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## **REQUOL Study**

***“Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants***

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# REQUOL Study

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## GLOSSARY

AF	Atrial Fibrillation
BMI	Body mass index
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/TIA/thrombo-embolism, Vascular disease, Sex Female SCORE
CRF	Case report form
DOAC	Direct oral anticoagulant
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol SCORE
HRQoL	Health-related quality of life
IC	Inclusion criterion
Max	Maximum
Min	Minimum
N	Number of patients
NVAF	Non-valvular atrial fibrillation
Q1	First quartile
Q3	Third quartile
SD	Standard deviation
VKA	Vitamin K antagonists

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## **1 INTRODUCTION**

Atrial fibrillation (AF) affects 1-2% of the general population, but especially patients aged from 80-85 years, in whom the prevalence rate can be as high as 16%. The first oral anticoagulants to prevent the risk of thromboembolic episodes in AF were vitamin K antagonists (VKA), warfarin and acenocoumarol. Management of these drugs continues to be problematic, as they require routine clotting monitoring, clinical supervision and ongoing patient education, affecting their daily habits and, hence, their quality of life. Data also shows that 80% of patients continue to receive acenocoumarol in Spain, 44-59% of them with an international normalized rate (INR) within the therapeutic range, and a mean time in therapeutic range (TTR) of 64%.

Direct oral anticoagulants (DOAC) maintain the beneficial effects of anticoagulant therapy and can increase patient perception of quality of life, as they do not require the strict monitoring necessary for VKAs. On the other hand, maintaining a stable anticoagulation level with DOACs eliminates the risk of uncontrolled patients and prevents increased numbers of doctor visits for this reason. In theory, this would have positive implications for quality of life. However, the evidence provided by the quality of life study does not appear to show that AF leads to major reductions in quality of life. In this respect, the cross-sectional study by Roalfe et al. in 1762 patients of more than 75 years of age with AF reached the conclusion that, in the absence of comorbidities, chronic AF has little impact on generic quality of life. This suggests that treatment strategies should focus on the prevention of complications such as stroke, so further studies are required on anticoagulant therapy and its impact on quality of life.

HRQoL was evaluated in a subgroup of the RE-LY population to determine the effect of choice of anticoagulant during a stable treatment phase in the first year of the study, in patients with no significant events such as stroke or important haemorrhages. HRQoL was evaluated by the EQ-5D questionnaire, a generic healthcare assessment tool. In one year, all the patients taking anticoagulants with no significant events presented a stable HRQoL. The scores obtained by dabigatran and warfarin were comparable. There are insufficient data regarding HRQoL in controlled and uncontrolled patients treated with oral anticoagulants.

This study was designed to describe HRQoL in uncontrolled patients with NVAF treated with conventional VKAs and controlled patients receiving a VKA or DOAC.

Given that the type of patients to be enrolled in this study are those seen in internal medicine, as they are elderly or chronic patients, largely hospitalised, polymedicated and with a high risk

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of haemorrhage and thromboembolism, this study will provide information about the HRQoL of these patients in relation to their anticoagulation status (controlled or uncontrolled).

### **2 OBJECTIVE AND DESIGN**

#### **2.1 Objectives of the analytical plan**

This document presents a proposed analytical plan for the final statistical analysis of the REQUOL study.

The analytical plan proposed below details the aspects to be learned about the study and the statistical methods of analysis to be used and applied to the collected data to comply with the primary objective and the secondary objectives.

#### **2.2 Primary study objective**

To describe HRQoL in uncontrolled patients treated with VKA and controlled patients treated with VKA or DOAC.

#### **2.3 Secondary objectives**

To describe the profile of uncontrolled patients.

#### **2.4 Study design**

Cross-sectional, multicentre, observational study.

#### **2.5 Study population**

The patients to be included will present NVAF and receive the same anticoagulant treatment (VKA or DOAC) for at least 6 months and up to 2 years. They will be seen in internal medicine departments.

In all, it is expected that approximately 330 patients will be included in the controlled group and 170 in the uncontrolled group.

