# 1. ABSTRACT

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| | |
|---|---|
| **Title of study:** | Pradaxa Initiation Post-Stroke Study: SITS-Pradaxa 1.<br>A retrospective analysis of existing data from the SITS-AF Registry on treatment initiation of dabigatran etexilate in non-valvular atrial fibrillation patients hospitalized with acute ischemic stroke |
| **Keywords:** | Stroke, non-valvular atrial fibrillation, prevention. |
| **Rationale and background:** | The optimal time range for initiation of dabigatran after acute ischemic stroke is not established. We aimed to evaluate the timing of dabigatran initiation in NVAF patients hospitalized after first ever acute ischemic stroke in routine clinical practice.<br>To address this question data from the SITS-AF Registry were extracted for retrospective analyses. |
| **Research questions, study objectives and outcomes:** | **Primary Objective:**<br>To evaluate the timing of dabigatran treatment initiation in patients with non-valvular atrial fibrillation (NVAF) after hospitalization for first ever ischaemic stroke (the index event) in order to prevent secondary stroke.<br>With primary outcome:<br>• Number of NVAF patients, according to the timing of dabigatran treatment initiation after the index event, categorized according to the following dabigatran initiation time periods: 0-24h, >24-72h, >3-7d >7-14d, >14-28d, >28d- 3m.<br>**Secondary Objectives:**<br>To describe baseline characteristics for patients treated with dabigatran according to time of dabigatran initiation.<br>To describe self-reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting.<br>To describe self-reported factors important for physician's decision as to which dabigatran dose was used in the post-ischemic stroke setting.<br>With the following secondary outcomes: |

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| | |
|---|---|
| | • Baseline and demographic characteristics of patients, who have been treated with dabigatran within 3 months after the index event, according to time of dabigatran initiation, based on information available for time of treatment initiation.<br>• Frequency of physician responses specifying the reasons for delay of dabigatran initiation, and where possible, also specified per dabigatran initiation time point.<br>• Frequency of physician responses specifying the reasons for choosing the 220 mg or 300 mg dabigatran daily dose. |
| **Study design:** | This was a retrospective observational study using existing data from the SITS-AF registry, exploring the use of dabigatran in NVAF patients after their first ever ischaemic stroke. |
| **Setting:** | European Stroke Centres continuously registering patients with NVAF presenting with their first ever stroke into the SITS-AF Registry during July 2014 to July 2018. For dabigatran patients, follow-up period was 3 months after the index event. |
| **Subjects and study size, including dropouts:** | Subjects: NVAF patients ≥ 18 years old, hospitalized after first-ever acute ischemic stroke receiving an oral anticoagulant (OAC) within 3 months after the index event during July 2014 to July 2018 from European centres.<br>Study size and dropout:<br>• Planned: Approximately 1000 NVAF patients who are treated with dabigatran etexilate within 3 months of their first ischemic stroke (index event) constitute the main analysis population.<br>• Actual: The dataset comprised of 1489 NVAF patients with first-ever acute ischaemic stroke (AIS) who received dabigatran treatment for secondary prevention. Information regarding dabigatran initiation timing was available in 1240 patients. |
| **Variables and data sources:** | Data source: SITS-International AF registry.<br>Main variables: Baseline and demographic characteristics, prestroke modified Rankin Scale (mRS), $CHADS_2$, $CHA_2DS_2$-VASc score (scoring |

