



Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
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.		
Keywords:	SPAF, dabigatran, NOAC management, NIS		
Rationale and background:	<p>Atrial fibrillation (AF) affects 1-2% of general population. In Spain, the latest data showed that prevalence of NVAf among general population is 4.4% in patients over 40 years-old and rises steeply above 60 years of age (3).</p> <p>One of the most concerning sequelae associated with AF is ischemic stroke with an incidence of about 5 % per year in the absence of appropriate prophylaxis (4). The current clinical guidelines for the management of atrial fibrillation recommend that patients with a CHA₂DS₂-VASc score higher than 1 for males or 2 for females receive preventive anticoagulant therapy (5).</p> <p>The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocoumarol. The management of these agents remains problematic because they require frequent routine coagulation monitoring and dose adjustment to maintain the intensity of anticoagulation within a safe and effective range. However, data show that 80% of patients receiving acenocoumarol in Spain, maintain a percentage of International Normalized Ratio (INRs) in therapeutic range between 44% -59% (6,7) and mean time in therapeutic range (TTR) of only 64% (6). Another recent study has showed that 40% of patients with NVAf who were receiving anticoagulation therapy with VKA in primary care in Spain had poor anticoagulation control (8).</p> <p>NOACs profile is safer in terms of intracerebral haemorrhage risk reduction, maintains the benefits of anticoagulant therapy and may increase perception of quality of life and satisfaction among patients because they do not necessitate the strict monitoring required for VKA. Likewise, maintaining a stable level of anticoagulation with NOACs prevents uncontrolled patients, improving patient outcomes and avoiding bleeding events (9).</p> <p>The importance of this proposed novel study lies in the new scenario in anticoagulation therapy in Spain which involves:</p>		
	- Recent publications in Real World Evidence (RWE) that compare efficacy, effectiveness and safety among different NOACs (10).		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
	<ul style="list-style-type: none"> - Recent launch of Praxbind to market (June 2016). - Changes in anticoagulants' prescription Spanish National guidelines - positioning therapeutic report (November 2016). (11) - Launch of new alternative (edoxaban) to market (September 2016). <p>All these topics could influence the prescription habits and the positioning of the different NOACs in different patient's profile, according to their clinical characteristics. Furthermore, patient could play a new role in this scenario, with a higher empowerment in decisions about his condition. Based on this assumption, it is considered interesting to describe the current anticoagulation management in Spain.</p>		
Research question and objectives:	<p>This study has been designed in order to describe the current anticoagulation management in Spain.</p> <p>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.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> - 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. <p>Further objectives:</p> <p>To evaluate the appropriateness of prescribed therapy based on Spanish health authorities' recommendations (positioning therapeutic report) per NOAC type and by autonomous community.</p>		
Study design:	<p>This was an observational, multicentre, cross-sectional study based on retrospective and newly collected data at the study visit. Cardiology departments from 102 sites in Spain were planned to be involved.</p> <p>The study was designed as an only visit performed by the patients as part of the routine follow-up on their disease.</p>		
Setting:	<p>Approximately 1000 patients with NVAF currently on NOAC treatment and having initiated their first NOAC starting from November 2016 (Health authorities positioning</p>		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
	<p>report publication) were planned to be included in the study. To minimize selection bias at the patient level, 10 consecutive patients from each site who met entry criteria were enrolled.</p> <p>It was necessary to ensure that study population was representative of the entire national territory. Cardiology departments, mainly in the public or private hospital setting (73 sites), who regularly prescribed NOACs for stroke prevention in NVAF patients were selected to participate. Few numbers of cardiologists from private consultations (9 sites) and private large clinics (5 sites) were also selected. Sites across the different geographical areas and according to the distribution of the overall population were selected in order to ensure representativeness of the NVAF population treated with NOACs.</p>		
Subjects and study size, including dropouts:	<p>Patients, mainly from the hospital setting, were included in the study if all of the following criteria were met:</p> <ol style="list-style-type: none"> 1. The patient was willing and provided written informed consent to participate in this study 2. The patient was at least 18 years of age 3. The patient had a diagnosis of non-valvular atrial fibrillation (NVAF) 4. The patient was on treatment with NOAC according to its approved local Summary of Product Characteristics (SmPC) and had initiated his first NOAC starting from November 2016 <p>Patients were excluded from participating in this study if they participated in any clinical trial of a drug or device, at the time of study initiation.</p>		
Variables and data sources:	<p>For the primary objective (variables collected at time of first NOAC initiation, baseline data collected from medical records):</p> <ul style="list-style-type: none"> - Age - CHA₂DS₂-VASc - HAS-BLED <p>Primary outcomes were defined as the CHA₂DS₂-VASc and HAS-BLED scores at the time of first NOAC initiation.</p>		
	<u>Covariates:</u>		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
<ul style="list-style-type: none"> - Demographic characteristics (gender, work status, life status) - Alcohol consumption - Physical activity - Weight - Systolic BP/Diastolic BP - AF diagnosis date - In case of previous treatment with VKA: treatment duration (start and stop date if available) and reasons for VKA treatment switch (collected as “reasons for NOAC prescription”). This variable has been considered for the secondary objective NOAC treatment management as well. - First NOAC initiated (active substance, dose, start date) - Kidney function (serum creatinine (mg/dl), creatinine clearance (Cockcroft-Gault equation) obtained from medical charts or auto-calculated) - Liver function (AST/ALT, total bilirubin) - Clinical history/Concomitant diseases (focused on those related with stroke and systemic embolism in patients with NVAf) - Concomitant treatments (focused on those related with stroke and systemic embolism prevention in patients with NVAf). <p>For the secondary objective:</p> <p>Secondary outcomes were defined as follows:</p> <ul style="list-style-type: none"> - Appropriateness of NOACs prescription - NOAC treatment management: <ul style="list-style-type: none"> o Duration of NOAC treatment o Number of visits to the physician (cardiologist) per year o Number of patients who required discontinuing the NOAC treatment, to adjust the NOAC dose or to change to a new NOAC 			
<ul style="list-style-type: none"> o Reason for treatment changes. o Number of patient with Previous Treatment with Vitamin K Antagonists 			

