Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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: 14 Apr 2014	**Study number:** 1160.157	**Version/Revision:** Version 1	**Version/Revision date:**
Title of study:	Comparative effectiveness of oral anticoagulants: A cohort study		
Keywords:	Dabigatran, warfarin, oral anticoagulants, thrombotic events, major bleeding		
Rationale and background:	A number of new oral anticoagulants have been developed and marketed. In Phase III studies, these drugs were found to be therapeutically advantageous or non-inferior over warfarin. In the coming years, as many as six new anticoagulants could be on the market with a lack of valid comparative evidence. This evaluation provides for the feasibility of a direct assessment of comparative effectiveness and safety across the anticoagulants. The current protocol addresses only the initial comparison between warfarin and dabigatran using data through June 2012.		
Research question and objectives:	The overall study objective is to quantify associations between anticoagulant use (warfarin and dabigatran) and the occurrence of selected outcomes, including major thromboembolic events, major bleeding events in patients with non-valvular atrial fibrillation (NVAF) at risk for stroke using a large US commercial health insurance database. The analyses described in this report are based on a cohort of patients identified between Jan 2009 and Jun 2012 in the UnitedHealth Research Database.		
Study design:	Observational cohort study		
Setting:	UnitedHealth July 2008 through June 2012		
Subjects and study size, including dropouts:	Patients ≥18 years with a diagnosis of NVAF at risk for stroke (CHA_2DS_2-VASc score ≥ 1) who initiated treatment with warfarin (N=7,724) or dabigatran (N=4,158) between October 2010 and June 2012. From this population, 2,991 patients initiating dabigatran were matched to 2,991 patients initiating warfarin, and these patients form the main study cohorts.		
Variables and data sources:	Exposure, outcomes, and baseline covariates were identified from UnitedHealth claims data from July 2008 through June 2012. Exposure is initiation of dabigatran or warfarin. Primary Outcomes are: stroke (hemorrhagic, ischemic, uncertain classification) and major bleeding.		

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	Secondary outcomes include stroke or systemic embolism, systemic embolism, ischemic stroke, hemorrhagic stroke, stroke uncertain classification, major intracranial bleeding, major extracranial bleeding, major GI bleeding, major upper GI bleeding, major lower GI bleeding, major urogenital bleeding, major other bleeding, TIA, MI, VTE (DVT or PE), DVT, PE.. Covariates include demographic information and clinical risk factors for study outcomes.		
Results:	Following PS-matching, 2,991 dabigatran patients had a mean age of 63.86 ± 10.99 years with 31.53% being female and 2,991 warfarin patients had a mean age of 63.26 ± 11.04 years with 29.32% being female. Among the matched dabigatran patients (96% with the 150 mg dose) providing 1,237 person-years of follow-up and the warfarin patients providing 950 person-years of follow-up, there were 36 strokes (IR = 29.09, presented as events/1000 PY) among dabigatran users vs. 30 (IR = 31.59) among warfarin users (HR=1.05, 95% CI=0.64-1.70). With slightly different person-years follow-up (1,233 dabigatran vs. 944 warfarin), there were 74 major hemorrhages (IR = 60.00) among dabigatran users vs. 63 (IR = 66.72) in warfarin users (HR=0.97, 0.69-1.36). For the outcome of stroke or systemic embolism (1,233 person-years of dabigatran exposure vs. 944 person-years of warfarin exposure), there were 49 events (IR = 39.73) among dabigatran users vs. 57 events (IR = 60.38) among warfarin users (HR= 0.74, 95% CI=0.50-1.08, while for systemic embolism including PE, there were 1,242 person-years of dabigatran exposure and 949 person-years of warfarin exposure during which there were 14 events (IR = 11.27) vs. 29 events (IR = 30.55) (HR=0.40, 95% CI=0.21-0.76), with much of this effect due to PE. For ischemic stroke (1,240 person-years vs. 947 person-years) there were 34 events (IR = 27.40) vs. 31 events (IR = 32.71) (HR=0.95, 95% CI =0.58-1.55). There were only 8 hemorrhagic strokes in total (5 among dabigatran treated patients and 3 among warfarin treated patients). Hazard Ratios with corresponding 95% CI for hemorrhagic stroke and remaining secondary outcomes are listed below: Hemorrhagic stroke HR: 1.36; 95% CI: (0.32 - 5.72) Stroke Uncertain HR: 1.60; 95% CI: (0.83 - 3.08) TIA HR: 1.01; 95% CI: (0.47 - 2.20) MI HR: 1.24; 95% CI: (0.62 - 2.45) VTE HR: 0.29; 95% CI: (0.15 - 0.59) DVT HR: 0.31; 95% CI: (0.15 - 0.67) PE HR: 0.27; 95% CI: (0.09 - 0.84)		

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	Major Intracranial bleeding HR: 1.45; 95% CI: (0.57 - 3.70) Major Extracranial bleeding HR: 0.95; 95% CI: (0.67 - 1.35) Major GI bleeding HR: 1.26; 95% CI: (0.79 - 2.01) Major Upper GI bleeding HR: 0.65; 95% CI: (0.21 - 1.98) Major Lower GI bleeding HR: 1.25; 95% CI: (0.78 - 2.01) Major Urogenital bleeding HR: NA; 95% CI: NA Other Major bleeding HR: 0.74; 95% CI: (0.48 - 1.14)		
Discussion:	Analyses suggested similarity of primary outcome occurrence between dabigatran and warfarin for stroke (HR = 1.05, 95% CI = 0.64-1.70) and major hemorrhage (HR = 0.97, 0.69-1.36) along with other effectiveness and safety outcomes, across a range of assumptions regarding exposure and within numerous subgroups and sensitivity analyses. Patients initiated on dabigatran appeared to be slightly more persistent with treatment, so this study reflects more person-time exposed to dabigatran than warfarin. These current feasibility results are limited by a small sample size, short follow up and few outcome events resulting in wide 95% confidence intervals. At this early stage, no comparative conclusions are possible. Future data in the context of the subsequent protocol (1160.207) will increase the number of patients and also expand to additional data sources.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim GmbH		
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