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| | |
|---|---|
| | of congestive heart failure, hypertension, age (≥ 75), diabetes mellitus, stroke/transient ischaemic attack (TIA), vascular disease, age 65-74, sex category) and HAS-BLED score (including scores for hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile International normalized ratio (INR), elderly (>65 years), drugs and alcohol use) , stroke severity per the National Institute of Health Stroke Scale (NIHSS), medication history, prior oral anticoagulant treatment and at the time of index event, lab test, imaging data at admission, time interval in days between index event and start of dabigatran and physicians' reasons for delaying dabigatran initiation. From the date of index event (first ever stroke) dabigatran patients were followed for 3 months. |
| **Statistical methods:** | Primary and secondary outcomes were summarized descriptively.<br>Univariate and multivariate linear regression models with the dependent variable of time-to-initiation were applied to assess which demographic and clinical factors are associated with initiation of dabigatran time.<br>No interim analysis was done for this study. |
| **Results:** | 1489 NVAF patients (mean age 75 ± 10, 52.9% female) with first-ever acute ischaemic stroke (AIS), who received dabigatran treatment for secondary prevention of stroke were included.<br>For 1240 patients (mean age 75 ± 10, 52.9% female) information on time of dabigatran initiation after the index event was available: the results are shown in the following table: |

| Dabigatran initiation time period | N | % |
|---|---|---|
| 0-24h | 73 | 5,9 |
| >24-72h | 190 | 15,3 |
| >3-7d | 344 | 27,7 |
| >7-14d | 410 | 33,1 |
| >14-28d | 174 | 14,0 |
| >28d-3m | 49 | 4,0 |
| **Total** | **1240** | **100,0** |

With h = hours, d = days, m = months.

Most patients (82%) initiated dabigatran within 14 days after the index

| **Name of company:** Boehringer Ingelheim | | | |
|---|---|---|---|
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

event.

Patients with lower stroke severity at baseline initiated dabigatran earlier: from median NIHSS 8 (Inter Quartile Range, IQR 6-13) for patients who initiated dabigatran within 7 days, to NIHSS 15 (9-19) who initiated between 28 days and 3 months.

Race or ethnicity data were not extracted according to protocol.

Baseline characteristics, for the 1489 NVAF patients who were initiated with dabigatran, reported with a frequency above 10% were: hypertension (77%), previous AF (55.7%), hyperglycemia (28.5%), diabetes (17.8%), use of an oral anticoagulant prior to the index event (14.5%), vascular disease (12.3%), signs of acute infarct (11.8%), congestive heart failure (10.6%). Median NIHSS at baseline was 11 (IQR 6-16).

Important demographic and baseline characteristics of patients, with known timing of dabigatran initiation after the index event are shown in the following table:

| **Timing dabigatran initiation No. of patients (N)** | **Overall N=1240** | **< 24 h N=73** | **> 24 – 72 h N=190** | **> 3 – 7 d N=344** | **> 7 – 14 d N=410** | **> 14 – 28 d N=174** | **>28d – 3m N=49** |
|---|---|---|---|---|---|---|---|
| Age (Mean, SD) (Median, IQ) | 75 ± 10 (69-82) | 72 ± 11 (69-75) | 74 ± 10 (73-76) | 75 ± 9 (73-76) | 75 ± 9 (74-77) | 76 ± 9 (74-78) | 77 ± 10 (73-80) |
| NIHSS baseline (Median, IQ) | 10 (6-16) | 8 (5-14) | 8 (5-14) | 8 (6-13) | 12 (7-17) | 14 (10-18) | 15 (9-19) |
| DBP (mm Hg, Mean, SD) | 85 ± 15 | 87 ± 12 | 83 ± 15 | 84 ± 14 | 85 ± 15 | 85 ± 17 | 91 ± 16 |
| History of / predisposition to bleeding (%) | 2.6% | 2.1% | 1.1% | 3.0% | 3.0% | 1.8% | 4.4% |
| Previous mRS (Median, IQ) | 0 (0-0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0-1) |
| Previous CHA2DS2-VASc (Mean, 95%CI) (Median, IQ) | 3.1 (3-3.2) 3 (2-4) | 2.9 (2.5-3.2) 3 (1-5) | 3.2 (3-3.4) 3 (1-5) | 3.2 (3-3.3) 3 (1-5) | 3.2 (3.1-3.4) 3 (1-5) | 3.3 (3.-3.5) 3 (1-5) | 3.4 (3.1-3.8) 3.5 (2.5-4.5) |
| Previous HAS-BLED (Mean, 95%CI) (Median, IQ) | 1.7 (1.7-1.8) 1 (1-2) | 1.1 (0.9-1.3) 1 (0-3) | 1.3 (1.2-1.3) 1 (0-2) | 1.2 (1.2-1.3) 1 (0-2) | 1.3 (1.2-1.4) 1 (0-1) | 1.2 (1-1.3) 1 (1-1) | 1.2 (1.1-1.4) 1 (0-2) |

