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Statistical Analysis Plan

BI Study Number 1160-0297

Protocol Version 1.0. Date: 24 May 2019

Non-Interventional, cross-sectional study to describe NOACs management in elderly patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-BELD Study

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan <Version 1.0, 08 JULY 2020> for Protocol 1160-0297.

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[redacted]

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1. ABBREVIATIONS

ACE	Angiotensin Converting Enzyme inhibitors
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AIDs	Acquired immune deficiency syndrome
ALT	Alanine Aminotransferase
ARB	Angiotensin-Receptor Blockers
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BID	Twice a day
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age (> 75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex Category
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	Case Report Form
eCRF	Electronic Case Report Form
EHRA	European Heart Rhythm Association
GFR	Glomerular Filtration Rate
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol.
ICH	Intracranial haemorrhage
ICH-GCP	Harmonized Tripartite Guideline for Good Clinical Practice
INR	International Normalized Ratio
LVEF	Left ventricular ejection fraction
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
PCI	Percutaneous coronary intervention

PT	Preferred Terms
QD	Once a day
SADR	Serious Adverse Drug Reaction
SAHS	Sleep apnoea-hypopnoea syndrome
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOPs	Standard Operating Procedures
TIA	Transitory ischemic attack
TLF	Tables/Listings/Figures
VKA	Vitamin K Antagonist

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of treatment patterns and patient profile. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 1.0, dated 24 May 2019 and case report forms (CRFs) version 2, dated 10 March 2020.

3. STUDY OBJECTIVES

This study has been designed in order to describe the current non-vitamin K antagonist oral anticoagulants (NOACs) management in elderly patients in Spain.

3.1 Primary Objectives

The primary objective is to describe the pattern of usage of NOACs prescribed according to their Summary of Product Characteristics (SmPC), by current NOAC type and dose, in elderly patients (≥75 years-old) with non-valvular atrial fibrillation (NVAF) at the time of the study visit.

3.2 Secondary Objectives

The secondary objectives are:

1. To describe patients' characteristics at the time of the study visit by current NOAC type stratified by duration since first NOAC initiation.
2. To describe OAC treatment management since first NOAC initiation until the study visit by duration since first NOAC initiation: previous vitamin K antagonists (VKA) treatment, first NOAC treatment duration, dose changes, switch between NOACs and

reasons for switch, total NOAC treatment duration and additional antiplatelet treatment.

3. To describe the Clinical Frailty Scale grading, CFS (1), at the time of the study visit, by current NOAC type.
4. To describe first NOAC usage by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.

Further objective: To evaluate the appropriateness of prescribed therapy based on Spanish health authorities' recommendations (2) (therapeutic positioning report) and other regional guidelines by NOAC type (if there are enough patients for a NOAC type), at the time of first NOAC initiation.

4. STUDY DESIGN

4.1 General Description

This is an observational, multicenter and cross-sectional study in NVAF elderly patients currently on NOAC treatment for their stroke prevention.

AF is classified as non-valvular AF in the absence of mitral stenosis or cardiac valvular prosthesis, since NOACs are not recommended for patients with mechanical heart valve (level of evidence B) or moderate to severe mitral stenosis (level of evidence C) (3).

The study will be conducted in approximately 50 sites in Spain. Investigators from different specialties are planned to be included as follows: 35 cardiologists, 10 hematologists and 5 geriatricians.

The design of the study imposes a single visit to be performed for the informed consent signature and data collection that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

A specific therapeutic strategy has already been assigned to each included patient, based on routine practice and without interference with the physician's prescription habits. The observational nature of the study is ensured as no diagnostic or therapeutic intervention outside of routine clinical practice will be applied.

Cardiology, hematology, geriatric services at a hospital setting, specialty medical offices and nursing homes, who regularly prescribe NOACs for stroke prevention in NVAF patients may be invited to participate.

The number of patients per site to be included in the study will be initially set up to a maximum of 10 patients per site. Once the 50% of the participating sites have been initiated, the recruitment will become competitive until the end of the study and the limitation of 10 patients per site will be removed to allow sites to continue with the recruitment.

4.2 Study size

It is planned that a total of approximately 500 patients will be recruited for the study. Based on such a sample size estimate, categorical variables of binomial proportions (e.g. sex) will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in the following Table 1. Calculations of the confidence intervals (CI) are based on the Clopper-Pearson method:

Table 1. Width of 95% confidence interval by prevalence

Prevalence of attribute	Sample size 500
10% Expected n 95% CI width	50 5.46%
20% Expected n 95% CI width	100 7.20%
30% Expected n 95% CI width	150 8.22%
40% Expected n 95% CI width	200 8.76%
50% Expected n 95% CI width	250 8.76%

4.3 Description of treatment

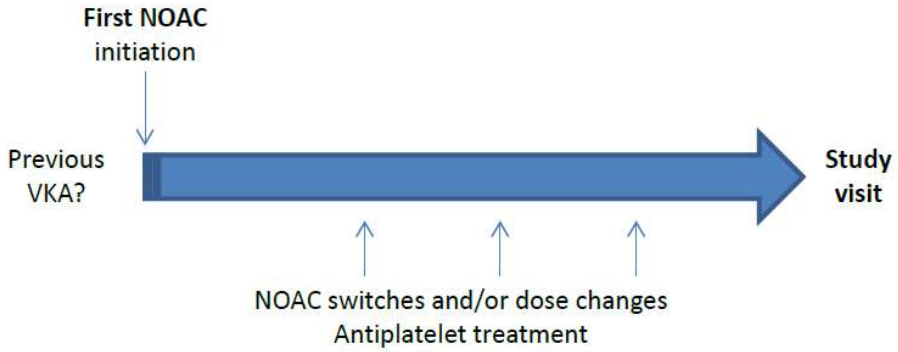
Patients in this study will be currently on treatment with NOAC for their NVAF, according to the indication approved in their SmPC, and initiated it at least 3 months before the study visit. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before considering the participation in the study.

In addition, no intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

4.4 Study flow/schedule

The design of the study imposes a single visit to be performed for the informed consent signature and data collection that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

Figure 1. Study scheme for study period



After signing the informed consent, investigator will assess the Clinical Frailty Scale (1), the Modified EHRA scale for AF related symptoms (4), the NYHA classification of heart failure (5) and the CHA2DS2-VASc and HAS-BLED scales and include the scores directly in eCRF after evaluating the patient's functional status and patient's medical records. The investigator will review the medical records in order to complete other variables needed to address study objectives that will mainly be obtained directly from patient medical records or requested to the patient at the study visit if not available in medical records. The end of the single study visit is the end of the study for each patient.

4.5 Schedule of Events

The schedule of events can be found in Section 6 of the protocol (Milestones).

4.6 Changes to Analysis from Protocol

Per protocol, the variable "reason for VKA switch will be described under the OAC treatment management outcome. Finally, reason for VKA treatment switch has not been collected specifically in the VKA section of the CRF. This has been deleted from section 14.2.2 of SAP.

New analysis not included in the final protocol have been considered:

- Antiplatelet treatment according to current NOAC type
- Treatment received at the moment of thromboembolic and bleeding events.
- For all NOACs, the different doses that patients take according to HAS-BLED score.
- Underdosed and overdosed patients (for current NOAC treatment).
- HAS-BLED total score according to NOAC and antiplatelet current treatment.
- Multivariate model to evaluate the association between the Clinical Frailty Scale (dependent variable) and the thromboembolic and the bleeding events (independent variables). To calculate this analysis, only events that have occurred subsequent to the start of anticoagulant therapy (not those prior to the start of VKA / NOACs) will be considered. Univariate analysis will be performed. All variables which have a P value of less than 0.1 will be included in the multivariate analysis.

5. PLANNED ANALYSES

5.1 Interim Analysis

No interim analysis has been planned.

5.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by [redacted] Real-World Evidence Solutions (RWES) Biostatistics following [redacted] SOPs. Final CSR will be performed using Boehringer Ingelheim template.

6. ANALYSIS SETS

6.1 All Subjects Enrolled Set [ENR]

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study.

6.2 Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled subjects who provide informed consent for this study (ENR set) and fulfill all selection criteria. This is called “eligible patients” in the protocol.

Patients will be included in FAS if all of the following criteria are met:

1. Patients are willing and provide written informed consent prior to participate in this study
2. Patients ≥ 75 years-old at the time of the study visit.
3. Patients with a diagnosis of non-valvular atrial fibrillation (NVAF).

4. Patients who are being treated with NOAC treatment according to the indication approved in the SmPC.
5. Patients who have started the NOAC treatment at least 3 months prior to the study visit.

Patients will be excluded from participating in this study, and will be excluded from this analysis set, if the following criterion is met:

1. Current participation in any clinical trial of a drug or device.
2. Patients who have any contraindication for NOAC treatment, according to the SmPC.

6.3 Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all enrolled subjects who receive at least one documented dose of Pradaxa®.

