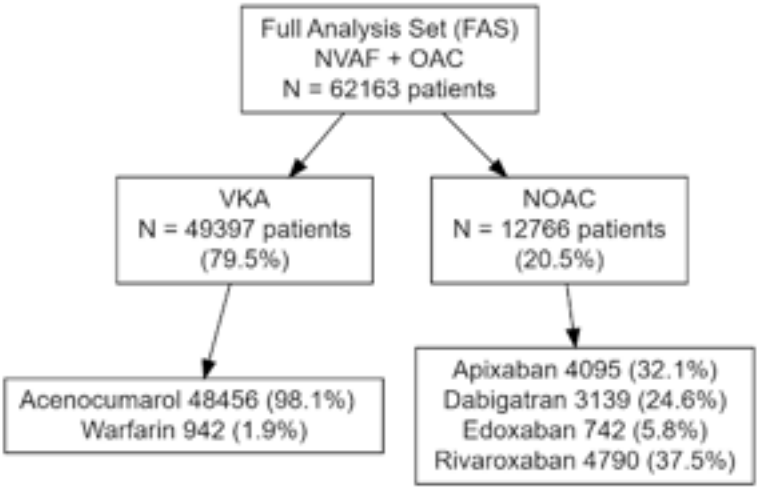


Table 6. Estimated incidence of NVAF by age*.

Age	Incidence of NVAF, ‰				
	2014	2015	2016	2017	2018
All	9.1	7.5	7.1	6.9	6.6
15-19	0.5	0.6	0.5	0.4	0.4
20-24	1.6	1.6	1.7	1.6	1.4
25-29	2.1	1.9	1.9	2.3	1.7
30-34	2.4	2.4	2.5	2.6	2.4
35-39	2.0	2.1	2.1	2.2	1.8
40-44	2.0	1.8	1.8	1.9	1.5
45-49	2.3	2.2	2.2	2.3	2.1
50-54	3.9	3.2	3.3	3.2	2.9
55-59	6.0	4.	4.6	4.6	4.0
60-64	10.0	8.3	8.1	7.8	7.2
65-69	14.3	11.4	11.2	10.8	10.6
70-74	24.7	16.7	16.5	15.8	14.7
75-79	35.3	31.0	28.8	28.6	30.0
80-84	47.9	36.1	34.7	32.9	31.4
85-89	67.5	50.8	44.3	42.2	41.5

90-94	72.7	55.8	47.5	43.5	46.0
>65	35.7	27.5	25.6	24.3	23.9
>95	134.6	100.0	83.3	71.1	84.1

** The yearly incidence was estimated until 2018 to include patient follow-up data from all participating sites.*

Table 7. Estimate prevalence of NVAF by age*.

Age	Prevalence of NVAF, %				
	2014	**2015**	**2016**	**2017**	**2018**
All	1.5	1.8	2.0	2.1	2.1
15-19	0.1	0.1	0.1	0.1	0.1
20-24	0.2	0.3	0.3	0.3	0.3
25-29	0.2	0.3	0.4	0.5	0.4
30-34	0.3	0.4	0.5	0.6	0.6
35-39	0.3	0.4	0.5	0.5	0.5
40-44	0.3	0.4	0.4	0.5	0.5
45-49	0.3	0.5	0.5	0.6	0.6
50-54	0.6	0.7	0.8	0.8	0.8
55-59	0.9	1.1	1.3	1.3	1.3
60-64	1.6	2.0	2.3	2.3	2.3
65-69	2.4	2.9	3.3	3.4	3.4
70-74	4.3	4.4	5.1	5.0	5.0
75-79	6.0	8.3	8.7	9.1	9.8
80-84	8.1	9.4	10.7	10.6	11.0
85-89	10.7	12.5	13.3	13.3	13.7
90-94	11.2	12.6	13.3	12.8	14.3
>65	5.9	6.9	7.6	7.6	7.8
>95	17.6	19.6	19.9	18.1	21.0

** The yearly prevalence was estimated until 2018 to include patient follow-up data from all participating sites.*

10.4. Descriptive analysis of the Study population (PO, SO-1)

10.4.1. *Baseline general characteristics*

Table 8. Baseline general characteristics for patients treated with OAC, overall and by OAC group.

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
Age			
Mean (SD)	76.62 (12.45)	74.95 (13.78)	77.06 (12.05)
Median (Q1, Q3)	78 (70, 84)	76 (67, 83)	79 (70, 84)
Missing (%)	0 (0%)	0 (0%)	0 (0%)
Gender			
Female	29503 (47%)	5586 (44%)	23917 (48%)
Male	32315 (52%)	7087 (56%)	25228 (51%)
Missing (%)	345 (0.6%)	93 (0.7%)	252 (0.5%)
Height (m)			
Mean (SD)	1.71 (0.75)	1.66 (0.63)	1.72 (0.77)
Median (Q1, Q3)	1.65 (1.56, 1.73)	1.66 (1.57, 1.75)	1.64 (1.56, 1.73)
Missing (%)	60009 (96.5%)	12331 (96.6%)	47678 (96.5%)
Weight (kg)			
Mean (SD)	88.48 (655.55)	76.89 (26.94)	91.09 (725.44)
Median (Q1, Q3)	76 (65, 89)	76 (65, 89.875)	76 (65, 89)
Missing (%)	58406 (94%)	12076 (94.6%)	46330 (93.8%)
BMI (kg/m^2)			
Mean (SD)	30.74 (7.41)	30 (7.09)	30.91 (7.47)
Median (Q1, Q3)	30.1 (25.925, 35)	29.73 (25.6, 33)	30.3 (26, 35)
Missing (%)	61136 (98.3%)	12576 (98.5%)	48560 (98.3%)
Drinking habit			
Alcoholic	2464 (4%)	436 (3%)	2028 (4%)
Ex-alcoholic	585 (1%)	102 (1%)	483 (1%)
Non-alcoholic	1045 (2%)	146 (1%)	899 (2%)
Missing (%)	58069 (93.4%)	12082 (94.6%)	45987 (93.1%)
Smoking habit			

Ex-smoker	4 (0%)	1 (0%)	3 (0%)
Smoker	3672 (6%)	761 (6%)	2911 (6%)
Non-smoker	15834 (25%)	3063 (24%)	12771 (26%)
Missing (%)	42653 (68.6%)	8941 (70%)	33712 (68.2%)

BMI, body mass index. Time window (First report, index date].

Table 9. Baseline general characteristics by NOAC or VKA subgroups.

	NOAC				VKA	
	Apixaban n= 4095	**Dabigatran n= 3139**	**Edoxaban n= 742**	**Rivaroxaban n= 4790**	**Acenocumarol n= 48456**	**Warfarin n= 942**
Age						
Mean (SD)	76.05 (13.41)	74.13 (13.37)	75.25 (14.59)	74.51 (14.17)	77.05 (12.05)	77.38 (11.73)
Median (Q1, Q3)	77 (68, 85)	75 (67, 83)	76 (68, 83.75)	76 (67, 83)	79 (70, 84)	79 (71, 85)
Missing (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender						
Female	1900 (46%)	1313 (42%)	315 (42%)	2058 (43%)	23442 (48%)	475 (50%)
Male	2165 (53%)	1809 (58%)	418 (56%)	2695 (56%)	24767 (51%)	461 (49%)
Missing (%)	30 (0.7%)	17 (0.5%)	9 (1.2%)	37 (0.8%)	247 (0.5%)	5 (0.5%)
Height (m)						
Mean (SD)	1.65 (0.81)	1.58 (0.33)	1.72 (0.55)	1.7 (0.61)	1.72 (0.77)	1.72 (0.89)
Median (Q1, Q3)	1.66 (1.58, 1.76)	1.64 (1.5675, 1.73)	1.65 (1.54, 1.77)	1.67 (1.6, 1.75)	1.65 (1.56, 1.73)	1.635 (1.545, 1.7025)
Missing (%)	3966 (96.8%)	3051 (97.2%)	705 (95%)	4609 (96.2%)	46765 (96.5%)	913 (97%)
Weight (kg)						
Mean (SD)	74.93 (23.65)	76.53 (25.97)	74.37 (19.93)	79.2 (30.85)	91.34 (730.93)	74.67 (22.64)
Median (Q1, Q3)	74 (63.25, 86)	77.35 (65, 90.7)	74.15 (65.45, 86.25)	78 (65, 93.2)	76 (65, 89)	75.5 (64.575, 83.9)
Missing (%)	3868 (94.5%)	3007 (95.8%)	686 (92.5%)	4515 (94.3%)	45435 (93.8%)	895 (95.1%)
BMI (kg/m^2)						
Mean (SD)	28.89 (5.61)	30.34 (8.06)	32.06 (8.43)	30.24 (7.28)	30.94 (7.46)	27.68 (8.06)

Median (Q1, Q3)	29.5 (25.475, 31.0025)	28.85 (24.385, 35.125)	30.9 (27.025, 33.35)	29.93 (26.225, 33.815)	30.4 (26, 35)	26.7 (22.7, 34.68)
Missing (%)	4043 (98.7%)	3103 (98.9%)	730 (98.4%)	4700 (98.1%)	47628 (98.3%)	932 (99%)
Drinking habit						
Alcoholic	152 (4%)	100 (3%)	36 (5%)	148 (3%)	1984 (4%)	44 (5%)
Ex-alcoholic	24 (1%)	26 (1%)	3 (0%)	49 (1%)	479 (1%)	4 (0%)
Non-alcoholic	37 (1%)	39 (1%)	13 (2%)	57 (1%)	885 (2%)	14 (1%)
Missing (%)	3882 (94.8%)	2974 (94.7%)	690 (93%)	4536 (94.7%)	45108 (93.1%)	879 (93.4%)
Smoking habit						
Ex-smoker	0 (0%)	1 (0%)	0 (0%)	0 (0%)	3 (0%)	0 (0%)
Smoker	245 (6%)	192 (6%)	46 (6%)	278 (6%)	2876 (6%)	35 (4%)
Non-smoker	969 (24%)	740 (24%)	204 (27%)	1150 (24%)	12576 (26%)	195 (21%)
Missing (%)	2881 (70.4%)	2206 (70.3%)	492 (66.3%)	3362 (70.2%)	33001 (68.1%)	711 (75.6%)

BMI, body mass index. Time window (First report, index date].

10.4.2. ***Baseline comorbidities***

Table 4. Baseline comorbidities for patients treated with OAC, overall and by OAC group.

	Overall (n=62163)	**NOAC (n=12766)**	**VKA (n=49397)**
Cardiovascular			
Hypertension	44508 (71.6%)	8636 (67.6%)	35872 (72.6%)
Heart failure	24917 (40.1%)	4432 (34.7%)	20485 (41.5%)
Diabetes mellitus	22289 (35.9%)	4105 (32.2%)	18184 (36.8%)
Coronary disease	5354 (8.6%)	1030 (8.1%)	4324 (8.8%)
Myocardial infarction	1927 (3.1%)	428 (3.4%)	1499 (3%)
Peripheral vascular disease	498 (0.8%)	65 (0.5%)	433 (0.9%)
Transient ischemic attack	3874 (6.2%)	834 (6.5%)	3040 (6.2%)
CHA_2DS_2-VASc Score			
0	1393 (2%)	555 (4%)	838 (2%)
1	4077 (7%)	1190 (9%)	2887 (6%)
2	8117 (13%)	1955 (15%)	6162 (12%)
3	13107 (21%)	2729 (21%)	10378 (21%)
4+	35124 (57%)	6244 (49%)	28880 (58%)
Missing (%)	345 (0.6%)	93 (0.7%)	252 (0.5%)
Others			
Renal disease	12347 (19.9%)	1965 (15.4%)	10382 (21%)
Hemodialysis	913 (1.5%)	52 (0.4%)	861 (1.7%)
Pulmonary disease	5811 (9.3%)	1018 (8%)	4793 (9.7%)
Sleep apnea	2785 (4.5%)	589 (4.6%)	2196 (4.4%)
Thrombocytopenia	1552 (2.5%)	229 (1.8%)	1323 (2.7%)
Dyspepsia	953 (1.5%)	191 (1.5%)	762 (1.5%)

CHA2DS2-VASc Score: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 6-74 years, Sex category Score. Time window (first report, Index date].

Table 5. Baseline comorbidities by NOAC or VKA subgroups

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
Cardiovascular						
Hypertension	2849 (69.6%)	2075 (66.1%)	525 (70.8%)	3187 (66.5%)	35219 (72.7%)	653 (69.4%)
Heart failure	1536 (37.5%)	1002 (31.9%)	288 (38.8%)	1606 (33.5%)	20100 (41.5%)	385 (40.9%)
Diabetes mellitus	1343 (32.8%)	1011 (32.2%)	253 (34.1%)	1498 (31.3%)	17870 (36.9%)	314 (33.4%)
Myocardial infarction	155 (3.8%)	105 (3.3%)	23 (3.1%)	145 (3%)	1473 (3%)	26 (2.8%)
Peripheral vascular disease	24 (0.6%)	13 (0.4%)	2 (0.3%)	26 (0.5%)	428 (0.9%)	5 (0.5%)
Transient ischemic attack	287 (7%)	242 (7.7%)	43 (5.8%)	262 (5.5%)	2980 (6.1%)	60 (6.4%)
Coronary disease	354 (8.6%)	235 (7.5%)	44 (5.9%)	397 (8.3%)	4251 (8.8%)	73 (7.8%)
CHA_2DS_2-VASc Score						
0	140 (3%)	161 (5%)	25 (3%)	229 (5%)	825 (2%)	13 (1%)
1	337 (8%)	324 (10%)	52 (7%)	477 (10%)	2824 (6%)	63 (7%)
2	550 (13%)	503 (16%)	130 (18%)	772 (16%)	6042 (12%)	120 (13%)
3	872 (21%)	668 (21%)	162 (22%)	1027 (21%)	10179 (21%)	199 (21%)
4+	2166 (53%)	1466 (47%)	364 (49%)	2248 (47%)	28339 (58%)	541 (57%)
Missing (%)	30 (0.7%)	17 (0.5%)	9 (1.2%)	37 (0.8%)	247 (0.5%)	5 (0.5%)
Others						
Renal disease	764 (18.7%)	352 (11.2%)	123 (16.6%)	726 (15.2%)	10147 (20.9%)	235 (25%)
Hemodialysis	24 (0.6%)	11 (0.4%)	2 (0.3%)	15 (0.3%)	841 (1.7%)	20 (2.1%)
Thrombo-cytopenia	83 (2%)	52 (1.7%)	14 (1.9%)	80 (1.7%)	1304 (2.7%)	19 (2%)

Dyspepsia	63 (1.5%)	51 (1.6%)	15 (2%)	62 (1.3%)	752 (1.6%)	10 (1.1%)
Pulmonary disease	336 (8.2%)	231 (7.4%)	56 (7.5%)	395 (8.2%)	4704 (9.7%)	89 (9.5%)
Sleep apnea	175 (4.3%)	156 (5%)	39 (5.3%)	219 (4.6%)	2167 (4.5%)	29 (3.1%)

CHA2DS2-VASc Score: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 6-74 years, Sex category Score. Time window (first report, Index date].

10.4.3. *Baseline concomitant medication*

Table 6. Baseline concomitant medication for patients treated with OAC, overall and by OAC group*

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
LMWH	16545 (26.6%)	2261 (17.7%)	14284 (28.9%)
Antiplatelet treatment			
Abciximab	13 (0%)	6 (0%)	7 (0%)
Acetilsalicilic acid	11047 (17.8%)	2324 (18.2%)	8723 (17.7%)
Cilostazol	149 (0.2%)	31 (0.2%)	118 (0.2%)
Clopidogrel	2890 (4.6%)	617 (4.8%)	2273 (4.6%)
Dipyridamole	112 (0.2%)	8 (0.1%)	104 (0.2%)
Epoprostenol	3 (0%)	0 (0%)	3 (0%)
Eptifibatide	0 (0%)	0 (0%)	0 (0%)
Iloprost	45 (0.1%)	4 (0%)	41 (0.1%)
Prasugrel	56 (0.1%)	11 (0.1%)	45 (0.1%)
Ticagrelor	175 (0.3%)	41 (0.3%)	134 (0.3%)
Ticlopidine	22 (0%)	6 (0%)	16 (0%)
Triflusal	247 (0.4%)	58 (0.5%)	189 (0.4%)
Insulin and analogs	4260 (6.9%)	719 (5.6%)	3541 (7.2%)
Oral hypoglycemic drugs			
Metformin	7577 (12.2%)	1464 (11.5%)	6113 (12.4%)
Sulfonilureas derivates	1565 (2.5%)	256 (2%)	1309 (2.6%)
Diuretics	27356 (44%)	4556 (35.7%)	22800 (46.2%)
Beta blockers	29880 (48.1%)	6393 (50.1%)	23487 (47.5%)
ACE inhibitors monodrugs	15967 (25.7%)	2748 (21.5%)	13219 (26.8%)
Angiotensin II antagonists monodrugs	15846 (25.5%)	3259 (25.5%)	12587 (25.5%)
Statins	22340 (35.9%)	4212 (33%)	18128 (36.7%)
Fibrates	1207 (1.9%)	214 (1.7%)	993 (2%)
Others			
Cholestyramine	64 (0.1%)	17 (0.1%)	47 (0.1%)
Colestipol	16 (0%)	5 (0%)	11 (0%)

Colextran	22 (0%)	5 (0%)	17 (0%)
Colesevelam	2 (0%)	1 (0%)	1 (0%)
Ezetimiba	1077 (1.7%)	248 (1.9%)	829 (1.7%)
Alirocumab	0 (0%)	0 (0%)	0 (0%)
Evolocumab	0 (0%)	0 (0%)	0 (0%)
Dronedarone	478 (0.8%)	128 (1%)	350 (0.7%)
NSAIDs	5890 (9.5%)	1156 (9.1%)	4734 (9.6%)

*ACE: Angiotensin-converting enzyme; NSAIDs: non-steroidal anti-inflammatory drugs; LMWH: Low molecular weight heparin. * Treatments of interest has been searched in all EHRs in a pre-index time-frame window (-6, +1 months) if not present at index date. The closest available entry to the index date will be chosen. Therefore, the treatments depicted in the table does not necessarily occur concomitantly in time. Time window Index date[-180d, +30d].*

Table 7. Baseline concomitant medication by NOAC or VKA subgroups*

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
LMWH	800 (19.5%)	479 (15.3%)	140 (18.9%)	842 (17.6%)	14018 (28.9%)	266 (28.3%)
Antiplatelet treatment						
Abciximab	3 (0.1%)	1 (0%)	1 (0.1%)	1 (0%)	5 (0%)	2 (0.2%)
Acetilsalicilic acid	859 (21%)	483 (15.4%)	152 (20.5%)	830 (17.3%)	8581 (17.7%)	142 (15.1%)
Cilostazol	12 (0.3%)	4 (0.1%)	0 (0%)	15 (0.3%)	115 (0.2%)	3 (0.3%)
Clopidogrel	219 (5.3%)	150 (4.8%)	37 (5%)	211 (4.4%)	2233 (4.6%)	40 (4.3%)
Dipyridamole	1 (0%)	2 (0.1%)	0 (0%)	5 (0.1%)	103 (0.2%)	1 (0.1%)
Epoprostenol	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	0 (0%)
Eptifibatide	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Iloprost	1 (0%)	2 (0.1%)	0 (0%)	1 (0%)	41 (0.1%)	0 (0%)
Prasugrel	2 (0%)	2 (0.1%)	0 (0%)	7 (0.1%)	45 (0.1%)	0 (0%)
Ticagrelor	12 (0.3%)	12 (0.4%)	3 (0.4%)	14 (0.3%)	131 (0.3%)	3 (0.3%)
Ticlopidine	0 (0%)	0 (0%)	0 (0%)	6 (0.1%)	16 (0%)	0 (0%)
Triflusal	27 (0.7%)	8 (0.3%)	6 (0.8%)	17 (0.4%)	188 (0.4%)	1 (0.1%)
Insulin and analogs	251 (6.1%)	180 (5.7%)	33 (4.4%)	255 (5.3%)	3462 (7.1%)	79 (8.4%)
Oral hypoglycemic drugs						
Metformin	467 (11.4%)	354 (11.3%)	85 (11.5%)	558 (11.6%)	5987 (12.4%)	126 (13.4%)
Sulfonilureas derivates	82 (2%)	56 (1.8%)	8 (1.1%)	110 (2.3%)	1277 (2.6%)	32 (3.4%)
Diuretics	1559 (38.1%)	1005 (32%)	260 (35%)	1732 (36.2%)	22275 (46%)	525 (55.8%)

Beta blockers	2159 (52.7%)	1474 (47%)	382 (51.5%)	2378 (49.6%)	23012 (47.5%)	475 (50.5%)
ACE inhibitors monodrugs	926 (22.6%)	651 (20.7%)	157 (21.2%)	1014 (21.2%)	12936 (26.7%)	283 (30.1%)
Angiotensin II antagonists monodrugs	1115 (27.2%)	732 (23.3%)	207 (27.9%)	1205 (25.2%)	12329 (25.4%)	258 (27.4%)
Statins	1407 (34.4%)	985 (31.4%)	234 (31.5%)	1586 (33.1%)	17733 (36.6%)	395 (42%)
Fibrates	74 (1.8%)	63 (2%)	7 (0.9%)	70 (1.5%)	966 (2%)	27 (2.9%)
Others						
Cholestyramine	9 (0.2%)	4 (0.1%)	2 (0.3%)	2 (0%)	46 (0.1%)	1 (0.1%)
Colestipol	4 (0.1%)	1 (0%)	0 (0%)	0 (0%)	11 (0%)	0 (0%)
Colextran	1 (0%)	1 (0%)	2 (0.3%)	1 (0%)	17 (0%)	0 (0%)
Colesevelam	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Ezetimiba	88 (2.1%)	46 (1.5%)	13 (1.8%)	101 (2.1%)	818 (1.7%)	11 (1.2%)
Alirocumab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Evolocumab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dronedarone	43 (1.1%)	23 (0.7%)	4 (0.5%)	58 (1.2%)	341 (0.7%)	9 (1%)
NSAIDs	378 (9.2%)	290 (9.2%)	78 (10.5%)	410 (8.6%)	4615 (9.5%)	119 (12.6%)

*ACE: Angiotensin-converting enzyme; NSAIDs: non-steroidal anti-inflammatory drugs; LMWH: Low molecular weight heparin. *Treatments of interest has been searched in all EHRs in a pre-index time-frame window (-6, +1 months) if not present at index date. The closest available entry to the index date will be chosen. Therefore, the treatments depicted in the table does not necessarily occur concomitantly in time. Time window Index date[-180d, +30d].*

10.4.4. *Follow-up medication*

Table 8. Follow-up medication for patients treated with OAC, overall and by OAC group

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
Follow-up, years*			
Mean (SD)	1.53 (1.6)	1.12 (1.35)	1.64 (1.64)
Median (Q1, Q3)	1 (0, 2.8)	0.5 (0, 2)	1.2 (0.1, 2.9)
Missing (%)	0 (0%)	0 (0%)	0 (0%)
Medication			
LMWH	14652 (23.6%)	1663 (13%)	12989 (26.3%)
Antiplatelet treatment			
Abciximab	17 (0%)	3 (0%)	14 (0%)
Acetilsalicilic acid	8431 (13.6%)	1340 (10.5%)	7091 (14.4%)
Cilostazol	152 (0.2%)	24 (0.2%)	128 (0.3%)
Clopidogrel	2373 (3.8%)	378 (3%)	1995 (4%)
Dipyridamole	158 (0.3%)	23 (0.2%)	135 (0.3%)
Epoprostenol	7 (0%)	1 (0%)	6 (0%)
Eptifibatide	0 (0%)	0 (0%)	0 (0%)
Iloprost	43 (0.1%)	11 (0.1%)	32 (0.1%)
Prasugrel	39 (0.1%)	2 (0%)	37 (0.1%)
Ticagrelor	109 (0.2%)	26 (0.2%)	83 (0.2%)
Ticlopidine	16 (0%)	1 (0%)	15 (0%)
Triflusal	139 (0.2%)	25 (0.2%)	114 (0.2%)
Insulin and analogs	4943 (8%)	600 (4.7%)	4343 (8.8%)
Oral hypoglycemic drugs			
Metformin	6557 (10.5%)	987 (7.7%)	5570 (11.3%)
Sulfonilureas derivates	1178 (1.9%)	147 (1.2%)	1031 (2.1%)
Diuretics	23304 (37.5%)	3249 (25.5%)	20055 (40.6%)
Beta bloqueant agents	23453 (37.7%)	4043 (31.7%)	19410 (39.3%)
ACE inhibitors monodrugs	13660 (22%)	1919 (15%)	11741 (23.8%)
Angiotensin II antagonists monodrugs	13071 (21%)	2216 (17.4%)	10855 (22%)
Statins	18205 (29.3%)	2831 (22.2%)	15374 (31.1%)

Fibrates	1178 (1.9%)	160 (1.3%)	1018 (2.1%)
Others			
Cholestyramine	120 (0.2%)	20 (0.2%)	100 (0.2%)
Colestipol	22 (0%)	3 (0%)	19 (0%)
Colextran	31 (0%)	4 (0%)	27 (0.1%)
Colesevelam	3 (0%)	1 (0%)	2 (0%)
Ezetimiba	1226 (2%)	200 (1.6%)	1026 (2.1%)
Alirocumab	0 (0%)	0 (0%)	0 (0%)
Evolocumab	0 (0%)	0 (0%)	0 (0%)
Dronedarone	583 (0.9%)	123 (1%)	460 (0.9%)
NSAIDs	8136 (13.1%)	1224 (9.6%)	6912 (14%)

*ACE: Angiotensin-converting enzyme; NSAIDs: non-steroidal anti-inflammatory drugs; LMWH: Low molecular weight heparin. Time window (Index date+30d, End of follow up] *Time window considered (Index date, End of follow-up].*

Table 9. Follow-up medication by NOAC or VKA subgroups.

