

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN



**Non-Interventional, cross-sectional study to describe
NOACs management in patients with non-valvular
atrial fibrillation (NVAF) in Spain**

STUDY NUMBER: 1160-0287

STUDY CODE: BOE-NOA-2017-01

Version 2.0, 1st April 2019

Prepared by:

Sponsor:  Boehringer
Ingelheim

1. SIGNATURE PAGE

Title: Non-interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-CONOCE Study

Study number: 1160-0287

Study code: BOE-NOA-2017-01

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Medical Project

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3. LIST OF ABBREVIATIONS

ACE inhibitor	Angiotensin converting enzyme inhibitors
ADR	Adverse drug reaction
AE	Adverse event
ARB	Angiotensin-receptor blockers
ATC	Anatomical, Therapeutic, Chemical classification system
COPD	Chronic obstructive pulmonary disease
DBP	Diastolic blood pressure
ICH	Intracranial haemorrhage
IQR	Interquartile range
MedDRA	Medical Dictionary for Regulatory Activities
NOAC	Non-Vitamin K antagonist oral anticoagulants/ New Oral Anticoagulants
NSAID	Nonsteroidal anti-inflammatory drug
NVAF	Non-Valvular Atrial Fibrillation
PT	Preferred Term
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TIA	Transient ischemic attack
VKA	Vitamin K antagonists

4. SYNOPSIS

4.1. TITLE OF STUDY

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

4.2. STUDY NUMBER

1160-0287 - BOE-NOA-2017-01

4.3. SPONSOR

Tel.: / Fax:

4.4. OBJECTIVES

This study has been designed in order to describe the current anticoagulation management in Spain.

❖ **Primary objective:**

- ☞ The primary objective of the study is to describe the usage of NOACs in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation.

❖ **Secondary objectives:**

- ☞ To evaluate the appropriateness of prescribed therapy based on Spanish health authorities' recommendations (positioning therapeutic report).
- ☞ To describe NOAC treatment management.
- ☞ To describe the patient's knowledge about anticoagulant treatment, independent of NOAC type.

4.5. STUDY DESIGN

- ❖ **Design:** This is an observational, multicenter, cross-sectional study based on newly collected data that will be conducted in cardiology departments, in at least 102 centers in Spain
- ❖ **Study disease:** Non-Valvular Atrial Fibrillation
- ❖ **Study medication:** NOACs (BI NOAC: Dabigatran etexilate-Pradaxa®)

"Non-interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain"

4.6. NUMBER OF PATIENTS

It is planned that a total of approximately 1000 patients, with NVAF currently on NOAC treatment and having initiated their first NOAC starting from November 2016 (Health Authorities positioning report publication), will be recruited for the study.

To minimize selection bias at the patient level, 10 consecutive patients from each site who meet entry criteria will be enrolled.

Cardiology departments, in a hospital setting, who regularly prescribe NOACs for stroke prevention in NVAF patients, will be selected to participate. The study will be performed among all the national territory.

4.7. STUDY POPULATION

To be eligible to participate in the study, patients must meet the following selection criteria.

The patient will be considered included when he/she agrees to participate in the study by signing the informed consent.

Patients, in the hospital setting, will be included in the study if all of the following criteria are met:

1. The patient is willing and provides written informed consent to participate in this study
2. The patient is at least 18 years of age
3. The patient has a diagnosis of non-valvular atrial fibrillation
4. The patient is on treatment with NOAC according to its approved local SmPC and has initiated his first NOAC starting from November 2016

Patients will be excluded from participating in this study if they currently participate in any clinical trial of a drug or device.

4.8. OUTCOMES

❖ Primary outcomes

- Usage of NOACs, in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation.

❖ Secondary outcomes

- The reasons for NOAC initiation collected during the study visit (at the time of patient enrollment).
- NOAC treatment management.
- Patient's knowledge about his condition.

5. GENERAL STATISTICAL METHODOLOGY

The content of the clinical database shall be transferred to SAS® data files for the statistical analysis. All the statistical analyses will be conducted using the statistical program SAS®v9.3 (SAS Institute Inc., Cary, NC, USA).

Description analyses of all the variables collected should be carried out. Depending on the type of variable, the following shall be presented:

- The categorical variables shall be summarized through frequencies and percentages.
- The continuous variables shall be summarized through measures of central tendency and dispersion: mean, standard deviation, median, interquartile range and extreme values (minimum and maximum).

The variables included in the study objectives will be summarized overall and by factors of interest.

The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria).