7. GENERAL CONSIDERATIONS

The design of the study imposes a single visit to be performed and that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

Data will be collected through an eCRF which will include all the study variables. Investigator will enter patient data in eCRF. Variables collected at the time of the study visit (including those related to the first NOAC initiation) will be obtained based on and limited to those available in the medical records of the selected patients. Demographic characteristics, smoking habit and alcohol consumption may be asked to the patient at the study visit if not available in the medical records. LVEF measurement will be obtained from the last images available for the patient.

Clinical Frailty Scale, modified EHRA scale for AF related symptoms, NYHA classification for heart failure, CHA2DS2-VASc and HAS-BLED scores will be assessed by the investigators at the study visit by evaluating the patient's functional status and medical records and the values will be directly included in the eCRF.

Final score for the Comorbidities Charlson Index will be automatically calculated based on the answers individually entered by the investigator in the eCRF for each index item (6).

Any required missing data to calculate the score for the scales or the Comorbidities Charlson Index may be asked to the patient at the study visit if not available in the medical records and should be documented, however the final score number obtained by the investigator from this information will not need to be included in medical records.

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Administrative reasons (i.e. study rejected by the hospital director)
3. Violation of GxP (as applicable), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

7.1 Reference Start/End Date

Reference start date is date of study visit, collected in the eCRF as a mandatory variable.

7.2 Common Calculations

7.2.1 Weight

Weight (kg) will be categorized in two categories according to dose adjustment criteria in NOAC:

- ≤60 kg
- >60 kg

7.2.2 Body Mass Index (BMI)

The formula to obtain Body Mass Index is the following: BMI (kg/ m^2) = weight (kg)/ height^2 (m) and BMI will be categorized into 5 categories according to the World Health Organization (WHO):

- Underweight: BMI< 18.5 kg/m^2
- Normal weight: 18.5 kg m^2<= BMI<= 25 kg/m^2
- Overweight: 25 kg/m^2< BMI<= 30 kg/m^2
- Obese: 30 kg/m^2<BMI<= 35 kg/m^2
- Severely Obese: BMI> 35 kg/m^2

7.2.3 Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) predicts the ten-year mortality for patients presenting one or more of the conditions in the model, where the age groups and each condition are awarded a specific number of points, some conditions weighing more than others, based on the adjusted risk of mortality. The more points given, the more likely the predicted adverse outcome. The index then sums the points and offers a 10-year survival/ mortality prognosis.

https://www.thecalculator.co/health/Charlson-Comorbidity-Index-(CCI)-Calculator-765.html
https://www.mdcalc.com/charlson-comorbidity-index-cci

Each of the conditions listed below are awarded 1, 2, 3 or 6 points depending on the mortality risk. CCI will be calculated as the sum of all points included in the following table:

Table 2. Point assigned to Charlson Comorbidity Index

	POINTS
Age	
50–59 years	+1
60–69 years	+2
70–79 years	+3
>=80 years	+4
Myocardial infarction	+1
Congestive Heart Failure (CHF)	+1
Peripheral vascular disease	+1
Cerebrovascular Accident or Transient ischemic attack	+1
COPD	+1
Connective tissue disease	+1
Peptic ulcer disease	+1
Liver disease	
Mild	+1
Moderate to severe	+3
Diabetes mellitus	
Uncomplicated	+1
End-organ damage	+2
Hemiplegia	+2
Moderate to severe* Chronic Kidney Disease (CKD)	+2
Solid tumor	
Localized	+2
Metastatic	+6
Leukemia	+2
Lymphoma	+2
AIDS	+6

7.2.4 Laboratory values

7.2.4.1 Serum creatinine

Serum creatinine will be categorized in two categories (7):

- Normal levels: 0.6-1.2 mg/dl in males and 0.5-1.1 mg/dl in females
- High/low levels

7.2.4.2 Creatinine clearance

Creatinine clearance will be estimated using Cockcroft-Gault formula (7):

CCr = (140 – Age(years)) x Weight (kg) x [0.85 if female] / 72 x [Serum Creatinine (mg/dL)]

Chronic Kidney Disease will be categorized according to these values, included in Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification:

- ≥90: Kidney damage with normal or increased glomerular filtration rate (GFR)
- 60-89: Kidney damage with mild decreased GFR
- 30-59: Moderate decrease in GFR
- 15-29: Severe decrease in GFR
- <15: Kidney failure

7.2.4.3 ALT, AST and bilirubin values

ALT, AST and bilirubin will be categorized in two categories, according to [redacted] (https://www [redacted].org/tests-procedures/liver-function-tests/about/pac-20394595):

ALT (GPT):

- Normal values: 7-55 UI/L
- High/low values

AST (GOT):

- Normal values: 8-48 UI/L
- High/low values

Bilirubin:

- Normal values: 0.2-1.2 mg/dl
- High/low values

7.2.4.4 Haemoglobin and platelets

Haemoglobin and platelets levels will be categorized in two categories, according to American cancer society (https://www.cancer.org/content/dam/CRC/PDF/Public/7174.pdf):

Haemoglobin:

- Normal values: 12-18 g/dL
- High/low values

Platelets:

- Normal values: 150-450 x103/µL
- High/low values

7.2.5 Time since NVAF diagnosis

The number of years since diagnosis will be obtained from number of years between date of NVAF diagnosis and date of study visit as follows:

Time of NVAF evolution (years) = (date of study visit – date of NVAF diagnosis + 1)/(365.25).

7.2.6 Duration of VKA treatment

VKA treatment duration in years will be calculated as number of months/12 (in case of months specified). In case of more than one VKA treatment, the total VKA treatment duration will be calculated as the sum of the years in treatment of each one.

7.2.7 Duration since the first NOAC

The number of months since the first NOAC initiation date until the study visit date will be obtained as follows:

Duration since the first NOAC (months) = (date of study visit – date of first NOAC + 1)/(30.5).

Duration since the first NOAC initiation until study visit will be categorized as >4 months and ≤4 months.

7.2.8 Duration since NVAF diagnosis until first NOAC initiation

The number of months since the NVAF diagnosis date until the first NOAC initiation date will be obtained as follows:

Duration since the NVAF diagnosis until first NOAC initiation (months) = (date of first NOAC – date of NVAF diagnosis + 1)/(30.5).

7.2.9 Duration of first NOAC treatment

The duration of the first NOAC treatment will be calculated as the number of years (or months, depending on the data) between stop date and start date for the NOAC treatment with the minimum start date:

Duration of the first NOAC (years) = (stop date of first NOAC – start date of first NOAC + 1)/(365.25)

or

Duration of the first NOAC (months) = (stop date of first NOAC – start date of first NOAC + 1)/(30.5)

In the case the first NOAC has not been finished, the study visit date will be considered as the stop date (censured cases).

7.2.10 Duration of new NOAC treatments

The duration of new NOAC treatment will be calculated as the number of years (or months, depending on the data) between stop date and start date for the new NOAC treatment:

Duration of the new NOAC (years) = (stop date of new NOAC – start date of new NOAC + 1)/(365.25).

or

Duration of the new NOAC (months) = (stop date of new NOAC – start date of new NOAC + 1)/(30.5).

In the case the new NOAC has not been finished, the study visit date will be considered as the stop date.

7.2.11 Total time in NOAC treatment

NOAC treatment duration in years will be calculated as the sum of the years of each NOAC treatment. The duration of the each NOAC treatment will be calculated as:

Duration of each NOAC (years) = (stop date of NOAC – start date of NOAC + 1)/(365.25).

For the last NOAC treatment (receiving at study visit) the stop date will be the study visit date.

In other hand, in the case there are periods of interruption of the NOAC treatment, only the time that they have been in treatment will be considered. In this case, the time in each period will be calculated from the previous formula, adding the different periods in treatment.

7.2.12 Number of switches

The number of switches will be defined as the number of changes to another NOAC.

7.2.13 Total time in treatment with antiplatelet agents

Time in treatment with antiplatelet agents (in years or months) will be calculated as the sum of the years of each antiplatelet treatment. The duration of each antiplatelet treatment will be calculated as:

Duration of the each antiplatelet (years) = (stop date of antiplatelet – start date of antiplatelet + 1)/(365.25).

or

Duration of the each antiplatelet (months) = (stop date of antiplatelet – start date of antiplatelet + 1)/(30.5).

For the last antiplatelet treatment (if it is received at study visit) the stop date will be the study visit date.

7.2.14 Clinical Frailty Scale (CFS)

The CFS score will be categorized in two categories, according to this ranges:

1) Frailty patients - CFS scoring >4
2) Non-frailty patients - CFS scoring ≤4

7.2.15 CHA2DS2-VASc Scale

The CHA2DS2-VASc total score will be categorized in three categories, according to the risk of stroke (8):

1) Low risk (score 0 in male; score 1 in female)
2) Moderate risk (score 1 in male; score 2 in female)
3) High risk (score ≥2 in male; score ≥3 in female)

   Note: In the last update of European Society of Cardiology (ESC) guidelines 2016 the "female gender" is no longer considered by itself as an increase of the risk.