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

Factors associated with initiation of dabigatran time:

Univariate analysis showed (see table below) that a higher NIHSS score at baseline and a higher pre-stroke mRS score were significantly correlated with a later dabigatran initiation.

| Variable | Mean ± Std. Deviation | P value | $r^2$ |
|---|---|---|---|
| Onset to OAC | 9,93 ± 9,02 | | |
| NIHSS Baseline (N=1183) | 11.4 ± 6 | < 0 001 | 0.07 |
| Previous mRS (N=1162) | 0.43 ± 0.93 | 0.01 | 0 005 |

Multivariate regression analysis of variables indicated in the table below showed that an older age, a higher DBP at baseline, a higher score on CHA2DS2-VASc were significantly associated with a later dabigatran initiation. We also found that a history or predisposition to bleeding was associated with an early dabigatran initiation. An explanation for this could be that in patients with a high burden of vascular risk factors the bleeding risk is not decisive because the embolic risk is higher than the haemorrhagic risk.

| Variable | Beta (ß) | Odds Ratio | 95% Confidence Interval | P value |
|---|---|---|---|---|
| Age | 0.12 | 1.13 | 1.02-1.25 | 0.016 |
| DBP | 0.12 | 1.12 | 1.04-1.21 | 0.002 |
| CHA2DS2-VASc | 0.1 | 1.10 | 1-1.21 | 0.04 |
| HAS-BLED | -0.1 | 0.9 | 0.45-1 | 0.051 |
| History/ Predisposition To Bleeding | -0.09 | 0.91 | 0.9-0.93 | 0.026 |

The physician's self-reported factors for delaying dabigatran initiation are shown in the next table. The most frequent reported reasons for delay were stroke severity, infarct (AIS) size, haemorrhagic transformation, patient's bleeding risk factors, location of the infarct and spontaneous intracranial haemorrhage.

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| Reasons for delay dabigatran initiation | N | Percent |
|---|---|---|
| Haemorrhagic transformation | 40 | 14,9% |
| Intracranial haemorrhage, spontaneous | 8 | 3,0% |
| Severity Infarct | 61 | 22,8% |
| Size of Infarct | 52 | 19,4% |
| Location Infarct | 14 | 5,2% |
| Intervention used to treat ischemic stroke | 8 | 3,0% |
| Altered coagulation parameters | 5 | 1,9% |
| Patients bleeding risk factors | 18 | 6,7% |
| Patients stroke risk factors | 6 | 2,2% |
| Patient preference | 4 | 1,5% |
| Recommendation from specialist | 6 | 2,2% |
| Practical considerations | 14 | 5,2% |
| Reason is not specified | 27 | 10,1% |
| Other reasons | 5 | 1,9% |
| **Total** | **268** | **100,0%** |

Note: Where 'Infarct' is mentioned, the index event (acute ischaemic stroke) is meant.

Analysis of the reported reasons for delay per dabigatran initiation time period showed that the highest number of reasons to delay dabigatran initiation were reported for the initiation time periods >7-14 days and >14-28 days (see next table)