If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. No type of imputation shall be made to the data and the data will be considered as missing.

The primary outcome is the usage of NOACs, in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation. Baseline (at time of first NOAC initiation) variables will be analysed descriptively by NOAC type. Treatment groups will be defined according to first NOAC prescribed.

Standardized differences between Dabigatran Etexilate and each of the other NOACs separately will be estimated for these variables (baseline characteristics). The formulas are:

For means:
$$d = \frac{(\bar{x}_{DE} - \bar{x}_C)}{\sqrt{(s_{DE}^2 + s_C^2)/2}}$$

For proportions:
$$d = \frac{(\hat{p}_{DE} - \hat{p}_C)}{\sqrt{\frac{\hat{p}_{DE}(1 - \hat{p}_{DE}) + \hat{p}_C(1 - \hat{p}_C)}{2}}}$$

Where DE is dabigatran etexilate and C is the comparator

Standardized differences higher than 10% (in absolute value) are indicative of imbalance between the compared groups.

The secondary outcomes will be carried out descriptively for the total sample, regardless of the type of NOAC prescribed to the patient.

These objectives include: evaluating whether the recommendations of the Spanish health authorities have been followed, describing the management of the treatment with NOAC and evaluating, through a simple questionnaire of 4 questions, the knowledge the patient has about his illness and the treatment the patient is receiving.

The adverse drug reactions (ADR) and fatal adverse events (AE) shall be tabulated by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities version 21 (MedDRA). A description of them shall be carried out: serious, relation, action taken, outcome, etc.

6. INCLUDED PATIENTS

The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria).

The following should be provided:

- ➔ Number of patients included in the study. Patients not included in the analysis will be shown in a table describing all protocol deviations.
- ➔ Number of patients included in each of the centers. The recruiting investigators within each participating center should be listed.
- ➔ Number of patients included by autonomous community.
- ➔ Number of patients included by type of NOAC and dose (first NOAC prescribed).

7. DESCRIPTION OF THE SAMPLE

7.1. DEMOGRAPHIC DATA

The quantitative variables will be described through the mean, median, standard deviation, interquartile range, minimum, maximum and the total number of patients with available data. These variables include:

- Age (years)

The qualitative variables will be described through their relative and absolute frequency distribution. These variables include:

- Sex
 - Male
 - Female

- Work status
 - Active
 - Inactive
 - Student
 - Retired
 - Not available
- Life status
 - Married
 - Single
 - Widower/widow
 - Divorced
 - Not available

7.2. PHYSICAL ASSESSMENT

The following should be provided, as continuous variables:

- Weight (Kg)
- SBP (mmHg)
- DBP (mmHg)

The number and percentage of patients that perform any physical activity should be provided.

7.3. CLINICAL HISTORY

The following should be provided:

- Number and percentage of patients depending on alcohol consumption: no consumption, moderate or high.
- Number and percentage of patients who presented or not concomitant diseases. Number and percentage of patients who presented or not each one of the following concomitant diseases:
 - ❖ Ischaemic stroke or TIA
 - ❖ Systemic embolism
 - ❖ Heart failure
 - ❖ Coronary artery disease
 - ❖ Ischaemic cardiomyopathy
 - ❖ Left ventricular dysfunction
 - ❖ Cerebrovascular disease
 - ❖ Renal disease
 - ❖ Liver disease
 - ❖ Bleeding
 - ❖ Other
 - ❖ Hypertension
 - ❖ Diabetes Mellitus
 - ❖ Hyperlipidaemia
 - ❖ COPD
 - ❖ Gastric and/or duodenal ulcer
 - ❖ Dementia
 - ❖ Anaemia
 - ❖ Rheumatic disease
 - ❖ Cancer
 - ❖ Prosthetic heart valves

In those patients who present other disease, not predefined, these should be detailed. They will be encoded through MedDRA dictionary based on PT and SOC.

7.4. CURRENT MEDICATION

In the same way as in the previous section, the number and percentage of patients who were or not receiving some other concomitant treatment will be provided.

A detailed description of the treatment will be made according to:

- ❖ ARB or ACE inhibitor
- ❖ Beta-blocker
- ❖ Calcium channel blockers
- ❖ Diuretics
- ❖ Amiodarone
- ❖ Statin
- ❖ Proton-pump inhibitor
- ❖ H₂ - receptor antagonist
- ❖ Aspirin
- ❖ Other antiplatelet agents
- ❖ Digoxin
- ❖ NSAID
- ❖ Verapamil/dronedarone
- ❖ Other antiarrhythmic
- ❖ Ketoconazole (systemic)
- ❖ Cyclosporine
- ❖ Litraconazole
- ❖ Other

The other non-predefined concomitant medication should be detailed. The other concomitant medication will be encoded through the ATC system code classification based on the active principal and the therapeutic group (first anatomical level).

