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: 09Mar2017	**Study number:** 1160.192	**Version/Revision:** 1.0	**Version/Revision date:** 09Mar2017
Title of study:	The Comparative Safety and Effectiveness of Warfarin and Dabigatran Utilized in the Humana Non-Valvular Atrial Fibrillation Patient Population – A Retrospective Database Analysis		
Keywords:	NVAF, dabigatran, warfarin, safety, efficacy		
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 agents. Up to this point, the safety and efficacy of dabigatran and warfarin in non-valvular atrial fibrillation (NVAF) patients had been compared based on randomized controlled trials (RCT) RE-LY, PETRO, PETRO-EX. Now that real world experience with dabigatran for NVAF patients has accrued, the safety and effectiveness for dabigatran and warfarin may also be assessed and compared in this setting. Boehringer Ingelheim Pharmaceuticals Inc. (BIPI) has an opportunity to collaborate with Humana to conduct comparative safety and effectiveness studies of dabigatran and warfarin using existing real world data from Humana's health plan operations.		
Research question and objectives:	Assess the safety and effectiveness of dabigatran compared to warfarin in patients diagnosed with non-valvular atrial fibrillation in the real-world setting using the Humana population.		
Study design:	A non-interventional study based on existing data was conducted including OAC-naïve new dabigatran (75 mg or 150 mg capsules administered orally, twice daily) or warfarin (1 to 10 mg tablets administered orally) users. Propensity score matching was used to control for channelling bias. Patients were followed-up until treatment discontinuation, switch to another OAC, disenrollment, end of the observation period, or death.		
Setting:	A claims based analysis of existing data was conducted using the Humana database. This is one of the largest Medicare Advantage claims databases in the US with national coverage and high proportions of members from Texas, Florida, and Ohio. A study period of October 1, 2009 through April 30, 2014 was utilized for the study.		

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Subjects and study size, including dropouts:	Main inclusion criteria: 1) Patients must have at least one inpatient, or one physician office visit (OV), emergency room (ER) visit with a diagnosis of AF (ICD-9-CM diagnosis code: 427.31 in any position) on the index date or during the pre-index period. 2) Patients must be continuously enrolled in a health plan during the pre-index period. 3) Patients must have a prescription for dabigatran or warfarin (this first prescription will be considered the "index date"). 4) Patients must be treatment naïve from all oral anticoagulant (OAC) use prior to first OAC prescription 5) Aged ≥18 years and <90 years of age on the index date. The index date is defined as the date of the first oral anticoagulant prescription. Main exclusion criteria: 1) Diagnosis of hyperthyroidism during the pre-index period 2) Having at least one claim with any of the following diagnosis or procedure codes within three months prior to the first diagnosis of AF: Cardiac surgery, Pericarditis, Myocarditis, Pulmonary Embolism 3) Having at least one medical claim for valvular heart disease during the pre-index period		
Variables and data sources:	Safety outcomes include major bleeding and hemorrhagic stroke; effectiveness outcome include ischemic stroke. The number and proportion of patients experiencing an outcome, rate of the outcome per 1,000 person years, and median time to first event were reported. • Primary: o Stroke (hemorrhagic, ischemic) o Major bleeding • Secondary: o Ischemic stroke o Hemorrhagic stroke o Major intracranial bleeding o Major extracranial bleeding • Major gastrointestinal (GI) bleeding o Major upper GI bleeding o Major lower GI bleeding • Major urogenital bleeding • Major other bleeding		