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
	<ul style="list-style-type: none"> ○ Duration of previous VKA treatment - Patient's knowledge about his/her condition <p><u>Variables collected at the time of the study visit, if required:</u></p> <ul style="list-style-type: none"> - In order to answer the secondary objective regarding patient's knowledge about his condition, all patients were asked four questions during the study visit. - In order to answer the secondary objective regarding treatment management, the following variables were to be collected during the study visit, if not present in patient's records: <ul style="list-style-type: none"> - History of NOAC treatments prior to current NOAC (if applicable): - Dose changes: start date - end date, new dose, reason - NOAC switch: start date - end date, dose and/or dose changes and reason - Frequency of visits to the physician (cardiologist). <p><u>Variables collected at time of first NOAC initiation, baseline data collected from medical records:</u></p> <p>The appropriateness of NOAC prescription based on national recommendations was described using a checklist that was validated with baseline variables already collected in patient's records.</p> <p>AE management and reporting procedures were implemented for the study. Any information identified during the review of patients records or during the study visit, which constituted an adverse reaction to a BI product or a fatal event in patients under dabigatran, were processed in line with applicable rules and regulations.</p>		
Statistical methods:	<p>In this non-interventional study, cross-sectional data at study baseline (defined at time of first NOAC initiation) was collected for NVAF patients currently receiving NOAC treatment.</p> <p>The analysis population consisted of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria).</p> <p>Descriptive analyses for all variables collected were developed. Categorical variables were summarized through frequencies and percentages. Continuous variables were summarized through measures of central tendency and dispersion: mean, standard deviation, median,</p>		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
	<p>interquartile range and extreme values (minimum and maximum). Since the study is descriptive, all variables included in the study objectives were summarized overall and by factors of interest.</p> <p>If patients had missing values for an outcome, those patients were excluded for that outcome's analysis and the data was considered as missing. Missing data was not imputed. For the primary outcome, baseline variables (at time of first NOAC initiation) were analysed descriptively overall and by NOAC type. Treatment groups were defined according to the first NOAC prescribed. Standardized differences between dabigatran and each of the other NOACs separately were estimated for these variables (baseline characteristics). Standardized differences higher than 10% (in absolute value) were indicative of imbalance between the compared groups.</p> <p>Secondary outcomes were carried out descriptively for the total sample, regardless of the type of NOAC prescribed to the patient.</p> <p>On the other hand, subgroup analysis were planned to be performed if sample size allowed it (at least 30 patients per subgroup):</p> <ul style="list-style-type: none"> - Exposure to VKA prior to first NOAC initiation - Appropriateness of prescribed NOAC therapy by NOAC and autonomous community - Subgroup analysis by time from 1st NOAC initiation to patient enrolment was also planned. (For this analysis a preliminary cut-off date of 3 months was defined). <p>No interim analysis was conducted for this study.</p>		
Results:	<p>Patients included for the study. Description of the sample:</p> <p>45 patients, out of the 1008 patients that were finally enrolled in the study, did not meet at least one of the selection criteria and were considered not eligible. Therefore, data analysis was finally carried out with 963 eligible patients, the mean age (\pmSD) being 73.6 ± 10.1 (median 74.8) years and the gender distribution being 57.8% males and 42.2% females. Race and ethnicity were not collected for this study. 905 (94%) out of 963 patients confirmed to have concomitant or relevant previous diseases, with hypertension (76.8%), hyperlipidaemia (38.9%), heart failure (23.4%) and diabetes mellitus (22.8%) being the most frequent of them.</p> <p>947 (98.3%) out of 963 patients confirmed to take concomitant medication, with angiotensin receptor blockers/angiotensin converting enzymes inhibitors (62.2%), beta-blockers (62%), diuretics (51.8%), statins (49.7%) and proton-pump inhibitors (37.4%), being the most frequently reported medications.</p>		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																																													
Name of finished medicinal product: Pradaxa®																																													
Name of active ingredient: B01AE07 - Dabigatran etexilate																																													
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																																										
<p>Regarding laboratory tests, the mean AST value (standard normal range 12-38 UI/L) was 26.1 UI/L (N=426 patients) and the mean ALT value (standard normal range 7-41 UI/L) was 26.3 UI/L (N=499 patients); the mean total bilirubin value (standard normal range 0.3-1.3 mg/dl) was 0.8 mg/dl (N=302 patients), and the mean creatinine clearance value (standard normal range >90 ml/min) was 73.4 ml/min (N=674 patients); 259 patients had the serum creatinine value (standard normal range <1.5 mg/dl) available with a mean of 0.94 mg/dl.</p> <p><u>Patients population description based on first NOAC prescribed:</u></p> <table border="1"> <thead> <tr> <th>First NOAC</th> <th>N</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Dabigatran</td> <td>314</td> <td>32.6</td> </tr> <tr> <td>Rivaroxaban</td> <td>253</td> <td>26.3</td> </tr> <tr> <td>Apixaban</td> <td>266</td> <td>27.6</td> </tr> <tr> <td>Edoxaban</td> <td>130</td> <td>13.5</td> </tr> <tr> <td>Total</td> <td>963</td> <td>100.0</td> </tr> </tbody> </table> <p>Primary objective: Baseline characteristics at the time of first NOAC initiation</p> <p><u>Age at the time of first NOAC:</u> as shown in the table, mean age at first NOAC initiation was similar among NOAC groups.</p> <table border="1"> <thead> <tr> <th>Age at first NOAC</th> <th>Mean</th> <th>S. Dev.</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>Global</td> <td>72.8</td> <td>10.1</td> <td>963</td> </tr> <tr> <td>Dabigatran</td> <td>72.8</td> <td>9.9</td> <td>314</td> </tr> <tr> <td>Rivaroxaban</td> <td>72.5</td> <td>10.7</td> <td>253</td> </tr> <tr> <td>Apixaban</td> <td>72.6</td> <td>9.8</td> <td>266</td> </tr> <tr> <td>Edoxaban</td> <td>74.0</td> <td>10.0</td> <td>130</td> </tr> </tbody> </table>				First NOAC	N	%	Dabigatran	314	32.6	Rivaroxaban	253	26.3	Apixaban	266	27.6	Edoxaban	130	13.5	Total	963	100.0	Age at first NOAC	Mean	S. Dev.	N	Global	72.8	10.1	963	Dabigatran	72.8	9.9	314	Rivaroxaban	72.5	10.7	253	Apixaban	72.6	9.8	266	Edoxaban	74.0	10.0	130
First NOAC	N	%																																											
Dabigatran	314	32.6																																											
Rivaroxaban	253	26.3																																											
Apixaban	266	27.6																																											
Edoxaban	130	13.5																																											
Total	963	100.0																																											
Age at first NOAC	Mean	S. Dev.	N																																										
Global	72.8	10.1	963																																										
Dabigatran	72.8	9.9	314																																										
Rivaroxaban	72.5	10.7	253																																										
Apixaban	72.6	9.8	266																																										
Edoxaban	74.0	10.0	130																																										