7.2.16 HAS-BLED Scale

The HAS-BLED total score will be categorized in three categories, according to the bleeding risk (9):

1) Low risk (score 0)
2) Intermediate risk (score 1-2)
3) High risk (score ≥3)

7.2.17 Underdosed or overdosed patient (current NOAC treatment)

The recommended dose of dabigatran is 150mg twice a day (BID). Patients who meet any of the following criteria should perform a dose adjustment to 110mg BID, so those who receive the recommended dose of 150mg BID will be classified as overdosed. Those who receive a 110mg BID dose and do not meet any of the following criteria will be classified as underdosed:

- Age ≥80 years
- Patients aged 75-79 years and HAS-BLED ≥ 3
- Moderate renal impairment (creatinine clearance 30-50mL/min)

The recommended dose of rivaroxaban is 20mg once a day (QD). Patients who meet the following criteria should perform a dose adjustment to 15mg QD, so those who receive the recommended dose of 20mg QD will be classified as overdosed. Those who receive a 15mg QD dose and do not meet following criteria will be classified as underdosed:

- Moderate renal impairment (creatinine clearance 30-50mL/min) or severe renal impairment (creatinine clearance 15-29mL/min)

The recommended dose of apixaban is 5mg BID. Patients who meet at least 2 of the following 3 criteria should perform a dose adjustment to 2.5mg BID, so those who receive the

recommended dose of 5mg BID will be classified as overdosed. Those who receive a 2.5mg BID dose and do not meet at least 2 of the 3 following criteria will be classified as underdosed:

- Age ≥80 years
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1,5 mg/dl or severe renal impairment (creatinine clearance 15-29mL/min)

The recommended dose of edoxaban is 60mg OD. Patients who meet at least 1 of the following 2 criteria should perform a dose adjustment to 30mg OD, so those who receive the recommended dose of 60mg OD will be classified as overdosed. Those who receive a 30mg OD dose and do not meet at least 1 of the 2 following criteria will be classified as underdosed:

- Body weight ≤ 60 kg
- Moderate or severe renal impairment (creatinine clearance 15-50mL/min)

A categorical variable for dose category with 3 levels will be described:

1) Appropriately dosed
2) Underdosed
3) Overdosed.

7.3 Software Version

All analyses will be conducted using SAS Enterprise Guide version 7.15.

8. STATISTICAL CONSIDERATIONS

Continuous variables will be described by the number of patients with valid/missing observations, mean, SD, median, 25 and 75 percentiles (Q1 and Q3, respectively), minimum and maximum and categorical variables will be described by frequencies and related percentages. Appendix 1 on page 42 shows the summary TLFs to be provided in the report of the study.

8.1 Statistical Bias Reduction

No statistical methods for handling bias will be used. Given the real-world nature of the data and the descriptive purposes of the study objectives no confounding factor have been identified.

Missing values and drop-outs will be counted in all description of variables, but no imputation will be considered.

8.2 Statistical Tests and Confidence Intervals

No statistical test will be performed.

8.3 Adjustments for Covariates and Factors to be Included in Analyses

No statistical modelling will be done. So, no adjustment for covariates and factors to be accounted for in the analyses are considered.

8.4 Missing data

Given the real-world nature of the data and the descriptive purposes of most of the study objectives, study variables will not be imputed. Missing values and drop-outs will be counted

in all description of variables, but no imputation will be considered. Only date data where the exact day is missing will be imputed, being replaced by the middle of the month.

8.5 Examination of Subgroups

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences within subgroups. The following subgroups will be assessed and described within the exploratory analysis sections (a minimum of 50 patients will be required for each subgroups).

For the primary objective (the pattern of NOAC usage):

- Sex:
  - Female
  - Male
- Age at the time of the study visit:
  - 75-79 years
  - 80-84 years
  - ≥85 years
- Presence of each comorbidities at the time of the study visit (heart failure, coronary artery disease, peripheral vascular disease diabetes, chronic kidney disease, liver disease, cancer):
  - No
  - Yes

For the secondary objectives (Patient's characteristics at the time of the study visit and OAC treatment management):

- Duration since the first NOAC initiation date until the study visit:

- ≤4 months
- > 4 months

9. OUTPUT PRESENTATIONS

Tables and Figures on page 42 describe the presentations for this study and therefore the format and content of the summary TLFs to be provided by [redacted]

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition, withdrawals, and protocol violations (as defined in section 6.2), including inclusion and exclusion criteria will be presented for all enrolled patients.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS.

The following demographic and other baseline characteristics, related to secondary outcome, will be collected from medical records or at study visit to describe the patient's characteristics:

Table 3. Patient characteristics at the time of study visit

Variable	Obtained from medical records	Obtained at the study visit
Demographic characteristics: Age, sex, height, weight, BMI, caregiver (Yes/No), place where patient is living (Home alone; At home with	x	x

Variable	Obtained from medical records	Obtained at the study visit
partner/other family member/a friend; Other's home (e.g family member's); Nursing home)		
Smoking habit (past/current/non-smoker) and alcohol consumption (casual or non-consumer/habitual/abuse/dependence)	x	x
Analytical lab results (from last available blood sample analysis): - Kidney function: serum creatinine (mg/dl), creatinine clearance (Cockcroft-Gault calculation) - Liver function: AST/ALT (UI/L), total bilirubin (mg/dl) - Haemoglobin (g/dl) and platelet levels (x uL)	x	
NVAF: - Diagnosis date (month and year) - Type (persistent, long standing persistent, permanent, paroxysmal) - Modified EHRA scale for AF related symptoms	x	x (mEHRA scale)
Procedures and interventions: - Cardioversion/Ablation (Yes/No) - Coronary interventions (Yes/No): Percutaneous coronary intervention (PCI)/Coronary Artery Bypass Grafting (CABG) - Pacemaker carrier (Yes/No)	x	

Variable	Obtained from medical records	Obtained at the study visit
Comorbidities and Clinical Risk Factors: - Heart Failure (Yes/No, New York Heart Association (NYHA) classification; Left Ventricular Ejection Fraction, LVEF, %) - Coronary artery disease (Yes/No) - Sleep apnoea-hypopnoea syndrome (SAHS) (Yes/No) - Hypertension (Yes/No) -Hyperlipidemia (Yes/No) - Comorbidity Charlson index (Yes/No; total score): myocardial infarction (already collected for history of thromboembolic events), congestive heart failure (already collected for the NHYA scale scoring), cerebral and peripheral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild/moderate/severe liver disease, diabetes, diabetes with end-organ damage, hemiplegia, moderate/severe renal disease, any solid tumor, metastatic solid tumor, leukemia, lymphoma AIDs, age (already collected as a demographic characteristic). -History of thromboembolic events (Yes/No, number and date): TIA, ischemic stroke, hemorrhagic stroke, embolism systemic, deep vein thrombosis, pulmonary embolism, stable angina, unstable angina, myocardial infarction with/without ST segment elevation; and bleeding events (Yes/No, number and date): intracranial, digestive, genitourinary, gingival, nasal, pulmonary, articular-muscular, conjunctival.	x	x (NYHA classification, Charlson Index)
CHA2DS2-VASc (total score)		x
HAS-BLED (total score)		x
Clinical Frailty Scale		x
Previous vitamin K antagonist (VKA) treatment (yes/no), type (acenocoumarol or warfarin), start date and treatment duration		
Other concomitant treatments (Total number of current concomitant drugs; Type (Yes/No, number): ARB or ACE inhibitor, Beta-blocker, Calcium channel blockers, Diuretics, Amiodarone, Statin, Proton pump inhibitor, H2-receptor antagonist, Digoxin, NSAIDs, Dronedarone, Other antiarrhythmics, ketoconazole (systemic), cyclosporine, itraconazole	x	

11.1 Derivations

Derived variables are specified in section 7.2 Common Calculations on page 18 in this SAP.

12. MEDICATIONS

Medications will be presented for FAS. In the case of previous treatment with VKA, type, treatment duration will be presented.

Other concomitant treatments in the study visit (ARB or ACE inhibitor, Beta-blocker, Calcium channel blockers, Diuretics, Amiodarone, Statin, Proton pump inhibitor, H2-receptor antagonist, Digoxin, NSAIDs, Dronedarone, Other antiarrhythmics, ketoconazole (systemic), cyclosporine, itraconazole) will be presented.

History and current antiplatelet treatment will be described.

13. STUDY MEDICATION EXPOSURE

Patients in this study will have been prescribed a NOAC treatment for their NVAF. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before considering the participation in the study.

14. OUTCOMES

14.1 Primary Outcome

The primary outcome is the pattern of usage of non-vitamin K oral anticoagulants (NOACs) prescribed according to their Summary of Product Characteristics (SmPC), based on the percentage of patients by NOAC type and dose the patient is taking at the time of the study visit. Timeframe to complete data collection for this outcome is one day, the study visit day.