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	o Transient ischemic attack (TIA) o Myocardial infarction (MI) o Venous thromboembolism (VTE) (DVT or PE) • Deep vein thrombosis (DVT) • Pulmonary embolism (PE) o Death (all-cause) A primary analysis was conducted that measured outcomes using coding algorithms to examine diagnosis codes in all service lines of medical claims in a hospitalization. This method can result in identification of multiple outcomes within a single hospitalization. In addition, a post-hoc analysis was conducted that measured outcomes using an algorithm to define the principal diagnosis. The principal diagnosis was defined as the primary diagnosis on the first room and board charge record within a hospital admission. This method results in identification of a single outcome for a hospitalization. Results from both the primary and post-hoc analyses are reported separately. The method used to measure outcomes in the post-hoc analysis is similar to methods in previous studies that used primary discharge diagnosis codes for outcome measurement. No interim analysis was conducted. Individual safety reporting is not applicable for this retrospective observational study in which all patient data were de-identified and analyzed in aggregate.
Results:	A total of 7,245 dabigatran and 14,490 warfarin users remained after propensity score matching (PSM, 1:2). Post-PSM dabigatran and warfarin cohorts showed no significant differences in baseline demographic characteristics. After PS matching, dabigatran and warfarin users had mean (standard deviation) ages of 73.9 (8.0) years and 74.0 (8.1) years, respectively, the proportion of males in both cohorts was 55.6% and the proportion of females in both cohorts was 44.4%. Comorbidity risk scores, stroke risk, and bleed risk scores were not significantly different. Mean durations of follow up for dabigatran and warfarin patients were 207 and 224 days, respectively. In the primary analysis of the primary outcomes, rates per 1,000 person year (PY) of stroke (17.4 vs. 25.7, p=0.0111) and major bleeding (54.1 vs. 70.9, p=0.0011) were significantly lower in the dabigatran cohort compared to the warfarin cohort (Table 1). Similarly, based on hazard ratios adjusted for covariates, risks for stroke (0.74, p=0.0149) and major bleeding (0.80, p=0.0023) were lower in the dabigatran cohort. In the primary analysis of secondary outcomes, rates per 1,000 PY of hemorrhagic stroke (1.5 vs 4.4, p=0.0068), major extracranial bleeding (54.4 vs. 66.1, p=0.0055),

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venous thromboembolism (12.2 vs. 23.0, p<0.0001), and all-cause death (36.6 vs. 49.8, p=0.0004) were significantly lower in the dabigatran cohort (Table 1). Rates per 1000 PY of ischemic stroke (21.7 vs. 26.4, p=0.0808), major intracranial bleeding (8.0 vs. 11.3, p=0.0749), TIA (10.7 vs. 13.0, p=0.261) and MI (13.6 vs. 16.1, p=0.2665) were not significantly different between the dabigatran and warfarin cohorts (Table 1). Based on hazard ratios adjusted for covariates, lower risks for hemorrhagic stroke (0.32, p=0.0097), major extracranial bleeding (0.82, p=0.0108), venous thromboembolism (0.52, p<0.0001), and all-cause death (0.73, p=0.001) were observed in the dabigatran cohort. For ischemic stroke, TIA and MI, the risk were lower though not statistically significant (p=0.081, 0.261, 0.267 respectively).

In the post-hoc analysis, rates of stroke per 1,000 PY were not significantly different between dabigatran and warfarin cohorts (12.4 vs. 16.1, p=0.0861, Table 2). However, rates of major bleeding per 1,000 PY were significantly lower in the dabigatran cohort compared to the warfarin cohort (35.6 vs. 46.9, p=0.0019, Table 2). Based on hazard ratios adjusted for covariates, lower risk for major bleeding (0.75, p=0.0028) was observed in the dabigatran cohort compared to the warfarin cohort. There was no statistically significant difference in the risk for stroke (0.76, p=0.0904) in the dabigatran cohort compared to the warfarin cohort.

In the post-hoc analysis of secondary outcomes, rates per 1,000 PY of hemorrhagic stroke (1.2 vs. 3.3, p=0.0271), major intracranial bleeding (4.4 vs. 8.6, p=0.0072), major extracranial bleeding (31.2 vs. 38.3, p=0.0284), and death (36.6 vs. 49.8, 0.0004) were significantly lower in the dabigatran cohort compared to warfarin cohort (Table 2). Rates per 1000 PY of ischemic stroke (11.2 vs. 12.9, p=0.3502), TIA (3.4 vs. 4.4, p=0.4407) and MI (8.0 vs. 7.5, p=0.8017) were not significantly different between the dabigatran and warfarin cohorts (Table 2). Based on hazard ratios adjusted for covariates, lower risks for hemorrhagic stroke (0.36, p=0.0366), major intracranial bleeding (0.50, p=0.0082), major extracranial bleeding (0.81, p=0.0394), and death (0.73, p=0.0007) were observed in the dabigatran cohort. Similarly, for ischemic stroke and TIA, the risks were lower though not statistically significant (p=0.350, 0.441, respectively).