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																																																			
Name of finished medicinal product: Pradaxa®																																																			
Name of active ingredient: B01AE07 - Dabigatran etexilate																																																			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																																																
<p>CHA₂DS₂-VASc Score: Mean CHA₂DS₂-VASc score was 3.3 (±1.5) for eligible patients. This value was similar for each of the 4 types of NOAC.</p> <table border="1"> <thead> <tr> <th>CHA₂DS₂-VASc score</th> <th>Mean</th> <th>S. Dev.</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>Global</td> <td>3.3</td> <td>1.5</td> <td>942</td> </tr> <tr> <td>Dabigatran</td> <td>3.2</td> <td>1.5</td> <td>308</td> </tr> <tr> <td>Rivaroxaban</td> <td>3.3</td> <td>1.6</td> <td>251</td> </tr> <tr> <td>Apixaban</td> <td>3.3</td> <td>1.5</td> <td>254</td> </tr> <tr> <td>Edoxaban</td> <td>3.3</td> <td>1.5</td> <td>129</td> </tr> </tbody> </table> <p>83% patients had a high risk of stroke (score ≥2 in male; score ≥3 in female), 15.3% moderate risk (score 1 in male; score 2 in female) and 1.7% low risk of stroke (score 0 in male; score 1 in female). There were not standardized differences between NOACs in patients with high thromboembolic risk, however, in case of patients with moderate risk, there was a standardized difference between dabigatran vs. rivaroxaban (10.3%).</p> <p>The baseline risk characteristics at the time of first NOAC initiation on CHA₂DS₂-VASc score by type of first prescribed NOAC are shown in the figure below.</p> <table border="1"> <thead> <tr> <th>NOAC</th> <th>Low</th> <th>Moderate</th> <th>High</th> </tr> </thead> <tbody> <tr> <td>Dabigatran</td> <td>1.0%</td> <td>17.2%</td> <td>81.8%</td> </tr> <tr> <td>Rivaroxaban</td> <td>4.0%</td> <td>13.5%</td> <td>82.5%</td> </tr> <tr> <td>Apixaban</td> <td>1.2%</td> <td>14.2%</td> <td>84.6%</td> </tr> <tr> <td>Edoxaban</td> <td>0.0%</td> <td>16.3%</td> <td>83.7%</td> </tr> <tr> <td>Global</td> <td>1.7%</td> <td>15.3%</td> <td>83.0%</td> </tr> </tbody> </table>				CHA ₂ DS ₂ -VASc score	Mean	S. Dev.	N	Global	3.3	1.5	942	Dabigatran	3.2	1.5	308	Rivaroxaban	3.3	1.6	251	Apixaban	3.3	1.5	254	Edoxaban	3.3	1.5	129	NOAC	Low	Moderate	High	Dabigatran	1.0%	17.2%	81.8%	Rivaroxaban	4.0%	13.5%	82.5%	Apixaban	1.2%	14.2%	84.6%	Edoxaban	0.0%	16.3%	83.7%	Global	1.7%	15.3%	83.0%
CHA ₂ DS ₂ -VASc score	Mean	S. Dev.	N																																																
Global	3.3	1.5	942																																																
Dabigatran	3.2	1.5	308																																																
Rivaroxaban	3.3	1.6	251																																																
Apixaban	3.3	1.5	254																																																
Edoxaban	3.3	1.5	129																																																
NOAC	Low	Moderate	High																																																
Dabigatran	1.0%	17.2%	81.8%																																																
Rivaroxaban	4.0%	13.5%	82.5%																																																
Apixaban	1.2%	14.2%	84.6%																																																
Edoxaban	0.0%	16.3%	83.7%																																																
Global	1.7%	15.3%	83.0%																																																