7.5. LABORATORY

The number and percentage of patients that had performed a laboratory test before the first NOAC will be provided, specifically if available data on renal function and hepatic function.

For kidney function, creatinine clearance (obtained from medical charts or auto-calculated by Cockroft-Gault equation) shall be described as continuous variable. And for liver function, the distribution of the following parameters will be described as continuous variables: AST, ALT and total bilirubin.

7.6. NON-VALVULAR ATRIAL FIBRILLATION DIAGNOSTIC

The time since when the patient was diagnosed NVAF until the date of starting the first NOAC shall be summarized for all patients and then separately for patients who received previous VKA treatment and patients who were directly treated with a NOAC.

The age at which the patient was diagnosed will also be provided.

7.7. PREVIOUS TREATMENT WITH VITAMIN K ANTAGONISTS

The number and percentage of patients who were treated previously with VKA (acenocumarol or warfarin), the time in treatment with them, the time from withdrawal to start first NOAC and the reasons for VKA switch will be provided.

8. PRIMARY OBJECTIVE

The main endpoint is the usage of NOAC in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of the start of the first NOAC. These baseline variables will be analyzed descriptively by type of NOAC. The treatment groups will be defined according to the first NOAC that has been prescribed.

Standardized differences between Dabigatran Etexilate and each of the other NOACs separately will be estimated for these variables. These variables are: age at the time of the first NOAC initiation, CHA₂DS₂-VASc Score and HAS-BLED Score.

In order to answer the primary objective to complement the three primary variables, the following baseline characteristics (covariates) will be also analyzed descriptively by type of NOAC:

- Demographic characteristics (gender, work status, life status)
- Alcohol consumption
- Physical activity
- Weight
- Systolic BP/Diastolic BP
- AF diagnosis date (time from diagnosis to first NOAC initiation, months)
- Duration of previous VKA treatment, if applicable
- Reasons for VKA treatment switch
- Kidney function
- Liver function
- Concomitant and relevant previous diseases
- Concomitant treatments

8.1. AGE AT THE TIME OF THE FIRST NOAC INITIATION

The age at the time of the start of the first NOAC will be calculated as the difference between the start date of the first prescribed NOAC and the date of birth of the patient.

Once calculated, the age will be described in terms of central tendency and dispersion providing mean, median, standard deviation, minimum, maximum and interquartile range for all patients and by type of first prescribed NOAC.

8.2. CHA₂DS₂-VASc SCORE

The CHA₂DS₂-VASc score is clinical prediction rule for estimating the risk of stroke in patients with atrial fibrillation, a common and serious heart arrhythmia associated with thromboembolic stroke. Then this score is used to determine whether or not anticoagulation therapy is required.

A high score corresponds to a greater risk of stroke, while a low score corresponds to a lower risk of stroke.

In this sense, the total score will be described as a quantitative variable through its mean, median, standard deviation, minimum, maximum, IQR and number of patients with non-missing values.

The total score shall be stratified by category according to the following classification, providing the relatives and absolutes frequencies:

- Low risk (score 0 in male; score 1 in female)
- Moderate risk (score 1 in male; score 2 in female)
- 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.*

8.3. HAS-BLED SCORE

The HAS-BLED score was developed as a practical risk score to estimate the 1-year for major bleeding in anticoagulated patients with atrial fibrillation and to identify potentially correctable bleeding risk factors such as uncontrolled hypertension, labile INRs, concomitant aspirin use and alcohol excess.

A high HAS-BLED score (≥ 3) is indicative of the need for regular clinical review and follow-up, but should not be used per se as a reason for stopping oral anticoagulation. Indeed, a high HAS-BLED score allows the clinician to 'flag up' patients at potential risk for serious bleeding.

The total HAS-BLED score will be described as a quantitative variable through its mean, median, standard deviation, minimum, maximum, interquartile range and number of patients available.