Table 1. Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Primary Analysis)

	N=7,245	**N=14,490**	
Primary Outcomes			
Stroke	90 (1.2%)	261 (1.8%)	0.0021

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	Rate per 1,000 PY (95% CI)	21.9 (17.4, 26.5)	29.3 (25.7, 32.9)	0.0111
	Major bleeding	253 (3.5%)	683 (4.7%)	0.0001
	Rate per 1,000 PY (95% CI)	61.7 (54.1, 69.3)	76.7 (70.9, 82.4)	0.0011
	Secondary Outcomes			
	Ischemic Stroke	89 (1.2%)	235 (1.6%)	0.0241
	Rate per 1,000 PY (95% CI)	21.7 (17.2, 26.2)	26.4 (23.0, 29.8)	0.0808
	Hemorrhagic Stroke	<10	39 (0.3%)	0.0044
	Rate per 1,000 PY (95% CI)	1.5 (0.3, 2.6)	4.4 (3.0, 5.8)	0.0068
	Major intracranial bleeding	33 (0.5%)	101 (0.7%)	0.032
	Rate per 1,000 PY (95% CI)	8.0 (5.3, 10.8)	11.3 (9.1, 13.6)	0.0749
	Major extracranial bleeding	223 (3.1%)	589 (4.1%)	0.0003
	Rate per 1,000 PY (95% CI)	54.4 (47.2, 61.5)	66.1 (60.8, 71.5)	0.0055
	Major GI bleeding	182 (2.5%)	392 (2.7%)	0.4023
	Rate per 1,000 PY (95% CI)	44.4 (37.9, 50.8)	44.0 (39.7, 48.4)	0.907
	Major upper GI bleeding	27 (0.4%)	80 (0.6%)	0.0748
	Rate per 1,000 PY (95% CI)	6.6 (4.1, 9.1)	9.0 (7.0, 10.9)	0.1534
	Major lower GI bleeding	178 (2.5%)	381 (2.6%)	0.4488
	Rate per 1,000 PY (95% CI)	43.4 (37.0, 49.8)	42.8 (38.5, 47.1)	0.9573
	Major urogenital bleeding	24 (0.3%)	108 (0.7%)	0.0002
	Rate per 1,000 PY (95% CI)	5.8 (3.5, 8.2)	12.1 (9.8, 14.4)	0.0006
	Major other bleeding	52 (0.7%)	162 (1.1%)	0.0048
	Rate per 1,000 PY (95% CI)	12.7 (9.2, 16.1)	18.2 (15.4, 21.0)	0.0185
	TIA	44 (0.6%)	116 (0.8%)	0.1162
	Rate per 1,000 PY (95% CI)	10.7 (7.6, 13.9)	13.0 (10.7, 15.4)	0.261
	Myocardial infarction	56 (0.8%)	143 (1.0%)	0.1185
	Rate per 1,000 PY (95% CI)	13.6 (10.1, 17.2)	16.1 (13.4, 18.7)	0.2665
	Venous thromboembolism	50 (0.7%)	205 (1.4%)	<.0001
	Rate per 1,000 PY (95% CI)	12.2 (8.8, 15.6)	23.0 (19.9, 26.2)	<.0001
	Deep Vein Thrombosis	39 (0.5%)	142 (1.0%)	0.0007
	Rate per 1,000 PY (95% CI)	9.5 (6.5, 12.5)	15.9 (13.3, 18.6)	0.0023
	Pulmonary Embolism	14 (0.2%)	81 (0.6%)	<.0001
	Rate per 1,000 PY (95% CI)	3.4 (1.6, 5.2)	9.1 (7.1, 11.1)	0.0003
	Death	150 (2.1%)	444 (3.1%)	<.0001
	Rate per 1,000 PY (95% CI)	36.6 (30.7, 42.4)	49.8 (45.2, 54.5)	0.0004

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*p-value for n/% is from chi-square test

Table 2. Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Post-hoc Analysis)