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																											
Name of finished medicinal product: Pradaxa®																											
Name of active ingredient: B01AE07 - Dabigatran etexilate																											
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																								
<p><u>HAS-BLED score:</u></p> <p>The mean global HAS-BLED score was 1.8 ± 1.1 and very similar for individual NOACs. For apixaban, the HAS-BLED score was slightly lower (1.7 ± 1.1) compared with the other types of first NOACs prescribed.</p> <table border="1"> <thead> <tr> <th>HAS-BLED score</th> <th>Mean</th> <th>S. Dev.</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>Global</td> <td>1.8</td> <td>1.1</td> <td>940</td> </tr> <tr> <td>Dabigatran</td> <td>1.8</td> <td>1.0</td> <td>308</td> </tr> <tr> <td>Rivaroxaban</td> <td>1.8</td> <td>1.1</td> <td>251</td> </tr> <tr> <td>Apixaban</td> <td>1.7</td> <td>1.1</td> <td>253</td> </tr> <tr> <td>Edoxaban</td> <td>1.8</td> <td>1.0</td> <td>128</td> </tr> </tbody> </table> <p>23.8% of patients had a high risk for hemorrhage (score ≥ 3), 67.2% moderate risk (score 1-2) and 8.9% had a low risk (score 0). There were not standardized differences higher than 10% between NOACs in patients with high bleeding risk. However, in patients with moderate bleeding risk, the standardized difference between dabigatran and rivaroxaban was 18.3% and, in patients with low bleeding risk, the standardized difference was higher than 10% between dabigatran and all the other types of NOACs. Dabigatran had most of the patients with moderate bleeding risk, and the lowest percentage of patients with a low bleeding risk.</p> <p>The baseline characteristics at the time of first NOAC initiation on HAS-BLED score by type of first prescribed NOAC are shown in the figure:</p>				HAS-BLED score	Mean	S. Dev.	N	Global	1.8	1.1	940	Dabigatran	1.8	1.0	308	Rivaroxaban	1.8	1.1	251	Apixaban	1.7	1.1	253	Edoxaban	1.8	1.0	128
HAS-BLED score	Mean	S. Dev.	N																								
Global	1.8	1.1	940																								
Dabigatran	1.8	1.0	308																								
Rivaroxaban	1.8	1.1	251																								
Apixaban	1.7	1.1	253																								
Edoxaban	1.8	1.0	128																								

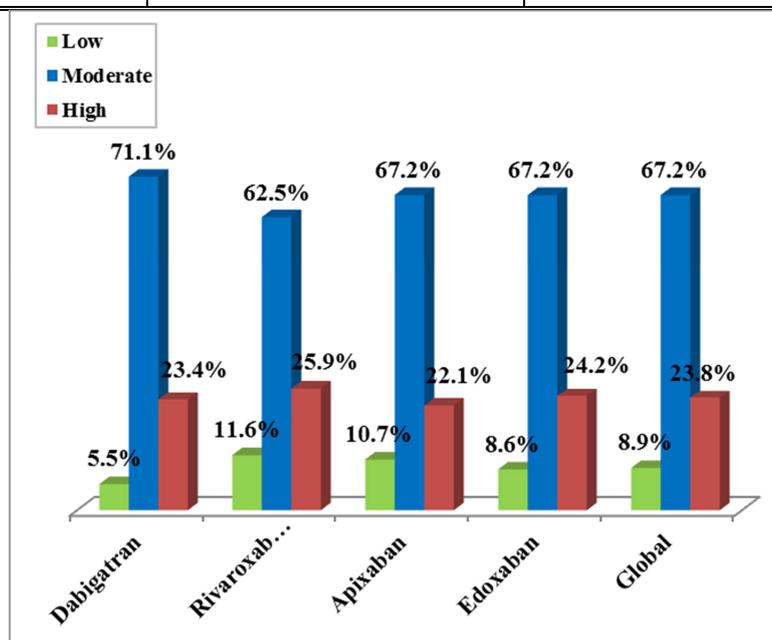
Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA

**Other covariates registered at the time of first NOAC initiation**

Previous and concomitant diseases: As shown in the table, a wide majority of patients, above 90% of patients and independently of the NOAC treatment, had concomitant diseases.

