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: If applicable, list centrally-authorised medicinal product(s) subject to the study.		Dabigatran and warfarin	
Name of active ingredient: List pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study		Dabigatran and warfarin	
Report date: 14 Jun 2018	**Study number:** 1160.0288	**Version/Revision:** Version 1	**Version/Revision date:**
Title of study:	Comparative Effectiveness and Safety between Warfarin and Dabigatran Using Real World Claims data of Japanese Non-valvular Atrial Fibrillation Patients		
Keywords:	Non-valvular atrial fibrillation, dabigatran, warfarin, claims data analysis, propensity score		
Rationale and background:	Real-world data about the characteristics of patients with non-valvular atrial fibrillation (NVAF) initiating an oral anticoagulant (OAC) in Japan has been scarce to date. The purpose of this study is to compare the effectiveness and safety of dabigatran and warfarin using the Medical Data Vision (MDV) database.		
Research question and objectives:	To compare the effectiveness (stroke and systemic embolism) and safety (major bleeding) in patients with NVAF and newly treated with dabigatran and warfarin in the real world Japanese setting using a claims database		
Study design:	A non-interventional study based on existing health insurance claims data		
Setting:	MDV clinical database between April 2010 and June 2016 was used. To reduce channeling bias, dabigatran and warfarin study groups were established using propensity score matching method, on a 1:1 fixed ratio. The nearest neighbor method of propensity score matching within a caliper of 0.10 of the standard deviation of the estimated logit was used to select the matched samples. For the primary and secondary outcome, incidence rates of each treatment group (warfarin and dabigatran) were provided, and all analyses were conducted on the propensity score matched sample. The hazard ratio of incidence for the dabigatran group as compared to the warfarin group and its 95% confidence interval (CI) were estimated using a Cox regression model with treatment group as the dependent variable. Kaplan Meier analysis with the number of patients at risk during the follow-up period after the index date and the number of events were provided.		

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Subjects and study size, including dropouts:	Inclusion criteria 1. >18 year-old with confirmed diagnosis of NVAF (International Classification of Diseases (ICD) 10 code I48) 2. New starters of either dabigatran or warfarin 3. No prescription of other OACs for 12 months prior to the index date, defined as the first prescription of OACs (the period is defined as baseline period) 4. Having an index date between 14 March 2011 to 30 June 2016 Exclusion criteria 1. Having less than 12 months of enrolment prior to the index date 2. Dialysis or kidney transplant recipients in baseline period 3. Having atrial flutter, valvular atrial fibrillation (AF), mechanical valve placement, rheumatic AF, mitral valve prolapse/regurge/stenosis in baseline period 4. Having record of deep vein thrombosis or pulmonary embolism < 6 months before AF diagnosis in baseline period		
Variables and data sources:	Variables are baseline characteristics of patients (age, sex, and clinical history), year of initiating treatment, medical history, type of OAC and its dosage, concomitant medications, events related to stroke, systemic embolism, major bleeding, transient ischemic attack (TIA), and myocardial infarction. Data source is MDV clinical database. The database is health insurance claims database. As of end of February 2016, MDV provides commercial claims for in and out-patients consisting of medical records from more than 12.94 million patients from 230 large acute care hospitals using Diagnosis Procedure Combination (DPC) system. Observation period was from 14 March 2010 to 30 June 2016 considering the launch date of dabigatran.		

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Results:	For eligible patients, dabigatran and warfarin were prescribed for 5,146 and 13,115 patients. After the propensity score matching, the number of matched patients was 4,606 for both treatment groups. The patients having 74±10 (mean±standard deviation (SD)) years old at 33% of female in the dabigatran group and those with 73±11 years old at 34% of female in the warfarin group was used in this analysis. There was no background factor with standardized difference (Std. Dif.) at more than 0.1. The incidence rate of stroke and systemic embolism in the dabigatran group was 2.898%, which was lower than that in the warfarin group (3.563%). The hazard ratio (95% CI) of incidence of stroke and systemic embolism for the dabigatran group compared to the warfarin group was 0.720 (0.534 - 0.970). The incidence rate of major bleeding in the dabigatran group (0.639%) was also lower than that in the warfarin group (1.128%), and the hazard ratio (95% CI) for the dabigatran group compared to the warfarin group was 0.549 (0.303 – 0.994). The Kaplan Meier curves for the incidence rate of (a) stroke and systemic embolism and (b) major bleeding are as below:		

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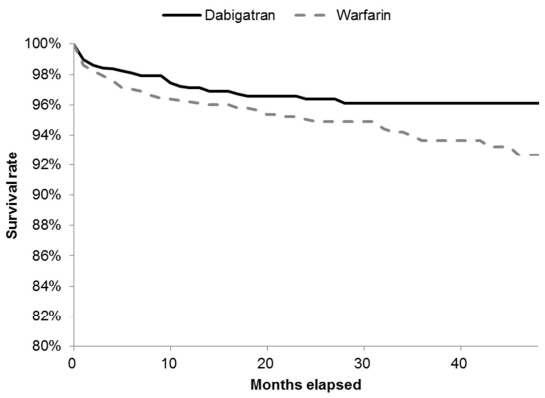
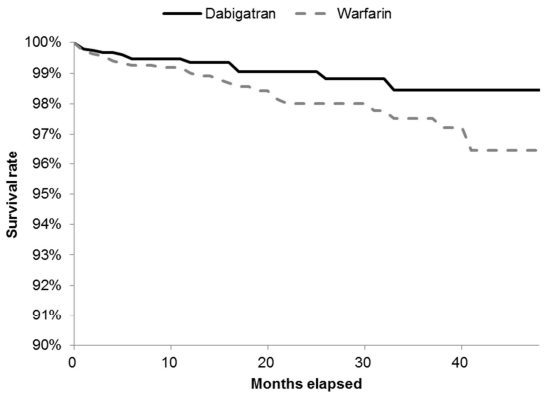
(a) Kaplan Meier curves for the incidence rate of stroke and systemic embolism



No. at risk

Dabigatran	4,606	1,167	717	455	273
Warfarin	4,606	1,006	565	339	156

(b) Kaplan Meier curves for the incidence rate of major bleeding



No. at risk

Dabigatran	4,606	1,191	728	459	278
Warfarin	4,606	1,012	568	341	158

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Discussion:	For Japanese patients with NVAF without any prescription of OACs, treatment with dabigatran is suggested to have a significantly higher effect in reducing the incidence of stroke and systemic embolism compared to warfarin. In terms of safety, treatment with dabigatran showed a significantly lower risk of major bleeding compared with warfarin. The effectiveness and safety of dabigatran when compared with warfarin were observed.		
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