Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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SYNOPSIS

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa® (dabigatran etexilate)			
Name of active ingredient: Pharmacotherapeutic group: antithrombotic, direct thrombin inhibitors, ATC code: B01AE07, active substance: dabigatran etexilate			
Report date: 01 Oct 2018	**Study number:** 1160.218	**Version:** 2.0	**Revision date:** 05 Oct 2018
Title of study:	AVANTI: Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF). Author: Dr. [redacted], Germany; Date: 01 Oct 2018		
Keywords:	Adherence, persistence, oral anticoagulants, dabigatran etexilate, atrial fibrillation		
Rationale and background:	AF, the most common cardiac arrhythmia, is associated with considerable morbidity and mortality, in particular due to a 4- to 5-fold risk of thromboembolic stroke. Oral anticoagulation (OAC) is recommended for stroke prevention. VKAs are frequently used for this purpose (in Germany mainly phenprocoumon). VKA treatment requires close laboratory monitoring of coagulation due to a narrow therapeutic range (International Normalized Ratio (INR) 2-3). The new oral anticoagulant (NOAC) Pradaxa® (dabigatran etexilate) is a direct thrombin inhibitor indicated for stroke prevention in non-valvular AF. As opposed to VKAs, the effect of dabigatran sets in rapidly. Successful anticoagulation requires treatment adherence and persistence. Whether persistence and adherence differ among patients treated with dabigatran etexilate or VKA has not yet been investigated in the German routine care setting.		
Research question and objectives:	The primary objective of this study was to compare persistence in patients treated with dabigatran etexilate or VKA. Secondary objectives were to compare adherence in patients treated with dabigatran etexilate or VKA, and to determine reasons for permanent treatment discontinuation.		
Study design:	This was an open, prospective, multicentre, non-interventional cohort study to collect data on persistence and adherence to anticoagulant therapy with dabigatran etexilate or VKA of patients with non-valvular AF in routine medical care.		

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Setting:	This study was conducted in a routine care setting in 280 sites (office-based cardiologists or primary care internists/general practitioners) in Germany. Patients with non-valvular AF, for whom anticoagulant treatment with dabigatran etexilate or VKA was indicated according to current guidelines and in line with the Summary of Product Characteristics (SPC), were included. Patients treated with VKA had theoretically also to be treatable with dabigatran etexilate and vice versa to ensure comparability of both patient populations. Each patient was followed up for 12 months. Information on each patient was recorded at five time points (at baseline and after approx. 3, 6, 9 and 12 months). The first patient was registered on 08 Oct 2014, the last patient on 29 Jan 2017. Last patient last visit (LPLV) was on 16 Feb 2018.		
Subjects and study size, including dropouts:	The study population consisted of male and female patients with non-valvular AF eligible for therapy with both dabigatran etexilate and VKA, for whom dabigatran etexilate /VKA was newly prescribed for stroke prevention. Inclusion criteria (IC) were: • Written informed consent of patient must be obtained (IC 01) • Patient with a diagnosis of non-valvular AF, not previously treated with oral anticoagulants (IC 02) • Patient is eligible for therapy with both dabigatran etexilate and VKA according to the respective SPCs, and routine diagnostic and treatment procedures envisaged independently of the study are not changed (IC 03) Exclusion criteria (EC) were: • Patient with general or special contraindications described in the SPC (EC 01) • Patient participates in another non-interventional study (NIS) or an interventional clinical trial simultaneously or within the last 30 days (EC 02) • Patient with anticoagulation treatment for a condition other than		

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	non-valvular AF (EC 03) • Pregnancy/breastfeeding (EC 04) Between 08 Oct 2014 and 30 Jan 2017, 1506 patients of 280 sites in Germany were registered. In total, 23 patients (1.53%) violated inclusion/exclusion criteria. 1421 patients had at least one documented prescription of dabigatran etexilate (n=771, 54.3%) or VKA (n=650, 45.7%) and were analyzed in the treated set (TS). Patients in the TS were matched 1:1 based on propensity score matching in order to ensure comparability of outcome variables between both treatment groups (dabigatran etexilate and VKA). 952 patients were analyzed in the matched group (MG) set, with 476 patients in each treatment group. Median age was 75 years (range 23 – 96 years). 798 patients (56.16%) were male, 623 (43.84%) were female.
Variables and data sources:	Data collection was performed prospectively. No clinical effectiveness data were collected. Outcome variables in this NIS were persistence and adherence to anticoagulant therapy with dabigatran etexilate or VKA. At the initial visit, sociodemographic data, data on medical history of AF, on initial anticoagulant treatment, and on prior and concomitant medication were collected. Continuation of treatment with dabigatran etexilate or VKA and, if applicable, reasons for discontinuation were recorded over the individual observation period of 12 months in approx. quarterly intervals (i.e. after approx. 3, 6, 9 and 12 months). The primary outcome variable was persistence, defined as the Kaplan Meier estimate at the 12-months visit. Secondary outcome variables were adherence, assessed by means of the Morisky questionnaire at the 6-month visit, and reasons for permanent treatment discontinuation. All study-relevant data were documented for each patient in a pseudonymized manner in the electronic case report form (eCRF). Data of completed Morisky questionnaires were entered into the eCRF by the CRO (Alcedis GmbH) via single data entry.