First NOAC	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Concomitant diseases	N	%	N	%	N	%	N	%
Yes	296	94.3	236	93.3	250	94.0	123	94.6
No	18	5.7	17	6.7	16	6.0	7	5.4
Total	314	100.0	253	100.0	266	100.0	130	100.0

There were standardized differences higher than 10% between NOACs for several concomitant diseases, with anaemia, cancer, rheumatic disease, gastric or duodenal ulcer, heart failure and coronary artery disease being the most relevant of them.

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																																																																			
Name of finished medicinal product: Pradaxa®																																																																			
Name of active ingredient: B01AE07 - Dabigatran etexilate																																																																			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																																																																
<p>Parameters of liver and kidney function: Similar mean values for AST, ALT and bilirubin were found among different NOAC groups. Creatinine clearance was between 70 and 75 ml/min for all patients. Laboratory parameters were calculated within the population of patients having these values entered in the eCRF.</p> <table border="1"> <thead> <tr> <th>Liver function</th> <th>Mean</th> <th>S. Dev.</th> <th>N</th> </tr> </thead> <tbody> <tr> <td colspan="4">AST (UI/L); standard normal ranges 12-38UI/L</td> </tr> <tr> <td>Dabigatran</td> <td>27.1</td> <td>17.1</td> <td>146</td> </tr> <tr> <td>Rivaroxaban</td> <td>24.4</td> <td>12.3</td> <td>102</td> </tr> <tr> <td>Apixaban</td> <td>26.3</td> <td>18.4</td> <td>120</td> </tr> <tr> <td>Edoxaban</td> <td>25.9</td> <td>13.2</td> <td>58</td> </tr> <tr> <td colspan="4">ALT (UI/L); standard normal range 7-41 UI/L</td> </tr> <tr> <td>Dabigatran</td> <td>26.1</td> <td>14.8</td> <td>157</td> </tr> <tr> <td>Rivaroxaban</td> <td>26.3</td> <td>20.6</td> <td>128</td> </tr> <tr> <td>Apixaban</td> <td>27.3</td> <td>25.7</td> <td>141</td> </tr> <tr> <td>Edoxaban</td> <td>25.0</td> <td>18.3</td> <td>73</td> </tr> <tr> <td colspan="4">Total bilirubin (mg/dl); standard normal range 0.3-1.3 mg/dl</td> </tr> <tr> <td>Dabigatran</td> <td>0.8</td> <td>0.4</td> <td>88</td> </tr> <tr> <td>Rivaroxaban</td> <td>0.9</td> <td>0.6</td> <td>90</td> </tr> <tr> <td>Apixaban</td> <td>0.8</td> <td>0.5</td> <td>86</td> </tr> <tr> <td>Edoxaban</td> <td>0.7</td> <td>0.3</td> <td>38</td> </tr> </tbody> </table>				Liver function	Mean	S. Dev.	N	AST (UI/L); standard normal ranges 12-38UI/L				Dabigatran	27.1	17.1	146	Rivaroxaban	24.4	12.3	102	Apixaban	26.3	18.4	120	Edoxaban	25.9	13.2	58	ALT (UI/L); standard normal range 7-41 UI/L				Dabigatran	26.1	14.8	157	Rivaroxaban	26.3	20.6	128	Apixaban	27.3	25.7	141	Edoxaban	25.0	18.3	73	Total bilirubin (mg/dl); standard normal range 0.3-1.3 mg/dl				Dabigatran	0.8	0.4	88	Rivaroxaban	0.9	0.6	90	Apixaban	0.8	0.5	86	Edoxaban	0.7	0.3	38
Liver function	Mean	S. Dev.	N																																																																
AST (UI/L); standard normal ranges 12-38UI/L																																																																			
Dabigatran	27.1	17.1	146																																																																
Rivaroxaban	24.4	12.3	102																																																																
Apixaban	26.3	18.4	120																																																																
Edoxaban	25.9	13.2	58																																																																
ALT (UI/L); standard normal range 7-41 UI/L																																																																			
Dabigatran	26.1	14.8	157																																																																
Rivaroxaban	26.3	20.6	128																																																																
Apixaban	27.3	25.7	141																																																																
Edoxaban	25.0	18.3	73																																																																
Total bilirubin (mg/dl); standard normal range 0.3-1.3 mg/dl																																																																			
Dabigatran	0.8	0.4	88																																																																
Rivaroxaban	0.9	0.6	90																																																																
Apixaban	0.8	0.5	86																																																																
Edoxaban	0.7	0.3	38																																																																