| **Name of company:** Boehringer Ingelheim | | | |
|---|---|---|---|
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| **Reasons for delay in dabigatran initiation** | **Start Dabigatran** | | | | | | **Total** |
|---|---|---|---|---|---|---|---|
| | < 24 h | >24 - 72 h | >3 - 7 days | >7 - 14 days | >14 - 28 days | >28 days - 3m | |
| Haemorrhagic transformation | 0 | 0 | 2 | 2 | 8 | 1 | 13 |
| ICH Spontaneous | 0 | 0 | 0 | 1 | 3 | 0 | 4 |
| Severity Infarct | 0 | 0 | 1 | 7 | 12 | 2 | 22 |
| Size of Infarct | 0 | 0 | 2 | 9 | 12 | 3 | 26 |
| Location Infarct | 0 | 0 | 0 | 3 | 2 | 0 | 5 |
| Intervention used to treat ischemic stroke | 0 | 0 | 0 | 2 | 3 | 0 | 5 |
| Altered coagulation parameters | 0 | 0 | 0 | 2 | 1 | 0 | 3 |
| Patients bleeding risk factors | 0 | 1 | 0 | 4 | 6 | 0 | 11 |
| Patients stroke risk factors | 0 | 0 | 0 | 2 | 2 | 1 | 5 |
| Recommendation from specialist | 0 | 0 | 0 | 0 | 2 | 1 | 3 |
| Practical considerations | 1 | 1 | 0 | 0 | 3 | 3 | 8 |
| Reason is not specified | 0 | 0 | 1 | 5 | 4 | 1 | 11 |
| Other reasons | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| **Total** | **1** | **2** | **6** | **26** | **42** | **10** | **87** |

The physicians self-reported reasons for choosing the dabigatran dose are shown in the table below, with the most important factors shown in 'bold' text: (in > 10% of the patients) : 'patient's age', 'stroke risk', 'renal function', 'recommendation from specialist', and for a relatively high proportion of patients the reason was not specified.

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 11 Jun 2020 | **Study number:** 1160-0235 | **Version/Revision:** 1.0 | **Version/Revision date:** NA |

| **Dabigatran dose at discharge:** | **110 mg b.i.d** | **150 mg b.i.d** |
|---|---|---|
| **Number of patients (N) with physicians reported reason for dose choice:** | **382** | **475** |
| **Reasons for dose choice:** | **Number of times (% of N)** | **Number of times (% of N)** |
| Haemorrhagic transformation | 6 (1.6%) | _____ |
| ICH spontaneous | 3 (0.8%) | 1 (0.2%) |
| Severity of stroke | 18 (4.7%) | 38 (8%) |
| Size of infarct | 13 (3.4%) | 16 (3.4%) |
| Location of infarct | 8 (2.1%) | 18 (3.8%) |
| Intervention used to treat stroke | 4 (1%) | 3 (0.6%) |
| Altered coagulation parameters | 7 (1.8%) | 10 (2.1%) |
| Patients bleeding risk | 24 (6.3%) | 34 (7.2%) |
| **Patients stroke risk** | **27 (7.1%)** | **89 (18.7%)** |
| **Recommendation from specialist** | **32 (8.4%)** | **50 (10.5%)** |
| **Reason is not specified** | **95 (24.9%)** | **216 (45.5%)** |
| Other reasons | 10 (2.6%) | 1 (0.2%) |
| **Patients age** | **209 (54.7%)** | **139 (29.3%)** |
| Co-medication | 11 (2.9%) | 5 (1.1%) |
| Co-morbidities | 16 (4.2%) | 19 (4%) |
| **Renal function** | **48 (12.6%)** | **47 (9.9%)** |

Since this was a retrospective study using existing data, no (serious) adverse events were collected.

| | |
|---|---|
| **Discussion:** | This is the first study reporting initiation time for dabigatran after an AIS. These results show that in clinical practice, dabigatran was most commonly initiated within 2 weeks of hospitalization for first-ever acute ischemic stroke in NVAF patients. The main reasons for delayed initiation were stroke severity/infarct size and haemorrhagic transformation. |
| **Marketing Authorisation Holder(s):** | Boehringer Ingelheim International GmbH, Ingelheim, Germany D-55216 Ingelheim am Rhein |
| **Names and affiliations of principal investigators:** | [redacted] MD, PhD. [redacted] Stockholm, SWEDEN. |