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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - dabigatran etexilate			
Report date: 18 Jan 2019	**Study number:** 1160-0280	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants. RE-QUOL study.		
Keywords:	Health-related Quality of Life, Nonvalvular Atrial Fibrillation, Anticoagulation control, Time in Therapeutic Range, Direct oral anticoagulants, Vitamin K antagonists.		
Rationale and background:	Atrial fibrillation (AF) affects 1-2% of general population, but specially persons between 80-85 years, in whom the prevalence can reach 16%. The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA). The management of these agents remains problematic because they need routine coagulation monitoring, clinical surveillance and continuous patient education, affecting to their daily habits and in consequence to their health-related quality of life (HRQoL). A most recent treatment called direct oral anticoagulants (DOAC) maintains the benefits of anticoagulant therapy and may increase perception of HRQoL among patients because they do not necessitate the strict monitoring required for VKA. On the other hand, maintaining a stable level of anticoagulation with DOAC prevents uncontrolled patients as well as the increased number of monitoring visits for this reason. Theoretically, this fact would have positive implications in HRQoL. However, the available evidence is inconsistent, with some studies reporting that patients have large decrements in their HRQoL due to AF, and, others suggesting that HRQoL might depend on other factors such as comorbidities or outcome events and not on AF *per se*. Importantly, there is a dearth of evidence regarding whether HRQoL perceptions of patients with AF on oral anticoagulants might be also affected by their anticoagulation control status.		
Research question and objectives:	The primary objective of the present study was to describe the HRQoL of nonvalvular AF (NVAF) patients with uncontrolled anticoagulation status treated with VKA, and of NVAF patients with controlled anticoagulation status treated with VKA or DOAC. The secondary objective was to describe the demographic and clinical profile of uncontrolled NVAF patients.		

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Study design:	This was an observational, multicentre and cross-sectional study conducted in Departments of Internal Medicine from 47 sites in Spain. The observational nature of the study was ensured as no diagnostic or therapeutic intervention outside of routine clinical practice was applied. The study was carried out in accordance with the requirements expressed in the Declaration of Helsinki as well as with current legislation in Spain concerning the conduct of observational studies (Ministerial Order SAS/3470/2009).
Setting:	This study was conducted in the Autonomous Communities of Madrid, Valencia and Andalucía (Spain). Forty-seven internal medicine specialists from 38 Hospital sites regularly prescribing DOACs and VKA for stroke prevention in NVAF according to the respective Summary of Product Characteristics (SmPC) participated in the study. The study consisted of a single visit to the Departments of Internal Medicine coinciding with one of the visits performed by the patients as part of routine follow-up of their disease. Patients were included in the study after signing the informed consent and were also asked to complete the study questionnaire during the study visit. Between April 2017 and January 2018, 535 patients were enrolled. The first patient was registered on 18th April 2017 and the last patient on 30th January 2018.
Subjects and study size, including dropouts:	Every physician was required to enrol the first consecutive patients meeting each of the following inclusion criteria and none of the following exclusion criteria. Inclusion criteria were: 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 the same anticoagulant therapy (VKA or DOAC) during at least 6 months and maximum 2 years. 5. If treated with VKA, availability of %TTR in past analytical records or enough amount of INR measures to calculate it. Exclusion criteria were: 1. Current participation in any clinical trial of a drug or device 2. Contraindication to the use of DOAC or VKA as described in the Summary of Product Characteristics (SmPC). A total of 535 patients were enrolled in the study. Thirty-four patients were excluded from the analysis (31 patients due to screening failures, and 3 patients due to not meeting inclusion criteria). Thus, 501 patients were included and analysed in this study. All 501 patients completed the single visit of this study. All the patients included in the study had NVAF and received anticoagulant treatment (VKA or DOAC) for at least 6 months and up to a maximum of 2 years. Patients treated with DOAC were classified as controlled. Patients treated with VKA were classified as controlled or uncontrolled group depending on the % Time in Therapeutic Range (TTR).

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<table>
<tr><td>Variables and data sources:</td><td>Primary variable: HRQoL based on the patients' ratings on the Sawicki questionnaire completed during the single study visit. This questionnaire includes 32 items grouped in 5 dimensions: general treatment satisfaction, self-efficacy (self-assessment of efficacy), strained social network, daily hassles and distress. High HRQoL perceptions were indicated by high scores in general treatment satisfaction and self-efficacy, and by low scores in strained social network, daily hassle and distress.

Secondary variables: uncontrolled patient profile. This variable included demographic characteristics (age, gender, work status, marital status, etc), left ventricular ejection fraction, kidney function (creatinine clearance), CHA_2DS_2-VASc, HAS-BLED, history of thromboembolic and bleeding events, concomitant diseases, concomitant treatments, frequency of visits to the physician, AF diagnosis date, VKA treatment, and time since anticoagulant treatment initiation.