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
Follow-up, years*						
Mean (SD)	0.95 (1.21)	1.38 (1.49)	0.5 (0.73)	1.18 (1.4)	1.65 (1.64)	1.36 (1.62)
Median (Q1, Q3)	0.4 (0, 1.6)	0.9 (0, 2.6)	0.1 (0, 0.8)	0.5 (0, 2.1)	1.2 (0.1, 2.9)	0.6 (0, 2.5)
Missing (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Medication						
LMWH	486 (11.9%)	454 (14.5%)	70 (9.4%)	653 (13.6%)	12739 (26.3%)	250 (26.6%)
Antiplatelet treatment						
Abciximab	1 (0%)	0 (0%)	1 (0.1%)	1 (0%)	13 (0%)	1 (0.1%)
Acetilsalicilic acid	417 (10.2%)	359 (11.4%)	60 (8.1%)	504 (10.5%)	6964 (14.4%)	127 (13.5%)
Cilostazol	10 (0.2%)	4 (0.1%)	1 (0.1%)	9 (0.2%)	128 (0.3%)	0 (0%)
Clopidogrel	119 (2.9%)	105 (3.3%)	17 (2.3%)	137 (2.9%)	1961 (4%)	34 (3.6%)
Dipyridamole	7 (0.2%)	8 (0.3%)	1 (0.1%)	7 (0.1%)	135 (0.3%)	0 (0%)
Epoprostenol	0 (0%)	1 (0%)	0 (0%)	0 (0%)	6 (0%)	0 (0%)
Eptifibatide	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Iloprost	0 (0%)	1 (0%)	1 (0.1%)	0 (0%)	36 (0.1%)	1 (0.1%)
Prasugrel	3 (0.1%)	2 (0.1%)	1 (0.1%)	5 (0.1%)	32 (0.1%)	0 (0%)
Ticagrelor	7 (0.2%)	10 (0.3%)	1 (0.1%)	8 (0.2%)	81 (0.2%)	2 (0.2%)
Ticlopidine	0 (0%)	0 (0%)	0 (0%)	1 (0%)	14 (0%)	1 (0.1%)
Triflusal	12 (0.3%)	6 (0.2%)	1 (0.1%)	6 (0.1%)	113 (0.2%)	1 (0.1%)

Insulin and analogs	186 (4.5%)	148 (4.7%)	23 (3.1%)	243 (5.1%)	4261 (8.8%)	82 (8.7%)
Oral hypoglycemic drugs						
Metformin	289 (7.1%)	264 (8.4%)	41 (5.5%)	393 (8.2%)	5483 (11.3%)	87 (9.2%)
Sulfonilureas derivates	36 (0.9%)	37 (1.2%)	9 (1.2%)	65 (1.4%)	1014 (2.1%)	17 (1.8%)
Diuretics	1059 (25.9%)	797 (25.4%)	136 (18.3%)	1257 (26.2%)	19688 (40.6%)	367 (39%)
Beta bloqueant agents	1252 (30.6%)	1037 (33%)	182 (24.5%)	1572 (32.8%)	19082 (39.4%)	328 (34.9%)
ACE inhibitors monodrugs	632 (15.4%)	496 (15.8%)	72 (9.7%)	719 (15%)	11533 (23.8%)	208 (22.1%)
Angiotensin II antagonists monodrugs	696 (17%)	586 (18.7%)	103 (13.9%)	831 (17.3%)	10668 (22%)	187 (19.9%)
Statins	869 (21.2%)	756 (24.1%)	138 (18.6%)	1068 (22.3%)	15103 (31.2%)	271 (28.8%)
Fibrates	53 (1.3%)	44 (1.4%)	7 (0.9%)	56 (1.2%)	998 (2.1%)	20 (2.1%)
Others						
Cholestyramine	8 (0.2%)	6 (0.2%)	2 (0.3%)	4 (0.1%)	98 (0.2%)	2 (0.2%)
Colestipol	1 (0%)	1 (0%)	0 (0%)	1 (0%)	19 (0%)	0 (0%)
Colextran	1 (0%)	0 (0%)	0 (0%)	3 (0.1%)	24 (0%)	3 (0.3%)
Colesevelam	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0.1%)
Ezetimiba	61 (1.5%)	54 (1.7%)	8 (1.1%)	77 (1.6%)	1020 (2.1%)	6 (0.6%)
Alirocumab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Evolocumab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dronedarone	35 (0.9%)	29 (0.9%)	4 (0.5%)	55 (1.1%)	452 (0.9%)	8 (0.9%)
NSAIDs	371 (9.1%)	335 (10.7%)	54 (7.3%)	464 (9.7%)	6775 (14%)	137 (14.6%)

*ACE: Angiotensin-converting enzyme; HMG CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; NSAIDs: non-steroidal anti-inflammatory drugs; LMWH: Low molecular weight heparin. Time window (Index date+30d, End of follow up]. *Time window considered (Index date, End of follow-up].*

10.4.5. *Baseline laboratory values*

Table 10. Baseline laboratory values for patients treated with OAC, overall and by OAC group.

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
INR*			
Mean (SD)	2.28 (1.56)	NA	2.28 (1.56)
Median (Q1, Q3)	1.9 (1.16, 2.8)	NA	1.9 (1.16, 2.8)
Missing (%)	26523 (53.7%)	NA	26523 (53.7%)
Hemoglobin (g/dL)†			
Mean (SD)	13.09 (2.11)	13.33 (2.09)	13.03 (2.11)
Median (Q1, Q3)	13.2 (11.7, 14.6)	13.5 (12, 14.8)	13.1 (11.6, 14.5)
Missing (%)	27731 (44.6%)	6073 (47.6%)	21658 (43.8%)
Hematocrit (%)			
Mean (SD)	39.77 (31.89)	40.2 (7.93)	39.67 (35.22)
Median (Q1, Q3)	40.4 (36, 44.2)	41 (36.9, 44.8)	40.2 (35.8, 44)
Missing (%)	38420 (61.8%)	8262 (64.7%)	30158 (61.1%)

*INR: International Normalized Ratio. * INR > 15 has been discarded in the analysis for considering outliers. †For hemoglobin data, a standard outlier elimination has been performed. Time window Index date[-180d, +30d].*

Table 11. Baseline laboratory values by NOAC or VKA subgroups.

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
INR*						
Mean (SD)	NA	NA	NA	NA	2.27 (1.56)	2.79 (1.71)
Median (Q1, Q3)	NA	NA	NA	NA	1.89 (1.15, 2.79)	2.425 (1.595, 3.42)
Missing (%)	NA	NA	NA	NA	26042 (53.7%)	481 (51.1%)
Hemoglobin (g/dL)†						
Mean (SD)	13.23 (2.06)	13.3 (2.1)	13.46 (2.04)	13.4 (2.11)	13.04 (2.11)	12.59 (2.15)
Median (Q1, Q3)	13.3 (11.9, 14.7)	13.4 (12, 14.8)	13.6 (12.175, 15)	13.6 (12, 14.9)	13.2 (11.6, 14.5)	12.7 (11.2, 14)
Missing (%)	1894 (46.3%)	1636 (52.1%)	322 (43.4%)	2221 (46.4%)	21240 (43.8%)	418 (44.4%)
Hematocrit (%)						
Mean (SD)	39.99 (7.9)	39.87 (8.81)	40.69 (7.63)	40.49 (7.46)	39.71 (35.46)	37.03 (9.82)
Median (Q1, Q3)	40.7 (36.5, 44.6)	40.7 (36.625, 44.5)	41.9 (37.6, 45.4)	41.4 (37.225, 45)	40.2 (35.8, 44)	39 (33, 42.475)
Missing (%)	2624 (64.1%)	2129 (67.8%)	493 (66.4%)	3016 (63%)	29503 (60.9%)	655 (69.6%)

*INR: International Normalized Ratio. *INR > 15 has been discarded in the analysis for considering outliers.. † For hemoglobin data, a standard outlier elimination has been performed. Time window Index date[-180d, +30d].*

10.4.6. *Baseline vital signs*

Table 12. Baseline vital signs for patients treated with OAC, overall and by OAC group.

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
Heart rate			
Mean (SD)	65.48 (33.03)	62.95 (34.9)	66.1 (32.43)
Median (Q1, Q3)	70 (50, 85)	67 (40, 82)	70 (50, 85)
Missing (%)	32589 (52.4%)	6948 (54.4%)	25641 (51.9%)
Systolic BP			
Mean (SD)	136.51 (42.64)	136.6 (50.34)	136.55 (40.49)
Median (Q1, Q3)	135 (119, 153)	134 (118, 151)	135 (119, 153)
Missing (%)	38435 (61.8%)	8159 (63.9%)	30276 (61.3%)
Diastolic BP			
Mean (SD)	75.54 (23.38)	76.84 (21.11)	75.22 (23.24)
Median (Q1, Q3)	75 (65, 85)	76 (66, 86)	75 (65, 85)
Missing (%)	38434 (61.8%)	8159 (63.9%)	30275 (61.3%)

BP: Blood Pressure. Time window Index date[-180d, +30d].

Table 19. Baseline vital signs by NOAC or VKA subgroups.

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
Heart rate (bpm)						
Mean (SD)	63.59 (39.23)	64.17 (31.1)	60.59 (32.52)	62.1 (33.51)	66.07 (32.51)	67.88 (28.03)
Median (Q1, Q3)	68 (40, 84)	69 (50, 83)	65 (40, 80)	66 (40, 80)	70 (50, 85)	70 (55, 84.75)
Missing (%)	2217 (54.1%)	1814 (57.8%)	363 (48.9%)	2554 (53.3%)	25150 (51.9%)	491 (52.2%)
Systolic BP (mmHg)						
Mean (SD)	136.28 (43.4)	135.63 (44.31)	134.58 (25.91)	137.82 (61.43)	136.58 (40.73)	135.17 (26.43)
Median (Q1, Q3)	133 (119, 150)	134 (116, 154)	135 (119, 150)	134 (120, 150)	135 (119, 153)	132.5 (117.75, 153)
Missing (%)	2558 (62.5%)	2108 (67.2%)	439 (59.2%)	3054 (63.8%)	29715 (61.3%)	561 (59.6%)
Diastolic BP (mmHg)						
Mean (SD)	77.46 (23.72)	76.04 (16.31)	77.61 (15.64)	76.62 (21.99)	75.23 (22.92)	74.55 (35.8)
Median (Q1, Q3)	76 (67, 87)	75 (65, 86)	78 (67, 88)	76 (66, 86)	75 (65, 85)	72 (63, 82)
Missing (%)	2559 (62.5%)	2108 (67.2%)	439 (59.2%)	3053 (63.7%)	29715 (61.3%)	560 (59.5%)

BP: Blood pressure. Time window Index date[-180d, +30d].

10.4.7. *Follow-up clinical events*

Table 13. Follow-up acute and chronic clinical events for patients treated with OAC, overall and by OAC group*.

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)
Follow-up, years			
Mean (SD)	1.53 (1.6)	1.12 (1.35)	1.64 (1.64)
Median (Q1, Q3)	1 (0, 2.8)	0.5 (0, 2)	1.2 (0.1, 2.9)
Missing (%)	0 (0%)	0 (0%)	0 (0%)
Acute clinical events			
Transient ischemic attack	5877 (9.5%)	903 (7.3%)	4974 (10.1%)
Thrombocytopenia	3531 (5.7%)	409 (3.3%)	3122 (6.3%)
Myocardial infarction	2830 (4.6%)	443 (3.6%)	2387 (4.8%)
Hemodialysis	1612 (2.6%)	136 (1.1%)	1476 (3%)
Chronic clinical events			
Heart failure	29037 (47%)	4261 (34.2%)	24776 (50.3%)
Renal disease	17942 (29.1%)	2438 (19.6%)	15504 (31.5%)
Diabetes mellitus	24085 (39%)	3703 (29.7%)	20382 (41.4%)
Hypertension	39267 (63.6%)	6499 (52.2%)	32768 (66.5%)
Dyspepsia	1306 (2.1%)	202 (1.6%)	1104 (2.2%)
Peripheral vascular disease	767 (1.2%)	96 (0.8%)	671 (1.4%)
Coronary disease	6202 (10.0%)	983 (7.9%)	5219 (10.6%)
Pulmonary disease	6948 (11.3%)	968 (7.8%)	5980 (12.1%)
Sleep apnea	3675 (6%)	644 (5.2%)	3031 (6.2%)

**For acute events, data included in the table refer to prevalent or incident acute comorbidities available in the EHRs during post-baseline period. For chronic events, data included in the table refer to incident chronic comorbidities available in the EHRs during post-baseline period, not being considered those present at index-date or baseline. Time window considered (Index date, End of follow-up].*

Table 14. Follow-up acute and chronic clinical events by NOAC or VKA subgroups*.

	NOAC				VKA	
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**
Follow-up, years						
Mean (SD)	0.95 (1.21)	1.38 (1.49)	0.5 (0.73)	1.18 (1.4)	1.65 (1.64)	1.36 (1.62)
Median (Q1, Q3)	0.4 (0, 1.6)	0.9 (0, 2.6)	0.1 (0, 0.8)	0.5 (0, 2.1)	1.2 (0.1, 2.9)	0.6 (0, 2.5)
Missing (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Acute clinical events						
Transient ischemic attack	268 (6.7%)	282 (9.2%)	33 (4.7%)	320 (6.8%)	4855 (10%)	119 (12.7%)
Thrombocytopenia	112 (2.8%)	128 (4.2%)	14 (2%)	155 (3.3%)	3057 (6.3%)	65 (6.9%)
Myocardial infarction	112 (2.8%)	128 (4.2%)	14 (2%)	155 (3.3%)	3057 (6.3%)	65 (6.9%)
Hemodialysis	53 (1.3%)	32 (1%)	4 (0.6%)	47 (1%)	1433 (3%)	43 (4.6%)
Chronic clinical events						
Heart failure	1339 (33.6%)	1154 (37.5%)	206 (29.3%)	1562 (33.4%)	24266 (50.2%)	510 (54.3%)
Renal disease	805 (20.2%)	619 (20.1%)	114 (16.2%)	900 (19.2%)	15147 (31.3%)	357 (38%)
Diabetes mellitus	1143 (28.7%)	1009 (32.7%)	173 (24.6%)	1378 (29.4%)	19991 (41.4%)	391 (41.6%)
Hypertension	2028 (50.9%)	1703 (55.3%)	322 (45.7%)	2446 (52.2%)	32170 (66.6%)	598 (63.7%)
Dyspepsia	57 (1.4%)	65 (2.1%)	8 (1.1%)	72 (1.5%)	1084 (2.2%)	20 (2.1%)
Peripheral vascular disease	35 (0.9%)	22 (0.7%)	4 (0.6%)	35 (0.7%)	663 (1.4%)	8 (0.9%)
Coronary disease	304 (7.6%)	239 (7.8%)	44 (6.2%)	396 (8.5%)	5111 (10.6%)	108 (11.5%)
Pulmonary disease	308 (7.7%)	220 (7.1%)	59 (8.4%)	381 (8.1%)	5861 (12.1%)	119 (12.7%)

Sleep apnea	198 (5%)	178 (5.8%)	21 (3%)	247 (5.3%)	2985 (6.2%)	46 (4.9%)

**For acute events, data included in the table refer to prevalent or incident acute comorbidities available in the EHRs during post-baseline period. For chronic events, data included in the table refer to incident chronic comorbidities available in the EHRs during post-baseline period, not being considered those present at index-date or baseline. Time window considered (Index date, End of follow-up].*

10.4.8. *Switch of Treatment*

Table 15. Switch for patients treated with OAC, overall and by OAC group.

	Overall (n=62163)	NOAC (n=12766)	VKA (n=49397)	Chi-squared
No switch in treatment	52291 (84.1%)	10081 (79%)	42210 (85.5%)	NA
Treatment switch	9872 (15.9%)	2685 (21%)	7187 (14.5%)	NA
Treatment after switch				p<2*10e-16
Apixaban	2818 (28.5%)	349 (13.0%)	2469 (34.3%)	
Dabigatran	1270 (12.9%)	189 (7.0%)	1081 (15.0%)	
Edoxaban	797 (8.1%)	67 (2.5%)	730 (10.2%)	
Rivaroxaban	1995 (20.2%)	178 (6.6%)	1817 (25.3%)	
Acenocumarol	2283 (23.1%)	1862 (69.3%)	421 (5.9%)	
Warfarin	709 (7.2%)	40 (1.5%)	669 (9.3%)	
Time to switch (days)				NA
N* (%)	9235 (14.9%)	1694 (13.3%)	7541 (15.3%)	
Mean (SD)	564.33 (479.09)	420.12 (379.86)	596.72 (492.92)	
Median (Q1, Q3)	431 (170, 835.5)	286 (113, 635.75)	470 (191, 883)	

Time window considered (Index date, End of follow-up].
** Data include both therapeutic switching and discontinuation patients, causing a numerical disparity with treatment switch-only cases*

Table 16. Switch by NOAC or VKA subgroups.

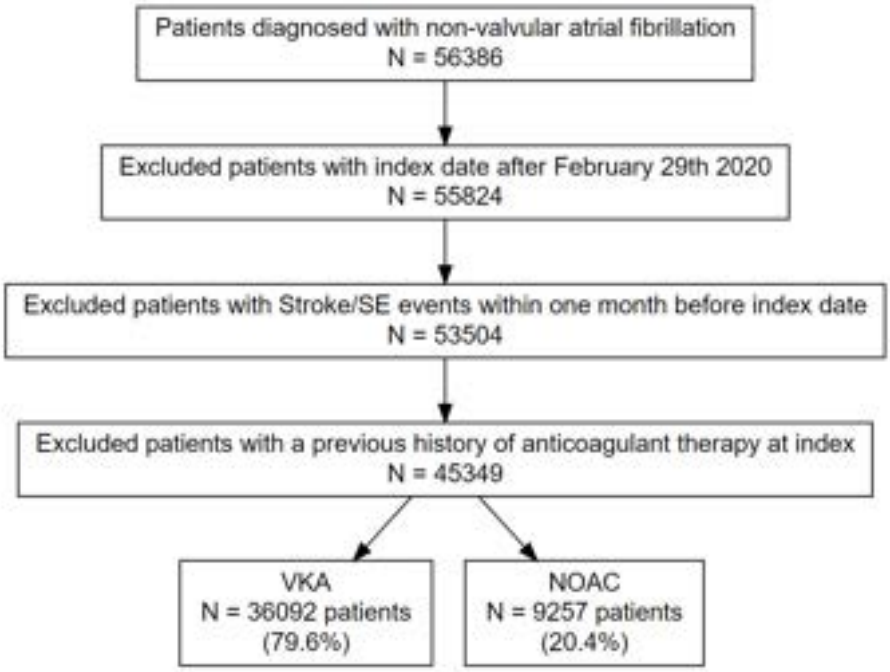
	NOAC				VKA		
	Apixaban n=4095	**Dabigatran n=3139**	**Edoxaban n=742**	**Rivaroxaban n=4790**	**Acenocumarol n=48456**	**Warfarin n=942**	**Chi-squared**
No switch in treatment	3421 (83.5%)	2360 (75.2%)	592 (79.8%)	3708 (77.4%)	41727 (86.1%)	483 (51.3%)	NA
Treatment switch	674 (16.5%)	779 (24.8%)	150 (20.2%)	1082 (22.6%)	6729 (13.9%)	458 (48.7%)	NA
Treatment after switch							p<2*10e-16
Apixaban	NA	135 (17.3%)	22 (14.7%)	192 (17.7%)	2455 (36.5%)	14 (3.1%)	
Dabigatran	65 (9.6%)	NA	8 (5.3%)	116 (10.7%)	1074 (16.0%)	7 (1.5%)	
Edoxaban	17 (2.5%)	24 (3.1%)	NA	26 (2.4%)	725 (10.8%)	5 (1.1%)	
Rivaroxaban	69 (10.2%)	95 (12.2%)	14 (9.3%)	NA	1806 (26.8%)	11 (2.4%)	
Acenocumarol	516 (76.6%)	511 (65.6%)	103 (68.7%)	732 (67.7%)	NA	421 (91.9%)	
Warfarin	7 (1.0%)	14 (1.8%)	3 (2.0%)	16 (1.5%)	669 (9.9%)	NA	
Time to switch (days)							
N (%)	414 (10.1%)	534 (17.0%)	69 (9.3%)	677 (14.1%)	7307 (15.1%)	235 (24.9%)	
Mean (SD)	353.81 (342.23)	469.22 (415.13)	244.29 (247.34)	439.86 (373.7)	602.32 (494.91)	421.92 (388.48)	
Median (Q1, Q3)	224 (98, 502.75)	323.5 (131, 732.75)	131 (81, 329)	338 (126, 679)	476 (195, 890.5)	310 (111, 641)	

Time window considered (Index date, End of follow-up].
** Data include both therapeutic switching and discontinuation patients, causing a numerical disparity with treatment switch-only cases*

10.5. Study population included in outcome analyses (SO-2 and SO-3)

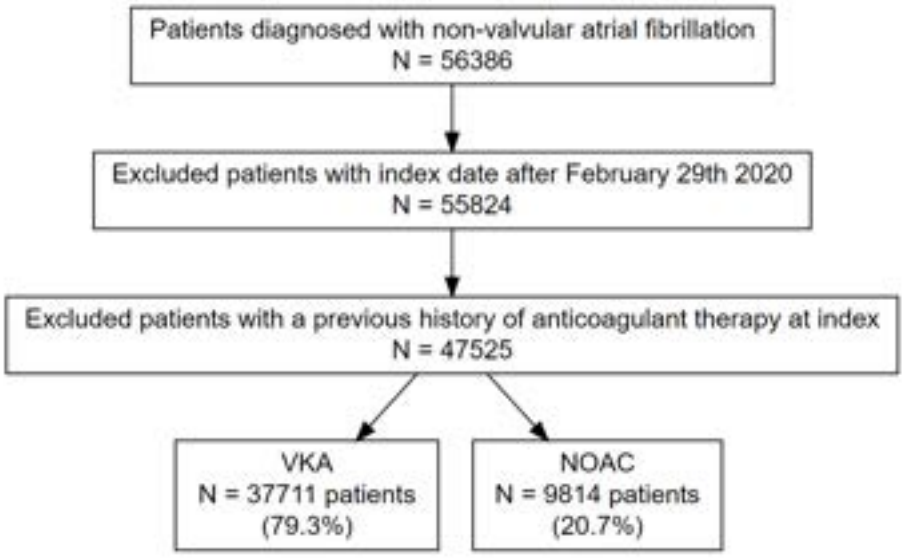
For SO-2 and SO-3 specific pAS for effectivity and safety outcomes were defined as described below.

Figure 5. Patients Criteria Selection of the Study Population with Stroke/SE Events



Patients with incident stroke events at index (defined as a stroke within the month previous to index) were excluded from stroke incident rate analysis to avoid the combination of primary vs. secondary events in the context of first NOAC/VKA treatment. SE: Systemic embolism.

Figure 6. Patients Criteria Selection of the Study Population with Major and Minor Bleeding



10.6. Annual incidences rates regarding effectivity and safety outcomes (SO-2)

10.6.1. *Effectivity outcomes*

Table 17. Incidence Rates of Stroke/SE and Ischemic Stroke Events patients treated with OAC, overall and by OAC group.

	Overall (n=45349)	NOAC (n=9257)	VKA (n=36092)
Stroke/SE			
N events (%)	1940 (4.28%)	248 (2.68%)	1692 (4.69%)
Incidence Rate (N per 100 per year)	1.61	1.26	1.68
Time to stroke SE (days)			
Mean (SD)	454.68 (473.82)	367.41 (410.30)	469.82 (482.47)
Median (Q1, Q3)	306.5 (48; 747)	190 (32; 609)	322 (53; 776)
Ischemic Stroke			
N events (%)	1414 (3.12%)	187 (2.02%)	1227 (3.4%)
Incidence Rate (N per 100 per year)	1.16	0.95	1.21
Time to Ischemic Stroke (days)			
Mean (SD)	480.15 (485.68)	382.12 (418.81)	497.72 (494.79)
Median (Q1, Q3)	327 (60; 790)	219 (39; 642)	342 (67; 807)

NOAC: Non-Vitamin K Oral Anticoagulants; VKA: Vitamin K Oral Anticoagulants; SD: standard deviation; SE: Systemic embolism. Time window considered (Index date, End of follow-up].

Table 18. Incidence Rates of Ischemic Stroke Events by NOAC or VKA.

	NOAC			VKA
	Apixaban (n=3144)	**Dabigatran (n=2290)**	**Rivaroxaban (n=3823)**	**Acenocumarol (n=36092)**
Ischemic Stroke				
N events (%)	68 (2.16%)	58 (2.53%)	61 (1.6%)	1227 (3.4%)
Incidence Rate (N per 100 per year)	1.11	1.11	0.73	1.21
Time to stroke Ischemic Stroke (days)				
Mean (SD)	299 (363.11)	336.85 (415.61)	488.91 (447.63)	497.72 (494.79)
Median (Q1, Q3)	109 (22; 516)	161 (32; 523)	388 (114; 755)	342 (67; 807)

NOAC: Non-Vitamin K Oral Anticoagulants; VKA: Vitamin K Oral Anticoagulants; SD: standard deviation. Time window considered (Index date, End of follow-up).

10.6.2. *Safety outcomes*

Table 19. Incidence Rates of Major and Minor Bleeding in patients treated with OAC, overall and by OAC group.

	Overall (n=47525)	NOAC (n=9814)	VKA (n=37711)
Major Bleeding			
N events (%)	5844 (12.3%)	819 (8.35%)	5025 (13.33%)
Incidence Rate (N per 100 per year)	4.98	4.12	5.15
Time to Major Bleeding (days)			
Mean (SD)	447.29 (484.41)	366.04 (413.75)	461.85 (494.63)
Median (Q1, Q3)	271 (47; 725)	194 (34; 617)	289.5 (50; 744)
Minor Bleeding			
N events (%)	9394 (19.77%)	1474 (15.02%)	7920 (21%)
Incidence Rate (N per 100 per year)	8.61	7.89	8.76
Time to Minor Bleeding (days)			
Mean (SD)	400.77 (445.42)	343.16 (397.13)	412.81 (453.97)
Median (Q1, Q3)	241 (42; 627)	182 (33; 540)	252 (45; 643)

NOAC: Non-Vitamin K Oral Anticoagulants; VKA: Vitamin K Oral Anticoagulants; SD: Standard deviation. Time window considered (Index date, End of follow-up].

Table 20. Incidence Rates of Major and Minor Bleeding by NOAC or VKA subgroups.

		NOAC		VKA
	Apixaban (n=3390)	**Dabigatran (n=2441)**	**Rivaroxaban (n=3983)**	**Acenocumarol (n=37711)**
Major Bleeding				
N events (%)	303 (8.94%)	215 (8.81%)	301 (7.56%)	5025 (13.33%)
Incidence Rate (N per 100 per year)	4.82	4.08	3.62	5.15
Time to stroke Major Bleeding (days)				
Mean (SD)	327.94 (398.08)	398.51 (430.26)	376.59 (413.55)	461.85 (494.63)
Median (Q1, Q3)	157 (34; 504)	237.5 (42; 687)	215 (28; 618)	289.5 (50; 744)
Minor Bleeding				

		NOAC		VKA
	Apixaban (n=3390)	**Dabigatran (n=2441)**	**Rivaroxaban (n=3983)**	**Acenocumarol (n=37711)**
N events (%)	478 (14.1%)	387 (15.85%)	609 (15.29%)	7920 (21%)
Incidence Rate (N per 100 per year)	8.01	7.82	7.84	8.76
Time to stroke Minor Bleeding (days)				
Mean (SD)	314.65 (387.13)	342.34 (397.82)	364.74 (403.08)	412.81 (453.97)
Median (Q1, Q3)	139 (28; 470)	193.5 (22; 553)	213.5 (43; 573)	252 (45; 643)

NOAC: Non-Vitamin K Oral Anticoagulants; VKA: Vitamin K Oral Anticoagulants; SD: standard deviation. Time window considered (Index date, End of follow-up].

10.7. Comparison rates of effectivity and safety outcomes (SO-3)

10.7.1. *Effectivity outcomes.*

Table 21. List of Confounders for the Propensity Score Matching for Stroke/SE and Ischemic Stroke per NOAC or VKA Type in pre-matched patients.