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																																																	
Name of finished medicinal product: Pradaxa®																																																	
Name of active ingredient: B01AE07 - Dabigatran etexilate																																																	
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																																														
		<table border="1"> <thead> <tr> <th>Kidney function</th> <th>Mean</th> <th>S. Dev.</th> <th>N</th> </tr> </thead> <tbody> <tr> <td colspan="4">Serum creatinine (mg/dl); standard normal range <1.5 mg/dl</td> </tr> <tr> <td>Dabigatran</td> <td>0.94</td> <td>0.21</td> <td>85</td> </tr> <tr> <td>Rivaroxaban</td> <td>0.93</td> <td>0.24</td> <td>72</td> </tr> <tr> <td>Apixaban</td> <td>0.93</td> <td>0.27</td> <td>61</td> </tr> <tr> <td>Edoxaban</td> <td>1.01</td> <td>0.32</td> <td>41</td> </tr> <tr> <td colspan="4">CrCl* (ml/min); standard normal range >90ml/min</td> </tr> <tr> <td>Dabigatran</td> <td>75.1</td> <td>26.1</td> <td>191</td> </tr> <tr> <td>Rivaroxaban</td> <td>73.7</td> <td>23.1</td> <td>181</td> </tr> <tr> <td>Apixaban</td> <td>72.9</td> <td>23.9</td> <td>197</td> </tr> <tr> <td>Edoxaban</td> <td>70.5</td> <td>20.9</td> <td>105</td> </tr> </tbody> </table>		Kidney function	Mean	S. Dev.	N	Serum creatinine (mg/dl); standard normal range <1.5 mg/dl				Dabigatran	0.94	0.21	85	Rivaroxaban	0.93	0.24	72	Apixaban	0.93	0.27	61	Edoxaban	1.01	0.32	41	CrCl* (ml/min); standard normal range >90ml/min				Dabigatran	75.1	26.1	191	Rivaroxaban	73.7	23.1	181	Apixaban	72.9	23.9	197	Edoxaban	70.5	20.9	105		
Kidney function	Mean	S. Dev.	N																																														
Serum creatinine (mg/dl); standard normal range <1.5 mg/dl																																																	
Dabigatran	0.94	0.21	85																																														
Rivaroxaban	0.93	0.24	72																																														
Apixaban	0.93	0.27	61																																														
Edoxaban	1.01	0.32	41																																														
CrCl* (ml/min); standard normal range >90ml/min																																																	
Dabigatran	75.1	26.1	191																																														
Rivaroxaban	73.7	23.1	181																																														
Apixaban	72.9	23.9	197																																														
Edoxaban	70.5	20.9	105																																														
*Autocalculated creatinine clearance or using Cockcroft-Gault equation																																																	
Concomitant treatments: A wide majority of patients, above 90% of patients and regardless the NOAC treatment, used concomitant treatments.																																																	
<table border="1"> <thead> <tr> <th rowspan="2">First NOAC</th> <th colspan="2">Dabigatran</th> <th colspan="2">Rivaroxaban</th> <th colspan="2">Apixaban</th> <th colspan="2">Edoxaban</th> </tr> <tr> <th>N</th> <th>%</th> <th>N</th> <th>%</th> <th>N</th> <th>%</th> <th>N</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Yes</td> <td>311</td> <td>99.0</td> <td>249</td> <td>98.4</td> <td>264</td> <td>99.2</td> <td>123</td> <td>94.6</td> </tr> <tr> <td>No</td> <td>3</td> <td>1.0</td> <td>4</td> <td>1.6</td> <td>2</td> <td>0.8</td> <td>7</td> <td>5.4</td> </tr> <tr> <td>Total</td> <td>314</td> <td>100.0</td> <td>253</td> <td>100.0</td> <td>266</td> <td>100.0</td> <td>130</td> <td>100.0</td> </tr> </tbody> </table>						First NOAC	Dabigatran		Rivaroxaban		Apixaban		Edoxaban		N	%	N	%	N	%	N	%	Yes	311	99.0	249	98.4	264	99.2	123	94.6	No	3	1.0	4	1.6	2	0.8	7	5.4	Total	314	100.0	253	100.0	266	100.0	130	100.0
First NOAC	Dabigatran		Rivaroxaban		Apixaban		Edoxaban																																										
	N	%	N	%	N	%	N	%																																									
Yes	311	99.0	249	98.4	264	99.2	123	94.6																																									
No	3	1.0	4	1.6	2	0.8	7	5.4																																									
Total	314	100.0	253	100.0	266	100.0	130	100.0																																									
There were standardized differences higher than 10% between NOACs for several concomitant treatments, with antiarrhythmic and antiplatelet treatments being the most relevant of them.																																																	
Secondary objectives:																																																	
Appropriateness of NOACs prescription: Based on national recommendations (positioning therapeutic report), the most common reason for the usage of the first NOAC was the difficulty with the VKA treatment in the maintenance of INR control within range (2-3) despite patient's good therapeutic compliance (271, 28.1% of patients). Other common reasons for the prescription of the first NOAC were the impossibility to have access to the conventional INR control (102, 10.6% of patients) or																																																	

