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® (Dabigatran etexilate), or warfarin			
Name of active ingredient: Dabigatran etexilate or warfarin			
Report date: 08 May 2018	**Study number:** 1160.219	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Association of select EMR-based covariates with oral anticoagulant medication selection Version and date: Version 1.0, 07 May 2018 Main author: [redacted], MS, PhD, [redacted], MD, ScD, [redacted], MD, MPH. All from the [redacted], USA		
Rationale and background:	A study of safety/effectiveness of NOACs is being conducted in health insurer claims databases that may incompletely capture select variables representing covariates. This validation study seeks to ascertain a select set of covariates in electronic medical records (EMRs) linked to a subset of patients within the insurance claims data to assess the potential for unmeasured confounding in observational studies based on insurance claims databases only.		
Research question and objectives:	The research question is whether select patient characteristics that may be incompletely captured by insurance claims data differ between NOAC and warfarin initiators. Objectives: 1) Descriptive: To identify select clinical covariates from electronic medical records that might be associated with initiation of oral anticoagulant medications (dabigatran or warfarin) in patients with NVAF at risk for stroke and are not usually well captured in the associated claims database. 2) Prediction Rule: To quantify the association between EMR-based clinical characteristics and patterns of insurance claims.		

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	3) Assess Balance: To assess the potential for unmeasured confounding in dabigatran vs warfarin comparative effectiveness and safety studies based on administrative claims databases
Study design:	A validation study. No drugs are being compared in this study, but patients on the following active drugs are included: dabigatran and warfarin as pre-specified in the protocol, rivaroxaban and apixaban as a post hoc analysis. The analyses were mostly descriptive. Representativeness of the linked EMR patients was assessed using absolute standardized differences (aSD) of the variables as compared to the unlinked patients. Objective 1 was addressed by calculating aSDs for the EMR characteristics for the corresponding treatment groups, before and after propensity score (PS) matching on the claims data. Objective 2 was addressed by fitting multivariate regression models to predict 5 continuous EMR variables (BMI, creatinine, time since first recording of AF, time since first recording of diabetes and HAS-BLED) and 5 binary EMR variables (AF, diabetes, stroke, bleeding history, hyperlipidemia). Objective 3 was addressed by predicting exposure (e.g. to dabigatran versus warfarin) by logistic regression from claims variables only, EMR variables only, or the combination of both in the PS matched sets and reporting the corresponding c-statistics. A c-statistic close to 0.5 would suggest low potential for confounding No interim analysis was planned for this study.
Population:	Patients from a US Truven MarketScan health insurance database (linked to electronic medical records in a subset) with a recorded diagnosis of atrial fibrillation without evidence of valvular aetiology and at risk for stroke who initiate dabigatran or warfarin between October 2010 and December 2014. As a post-hoc analysis, patients initiating rivaroxaban and apixaban were also included.

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	Inclusion criteria: • A recorded diagnosis of atrial fibrillation. • Initiation of anticoagulant medication • At least 18 years of age on the date of anticoagulant initiation. • CHA_2DS_2-VASc score ≥ 1 • Presence of electronic medical records (for the EMR-based subset) Exclusion criteria: • Patients with missing or ambiguous age or sex information. • Patients with evidence of valvular disease. • Patients with less than 12 months enrolment preceding the date of anticoagulant initiation. • Patients with a dispensing of any oral anticoagulant during the 12 months preceding the date of anticoagulant initiation • Patients with a nursing home stay during the 12 months preceding the date of anticoagulant initiation
Variables:	Patient characteristics derived from insurance claims (claims-based covariates) This study characterized patients initiating oral anticoagulant medications with respect to select characteristics, as documented in claims data and in electronic medical records prior to and including the date of initiation. These EMR characteristics are considered ‘outcomes’ in this study and include:

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	Primary Outcomes • Obesity • Smoking • Alcohol consumption • Abnormal renal function • Bleeding history or predisposition • Renal function (estimated GFR) • Serum Creatinine • Abnormal liver function Secondary Outcomes • Duration of atrial fibrillation • History of adherence • History/duration of hypertension • Uncontrolled Hypertension • History/duration of CHF • Prior TIA • Diabetes • Hyperlipidemia • HAS-BLED Score • Use of antiplatelets or NSAIDs Further Outcomes • INR Binary EMR variables capturing the presence or absence of a condition were considered to be truly absent if not recorded in the		