Measure	Dabigatran	Warfarin	p-value*
	N=7,245	**N=14,490**	
Primary Outcomes			
Stroke	51 (0.7%)	143 (1.0%)	0.0365
Rate per 1,000 PY (95% CI)	12.4 (9.0, 15.8)	16.1 (13.4, 18.7)	0.0861
Major bleeding	146 (2.0%)	418 (2.9%)	0.0001
Rate per 1,000 PY (95% CI)	35.6 (29.8, 41.4)	46.9 (42.4, 51.4)	0.0019
Secondary Outcomes			
Ischemic Stroke	46 (0.6%)	115 (0.8%)	0.1983
Rate per 1,000 PY (95% CI)	11.2 (8.0, 14.5)	12.9 (10.6, 15.3)	0.3502
Hemorrhagic Stroke	<10	29 (0.2%)	0.0211
Rate per 1,000 PY (95% CI)	1.2 (0.2, 2.3)	3.3 (2.1, 4.4)	0.0271
Major intracranial bleeding	18 (0.2%)	77 (0.5%)	0.0029
Rate per 1,000 PY (95% CI)	4.4 (2.4, 6.4)	8.6 (6.7, 10.6)	0.0072
Major extracranial bleeding	128 (1.8%)	341 (2.4%)	0.005
Rate per 1,000 PY (95% CI)	31.2 (25.8, 36.6)	38.3 (34.2, 42.3)	0.0284
Major GI bleeding	117 (1.6%)	256 (1.8%)	0.4165
Rate per 1,000 PY (95% CI)	28.5 (23.4, 33.7)	28.7 (25.2, 32.3)	0.8208
Major upper GI bleeding	22 (0.3%)	61 (0.4%)	0.1862
Rate per 1,000 PY (95% CI)	5.4 (3.1, 7.6)	6.8 (5.1, 8.6)	0.3055
Major lower GI bleeding	97 (1.3%)	202 (1.4%)	0.7418
Rate per 1,000 PY (95% CI)	23.6 (18.9, 28.3)	22.7 (19.6, 25.8)	0.8465
Major urogenital bleeding	<10	40 (0.3%)	<.0001
Rate per 1,000 PY (95% CI)	0.2 (0.0, 0.7)	4.5 (3.1, 5.9)	<.0001
Major other bleeding	11 (0.2%)	52 (0.4%)	0.0074

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Rate per 1,000 PY (95% CI)	2.7 (1.1, 4.3)	5.8 (4.3, 7.4)	0.0138
Transient Ischemic Attack	14 (0.2%)	39 (0.3%)	0.2847
Rate per 1,000 PY (95% CI)	3.4 (1.6, 5.2)	4.4 (3.0, 5.8)	0.4407
Myocardial infarction	33 (0.5%)	67 (0.5%)	0.9435
Rate per 1,000 PY (95% CI)	8.0 (5.3, 10.8)	7.5 (5.7, 9.3)	0.8017
Venous thromboembolism	<10	31 (0.2%)	0.1457
Rate per 1,000 PY (95% CI)	2.2 (0.8, 3.6)	3.5 (2.3, 4.7)	0.2083
Deep Vein Thrombosis	<10	12 (0.1%)	0.4793
Rate per 1,000 PY (95% CI)	1.0 (0.0, 1.9)	1.3 (0.6, 2.1)	0.5331
Pulmonary Embolism	<10	19 (0.1%)	0.1937
Rate per 1,000 PY (95% CI)	1.2 (0.2, 2.3)	2.1 (1.2, 3.1)	0.2646
Death	150 (2.1%)	444 (3.1%)	<.0001
Rate per 1,000 PY (95% CI)	36.6 (30.7, 42.4)	49.8 (45.2, 54.5)	0.0004

*p-value for n/% is from chi-square test

Discussion:

Safety and efficacy of dabigatran compared to warfarin in treatment of patients with NVAF have been studied previously.

The RE-LY trial found that dabigatran administered at a dose of 110 mg twice daily was associated with similar rates of stroke and systemic embolism as warfarin, as well as lower rates of major bleeding (P09-11669). However, the 150 mg dose of dabigatran was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to warfarin (P09-11669).

In a retrospective database study of Medicare patients, Graham et al (2014) found that dabigatran was associated with lower risk of intracranial bleeding and death compared with warfarin (P14-15648). However, Graham et al also found lower risks for ischemic stroke and increased risk of major gastrointestinal haemorrhage associated with dabigatran compared to warfarin.

In another retrospective study using the US Department of Defense database, Villines et al found lower risks for stroke, major bleeding, major intracranial bleeding, urogenital and other bleeding, and death in the dabigatran cohort compared to warfarin cohort (P15-10687). However, Villines et al found a higher risk for major lower GI bleeding in the dabigatran cohort compared to the warfarin cohort (P15-10687).

Seeger et al (2016) conducted a retrospective study comparing dabigatran and warfarin using commercial health insurance databases (P15-10670). They found a

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	lower risk of major haemorrhage with dabigatran compared to warfarin, which is comparable with our study. Seeger et al also found a lower risk of stroke with dabigatran compared to warfarin. Overall, the results of this study are in agreement with previous studies that demonstrate improved safety outcomes, e.g. major bleeding, hemorrhagic stroke etc, and similar efficacy outcomes, e.g. ischemic stroke, in NVAF patients treated with dabigatran compared to warfarin.		
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