Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Dabigatran etexilate			
Name of active ingredient: Dabigatran etexilate			
Report date: 18 Feb 2020	**Study number:** 1160.188	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	ChaRactErization of patients following aCute venous thrOmboembolism (VTE) and assessment of safety and effectiveness of dabigatran etexilate (DE) in the tReatment and secondarY prevention of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in comparison to vitamin K antagonist (VKA) in routine clinical practice - **RE-COVERY DVT/PE** Main author: [redacted], Ph.D. Boehringer Ingelheim (Canada) Ltd./Ltée		
Keywords:	International, multicentre, prospective, non-interventional study programme		
Rationale and background:	The collection of clinical practice data is important for studying large patient numbers that include a broad spectrum of comorbidities and co-medication use with the use of a new drug. Observational studies can provide complementary data, including safety data and health care resource utilisation. This can expand the knowledge previously collected from randomized clinical trials, which generally have stricter entry criteria and structured monitoring schemes. With the approval of non-VKA oral anticoagulants (NOACs) for the treatment and secondary prevention of recurrent VTE, the use of older, traditional treatments, such as VKA, may change and it is therefore important to understand how patients with different characteristics are treated in routine clinical practice. In addition, there may be geographical differences in treatment patterns based on a number of factors including patient comorbidities and co-medication use or cost and access to newer therapies. Dabigatran etexilate (dabigatran) safety and efficacy with the 150 mg twice daily (b.i.d.) dose has been demonstrated in large randomized clinical trials for several indications (e.g., VTE, stroke prevention in atrial fibrillation (AF)). However, the safety and effectiveness of 110 mg b.i.d. dabigatran compared with VKA for the treatment and secondary prevention of VTE has not been investigated in randomized clinical trials. Health authorities, however, have also requested the lower dose (110 mg b.i.d) for use in the treatment and secondary prevention of VTE in special		

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	populations (e.g., elderly or patients concomitantly taking verapamil). This observational study provides an opportunity to collect clinical data in a broader patient population including all available dosages of dabigatran.		
Research question and objectives:	There were two primary objectives in this study: • Objective 1: To characterise the DVT / PE patient population including the initial acute event phase. All patients with a DVT and/or PE were enrolled for cross-sectional characterisation of the VTE patient population and descriptions of current treatment patterns, and stratified by geographical location. • Objective 2: To analyse the safety and effectiveness of dabigatran regimens in the treatment of DVT and PE over 1 year of follow-up in comparison to a VKA regimen. The following secondary research questions were investigated: • With the approval of dabigatran and other NOACs, what treatments are being administered for acute VTE in routine clinical practice in the different regions of the world? • When presenting with an acute VTE event, what factors influence the choice of treatment for the event? • What is the safety and effectiveness of dabigatran versus VKA under conditions of routine clinical practice?		
Study design:	RE-COVERY is a large, multi-national, multi-centre observational study based on new data collection. The study enrolled and characterised patients diagnosed with an acute DVT and/or PE from 229 sites from 5 regions: Europe, North America, Middle East, Asia and Latin America. Patients treated with dabigatran or VKA were followed up for the occurrence of outcome events for up to one year.		
Setting:	Participation of a country required the approval of dabigatran for the VTE indication prior to study initiation within that country. Selected sites within each country included those physicians (e.g., specialist and general practitioners) and facilities (e.g., general practice offices, specialist offices, hospitals, outpatient care centres and anticoagulation clinics) that reflected the clinical practice within that country.		
Subjects and study size, including	For Objective 1: The first part of the study enrolled and characterised adult patients diagnosed with an acute DVT and/or PE within 14 days but not		

