Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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**.

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: dabigatran etexilate			
Report date: **16 May 2018**	**Study number:** 1160.274	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	The Comparative Safety and Effectiveness of Dabigatran, versus Rivaroxaban, and Apixaban Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation (NVAF) Patient Population-A Retrospective Database Analysis		
Keywords:	atrial fibrillation, dabigatran, rivaroxaban, apixaban, anticoagulants		
Rationale and background:	Due to the emergence of multiple pharmaceutical alternatives to warfarin, physicians in the US are faced with many anticoagulation options. To help inform their decisions, physicians want to know the comparative safety and efficacy profiles of these new agents. Now that real world experience with dabigatran for NVAF patients has accrued, the safety and effectiveness for dabigatran, rivaroxaban, and apixaban may also be assessed and compared in this setting. Boehringer Ingelheim Pharmaceuticals Inc. (BIPI) had an opportunity to collaborate with DoD to conduct comparative safety and effectiveness studies of dabigatran, rivaroxaban, and apixaban using already existing real world data from DoD's claims and EMR data.		
Research question and objectives:	To assess the safety and effectiveness of newly initiated dabigatran NVAF patients in comparison to newly initiated rivaroxaban patients and newly initiated apixaban patients in two separate study cohorts: • dabigatran vs. rivaroxaban • dabigatran vs. apixaban		
Study design:	Non-interventional study based on existing data with propensity score matching (PSM)		
Setting:	US Department of Defense claims database, July 1, 2010 to June 30, 2016		

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Subjects and study size, including dropouts:	NVAF patients, ≥ 18 years of age, enrolled within the DoD Military Health System (MHS) who had newly initiated dabigatran, rivaroxaban or apixaban, had no NOAC exposure for at least 12 months prior to the first dispensed (index) NOAC. Patients also had to be treatment naïve to OAC use for at least 12 months prior to index NOAC. Initial study feasibility counts showed these patient numbers in two separate study cohorts: • dabigatran (n=16,604) vs. rivaroxaban (n=25,215); July 1, 2011 to June 30, 2016 • dabigatran (n=6,050) vs. apixaban (n=20,930); December 28, 2012 to June 30, 2016 Applying additional inclusion/exclusion criteria for actual analysis, including the requirement of patients to have 6 months of data from index date, resulted in the following patient numbers: • dabigatran (n=12,763) vs. rivaroxaban (n= 17,177) • dabigatran (n=4,802) vs. apixaban (n=12,594) One-to-one propensity-matching further reduced the number of patients dispensed comparator NOAC, yielding the following final patient numbers: • dabigatran (n=12,763) vs. rivaroxaban (n=12,763) • dabigatran (n=4,802) vs. apixaban (n=4,802)		

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Variables:	Covariates (used for PSM)
	• Gender
	• Age
	• Geographic location
	• Baseline comorbid conditions
	• Pre-index medication use for comorbidities
	• Baseline Charlson comorbidity index
	• Baseline stroke risk ($CHADS_2$ and CHA_2DS_2-VASc)
	• Baseline bleeding risk (modified HAS-BLED)
	• Index exposure
	Primary outcomes
	• Stroke overall (hemorrhagic, ischemic, uncertain)
	• Major bleeding, overall
	Secondary outcomes
	• Ischemic stroke
	• Hemorrhagic stroke
	• Major intracranial bleeding
	• Major extracranial bleeding
	  ○ Major GI bleeding
	  ○ Major urogenital bleeding
	  ○ Major other bleeding
	• TIA
	• All-cause mortality
	Further outcomes
	• MI
	• VTE
	  ○ DVT
	  ○ PE

Data sources:	DoD Military Health System Data Repository

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Results:	In a 1:1 propensity-score matched sample of dabigatran patients (n=12,763) and rivaroxaban patients (n=12,763), event rates per 1000 person-years for stroke were 5.2 in dabigatran patients and 6.9 in rivaroxaban patients. In Cox proportional-hazards regression analysis using the same PSM sample, the hazard ratio (HR) for stroke comparing dabigatran to rivaroxaban was 0.77 (95% CI 0.57 to 1.04, p=0.08). Rates for major bleeding were 18.2 and 22.4 per 1000 person-years in dabigatran patients and rivaroxaban patients, respectively. The corresponding HR was 0.82 (95% CI 0.70 to 0.97, p=0.02). After 4,802 dabigatran patients were propensity-score matched to 4,802 apixaban patients, event rates per 1000 person-years for stroke were 4.6 in dabigatran patients and 3.6 in apixaban patients. The HR for stroke for dabigatran vs. apixaban treatment was 1.26 (95% CI 0.66 to 2.39, p=0.49). For major bleeding, event rates per 1000 person-years were 16.9 in dabigatran patients and 12.4 in apixaban patients. The HR was 1.37 (95% CI 0.97 to 1.94, p=0.07). Results of secondary outcomes and further analyses are described in detail in this report.
Discussion:	This study sampled patients with NVAF from a US database of 10 million active patients to assess incident stroke and major bleedings associated with pharmacy dispensings of three drugs, dabigatran, rivaroxaban and apixaban. Dabigatran users demonstrated a statistically significant lower risk of major bleeding compared to rivaroxaban users and no difference compared to apixaban users. Neither cohort demonstrated a significant difference in stroke risk. Results of this study may better inform clinical decisions in management of NOAC usage for NVAF patients within the United States.