			NOAC		VKA
	Overall (n=45349)	**Apixaban (n=3144)**	**Dabigatran (n=2290)**	**Rivaroxaban (n=36092)**	**Acenocumarol (n=21881)**
Demographic and Social Characteristics					
Gender					
Female	21207 (47%)	1451 (46%)	925 (40%)	1580 (41%)	17251 (48%)
Male	23858 (53%)	1666 (53%)	1350 (59%)	2207 (58%)	18635 (52%)
Missing (%)	284 (0.6%)	27 (0.9%)	15 (0.7%)	36 (0.9%)	206 (0.6%)
Age at index					
Mean (SD)	76.39 (12.71)	75.71 (13.86)	73.44 (13.94)	73.76 (14.7)	76.92 (12.23)
Median (Q1, Q3)	78 (69, 84)	77 (68, 84)	75 (66, 83)	75 (66, 83)	78 (70, 84)
(Min, Max)	(18-218)	(20-152)	(21-152)	(21-153)	(18-218)
Missing (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Drinking habit					
alcoholic	2194 (5%)	110 (3%)	88 (4%)	171 (4%)	1825 (5%)
ex-alcoholic	374 (1%)	21 (1%)	16 (1%)	36 (1%)	301 (1%)
No alcoholic	81 (0%)	2 (0%)	3 (0%)	4 (0%)	72 (0%)
Missing (%)	42700 (94.2%)	3011 (95.8%)	2183 (95.3%)	3612 (94.5%)	33894 (93.9%)

			NOAC		VKA
	Overall (n=45349)	**Apixaban (n=3144)**	**Dabigatran (n=2290)**	**Rivaroxaban (n=36092)**	**Acenocumarol (n=21881)**
Comorbidities					
Bleeding baseline*	11217 (24.7%)	680 (21.6%)	507 (22.1%)	756 (19.8%)	9274 (25.7%)
Anemia baseline	14193 (31.3%)	708 (22.5%)	519 (22.7%)	832 (21.8%)	12134 (33.6%)
Thrombocytopenia	1019 (2.2%)	65 (2.1%)	37 (1.6%)	61 (1.6%)	856 (2.4%)
Ischemic stroke*	2052 (4.5%)	162 (5.2%)	115 (5%)	168 (4.4%)	1607 (4.5%)
Peripheral vascular disease*	124 (0.3%)	8 (0.3%)	2 (0.1%)	11 (0.3%)	103 (0.3%)
Myocardial infarction*	1363 (3%)	86 (2.7%)	63 (2.8%)	108 (2.8%)	1106 (3.1%)
Coronary disease*	4164 (9.2%)	284 (9%)	169 (7.4%)	345 (9%)	3366 (9.3%)
Heart failure*	17770 (39.2%)	1197 (38.1%)	686 (30%)	1337 (35%)	14550 (40.3%)
Diabetes mellitus*	20794 (45.9%)	1289 (41%)	905 (39.5%)	1517 (39.7%)	17083 (47.3%)
TIA*	2120 (4.7%)	165 (5.2%)	118 (5.2%)	148 (3.9%)	1689 (4.7%)
Hypertension*	33814 (74.6%)	2286 (72.7%)	1557 (68%)	2687 (70.3%)	27284 (75.6%)
Dyspepsia	668 (1.5%)	57 (1.8%)	30 (1.3%)	50 (1.3%)	531 (1.5%)
Renal disease*	8150 (18%)	572 (18.2%)	220 (9.6%)	555 (14.5%)	6803 (18.8%)
Cirrhosis*	543 (1.2%)	30 (1%)	17 (0.7%)	40 (1%)	456 (1.3%)
Multi-comorbidity index†	8158 (18%)	516 (16.4%)	268 (11.7%)	529 (13.8%)	6845 (19%)
Treatments					
Antiplatelets	9682 (21.3%)	696 (22.1%)	397 (17.3%)	777 (20.3%)	7812 (21.6%)
Insulin and analogs	3587 (7.9%)	183 (5.8%)	150 (6.6%)	208 (5.4%)	3046 (8.4%)
ACEs/ARBs	22699 (50.1%)	1493 (47.5%)	1010 (44.1%)	1747 (45.7%)	18449 (51.1%)

			NOAC		VKA
	Overall (n=45349)	**Apixaban (n=3144)**	**Dabigatran (n=2290)**	**Rivaroxaban (n=36092)**	**Acenocumarol (n=21881)**
OHD	6280 (13.8%)	407 (12.9%)	303 (13.2%)	474 (12.4%)	5096 (14.1%)
Lipid lowering drugs	2299 (5.1%)	179 (5.7%)	105 (4.6%)	191 (5%)	1824 (5.1%)
Diuretics	20952 (46.2%)	1274 (40.5%)	810 (35.4%)	1422 (37.2%)	17446 (48.3%)
Beta blocker agents	23351 (51.5%)	1787 (56.8%)	1235 (53.9%)	2046 (53.5%)	18283 (50.7%)
NSAIDs	4829 (10.6%)	320 (10.2%)	243 (10.6%)	385 (10.1%)	3881 (10.8%)

*ACE: Angiotensin converting enzyme inhibitors; ARB Angiotensin-receptor blockers; NOAC: Non-Vitamin K Oral Anticoagulants; NSAIDs: Non-steroidal anti-inflammatory drugs; OHD: Oral hypoglycemic medications; TIA: Transient ischemic attack; VKA: Vitamin K Oral Anticoagulants; SD: Standard deviation. †Multi-comorbidity index is a binary variable in which each comorbidity marked with * was included as +1. Comorbidity is considered negative when index <3, and positive when ≥3. Time window considered (First report, Index date].*

Figure 7. Evaluation of PSM (love plot).

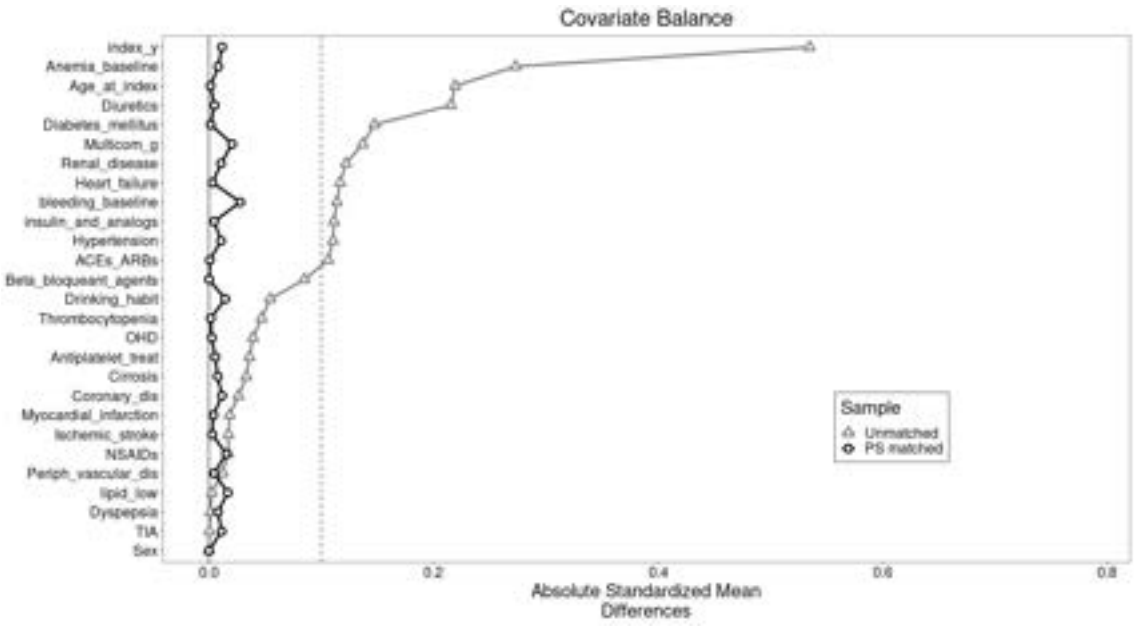


Figure 8. Kaplan-Meier curve for Time to Stroke/SE after PSM for NOAC vs VKA (full scale).

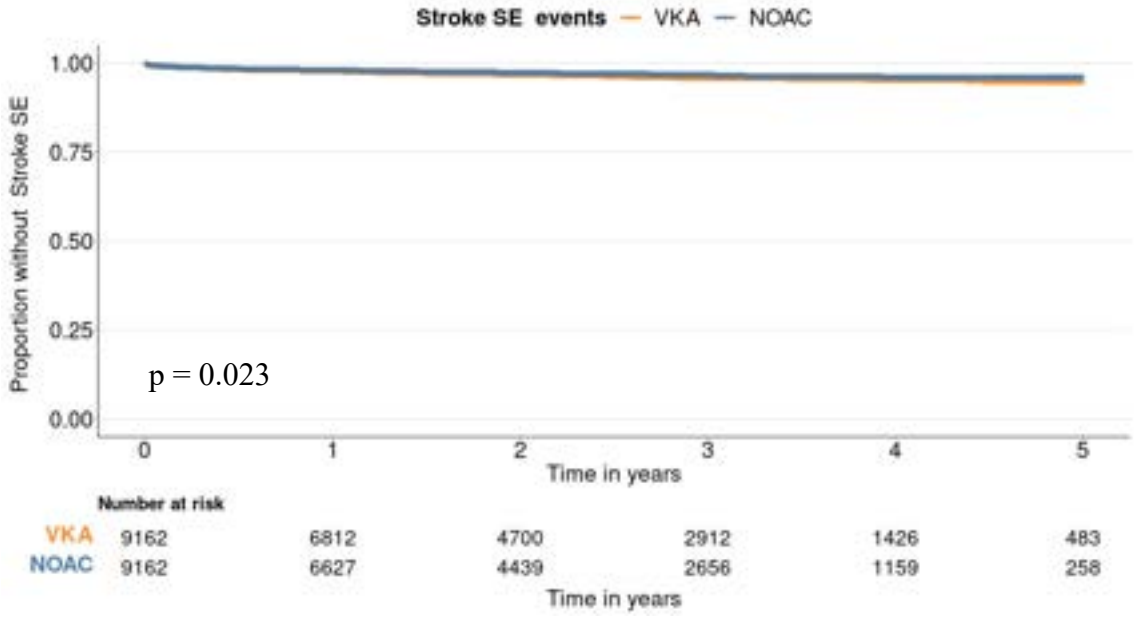


Figure 9. Kaplan-Meier curve for Time to Stroke/SE after PSM for NOAC vs VKA (partial scale).

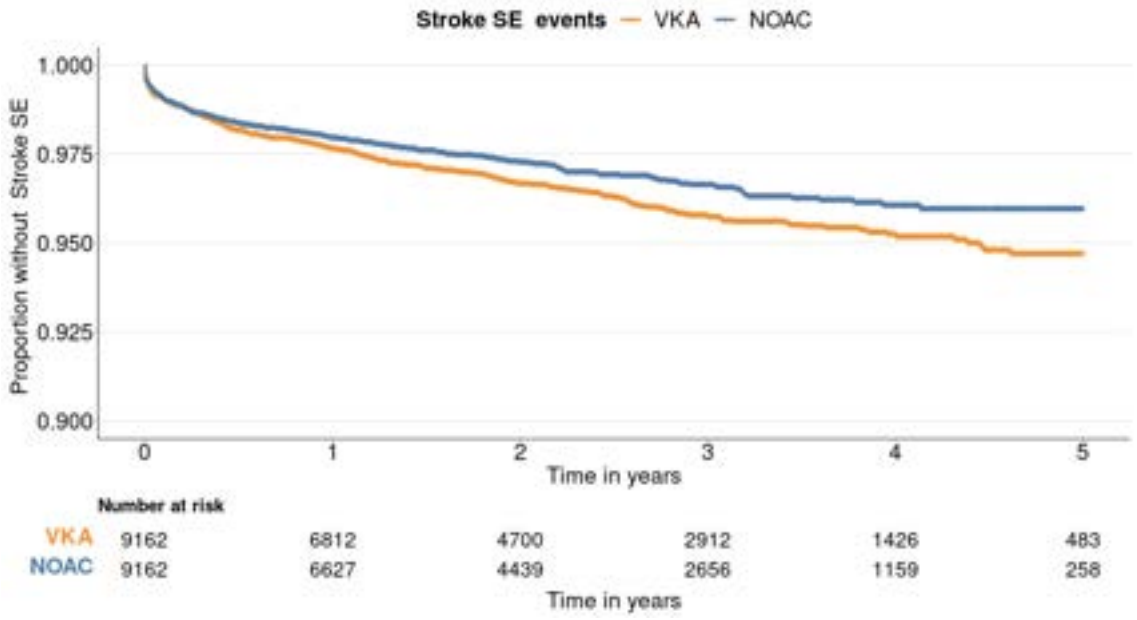
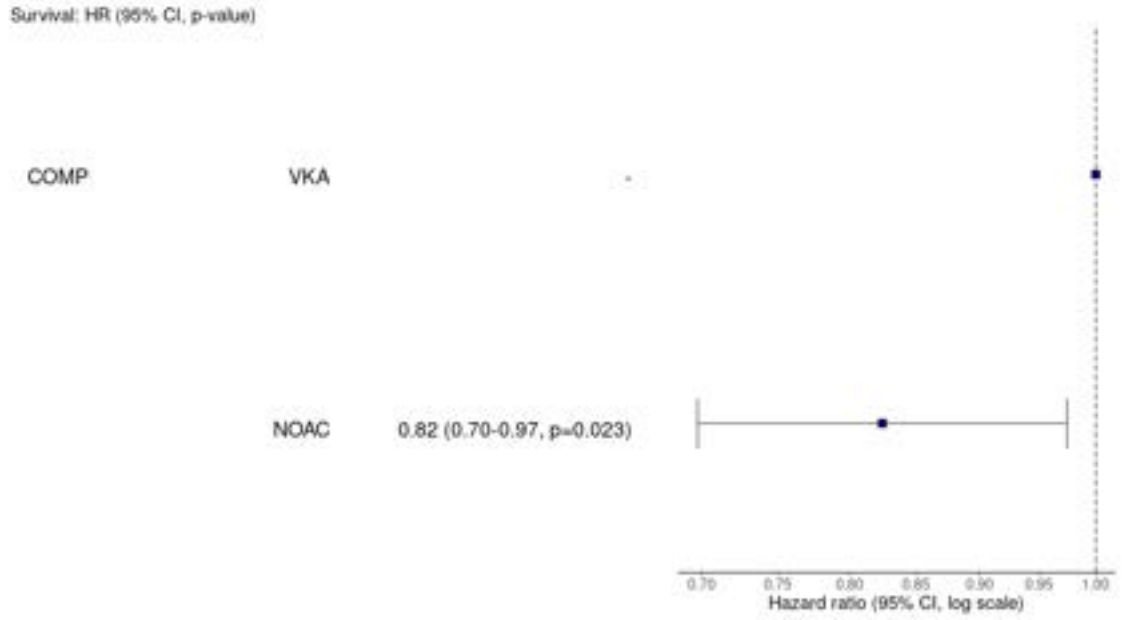


Figure 10. Univariate cox regression for time to event comparison of NOAC vs VKA for Stroke/SE after PSM.



10.7.2. ***Safety outcomes.***

Table 29. List of Confounders for the Propensity Score Matching for Major and Minor Bleeding per NOAC or VKA Type in pre-matched patients.

			NOAC		VKA
	Overall (n=47525)	**Apixaban (n=3390)**	**Dabigatran (n=2441)**	**Rivaroxaban (n=3983)**	**Acenocumarol (n=37711)**
Demographic and Social Characteristics					
Gender					
Female	22269 (47%)	1569 (46%)	990 (41%)	1654 (42%)	18056 (48%)
Male	24966 (53%)	1793 (53%)	1436 (59%)	2293 (58%)	19444 (52%)
Missing (%)	290 (0.6%)	28 (0.8%)	15 (0.6%)	36 (0.9%)	211 (0.6%)
Age at index					
Mean (SD)	76.44 (12.65)	75.91 (13.66)	73.54 (13.74)	73.88 (14.6)	76.94 (12.19)
Median (Q1, Q3)	78 (69, 84)	77 (68, 84.75)	75 (66, 83)	75 (66, 83)	78 (70, 84)
(Min, Max)	(18-218)	(20-152)	(21-152)	(21-153)	(18-218)
Missing (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Drinking habit					
alcoholic	2335 (5%)	131 (4%)	96 (4%)	181 (5%)	1927 (5%)
ex-alcoholic	395 (1%)	23 (1%)	18 (1%)	38 (1%)	316 (1%)
No alcoholic	84 (0%)	3 (0%)	3 (0%)	4 (0%)	74 (0%)
Missing (%)	44711 (94.1%)	3233 (95.4%)	2324 (95.2%)	3760 (94.4%)	35394 (93.9%)
Comorbidities					
Bleeding baseline*	12386 (26.1%)	829 (24.5%)	591 (24.2%)	843 (21.2%)	10123 (26.8%)
Anemia baseline	14797 (31.1%)	750 (22.1%)	552 (22.6%)	867 (21.8%)	12628 (33.5%)
Thrombocytopenia	1079 (2.3%)	67 (2%)	41 (1.7%)	66 (1.7%)	905 (2.4%)
Ischemic stroke*	4182 (8.8%)	406 (12%)	265 (10.9%)	326 (8.2%)	3185 (8.4%)
Peripheral vascular disease*	130 (0.3%)	8 (0.2%)	2 (0.1%)	11 (0.3%)	109 (0.3%)
Myocardial infarction*	1696 (3.6%)	120 (3.5%)	95 (3.9%)	133 (3.3%)	1348 (3.6%)
Coronary disease*	4393 (9.2%)	320 (9.4%)	183 (7.5%)	355 (8.9%)	3535 (9.4%)
Heart failure*	18665 (39.3%)	1300 (38.3%)	742 (30.4%)	1396 (35%)	15227 (40.4%)
Diabetes mellitus*	21892 (46.1%)	1414 (41.7%)	979 (40.1%)	1594 (40%)	17905 (47.5%)

			NOAC		VKA
	Overall (n=47525)	**Apixaban (n=3390)**	**Dabigatran (n=2441)**	**Rivaroxaban (n=3983)**	**Acenocumarol (n=37711)**
TIA*	2549 (5.4%)	224 (6.6%)	157 (6.4%)	177 (4.4%)	1991 (5.3%)
Hypertension*	35540 (74.8%)	2485 (73.3%)	1673 (68.5%)	2815 (70.7%)	28567 (75.8%)
Dyspepsia	693 (1.5%)	58 (1.7%)	35 (1.4%)	50 (1.3%)	550 (1.5%)
Renal disease*	8548 (18%)	623 (18.4%)	236 (9.7%)	582 (14.6%)	7107 (18.8%)
Cirrhosis*	566 (1.2%)	31 (0.9%)	17 (0.7%)	42 (1.1%)	476 (1.3%)
Multi-comorbidity index†	9349 (19.7%)	665 (19.6%)	340 (13.9%)	615 (15.4%)	7729 (20.5%)
Treatments					
Antiplatelets	10495 (22.1%)	821 (24.2%)	446 (18.3%)	833 (20.9%)	8395 (22.3%)
Insulin and analogs	4024 (8.5%)	222 (6.5%)	179 (7.3%)	234 (5.9%)	3389 (9%)
ACEs/ARBs	23974 (50.4%)	1637 (48.3%)	1085 (44.4%)	1826 (45.8%)	19426 (51.5%)
OHD	6621 (13.9%)	434 (12.8%)	322 (13.2%)	505 (12.7%)	5360 (14.2%)
Lipid lowering drugs	2404 (5.1%)	188 (5.5%)	116 (4.8%)	198 (5%)	1902 (5%)
Diuretics	21948 (46.2%)	1366 (40.3%)	852 (34.9%)	1475 (37%)	18255 (48.4%)
Beta blocker agents	24529 (51.6%)	1913 (56.4%)	1315 (53.9%)	2129 (53.5%)	19172 (50.8%)
NSAIDs	5060 (10.6%)	343 (10.1%)	259 (10.6%)	397 (10%)	4061 (10.8%)

*ACE: Angiotensin converting enzyme inhibitors; ARB Angiotensin-receptor blockers; NOAC: Non-Vitamin K Oral Anticoagulants; NSAIDs: Non-steroidal anti-inflammatory drugs; OHD: Oral hypoglycemic medications; TIA: Transient ischemic attack; VKA: Vitamin K Oral Anticoagulants; SD: standard deviation. † Multi-comorbidity index is a binary variable in which each comorbidity marked with * was included as +1. Comorbidity is considered negative when index <3, and positive when ≥3. Time window considered (First report, Index date].*

Figure 11. Evaluation of PSM (love plot).

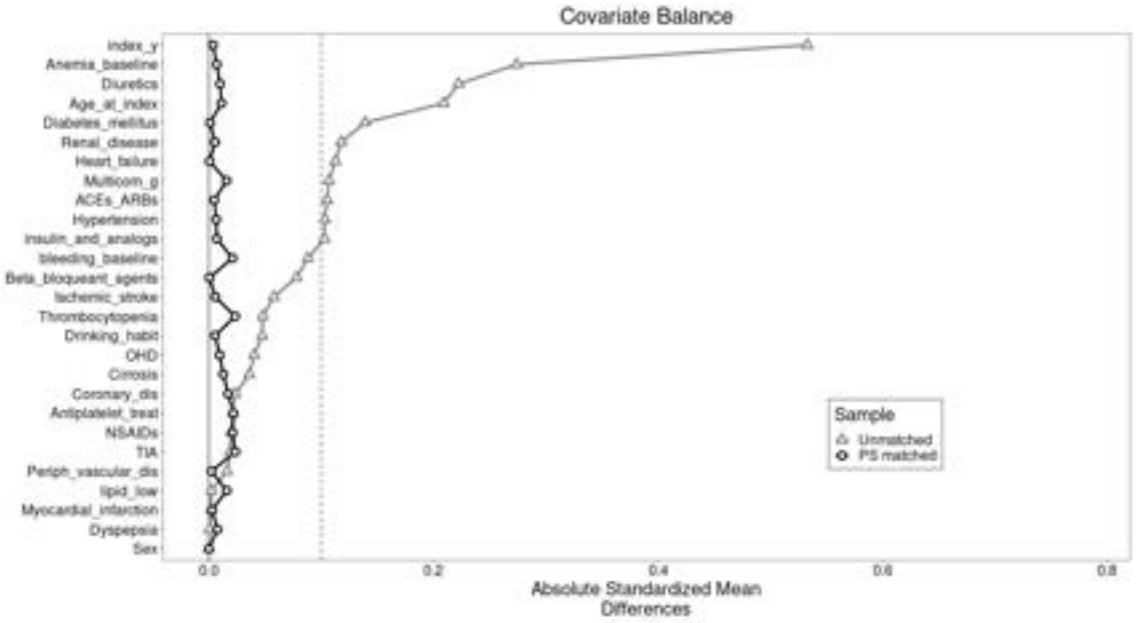


Figure 12. Kaplan-Meier curve for Time to Major Bleeding after PSM for NOAC vs VKA (full scale).

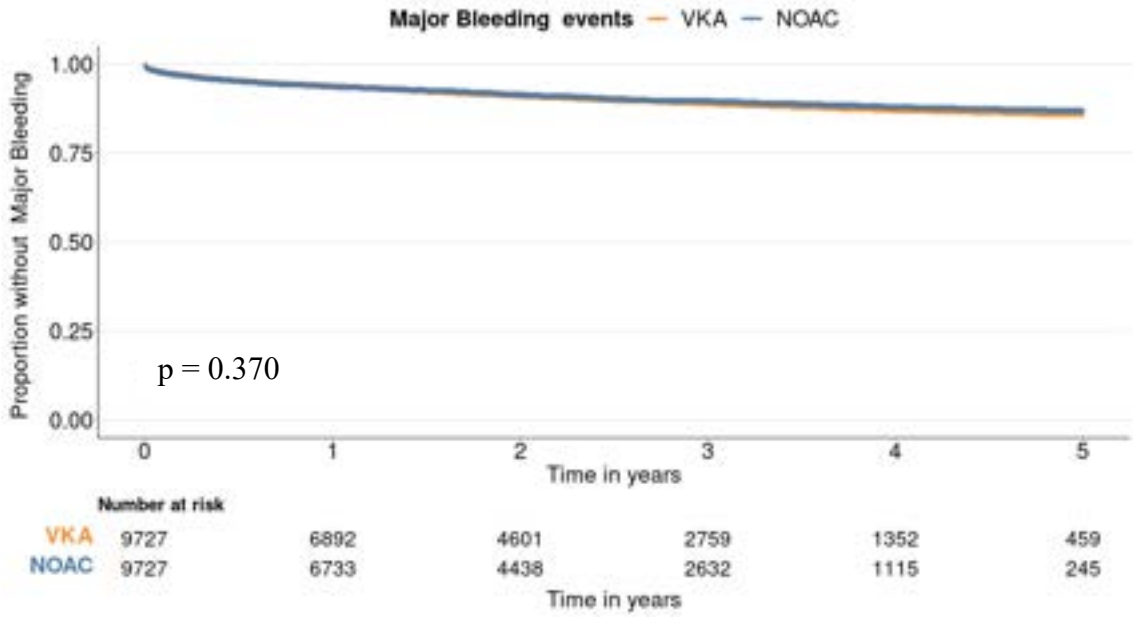


Figure 13. Kaplan-Meier curve for Time to Major Bleeding after PSM for NOAC vs VKA (partial scale).

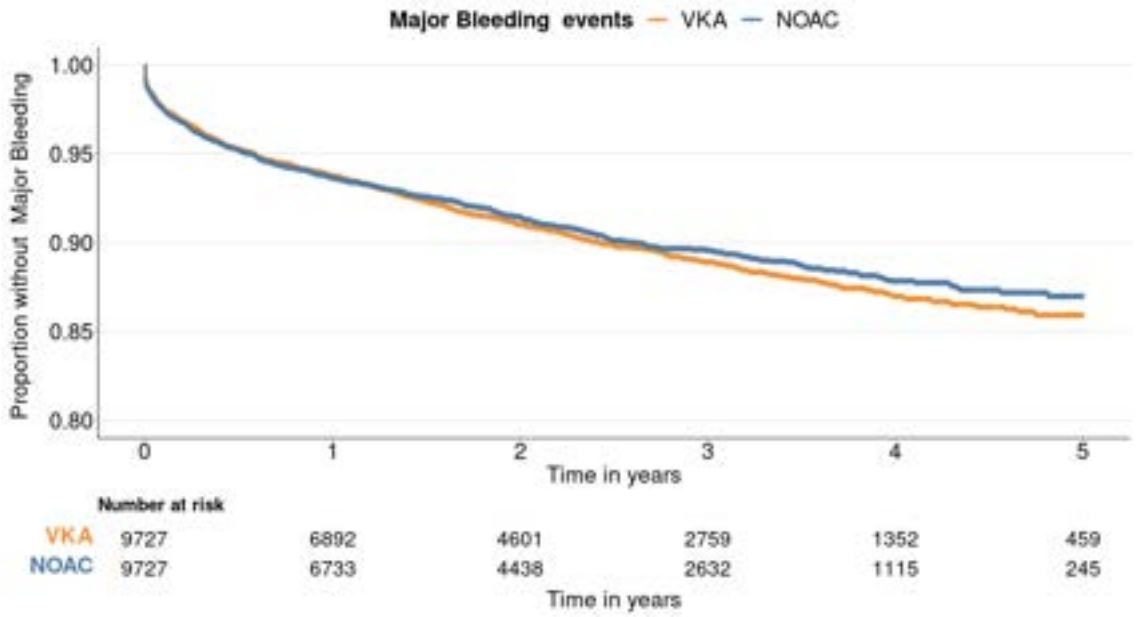


Figure 14. Univariate cox regression for time to event comparison of NOAC vs VKA for Major Bleeding after PSM

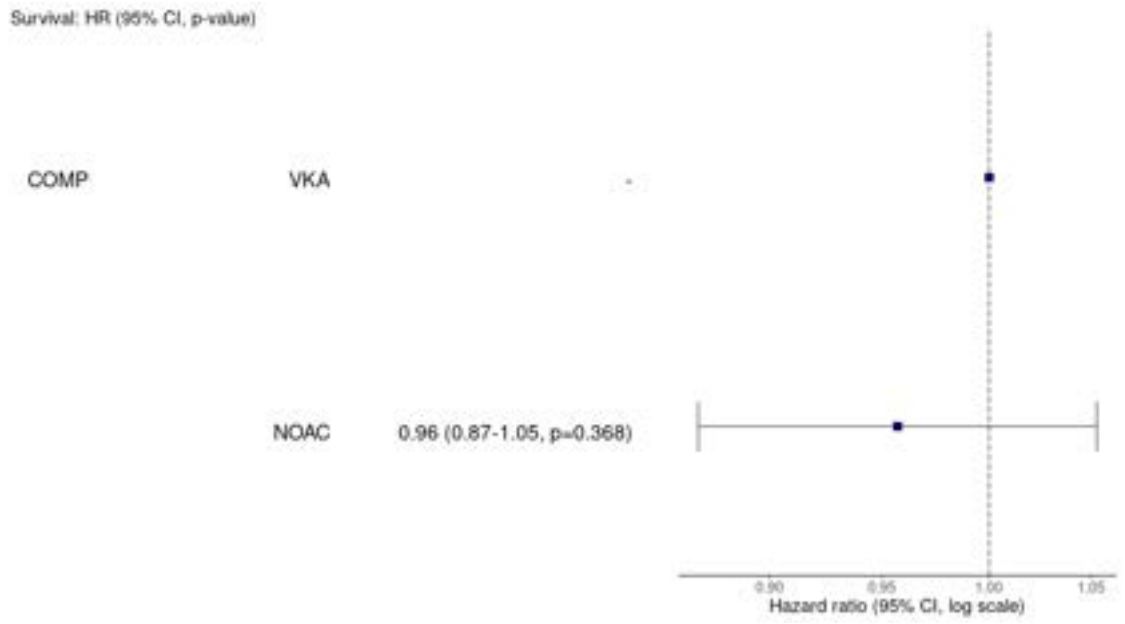


Figure 15. Kaplan-Meier curve for Time to Minor Bleeding after PSM for NOAC vs VKA (full scale).

