Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: If applicable, list centrally-authorised medicinal product(s) subject to the study.			
Name of active ingredient: List pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study			
Report date: 13 May 2018	**Study number:**	**Version/Revision:** Version 1	**Version/Revision date:**
Title of study:	Medical Need of Non-vitamin K Oral Anti-coagulant Reversal in Japan: Epidemiological Assessment of Emergency Surgery, Major Bleeding due to Trauma and Fracture, using Large Scale Claims Database		
Keywords:	Non-valvular atrial fibrillation, Non-vitamin K Oral Anti-coagulant Reversal, Japan, claims data analysis		
Rationale and background:	As part of medical need assessment for anti-coagulant reversals, it is necessary to investigate the number of patients using the drugs undergoing emergency surgery or major bleeding from trauma or fracture. However, there has been no such epidemiological assessment in Japan. Therefore we conducted this assessment in this study.		
Research question and objectives:	The objective of this study is to assess the incidence of emergency surgery and major bleeding associated with fracture and head trauma in Japanese patients prescribed with oral anti-coagulants such as warfarin, dabigatran, apixaban, rivaroxaban and edoxaban.The primary objective is to assess the incidence of emergency surgery, major bleeding due to trauma, and major bleeding due to fracture, overall and stratified by age (<64, 65-74, >75) for adult patients initiating an oral anticoagulant for non-valvular atrial fibrillation (NVAF). The secondary objective is to estimate the overall and age stratified incidence of cardiac tamponade and pericardiocentesis. Further objective is to describe the types of emergency surgeries.		
Study design:	Non-interventional study based on existing health insurance claims data		
Setting:	Medical Data Vision (MDV) clinical database was used. <u>Inclusion criteria</u> 1. >18 year old NVAF patients 2. Prescribed dabigatran, rivaroxaban, apixaban, edoxaban or warfarin 3. Patients with confirmed date of initiation of OACs 4. Patients with a minimum of 6 months of enrolment data prior to index date		

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	5. Patients have an index date between 14th of March 2011 to 30 June, 2016 Exclusion criteria 1. Patients receiving two or more oral anti-coagulants at the same time at index date 2. Patients with prescriptions of index treatment in the 6 months prior to index date 3. Patients without enrolment period of at least six month in the database Definition of terminology 1. Index date: the date of first oral anticoagulant prescription, namely dabigatran, apixaban, rivaroxaban, edoxaban and warfarin 2. Follow-up period: the day after index date to the earliest of treatment discontinuation, the end of continuous enrolment in the database, the end of study period, the first occurrence of the event of interest, or death. 3. Any OAC treatment discontinuation: treatment gap of any one of OACs for more than 14 days including the time after switch from one OAC to another OAC (primary analysis) *4.* Index OAC treatment discontinuation: treatment gap of the index OAC treatment for more than 14 days, not including the time after switch from one OAC to another (further analysis)
Subjects and study size, including dropouts:	The previous study 1160.279 has identified the patients with confirmed 6 months of baseline period and no OAC treatment (defining "treatment naïve" new starter population). The total of these patients was 62,888. The mean on-treatment follow-up duration for all OACs new starters combined in patients with one year of baseline period was 121 days. The mean on-treatment follow-up duration for all OACs new starters combined with 6 months of baseline period is unknown.
Variables and data sources:	Variables are the number of emergency surgeries, major bleeding due to fracture, major bleeding due to trauma, cardiac tamponade and pericardial effusion. Co-variates are baseline characteristics of patients (age, sex, and clinical history), medical history, type of OAC, concomitant medications, events related to bleeding, trauma and fracture.

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	Data sources are MDV clinical database. The database is health insurance claims database. As of end of February 2016, MDV has accumulated claims records from 12.94 million patients, both in and out-patients, from more than 230 large acute, sub-acute and outpatient care DPC hospitals.		
Results:	The number of patients meeting the inclusion and exclusion criteria was 53,969. The age (average±standard deviation (SD)) and percentage of female in these patients were 76±10 with 40% female. Followings are the results of the analyses which included time after switch of OAC. Age stratified data are described in parenthesis. The number of patients with emergency surgery or major bleeding due to fracture/trauma was 133 (14, 35, and 84 for the patient group with age <=64, 65-74 and >=75, respectively). The number of patients with cardiac tamponade and pericardiocentesis was 1. The number of patients with emergency surgery of cardiovascular system was 30 (2, 9, and 19 for the patient group with age <=64, 65-74 and >=75, respectively). The number of patients with emergency surgery of abdomen was 39 (5, 10, and 24 for the patient group with age <=64, 65-74 and >=75, respectively). The number of patients with emergency surgery of urinary system/adrenal glands was 3 (1, 2, and 0 for the patient group with age <=64, 65-74 and >=75, respectively). Comparable results were obtained from analyses which excluded time after switch of OAC. Patient characteristics showed that arterial hypertension was the most frequent diseases within 6 months baseline period. The average±SD of Charlson co-morbidity index was 1.7±2.1. As concomitant medication with OAC, amiodarone and clopidogrel were prescribed in less than 10% of the patients, whereas the other investigated medications were prescribed in over 10 % of the patients.		
Discussion:	We performed epidemiological assessment of emergency surgery, major bleeding due to trauma and fractures by using large scale claims database to investigate the use of non-vitamine K Oral Anti-coagulant reversal in Japan. The number of patients meeting the inclusion and exclusion criteria was 53,969. Among them, the number of patients with emergency surgery or major bleeding due to fracture/trauma, the number of patients with emergency surgery of cardiovascular system, and the number of patients with emergency surgery of abdomen were all less than 150. The incidence of cardiac tamponade and pericardiocentesis, and the incidence of		

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	emergency surgery of urinary system or adrenal glands were extremely rare and only few cases were found.		
Marketing Authorisation Holder(s):	Nippon Boehringer Ingelheim Co., Ltd. 2-1-1 Osaki, Shinagawa-ku, Tokyo 141-6017, Japan		
Names and affiliations of principal investigators:	[redacted] [redacted] [redacted] [redacted], Japan		