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: 10 October 2018	**Study number:** 1160.207	**Version/Revision:** Version 1	**Version/Revision date:** N/A
Title of study:	Sequential expansion of 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 were marketed during the study period. In Phase III studies, these drugs were found to be therapeutically advantageous or non-inferior over warfarin; however, their long-term safety and effectiveness have not been characterized in a real-world setting. The current report includes comparisons between patients who initiated treatment either with warfarin or dabigatran. Comparisons were also made between other new oral anticoagulants (NOACs) (rivaroxaban or apixaban as they became available for stroke prevention in NVAF) and warfarin during the period October 2010 – September 2015.		
Research question and objectives:	The overall study objective is to conduct a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating dabigatran (compared to warfarin) and other NOACs as they become available, (compared to warfarin), and are followed longitudinally for the occurrence of a variety of health outcomes. Objectives: Primarily, to conduct direct comparisons over time between dabigatran and warfarin and to quantify the association between anticoagulant choice and the occurrence of specific outcomes of interest. Secondarily, to monitor the number of patients initiating other NOAC medications and, when sufficient, to compare the study outcomes between other NOAC medications and warfarin. The analyses described in this report are based on cohorts of patients identified between October 2010 and September 2015 in the MarketScan and Optum Research Databases.		
Study design:	Observational cohort study		
Setting:	US MarketScan® Commercial Claims and Encounters database and Medicare Supplement (MarketScan) and Optum Clinformatics Research Database (Optum): July 2008 through September 2015. Data from July 2008 through September 2010 (July 2008 to December 2008 for covariate assessment) are used for estimation of Disease Risk Scores.		

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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 either with warfarin (MarketScan: N=76,055, Optum: N=26,149), dabigatran (MarketScan: N=27,456, Optum: N=7,668), rivaroxaban (MarketScan: 40,207; Optum: 14,852) or apixaban (MarketScan: 19,729; Optum: 9,112) between October 2010 and September 2015. Overall mean age in MarketScan was 69.3y ± 12.3 and Optum was 68.9y ± 11.9. Gender distribution in MarketScan was 61.9% male and in Optum was 62.2% male. Overall mean age combined was 69.2y ± 12.2. Gender distribution combined was 62.0% male. From this population, 29,448 patients initiating dabigatran (MarketScan: 23,323, Optum: 6,125), 35,520 patients initiating rivaroxaban (MarketScan: 25,147, Optum 10,373) and 19,588 patients initiating apixaban (MarketScan: 12,523; Optum: 7,065) were propensity score (PS)-matched on a 1:1 basis to patients initiating warfarin. The matched patients form the main study cohort.		
Variables and data sources:	Baseline covariates, exposure, and study outcomes of interest were identified from 2 US commercial health insurance claims data sources (MarketScan and Optum Clinformatics) during the period of July 2008 – September 2015. Warfarin initiators between January 2009 and September 2010 were used to develop disease risk scores, with data from July 2008 to December 2008 being used for covariate assessment for the disease risk score. These disease risk scores were used to adjust for potential residual confounding in sensitivity analyses. Exposure is initiation of any NOAC or warfarin. Primary outcomes of interest are: stroke (hemorrhagic, ischemic or uncertain classification) and major bleeding. Secondary outcomes of interest include stroke or systemic embolism, systemic embolism, ischemic stroke, hemorrhagic stroke, stroke of uncertain classification, major intracranial bleeding, major extracranial bleeding, major GI bleeding, major upper GI bleeding, major lower GI bleeding, major urogenital bleeding, other major bleeding, transient ischemic attack (TIA), myocardial infarction (MI), venous thromboembolism (DVT or PE), deep vein thrombosis (DVT), and pulmonary embolism (PE). Further outcomes include hepatotoxicity, and all-cause mortality. Covariates include demographic information, calendar time, prior medication use, clinical risk factors for study outcomes of interest, and healthcare utilization measures (e.g., number of medications, number of office visits). Analyses involved description and comparison of above mentioned baseline characteristics among initiators of different anticoagulants. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were estimated in PS and calendar quarter matched cohorts. The study implemented sequential analysis with the first interim analysis covering the period October 2010-December		