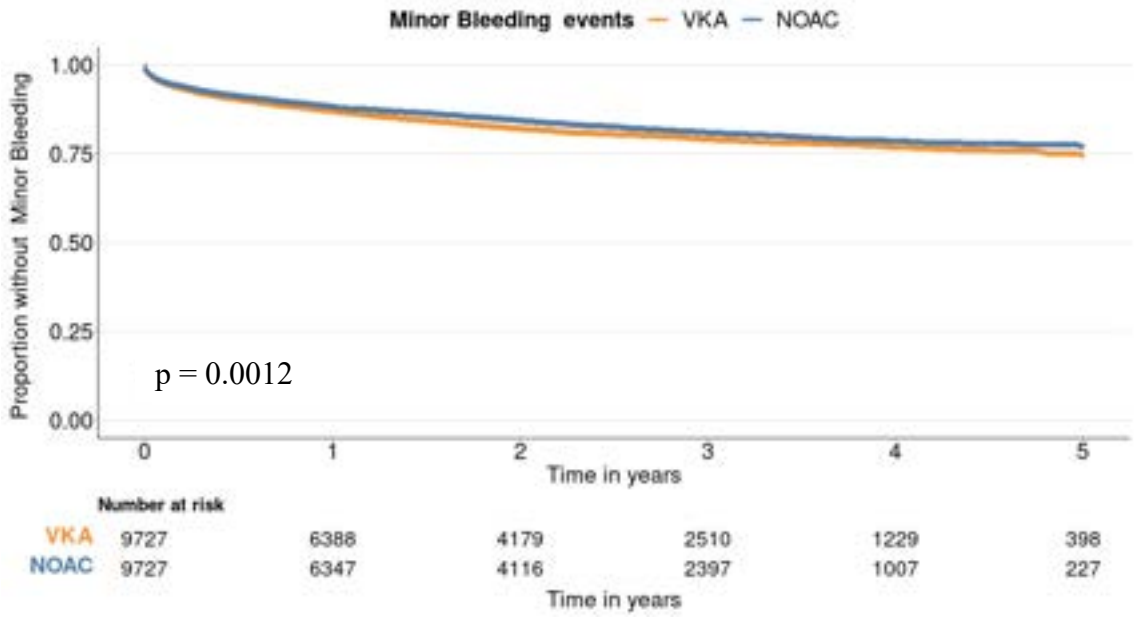


Figure 16. Kaplan-Meier curve for Time to Minor Bleeding after PSM for NOAC vs VKA (partial scale).

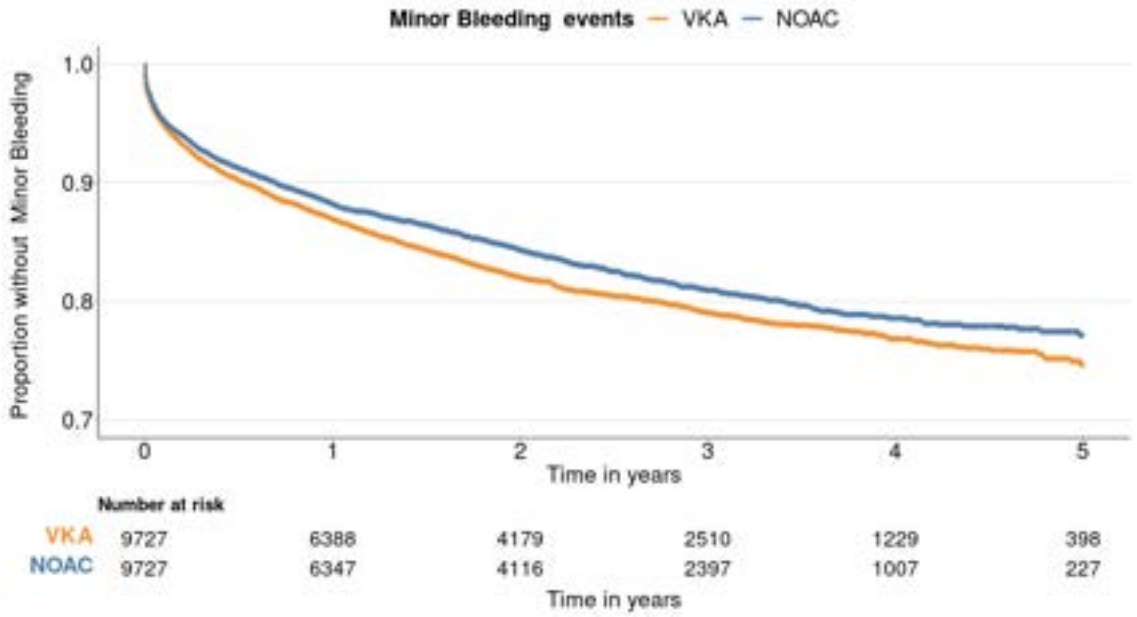
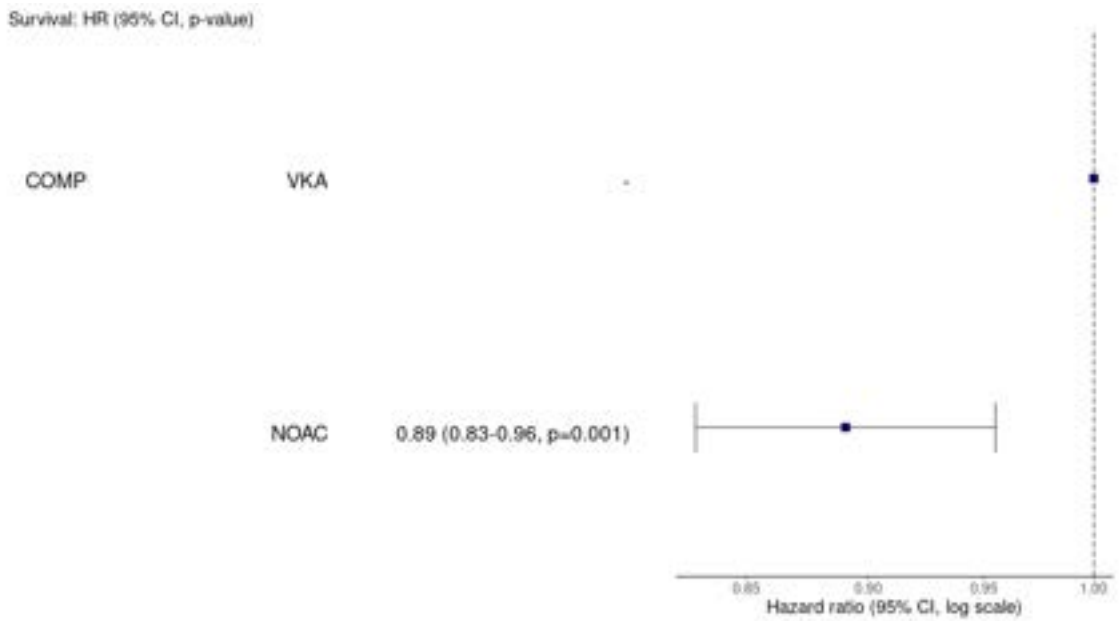


Figure 17. Univariate cox regression for time to event comparison of NOAC vs VKS for Minor Bleeding after PSM.



10.8. Main results

A total of 62,163 patients diagnosed with NVAF and treated with OAC were included in the study. Estimated incidence of NVAF decreased during the study period, from 2014 to 2018 (9.1, 7.5, 7.1, 6.9 and 6.6%) being higher in those patients older than 65 years (35.7, 27.5, 25.6, 24.3 and 23.9%). Regarding the type of oral anticoagulation, 12,766 (20.5%) received NOACs and 49,397 (79.4%) received VKAs. Globally, the medication most frequently detected was acenocoumarol which was found in 48,456 (77.9%) cases. Among NOAC, rivaroxaban was the most common treatment detected (37.5%), followed by apixaban (32.1%), dabigatran (24.6%) and edoxaban (5.8%).

10.8.1. *Descriptive analysis of the Study population*

Median age of patients receiving NOAC was 76 (67, 83) years whilst patients receiving VKA had 79 (70, 84) years. A total of 51% and 56% of males were seen in both groups, with a median BMI of 30.3 (26, 35) Kg/m^2 and 29.7 (25.6, 33) Kg/m^2, respectively. Cardiovascular were the most frequent comorbidities observed, with higher frequencies in VKA than in NOAC groups (hypertension: 72.6% and 67.6%; heart failure: 41.5% and 34.7% and diabetes mellitus: 36.8% and 32.2%). In this regard, more patients in VKA group had a CHA_2DS_2-VASc Score equal or higher than 4 points (58% and 49%). Same trend was observed when stratifying by study subgroups. Interestingly, among patients receiving NOAC, those receiving edoxaban and apixaban presented higher frequencies of cardiovascular comorbidities (hypertension: 70.8% and 69.6%; heart failure: 38.8% and 37.5% and diabetes mellitus: 34.1% and 32.8%). Beta-

blockers were the most frequent concomitant medication used at baseline in all the included patients (48.1%), followed by diuretics (44.0%), statins (35.9%), LMWH (26.6%), ACE inhibitors (25.7%), angiotensin II antagonists (25.5%) and acetylsalicylic acid (17.8%). Patients receiving VKA were more frequently under concomitant medications than NOAC patients, especially diuretics (46.2% and 35.7% respectively), statins (36.7% and 33.0% respectively), and LMWH (28.9% and 17.7% respectively). Remarkably, acetylsalicylic acid was more used in patients treated with apixaban (21.0%) and edoxaban (20.5%) than in patients receiving both VKA, acenocoumarol (17.7%) and warfarin (15.1%). On the other hand, beta-blockers and diuretics were the most frequent medication used during the follow-up (37.7% and 37.5%), followed by statins (29.3%) and LMWH (23.6%), Baseline laboratory values including hemoglobin and hematocrit as well as vital signs at baseline were within normality ranges in both groups and in all specific treatment subgroups. INR at baseline in the VKA group was higher in those patients receiving warfarin than in those receiving acenocoumarol [2.42 (1.59, 3.42) and 1.89 (1.15, 2.79)]. The median follow-up time for the entire sample was 1 (0.2, 8) year, 1.2 (0.1, 2.9) years for patients in the VKA group and 0.5 (0.0, 2.0) years for patients in the NOAC group. All medications were more frequently used in patients from the VKA group than from the NOAC group during the follow up. Clinical events during the follow up occurred more frequently in patients treated with VKA than in patients treated with NOAC, especially TIA as acute event (10.1% and 7.3%) and hypertension (66.5% and 52.2%), heart failure (50.3% and 34.2%), diabetes mellitus (41.4% and 29.7%) and renal disease (31.5% and 19.6%) as chronic clinical events.

OAC treatment switch was detected in a total of 21% of patients in the NOAC group and 14.5% in the VKA group. Dabigatran and warfarin were the most common treatment switched in each group (24.8% and 48.7% respectively). In VKA patients in whom treatment was switched, 34.3% switched to apixaban whilst in NOAC group a 69.3% switched to acenocoumarol, depicting its tendency to become the final treatment for most patients. Median time to switch was 286 (113, 636) days in NOAC and 470 (191, 883) days in VKA without statistical differences.

10.8.2. ***Annual incidence rates regarding effectivity and safety outcomes***

For the analysis of effectivity outcomes, a total of 45,349 patients were included, 36,092 (79.6%) in the VKA group and 9,257 (20.4%) in the NOAC group. Patients with ischemic events (stroke/SE) and its incidence rate were lower in NOAC than VKA (2.7% and 4.7%, as well as 1.26 and 1.68 per 100 per year, respectively) appearing the event after a median of 322 (53, 776) and 190 (32, 609) days from the inclusion. Like stroke/SE events, ischemic stroke was also less frequently observed in the NOAC group (2.0% and 3.4%) with lower incidence rates (0.95 and 1.21 per 100 per year) with a median time between the inclusion and the event of 219 (39, 642) and 342 (67, 807) days respectively. The highest incidence rate was observed in the acenocoumarol group.

For the analysis of safety outcomes, a total of 47,525 patients were included, 37,711 (79.3%) in the VKA group and 9,814 (20.7%) in the NOAC group. Fewer patients in the NOAC group presented major and minor bleeding events than VKA patients (8.3%;and 13.3%, 15.0% and

21.0%) resulting in lower annual incidence rates (4.12 and 5.15 per 100 per year; 7.89 and 8.76 per 100 per year). Most of major bleedings were seen in patients receiving acenocoumarol rather than apixaban, dabigatran or rivaroxaban (13.3%, 8.9%, 8.8% and 7.6%), This trend was maintained in minor bleedings which were more frequently seen (21%, 14.1%, 15.8% and 15.3%).

10.8.3. ***Comparison rates of effectivity and safety outcomes***

After a PSM was performed including demographics, comorbidities, and treatment variables, up to 9,162 patients from each group, NOAC and VKA, were matched . Our results show that NOAC patients were freer from stroke/SE events than VKA patients (p=0.023). In addition, univariate Cox regression analysis revealed that the NOAC group had an 18% lower risk for stroke than the VKA group (HR: 0.82, 95% CI 0.70-0.97; p= 0.023).

Concerning major and minor bleeding, and after matching a total of 9,727 patients, we observed that there were no differences in terms of major bleeding between the NOAC and the VKA groups but a higher proportion of patients without minor bleeding was detected in the NOAC group (p=0.0012) with a significant lower risk of minor bleeding (HR: 0.89, 95% CI 0.83-0.96; p=0.001).

10.9. Other analyses

See section 15.

10.10. Adverse events / adverse reactions

This study involves a combination of existing structured data and unstructured data, which have been converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as NLP.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. DISCUSSION

11.1. Key results

1. The NVAF estimated incidence and prevalence increased significantly over the 65 years.

2. Acenocumarol was the OAC drug most frequently reported (77.9%).

3. Rivaroxaban and Apixaban were the NOAC most reported (37.5% and 32.1%).

4. VKA patients were older, with higher cardiovascular comorbidities, higher CHA2DS2-VASc Score values and received more concomitant medications than NOAC patients at baseline. They also received more medications and presented more frequently clinical events during the follow up.

5. OAC switch was detected in a total of 21% of patients in the NOAC group and 14.5% in the VKA. More frequent switches were from NOAC to acenocoumarol (69.3%) and from VKA to apixaban (34.3%).

6. Effectivity outcomes as overall ischemic episodes (stroke/SE and ischemic stroke) were more frequent, and its incidence rates were lower in the NOAC patients than VKA.

7. Safety outcomes as major and minor bleeding events were more frequent, and its incidence rates were lower in the NOAC group than in the VKA group.

8. NOAC patients were freer from stroke/SE events than VKA patients (p=0.023). NOAC group had an 18% lower risk for stroke than the VKA group (HR: 0.82, 95% CI 0.70-0.97; p= 0.023).

9. Higher proportion of patients without minor bleeding was detected in the NOAC group (p=0.0012) with a significant lower risk of minor bleeding (HR: 0.89, 95% CI 0.83-0.96; p=0.001).

11.2. Limitations

1. Selection of population in Phase II and III to answer the objectives related with effectivity and safety outcomes, was based on patients with no previous information of anticoagulant treatment before the study period to ensure the adequacy of the groups to compare. Due to the complications to disambiguate incident and prevalent patients for anticoagulant use (i.e., patients treated in primary care centers or derived from other sites) we expected certain bias in this classification model. However, as proportion of patients detected after all the applied filters agreed with the expected one, we think that this bias could be not relevant when interpreting the results.

2. The use of exclusively hospital population could limit the extrapolation of our results to general population with NVAF.

3. The detection of laboratory, pharmacy, and vital signs variables, using only the information written by physicians rather than structured data in the EHRs, resulted in a high number of missing for these variables. However, the multicenter nature of the study including large amount of data could mitigate this limitation.

4. The performance of the model for the variables bleeding and intracranial hemorrhage was poorer than for other relevant variables, which could be traduced in a misidentification and/or misclassification of some patients with these complications. Given all that, the interpretention of non-statistically significant effects could be limited.

11.3. Interpretation

The study aimed to describe the demographic and clinical characteristics of patients with NVFA receiving OAC drugs, as well as to analyze treatment pathways and compare the rates of effectivity and safety related outcomes as stroke, SE, major and minor bleeding across different subgroups. The findings indicate that, NOACs have a better safety and effectivity profile than traditional anticoagulants. Otherwise, VKA and specifically the acenocoumarol are the most used anticoagulants in the patients with NVFA. The VKA patients were older, had higher cardiovascular comorbidities, and higher CHA2DS2-VASc Score values than NOAC patients. Overall, stroke episodes and the subtype ischemic were less frequent in the NOAC patients, and the incidence rate for major and minor bleeding was lower in the NOAC group than in the VKA group. After performing survival analysis using K-M and Cox in previously matched patients, the study found that patients in NOAC group presented a significant lower risk of stroke and minor bleeding, but there were no statistically significant differences in major bleeding.

These results are surely influenced by the characteristics of the Spanish healthcare system from which the data was extracted, in which the use of NOACs was restricted due to economic issues and not due to effectivity or safety-related data. In line with the nature of the data, exclusively of hospital origin, the demographic characteristics, comorbidities, and complications may not accurately reflect the entire population with NVAF receiving anticoagulant treatment or the cohorts reported in the literature so far. However, we believe that the large sample of patients obtained in our study and the rigorous statistical analysis applied in the evaluation of outcomes provide reliable and highly relevant information that will help to improve the use of these drugs in real-word scenarios.

11.4. Generalizability

This is a multicenter study carried out in 15 Spanish hospitals including more than 60,000 patients and with real life data. The data extraction from the EHRs was performed using the innovative EHRead technology that includes NLP and ML. This is a methodology validated in the literature and, in addition, in our study the performance of the most important variables in the external validation resulted in good metrics, most of them greater than 0.7. Because of that, we think that the results of this study could be generalized in our environment with a significant impact on the field.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

In patients with NVFA, VKA and specially acenocoumarol, are the most used anticoagulants. Globally, OAC are used in elder patients with cardiovascular comorbidities and high CHA2DS2-VASc Score values. In this RWE study including more than 60,000 patients in Spain, we found that, NOAC in comparison with VKA had a better effective and safety profile regarding the development of ischemic or bleeding events after a PSM to control confounders. These results could have an important clinical impact in patients with AF when deciding the best therapeutic strategy.

14. MANUSCRIPT PROPOSAL

14.1. First Manuscript

14.1.1. *Project title*

AF In Real practice on Management of oral Anticoagulation– AFIRMA 4.0.

14.1.2. *Manuscript title*

Real-world description of oral anticoagulant treatment in nonvalvular atrial fibrillation: Using natural language processing and machine learning.

14.1.3. *Objectives*

To describe the demographic and clinical characteristics of Nonvalvular Atrial Fibrillation (NVAF) patients receiving oral anticoagulant treatment (Vitamin K Antagonists [VKA] or Direct-Acting Anticoagulants [DOAC]) through natural language processing (NLP) and machine learning (ML).

14.1.4. *Methods*

1. Study design
2. Study population and subgroups (including definition of inclusion-exclusion criteria and other filters needed to select study population and subgroups)
3. NLP and ML (Savana's methodology) including study variables (focusing on the definition of variables, timelines and windows, SNOMED-CT, AI modules applied, internal and external validation, etc.).
4. Statistical methods (descriptive analysis)
5. Ethical issues

14.1.5. *Results*

Results will be distributed between the main manuscript and supplemental material. Below there is a summary of the available results, but only a selection of them will be agreed to be included to the manuscript:

1. EHRead- performance evaluation (CSR table 5 and 6).
2. Study Population (flow chart- CSR figure 4)
3. Descriptive results: The results will be shown for the overall sample, DOAC and VKA groups.
    - Demographic and baseline comorbidities (CSR Table 9 and 11)
    - Concomitant medication (CSR Table 13)

- Baseline laboratory values and vital signs (CSR table 17 and 19)
- Switch of treatment: These results will be shown for specific formulations (CSR table 24).

14.1.6. ***Key results***

1. Acenocumarol (VKA) was the OAC drug most frequently reported.
2. Rivaroxaban and Apixaban were the DOAC most reported.
3. VKA patients were older, had more comorbidities, higher CHA2DS2-VASc Scores, and received more medications than NOAC patients at baseline.
4. OAC switch was detected in a total of 21% of patients in the DOAC group and 14.5% in the VKA group. More frequent switches were from DOAC to acenocumarol and from VKA to apixaban.

14.1.7. ***Other results to discuss***

1. Usefulness and limitations of NLP and ML in the field of the study (cardiology).
2. Future lines of work with NLP could enable addressing gaps present in the current literature (e.g., comparative effectiveness and safety of DOACs and VKAs in patients with nonvalvular atrial fibrillation)

14.2. Second Manuscript

14.2.1. ***Project title:***

AF In Real practice on Management of oral Anticoagulation– AFIRMA 4.0

14.2.2. ***Manuscript title***

Real-World Insights: Safety and Efficacy of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Leveraging Natural Language Processing and Machine Learning.

Clarification Note: For scientific publications, the term "New Oral Anticoagulant (NOAC)" as used in the CSR will be replaced with the current terminology, "Direct Oral Anticoagulant (DOAC).

14.2.3. *Objectives*

In patients with nonvalvular atrial fibrillation (NVAF), to compare the efficacy and safety outcomes of Vitamin K antagonists (VKA) versus direct oral anticoagulants (DOAC).

14.2.4. ***Results***

1. EHRead performance
2. Study population (Flow chart- Figure 18 Section 15 CSR).
3. **Descriptive results:** The results will be shown for the overall sample, DOAC and VKA groups.
    - Demographics, baseline comorbidities and CHA_2DS_2-VASc score (Table 39-Section 15 CSR)
    - Concomitant medication (Table 39-Section 15 CSR)
4. **Incidence rates of effectivity, security outcomes and death**.
    - Transitory Ischemic Accident (TIA) and Stroke/Systemic embolism (SE) (Table 31-Section 15 CSR)
    - Incidence rates of Major Bleeding and Minor bleeding (Table 33-Section 15 CSR)
    - Incidence rates of death (Table 37-Section 15 CSR)
5. **Comparison rates of effectivity and security outcomes**
    - Love plot PSM (figure 19- Section 15 CSR)
    - Kaplan-Meir curve for time to TIA (Figures 20 and 21, Section 15 CSR) including HR from Cox univariate analysis (Figure 22, Section 15 CSR)

- Kaplan-Meir curve for time to Stroke/SE/TIA (Figures 23 and 24, Section 15 CSR) including HR from Cox univariate analysis (Figure 25, Section 15 CSR)
- Kaplan-Meir curve for time to death (Figures 26 and 27, Section 15 CSR) including HR from Cox univariate analysis (Figure 28, Section 15 CSR)

14.2.5. ***Key results***

1. The incidence rates of effectivity, security outcomes were lower in the DOAC patients than VKA.
2. The incidence rates of major and minor bleeding events were lower in the DOAC patients than VKA.
3. The incidence rates of death events were lower in the DOAC patients than VKA.
4. DOAC group had lower risk of AIT and stroke/SE events compared to VKA patients.
5. DOAC group had lower risk of minor bleeding compared to VKA patients without differences in major bleeding between groups.
6. DOAC group had lower risk of death compared with VKA patients.

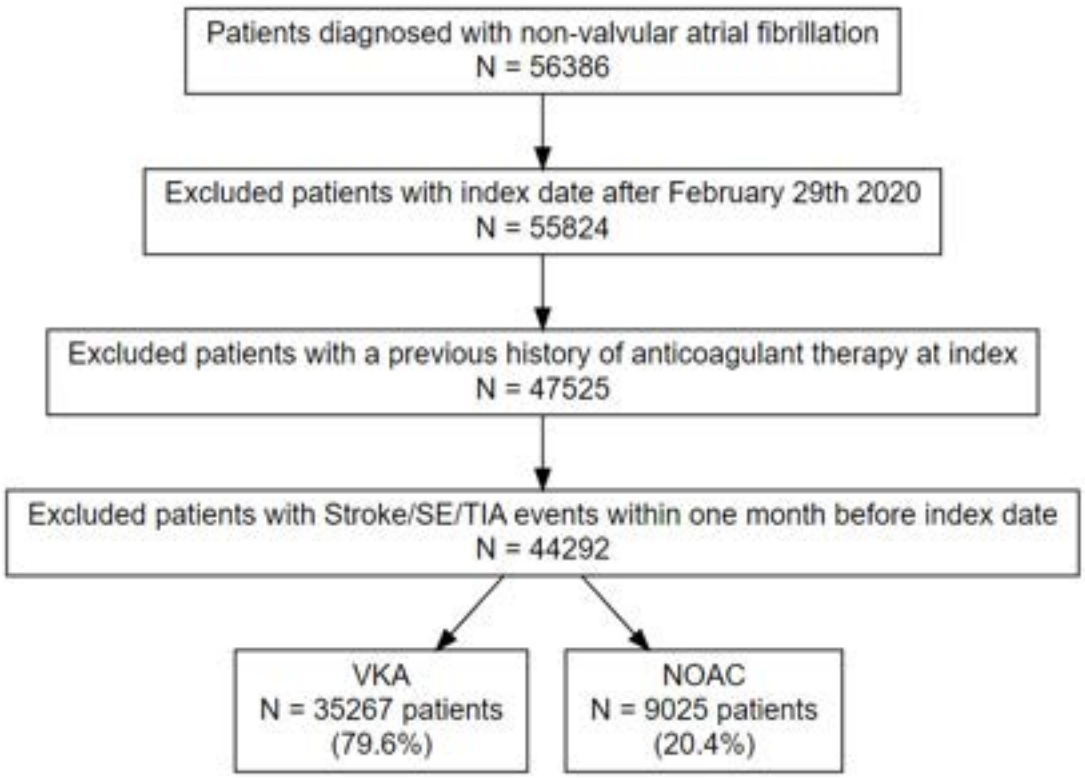
15. RESULTS TO BE CONSIDERED FOR INCLUSION IN THE SECOND MANUSCRIPT

Changes from CSR:

- The effectivity outcomes previously presented in the CSR included Stroke and Systemic embolism (SE). The outcomes presented in the current analysis include Stroke, SE and also Transient ischemic attack (TIA).
- Major and minor bleeding events are described in CSR. For the current analysis, the definition of gastrointestinal bleeding (previously considered always within major bleeding) has been updated. Gastrointestinal bleeding is now considered as major bleeding if it was presented together with a transfusion. Gastrointestinal bleeding not presented with transfusion is now considered minor bleeding.
- The proportion and incidence from bleeding types are included in the current analysis.
- Death analysis is included as a new outcome in the current analysis (mortality).