Table 4. Primary variable collected at the time of the study visit

Variable	Obtained from medical records
Current NOAC active substance and dose	x

14.1.1 Primary Analysis of Primary Outcome

The primary outcome analysis will be performed for the FAS. For the primary objective, the pattern of usage of NOAC will be described as the percentage of patients by NOAC type and dose.

The pattern of NOAC usage will be also analyzed descriptively by the following subgroups, if a minimum of 50 patients have been included in the required subgroups:

- Sex (female, male)
- Age at the time of the study visit (75-79, 80-84, ≥85 years)
- Comorbidities at the time of the study visit: heart failure, coronary artery disease, peripheral vascular disease, diabetes, chronic kidney disease, liver disease and cancer.

14.2 Secondary Outcomes

14.2.1 Patient's characteristics

Patient's characteristics at the time of the study visit by the NOAC type that the patient is taking at the time of the study visit. Patients will be also stratified by the duration since the

first NOAC initiation date until the study visit date (>4 months / ≤4 months) (See Patient's characteristics: refer to Section 11, Table 3.).

14.2.2 OAC treatment management

OAC treatment management (since first NOAC initiation until the study visit date), based on the following variables:

- Previous vitamin K antagonist (VKA) treatment (yes/no), VKA treatment duration in years
- Duration since NVAF diagnosis until first NOAC initiation,
- Duration of first NOAC treatment (first NOAC active substance, start and stop date, first NOAC dose and its dose changes),
- Switch to new NOAC (active substance, start/stop date, dose and dose changes, reason for switch to new NOAC): number of patients that switch their first or further NOAC and mean number of switches.
- Total time in NOAC treatment
- History and current antiplatelet treatment (yes/no, start date, end date, active substance).

Patients will be also stratified by the duration since the first NOAC initiation date until the study visit date (> 4 months / ≤4 months).

14.2.3 Clinical Frailty Scale

Clinical Frailty Scale grading at the time of the study visit, by current NOAC type.

14.2.4 Prevention strategy

The first NOAC usage by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.

14.3 Analysis of Secondary Outcomes

All analysis of secondary outcomes will be performed for the FAS.

14.3.1 Patient's characteristics

Patient's characteristics at the time of the study visit will be summarized descriptively by current NOAC type. Patients will be also stratified by duration since the first NOAC initiation until the study visit date (>4 months / ≤4 months). All covariates related to patient's characteristics (refer to Section 11 , Table 3.) will be analyzed descriptively by NOAC type and by the duration since the first NOAC initiation. Standardized differences between Pradaxa® and other NOACs will be estimated for these covariates. For this, a minimum of 50 patients is required for each group.

14.3.2 OAC treatment management

For OAC treatment management, descriptive analysis of previous VKA treatment (yes/no), VKA treatment duration in years, first NOAC treatment duration, first NOAC dose and dose changes, new NOAC treatment duration, new NOAC dose and dose changes. Duration since NVAF diagnosis until first NOAC initiation and total time in NOAC treatment will be described. Also, the reason for switches, the number of patients that switched their first or further NOAC and mean number of switches will be presented. Antiplatelet use will be also summarized.

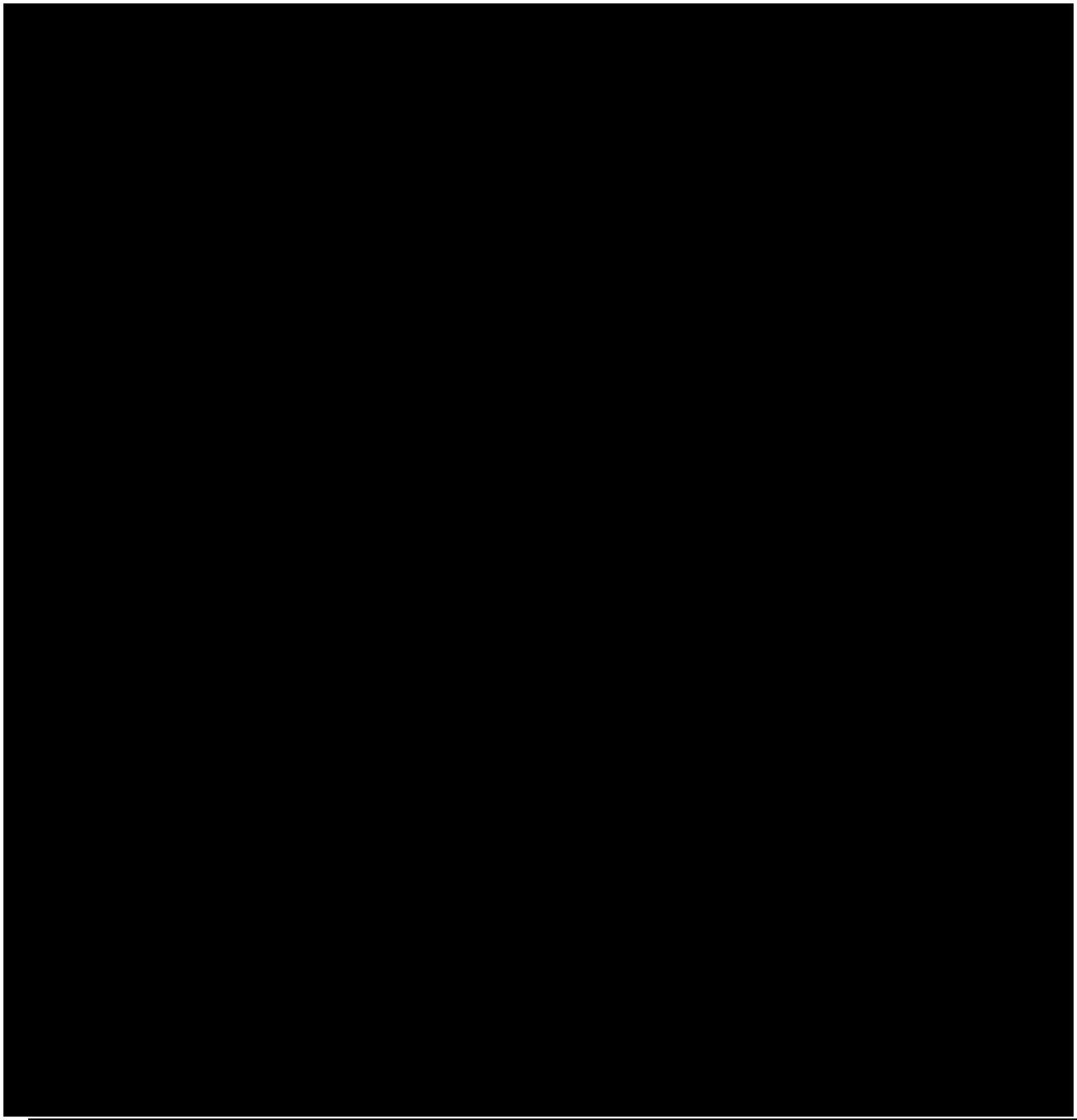
The subgroup analysis of these outcomes by the duration since the first NOAC initiation until the study visit date (> 4 months / ≤ 4 months) will also be performed. For this subgroup analysis, a minimum of 50 patients is required for each group.

14.3.3 Clinical Frailty Scale

Clinical Frailty Scale grading at the time of the study visit by current NOAC type will be described as the number of patients on each category of frailty as evaluated by the investigator according to patient's records. In addition, CFS score will be summarized in the following two categories: Frailty patients (CFS scoring >4) and Non-frailty patients (CFS scoring ≤4).

14.3.4 Prevention strategy

First NOAC usage will be described by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.



14.6 Exploratory analysis

History and current antiplatelet treatment will be described by current NOAC type.

Treatment received at the time of thromboembolic and bleeding events will be described, including NOAC, VKA and antiplatelet treatments.

Doses of current NOAC treatment received by the patient will be described according to HAS-BLED score (as low, intermediate and high risk).

The percentage of underdosed and overdosed patients for current NOAC treatment will be described.

HAS-BLED total score (as <3, 3-5, ≥5) will be described according to NOAC and antiplatelet current treatment.

Multivariate logistic regression will be used to evaluate the association between the Clinical Frailty Scale (dependent variable: Frailty patients - CFS scoring >4 vs Non-frailty patients - CFS scoring ≤4) and the thromboembolic and the bleeding events (independent variables). To calculate this analysis, only events that have occurred subsequent to the start of anticoagulant therapy (not those prior to the start of VKA / NOACs) will be considered. Other factors will be age, sex, BMI, smoking habit, alcohol consumption, time since NVAF diagnosis, NVAF type, modified EHRA scale, procedures and interventions, comorbidity Charlson index and clinical risk factors. Univariate analysis will be performed. All variables which have a P value of less than 0.1 will be included in the multivariate analysis.