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dropouts:	more than 6 months after diagnosis of the acute VTE. For Objective 2: The second part of the study enrolled and characterised adult patients diagnosed with an acute DVT and/or PE within 14 days but not more than 30 days from diagnosis who were treated with dabigatran or VKA. Patients who enrolled in Objective 1 and were treated with VKA or dabigatran were also eligible for Objective 2. It was planned that approximately 6000 patients would be enrolled for Objective 1. This was not based on formal sample size calculations as there were no hypotheses tested. In combination with additional non-statistical considerations, a total sample size of up to 5000 patients (i.e., 2,500 patients per group) from approximately 300 sites around the world was deemed appropriate for the planned analyses for Objective 2 on an exploratory basis. *Analysis Populations*: Objective 1: The planned analysis for Objective 1 was based on all eligible patients (i.e. all patients who fulfilled all inclusion criteria and no exclusion criteria.) Objective 2: Three patient sets were defined: "all eligible", “all eligible treated”, and “restricted”; the following rules were used to assess if a patient is included in an analysis set: • All Eligible: If a patient fulfilled all inclusion criteria and no exclusion criteria. • All Eligible Treated: If a patient fulfilled all inclusion criteria and no exclusion criteria and took prescribed treatment at least once. • Restricted: The restricted population was composed of all eligible patients within the trimmed patient set which lay within the region of propensity score overlap.		
Variables and data sources:	*Variables*: For Objective 1: The patient’s baseline characteristics including demographic information, co-medication and co-morbidities, basic physical examination and laboratory information, VTE event information including treatment selected, event type, and history of VTE event were collected at the time of the acute VTE event. The following primary outcome measures were analysed on data that were collected at the time of the acute VTE event:		

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- Demographic information (age and gender)
- VTE event information (event type and treatment for event)

For Objective 2:

The same baseline outcome measures were collected as described above at time of the acute VTE event. During the follow-up of patients treated with dabigatran or VKA, details regarding changes to their anticoagulation therapy (e.g., dose adjustments, discontinuation of treatment, and reason for discontinuation), outcome events, adverse drug reactions and changes to concomitant medications were collected. Health care resource utilisation and patient's satisfaction with their anticoagulation therapy were assessed using the Perception of anticoagulation treatment questionnaire 2 (PACT-Q2).

The following primary outcomes were analysed:

- Primary safety outcome measure: Major bleeding and clinically relevant non major bleeding (CRNMB) based on International Society on Thrombosis and Haemostasis (ISTH) criteria
- Primary effectiveness outcome measure: symptomatic recurrent VTE including VTE-related mortality

A patient is considered to have major bleeding if the bleeding is fatal and/or meets at least one of the following criteria:

- Overt bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal, or intramuscular with compartmental syndrome, retroperitoneal bleeding, intraarticular bleeding or pericardial bleeding

A patient is considered to have CRNMB if the bleeding caused at least one of the following actions:

- Leading to hospitalization or increased the level of health care
- Requiring medical intervention by a healthcare professional
- Prompting a face to face evaluation

The following secondary outcomes were analysed:

- Recurrent DVT and/or PE
- VTE-related mortality

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	• All-cause mortality For Objective 2, the main effectiveness outcomes were analysed on the restricted set and the safety outcomes were analysed on the all eligible treated set. *Data Sources*: RE-COVERY is a study based on new data collection. Data were collected based on assessment of the patient (e.g., physical examination and patient interview), review of hospital / medical records and available laboratory and diagnostic test reports. Patient reported outcomes (PROs) were assessed by using a validated questionnaire. *Interim Analyses*: For Objective 1, an interim analysis was planned for each year after approximately 2,000 patients had been enrolled until the target enrollment of 6,000 patients had been reached over a 3-year period. The protocol was then amended perform one interim analysis of data from approximately the first 3,000 patients. However, enrollment into Objective 1 proceeded more quickly than originally anticipated such that the interim analysis was considered impractical and of limited value. Therefore, the study team continued Objective 1 enrollment without performing an interim analysis until the total target of 6,000 patients was reached and analyzed in full in the final analysis. For Objective 2, an interim analysis that assessed the comparability of patients in the dabigatran and VKA groups based on propensity scores was performed when the target sample size was reached. This analysis was also repeated at the time of final analysis.		
Results:	**Objective 1**: A total of 6194 consecutive patients were enrolled from 34 countries from five regions: Europe, North America, Middle East, Asia and Latin America. Of these, 6095 patients were deemed eligible for analysis. The majority of eligible patients were from Europe (3618 patients, 59.4%) followed by North America (970 patients, 15.9%), Middle East (668 patients, 11.0%), Asia (600 patients, 9.8%), and Latin America (239 patients, 3.9%). Collectively, NOACs were prescribed more frequently than VKA or other anticoagulant treatment options (54% NOACs vs. 23% for both of the latter two groups, respectively), but there was substantial regional variation. NOACs were prescribed for approximately 52% of patients in North America and 61% of patients in Europe and Asia but at a much lower frequency in Latin America (29%) and the Middle East (21%). DVT was the predominant index event (59.8%) followed by PE (26.1%)		