15.1. Study population included in the outcome analysis.

Figure 18. Patients Criteria Selection of the Study Population with Stroke/SE/TIA



Patients with incident stroke/SE/TIA events at index (defined as an event within the month previous to index) were excluded from the analysis to avoid the combination of primary vs. secondary events in the context of first NOAC/VKA treatment. SE: Systemic embolism. TIA: Transient Ischemic Atack.

15.2. Annual incidences rates

15.2.1. ***Effectivity outcomes***

Table 22. Incidence Rates of Stroke/SE/TIA in patients treated with OAC, overall and by OAC group.

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
TIA			
N events (%)	886 (2)	100 (1.11)	786 (2.23)
Incidence Rate (N per 100 per-year)	0.74	0.52	0.79
Time to TIA (days)			
Mean (SD)	499.85 (482.56)	417.43 (435.37)	512.06 (488.19)
Median (Q1; Q3)	360.5 (76.25; 825.25)	268 (43.5; 664)	386 (80; 836)
Stroke/SE/TIA			
N events (%)	2548 (5.75)	314 (3.48)	2234 (6.33)
Incidence Rate (N per 100 per-year)	2.19	1.65	2.3
Time to Stroke/SE/TIA (days)			
Mean (SD)	450.1 (467.09)	382.93 (421.41)	461.09 (473.31)
Median (Q1; Q3)	306 (48; 735)	222 (36; 633)	318.5 (50; 752)

TIA: Transient ischemic attack; SE: systemic embolism; SD: standard deviation. Time window considered (Index date, End of follow-up].

Table 23. Incidence Rates of Stroke/SE/TIA in patients treated with NOAC or VKA subgroups.

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
TIA				
N events (%)	786 (2.23%)	35 (1.14%)	33 (1.49%)	32 (0.85%)
Incidence Rate (N per 100 per year)	0.79	0.59	0.64	0.39

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
Time to TIA (days)				
Mean (SD)	512.06 (488.19)	363.67 (435.36)	388.89 (443.88)	487.77 (427.04)
Median ((Q1-Q3)	386 (80; 836)	199.5 (23.25; 484.25)	236 (28.75; 634.5)	319 (155; 797)
Stroke/SE/TIA				
N events (%)	2234 (6.33)	114 (3.73)	90 (4.06)	110 (2.93)
Incidence Rate (N per 100 per year)	2.3	1.94	1.79	1.35
Time to Stroke/SE/TIA (days)				
Mean (SD)	461.09 (473.31)	341.26 (409.94)	351.16 (417.52)	439.49 (429.54)
Median (Q1; Q3)	318.5 (50; 752)	160 (23; 512)	179.5 (31; 566.5)	307 (52; 722)

TIA: Transient ischemic attack; SE:systemic embolism; SD: standard deviation. Time window considered (Index date, End of follow-up].

15.2.2. ***Safety outcomes***

Table 24. Incidence Rates of Major and Minor bleeding Events in patients treated with OAC, overall and by OAC group.

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Major Bleeding			
N events (%)	4178 (9.43)	540 (5.98)	3638 (10.32)
Incidence Rate (N per 100 per-year)	3.7	2.88	3.86
Time to Major Bleeding (days)			
Mean (SD)	478.01 (493.8)	387.2 (428.19)	493.04 (502.29)
Median (Q1; Q3)	314 (61; 774)	213.5 (40; 667.75)	331 (66; 798)
Minor Bleeding			

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
N events (%)	10412 (23.51)	1574 (17.44)	8838 (25.06)
Incidence Rate (N per 100 per-year)	10.61	9.39	10.86
Time to Minor Bleeding (days)			
Mean (SD)	391.76 (437.98)	340.61 (389.65)	401.9 (446.25)
Median (Q1; Q3)	231 (43; 613)	184 (36; 540)	241.5 (45; 624)

SD: standard deviation. Time window considered (Index date, End of follow-up].

Table 25. Incidence Rates of Major and Minor bleeding Events in patients treated with NOAC or VKA subgroups.

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
Major Bleeding				
N events (%)	3638 (10.32)	197 (6.44%)	144 (6.5%)	199 (5.31%)
Incidence Rate (N per 100 per year)	3.86	3.43	2.9	2.48
Time to Major Bleeding (days)				
Mean (SD)	493.04 (502.29)	355.11 (423.83)	440.1 (451.82)	376.21 (411.52)
Median (Q1; Q3)	331 (66; 798)	184 (31; 597)	284 (54.5; 736.25)	232 (36; 626)
Minor Bleeding				
N events (%)	8838 (25.06)	503 (16.44%)	399 (18%)	672 (17.93%)
Incidence Rate (N per 100 per year)	10.86	9.64	9.01	9.45
Time to Minor Bleeding (days)				
Mean (SD)	401.9 (446.25)	308.05 (361.13)	347.32 (406.59)	360.13 (398.06)
Median (Q1; Q3)	241.5 (45; 624)	150 (39; 470)	193.5 (24; 557.5)	209.5 (43; 567.75)

SD: standard deviation. Time window considered (Index date, End of follow-up].

Table 26. Incidence Rates of different Bleeding Events in patients treated with OAC, overall and by OAK group.

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Fatal Bleeding			
N events (%)	125 (0.28)	18 (0.2)	107 (0.3)
Incidence Rate (N per 100 per year)	0.10	0.09	0.11
Critical Bleeding			
N events (%)	1366 (3.08)	178 (1.97)	1188 (3.37)
Incidence Rate (N per 100 per year)	1.15	0.92	1.20
Hemorrhagic Stroke			
N events (%)	190 (0.43)	36 (0.4)	154 (0.44)
Incidence Rate (N per 100 per year)	0.16	0.18	0.15
Intracranial hemorrhage			
N events (%)	1109 (2.5)	142 (1.57)	967 (2.74)
Incidence Rate (N per 100 per year)	0.93	0.73	0.97
Pericardial Bleeding			
N events (%)	36 (0.08)	3 (0.03)	33 (0.09)
Incidence Rate (N per 100 per year)	0.03	0.02	0.03
Retroperitoneal Bleeding			
N events (%)	109 (0.25)	10 (0.11)	99 (0.28)
Incidence Rate (N per 100 per year)	0.09	0.05	0.10
Intraocular Bleeding			
N events (%)	2 (0)	0 (0)	2 (0.01)
Incidence Rate (N per 100 per year)	0.00	0.00	0.00
Intraspinal Bleeding			
N events (%)	0 (0)	0 (0)	0 (0)
Incidence Rate (N per 100 per year)	0.00	0.00	0.00
Gastrointestinal Bleeding			
N events (%)	714 (1.61)	94 (1.04)	620 (1.76)
Incidence Rate (N per 100 per year)	0.60	0.48	0.62
Bleeding and anemization			
N events (%)	2499 (5.64)	294 (3.26)	2205 (6.25)

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Incidence Rate (N per 100 per year)	2.15	1.53	2.27
Bleeding and transfusion			
N events (%)	1418 (3.2)	186 (2.06)	1232 (3.49)
Incidence Rate (N per 100 per year)	1.20	0.96	1.24
Surgical site bleeding and anemization			
N events (%)	18 (0.04)	4 (0.04)	14 (0.04)
Incidence Rate (N per 100 per year)	0.01	0.02	0.01
Surgical site bleeding and transfusion			
N events (%)	20 (0.05)	1 (0.01)	19 (0.05)
Incidence Rate (N per 100 per year)	0.02	0.01	0.02
Major Bleeding			
N events (%)	4178 (9.43)	540 (5.98)	3638 (10.32)
Incidence Rate (N per 100 per year)	3.70	2.88	3.86
Minor Bleeding			
N events (%)	10412 (23.51)	1574 (17.44)	8838 (25.06)
Incidence Rate (N per 100 per year)	10.61	9.39	10.86
Clinically relevant minor bleeding			
N events (%)	2693 (6.08)	446 (4.94)	2247 (6.37)
Incidence Rate (N per 100 per year)	2.32	2.36	2.31

Time window considered (Index date, End of follow-up].

Table 27. Incidence Rates of different Bleeding Events in patients treated with NOAC or VKA subgroups.

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
Fatal Bleeding				
N events (%)	107 (0.3)	7 (0.23)	2 (0.09)	9 (0.24)
Incidence Rate (N per 100 per year)	0.11	0.12	0.04	0.11
Critical Bleeding				
N events (%)	1188 (3.37)	68 (2.22)	47 (2.12)	63 (1.68)
Incidence Rate (N per 100 per year)	1.20	1.14	0.92	0.77

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
Hemorrhagic Stroke				
N events (%)	154 (0.44)	14 (0.46)	11 (0.5)	11 (0.29)
Incidence Rate (N per 100 per year)	0.15	0.23	0.21	0.13
Intracranial hemorrhage				
N events (%)	967 (2.74)	53 (1.73)	37 (1.67)	52 (1.39)
Incidence Rate (N per 100 per year)	0.97	0.89	0.72	0.63
Pericardial Bleeding				
N events (%)	33 (0.09)	2 (0.07)	1 (0.05)	0 (0)
Incidence Rate (N per 100 per year)	0.03	0.03	0.02	0.00
Retroperitoneal Bleeding				
N events (%)	99 (0.28)	6 (0.2)	2 (0.09)	2 (0.05)
Incidence Rate (N per 100 per year)	0.10	0.10	0.04	0.02
Intraocular Bleeding				
N events (%)	2 (0.01)	0 (0)	0 (0)	0 (0)
Incidence Rate (N per 100 per year)	0.00	0.00	0.00	0.00
Intraspinal Bleeding				
N events (%)	0 (0)	0 (0)	0 (0)	0 (0)
Incidence Rate (N per 100 per year)	0.00	0.00	0.00	0.00
Gastrointestinal Bleeding				
N events (%)	620 (1.76)	29 (0.95)	25 (1.13)	40 (1.07)
Incidence Rate (N per 100 per year)	0.62	0.48	0.48	0.48
Bleeding and anemization				
N events (%)	2205 (6.25)	110 (3.59)	83 (3.74)	101 (2.69)
Incidence Rate (N per 100 per year)	2.27	1.87	1.64	1.23
Bleeding and transfusion				
N events (%)	1232 (3.49)	62 (2.03)	53 (2.39)	71 (1.89)
Incidence Rate (N per 100 per year)	1.24	1.04	1.03	0.86
Surgical site bleeding and anemization				
N events (%)	14 (0.04)	1 (0.03)	0 (0)	3 (0.08)
Incidence Rate (N per 100 per year)	0.01	0.02	0.00	0.04
Surgical site bleeding and transfusion				

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
N events (%)	19 (0.05)	0 (0)	0 (0)	1 (0.03)
Incidence Rate (N per 100 per year)	0.02	0.00	0.00	0.01
Major Bleeding				
N events (%)	3638 (10.32)	197 (6.44)	144 (6.5)	199 (5.31)
Incidence Rate (N per 100 per year)	3.86	3.43	2.90	2.48
Minor Bleeding				
N events (%)	8838 (25.06)	503 (16.44)	399 (18)	672 (17.93)
Incidence Rate (N per 100 per year)	10.86	9.64	9.01	9.45
Clinically relevant minor bleeding				
N events (%)	2247 (6.37)	153 (5)	117 (5.28)	176 (4.7)
Incidence Rate (N per 100 per year)	2.31	2.63	2.36	2.18

Time window considered (Index date, End of follow-up].

15.2.3. ***Mortality***

Table 28. Incidence Rates of Death Events in patients treated with OAC, overall and by OAC group.

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Mortality			
N events (%)	2988 (6.75)	336 (3.72)	2652 (7.52)
Incidence Rate (N per 100 per-year)	2.46	1.72	2.61
Time to Death (days)			
Mean (SD)	432.99 (439.61)	330.44 (362.59)	445.98 (446.81)
Median (Q1; Q3)	282.5 (56; 707)	198 (42.75; 524.25)	297 (61.75; 733)

SD: standard deviation. Time window considered (Index date, End of follow-up].

Table 29. Incidence Rates of Death Events in patients treated with NOAC or VKA subgroups.

	Acenocumarol (n=35267)	Apixaban (n=3060)	Dabigatran (n=2217)	Rivaroxaban (n=3748)
Mortality				
N events (%)	2652 (7.52%)	125 (4.08%)	74 (3.34%)	137 (3.66%)
Incidence Rate (N per 100 per year)	2.61	2.07	1.43	1.64
Time to Death (days)				
Mean (SD)	445.98 (446.81)	291.74 (307.86)	376.05 (419.82)	341.12 (374.45)
Median (Q1; Q3)	297 (61.75; 733)	175 (45; 466)	189.5 (42.5; 676)	220 (42; 486)

SD: standard deviation. Time window considered (Index date, End of follow-up].

15.3. Comparison rates

Table 30. List of Confounders for the Propensity Score Matching per NOAC or VKA Type in pre-matched patients

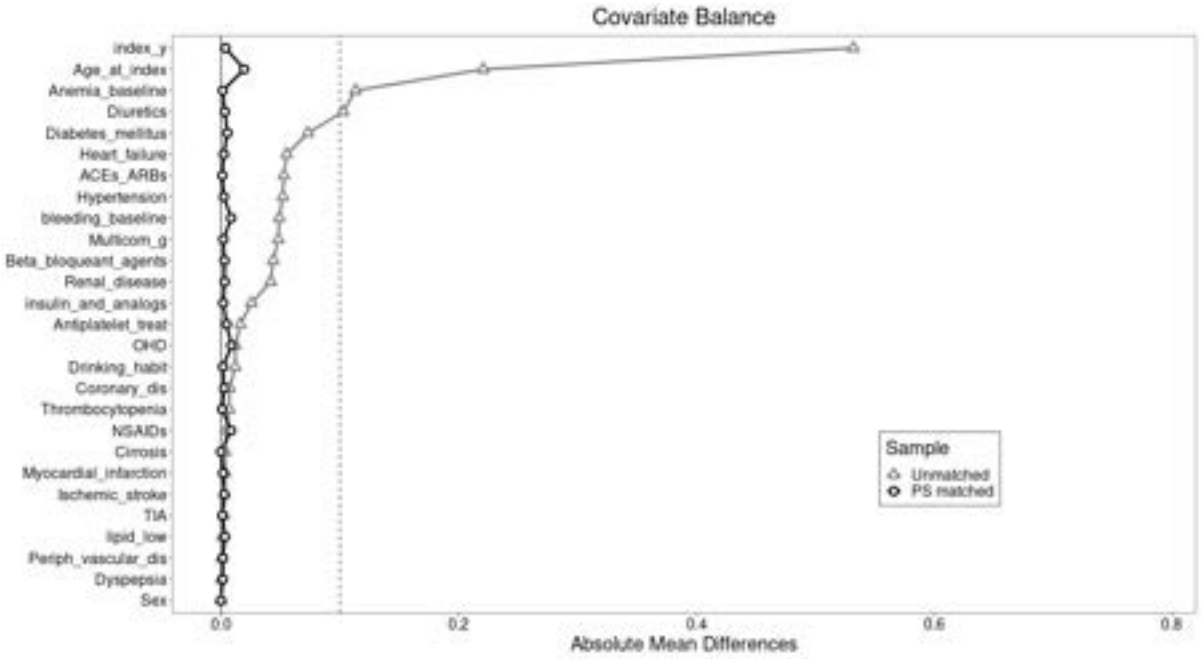
	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Bleeding baseline*	10683 (24.1%)	1821 (20.2%)	8862 (25.1%)
Hypertension*	32954 (74.4%)	6339 (70.2%)	26615 (75.5%)
Diabetes mellitus*	20262 (45.7%)	3602 (39.9%)	16660 (47.2%)
Renal disease*	7923 (17.9%)	1314 (14.6%)	6609 (18.7%)
Sex			
Missing (%)	279 (0.6%)	78 (0.9%)	201 (0.6%)
Female	20709 (47%)	3864 (43%)	16845 (48%)
Male	23304 (53%)	5083 (56%)	18221 (52%)
TIA*	1063 (2.4%)	199 (2.2%)	864 (2.4%)
Anemia baseline	13849 (31.3%)	2008 (22.2%)	11841 (33.6%)
Ischemic stroke*	1919 (4.3%)	412 (4.6%)	1507 (4.3%)
Thrombocytopenia	978 (2.2%)	150 (1.7%)	828 (2.3%)
Age at index			
Missing (%)	0 (0%)	0 (0%)	0 (0%)

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)
Mean (SD)	76.35 (12.74)	74.3 (14.31)	76.88 (12.26)
Median (Q1, Q3)	78 (69, 84)	75 (66, 83)	78 (70, 84)
(Min, Max)	(18-218)	(20-153)	(18-218)
Peripheral vascular disease*	123 (0.3%)	21 (0.2%)	102 (0.3%)
Myocardial infarction*	1297 (2.9%)	240 (2.7%)	1057 (3%)
Coronary disease*	4048 (9.1%)	775 (8.6%)	3273 (9.3%)
Cirrhosis*	528 (1.2%)	82 (0.9%)	446 (1.3%)
Drinking habit			
Missing (%)	41712 (94.2%)	8599 (95.3%)	33113 (93.9%)
alcoholic	2142 (5%)	350 (4%)	1792 (5%)
ex-alcoholic	360 (1%)	67 (1%)	293 (1%)
No alcoholic	78 (0%)	9 (0%)	69 (0%)
Heart failure*	17348 (39.2%)	3140 (34.8%)	14208 (40.3%)
Dyspepsia	654 (1.5%)	132 (1.5%)	522 (1.5%)
Antiplatelet treat	9332 (21.1%)	1785 (19.8%)	7547 (21.4%)
Insulin and analogs	3449 (7.8%)	519 (5.8%)	2930 (8.3%)
ACEs ARBs	22080 (49.9%)	4125 (45.7%)	17955 (50.9%)
OHD	6121 (13.8%)	1158 (12.8%)	4963 (14.1%)
lipid low	2249 (5.1%)	468 (5.2%)	1781 (5.1%)
Diuretics	20459 (46.2%)	3430 (38%)	17029 (48.3%)
Beta blocking agents	22798 (51.5%)	4951 (54.9%)	17847 (50.6%)
NSAIDs	4706 (10.6%)	927 (10.3%)	3779 (10.7%)
Multi-comorbidity Index[†]	7609 (17.2%)	1204 (13.3%)	6405 (18.2%)
CHADVASC Group			
Missing (%)	279 (0.6%)	78 (0.9%)	201 (0.6%)
0	1017 (2%)	445 (5%)	572 (2%)
1	2652 (6%)	805 (9%)	1847 (5%)
2	5542 (13%)	1371 (15%)	4171 (12%)
3	9103 (21%)	1928 (21%)	7175 (20%)
4+	25699 (58%)	4398 (49%)	21301 (60%)

	Overall (n=44292)	NOAC (n=9025)	VKA (n=35267)

*ACE: Angiotensin converting enzyme inhibitors; ARB Angiotensin-receptor blockers; NOAC: Non-Vitamin K Oral Anticoagulants; NSAIDs: Non-steroidal anti-inflammatory drugs; OHD: Oral hypoglycemic medications; TIA: Transient ischemic attack; SD: Standard deviation. †Multi-comorbidity index is a binary variable in which each comorbidity marked with * was included as +1. Comorbidity is considered negative when index <3, and positive when ≥3. Time window considered (First report, Index date].*

Figure 19. Evaluation of PSM (love plot)



15.3.1. *Effectivity outcomes*

Figure 20. Kaplan-Meier curve for Time to TIA after PSM for NOAC vs VKA (full scale).

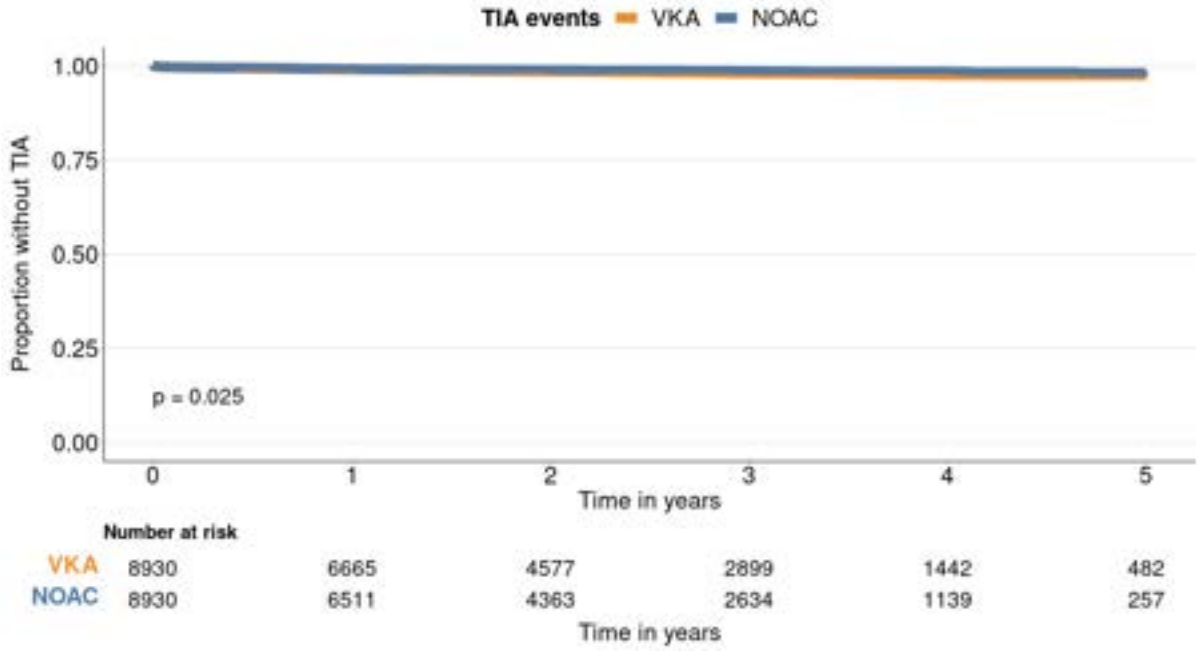


Figure 21. Kaplan-Meier curve for Time to TIA after PSM for NOAC vs VKA (partial scale).

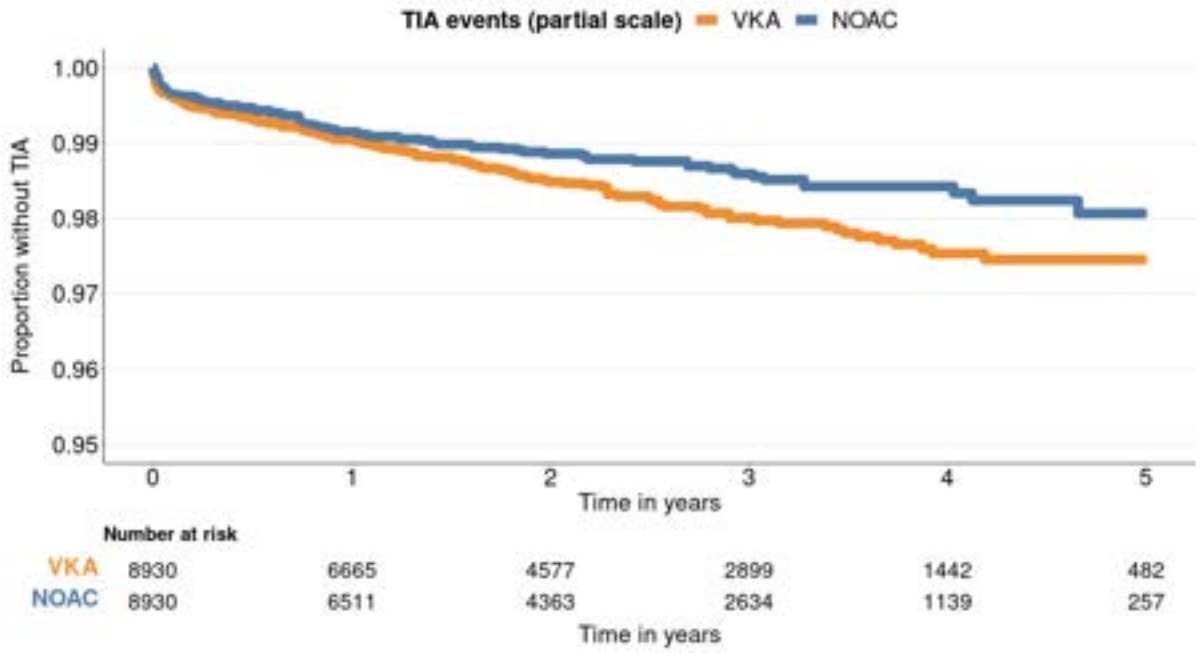


Figure 22. Univariate cox regression for time to event comparison of NOAC vs VKA for TIA after PSM

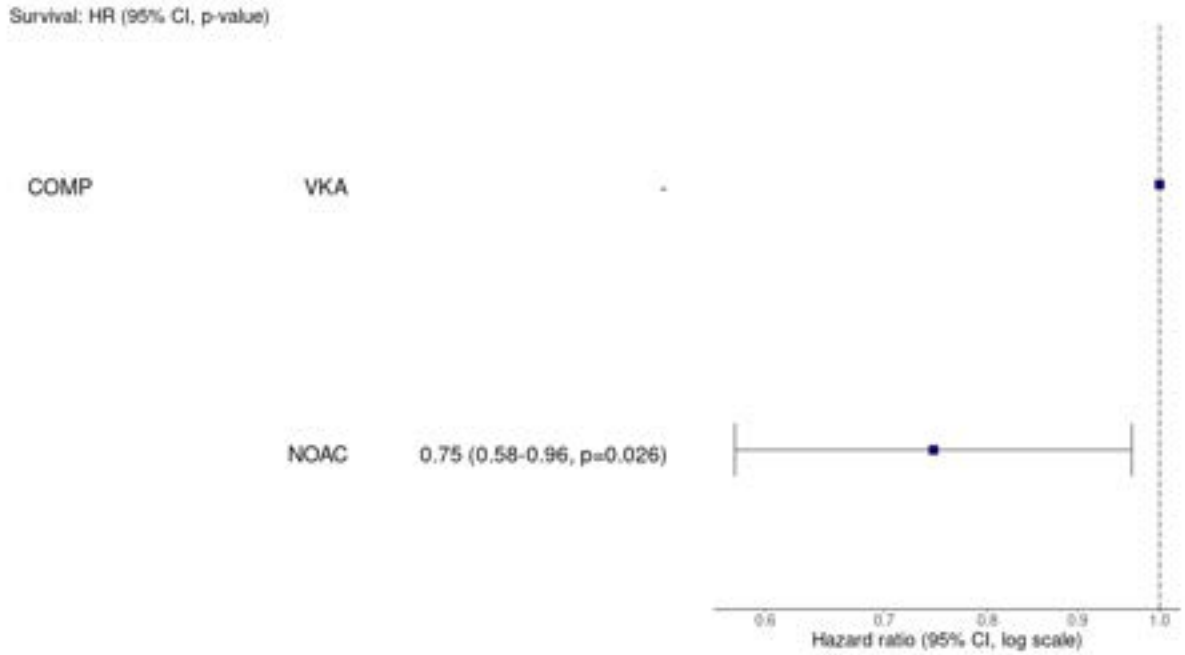


Figure 23. Kaplan-Meier curve for Time to Stroke/SE/TIA after PSM for NOAC vs VKA (full scale).

