Risk of stroke and bleeding in nonvalvular atrial fibrillation treated with apixaban compared to warfarin in the Sentinel System

Marie C. Bradley[1], PhD, MPharm, MSc.PH, Emily C. Welch[2], MPH, Efe Eworuke[1], PhD, MSc, B.Pharm, David J. Graham[1], MD, MPH, Rongmei Zhang[3], PhD, Ting-Ying Huang[2], PhD

[1]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration. Silver Spring, MD [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA [3]Office of Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

Acknowledgement: The authors thank the Sentinel Data Partners who provided data used in the analysis. This project was funded by the US Food and Drug Administration via Contract No HHSF223201400030I and HHSF223200910006I. The views expressed are those of the authors and not intended to convey official US Food and Drug Administration policy or guidance.

Background and Objective

- Use of Apixaban, a non-vitamin K antagonist oral anticoagulant (NOAC), has been increasing in recent years in the US.
- A previous FDA study[1] reported a favorable benefit risk profile for apixaban compared to warfarin for stroke prevention in older nonvalvular atrial fibrillation (NVAF) patients.
- However, that study was restricted to Medicare beneficiaries aged ≥ 65 years and it remained unclear whether this favorable benefit risk profile persists in other populations including younger users aged < 65 years.

Objective: To examine if a similar benefit risk profile for apixaban compared to warfarin was observed in the FDA Sentinel System and if it varied by age group.

Methods

- Retrospective new user cohort study in the Sentinel System from December 28, 2012 to June 30, 2018 (Figure 1)
- Identified new initiators of apixaban or warfarin, aged ≥ 21 years with a diagnosis of NVAF in the previous 183 days
- Outcomes: inpatient principal diagnosis for gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH) or ischemic stroke were defined using previously validated algorithms based on ICD-9-CM diagnosis codes. We adapted this to include ICD-10-CM coding using forward-backward mapping via the General Equivalence Mapping.
- Excluded Medicare fee-for-service population in order to better differentiate study population from prior Medicare study
- Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95 % confidence intervals (95% CI) for each outcome in propensity score matched apixaban users compared to warfarin users. A subgroup analysis by age (21-64, 65-74 and 75+ years) was also conducted.