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and both (14.2%). Overall, NOACs were prescribed more frequently than VKA or parenteral anticoagulant treatment regardless of index event.

Approximately half of the eligible patients were male (50.2%). The majority of all eligible patients were Caucasian (75.5%) followed by Asian (10.9%) and Black or African American (3.0%); other race categories were reported by fewer than 2% of patients or unknown (10.2%). The mean (standard deviation [SD]) age of the eligible population was 61.5 (17.0) years. More than half of the population was overweight or obese, and the most common risk factors for VTE were hypertension (34.7%), diabetes mellitus (11.4%), cancer (11.0%), prior DVT (8.9%), and trauma/surgery (7.4%). While some variation was observed across treatment groups in terms of baseline demographic and disease features, the most notable treatment group imbalance was presence of cancer. Specifically, the cohort of patients who received parenteral anticoagulant treatment without oral anticoagulant treatment comprised a greater proportion of patients with cancer (28.7%) compared with NOACs or VKA (4-7%).

Objective 2: The Objective 2 part of study enrolled 3079 patients, and of these, 3009 patients were deemed eligible for the outcome analyses, including 1688 patients who received dabigatran and 1321 patients who received VKA. The all eligible treated set comprised a total of 2989 patients, including 1682 treated with dabigatran and 1307 treated with VKA. Twenty patients (<1%) were excluded from the all eligible treated set to compose the restricted set, which comprised a total of 2969 patients, including 1681 treated with dabigatran and 1288 treated with VKA.

Of the 1688 all eligible patients who received dabigatran, 80.0% were treated with 150 mg b.i.d., 13.3% were treated with 110 mg b.i.d., 4.3% were treated with 75 mg b.i.d., and 2.2% were treated with other dose of dabigatran. DVT was the predominant index event (60.2%) followed by PE (20.5%) or both (19.3%).

The majority of all eligible patients (64.1%) were from Europe followed by Asia (13.7%), Middle East (12.6%), Latin America (7.1%), North America (1.8%), and Other (New Zealand; 0.7%). Dabigatran was prescribed more frequently than VKA in Europe and Asia, whereas the use of VKA was favoured in the Middle East, Latin America, and North America.

The mean (SD) age of patients in the all eligible patient set was 58.6 (16.5) years with 59.0% of the patients younger than 65. Most patients in the all eligible patient set were Caucasian (81.0%) followed by Asian (14.4%) and multiple answers (2.2%); other categories were reported by fewer than 2%

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of patients. The all eligible patient set included more men (53.1%) than women (46.9%). The mean creatinine clearance (CrCl) of the overall eligible patient population was 97.45 mL/min, but the mean CrCl was lower in patients who received VKA than those who received dabigatran (93.76 mL/min vs. 100.29 mL/min, respectively). The five most commonly reported comorbidities in the all eligible patient set included hypertension (31.5%), diabetes mellitus (8.5%), varicose vein (4.9%), dyslipidaemia (4.0%), and coronary artery disease (3.8%). Overall, the demographic and baseline characteristics of all eligible patients in Objective 2 were similar to those who participated in Objective 1.

Patients were followed for up to 12 months. The mean (SD) exposure for all eligible patients treated with dabigatran was 256.9 (119.9) days and for those treated with VKA was 268.8 (128.0) days. Exposure time was similar for patients in the restricted set. More than half of the patients in both cohorts received more than 270 days of treatment with dabigatran or VKA. Time in therapeutic range (TTR) was calculated from INR results for patients who received VKA. The average TTR (2.0 to 3.0) during the study was 45.6% for patients who received VKA and had INR measurements available.