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																														
Name of finished medicinal product: Pradaxa®																														
Name of active ingredient: B01AE07 - Dabigatran etexilate																														
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																											
		<p>a known hypersensitivity or specific contraindication to the use of acenocoumarol or warfarin (88, 9.1% of patients). Further details are in the table below.</p> <table border="1"> <caption>Reasons for NOAC Initiation</caption> <thead> <tr> <th>Reason</th> <th>Percentage</th> <th>n</th> </tr> </thead> <tbody> <tr> <td>Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin</td> <td>9.1%</td> <td>88</td> </tr> <tr> <td>Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase)</td> <td>1.0%</td> <td>10</td> </tr> <tr> <td>Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH</td> <td>1.7%</td> <td>16</td> </tr> <tr> <td>Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control</td> <td>1.7%</td> <td>16</td> </tr> <tr> <td>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</td> <td>28.1%</td> <td>271</td> </tr> <tr> <td>Impossibility of access to conventional INR control</td> <td>10.6%</td> <td>102</td> </tr> <tr> <td>Other reason</td> <td>35.5%</td> <td>342</td> </tr> <tr> <td>Unknown</td> <td>12.3%</td> <td>118</td> </tr> </tbody> </table>		Reason	Percentage	n	Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin	9.1%	88	Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase)	1.0%	10	Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH	1.7%	16	Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control	1.7%	16	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	28.1%	271	Impossibility of access to conventional INR control	10.6%	102	Other reason	35.5%	342	Unknown	12.3%	118
Reason	Percentage	n																												
Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin	9.1%	88																												
Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase)	1.0%	10																												
Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH	1.7%	16																												
Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control	1.7%	16																												
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	28.1%	271																												
Impossibility of access to conventional INR control	10.6%	102																												
Other reason	35.5%	342																												
Unknown	12.3%	118																												
		<p>By grouping the different reasons for the initiation of the first NOAC into “clinical reasons” (combination of the first four reasons) or “situations related to INR control” (5th and 6th reasons of the listing shown in the above figure), we found that the most common reasons leading to the prescription of the first NOAC were related to “situations regarding INR control” (38.7%), while “clinical reasons” were reported for 13.5% of patients, and “Other reasons” were reported for the 35.5 % of patients. Within the section "Other reasons", "decision of the investigator/patient" (230/342) was reported the most frequently. (The figure below represents the strength (23.9%) of this reason in relation to the rest of the reasons already mentioned). This distribution differs from the positioning therapeutic report in which the investigator/patients decision is not considered.</p>																												

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

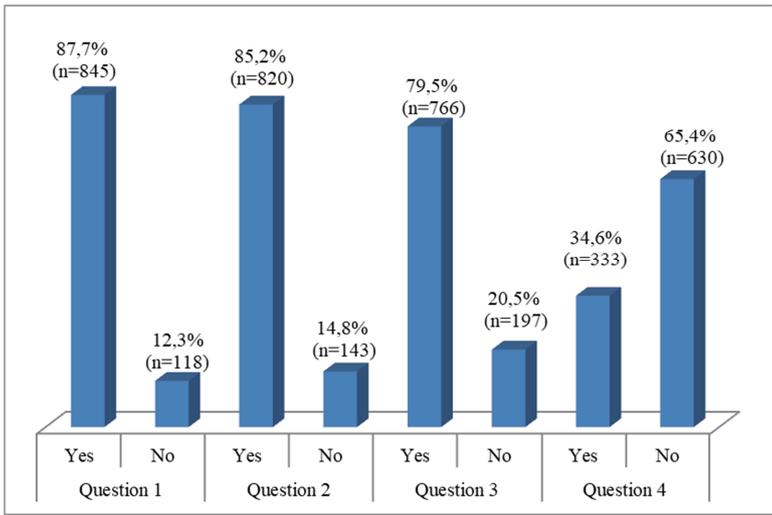
Name of company: Boehringer Ingelheim															
Name of finished medicinal product: Pradaxa®															
Name of active ingredient: B01AE07 - Dabigatran etexilate															
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA												
<table border="1"> <caption>Reason for prescription of the first NOAC</caption> <thead> <tr> <th>Reason</th> <th>% patients</th> </tr> </thead> <tbody> <tr> <td>Clinical reasons</td> <td>13.5</td> </tr> <tr> <td>Related to INR control</td> <td>38.7</td> </tr> <tr> <td>Investigator - patient decision</td> <td>23.9</td> </tr> <tr> <td>Other</td> <td>11.6</td> </tr> <tr> <td>Unknown</td> <td>12.3</td> </tr> </tbody> </table>				Reason	% patients	Clinical reasons	13.5	Related to INR control	38.7	Investigator - patient decision	23.9	Other	11.6	Unknown	12.3
Reason	% patients														
Clinical reasons	13.5														
Related to INR control	38.7														
Investigator - patient decision	23.9														
Other	11.6														
Unknown	12.3														
<p><u>NOAC treatment management:</u> Dabigatran (32.6%) was shown to be the most common first NOAC prescribed. All NOACs were prescribed according to the indication of each corresponding SmPC. Duration of NOAC treatment had a mean value of 9.6 (± 6.5) months for all NOAC considered and 9.4 (± 6.5) months for the first NOAC. 56 (5.8%) patients required changes in their NOAC treatment concerning the initial NOAC prescribed. Of those, 4 patients (0.4%) discontinued the NOAC treatment, 20 patients (2.1%) required a dose adjustment, and 32 patients (3.3%) changed to a new NOAC. Regarding the doses of NOAC prescribed, apixaban 5 mg was the most commonly dose used (220 patients, 22.8%), followed by dabigatran 150 mg (198 patients, 20.6%) and rivaroxaban 20 mg (197 patients, 20.5%). The most common dose of the new NOAC prescribed was apixaban 5mg (8 patients), followed by dabigatran 110mg (5 patients), dabigatran 150mg (4 patients), rivaroxaban 20mg (4 patients) and edoxaban 60mg (4 patients). Mean frequency of visits to the physician (cardiologist) was 2.0 (± 1.1) per year.</p> <p>44% of all patients had previous treatment with VKA, ranging from 37.6% for apixaban to 49.4% for rivaroxaban. Mean duration (months) of previous VKA treatment was 34.0 (edoxaban), 37.0 (rivaroxaban), 46.6 (dabigatran), and 54.5 (apixaban).</p>															