#### **2.6 Inclusion criteria**

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

1. The patient is willing to participate and grants his or her informed consent to participate in the study in writing.
2. The patient is at least 18 years old.
3. The patient has a diagnosis of NVAF.

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4. The patient has been receiving the same anticoagulant treatment (VKA or DOAC) for at least 6 months and no more than 2 years.
5. If he/she receives treatment with VKA, availability of TRT% in previous analytical records or sufficient INR measures to calculate same.

### **2.7 Exclusion criteria**

Patients will be excluded from the study if they meet 1 or more of the following criteria:

1. Participation in any clinical trial of a drug or medical device.
2. Contraindications for the use of DOAC or VKA as described in the summary of product characteristics.

## **3 STATISTICAL ANALYSIS METHODS**

Following are the analytical methods to be used both to attain the study's objectives and to describe the variables.

The quantitative variables will be described with centralisation and dispersion measures (mean, median, SD (standard deviation), Q1 (first quartile), Q3 (third quartile), minimum and maximum). The qualitative variables are described by absolute and relative frequencies.

In the descriptive analysis of the qualitative variables there will be two percentage columns, the total (%) and valid (% valid) percentages, in other words the sum of valid responses plus missing values and the percentage of the total valid responses.

The data shall be analysed by SPSS v18.0 or later.

### **3.1 Database closure agreement**

Once the database is closed for the analysis, if abnormal and/or inconsistent values are detected in a results table, the database shall not be re-opened for modification, but the abnormal datum and the way in which it was processed will be informed and agreed with the sponsor (such as by assignment of missing datum or elimination of the case, depending on the statistical method to be used in the analysis in question). Missing data shall not count and shall be considered as missing.

Any change to said table will be described in writing in the report, as shall the procedure applied (such as assignment of missing datum, interpolation, elimination of the case, etc.).

For the final statistical analysis, the database shall be re-opened and the study data and affected tables will be changed only if a change in the contractual conditions is considered with the sponsor.

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## 4 POPULATION TO BE ANALYSED

The different populations included in the analysis are defined below:

- **Eligible patients** are defined as those who meet all the inclusion criteria and none of the exclusion criteria described in the protocol.

The CRF will contain information about the screening criteria in binary variable form (Yes/No) for each of the described items.

Several of these criteria can be verified with the data recorded in the CRF. The criteria to be verified to define the assessable population are described below:

### **SCREENING CRITERIA:**

- *The patient is willing to participate and grants his or her informed consent to participate in the study in writing.* The date of informed consent must be provided; it must be before or on the same date as the baseline visit.
- *The patient is at least 18 years old.* The patients' age must be 18 years or more (calculated from date of birth to the date of the baseline visit).
- *The patient has a diagnosis of NVAf.* The information regarding the NVAf-type variable must be completed.
- *The patient has been receiving the same anticoagulant treatment (VKA or DOAC) for at least 6 months and up to 2 years.* Time of treatment from the treatment start date to the date of the baseline visit must be at least 6 months and no greater than 2 years.
- *If he/she receives treatment with VKA, availability of TRT% in previous analytical records or sufficient INR determinations to calculate same.* If the patient is receiving treatment with VKA, the TRT% figure must be completed.

If there is a contradiction between the binary variables and the information shown in the CRF in question, the latter shall be assumed to be valid.

The number of unassessable patients in the study shall be provided, together with the reasons for their non-inclusion.

**The analyses will be performed with the eligible patients.**

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## 5 DESCRIPTIVE ANALYSIS.

### 5.1 Groups

The number of controlled vs uncontrolled patients shall be described.

The allocation of each patient to each group is performed automatically by the platform where the data are collected during the study and is performed at the time the VKA and TTR data are collected.

Patients receiving AVK and TTR (Rosendaal method) <65%, or TTR (direct method) <60% are assigned to the uncontrolled group. The rest of the patients are assigned to the controlled group.

### 5.2 Demographic data

All the analyses in this section shall be performed for the controlled, uncontrolled and total populations.

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- Age (calculated on the date of the baseline visit)

The categorical variables to be described are: N and (%):

- Age (>=75 years, 65-<75 years, and <65 years)
- Gender
- Race
- Work status
- Life status

### 5.3 Non-valvular atrial fibrillation

All the analyses in this section shall be performed for the controlled, uncontrolled and total populations.