Results of the primary safety and effectiveness outcomes on the restricted set for Objective 2 were as follows:

- The incidence rate of ISTH major bleeding and CRNMB was 2.63 events (95% CI: 1.79, 3.74) per 100 patient-years for dabigatran-treated patients and 4.48 events (95% CI: 3.23, 6.06) per 100 patient-years for VKA-treated patients (HR = 0.634; 95% CI: 0.322, 1.249). While the risk for major bleeding and CRNMB was lower for dabigatran than VKA, the difference was not statistically significant based on the 95% CI of the HR.
- The incidence rate of symptomatic recurrent VTE including VTE-related mortality was 1.53 events (95% CI: 0.91, 2.42) per 100 patient-years for those receiving dabigatran and 2.01 events (95% CI: 1.21, 3.14) per 100 patient-years for those receiving VKA (HR=0.778; 95% CI: 0.300, 2.017). While the risk of symptomatic recurrent VTE, including VTE-related mortality, was lower for dabigatran, the difference was not statistically significant based on the 95% CI of the HR.

Results of the secondary outcomes on the restricted set for Objective 2 were as follows:

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- The incidence rate of recurrent DVT and/or PE was 1.61 events (95% CI: 0.97, 2.52) per 100 patient-years for patients receiving dabigatran and 2.22 events (95% CI: 1.38, 3.40) per 100 patient-years for patients receiving VKA (HR=0.751; 95% CI: 0.299, 1.885).
- No patient who received dabigatran had VTE-related mortality. The incidence of VTE-related mortality was 0.42 events (95% CI: 0.11, 1.08) per 100 patient-years in the cohort of patients who received VKA.
- The incidence rate of all-cause mortality during the 12-month study was 2.12 events (95% CI: 1.37, 3.12) per 100 patients-years for patients who received dabigatran and 3.06 events (95% CI: 2.05, 4.39) per 100 patients-years for patients who received VKA (HR=0.857; 95% CI: 0.402, 1.828).

Key safety findings from this study, including ADRs and all fatal AEs, are summarised below by treatment group for the all eligible treated set:

	Dabigatran	VKA	Total
Number of patients	1682	1307	2989
Patients with any ADR, N (%)	87 (5.2)	66 (5.0)	153 (5.1)
Patients with any severe ADR, N (%)	6 (0.4)	12 (0.9)	18 (0.6)
Patients with serious ADR, N (%)	19 (1.1)	24 (1.8)	43 (1.4)
Patients with serious and fatal ADR, N (%)	4 (0.2)	4 (0.3)	8 (0.3)
Patients with ADR leading to treatment discontinuation	50 (3.0)	37 (2.8)	87 (2.9)
Patients with any fatal AE	47 (2.8)	48 (3.7)	95 (3.2)

Gastrointestinal disorders were the most commonly reported ADRs (1.7% of all eligible treated patients) and serious ADRs (0.4% of all eligible treated patients) by MedDRA system organ class than other categories. The most commonly reported ADRs by MedDRA preferred term were haematuria (0.6% of patients), epistaxis (0.4% of patients), and abdominal pain upper (0.3% of patients).

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Discussion:	The RE-COVERY DVT/PE is the first non-interventional, prospective study providing long-term safety and effectiveness outcome data comparing dabigatran with VKA treatment in a large cohort of consecutively enrolled patients with DVT, PE, or both. The incidence rates of major bleeding, CRNMB, recurrent VTE, life-threatening bleeding, and all-cause mortality were low and consistent with results from pivotal trials and other registry studies. Compared with VKA, the risks of primary safety and effectiveness outcome events among patients receiving dabigatran were lower but not statistically significant based on the 95% CI of the HR. In summary, results from this study were consistent with those from controlled, pivotal trials supporting an effective and favourable safety profile of dabigatran for the treatment and secondary prevention of VTE in the routine clinical practice setting.		
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