Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: dabigatran etexilate			
Report date: 09Mar2016	**Study number:** 1160.183	**Version/Revision:** 1.0	**Version/Revision date:** December 8, 2015
Title of study:	*The Comparative Safety and Effectiveness of Dabigatran and Warfarin Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-A Retrospective Database Analysis*		
Keywords:	Atrial Fibrillation, Anticoagulants, Warfarin, Dabigatran,		
Rationale and background:	The comparative safety and efficacy of dabigatran versus warfarin managed to a target INR of 2.0-3.0 for stroke and systemic embolism risk reduction in patients with NVAF has been demonstrated in the Randomized Evaluation of Long-Term Anticoagulation therapy (RE-LY) trial. In this randomized controlled clinical trial, a total of over 18,000 patients were randomized to 1 of 2 doses of dabigatran (110 mg or 150 mg bid) or to warfarin managed for a target international normalize ratio (INR) of 2.0 to 3.0. The study was blinded for dabigatran dose (110 mg vs 150 mg) but open for dabigatran versus warfarin. In RE-LY, dabigatran 110 mg was associated with similar rates of stroke and systemic embolism as warfarin but lower rates of major bleeding, whereas dabigatran 150 mg was associated with lower rates of stroke and systemic embolism as warfarin but similar rates of major bleeding. Because there may be differences in the selection, treatment, and management of patients in routine clinical practice compared to randomized controlled clinical trials, evaluation of safety and effectiveness in clinical practice settings is also important, and was undertaken via this study. Studies have already emerged looking at early real-world data comparing dabigatran and warfarin (***P12-13120***, ***P12-14118***, ***P13-04200***; however, many of these studies have not considered some of the biases that occur in real-world data sources, such as treatment and selection biases. Boehringer Ingelheim Pharmaceuticals Inc. (BIPI) had an opportunity to collaborate with Department of Defense (DoD) to conduct an administrative claims database comparative safety and effectiveness study of dabigatran and warfarin. This study aimed to mitigate many of the potential biases and limitations of observational studies via vigorous methodology including inclusion of only newly diagnosed, newly treated patients, propensity score matching to derive cohorts for comparison, and adjustments for covariates if needed based on imbalances left following PSM. Additionally, stopping rules were pre-specified to ensure that PSM analyses of outcomes were only performed if there were enough patients per cohort to support a robust analysis.		
Research question	Study Objective		

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and objectives:	To assess the safety and effectiveness of dabigatran compared to warfarin in patients diagnosed with non-valvular atrial fibrillation in the DoD population.		
Study design:	Existing data cohort design with propensity score matching		
Setting:	US Department of Defense claims database, October 1, 2009 to July 31, 2013.		
Subjects and study size, including dropouts:	Treatment-naïve patients aged 18-89 years, with first prescription claim for dabigatran (either FDA-approved dose) or warfarin between October 1, 2010 and July 31, 2012 (index date) and a diagnosis of NVAF during the 12 months before index date. Study included 12,793 patients per treatment group (dabigatran or warfarin) following propensity score-matching (PSM).		
Variables and data sources:	The study used the US Department of Defense claims database data from October 1, 2009 to July 31, 2013. Primary outcomes were stroke and major bleeding. Secondary outcomes were ischemic and hemorrhagic stroke; major intracranial, extracranial, gastrointestinal, urogenital, or other bleeding; transient ischemic attack; myocardial infarction; venous thromboembolism; deep vein thrombosis; pulmonary embolism; and death. Time to event was investigated using Kaplan-Meier survival analyses. Outcomes comparisons were made based on Cox-proportional hazards models of PSM groups.		
Results:	The dabigatran group experienced fewer strokes (adjusted hazard ratio [95% confidence intervals] of 0.73 [0.55-0.97]); hemorrhagic strokes (0.32 [0.14-0.73]); major intracranial bleeding (0.49 [0.30-0.79]); major urogenital (0.36 [0.18-0.74]) and other (0.38 [0.22-0.66]) bleeding; myocardial infarctions (0.65 [0.45-0.95]); and deaths (0.64 [0.55-0.74]) than the warfarin group. Major lower gastrointestinal bleeding events were more frequent (1.30 [1.04-1.62]) in the dabigatran group.		
Discussion:	The overall results of this study comparing the effectiveness and safety of dabigatran and warfarin in a large population of patients in clinical practice are consistent with those of the RE-LY randomized clinical trial. Compared with warfarin, dabigatran treatment was associated with fewer events across most outcomes measured, including stroke, major bleeding, myocardial infarction, and death, but more frequent gastrointestinal bleeding.		
Supplemental Analysis	The supplemental analysis consists of patients taking dabigatran 150 mg only at index. Patients with both 150mg and 75mg dabigatran at index were excluded. Patients were required to have at least one post-index day of dabigatran 150 mg and the follow-up was stopped when the patient started using another oral anticoagulant, which includes 75 mg dabigatran. A new propensity score model for treatment probability was generated for 150 mg dabigatran patients and warfarin patients Overall, the results of these analyses are the same as the previous analyses, except less statistical power is evident in the results. The fewer patients in this subset		

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	analysis were overall younger and healthier than the patients in the original analysis, and fewer outcome events were observed. The subset analysis also had slightly less follow-up time for the dabigatran patients due to ending follow-up if and when they started taking 75 mg dabigatran.		
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