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	EMR. Outcomes described in terms of duration correspond to time prior to initiation of anticoagulation based on the earliest date observed in the EMR data; patients without the condition are excluded from the calculations. HAS-BLED was calculated in the primary analysis including labile INR defined as the most recent INR <2 or >3 prior to cohort entry. In case INR was not documented, the patient was considered as having stable INR.		
Results	Pre-specified analyses were for patients on dabigatran or warfarin. As a post-hoc analysis, patients initiating rivaroxaban and apixaban were also included. • During the study period (Oct 2010 – Dec 2014), we identified 140,187 anticoagulant initiators who met the study inclusion criteria: 26,199 new dabigatran users, 70,071 new warfarin users, 32,595 rivaroxaban users and 11,322 apixaban users. • From the claims cohort, we successfully linked 1,130 dabigatran initiators (4.3%) and 2,566 warfarin initiators (3.7%) to the electronic medical records. In addition, 1,602 rivaroxaban initiators and 637 apixaban initiators were successfully linked, leaving a total EMR-linked subset of 5,935 anticoagulant initiators (4.2% of the claims-based cohort). • Mean age of the linked dabigatran patients was 65.1 (±11.4) years; 432 (38.2%) were female. Mean age of the linked warfarin patients was 69.3 (±11.3) years; 1,006 (39.2%) were female. Mean age of the linked rivaroxaban patients was 66.2 (±11.1) years; 600 (37.5%) were female. Mean age of the linked apixaban patients was 67.3 (±11.4) years; 250 (39.2%) were female. Overall, for the 5,935 linked patients, the mean		

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age was 67.4 (±11.4) and 2,288 (38.6%) were female. Race and ethnicity were not collected in this study, and no specific baseline measures were used in the analysis of the primary outcomes.

- Linked dabigatran and warfarin patients were comparable (absolute standardized difference, aSD ≤ 10%) to their unlinked counterparts, except for age (linked patients were younger, mean age 65.1 vs 67.2 for dabigatran and 69.3 vs 71.0 for warfarin), number of laboratory tests (mean number 16.0 vs 12.6 for dabigatran and 19.2 vs 16.0 for warfarin), number of medications (mean number 12.1 vs 11.2 for dabigatran and 13.1 vs 12 for warfarin) and number of office visits (mean number 13.1 vs 11.3 for dabigatran and 16.1 vs 13.5 for warfarin), which were all higher for linked patients. For dabigatran, both CHADS2 (average 1.7 vs 1.9) and CHA_2DS_2-VASc (average 2.7 vs 2.9) were lower for linked than for unlinked patients.
- Before PS-matching (PSM) based on claims variables only in the EMR-linked subset, we observed imbalances in EMR based variables between each NOAC and warfarin.
- After PSM, there were 846 dabigatran initiators matched (75% of the linked patients) 1:1 to warfarin initiators, for a total of 1,692 initiators. There were 874 rivaroxaban-warfarin pairs and 355 apixaban-warfarin pairs.
- History of adherence was not available in the EMR. Some EMR variables had high (>85%) proportions of missing values. They included smoking, alcohol consumption, and systolic blood pressure. Some others were only observed for a small subset (<5%) of patients: abnormal liver function, bleeding history or predisposition, transient ischemic attack.
- The results for the primary outcomes for dabigatran and

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warfarin (always reported in that order) are summarized below:

- Obesity: after PSM, 24% and 22% of dabigatran and warfarin patients, respectively, had missing body mass index (BMI). 57% and 54% were obese (BMI>30), corresponding to an aSD of 7%.
- Smoking: information was missing for 90% and 89% of patients respectively, making the aSD of 1% challenging to interpret.
- Alcohol consumption: information was missing for 98% of patients in both treatment groups; the aSD of 20% for the proportion of heavy drinkers is therefore not very meaningful.
- Abnormal renal function: documented in the EMRs for 6.5% and 8.0% of dabigatran and warfarin patients respectively, corresponding to an aSD of 6%.
- Bleeding history or predisposition: documented for 3.7% and 4.6% of patients; the corresponding aSD of 5% should be interpreted with caution given the low prevalence of documentation of this outcome.
- Renal function (eGFR): information on estimated glomerular filtration rate (eGFR) was missing for 48% of patients in each group. Mean eGFR was 85.4 (±21.9) and 83.4 (±23.5) ml/min/1.73m² respectively, corresponding to an aSD of 9%.
- Serum creatinine was missing for 48% of patients in each group. Mean serum creatinine was 1.0 (±0.3) and 1.0 (±0.4) mg/dl respectively, corresponding to an aSD of 12%.
- Abnormal liver function was documented for 6.5% and

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8.0% of patients respectively, corresponding to an aSD of 6%.