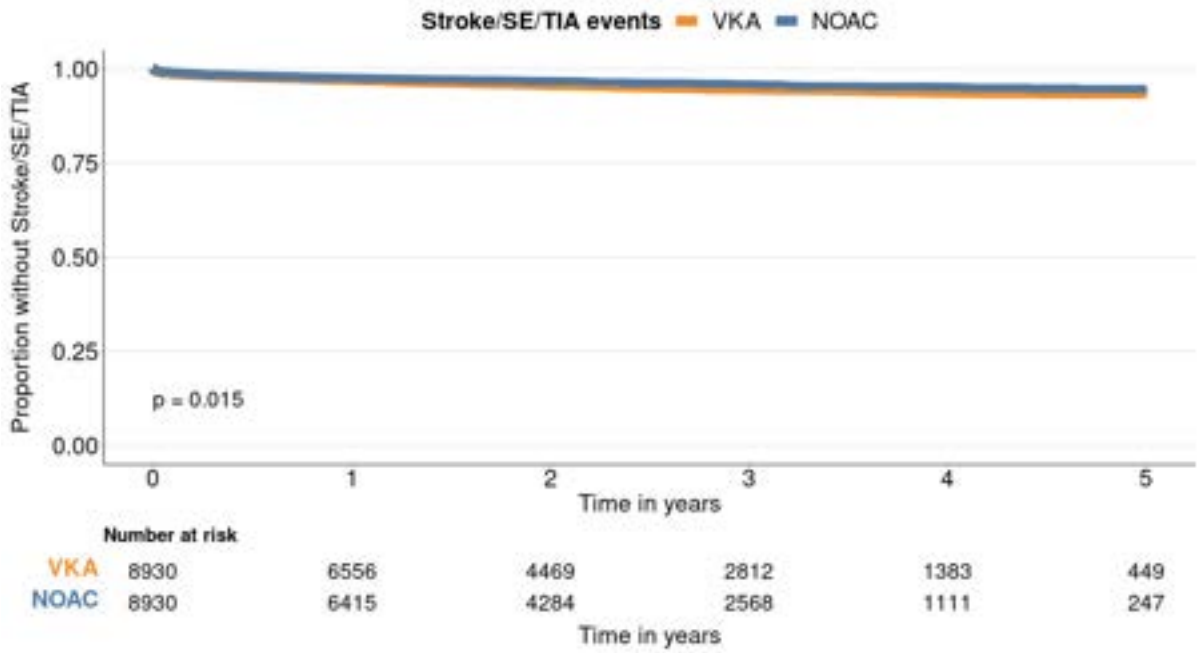


Figure 24. Kaplan-Meier curve for Time to Stroke/SE/TIA after PSM for NOAC vs VKA (partial scale).

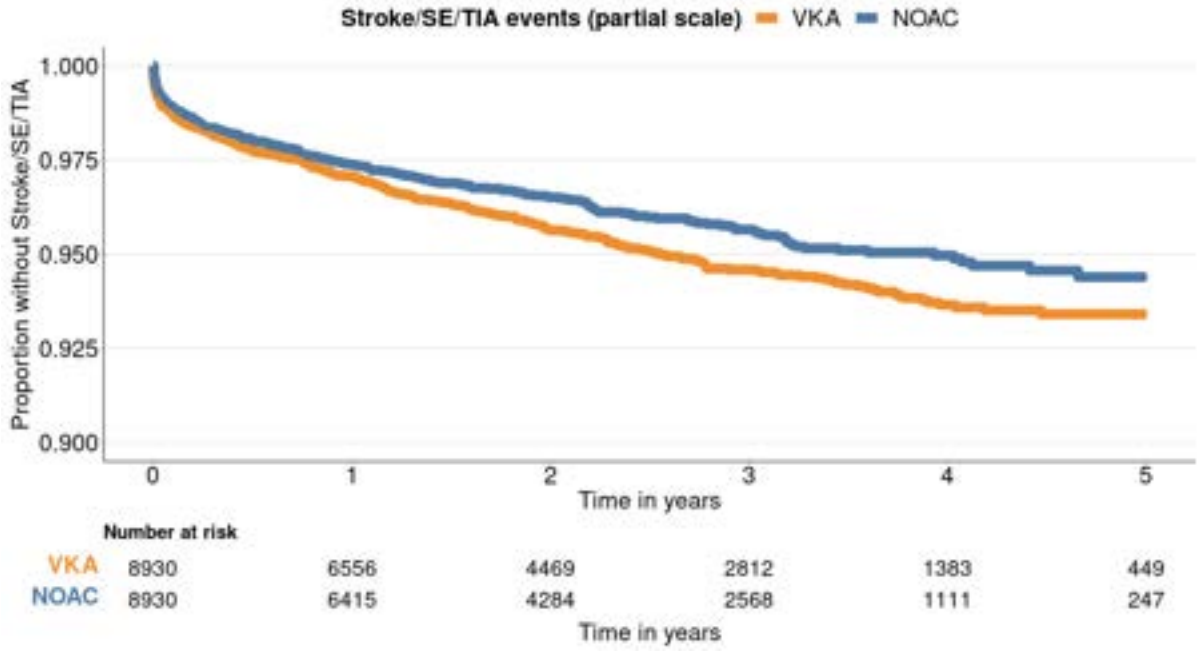
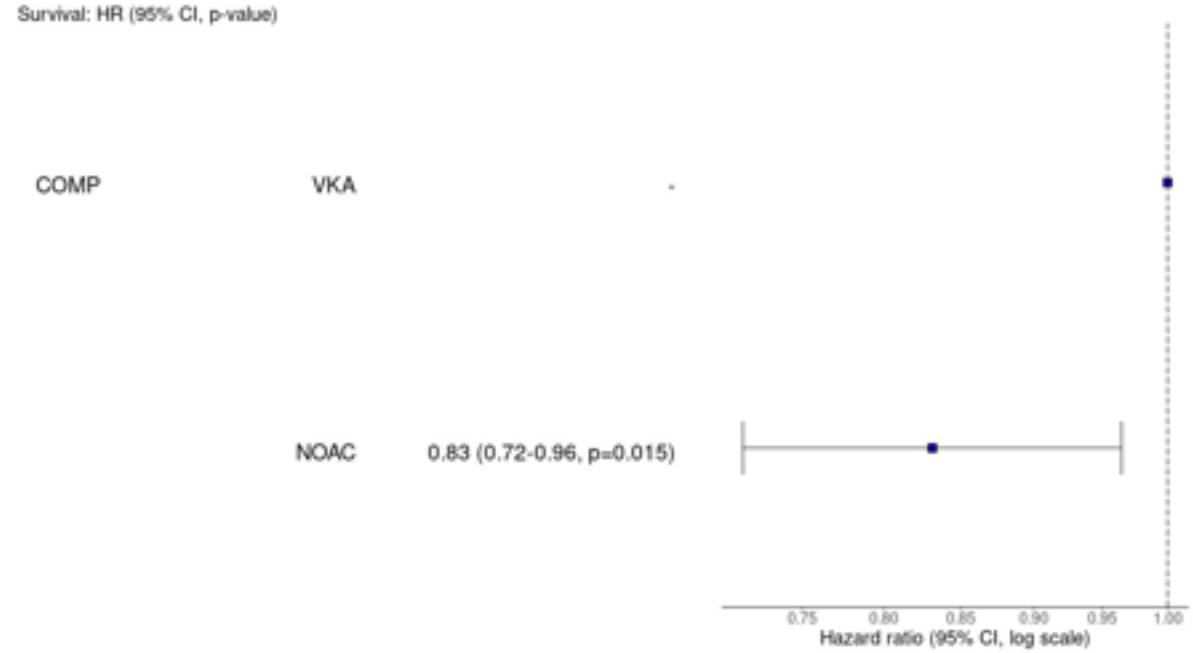


Figure 25. Univariate cox regression for time to event comparison of NOAC vs VKA for Stroke/SE/TIA after PSM.



15.3.2. *Safety outcomes*

Figure 26. Kaplan-Meier curve for Time to Major Bleeding after PSM for NOAC vs VKA (full scale).

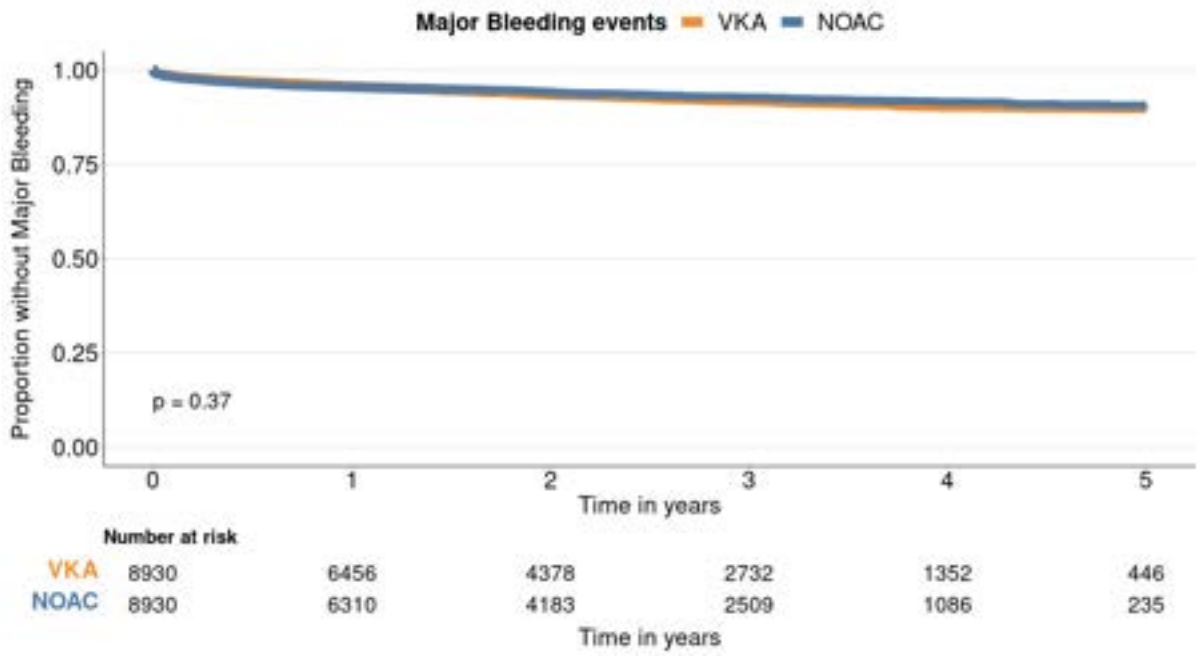


Figure 27. Kaplan-Meier curve for Time to Major Bleeding after PSM for NOAC vs VKA (partial scale).

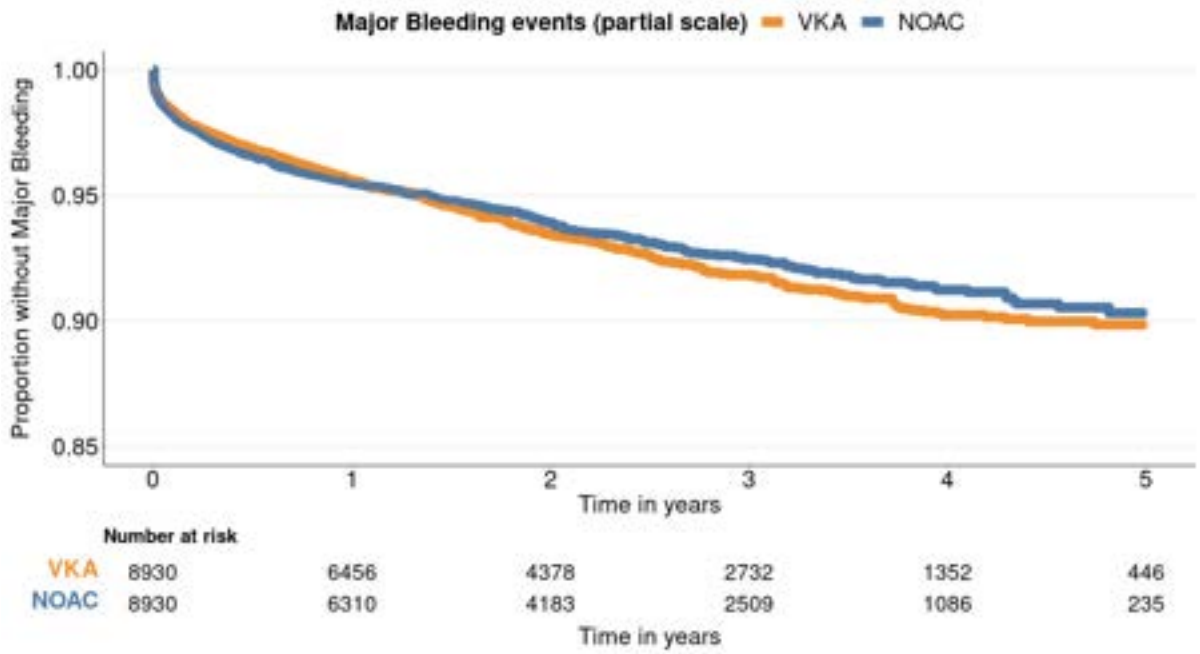


Figure 28. Univariate cox regression for time to event comparison of NOAC vs VKA for Major Bleeding after PSM.

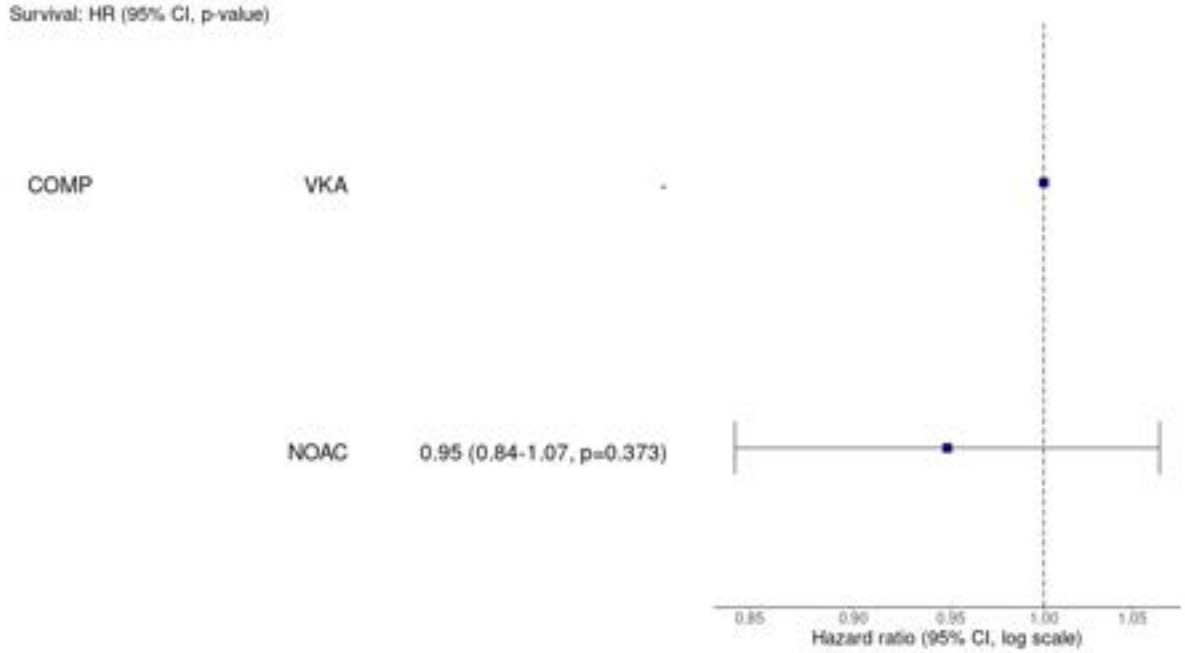


Figure 29. Kaplan-Meier curve for Time to Minor Bleeding after PSM for NOAC vs VKA (full scale).

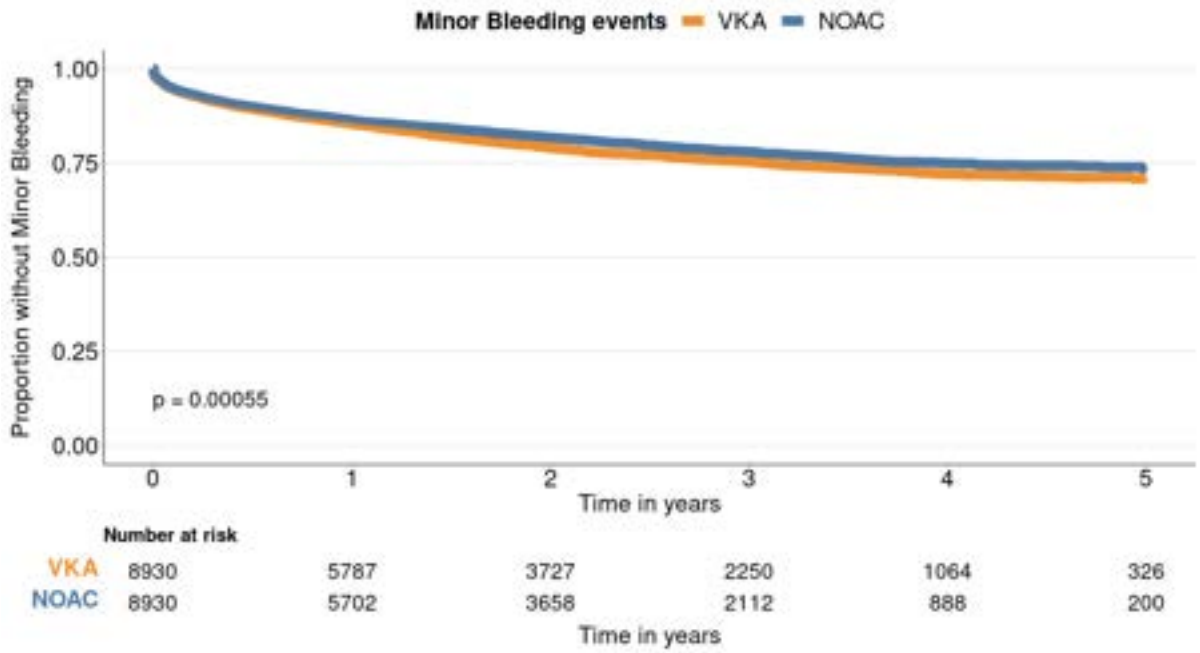


Figure 30. Kaplan-Meier curve for Time to Minor Bleeding after PSM for NOAC vs VKA (partial scale).

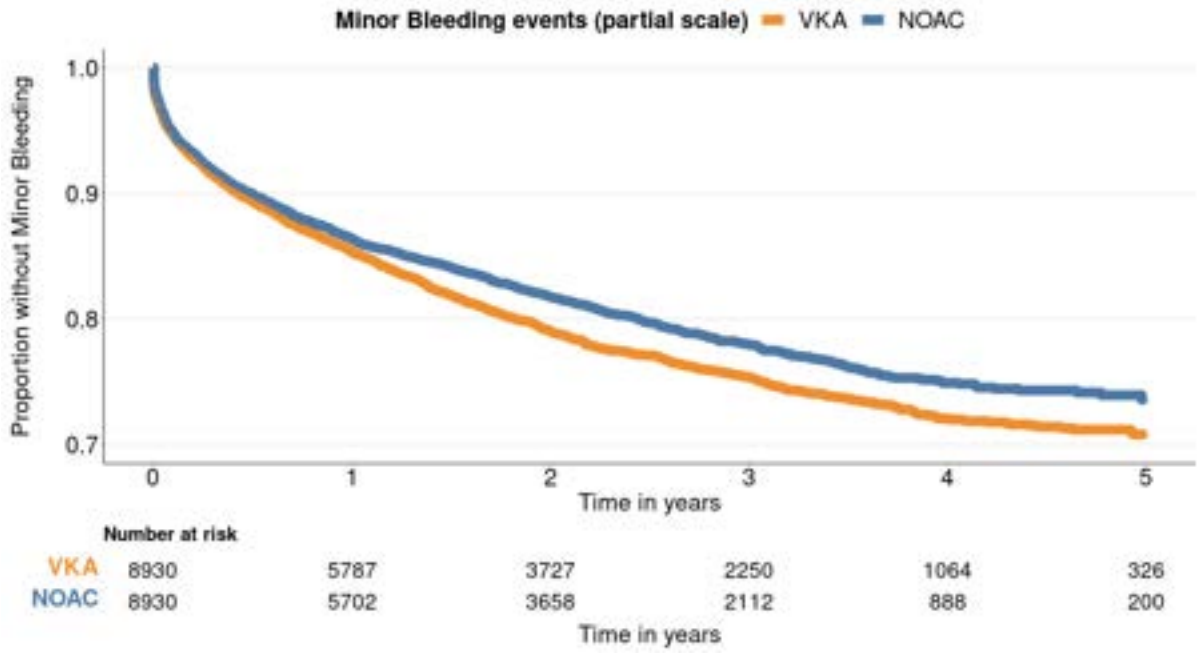
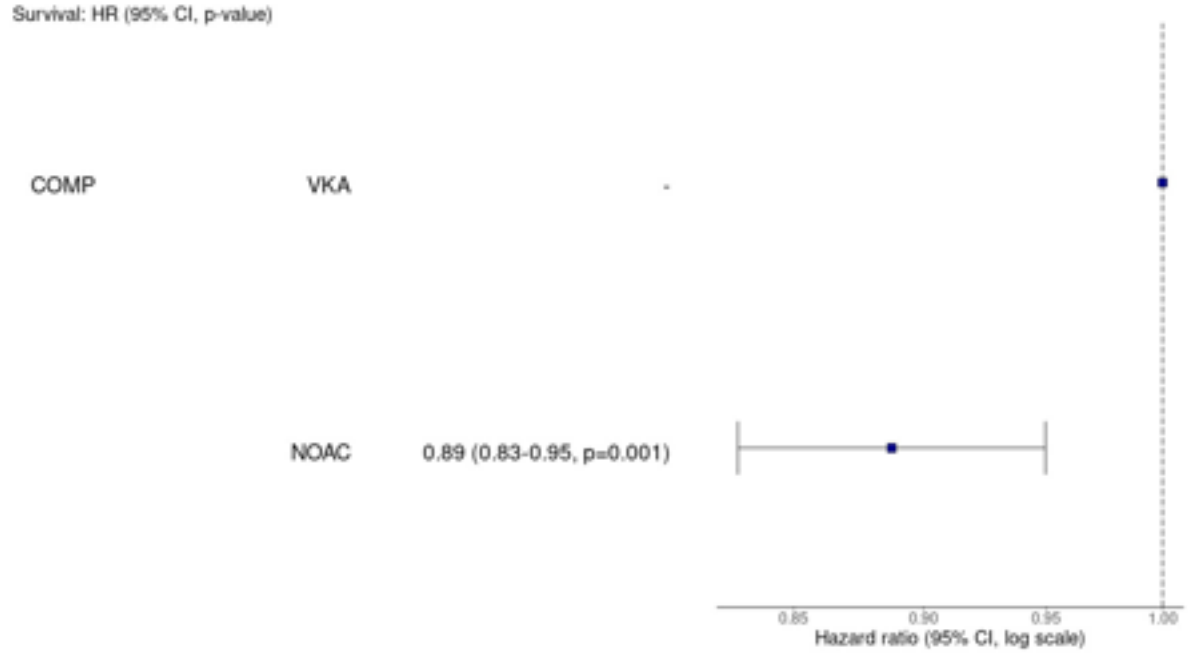


Figure 31. Univariate cox regression for time to event comparison of NOAC vs VKA for Minor Bleeding after PSM.



15.3.3. *Mortality*

Figure 32. Kaplan-Meier curve for Survival Time after PSM for NOAC vs VKA (full scale).

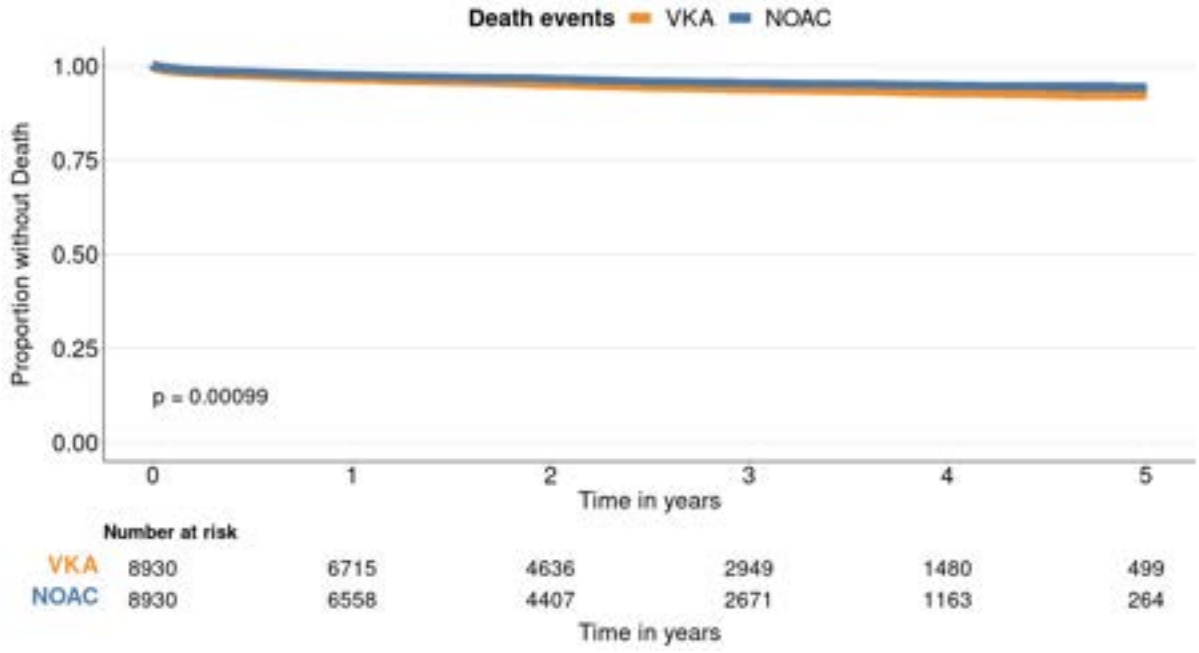


Figure 33. Kaplan-Meier curve for Survival Time after PSM for NOAC vs VKA (partial scale).