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim																												
Name of finished medicinal product: Pradaxa®																												
Name of active ingredient: B01AE07 - Dabigatran etexilate																												
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA																									
<p><u>Patient's knowledge about his/her condition:</u> Almost 80% of patients reported to have knowledge about their disease and about the anticoagulation treatment that they were receiving. On the other hand, nearly 35% of patients cared about taking their treatment.</p>  <table border="1"> <thead> <tr> <th>Question</th> <th>Yes (%)</th> <th>Yes (n)</th> <th>No (%)</th> <th>No (n)</th> </tr> </thead> <tbody> <tr> <td>Question 1</td> <td>87.7%</td> <td>845</td> <td>12.3%</td> <td>118</td> </tr> <tr> <td>Question 2</td> <td>85.2%</td> <td>820</td> <td>14.8%</td> <td>143</td> </tr> <tr> <td>Question 3</td> <td>79.5%</td> <td>766</td> <td>20.5%</td> <td>197</td> </tr> <tr> <td>Question 4</td> <td>34.6%</td> <td>333</td> <td>65.4%</td> <td>630</td> </tr> </tbody> </table> <p>Question 1. Do you know why are you being treated with an anticoagulant?</p> <p>Question 2. Do you know which is the effect of the anticoagulant treatment?</p> <p>Question 3. Do you know what could happen if you do not take the anticoagulant treatment?</p> <p>Question 4. Do you mind taking the anticoagulant treatment?</p> <p>Only one subgroup analysis could be finally performed due to the sample size required for each subgroup (at least 30 patients per subgroup were required to perform the analysis). It was the subgroup analysis by time from 1st NOAC initiation to patient enrolment: 195 (20.2%) patients were newly initiated (1st NOAC was initiated within 3 months before the enrolment), with a mean age at first NOAC initiation of 71.4 years old, a CHA2DS2-VASc mean score of 3.0 and a HAS-BLED mean score of 1.6.</p> <p>768 (79.8%) patients were non-newly initiated, with a mean age of 73.2 years old, a CHA2DS2-VASc mean score of 3.4 and a HAS-BLED mean score of 1.8; 195 (20.2%).</p>				Question	Yes (%)	Yes (n)	No (%)	No (n)	Question 1	87.7%	845	12.3%	118	Question 2	85.2%	820	14.8%	143	Question 3	79.5%	766	20.5%	197	Question 4	34.6%	333	65.4%	630
Question	Yes (%)	Yes (n)	No (%)	No (n)																								
Question 1	87.7%	845	12.3%	118																								
Question 2	85.2%	820	14.8%	143																								
Question 3	79.5%	766	20.5%	197																								
Question 4	34.6%	333	65.4%	630																								

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
	<u>Safety results:</u> ADR and fatal AE were not included in the objectives of this non-interventional study, and they were only collected for one of the NOACs (dabigatran) to meet with the regulatory and pharmacovigilance requirements. From the information collected on dabigatran, no new or relevant safety information has been identified.		
Conclusion:	<p>From the mean values obtained for each of the baseline characteristics analysed in this study, we could conclude that the typical patient profile with NVAf who initiates treatment with a NOAC is a patient of advanced age, with a high stroke risk, moderate haemorrhagic risk, multiple comorbidities and concomitant treatments, and mainly without serious alterations of the hepatic and renal function. Comorbidities and concomitant treatments may influence the selection of NOAC. However, thromboembolic or haemorrhagic risks do not seem to have any impact on product selection as both CHA2DS2-VASc scores and HAS-BLED scores were very similar for all NOACs.</p> <p>In general, the Spanish health authorities criteria (therapeutic positioning report) were followed when prescribing a NOAC, although investigator criteria and patient's preferences were also considered for this decision. Patients undergoing treatment with NOAC seemed to have good understanding of their anticoagulation treatment and its relevance. The majority of patients also accepted well their treatment with a NOAC, although the number of patients (333, 34.6%) that reported to have any concern regarding the intake of the treatment should be further explored.</p> <p>The study only allowed the inclusion of patients that had started their NOAC treatment from November 2016 onwards, and recruitment was focused in the hospital setting. These limitations should be considered when interpreting the results of this study.</p> <p>The reported serious and non-serious adverse drug reactions collected for dabigatran in this study were consistent with the known/listed side effects of the molecule. Overall, no changes were observed in the safety profile of dabigatran.</p>		
Marketing Authorisation Holder(s):	<p><u>MAH:</u> Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein</p> <p><u>This study is initiated, managed and sponsored by:</u> Boehringer Ingelheim España, S.A C/ Prat de la Riba, 50</p>		

Non-interventional Study Report

BI Study Number 1160-0287

c30745952-01

Proprietary confidential information © 2020 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Report date: 09 Jan 2020	Study number: 1160-0287	Version/Revision: 01	Version/Revision date: NA
08174 Sant Cugat del Vallès (Barcelona)			
Names and affiliations of principal investigators:	Coordinating Investigators: <div style="background-color: black; height: 15px; width: 100%;"></div> <div style="background-color: black; height: 15px; width: 80%;"></div> <div style="background-color: black; height: 15px; width: 70%;"></div>		