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Results:	In the MG (n=952), median age at registration was 75 years (range: 38 – 96 years). 56% of patients were male. 97 patients had prematurely discontinued treatment at the 12-month visit; 49 of those were treated with dabigatran etexilate and 48 with VKA. 89.5% (95% CI: 86.3 - 91.9%) of patients treated with dabigatran etexilate and 89.5% (95% CI: 86.3 - 92.0%) of patients treated with VKA were persistent after one year according to the Kaplan-Meier estimator. The stratified log-rank test did not reveal a difference in persistence between both treatment groups (p=0.8496). Almost half (46.3%) of the patients had a medium level of adherence (Morisky score of 1 or 2); in the dabigatran etexilate group it were 45.8%, and in the VKA group 46.9%. 5% had a high level of adherence (Morisky score of 0); in the dabigatran etexilate group it were 5.9%, and in the VKA group 4.0%. About 1/5 had a low level of adherence (Morsiky score > 2); in the dabigatran etexilate group it were 19.1%, and in the VKA group 23.7%. On a scale from 0 to 8, the median Morisky score was 1 (range 0 to 8); in the dabigatran etexilate group it was 1, and in the VKA group it was 2. Only a minor proportion of patients did not continue the initial treatment at the respective visits (8.4% at visit 2, 6.1% at visit 3, 3.9% at visit 4, and 2.9% at visit 5), being similar in both treatment groups. The major reason for switching to another anticoagulant treatment (3.1% at visit 2, 2.4% at visit 3, 2.0% at visit 4, and 1.6% at visit 5) was “decision of physician”, followed by “patient’s wish”, and for patients with VKA “insufficient INR control”. The major reason for permanent treatment discontinuation at visit 2 was “patient’s wish”, for patients treated with dabigatran etexilate also “decision of physician”; at visit 3 it was “SAE” and “decision of physician”, for patients treated with VKA also “patient’s wish”; at visit 4 only VKA-treated patients permanently discontinued treatment, mainly due to “decision of physician”; at visit 5 dabigatran etexilate-treated patients discontinued mainly due to “patient’s wish”, VKA-treated patients due to “decision of physician”. In the TS (n=1421), a total of 296 treatment-emergent adverse events (TEAEs) were observed in 174 patients (12.2%; dabigatran etexilate		

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	group: 13.9%, VKA group: 10.3%). TEAEs were deemed drug-related by the investigator for 46 patients (3.2%; dabigatran etexilate group: 4.8%, VKA group: 1.4%), and led to discontinuation of study medication in 54 patients (3.8%; dabigatran etexilate group: 4.9%, VKA group: 2.5%). 84 patients (5.9%) had serious TEAEs (dabigatran etexilate group: 5.8%, VKA group: 6.0%). TEAEs were fatal for 15 patients (1.1%), 10 were treated with dabigatran etexilate (1.3%) and 5 with VKA (0.8%).		
Discussion:	Persistence and adherence are crucial for the success of anticoagulant therapy for stroke prevention in patients with AF. 1-year persistence in a real-life setting, as determined in this study, was high and independent of the precribed therapy (dabigatran etexilate or VKA), thus seeming unaffected by the lack of routine coagulation monitoring required for VKA. Very low rates of major bleeding with none of them being fatal indicate an overall good safety profile for both dabigatran etexilate and VKA.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 55216 Ingelheim, Germany		
Names and affiliations of principal investigators:	Investigators of each participating site are listed in a stand-alone document (see Annex 1: List of stand-alone documents, which is available upon request).		