15. SAFETY

All outputs for safety analysis will be based on the Safety Analysis Set.

15.1 Adverse Drug Reactions

The percentage of patients experiencing Adverse Drug Reactions related with BI product Pradaxa®, will be presented. Number and percentage of patients reporting each type of ADRs (SOC and PT) will be reported. ADRs will be described according to type, duration (days), seriousness, reason for seriousness and outcome. Adverse Drug Reaction term (open string variable) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, the latest version available.

15.2 Serious Adverse Drug Reactions

Serious Adverse Drug Reactions (SADRs) are those ADRs recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of SADRs by SOC and PT will be prepared.

The percentage of patients experiencing serious related drug reactions (SADRs) with Pradaxa® will be presented. Number and percentage of patients reporting each type of SADRs will be reported.

15.3 Deaths

If any subjects die during Pradaxa® treatment, recorded on the "results in death" or outcome of event" as "fatal" on the (e)CRF, the information will be presented in a summary table and a data listing.

16. REFERENCES

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17. APPENDIX 1. MOCK TABLES

17.1 Eligibility

Table 5. Eligibility criteria – Patients in the FAS

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
Total enrolled patients						
Eligible patients	Eligible patients (FAS)					
	Non-Eligible patients					
Reasons for non-eligible patients	Inclusion criteria 1					
	Inclusion criteria 2					

Table 6. Main stratification variables

		Total
Total eligible (FAS)		
NOAC type at study visit	Total Dabigatran Rivaroxaban Apixaban Edoxaban	
Duration since the first NOAC initiation date until the study visit	≤4 months > 4 months	

17.2 Patient's characteristics

Total column will include description of total eligible sample (FAS).

17.2.1 Patient's characteristics according to current NOAC type

Table 7. Socio-demographic variables and habits according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
Age	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Age group	Valid N 75-79 years 80-84 years ≥85 years N missing						
Sex	Valid N Male, n (%) Female, n (%) N missing						
Weight (Kg)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Weight (Kg) cat	Valid N ≤60 kg, n (%) >60 kg, n (%) N missing						
Height (cm)	Valid N Mean (SD)						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
	Median (Q1-Q3) Min-Max N missing						
BMI (Kg/m2)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
BMI cat	Valid N Underweight: BMI< 18.5 kg/m2 Normal weight: 18.5 kg/m2<= BMI<= 25 kg/m2 Overweight: 25 kg/m2< BMI<= 30 kg/m2 Obese: 30 kg/m2<BMI<= 35 kg/m2 Severely Obese: BMI> 35 kg/m2 N missing						
Caregiver	Valid N No Yes N missing						
Place where patients is living	Valid N Home alone At home with partner/other family member/a friend Other's home (e.g. family member's) Nursing home N missing						
Smoking habit	Valid N Ex-smoker						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
	Smoker Non-smoker N missing						
Alcohol consumption	Valid N Casual Habitual Abuse Dependence N missing						

Table 8. Analytical laboratory results from the last available blood sample analysis according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
Serum creatinine (mg/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Serum creatinine Normal levels: 0.6-1.2 mg/dl in males 0.5-1.1 mg/dl in females	Valid N Normal levels High/low level N missing						
Creatinine clearance (ml/min)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Creatinine clearance (ml/min): Cockcroft and Gault formula	Valid N Mean (SD) Median (Q1-Q3)						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
	Min-Max N missing						
Creatinine clearance – range (ml/min/1.73m^2)	Valid N <15 15-29 30-59 60-89 ≥90 N missing						
AST (UI/L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
AST Normal values : 7-55 UI/L	Valid N Normal value High/low value N missing						
ALT (UI/L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
ALT Normal values: 8-48 UI/L	Valid N Normal value High/low value N missing						
Total bilirubin (mg/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Total bilirubin Normal values: 0.2-1.2 mg/dl	Valid N Normal value High/low value						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
	N missing						
Haemoglobin (g/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Haemoglobin Normal values: 12-18 g/dl	Valid N Normal value High/low value N missing						
Platelet levels (x10^3/µL)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Platelet Normal values: 150 – 450 x103/µL	Valid N Normal value High/low value N missing						

Table 9. NVAF variables according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
Years since NVAF diagnosis	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Years since NVAF diagnosis (patients treated previously with VKA)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
Years since NVAF diagnosis (patients treated with NOAC as first anticoagulant)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Type of NVAF	Valid N Persistent Long standing persistent Permanent Paroxysmal N missing						
Modified EHRA scale for AF related symptoms	Valid N 1-none 2a-mild 2b-moderate 3-severe 4-disabling N missing						

Table 10. Procedures and interventions according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
Cardioversion	Valid N No Yes N missing						
Ablation	Valid N No Yes N missing						
Coronary interventions	Valid N No						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others)
	Yes N missing						
Type of coronary interventions	Valid N Percutaneous coronary intervention Coronary artery bypass grafting N missing						
Pacemaker carrier	Valid N No Yes N missing						

Table 11. Clinical risk factors according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
Heart failure	Valid N No Yes N missing						
NYHA classification	Valid N A - No objective evidence of cardiovascular disease B - Objective evidence of minimal cardiovascular disease C - Objective evidence of moderately severe cardiovascular disease D - Objective evidence of severe cardiovascular disease N missing						
Left ventricular ejection fraction (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	N missing						
Coronary artery disease	Valid N No Yes N missing						
Sleep apnoea-hypopnoea syndrome	Valid N No Yes N missing						
Hypertension	Valid N No Yes N missing						
Hyperlipidemia	Valid N No Yes N missing						

Table 12. Charlson Comorbidity Index according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
Myocardial infarction	Valid N No Yes N missing						
Congestive heart failure	Valid N No Yes N missing						
Peripheral vascular disease	Valid N No						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	Yes N missing						
Cerebrovascular disease	Valid N No Yes N missing						
Dementia	Valid N No Yes N missing						
COPD	Valid N No Yes N missing						
Connective tissue disease	Valid N No Yes N missing						
Peptic ulcer disease	Valid N No Yes N missing						
Liver disease	Valid N Mild Moderate to severe N missing						
Diabetes mellitus	Valid N Uncomplicated End-organ damage N missing						
Hemiplegia	Valid N No Yes						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	N missing						
Moderate to severe renal disease	Valid N No Yes N missing						
Solid tumor	Valid N Localized Metastasic N missing						
Leukemia	Valid N No Yes N missing						
Lymphoma	Valid N No Yes N missing						
AIDS	Valid N No Yes N missing						
Age-adjusted Charlson Comorbidity index score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						

Table 13. History of thromboembolic events according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
History of thromboembolic events	Valid N No Yes N missing						
Number of total thromboembolic events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
TIA	Valid N No Yes N missing						
Number of TIA	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Ischemic stroke	Valid N No Yes N missing						
Number of ischemic strokes	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Hemorrhagic stroke	Valid N No Yes N missing						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
Number of hemorrhagic strokes	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Embolism systemic	Valid N No Yes N missing						
Number of embolism systemic	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Deep vein thrombosis	Valid N No Yes N missing						
Number of deep vein thrombosis	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Pulmonary embolism	Valid N No Yes N missing						
Number of pulmonary embolisms	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Stable angina	Valid N No Yes						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	N missing						
Number of stable anginas	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Unstable angina	Valid N No Yes N missing						
Number of unstable anginas	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Myocardial infarction with ST segment elevation	Valid N No Yes N missing						
Number of myocardial infarctions with ST segment elevation	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Myocardial infarction without ST segment elevation	Valid N No Yes N missing						
Number of myocardial infarctions without ST segment elevation	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						

Table 14. History of bleeding events according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
History of bleeding events	Valid N No Yes N missing						
Number of total bleeding events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Intracranial	Valid N No Yes N missing						
Number of intracranial events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Digestive	Valid N No Yes N missing						
Number of digestive events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Genitourinary	Valid N No Yes N missing						
Number of genitourinary events	Valid N Mean (SD)						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	Median (Q1-Q3) Min-Max N missing						
Gingival	Valid N No Yes N missing						
Number of gingival events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Nasal	Valid N No Yes N missing						
Number of nasal events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Pulmonary	Valid N No Yes N missing						
Number of pulmonary events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Articular-muscular	Valid N No Yes N missing						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
Number of articular-muscular events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
Conjunctival	Valid N No Yes N missing						
Number conjunctival events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						

Table 15. Risk of stroke (CHA2DS2-VASc) and risk of major bleeding (HAS-BLED) according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
CHA2DS2-VASc score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
CHA2DS2-VASc (risk of stroke)	Valid N Low risk *(score 0 in male; 1 in female)* Moderate risk *(score 1 in male; 2 in female)* High risk *(score ≥2 in male; ≥3 in female)* N missing						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
HAS-BLED score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing						
HAS-BLED (risk of bleeding)	Valid N Low risk *(score 0)* Intermediate risk *(score 1-2)* High risk *(score ≥3)* N missing						

