SUMMARY OF FDA SENTINEL MODULAR PROGRAM ANALYSES OF ACUTE MYOCARDIAL INFARCTION COMPARING NEW DABIGATRAN AND WARFARIN USERS WITH ATRIAL FIBRILLATION

PURPOSE

This document summarizes results of targeted analyses for the outcome of acute myocardial infarction in a cohort of new users of dabigatran vs. warfarin using the Level 2 (L2) FDA Sentinel Propensity Score-Matching Modular Program. The main motivation for conducting these analyses was to test the feasibility and utility of standardized programming in the propensity score-matching modular program against customized programming employed in the protocol-based assessment (PBA) that is described in the associated paper. L2 analyses were run on all primary outcomes in the PBA (i.e., ischemic stroke, intracranial hemorrhage [with and without trauma-related events], all stroke, major extracranial bleeding and gastrointestinal bleeding), were initiated independent of the primary study team, and produced consistent results except for the analyses of acute myocardial infarction. This document reports results of the L2 analyses for acute myocardial infarction as compared with results of the reported PBA.

DESIGN

The data source for the L2 and PBA analyses in this document were as similar as possible given the available technical options in the L2 modular programs and given the dynamic nature of the FDA Sentinel Distributed Database in which contributing Data Partners update their data on a regular basis. Both approaches employed a "new user" cohort design using data from the same Data Partners in the FDA Sentinel network with identical study periods but different data extraction times.

The following differences in study design led to differences in the analytic dataset. The PBA included prior history of deep vein thrombosis, pulmonary embolism, and joint replacement in the propensity score model whereas the L2 excluded patients with these conditions at baseline. Other differences in the propensity score model are as follows: The PBA included 64 covariates while the L2 had 74 covariates; additional covariates in the L2 analysis included prior history of study outcomes and several health services utilization variables. The covariate identification period was also different, with baseline covariates identified from days -365 to 0 (i.e., inclusive of the cohort entry date) in the PBA and from days -365 to -1 (i.e., exclusive of the index date) in the L2 analysis. Finally, there were also some differences in the National Drug Codes used to identify medications.

With regard to follow-up assessment, the medication stockpiling algorithm was different in the two designs. In both analyses, time on treatment was extended beyond the end of the last dispensing to account for possible overlapping days in consecutive dispensing periods (referred to as stockpiling). However, the PBA analysis capped the extension to 7 days whereas the L2 analysis capped the extension to 23% of the last dispensing's duration. The majority of dispensing durations were for 30 days, so the L2 cap on extension corresponds to 6.9 days for most patients in the L2 analysis. The extract, transform and load (ETL) data end dates for the PBA ranged from 12/31/2012 to 5/31/2014 whereas the ETL data end dates for the L2 ranged from 4/30/2014 to 3/31/2015 across the eight contributing Data Partners.

ANALYSES

L2 analyses of acute myocardial infarction between new dabigatran and warfarin users with atrial fibrillation adjusted for confounding using 1:1 propensity score-matching in the same way the PBA analyses did (i.e., same caliper distance and nearest neighbor matching algorithm). Hazard ratios were estimated using Cox regression stratified by Data Partner (unconditional approach) or Cox regression stratified jointly by Data Partner and matched pair (conditional approach). Stratifying Cox regression by Data Partner and matched pair (conditional approach) can reduce the number of informative events (i.e., those events contributing to the likelihood estimating the hazard ratio) compared to the unconditional analytic approach. The reason is that only those events occurring before either patient in a pair is censored are considered informative using a conditional analytic approach.

RESULTS

Among 25,385 matched pairs of new dabigatran and warfarin users, the mean (SD) duration of continuous exposure was 122.1 (148.7) days for dabigatran and 107.8 (127.9) days for warfarin, with median (interquartile range) of 66 (36 to 143) days and 66 (36 to 126) days, respectively. In the L2 analysis, we observed an incidence of acute myocardial infarction of

0.73 per 100 person-years for dabigatran and 0.60 per 100 person-years for warfarin (**Table**). Using either an unconditional or conditional analytic approach, there was a numerically higher but not statistically significant association between dabigatran and acute myocardial infarction compared with warfarin (**Table**).

Table. Drug exposure and incidence of acute myocardial infarction among 25,385 matched new users of dabigatran or warfarin in the L2 analysis.

Mean days of follow-up		Number of acute myocardial infarction events*		Incidence rate per 100 person-years		Hazard ratio (95% confidence interval)	
						Unconditional Analytic Approach	Conditional Analytic Approach
Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin		
122	108	62	45*	0.73	0.60	1.24 (0.85-1.83)	1.50 (0.89-2.51)

*Total events are informative for the unconditional analytic approach but not necessarily informative for the conditional analytic approach