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variables:

- Time since diagnosis, calculated as the time from date of diagnosis to the date of the baseline visit



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- Age at date of diagnosis
- Time since treatment initiation, calculated as the time from the treatment start date to the date of the baseline visit
- Time during which the patient has not been controlled, calculated as 100-TTR% (Rosendaal method)

The categorical variables to be described are: N and (%):

- TTR% (Rosendaal method): TTR < 65%, TTR >=65%
- TTR% (direct method): TTR < 60%, TTR >=60%
- Type of NVAf
- Current type of anticoagulant medication
- Specify VKA

## **6 DESCRIPTIVE ANALYSIS. UNCONTROLLED PATIENTS**

### **6.1 Physical examination**

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variables:

- Weight
- Height
- BMI

### **6.2 Blood tests**

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- Creatinine clearance. A single variable will be created for the creatinine clearance value. The auto-calculated creatinine value will be used if available; otherwise the auto-calculated value will be imputed according to the collected creatinine value.

### **6.3 Ejection fraction**

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- Quantitative-LVEF

The categorical variable to be described is: N and (%):

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- Qualitative-LVEF (Normal ( $\geq 50\%$ ), slightly depressed (49-31%), moderately (40-31%), severely ( $\leq 30\%$ ))

### 6.4 CHA<sub>2</sub>DS<sub>2</sub>VASc

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- CHA<sub>2</sub>DS<sub>2</sub>VASc score: The score is calculated according to the following algorithm.

Variable	Score if answer is "Yes"
Congestive heart failure	1
Hypertension	1
Age $\geq 75$ years	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease (history of myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65-74	1
Female sex	1

N and (%) will be presented for the following categorical variable:

- CHA<sub>2</sub>DS<sub>2</sub>VASc score (Low risk (score=0), intermediate risk (score=1), high risk (score  $\geq 2$ ))

### 6.5 HAS-BLED

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- HAS-BLED score, where the score is calculated according to the following algorithm.

Variable	Score if answer is "Yes"
Hypertension	1
Impaired renal function	1
Impaired hepatic function	1
Prior history of stroke = Stroke/TIA	1
Labile INR	1
History of or predisposition to bleeding	1
Age > 65 years	1
Pro-haemorrhagic drugs	1
Alcohol	1

N and (%) will be presented for the following categorical variable:

- HAS-BLED score (Low risk (Score <3), high risk (score  $\geq 3$ ))

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### **6.6 Thromboembolic events**

The categorical variables to be described are: N and (%):

- Has the patient ever suffered a thromboembolic event?
- List of presented thromboembolic events

### **6.7 Haemorrhagic events**

The categorical variables to be described are: N and (%):

- Has the patient ever suffered a haemorrhagic event?
- List of presented haemorrhagic events
- Severity of haemorrhagic events

### **6.8 Frequency of visits to the doctor**

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for the following continuous variable:

- Number of visits to internal medicine specialist per year

### **6.9 Comorbidities**

The categorical variables to be described are: N and (%):

- Present at least one of the diseases contained in the CRF
- Each of the diseases contained in the CRF
- For each disease, how many are still active

### **6.10 Concomitant treatments**

The categorical variables to be described are: N and (%):

- Treatment
- Indication

## **7 ADVERSE EVENT**

All the analyses in this section shall be performed for the controlled, uncontrolled and total populations.

The categorical variables to be described are: N and (%):

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- Number of patients who present at least one adverse event
- Number of patients who present at least one serious adverse event
- Number of patients who present at least one adverse event related to Pradaxa®
- Number of patients who present each of the collected adverse events
- A list of serious adverse events will be presented
- A list of adverse events related to Pradaxa® will be presented

## **8 ANALYSIS OF THE OBJECTIVES**

### **8.1 Primary objective**

***To describe HRQoL in uncontrolled patients treated with VKA and controlled patients treated with VKA or DOAC.***

All the analyses in this section shall be performed for the controlled, uncontrolled and total populations.