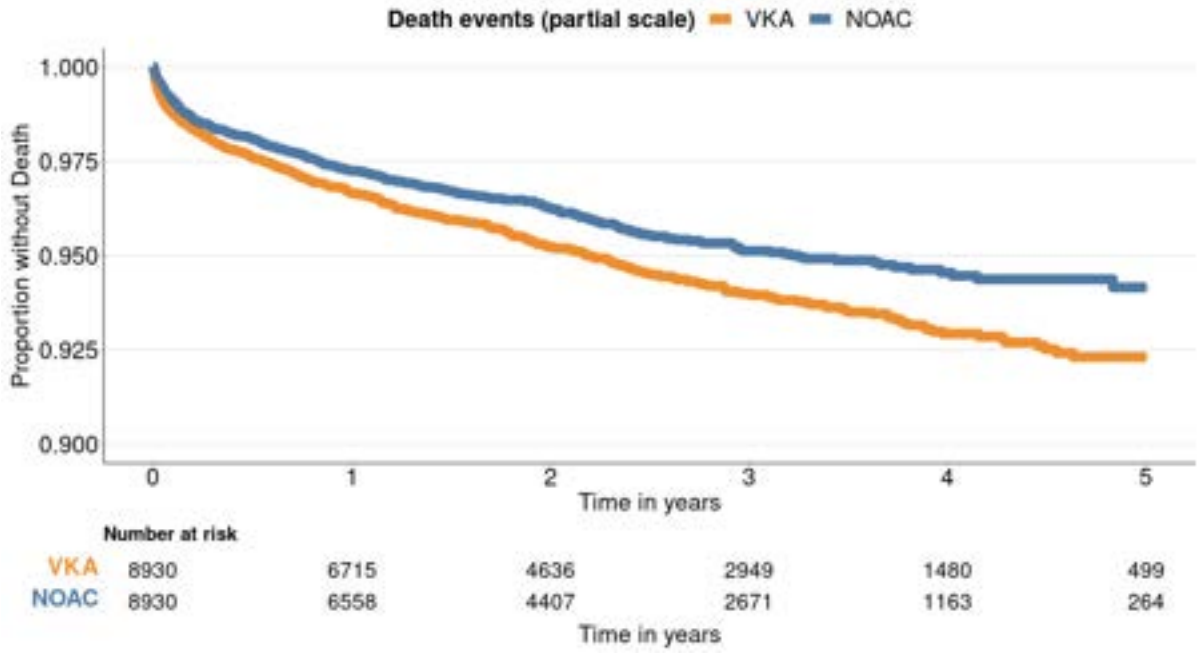
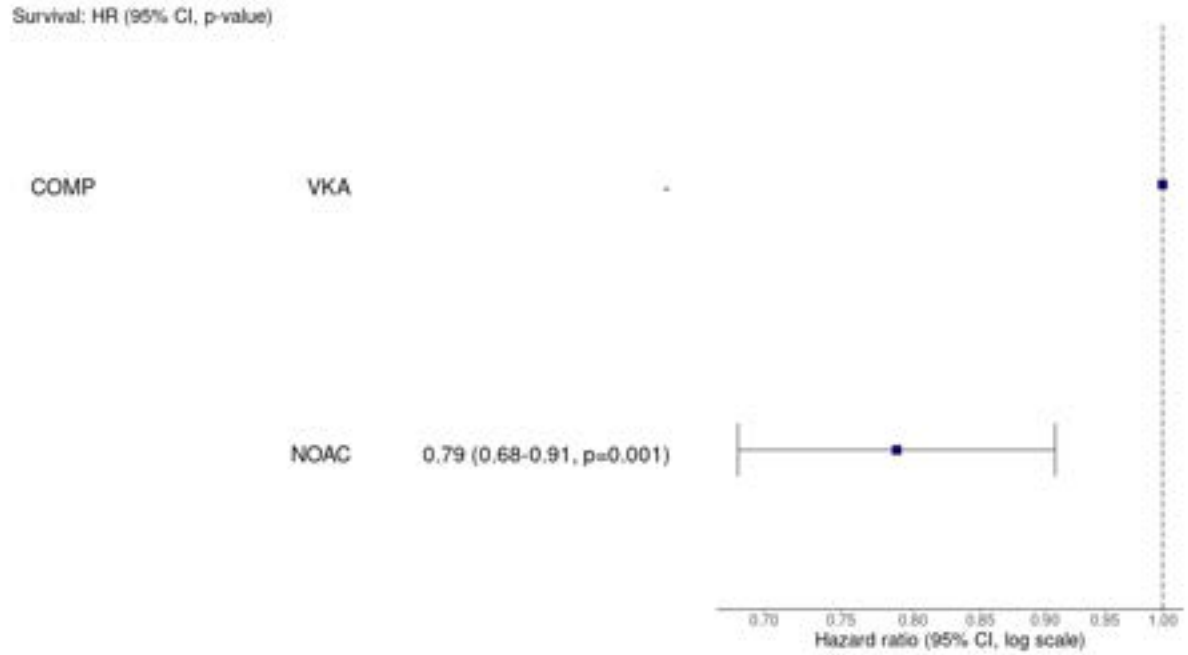


Figure 34. Univariate cox regression for time to event comparison of NOAC vs VKA for Death after PSM.



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17. LIST OF SOURCE TABLES AND FIGURES

Not Applicable

18. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

18.1. Appendix 1. Signatures

Pfizer	CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE	
Identifier	**Version**	**Title**
CT24-WI-GL15-RF06	2.0	NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT/MANUSCRIPT SIGNATURES

APPENDIX 1. SIGNATURES

PROTOCOL NUMBER:	*B0661131*
TITLE OF STUDY:	*Atrial Fibrillation In Real practice on Management of oral Anticoagulation– AFIRMA 4.0*
FINAL STUDY REPORT VERSION:	*B0661131. Non-interventional final study report. 13october 2023.*

Confirmation: I confirm that this study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study.

Pfizer NI study lead/LIS1 study lead
Susana Fernández de Cabo, Sr Medical Team Lead

Susana Fernandez de Cabo
Signature: **Date:** 15 Nov 2023 10:40:055-0500

Principal investigator
Juan Cosin Sales, Cardiologist H. Arnau de Vilanova, Valencia

Juan Cosín Sales
Signature: **Date:** 15 Nov 2023 16:29:057-0500

Approval of final study report

Medical Director Internal Medicine & Hospital, Spain
Francisco Jesús Mesa Banqueri

Francisco Jesús Mesa
Signature: **Date:** 16 Nov 2023 12:07:024-0500

18.2. Appendix 2. Protocol

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	***AF In Real practice on Management of oral Anticoagulation– AFIRMA 4.0***
Protocol number	*B0661131*
Protocol version identifier	*0.4*
Date	*20th September 2019*
EU Post Authorization Study (PAS) register number	*Study not registered*
Active substance	*Oral anticoagulants (OACs)*
Medicinal product	*Apixaban, rivaroxaban, edoxaban, dabigatran, warfarin, and acenocumarol.*
Product reference	*Apixaban*
Procedure number	Not applicable
Marketing Authorization Holder(s) (MAH)	*Pfizer SLU* *Spain*
Joint PASS	*No*
Research question and objectives	PRIMARY: To describe the demographic and clinical characteristics, including comorbidities, for OAC patients who were prescribed apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol or warfarin. SECONDARY: • To describe treatment pathways, including: initial treatment, switching treatment, treatment after switch, discontinuation, reasons for

	switching and discontinuation, and clinical events preceding or following a switch of treatment. • To describe report annual incidence rates of stroke/SE, major and minor bleedings for patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin. • To compare the rates of stroke/SE, major and minor bleedings and evaluated comparative rates across various subgroups among NVAF patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin. • To describe bleeding and stroke-related health care resource utilization in the study populations. • The study will occur over three phases: an initial one describing patient characteristics and treatment pathways; the second one with a description of the minor bleeding events and comparative analysis between treatments; and a third one describing stroke/SE and major bleedings and a comparative analysis between treatments. The power and estimated sample size will be verified before conducting any comparative analysis between treatments.
Country(-ies) of study	*Spain.*
Author	*Susana Fernandez de Cabo* *Daniel Arumi* *Departamento Médico, Pfizer España* *Susana.FernandezdeCabo@pfizer.com* *Daniel.arumi@pfizer.com*

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	*Pfizer SLU* *Avda. Europa 20B, 28108 Alcobendas (Madrid) Spain*

MAH contact person	*Susana Fernandez de Cabo* *Daniel Arumi* *Dpto. Médico, Pfizer España* *Susana.FernandezdeCabo@pfizer.com* *Daniel.arumi@pfizer.com*

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AI	Artificial intelligence
AF	Atrial fibrillation
EHR	Electronic health records
INR	International normalized ratio
NLP	Natural language processing
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulants
SAP	Statistical analysis plan
SE	Systemic embolism
TTR	Time in therapeutic range
VKA	Vitamin K antagonists

3. RESPONSIBLE PARTIES

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Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Susana Fernández de Cabo *Daniel Arumi* *Juan Cosín*	Sr Medical Advisor Medical Director CV Cardiólogo	Pfizer Spain Pfizer Spain H. Arnau de Valencia	Avda. Europa 20B. Alcobendas 28108 Madrid Carrer de Sant Clement, 12, 46015 València

4. ABSTRACT

Tittle	***AF In Real practice on Management of oral Anticoagulation – AFIRMA 4.0***
Version number	0.4
Date of protocol	20th September 2019
Main author/ Affiliation	Susana Fernandez de Cabo/ Pfizer Daniel Arumi / Pfizer
Rationale and background	Options for anticoagulation have been expanding steadily over the past few decades, providing a greater number of oral anticoagulant (OAC) agents for prevention and management of thromboembolic disease. In addition to the standard treatment with vitamin K antagonists (VKA) (i.e. warfarin and acenocumarol), new oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOACs) that directly target the activity of thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have recently revolutionized thromboprophylaxis for stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF). Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits. Thus, advantages and disadvantages of each agent must be individualized to the patient and clinical setting. The clinical indications for direct thrombin inhibitors and direct factor Xa inhibitors include the prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ⩾ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ⩾ II).The most studied disease is NVAF unlike the rest of indications. One reason can be that despite good progress in the management of patients with AF, this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. So understanding treatment patterns and clinical and economic outcomes of NVAF treatment is critical to develop effective strategies to reduce the overall disease burden. NOACs are an alternative for VKA for most patients with NVAF, in whom oral anticoagulant therapy is chosen, and are the preferred choice in those AF populations with increased risks of both thromboembolic and bleeding events. These agents have an improved efficacy/safety ratio, a predictable anticoagulant effect without need for routine monitoring, and fewer food and drug interactions compared with VKAs. However, the proper use of NOACs requires a careful approach to many practical aspects.

	The growing need for real-world evidence (RWE) is motivated to complement data from clinical trials and has increasingly been used in the process of decision-making. Despite previous observational studies have already been performed in different populations with NVAF treated with NOACs, there is still a need for further studies in RWE. In this context, we propose to use SAVANA, an innovating data-driven system based on NLP and big data techniques, designed to analyse unstructured data contained in the electronic medical files.
Research questions and objectives	PRIMARY: To describe the demographic and clinical characteristics, including comorbidities, for OAC patients who were prescribed apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol or warfarin. SECONDARY: • To describe treatment pathways, including: initial treatment, switching treatment, treatment after switch, discontinuation, reasons for switching and discontinuation, and clinical events preceding or following a switch of treatment. • To describe report annual incidence rates of stroke/SE, major and minor bleedings for patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin. • To compare the rates of stroke/SE, major and minor bleedings and evaluated comparative rates across various subgroups among NVAF patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin ** • To describe bleeding and stroke-related health care resource utilization in the study populations. • The study will occur over three phases: an initial one describing patient characteristics and treatment pathways; the second one with a description of the minor bleeding events and comparative analysis between treatments; and a third one describing stroke/SE and major bleedings and a comparative analysis between treatments. The power and estimated sample size will be verified before conducting any comparative analysis between treatments. ** Power calculations will be undertaken to determine the feasibility of conducting comparative analyses. The following comparison will be carried out: 1. NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) compared to VKA (acenocumarol and warfarin) 2. Each NOAC compared to VKA

	3. Comparisons between NOACs
Study design	This is designed as an observational retrospective cohorts study based on real-world data through the reuse of EHRs, using Natural Language Processing (NLP) and Artificial Intelligence (AI) techniques developed by Savana. The study period will be from January 2014 through December 2018 (or most recent data available).
Population	All adult patients with a diagnosis of NVAF who were prescribed an OACs (apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin).
Variables	• Baseline characteristics: Spanish geographic region, specialty, age, gender, Deyo-Charlson Comorbidity Index, CHA_2DS_2, CHA_2DS_2-VASc, and HAS-BLED score, baseline prior bleed and prior stroke, comorbidities (diabetes mellitus, renal disease, hemodialysis, hypertension, etc.), alcohol/drug abuse, smoking status, and medication use. • Stroke or SE, major bleeding, gastrointestinal bleeding, intracranial hemorrhage, minor bleeding, INR (determination (at stroke or bleed and prior to the moment of medication switch) and TTR. • Other: Discontinuation and switch among anticoagulants.
Data source	A selection of Spanish hospitals will be defined having an unbiased representation of NVAF population, in order to extract all the data available in EHR's from this disease. EHR's include data collected from all available health care sites (inpatient hospital, outpatient hospital, and emergency room), for virtually all types of provided services. Savana has developed a technology (EHRead) to process and structure EHRs, based on NLP and AI. Information will cover the last 5 years (2014 to present) from the selected Spanish centres.
Study size	Given the descriptive nature of this study, no hypothesis testing will be performed and determination of a minimum sample size is not required. Nevertheless, in order to provide reliable results that could give value to the analysis, a recommended sample size has been calculated.
Data analysis	All statistical analysis and methodology are detailed in the Statistical Analysis Plan (SAP).

Milestones	**Milestone**	**Planned date**
	Start of data colletion	November 2019
	Final data colletion SAP for review	September 2020
	Final study report	November 2020

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data colletion	November 2019
Final data colletion	September 2020
Final study report	November 2020

*Depends on each hospital.

7. RATIONALE AND BACKGROUND

Options for anticoagulation have been expanding steadily over the past few decades, providing a greater number of oral anticoagulant (OAC) agents for prevention and management of thromboembolic disease. In addition to the standard treatment with vitamin K antagonists (VKA) (i.e. warfarin and acenocumarol), new oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOACs) that directly target the activity of thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have recently revolutionized thromboprophylaxis for stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF) (1). Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits. Thus, advantages and disadvantages of each agent must be individualized to the patient and clinical setting (2).

The clinical indications for direct thrombin inhibitors and direct factor Xa inhibitors include the prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age $\geqslant$ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class $\geqslant$ II).The most studied disease is NVAF unlike the rest of indications (3-6). One reason can be that despite good progress in the management of patients with AF, this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world (7). Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. So understanding treatment patterns and clinical and economic outcomes of NVAF treatment is critical to develop effective strategies to reduce the overall disease burden (8).

NOACs are an alternative for VKA for most patients with NVAF, in whom oral anticoagulant therapy is chosen, and are the preferred choice in those AF populations with increased risks of both thromboembolic and bleeding events (9). These agents have an improved efficacy/safety ratio (10-13), a predictable anticoagulant effect without need for routine monitoring, and fewer food and drug interactions compared with VKAs (14). However, the proper use of NOACs requires a careful approach to many practical aspects, including to obtain the safety profile of patients in treatment with NOACs, that led to the inictiation of this study.

The growing need for real-world evidence (RWE) is motivated to complement data from clinical trials and has increasingly been used in the process of decision-making. Despite previous observational studies have already been performed in different populations with NVAF treated with NOACs (15, 16), there is still a need to obtain local RWE including the treatment with acenocumarol, the most used VKA in Spain. Recently the REBASA study, a retrospective study using partial local databases of patients treated with apixaban or acenocumarol to compare the risk of stroke, systemic thromboembolism and bleeding, was performed using data from selected hospitals in Spain.

Based on all the above, we intend to perform a study of NVAF patients based on real-world data through the reuse of electronic health records (EHRs), using SAVANA, a data-driven system based on NLP and big data techniques, designed to analyse unstructured data contained in the electronic medical files. We will use the information obtained from the REBASA study in order to contrast our findings.

7.1. Rationale for the use of NLP, big data and artificial intelligence in the generation of real-world evidence

Classical clinical registries are beneficial in terms of high quality and homogeneity of data, as they are manually populated, ad hoc for each of the included patients. However, there are three main issues to be considered:

1. Because it is a time consuming task for clinicians, the number of patients that can be included is extremely low.
2. Because the patients included are specifically addressed, there are observation biases implicit during the data gathering.
3. Because it is a time consuming task, the number of variables that can be included is very limited and influenced by the previous state of knowledge.

Applying NLP on clinical records, however, allows the extraction of the whole track record, including all patients from the participant center. Following the points mentioned above,

1. The number of patients is as extense as the total amount of existing ones (including patients not alive or not being followed anymore).
2. The nature of the information is not influenced by the study or the observer; on the contrary, it comes from clinical reality.
3. The number of considered variables is as extense as the total amount of clinical information gathered along the previous contacts with the center; this allows the analysis to find new possible associations that can be furthered checked.

Accepting there are certain variables which will not be annotated by physicians in the clinical records, all three reasons above stated, explain why the advantages of RWE studies using text mining, compensate or even overcome the limitations, when comparing to traditional registry studies.

Many matters have been raised regarding the use and exploitation of structured databases for research purposes, as this is the case with the largest regional database in Spain, the Information System for Research in Primary Care (SIDIAP, from its abbreviation in Spanish) from the Catalonia Region. This is predominantly concerned with primary care data and limited information owned by the regional Public Health Services (17-19). In these published studies, it is most often used in the context of descriptive analyses of outcomes likely to be captured by primary care physicians (eg descriptive analyses of incidence and prevalence of dementia in Ponjoan et al; smoking behaviour in Pons-Vigues et al and prevalence of health conditions/co-morbidities in Violán et al.). Furthermore, some of the research has indicated that the prevalence of co-morbid conditions is also dependent upon the source of data used, with some differences between SIDIAP and the results from a health survey, as reported by Violán et al. Additionally, the use of the SIDIAP dataset for effectiveness comparative purposes is useless, as there is inadequate capture of important endpoints to support the differentiation of a particular drug (i.e. apixaban), and the risk of all appropriate confounders may not be adequately captured for balancing patient covariates. Therefore, there is a need to identify new ways of generating data that will support differentiation of drugs on routine clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to perform a study of NVAF patients based on real-world data through the reuse of electronic health records (EHRs). This approach avoids missing valuable information, and reduces biases normally present in this type of studies. In particular, the following objectives will be explored:

PRIMARY:

To describe the demographic and clinical characteristics, including comorbidities, for OAC patients who were prescribed apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol or warfarin.

SECONDARY:

- To describe treatment pathways, including: initial treatment, switching treatment, treatment after switch, discontinuation, reasons for switching and discontinuation, and clinical events preceding or following a switch of treatment.

- To describe report annual incidence rates of stroke/SE, major and minor bleedings for patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin.
- To compare the rates of stroke/SE, major and minor bleedings and evaluated comparative rates across various subgroups among NVAF patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin*.
- To describe bleeding and stroke-related health care resource utilization in the study populations.
- The study will occur over three phases: an initial one describing patient characteristics and treatment pathways; the second one with a description of the minor bleeding events and comparative analysis between treatments; and a third one describing stroke/SE and major bleedings and a comparative analysis between treatments. The power and estimated sample size will be verified before conducting any comparative analysis between treatments.

9. RESEARCH METHODS

9.1. Study design

This is designed as an observational retrospective cohorts study based on real-world data through the reuse of EHRs, using Natural Language Processing (NLP) and Artificial Intelligence (AI) techniques developed by Savana.

Savana will include information from all EHRs from the available centres. These records will include inpatient and outpatient hospital and emergency room.

9.2. Setting

The study will be conducted in Spain. The study period will be from January 2014 through December 2018 (or most recent data available). In order not to lose valuable information, each patient will be followed as long as it is allowed. The selection criteria are detailed below.

*Power calculations will be undertaken to determine the feasibility of conducting comparative analyses. The following comparison will be carried out:

1. NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) compared to VKA (acenocumarol and warfarin)
2. Each NOAC compared to VKA
3. Comparisons between NOACs

9.2.1. Inclusion criteria

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

1. Were diagnosed NVAF and are taking NOACs (apixaban, rivaroxaban, dabigatran and edoxaban), or VKA (acenocumarol, warfarin) during the identification period, either as treatment-naïve or treatment-experienced (switching OAC treatments, NOACs/VKA).
2. Aged ⩾18 years at the index date

9.2.2. Exclusion criteria

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

1. Rheumatic mitral valvular heart disease and mitral valve stenosis.
2. Venous thromboembolism (VTE).
3. Pregnancy.

After applying the inclusion and exclusion criteria, eligible patients will be assigned to one of the OAC cohort based and we will analyze separately those patients that newly initiated OAC therapy (apixaban, dabigatran, rivaroxaban, edoxaban, warfarin, or acenocumarol) against those that switched OACs therapies. For further details, please refer to section Analysis sets/Population of the Statystical analysis plan of the present study.

9.3. Variables

Given that this is a Big Data-based study, the potential number of variables that may be included is only limited to the information contained in the EHRs. All mentioned variables will be included provided that they are found correctly in the text. It is therefore understood that it is impossible to guarantee that all the desired variables are included in the final study. On the other hand, this technology enables to create new variables, which can neither be described in advance.
A complete and detailed guidance on the evaluation of the variables and outcomes are presented in the SAP.

9.3.1. Baseline characteristics

- Spanish geographic region
- Specialty
- Age: (18-64 years; 65-74 years; 75-85 years; >65; >75; >85)
- Gender: (male/female)

- Weigth
- Baseline Deyo-Charlson Comorbidity Index
- CHA_2DS_2 and CHA_2DS_2-VASc score
- HAS-BLED score:
  - Baseline prior bleed
  - Baseline prior stroke
- Comorbidities: Diabetes mellitus, renal disease, hemodialysis, hypertension, congestive heart failure, thrombocytopenia, myocardial infarction, dyspepsia, peripheral vascular disease, TIA, coronary artery disease, chronic pulmonary disease, sleep apnea syndrome, etc.
- Alcohol/drug abuse
- Smoking status
- OAC therapy
  - Type
  - Time under treatment
  - Treatment switch and reason (if available)
- Prior OAC therapy (if applies)

9.3.2. Effectiveness variables

Stroke or SE will be identified in the EHR by means of NLP and AI techniques. Stroke/SE will be classified into 3 categories: ischemic stroke, hemorrhage stroke, and SE.

9.3.3. Safety variables

The following variables will be identified in the EHR by means of NLP and AI techniques: major bleeding, gastrointestinal bleeding, intracranial hemorrhage, minor bleeding, International Normalized Ratio (INR) determination at stroke or bleed and prior to the moment of medication switch, and the time in therapeutic range (TTR), which is defined as the duration of time in which the patient's INR values were within a desired range.

A variety of definitions of major bleeding have been used in published clinical studies, and this diversity adds to the difficulty in comparing data between trials and in performing meta-analyses. The definition of major bleeding in non - surgical patients was discussed at the Control of Anticoagulation Subcommittee of the *International Society on Thrombosis and Haemostasis* (20). A definition was developed that should be applicable to studies with all agents that interfere with haemostasis, including anticoagulants, platelet function inhibitors and fibrinolytic drugs.

Major Bleeding

- **Major Bleeding in Non-Surgical Patients**

  1. Fatal bleeding, and/or
  2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra - articular or pericardial, or intramuscular with compartment syndrome, and/or
  3. Bleeding causing a fall in hemoglobin level of 2g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

- **Major Bleeding in Surgical Patients**

  1. Fatal bleeding, and/or
  2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon. and/or
  3. Extrasurgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding. and/or
  4. Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection. and/or
  5. Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.
  6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).
  7. The population is those who have received at least one dose of the study drug.

Minor Bleeding

All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not.

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

1. A hospital admission for bleeding, or
2. A physician guided medical or surgical treatment for bleeding, or
3. A change in antithrombotic therapy (including interruption or discontinuation of study drug).

9.3.4. Other variables

- Discontinuation, defined as the first day of a period of at least 30 consecutive days (grace period) after Savana detects a discontinuation in the EHR. Reason for discontinuation (if available) will be identified in the EHR by means of NLP and AI techniques
- Switch among anticoagulants, defined as a prescription filled for non-index anticoagulants within ±30 days after the date of discontinuation. Reason for switch among anticoagulants (if available) will be identified in the EHR by means of NLP and AI techniques.

9.4. Data sources

A selection of Spanish hospitals will be defined having an unbiased representation of NVAF population, in order to extract all the data available in EHR's from this disease.

EHR's include data collected from all available health care sites (inpatient hospital, outpatient hospital, and emergency room), for virtually all types of provided services.

Savana has developed a technology (EHRead) to process and structure EHRs, based on NLP and AI. Information will cover the last 5 years (2014 to present) from the selected Spanish centres.

9.5. Study size

Given the descriptive nature of this study, no hypothesis testing will be performed and determination of a minimum sample size is not required. Nevertheless, in order to provide reliable results that could give value to the analysis, a recommended sample size will be calculated.

The calculation takes into account that some of the descriptive analysis are going to be performed by sub-groups (e.g. OAC treatment). Assuming a 5% as the minimum percentage of patients, the sample size of a sub-group could be calculated as:

$$n = \frac{P \cdot (1 - P) \cdot Z_{1-\alpha/2}^2}{d^2}$$

where,

P is the proportion of the class (10%),
Z is the inverse of the standard normal distribution,
α significance level of 5%,
d is the desired precision, representing half of the desired confidence interval width

For the description of demographic and clinical characteristics it is recommended to count with at least 384 patients with an OAC prescription within each sub-group, assuming a maximum percentage of patients in a class of 50% (most conservative value) and a precision d of 5% (pp). This makes a total of 7,683 patients with OAC prescription (384/0.05).

In the case of annual incidence rates (Stroke/SE, Major and Minor Bleedings), and considering the scenarios described in Figure 1, we would need at least 1,825 patients with an OAC prescription within each sub-group, and a total of 36,494 patients with OAC prescription (1,825/0.05).

	Annual Incidence Rate		
Precision	1.00%	5.00%	10.00%
0.50%	1,521		
1.00%		1,825	
2.00%			864

Figure 1 Incidence and precision scenarios

Considering an AF prevalence of 1% (21) this involves searching for NVAF cases from a population of approximately 3,700,000 patients. The number of sites participating in the study will be 20, which entails counting with around 6.000.000 patients a figure that widely satisfy the minimum sample size. Once the study initiates, the sample size will be reviewed with information from the first enrolled hospitals, in order to ensure its adequacy.

In order to achive comparative analysis planned in the third secondary objective, the rate of the different events of interest in each cohort will be evaluated with Cox proportional hazard models, assuming a power of 80% and a significance level of 5%.

9.6. Data management

With the growing availability of large EHRs, new methodology is needed. Classical research is time-consuming in comparison to a few seconds search in a well designed database researcher. This is why clinical researchers are increasingly interested in secondary use of clinical data.

9.6.1. Data acquisition at site

The Data Acquisition phase is responsibility of the Site, because at this stage, the EMR is considered personal data by EU's General Data Protection Regulation (EU GDPR) or Protected Health Information (PHI) by Health Insurance Portability and Accountability Act (HIPAA). By getting the data through this phase, several mechanisms will be established in order to transform the EMR into anonymous, pseudonymized Clinical Information that won't be considered personal data.

This stage consists in an Extract, Transfer, Load (ETL) that intends to pre-process the data on-site in order to transfer a minimal set needed by Savana's EHRead technology (see below).

9.6.1.1. Extraction stage

The main objective of this stage is to minimize the disruption of EMR production environments. Clinical production environments aren't usually designed to run ETLs and/or processing such as anonymization and pseudonymization. The recommended approach is to extract the data into a storage that Site IT Department can control during the Acquisition phase. This will also provide additional benefits as Site Data Controller can enable traceability of the extracted data.