Table 16. Concomitant treatments to NOAC at study visit according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
ARB or ACE inhibitor	Valid N No Yes N missing						
Beta-blocker	Valid N No Yes N missing						
Calcium channel blockers	Valid N No Yes N missing						
Diuretics	Valid N No Yes						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	N missing						
Amiodarone	Valid N No Yes N missing						
Statin	Valid N No Yes N missing						
Proton pump inhibitor	Valid N No Yes N missing						
H2-receptor antagonist	Valid N No Yes N missing						
Digoxin	Valid N No Yes N missing						
NSAIDs	Valid N No Yes N missing						
Dronedarone	Valid N No Yes						

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total	Standardized differences (Pradaxa® vs others
	N missing						
Ketoconazole	Valid N No Yes N missing						
Cyclosporine	Valid N No Yes N missing						
Itraconazole	Valid N No Yes N missing						
Other antiarrhythmics	Valid N No Yes N missing						

17.2.2 Patient's characteristics according to duration since the first NOAC initiation

Table 17. Socio-demographic variables and habits according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Age	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Age group	Valid N 75-79 years 80-84 years ≥85 years N missing			
Sex	Valid N Male, n (%) Female, n (%) N missing			
Weight (Kg)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Weight (Kg) cat	Valid N ≤60 kg, n (%) >60 kg, n (%) N missing			
Height (cm)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
BMI (Kg/m2)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

		≤4 months	>4 months	Total
BMI cat	Valid N Underweight: BMI< 18.5 kg/m2 Normal weight: 18.5 kg/m2<= BMI<= 25 kg/m2 Overweight: 25 kg/m2< BMI<= 30 kg/m2 Obese: 30 kg/m2<BMI<= 35 kg/m2 Severely Obese: BMI> 35 kg/m2 N missing			
Caregiver	Valid N No Yes N missing			
Place where patient is living	Valid N Home alone At home with partner/other family member/a friend Other's home (e.g. family member's) Nursing home N missing			
Smoking habit	Valid N Ex-smoker Smoker Non-smoker N missing			
Alcohol consumption	Valid N Casual Habitual Abuse Dependence N missing			

Table 18. Analytical laboratory results from the last available blood sample analysis according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Serum creatinine (mg/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Serum creatinine Normal levels: 0.6-1.2 mg/dl in males 0.5-1.1 mg/dl in females	Valid N Normal levels High/low level N missing			
Creatinine clearance (ml/min)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Creatinine clearance (ml/min): Cockcroft and Gault formula	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Creatinine clearance – range (ml/min/1.73m^2)	Valid N <15 15-29 30-59 60-89 ≥90 N missing			
AST (UI/L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
AST Normal values: 7-55 UI/L	Valid N Normal value High/low value			

		≤4 months	>4 months	Total
	N missing			
ALT (UI/L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
ALT Normal values: 8-48 UI/L	Valid N Normal value High/low value N missing			
Total bilirubin (mg/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Total bilirubin Normal values: 0.2-1.2 mg/dl	Valid N Normal value High/low value N missing			
Haemoglobin (g/dl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Haemoglobin Normal values: 12-18 g/dl	Valid N Normal value High/low value N missing			
Platelet levels (xµL)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Platelet levels Normal values: 150 – 450 $x10^3/\mu L$	Valid N Normal value High/low value N missing			

Table 19. NVAF variables according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Years since NVAF diagnosis	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Years since NVAF diagnosis (patients treated previously with VKA)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Years since NVAF diagnosis (patients treated with NOAC as first anticoagulant)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Type of NVAF	Valid N Persistent Long standing persistent Permanent Paroxysmal N missing			
Modified EHRA scale for AF related symptoms	Valid N 1-none 2a-mild 2b-moderate 3-severe 4-disabling N missing			

Table 20. Procedures and interventions according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Cardioversion	Valid N No Yes N missing			
Ablation	Valid N No Yes N missing			
Coronary interventions	Valid N No Yes N missing			
Type of coronary interventions	Valid N Percutaneous coronary intervention Coronary artery bypass grafting N missing			
Pacemaker carrier	Valid N No Yes N missing			

Table 21. Clinical risk factors according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Heart failure	Valid N No Yes N missing			
NYHA classification	Valid N A - No objective evidence of cardiovascular disease B - Objective evidence of minimal cardiovascular disease			

		≤4 months	>4 months	Total
	C - Objective evidence of moderately severe cardiovascular disease D - Objective evidence of severe cardiovascular disease N missing			
Left ventricular ejection fraction (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Coronary artery disease	Valid N No Yes N missing			
Sleep apnoea-hypopnoea syndrome	Valid N No Yes N missing			
Hypertension	Valid N No Yes N missing			
Hyperlipidemia	Valid N No Yes N missing			

Table 22. Comorbidity Charlson Index according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Myocardial infarction	Valid N No Yes N missing			
Congestive heart failure	Valid N No Yes			

		≤4 months	>4 months	Total
	N missing			
Peripheral vascular disease	Valid N No Yes N missing			
Cerebrovascular disease	Valid N No Yes N missing			
Dementia	Valid N No Yes N missing			
COPD	Valid N No Yes N missing			
Connective tissue disease	Valid N No Yes N missing			
Peptic ulcer disease	Valid N No Yes N missing			
Liver disease	Valid N Mild Moderate to severe N missing			
Diabetes mellitus	Valid N Uncomplicated End-organ damage N missing			
Hemiplegia	Valid N No Yes N missing			

		≤4 months	>4 months	Total
Moderate to severe renal disease	Valid N No Yes N missing			
Solid tumor	Valid N Localized Metastasic N missing			
Leukemia	Valid N No Yes N missing			
Lymphoma	Valid N No Yes N missing			
AIDS	Valid N No Yes N missing			
Age-adjusted Charlson Comorbidity index score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 23. History of thromboembolic events according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
History of thromboembolic events	Valid N No Yes N missing			
Number of total thromboembolic events	Valid N Mean (SD) Median (Q1-Q3) Min-Max			

		≤4 months	>4 months	Total
	N missing			
TIA	Valid N No Yes N missing			
Number of TIA	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Ischemic stroke	Valid N No Yes N missing			
Number of ischemic strokes	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Hemorrhagic stroke	Valid N No Yes N missing			
Number of hemorrhagic strokes	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Embolism systemic	Valid N No Yes N missing			
Number of embolism systemic	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Deep vein thrombosis	Valid N			

		≤4 months	>4 months	Total
	No Yes N missing			
Number of deep vein thrombosis	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Pulmonary embolism	Valid N No Yes N missing			
Number of pulmonary embolisms	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Stable angina	Valid N No Yes N missing			
Number of stable anginas	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Unstable angina	Valid N No Yes N missing			
Number of unstable anginas	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Myocardial infarction with ST segment elevation	Valid N No Yes			

		≤4 months	>4 months	Total
	N missing			
Number of myocardial infarctions with ST segment elevation	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Myocardial infarction without ST segment elevation	Valid N No Yes N missing			
Number of myocardial infarctions without ST segment elevation	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 24. History of bleeding events according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
History of bleeding events	Valid N No Yes N missing			
Number of total bleeding events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Intracranial	Valid N No Yes N missing			
Number of intracranial events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

		≤4 months	>4 months	Total
Digestive	Valid N No Yes N missing			
Number of digestive events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Genitourinary	Valid N No Yes N missing			
Number of genitourinary events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Gingival	Valid N No Yes N missing			
Number of gingival events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Nasal	Valid N No Yes N missing			
Number of nasal events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Pulmonary	Valid N No			

		≤4 months	>4 months	Total
	Yes N missing			
Number of pulmonary events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Articular-muscular	Valid N No Yes N missing			
Number of articular-muscular events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Conjunctival	Valid N No Yes N missing			
Number conjunctival events	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 25. Risk of stroke (CHA2DS2-VASc) and risk of major bleeding (HAS-BLED) according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
CHA2DS2-VASc score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
CHA2DS2-VASc (risk of stroke)	Valid N Low risk *(score 0 in male; 1 in female)*			

		≤4 months	>4 months	Total
	Moderate risk *(score 1 in male; 2 in female)* High risk *(score ≥2 in male; ≥3 in female)* N missing			
HAS-BLED score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
HAS-BLED (risk of bleeding)	Valid N Low risk *(score 0)* Intermediate risk *(score 1-2)* High risk *(score ≥3)* N missing			

Table 26. Concomitant treatments to NOAC at study visit according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
ARB or ACE inhibitor	Valid N No Yes N missing			
Beta-blocker	Valid N No Yes N missing			
Calcium channel blockers	Valid N No Yes N missing			
Diuretics	Valid N No Yes N missing			
Amiodarone	Valid N No			