Quality of Life shall be based on the patients' assessments, by completing the Sawicki questionnaire during the single study visit. This questionnaire includes 32 items grouped in 5 dimensions: overall treatment satisfaction, self-efficacy, strained social disturbances, daily hassles and distress. The highest scores show less quality of life (validated adapted Spanish questionnaire<sup>1</sup>). The response options for each question are: 1=Not at all, 2=Very slightly, 3=Slightly, 4=Moderately, 5=Quite a lot, 6=Very much. The responses correspond to a quantitative scale from 1 to 6.

<sup>1</sup>Reference: Sanchez GR, Yanes BM, Cabrera MA, Ferrer Garcia-Borras JM, Alvarez NR, Barrera LE. [Cross-cultural adaptation of a questionnaire for measuring the quality of life of patients taking oral anticoagulants]. *Aten Primaria* 2004;34(353):353-9.

The categorical variable to be described is: N and (%):

- Number of patients who completed the questionnaire

The summary score for each dimension is calculated by dividing the total score of the items that comprise each dimension by the number of items included in that dimension (arithmetical mean of the items in question).

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**Treatment Satisfaction:** Arithmetical mean of the scores of items 4, 12, 14, 15, 21 and 27 (the results of each item in this dimension must be inverted:  $n+1$ -score of the item,  $n$  is the number of scales, in this case  $n=6$ )

**Self-efficacy:** Arithmetical mean of the scores of items 5, 9, 18 and 24

**Stress:** Arithmetical mean of the scores of items 1, 8, 10, 13, 19, 25, 26, 28, 30, 31

**Limitations:** Arithmetical mean of the scores of items 2, 3, 6, 7, 11, 22, 23

**Social disturbances :** Arithmetical mean of the scores of items 16, 17, 20, 29, 32

The descriptive statistic (Mean, SD, Median,  $Q_1$ ,  $Q_3$ , Min, Max) will be shown for each of the questionnaire's items (in the inverted items, the inverted value will be provided):

1. My treatment makes me feel worried or stressed
2. The effort of controlling my blood clotting causes me discomfort when I leave the house
3. My treatment prevents me from organising my leisure time how I wish
4. I am dissatisfied with the amount of time I invest in controlling my clotting
5. I believe I have learned to control my treatment
6. The risk of cutting myself prevents me from performing housework
7. I avoid some activities (e.g. Cycling) due to the risk of accidents
8. My treatment is a cause of concern for my family
9. I can deal with the treatment-related problems that arise
10. I am worried about my future health
11. I am afraid of doing exercise for fear that I will hurt myself
12. I am dissatisfied with the time it takes to get results
13. I am worried that my treatment may shorten my life
14. I dislike having to plan my activities in advance
15. I am worried by the uncertainty I feel while awaiting results
16. I see my friends less since following this treatment
17. I avoid going on holiday because I do not know the negative effects different foods may have on my treatment
18. I am well informed about what to do to achieve results within the acceptable limits
19. I feel dependent on my anticoagulation medication
20. I avoid travelling because I fear that I may not receive suitable treatment in case my results are too low or high
21. I am fed up with the amount of time I lose at the doctor's surgery
22. I would do more sports if I did not take anticoagulants
23. I have problems at work because of frequent absences caused by my treatment
24. I am sure I am able to control my treatment
25. I tend to worry about things

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26. Despite regular visits to the doctor, I feel limited
27. I am annoyed that many people do not understand the problems related to my treatment
28. When I go to the dentist or other doctors. I am concerned that they might not know enough about anticoagulation
29. The treatment has affected my sex life
30. I dislike being treated like an invalid
31. I am worried about the side effects of my anticoagulant treatment
32. I am worried about other people's reactions to my treatment

The descriptive statistic (Mean, SD, Median, Q<sub>1</sub>, Q<sub>3</sub>, Min, Max) will be shown for each of the previously calculated dimensions:

- Treatment Satisfaction
- Self-efficacy
- Stress
- Limitations
- Social disturbances

### **8.2 Secondary objectives**

***To describe the profile of uncontrolled patients.***

This objective is met by the descriptive analysis of the variables, as specified in section 6 herein.