The total score shall be stratified by category, according to the following classification, and shall be provide the distribution of the relatives and absolutes frequencies:

Score	Bleeding risk*
0	Low risk
1-2	Intermediate risk
≥ 3	High risk

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. *Chest* 2010;138: 1093-100

* The risk is based on the possibility of developing a hemorrhagic process (intracranial hemorrhage, hemorrhage requiring hospitalization or transfusion or a decrease in hemoglobin $> 2\text{ g/l}$)

9. SECONDARY OBJECTIVES

9.1. APPROPRIATENESS OF NOACs PRESCRIPTION

First of all, appropriateness of NOAC prescription based on national recommendations (positioning therapeutic report) is planned, for the entire eligible patients. For this, it will be reviewed if the presence of at least one of the below clinical situations or situations related to INR control were met.

- Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin.
- Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase).
- Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH.
- Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control.
- Patients who have started treatment with VKA in which it is not possible to maintain INR control within range (2-3) despite good therapeutic compliance.
- Impossibility of access to conventional INR control.
- Other reason
- Unknown

The reasons for initiation of the first NOAC will be described in first place, broken down between clinical reasons or situations related to INR control. In case of other reason, it should be specified.

9.2. NOAC TREATMENT MANAGEMENT

A description of the first prescribed NOAC and other NOACs (if applicable) will be made, indicating:

- ✓ Number and percentage of patients according to NOAC type and dose
- ✓ Time in treatment calculated as the difference between start date and end date, if both are available and in other case informed consent date will be used (time to beginning study); it will be described as quantitative variable.
- ✓ NOAC Dose; it will be described as qualitative variable.
- ✓ Number and percentage of patients who need discontinue treatment or dose adjustment or change a new NOAC; in this case, reason for change.
- ✓ Number and percentage of patients who change other NOAC, including type of new NOAC or new doses, time in treatment if start and end dates, and time after first NOAC.

On the other hand, frequency of visits to the physician will be assessed quantitatively and qualitatively.

A descriptive analysis of the history of thromboembolic and hemorrhagic events presented by the patients will be carried out. First, the number and percentage of patients with or without thromboembolic and hemorrhagic events would be provided. A description will be made of the type of event suffered, if it was related to NOAC and as well as the number of times, for the following two types of events:

Thromboembolic events:

- TIA
- Ischaemic stroke
- Haemorrhagic stroke
- Embolism systemic
- Deep vein thrombosis
- Pulmonary embolism
- Stable angina
- Unstable angina
- Myocardial infarction without ST segment elevation
- Myocardial infarction with ST segment elevation

Bleeding events:

- Intracranial
- Digestive
- Genitourinary
- Gingival
- Nasal
- Pulmonary
- Articular-muscular
- Conjunctival
- Other

9.3. PATIENT'S KNOWLEDGE ABOUT HIS CONDITION

At the time of inclusion, the physician will perform a small questionnaire to the patient, with answers yes/no to assess the knowledge that the own patient has about his illness and the anticoagulant treatment prescribed.

These questions would be:

- a) Do you know why you are being treated with an anticoagulant?
- b) Do you know which the effect of the anticoagulant treatment is?
- c) Do you know what could happen if you don't take the anticoagulant treatment?
- d) Do you mind taking the anticoagulant treatment?

Answers (yes/no) to the questions above will be described by means its distribution of relatives and absolutes frequencies, for the whole study population, independent of NOAC type. Each question will be analyzed separately.

11. SAFETY PROFILE

11.1. ADVERSE DRUG REACTION AND FATAL ADVERSE EVENTS

The adverse drug reaction (ADR) and fatal adverse events shall be tabulated by System Organ Class (SOC) and Preferred Term (PT) using the *Medical Dictionary for Regulatory Activities* last version (MedDRA). The general summary of the AE should include the following:

- Number and percentage of patients who presented at least one ADR
- Number and percentage of patients who presented at least one serious ADR
- Number and percentage of patients who presented non-serious ADRs
- Number and percentage of patients who presented at least one fatal AE
- Number and percentage of patients who presented at least one fatal AE related with Pradaxa®
- Number and percentage of patients reported for each SOC and PT (Take into account that the percentages shall be by patient, not by event, and each patient only shall be counted once within each SOC and PT)

In patients who presented an AE, a description of the AE should be provided:

- Serious
- Seriousness reason
 - Death
 - Life-threatening
 - Persistent or significant incapacity
 - Requires/prolonged hospitalization
 - Congenital abnormality/birth defect
 - Other
- Duration
- Related with Pradaxa®
- Action taken with Pradaxa®
 - Dose not changed
 - Dose reduced
 - Dose increased
 - Drug withdrawn
- Outcome
 - Recovered
 - Recovered with sequelae
 - Not recovered
 - Fatal
 - Unknown

Finally, a list of all serious adverse events and a list of all adverse events related to Pradaxa® will be provided.