- The results for the secondary outcomes for dabigatran and warfarin (always reported in that order) are summarized below:
  - Duration of AF was estimated in 46% (dabigatran) and 41% (warfarin) of patients with EMR documentation of atrial fibrillation. It was 22.7 (±35.2) and 25.4 (±33.0) months respectively, corresponding to an 8% aSD.
  - History of adherence was not documented in the EMR and no analyses were possible.
  - History of hypertension was documented in 84% and 86% of patients respectively (6% aSD). Mean duration of hypertension was 43.6 (±43.7) and 40.9 (±40.6) months respectively, corresponding to a 6% aSD.
  - Uncontrolled hypertension was based on systolic blood pressure, which was missing for 99% of patients in both groups. None of the patients with available information was identified as having uncontrolled hypertension.
  - History of congestive heart failure (CHF) was documented for 5% and 6% of patients (aSD 4%). Mean duration of CHF was 26.0 (±30.1) and 33.9 (±38.0) months respectively, corresponding to a 23% aSD.
  - Prior transient ischemic attack (TIA) was documented for 1.4% and 2.4% of patients respectively. The corresponding aSD of 7% should be interpreted with caution given the low prevalence of documented TIA.
  - Diabetes (type I or II) was documented for 14.7% and 14.5% of patients respectively, corresponding to a 0% aSD.

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- Hyperlipidemia was documented for 35.6% and 34.0% of patients respectively, corresponding to a 3% aSD.
- The mean HAS-BLED score was well balanced (aSD=6%) however this score relies on availability of the international normalized ratio (INR) which was missing for 88% and 79% of patients respectively (who were then considered to have stable INR).
- Use of antiplatelets or non-steroidal inflammatory drugs (NSAIDs) was documented for 17.1% and 18.7% of patients respectively, corresponding to a 4% aSD.

- To summarize, and also taking the groups matched to apixaban and rivaroxaban into consideration, balance (aSD ≤ 10%) was observed for most EMR variables even though these variables were not included in the PS used for matching.
- Imbalances (aSD > 10%) that persisted after PSM included a shorter duration of congestive heart failure (all NOACs), time since first recording ("duration") of TIA (longer for dabigatran but shorter for other NOACs), duration of diabetes (longer for dabigatran and rivaroxaban, shorter for apixaban), shorter duration of hyperlipidemia (apixaban only) and lower proportion of smokers (apixaban only). Many of the imbalances that persisted were also driven by the large amount of missing data for variables such as smoking status or extremely low prevalence in the EMR subset of the variable, such as TIA.
- The performance of models predicting continuous EMR variables, such as an actual laboratory value or duration of conditions, ranged from poor to moderate. However, models predicting the presence or absence of an EMR variable (typically a diagnosis of a condition of interest which was

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	also recorded in the claims data) showed high predictive accuracy. • When evaluating the potential for unmeasured confounding from EMR variables by assessing change in discrimination of PS models (when EMR variables are included as predictors) predicting initiation of NOAC vs. warfarin, we observe a small change in the c-statistic (for dabigatran vs warfarin, 0.56 when including claims variables only and 0.64 when including EMR variables in addition) across all NOACs suggesting that the EMR variables may represent some unmeasured confounding variables. • Bias analyses however confirmed that remaining numeric imbalances would not cause meaningful confounding (<5% bias).		
Conclusion	This validation study was conducted within a claims-based cohort of commercially insured EMR-linked and unlinked patients initiating oral anticoagulants. Most claims-based characteristics between EMR-linked and unlinked patients were similar suggesting that the results would broadly apply to the overall population. Overall, after PS matching within the EMR-linked subset, patient characteristics between NOAC initiators and initiators of warfarin were well balanced, even though the EMR variables were not included in the PS. The few imbalances that persisted make confounding bias unlikely, as assessed by quantitative bias analyses.		