		≤4 months	>4 months	Total
	Yes N missing			
Statin	Valid N No Yes N missing			
Proton pump inhibitor	Valid N No Yes N missing			
H2-receptor antagonist	Valid N No Yes N missing			
Digoxin	Valid N No Yes N missing			
NSAIDs	Valid N No Yes N missing			
Dronedarone	Valid N No Yes N missing			
Ketoconazole	Valid N No Yes N missing			
Cyclosporine	Valid N No Yes N missing			
Itraconazole	Valid N No Yes N missing			

		≤4 months	>4 months	Total
Other antiarrhythmics	Valid N No Yes N missing			

17.3 Outcomes

17.3.1 Primary outcome: Current NOAC

Table 27. Type of NOAC, dose and duration since first NOAC initiation at study visit according to sex

		Male	Female	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			

		Male	Female	Total
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 28. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to age

		75-79 years	80-84 years	≥85 years	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing				
Dabigatran dose	Valid N 110mg BID 150mg BID N missing				
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing				
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing				
Edoxaban dose	Valid N 30mg QD 60mg QD N missing				
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max				

		75-79 years	80-84 years	≥85 years	Total
	N missing				

BDI: twice a day; QD: once a day

Table 29. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to heart failure

		Heart failure		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 30. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to coronary artery disease

		Coronary artery disease		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 31. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to peripheral vascular disease

		Peripheral vascular disease		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 32. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to diabetes

		Diabetes		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 33. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to chronic kidney disease

		Chronic kidney disease		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 34. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to liver disease

		Liver disease		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

Table 35. Type of NOAC, dose and duration since fist NOAC initiation at study visit according to cancer

		Cancer		
		No	Yes	Total
Current NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Dabigatran dose	Valid N 110mg BID 150mg BID N missing			
Rivaroxaban dose	Valid N 15mg QD 20mg QD N missing			
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing			
Edoxaban dose	Valid N 30mg QD 60mg QD N missing			
Years since first NOAC initiation to study visit	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

BDI: twice a day; QD: once a day

17.3.2 Secondary outcome: OAC treatment management

Table 36. Previous VKA treatment and duration according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Previous VKA	Valid N No Yes N missing			
Type of VKA	Valid N Acenocoumarol Warfarin N missing			
Years with Acenocoumarol	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Years with Warfarin	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Total VKA treatment duration in years	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 37. Durations since NVAF diagnosis until first NOAC initiation, first NOAC received, first NOAC dose, dose changes and first NOAC treatment duration according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Months since NVAF diagnosis until first NOAC initiation	Valid N Mean (SD) Median (Q1-Q3)			

		≤4 months	>4 months	Total
	Min-Max N missing			
First NOAC received	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
First NOAC dose: Dabigatran	Valid N 110mg BID 150mg BID N missing			
First NOAC dose: Rivaroxaban	Valid N 15mg QD 20mg QD N missing			
First NOAC dose: Apixaban	Valid N 2.5mg BID 5mg BID N missing			
First NOAC dose: Edoxaban	Valid N 30mg QD 60mg QD N missing			
Changes in first NOAC dose	Valid N No Yes (increase) Yes (decrease) N missing			
First NOAC treatment duration in years*	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Reason for first NOAC treatment discontinuation*	Valid N Lack of effectiveness Investigator decision			

		≤4 months	>4 months	Total
	Patient decision Adverse event N missing			
Reason for first NOAC treatment change dose*	Valid N Lack of effectiveness Investigator decision Patient decision Adverse event N missing			

BDI: twice a day; QD: once a day

*Only patients who stopped first NOAC treatment

Table 38. Number of switches to a new NOAC and reason for switches according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Number of switches to a new NOAC	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Number of switches to a new NOAC	Valid N 0 1 2 3 … N missing			
Switchers	Valid N* Dabigatran to Rivaroxaban Dabigatran to Apixaban Dabigatran to Edoxaban Rivaroxaban to Dabigatran Rivaroxaban to Apixaban Rivaroxaban to Edoxaban			

		≤4 months	>4 months	Total
	Apixaban to Dabigatran Apixaban to Rivaroxaban Apixaban to Edoxaban Edoxaban to Dabigatran Edoxaban to Rivaroxaban Edoxaban to Apixaban N missing			
Reason for switch	Valid N* Lack of effectiveness Investigator's decision Patient's decision Adverse effect N missing			

*Valid N corresponds to the total of switches

Table 39. New NOAC received, new NOAC dose and new NOAC treatment duration according to duration since the first NOAC initiation (SECOND NOAC)

		≤4 months	>4 months	Total
Second NOAC received	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing			
Second NOAC dose: Dabigatran	Valid N 110mg BID 150mg BID N missing			
Second NOAC dose: Rivaroxaban	Valid N 15mg QD 20mg QD N missing			
Second NOAC dose: Apixaban	Valid N 2.5mg BID 5mg BID N missing			

		≤4 months	>4 months	Total
Second NOAC dose: Edoxaban	Valid N 30mg QD 60mg QD N missing			
Changes in second NOAC dose	Valid N No Yes (increase) Yes (decrease) N missing			
Second NOAC treatment duration in years*	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Reason for second NOAC treatment discontinuation*	Valid N Lack of effectiveness Investigator decision Patient decision Adverse event N missing			
Reason for second NOAC treatment change dose*	Valid N Lack of effectiveness Investigator decision Patient decision Adverse event N missing			

BDI: twice a day; QD: once a day

*Only patients who stopped second NOAC treatment

Table 39. will be repeated for each treatment switch during follow-up.

Table 40. Total time (in years) in NOAC treatment

		≤4 months	>4 months	Total
Total time in NOAC treatment (in years)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Total time in NOAC treatment (cat)	Valid N <1 year 1-2 years 2-3 years >3 years N missing			

Table 41. History and current antiplatelet treatment according to duration since the first NOAC initiation

		≤4 months	>4 months	Total
Antiplatelet treatments received (all)	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing			
Time in treatment with antiplatelet agents (in years)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Current antiplatelet treatment (at study visit)	Valid N None			

		≤4 months	>4 months	Total
	Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing			

17.3.3 Secondary outcome: Clinical Frailty Scale

Table 42. Clinical Frailty Scale grading at the time of the study visit according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
CFS score	Valid N 1-Very fit 2-Well 3-Managing well 4-Vulnerable 5-Mildly frail 6-Moderately frail 7-Severely frail 8-Very severely frail 9-Terminally ill N missing					
CFS (categorized)	Valid N Non-frailty patients (CFS scoring ≤4) Frailty patients (CFS scoring >4) N missing					

17.3.4 Secondary outcome: Prevention strategy

Table 43. First NOAC usage at the time of first NOAC initiation according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
Reason for prescription of the first NOAC	Valid N Primary prevention Secondary prevention N missing					

[redacted]

17.4 Additional tables

Table 45. Historic and current antiplatelet treatment according to current NOAC type

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
Antiplatelet treatments received (all)	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole					

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
	Others N missing					
Time in treatment with antiplatelet agents (in years)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing					
Current antiplatelet treatment (at study visit)	Valid N None Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing					

Table 46. Treatment received at the moment of thromboembolic events (1st part)

		TIA	Ischemic stroke	Hemorrhagic stroke	Embolism systemic	Deep vein thrombosis
Treatment (VKA/NOAC/ antiplatelet)	Valid N* No Yes N missing					
VKA	Valid N* No Yes N missing					
Type of VKA	Valid N Acenocoumarol Warfarin N missing					

		TIA	Ischemic stroke	Hemorrhagic stroke	Embolism systemic	Deep vein thrombosis
NOAC	Valid N* No Yes N missing					
Type of NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing					
Antiplatelet	Valid N* No Yes N missing					
Type of antiplatelet	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing					

*Number of events in each column.

One event could be associated with more than one treatment

Table 47. Treatment received at the moment of thromboembolic events (2nd part)

		Pulmonary embolism	Stable angina	Unstable angina	Myocardial infarction with ST segment elevation	Myocardial infarction without ST segment elevation
Treatment (VKA/NOAC/ antiplatelet)	Valid N* No Yes N missing					
VKA	Valid N* No Yes N missing					
Type of VKA	Valid N Acenocoumarol Warfarin N missing					
NOAC	Valid N* No Yes N missing					
Type of NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing					
Antiplatelet	Valid N* No Yes N missing					
Type of antiplatelet	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol					

		Pulmonary embolism	Stable angina	Unstable angina	Myocardial infarction with ST segment elevation	Myocardial infarction without ST segment elevation
	Triflusal Dipyridamole Others N missing					

*Number of events in each column

One event could be associated with more than one treatment

Table 48. Treatment received at the moment of bleeding events (1st part)

		Intracranial	Digestive	Genitourinary	Gingival
Treatment (VKA/NOAC/ antiplatelet)	Valid N* No Yes N missing				
VKA	Valid N* No Yes N missing				
Type of VKA	Valid N Acenocoumarol Warfarin N missing				
NOAC	Valid N* No Yes N missing				
Type of NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing				
Antiplatelet	Valid N*				

