Individuals and Organizations Completing Research in the IMEDS Lab
Sanofi Investigators

Sanofi Investigators (January 31, 2014)

Overview: This project will focus on evaluating one Mini-Sentinel protocol-based assessment using IMEDS Research Lab in support of IMEDS Methods Research Agenda

Objectives:
1. To estimate the incidence of ischemic stroke and intracranial hemorrhage among new initiators of new oral anticoagulants – debigatran and rivoroxaban in atrial fibrillation patients in a real-world setting
2. To compare the incidence of ischemic stroke and intracranial hemorrhage among new initiators of the above new oral anticoagulants with those among new initiators of warfarin in atrial fibrillation patients in a real-world setting

Study Design: A new user cohort design

Study Population: The US MarketScan Commercial Claims and Encounters database (CCAE), the Medicare Supplemental Beneficiaries database (MDCR) and the Multi-State Medicaid database (MDCD) from Thomson Reuters (New York, NY) in IMEDS Research Lab will be used.

The databases from IMEDS Research Lab may be different than those used in Mini-Sentinel protocol-based assessment. In order to compare results with Mini-Sentinel protocol-based assessment and assess whether there is impact of using different data models (e.g. Mini-Sentinel Common Data Model (CDM) vs. OMOP CDM), we plan to replicate similar analysis using in-house US MareketScan databases, which will be transformed to Mini-Sentinel CDM for comparison purpose.

Eligible participants are adult (age ≥21 years) patients with diagnosed nonvalvular atrial fibrillation and who are new users of dabigatran, rivoroxaban, or warfarin. Patients with recent joint replacement or arthroplasty surgery will be excluded.

Exposure Measurement: For eligible patients, new use of dabigatran will be defined as the date of first datigatran prescription in the database. Similarly, for eligible patients, new use of rivoroxaban or warfarin will be defined as the date of first prescriptions for these medications in the database. Exposure to dabigatran, rivoroxaban, or warfarin will be considered to end for each patient on the final day of the last recorded prescription's days' supply.

Outcomes of Interest: The primary outcomes are ischemic stroke and intracranial hemorrhage.

- **Ischemic stroke** will be identified using hospital claims for primary discharge diagnoses indicating potential stroke events (ICD-9-CM codes 433.x1, 434.x1, 436.0)
- **Intracranial hemorrhage** will be identified using hospital claims for relevant primary and secondary discharge diagnoses (ICD-9-CM codes 430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0) We will also conduct a sensitivity analysis that excludes intracranial haemorrhage associated with major trauma (i.e., codes 852.0x, 852.2x, 852.4x, 853.0).

Statistical Analysis: Statistical analyses will be performed using SAS software package (SAS, version 9.1; SAS Institute. Descriptive analysis will be used as primary analysis to obtain incidence rates of ischemic stroke and intracranial hemorrhage among new initiators of debigatran, rivoroxaban and warfarin.

We will estimate the incidence rates of the event of interest during the follow-up period for the study cohorts. For each event of interest, the numerator for the incidence rate represents the count of patients who develop the event of interest during the follow-up period. The denominator for the rate will be calculated by summing the individual person-time experience contributed by each patient at risk. The standard errors of the incidence rate will be estimated based on a Poisson distribution.

Feasibility assessment will be performed to check if there is sufficient number of debigatran and rivoroxaban users for multivariate regression analysis for direct comparison between cohorts prior to start of the study.

In addition to sample size, baseline characteristics and propensity score distributions between drug cohorts will be compared. Propensity score matching may be performed if there is substantial overlap in the distributions between the two cohorts. If there is little overlap in the distributions between the two cohorts, other methods of controlling for confounding may be used, e.g. stratification. Results from direct comparison between two cohorts will be interpreted with caution given there may be other unmeasured confounding factors.

Cox proportional hazards regression modeling will be used to estimate hazard ratios and 95% confidence intervals to compare the risk of the event between the two study cohorts.

Impact: This project will support one of the IMEDS Methods Research Agenda to evaluate the protocol-based Mini-Sentinel findings using IMEDS data and CDMs.

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Timelines:
1. Study protocol/ analysis plan to be developed by March 31, 2014
2. Access IMEDS Research Lab and conduct data analysis from April 1 - September 30, 2014