9.6.2. Quality of data

Savana has developed EHRead, a powerful technology that applies NLP, Machine Learning and Deep Learning to analyze the unstructured free text information written in millions of EHRs and automatically extracts highly valuable medical information (22). It does so by combining in its pipeline modules for, among others, sentence segmentation, tokenization, text normalization, acronym disambiguation, negation detection, and a multi-dimensional ranking scheme which combines linguistic knowledge, statistical evidence and state-of-the-art continuous vector representations of words and documents in the clinical domain learned via shallow neural networks.

Data from patients is processed in the informatics of each hospital and sent to Savana in an anonymous way. We never receive any identifiable data. Savana works closely with the Spanish Data Protection Agency. All actions will be taken in accordance with the Code of Good Data Protection Practices for Big Data Projects of the Spanish Data Protection Agency,

the Spanish Data Protection Act (LOPD 03/2018) or another that may replace it, and the European Data Protection regulation. Note that the end output of this methodology is fully dissociated and anonymized.

9.6.3. Evaluation

The evaluation of the ability of Savana to accurately extract those records in which mentions of the pathology under study are registered will be conducted in each participating hospital once all centers have been processed. Further information has been detailed in section 9.7.Data analysis

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Evaluation/Validation of SAVANA's performance

Parallelly, at each participating site, an evaluation/validation will be performed to assess the performance of SAVANA at accurately identifying records that contains mentions of the pathology under study and its related clinical entities. Then, a gold standard that contains records with and without mention of the pathology will be built-up, in order to evaluate the SAVANA's ability to detect these mentions.

This evaluation/validation process will be conducted in two consecutive phases that are detailed as follows:

Phase 1: Building the Gold standard

a) Size: the number of records that will be used in the gold standard is determined by the SLiCE, a calculator that indicates the minimum number of records to be annotated to obtain the expected levels of confidence.

b) Text collection: a set of records related to the clinical specialties of the pathology under study are randomly collected from all participating centers to build up the gold standard. It is really important that the gold standard contains records from the different participating centers to assess the SAVANA performance in all of them and ensure that the performance is independent of each center. Otherwise, the evaluation will be biased by the subset of centers selected.

c) Annotations process: two researches (i.e. annotator 1 and annotator 2) will annotate a set of randomly selected records, following the annotation guidelines written by the medical

team of SAVANA. Once they are finished, in the case these two annotators have discrepancies, a third research will act as a judge to solve the discrepancies and will judge how to proceed, in order to obtain the gold standard.

Phase 2: Evaluation

Once the gold standard has been created, this dataset is split into two subsets:

- Training set: it is used to train the model (select the parameters that better fits the model).
- Hold-Out set/Test set: it is used to measure how well the model performs at making predictions.

The size of this sub-sets will depend on the number of documents that finally make up the gold standard. Traditionally, the training set is constituted with 70-80% of the data set and the remaining 30-20% is employed for testing. Thus, this will be our approach.

It is really important that the performance of the model should be measured in the hold-out set to reflect how the model performs in a different dataset of the one that has been used to construct the model.

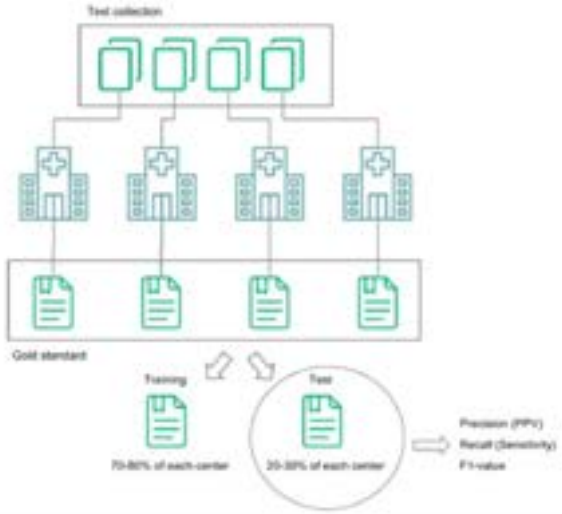

Figure 2. Workflow of the evaluation/validation of SAVANA's performance

From the evaluation on the hold out/test, we will obtain a confusion matrix which will provide relevant information about the performance of the model. A confusion matrix is a table with four different combinations of predicted (SAVANA) and actual values (gold standard):

Table 1. Example of confusion matrix

	Gold standard (Positive)	**Gold standard (Negative)**
Savana (Positive)	True Positive (TP)	False Positive (FP)
Savana (Negative)	False Negative (FN)	True Negative (TN)

As depicted in Figure 2, in order to evaluate the performance of SAVANA at identifying the clinical entities, we will calculate the following metrics on hold-out/test set:

- Precision (Positive Predictive Value - PPV): The proportion of correctly predicted positive cases to the total predicted positive observations.

  TP / (TP+FP)

- Recall (Sensitivity) = The proportion of correctly predictive positive observation to all observation in actual values.

  TP / (TP+FN)

- *F-Score*: Measure Recall and Precision at the same time giving an overall performance measure. It uses Harmonic Mean in place of Arithmetic Mean of precision and recall. Thus, this score takes both false positive and false negative into account.

  2*Recall*Precision/(Recall+Precision)

Accuracy is another metric that could be used to evaluate the performance of the model since it is the proportion of correctly predicted observation of the total observations. However, accuracy is a great measure when we have a balanced dataset. Otherwise, we should employ other metrics to evaluate the performance since accuracy could give false assumptions. For this reason, *F-Score* is employed in this evaluation.

9.7.1. Conducting the Evaluation/Validation

It is really important that the gold standard contains records from different participating centers to assess the SAVANA's performance status and to ensure that the performance is independent from each center. Therefore, the evaluation/validation of SAVANA will be conducted once all the centers have already been processed.

In this context, a phased-approach for the study will be used that will stop the analysis if any issues, in terms of validity, are identified at the earlier stages of the study, before any comparative analysis are performed. It is possible to determine that if the system obtains a Precision (i.e. PPV) > 85%, we could consider that the system is robust and

reliable to continue with the study. With respect to the Recall measure, we will find an optimal cutoff point to achieve the maximum recall with the predefined PPV of 85%. A diagram of this process is shown in Figure 3.

Figure 3. Diagram of the process carried out in each phase

Based on all the above, before conducting any statistical analysis for the study, the evaluation/validation will be carried out. Depending on the results, we will move forward or not from one phase to the next one. Moreover, in those phases where a comparative analysis is required, the estimated sample size will be then verified. The pre-specify phases will be:

Phase I: Description and validation of diagnosis and baseline characteristics*

Phase II: Description and validation of minor bleedings*

a. Comparative analysis of minor bleedings**

Phase III: Description and validation of stroke/SE and major bleedings*

a. Comparative analysis of stroke/SE and major bleedings**

*It will be considered patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin.

**Power calculations will be undertaken to determine the feasibility of conducting comparative analyses. The following comparison will be carried out:

1. NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) compared to VKA (acenocumarol)
2. Each NOAC compared to VKA
   a. Apixaban compared to acenocumarol
   b. Dabigatran compared to acenocumarol
   c. Rivaroxaban compared to acenocumarol
   d. Edoxaban compared to acenocumarol
3. Comparisons between NOACs
   a. Apixaban compared to dabigatran
   b. Apixaban compared to rivaroxaban
   c. Apixaban compared to edoxaban

d. Dabigatran compared to rivaroxaban
e. Dabigatran compared to edoxaban
f. Rivaroxaban compared to edoxaban

9.8. Quality control

SAVANA will ensure the quality of the database by reviewing the completion and accuracy of the data.

9.9. Limitations of the research methods

Limitations of this study are those related to an observational retrospective design. Potential limitations in terms of the accuracy of the system are accounted for in the measurement of its estimated error, and will ultimately be corrected with the manual validation.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information. *If* automated/algorithmic methods, such as natural language processing, will be used to convert unstructured data to structured data during the implementation of the protocol, no patient personal data will be accessed.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Patient withdrawal

Not applicable.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. 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 the 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), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

IP list (when available)

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

For PASS protocols submitted in the EU, a copy of the ENCePP Checklist for Study protocols (available at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml*) should be completed and signed by the main author of the study protocol, and included in Annex 2.*

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

18.3. Appendix 3. Investigators and corresponding Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs)

Not applicable

18.4. Appendix 4. Statistical Analysis Plan

Non-Interventional Study Protocol
B0661131

AF In Real practice on Management of oral Anticoagulation– AFIRMA 4.0

Statistical Analysis Plan
(SAP)

Version: *1.2*

Author: *Pérez Ramos, Laura (Biostatistics, SAVANA)*

Date: *7 – May- 2021*

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

This new version contains the following modifications:

- Section 3.2: *"No adjustments for multiple comparisons will be made"* modified to *"Multiple comparisons will be adjusted with the false discovery rate (FDR) correction"*.
- Section 5.1: New definitions added to:
  - Treatment switch
  - Treatment discontinuation
- Section 5: *"On the other hand, this technology enables to create new variables, which can neither be described in advance."* Deleted from section 5.

No additional modifications added.

2 INTRODUCTION

Options for anticoagulation have been expanding steadily over the past few decades, providing a greater number of oral anticoagulant (OAC) agents for prevention and management of thromboembolic disease. In addition to the standard treatment with vitamin K antagonists (VKA) (i.e. warfarin and acenocumarol), new oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOACs) that directly target the activity of thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have recently revolutionized thromboprophylaxis for stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF) (1). Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits. Thus, advantages and disadvantages of each agent must be individualized to the patient and clinical setting (2).

The clinical indications for direct thrombin inhibitors and direct factor Xa inhibitors include the prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).The most studied disease is NVAF unlike the rest of indications (3-6). One reason can be that despite good progress in the management of patients with AF, this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world (7). Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. So understanding treatment patterns and clinical and economic outcomes of NVAF treatment is critical to develop effective strategies to reduce the overall disease burden (8).

NOACs are an alternative for VKA for most patients with NVAF, in whom oral anticoagulant therapy is chosen, and are the preferred choice in those AF populations with increased risks of both thromboembolic and bleeding events (9). These agents have an improved efficacy/safety ratio (10-13), a predictable anticoagulant effect without need for routine monitoring, and fewer food and drug interactions compared with VKAs (14). However, the proper use of NOACs requires a careful approach to many practical aspects.

The growing need for real-world evidence (RWE) is motivated to complement data from clinical trials and has increasingly been used in the process of decision-making. Despite previous observational studies have already been performed in different populations with NVAF treated with NOACs (15, 16), there is still a need to obtain local RWE including the treatment with acenocumarol, the most used VKA in Spain. Recently the REBASA study, a retrospective study using partial local databases of patients treated with apixaban or acenocumarol to compare the risk of stroke, systemic thromboembolism and bleeding, was performed using data from selected hospitals in Spain.

Based on all the above, we intend to perform a study of NVAF patients based on real-world data through the reuse of electronic health records (EHRs), using SAVANA, a data-driven system based on NLP and big data techniques, designed to analyse unstructured data contained in the electronic medical files. We will use the information obtained from the REBASA study in order to contrast our findings.

2.1 STUDY DESIGN

This is designed as an observational retrospective cohorts study based on real-world data through the reuse of EHRs, using Natural Language Processing (NLP) and Artificial Intelligence (AI) techniques developed by Savana.
Savana will include information from all EHRs from the available centres. These records will include inpatient and outpatient hospital and emergency room.

Study population

The study will be conducted in Spain. The study period will be from January 2014 through December 2018 (or most recent data available). In order not to lose valuable information, each patient will be followed as long as it is allowed.

Inclusion criteria

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

1. Were diagnosed NVAF and are taking NOACs (apixaban, rivaroxaban, dabigatran and edoxaban), or VKA (acenocumarol, warfarin) during the identification period, either as treatment-naïve or treatment-experienced (switching OAC treatments, NOACs/VKA).

2. Aged ≥ 18 years at the index date.

Exclusion criteria

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

1. Rheumatic mitral valvular heart disease and mitral valve stenosis.
2. Venous thromboembolism (VTE).
3. Pregnancy.
4. No follow-up information.

After applying the inclusion and exclusion criteria, eligible patients will be assigned to one of the OAC cohort based and we will analyze separately those patients that on the newly initiated OAC therapy (apixaban, dabigatran, rivaroxaban, edoxaban, warfarin, or acenocumarol) against those that switched OACs therapies. For further details, please refer to section Analysis sets/Population of the Statystical analysis plan of the present study.

Data source

A selection of Spanish hospitals will be defined having an unbiased representation of NVAF population, in order to extract all the data available in EHR's from this disease.

EHR's include data collected from all available health care sites (inpatient hospital, outpatient hospital, and emergency room), for virtually all types of provided services.

Savana has developed a technology (EHRead) to process and structure EHRs, based on NLP and AI. Information will cover the last 5 years (2014 to present) from the selected Spanish centres.

2.2 STUDY OBJECTIVES

The overall objective is to perform a study of NVAF patients based on real-world data through the reuse of electronic health records (EHRs). This approach avoids missing valuable information and reduces biases normally present in this type of studies. In particular, the following objectives will be explored:

PRIMARY:

To describe the demographic and clinical characteristics, including comorbidities, for OAC patients who were prescribed apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol or warfarin.

SECONDARY:

- To describe treatment pathways, including initial treatment, switching treatment, treatment after switch, discontinuation, reasons for switching and discontinuation, and clinical events preceding or following a switch of treatment.
- To describe annual incidence rates of stroke/SE, major and minor bleedings for patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin.
- To compare the rates of stroke/SE, major and minor bleedings and evaluated comparative rates across various subgroups among NVAF patients receiving apixaban, dabigatran, rivaroxaban, edoxaban, acenocumarol and warfarin.
- To describe bleeding and stroke-related health care resource utilization in the study populations.
- The study will occur over three phases: an initial one describing patient characteristics and treatment pathways; the second one with a description of the minor bleeding events and comparative analysis between treatments; and a third one describing stroke/SE and major bleedings and a comparative analysis between treatments. The power and estimated sample size will be verified before conducting any comparative analysis between treatments.

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

This study includes an exploratory element and specific hypotheses to be tested. Statistically significant differences for each event of interest (minor bleeding, major bleeding and stroke/SE) will be analyzed. The comparisons to be carried out are the following.

1. NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) compared to each VKA (acenocumarol and warfarin) and to both aggregated.

2. Pairwise comparisons between all four NOACs.

The null hypothesis for each statistical inference is defined as no difference between patients in both groups for the selected outcome.

3.2 STATISTICAL DECISION RULES

The alpha level will be 0.05, 2-sided. Multiple comparisons will be adjusted with the false discovery rate (FDR) correction.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Full analysis set is defined as all patients who fulfill all the eligibility criteria (please, refer to *Study population* in Section 2.1) to be eligible to participate in the study.

The first NOAC or VKA pharmacy claim date during the identification period is designated as the index date for patients who fulfill all the eligibility criteria (*Study population* in Section 2.1).

4.2 SAFETY ANALYSIS SET

The safety analysis set is the same as the full analysis set.

4.3 OTHER ANALYSIS SET

After applying the inclusion and exclusion criteria, eligible patients will be assigned to one of the OAC cohort based on the newly initiated OAC (apixaban, dabigatran, rivaroxaban, edoxaban, warfarin, or acenocumarol).

One-to-one propensity score matching (PSM) will be conducted between NOACs and acenocumarol (apixaban versus acenocumarol, dabigatran versus acenocumarol, rivaroxaban versus acenocumarol and edoxaban versus acenocumarol) and between the NOACs (apixaban versus dabigatran, apixaban versus rivaroxaban, apixaban versus edoxaban, dabigatran versus rivaroxaban, dabigatran versus edoxaban and rivaroxabán versus edoxaban). As well as overall NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) versus VKA (acenocumarol and warfarin). Patients will be matched 1:1 in each data set based on the propensity scores generated.

4.4 SUBGROUPS

Not applicable.

5 ENDPOINTS AND COVARIATES

Given that this is a Big Data-based study, the potential number of variables that may be included is only limited to the information contained in the EHRs. All mentioned variables will be included provided that they are found correctly in the text. It is therefore understood that it is impossible to guarantee that all the desired variables are included in the final study.

The following variables will be searched for in the EHR by means of NLP and AI techniques.

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Variable	Role	Operational definition *
Baseline comorbidities	Baseline characteristic and potential confounder	A flag will be created for patients with comorbidities: Diabetes mellitus, renal disease, haemodialysis, hypertension, congestive heart failure, thrombocytopenia, myocardial infarction, dyspepsia, peripheral vascular disease, TIA, coronary artery disease, chronic pulmonary disease, etc. claims in the baseline period
Baseline medication Use	Baseline characteristic and potential confounder	Individual flags will be created for patients with prescription claims for medication use.
Baseline laboratory values	Baseline characteristic and potential confounder	Individual flags will be created for patients with prescription claims for laboratory values.
Treatment switch	Outcomes	Switch among anticoagulants, defined as the annotation of a new anticoagulant drug within the study period.
Reason for treatment switch (if available)	Outcomes	Reason for switch among anticoagulants (if available)
Discontinuation	Outcome	Discontinuation will be identified from direct annotations in electronic health records. When no annotation is made, treatment administration continuation is assumed.
Time-to-discontinuation	Outcome	Time to discontinuation will be defined as the number of days from the date of the first Drug X prescription to the date of discontinuation.

5.2 SAFETY ENDPOINTS

Variable	Role	Operational definition *
Time to minor bleeding	Secondary endpoint	Time to minor bleeding will be calculated as the number of days from the index date to the date of minor bleeding. Consider only for patients without treatment switch.
Time to major bleeding	Secondary endpoint	Time to major bleeding will be calculated as the time from the index date to the date of stroke/SE or major bleeding. Consider only for patients without treatment switch.
Time to stroke/SE	Secondary endpoint	Time to stroke/SE will be calculated as the time from the index date to the date of stroke/SE or major bleeding. Consider only for patients without treatment switch.
Major bleeding	Outcome	A flag will be created for patients with any major bleeding claims since the baseline period.
Gastrointestinal bleeding	Outcome	A flag will be created for patients with any gastrointestinal bleeding claims since the baseline period.
Minor bleeding	Outcome	A flag will be created for patients with any minor bleeding claims since the baseline period.
Intracranial haemorrhage	Outcome	A flag will be created for patients with any intracranial bleeding claims since the baseline period.
Stroke or SE	Outcome	A flag will be created for patients with any stroke or SE claims since the baseline period. Stroke or SE will be classified into 3 categories: ischemic stroke, haemorrhage stroke, and SE.
Comorbidities	Post-Baseline characteristic	A flag will be created for patients with comorbidities: Diabetes mellitus, renal disease, haemodialysis,

		hypertension, congestive heart failure, thrombocytopenia myocardial infarction, dyspepsia, peripheral vascular disease, TIA, coronary artery disease, chronic pulmonary disease, etc. claims since the baseline period
International Normalized Ratio (INR) determination	Outcome	International Normalized Ratio (INR) determination a stroke or bleed and prior to the moment of medication switch
Time in therapeutic range (TTR)	Outcome	TTR will be defined as the duration of time in which the patient's INR values were within a desired range

A variety of definitions of major bleeding have been used in published clinical studies, and this diversity adds to the difficulty in comparing data between trials and in performing meta-analyses. The definition of major bleeding in non-surgical patients was discussed at the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (17). A definition was developed that should be applicable to studies with all agents that interfere with haemostasis, including anticoagulants, platelet function inhibitors and fibrinolytic drugs.

Major Bleeding

- **Major Bleeding in Non-Surgical Patients**

1. Fatal bleeding, and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or

3. Bleeding causing a fall in haemoglobin level of 2g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

- **Major Bleeding in Surgical Patients**

1. Fatal bleeding, and/or

2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon. and/or

3. Extrasurgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding. and/or

4. Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by

delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection. and/or

5. Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.

6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).

Minor Bleeding

All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not.

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

1. A hospital admission for bleeding, or

2. A physician guided medical or surgical treatment for bleeding, or

3. A change in antithrombotic therapy (including interruption or discontinuation of study drug).

5.3 OTHER ENDPOINTS

None.

5.4 COVARIATES

Variable	Role	Operational definition [a]
Age	Baseline characteristic and potential confounder	Age will be defined as of the index date.
Age group	Baseline characteristic and potential confounder	Age will be classified in the following levels: 18-64 years; 65-74 years; 75-85 years; >65; >75; >85
Weight	Baseline characteristic and potential confounder	Weight will be defined as of the index date.
Gender	Baseline characteristic and potential confounder	Male/Female
Spanish Geographic Region	Baseline characteristic and potential confounder	Geographic region will be captured from enrollment data.
Baseline Deyo-Charlson Comorbidity Index	Baseline characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be created during the baseline.

CHA2DS2 and CHA2DS2-VASc score	Baseline characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be created during the baseline.
HAS-BLED score	Baseline characteristic and potential confounder	HAS-BLED score will be created during the baseline prior bleed/ stroke.
Alcohol	Baseline characteristic and potential confounder	Alcohol will be defined as of the index date.
Drug abuse	Baseline characteristic and potential confounder	Drug abuse will be defined as of the index date.
Smoking status	Baseline characteristic and potential confounder	Smoking status will be defined as of the index date.
Baseline comorbidities	Baseline characteristic and potential confounder	A flag will be created for patients with comorbidities: Diabetes mellitus, renal disease, hemodialysis, hypertension, congestive heart failure, thrombocytopenia, myocardial infarction, dyspepsia, peripheral vascular disease, TIA, coronary artery disease, chronic pulmonary disease, sleep apnea syndrome, etc. claims in the baseline period
Treatment naïve	Baseline characteristic and potential confounder	Treatment naïve will be define as if patients are not treatment experienced.

6 HANDLING OF MISSING VALUES

Due to the nature of data source (unstructured free-text of the EHR generated during routine clinical practice), missing data elements in EMRs have to be differentiated between "true zero", or null. Bearing in mind that physicians tend to write down relevant data, in terms of data calculations, these patients must be included in the percentage calculations unless otherwise specified. The number of patients with missing data will be shown in the analysis for discrete and continuous variables.

In general, no imputation is planned for missing data, but missing data mechanisms will be evaluated to determine appropriate methods for handling missing data when necessary (e.g. multiple imputation). A thorough description of the imputation procedure to ensure the transparency and reproducibility of the analysis will be provided.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Frequency tables will be performed for categorical variables, whereas continuous variables will be described by means of summary tables that may include the mean, standard deviation, median and quartiles of each variable. The number of non-evaluable outcomes and of missing data will also be provided. Transformations will be considered where appropriate.

A sensitivity analysis will be performed to deal outliers if necessary.

Data such as medical history, life-style conditions, family history, signs and symptoms, general findings, evaluation findings and surgical interventions are coded according to the SAVANA terminology (SNOMED CT based) and will be tabulated by SOC/location and PT. Medications and substance use are coded according to the Anatomical Therapeutic Chemical (ATC) classification system and will be tabulated by ATC levels 1 and 5 (18).

Due to the non-randomized nature of the study, the propensity score matching (PSM) technique will be used to control for confounders when comparing the cohorts. A 1:1 PS matched sample will be used as the overall sample to explore treatment effect heterogeneity of paired comparisons throughout the range of patients' baseline characteristics.

After PSM, no significant differences are expected among all pre-index measures between the patient cohorts, and the treatment effect that is calculated based on the matched population is considered to be the true effect. PSM with a different ratio (1:2 or 1:3) can also be considered if the matched sample size using a ratio of 1:1 is too small. Covariates to be included in the logistic regression model will include variables such as age, geographic region, CCI score, and comorbidities. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing the pre-matched descriptive tables and post-matched pre-index measures.

R software v. 4.0.3 or superior will be used for all statistical analysis outputs.

7.2 STATISTICAL ANALYSES

7.2.1 Safety Analyses

Post-baseline data, corresponding to the follow up period, such as clinical characteristics, physical examination, vital signs, laboratory values, relevant medical history, complications, signs and symptoms, general findings, evaluation findings, surgical interventions and medications and substance use will be described.

In case of laboratory values with multiple measurements per subject before the time of evaluation, the last value prior to or on the first day of procedure will be considered.

7.2.2 Analyses of primary endpoint

Summary tables will be prepared with the patient demographics, clinical characteristics, life-style conditions, laboratory values, family history, relevant medical history, signs and symptoms, general findings, evaluation findings, surgical interventions and medications and substance use at baseline and follow up period in order to respond to the first primary objective. Additional variables which are annotated by physicians in the clinical records could be added.

Analysis of the primary endpoints will be performed in the Full analysis set population.

7.2.3 Analyses of secondary endpoints

Summary tables will be prepared in order to describe treatment pathway, including initial treatment, switching treatment, treatment after switch, discontinuation, reasons for switching and discontinuation (if available), and clinical events preceding or following a switch of treatment.

To evaluate the second secondary objective, it will be considered the cumulative incidence rate for clinical outcomes (minor/major bleeding event and stroke/SE). The incidence rate will be calculated as the number of patients who experience the event divided by the observed time at risk. An unadjusted Kaplan Meier curve will be drawn to illustrate time-to-event.

In order to evaluate the third secondary objective, after PSM, the rate of stroke/SE and minor and major bleeding in each PSM cohort will be evaluated with Cox proportional hazard models. OAC treatments will be included as predictor variables with no other covariates .

Healthcare resource use analyses will consider hospitalizations and visits to specialist services, according to their relationship with bleeding and stroke-related complications, in terms of mean length of admission days per patient and number of visits to each specialist services during the follow up period respectively.

Analysis of the secondary endpoints will be performed in the Full analysis set population as well as each data set based on the propensity scores generated.

8 LIST OF TABLES AND TABLE SHELLS

Will be included once protocol is approved.

9 REFERENCES

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10 APPENDICES

None.

10.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

None.

A1.2 Further definition of endpoints

None.

10.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

A2.1 Further Details of the Statistical Methods

None.

10.3 APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

Data such as medical history, life-style conditions, family history, signs and symptoms, general findings, evaluation findings and surgical interventions are coded according to the SAVANA terminology (SNOMED CT based) and will be tabulated by SOC/location and PT. Medications and substance use are coded according to the Anatomical Therapeutic Chemical (ATC) classification system and will be tabulated by ATC levels 1 and 5 (18).

18.5. Appendix 5. Sample Case Report Form (CRF) / Data Collection Tool (DCT))

Not applicable

18.6. Appendix 6. Sample standard subject Information Sheet and Informed Consent Document (ICD)

Not applicable

18.7. Appendix 7. List of subject data listings

Not applicable

18.7.1. ***Appendix 7.1 Withdrawn Subjects***

18.7.2. ***Appendix 7.2 Protocol Deviations***

18.7.3. ***Appendix 7.3 Subjects Excluded from the Analysis***

18.7.4. ***Appendix 7.4 Demographic Data***

18.7.5. ***Appendix 7.5 Medication/Treatment Data***

18.7.6. ***Appendix 7.6 Endpoint Data***

18.7.7. ***Appendix 7.7 Adverse Events***

This study involved a combination of existing unstructured and structured data from EHRs (secondary use of data). Data from EHRs were pseudonymized and aggregated into a single database, thus precluding Savana and the investigator from tracing terms potentially related with adverse events (AEs) to individual patients. Following the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (module VI: collection, management, and submission of reports of suspected adverse reactions to medicinal products, Rev 2 and module VIII: post-authorization safety studies, Rev3) regarding AE reporting in non-interventional post-authorization studies with a design based on secondary use of data, no individual case safety reports were submitted.

18.7.8. ***Appendix 7.8 Laboratory listings***

18.8. Appendix 8. Additional documents

Not applicable