Data collection was limited to those available in the medical records of selected patients and the HRQoL questionnaire, within the routine clinical practice and without interference with the physician's prescription habits.</td></tr>
<tr><td>Statistical Methods</td><td>To describe the quality of life among patients controlled and uncontrolled: the scores of each individual question in the Sawicki questionnaire were summarized descriptively in the controlled and uncontrolled patients. In addition, the summary score for each dimension of the questionnaire was calculated for each patient and summarized in the same way as the individual questions.

To describe the profile of uncontrolled patients treated with vitamin K antagonists: The specified variables assessed were summarized descriptively.

The quantitative variables were described with centralisation and dispersion measures, including: N, mean, median, SD (standard deviation), Q1 (first quartile), Q3 (third quartile), minimum and maximum.

The qualitative variables were described by absolute and relative frequencies. In the descriptive analysis of the qualitative variables two percentages were calculated: the total percentage (%) which was the percentage of the sum of valid responses plus missing values, and the valid percentage (% valid) which was the percentage of the total valid responses. The valid percentages (% valid) of the qualitative variables have been reported unless otherwise specified. All possible categories of the qualitative variables were presented.

Missing data were not imputed.</td></tr>
<tr><td>Results:</td><td>Analysis of the responses to the HRQoL questionnaire showed that the mean values (± SD) for the 5 dimensions were:
<table>
<tr><th>Dimensions of the Sawicki questionnaire</th><th>Controlled
Mean (SD)</th><th>Uncontrolled
Mean (SD)</th></tr>
<tr><td>General treatment satisfaction</td><td>4.9 (1.0)</td><td>3.6 (1.3)</td></tr>
<tr><td>Self-efficacy</td><td>4.3 (1.0)</td><td>3.6 (1.0)</td></tr>
<tr><td>Distress</td><td>3.1 (0.9)</td><td>3.9 (1.1)</td></tr>
<tr><td>Daily hassles</td><td>2.1 (0.8)</td><td>3.0 (1.0)</td></tr>
<tr><td>Strained social network</td><td>1.8 (0.9)</td><td>2.6 (1.2)</td></tr>
</table></td></tr>
</table>

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Data related to age, gender and race of controlled and uncontrolled patients is showed below:

		Controlled	Uncontrolled
Age [years], Mean (SD)		79.3 (8.8)	80.4 (8.7)
Gender [n (%)]	Female	152 (46.1)	95 (55.6)
	Male	178 (53.9)	76 (44.4)
Race [n (%)]	Caucasian	330 (100.0)	171 (100.0)

Data on work status of uncontrolled patients showed that the majority (73.7%) were retired. Marital status in these patients was distributed as follows: 46.2% married, 45.6% widowed, 4.7% single, and 3.5% divorced.

Descriptive analysis of uncontrolled patients also showed that this group had a mean (± SD) weight of 76.5 (± 16.1) kg, height of 163.1 (± 8.8) cm, and BMI of 28.7 (± 5.4) kg/m^2. The mean (± SD) was 57.2 (± 26.6) ml/min for creatinine clearance, 56.1 (±11.2) % for LVEF, 4.5 (± 1.4) for the CHA_2DS_2-VASc score, and 3.6 (± 1.1) for the HAS-BLED score. The percentage of patients who had ever suffered a thromboembolic and haemorrhagic event was 35.1% and 14.6%, respectively. The mean (± SD) number of visits to the internal medicine specialist was 3.1 (± 1.9) per year. Almost all patients had at least one other disease recorded and a concomitant treatment recorded (98.8% and 97.1%, respectively). Mean (± SD) time since diagnosis was 2.5 (± 3.2) years, age at diagnosis was 77.3 (± 8.7) years, and time since initiating treatment was 14.8 (± 6.3) years. The most common type of NVAF among uncontrolled patients was permanent (56.1%), followed by paroxysmal (29.8%), and persisting (13.5%).

One serious adverse event (upper gastrointestinal haemorrhage) related to dabigatran etexilate was reported. No fatal adverse events were reported.

Discussion:

The study presented HRQoL perceptions of NVAF patients on anticoagulants, either controlled or uncontrolled, assessed by the validated Spanish adaptation of the Sawicki questionnaire, which included five different dimensions (general treatment satisfaction, self-efficacy, distress, daily hassles and strained social network). From a descriptive point of view, controlled patients (treated with DOAC or VKA) had mean scores closer to a high perceived HRQoL in the 5 dimensions of the questionnaire, with remarkably high scores for general treatment satisfaction. These results suggest that TTR control might influence perceptions of HRQoL and highlight the importance of evaluate anticoagulation status, when assessing HRQoL.

An understanding of the factors that influence HRQoL is required in order to adapt economic evaluations to the characteristics of a specific patient population and assess the clinical and cost-effectiveness of different therapeutic alternatives. Our study provided a detailed description of the demographic and clinical profile of uncontrolled NVAF patients on anticoagulants, which should warrant further exploration of the extent to which particular demographic and clinical characteristics of these patients might influence perceptions of their HRQoL.

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