		Intracranial	Digestive	Genitourinary	Gingival
	No Yes N missing				
Type of antiplatelet	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing				

*Number of events in each column

One event could be associated with more than one treatment

Table 49. Treatment received at the moment of thromboembolic events (2nd part)

		Nasal	Pulmonary	Articular-muscular	Conjunctival
Treatment (VKA/NOAC/ antiplatelet)	Valid N* No Yes N missing				
VKA	Valid N* No Yes N missing				
Type of VKA	Valid N Acenocoumarol Warfarin N missing				
NOAC	Valid N* No				

		Nasal	Pulmonary	Articular-muscular	Conjunctival
	Yes N missing				
Type of NOAC	Valid N Dabigatran Rivaroxaban Apixaban Edoxaban N missing				
Antiplatelet	Valid N* No Yes N missing				
Type of antiplatelet	Valid N Aspirin Clopidogrel Prasugrel Ticlopidine Ticagrelor Cilostazol Triflusal Dipyridamole Others N missing				

*Number of events in each column

One event could be associated with more than one treatment

Table 50. Current NOAC dose according to HAS-BLED

		HAS-BLED			
		Low risk	Intermediate risk	High risk	Total
Dabigatran dose	Valid N 110mg BID 150mg BID N missing				
Rivaroxaban dose	Valid N				

		HAS-BLED			
		Low risk	Intermediate risk	High risk	Total
	15mg QD 20mg QD N missing				
Apixaban dose	Valid N 2.5mg BID 5mg BID N missing				
Edoxaban dose	Valid N 30mg QD 60mg QD N missing				

Table 51. Overdosing and underdosing of current NOACs

		Appropriately dosed (n,%)	Underdosed (n,%)	Overdosed (n,%)
Dabigatran	Dabigatran (Age <80 years)			NA
	Dabigatran (Age ≥80 years)		NA	
	Dabigatran (75-79 years and HAS-BLED < 3)			NA
	Dabigatran (75-79 years and HAS-BLED ≥ 3)		NA	
	Dabigatran (creatinine clearance >50mL/min)			NA
	Dabigatran (creatinine clearance 30-50mL/min)		NA	
Rivaroxaban	Rivaroxaban (creatinine clearance >50mL/min)			NA

		Appropriately dosed (n,%)	Underdosed (n,%)	Overdosed (n,%)
	Rivaroxaban (creatinine clearance ≤50mL/min)		NA	
Apixaban	Apixaban (Age <80 years)			NA
	Apixaban (Age ≥80 years)		NA	
	Apixaban (Body weight > 60 kg)			NA
	Apixaban (Body weight ≤ 60 kg)		NA	
	Apixaban (Serum creatinine < 1,5 mg/dl or creatinine clearance ≥30mL/min)			NA
	Apixaban (Serum creatinine ≥ 1,5 mg/dl or creatinine clearance <30mL/min)		NA	
Edoxaban	Edoxaban (Body weight > 60 kg)			NA
	Edoxaban (Body weight ≤ 60 kg)		NA	
	Edoxaban (creatinine clearance >50mL/min)			NA
	Edoxaban (creatinine clearance 15-50mL/min)		NA	

Table 52. HAS-BLED score according NOAC+antiplatelet current treatment

		HAS-BLED score				
		Valid N	<3	3-5	≥5	N missing
Current treatment	Dabigatran+aspirin					
	Dabigatran+clopidogrel					
	Dabigatran+peasugrel					
	…					
	… (for all combinations)					

Row percentage will be calculated

Table 53. Multivariate logistic model to evaluate the association between the Clinical Frailty Scale and the thromboembolic and the bleeding events

Variable	Estimate	Standard error	t-value	Pr>|t|	OR

*dependent variable: CFS in two categories: Frailty patients - CFS scoring >4 vs Non-frailty patients - CFS scoring ≤4)
*independent variables: thromboembolic and bleeding events. Other factors will be age, sex, BMI, smoking habit, alcohol consumption, time since NVAF diagnosis, NVAF type, modified EHRA scale, procedures and interventions, comorbidity Charlson index and clinical risk factors. Univariate analysis will be performed and all variables which have a P value of less than 0.1 will be included in the multivariate analysis.

17.5 Adverse Drug Reactions

Table 54. Patients with ADRs associated to BI product Pradaxa®

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
ADRs associated to BI product (Pradaxa®)	Total patients No Yes			
Type of ADR (multi-response)	SOC1 PT11 PT12 … SOC2 PT21 PT22 … …			
ADR outcome (multi-response)	Recovered Not yet recovered			

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
	Recovered with sequelae Unknown Fatal			
Action Taken with Pradaxa (multi-response)	Dose not changed Dose reduced Dose increased Drug withdrawn			

Percentage calculated at patient level

Patients in the Safety Analysis Set. Subjects who receive at least one documented dose of study medication (Pradaxa®)

Table 55. Description of ADRs associated to BI product Pradaxa®

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
ADRs associated to BI product (Pradaxa®)	Total ADRs			
Type of ADR	SOC1 PT11 PT12 … SOC2 PT21 PT22 … …			
ADR outcome	Recovered Not yet recovered Recovered with sequelae Unknown Fatal			
Action Taken with Pradaxa	Dose not changed Dose reduced Dose increased Drug withdrawn			

Percentage calculated at event level

Patients in the Safety Analysis Set. Subjects who receive at least one documented dose of study medication (Pradaxa®)

17.6 Serious Adverse Drug Reactions

Table 56. Patients with SADRs associated to BI product Pradaxa®

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
SADRs associated to BI product (Pradaxa®)	Total patients No Yes			
Type of SADR (multi-response)	SOC1 PT11 PT12 … SOC2 PT21 PT22 … …			
Reason for seriousness (multi-response)	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome (multi-response)	Recovered Not yet recovered Recovered with sequelae Unknown Fatal			
Action Taken with Pradaxa (multi-response)	Dose not changed Dose reduced			

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
	Dose increased Drug withdrawn			

Percentage calculated at patient level

Patients in the Safety Analysis Set. Subjects who receive at least one documented dose of study medication (Pradaxa®)

Table 57. Description of SADRs associated to BI product Pradaxa®

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
SADRs associated to BI product (Pradaxa®)	Total SADRs			
Type of SADR (multi-response)	SOC1 PT11 PT12 … SOC2 PT21 PT22 … …			
Reason for seriousness	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome	Recovered Not yet recovered Recovered with sequelae Unknown Fatal			
Action Taken with Pradaxa	Dose not changed Dose reduced			

		Pradaxa 110mg	Pradaxa 150mg	Pradaxa (110 and 150 mg)
	Dose increased Drug withdrawn			

Percentage calculated at event level

Patients in the Safety Analysis Set. Subjects who receive at least one documented dose of study medication (Pradaxa®)

17.7 Deaths

Table 58. List of deaths

PATCOD	Adverse Event Term	MedDRA Code	Onset date	End date	Outcome	Relationship with BI product

Certificate Of Completion

Envelope Id: D723D9040648460CA7C694EF256B7271
Status: Completed
Subject: Please DocuSign: SAP_REBELD_version1.0_08072020.pdf
Source Envelope:
Document Pages: 108
Signatures: 4
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Enabled
[redacted]
Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
7/10/2020 9:58:14 AM
Holder: [redacted]
Location: DocuSign
[redacted]

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 7/10/2020 10:04:50 AM Viewed: 7/10/2020 10:51:57 AM Signed: 7/10/2020 10:55:25 AM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Soy el autor de este documento	
Electronic Record and Signature Disclosure: Accepted: 7/10/2020 10:51:57 AM ID: [redacted]		
[redacted]	[redacted]	Sent: 7/10/2020 10:55:36 AM Resent: 7/13/2020 9:56:55 AM Viewed: 7/13/2020 10:27:28 AM Signed: 7/13/2020 10:28:45 AM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): He revisado este documento	
Electronic Record and Signature Disclosure: Accepted: 7/13/2020 10:27:28 AM ID: [redacted]		

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 7/13/2020 10:28:55 AM Viewed: 7/13/2020 11:04:08 AM Signed: 7/13/2020 11:05:15 AM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 6/16/2020 9:11:06 AM ID: [redacted]		
[redacted]	[redacted]	Sent: 7/13/2020 11:05:24 AM Viewed: 7/13/2020 5:35:06 PM Signed: 7/13/2020 5:36:47 PM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	
Electronic Record and Signature Disclosure: Accepted: 7/10/2020 2:33:16 AM ID: [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
[redacted]	COPIED	Sent: 7/13/2020 5:36:57 PM
[redacted] Validated Production Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign		

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/13/2020 5:36:57 PM

Envelope Summary Events	Status	Timestamps
Certified Delivered	Security Checked	7/13/2020 5:36:57 PM
Signing Complete	Security Checked	7/13/2020 5:36:57 PM
Completed	Security Checked	7/13/2020 5:36:57 PM

Payment Events	Status	Timestamps

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