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	2012 with subsequent analyses covering 6-month intervals accumulating additional data each time.		
Results:	In the MarketScan cohort 23,323 dabigatran patients (62.8% were male) with a mean age of 68.5±11.9 years were matched to 23,323 warfarin patients (63.2% were male) with a mean age of 68.3±12.1 years. In the Optum cohort, 6,125 dabigatran patients (67.5% were male) with a mean age of 65.2±11.4 years were matched to 6,125 warfarin patients (67.9% were male) with a mean age of 65.2±11.5 years. After PS matching, the characteristics of dabigatran and warfarin initiators were well balanced across databases with no individual characteristic appearing out of balance as assessed by absolute standardized differences between the groups being less than 0.1 for all covariates. Mean follow-up for the events of stroke among dabigatran patients in MarketScan was 0.52 years and among dabigatran patients in Optum the mean follow-up was 0.47 years. Among warfarin patients, the mean follow-up was 0.42 years for the MarketScan and 0.37 years for the Optum cohorts. Among the 29,448 matched dabigatran patients in the pooled analysis (MarketScan: 23,323, Optum 6,125) providing 14,981.1 person-years of follow-up (MarketScan: 12,095.6 PY; Optum: 2,885.5 PY), there were a total of 104 strokes (MarketScan: 78 events, incidence rate (IR) = 0.64 per 100 PY, 95% confidence interval (CI) = 0.51-0.80; Optum: 26 events, IR = 0.90 per 100 PY, 95% CI = 0.60-1.30). Among the 29,448 matched warfarin patients providing 12,114.2 person-years of follow-up (MarketScan: 9847.0 PY; Optum: 2,267.1 PY), there were a total of 120 stroke events (MarketScan: 97 events, IR = 0.99 per 100 PY, 95% CI = 0.80-1.20; Optum: 23 events, IR = 1.01 per 100 PY, 95% CI = 0.66-1.50). The pooled HR was 0.75 with 95% CI = 0.58 – 0.98 (MarketScan: HR=0.69, 95% CI=0.52-0.94; Optum: HR=1.00, 95% CI = 0.57-1.76). For the primary outcome of major bleeding, the pooled analysis provided 14,880.4 person-years of FU among dabigatran initiators and 12,012.1 person-years of FU among warfarin initiators (MarketScan: 12,000.2 PY for dabigatran vs. 9,757.5 PY for warfarin; Optum: 2,880.2 PY for dabigatran vs. 2,254.5 PY for warfarin). There were a total of 593 major bleeding events among dabigatran users (MarketScan: 523 events, IR = 4.36 per 100 PY, 95% CI = 4.00 - 4.74; Optum: 70 events, IR = 2.43 per 100 PY, 95% CI = 1.91 - 3.05) vs. 709 events among warfarin users (MarketScan: 591 events, IR = 6.06 per 100 PY, 95% CI = 5.58 – 6.56; Optum: 118 events, IR = 5.23 per 100 PY, 95% CI = 4.35-6.24), leading to a pooled HR of 0.72, 95% CI = 0.65 – 0.80 (MarketScan: HR= 0.76, 95% CI = 0.68 - 0.86, Optum: HR = 0.51, 95% CI = 0.38 - 0.69).		

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Pooled hazard ratios for dabigatran versus warfarin with corresponding 95% CI for secondary outcomes are listed below:

	Dabigatran events	**Warfarin events**	**HR**	**95% CI**
Stroke or systemic embolism	137	137	0.87	0.69 - 1.11
Systemic embolism	35	17	1.85	1.03 - 3.30
Ischemic stroke	94	97	0.84	0.63 - 1.12
Hemorrhagic stroke	10	23	0.37	0.18 - 0.78
Transient Ischemic attack (TIA)	32	52	0.53	0.34 - 0.82
Myocardial Infarction (MI)	72	73	0.83	0.60 - 1.15
Venous Thromboembolism (VTE)	100	138	0.65	0.50 - 0.84
Deep Vein Thrombosis (DVT)	69	95	0.65	0.47 - 0.88
Pulmonary embolism (PE)	43	56	0.70	0.47 - 1.04
Major Intracranial bleeding	32	71	0.39	0.25 - 0.59
Major Extracranial bleeding	563	645	0.75	0.67 - 0.84
Major GI bleeding	357	340	0.89	0.77 - 1.04
Major upper GI bleeding	77	109	0.60	0.44 - 0.80
Major lower GI bleeding	326	299	0.93	0.79 - 1.08
Major urogenital bleeding	1	0	NA*	NA*
Other major bleeding	346	441	0.68	0.59 - 0.78
Hepatotoxicity	26	36	0.63	0.38 - 1.05
Death	115	118	0.83	0.64 - 1.08

*Major urogenital bleeding: Across databases, only one event was observed among dabigatran initiators versus no event among warfarin initiators. Therefore HR estimation is not possible.

In the secondary analyses involving other NOACs, 35,520 rivaroxaban patients were PS-matched to an equal number of warfarin initiators. The analyses suggested a reduced risk of stroke (ischemic or hemorrhagic or uncertain classification) for rivaroxaban with a pooled HR of 0.77 with 95%

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	CI = 0.61 – 0.98 (MarketScan: HR=0.75, 95% CI=0.57-0.98; Optum: HR=0.84, 95% CI = 0.53-1.35), but suggested no reduced risk for major bleeding with a pooled HR of 1.02, 95% CI = 0.94 – 1.12 (MarketScan: HR= 1.01, 95% CI = 0.92 – 1.12, Optum: HR = 1.06, 95% CI = 0.88 – 1.26). A total of 19,588 apixaban patients were PS-matched to an equal number of warfarin initiators. The analyses favored apixaban with a reduced risk of stroke (ischemic or hemorrhagic or uncertain classification) with a pooled HR of 0.69 with 95% CI = 0.50 – 0.96 (MarketScan: HR=0.58, 95% CI=0.38-0.89; Optum: HR=0.90, 95% CI = 0.53-1.51), and a reduced risk for major bleeding with a pooled HR of 0.56, 95% CI = 0.49 – 0.64 (MarketScan: HR= 0.58, 95% CI = 0.49 – 0.68, Optum: HR = 0.51, 95% CI = 0.39 – 0.66).		
Discussion:	The final analyses from this monitoring program remain consistent with what we observed in the interim reports which suggested a reduced risk of both primary outcomes (stroke and major bleeding) with dabigatran relative to warfarin. The primary outcomes were studied across a range of assumptions regarding exposure and within numerous subgroups and these sensitivity analyses were consistent with the results from the primary analyses. Although pooled results in the full cohort are robust, comparative conclusions within some subgroups separately by database remain limited by patient numbers and relatively short follow-up. For the secondary comparisons, analyses suggested a reduced risk of stroke but a similar risk of major bleeding for the comparison of rivaroxaban versus warfarin. For the comparison of apixaban versus warfarin, the analyses suggested a reduced risk for both stroke and major bleeding.		
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