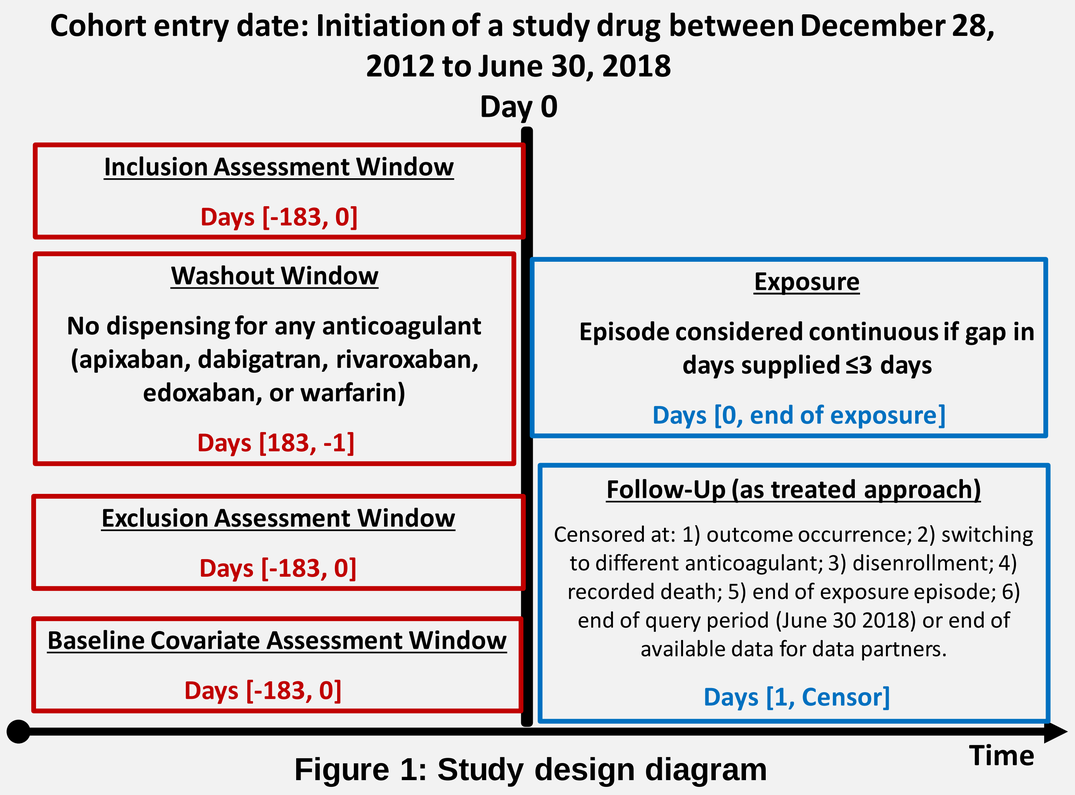

Figure 1: Study design diagram

Exclusion criteria

- Evidence of any study outcome
- Deep vein thrombosis, pulmonary embolism, joint replacement, mitral stenosis, valve replacement or valve repair

Inclusion criteria

- Continuous enrollment in health and prescription drug plans (gap ≤45 days allowed)
- NVAF diagnosis
- Age ≥21 years (day 0)

Baseline Covariates

- Demographics (day 0)
- Medical conditions and medication use
- Combined comorbidity score [2]
- Health care utilization

Results

- 99, 442 apixaban and 94,189 warfarin initiators were identified from 7 Sentinel data partners.
- After matching, 55.3% and 58.4% of the apixaban and warfarin cohorts respectively were included (n=55,038 in each cohort).
- After propensity score matching both exposure groups were closely balanced for all covariates (data not shown).
- Overall, a reduced risk of GI bleeding, ICH and ischemic stroke was seen in apixaban users compared to warfarin users (Table 1).
- The reduced risk of GI bleeding and stroke persisted across all age groups and was lowest in those aged 21-64 years (Tables 2, 3 & 4).

Table 1:Adjusted HRs (95% CIs) for GI bleeding, ICH, and Ischemic stroke in apixaban compared to warfarin users all age groups combined

	Person Years (PY) at Risk	Number of Events	Incidence Rate per 1,000 PY	Hazard Ratio (95% CI)
GI bleeding				
Apixaban	20,470.14	304	14.85	**0.57 (0.50-0.66)**
Warfarin	25,243.38	631	25.00	
ICH				
Apixaban	20,517.02	71	3.46	**0.53 (0.40-0.70)**
Warfarin	25,411.13	171	6.73	
Ischemic stroke				
Apixaban	20,493.77	108	5.27	**0.56 (0.45-0.71)**
Warfarin	25,381.00	226	8.90	

Tables 2, 3 & 4-Adjusted HRs (95% CIs) for GI bleeding, ICH, and Ischemic stroke in apixaban compared to warfarin users by age group

GI bleeding	Number of New Users	Incidence Rate per 1,000 PY	Hazard Ratio (95% CI)
Age: 21-64 years			
Apixaban	14,172	4.73	**0.34 (0.21-0.54)**
Warfarin	14,172	14.82	
Age: 65-74 years			
Apixaban	17,804	13.21	**0.51 (0.40-0.65)**
Warfarin	17,804	24.36	
Age: 75+ years			
Apixaban	20,977	22.50	**0.68 (0.56-0.82)**
Warfarin	20,977	30.57	

ICH	Number of New Users	Incidence Rate per 1,000 PY	Hazard Ratio (95% CI)
Age: 21-64 years			
Apixaban	14,172	1.03	**0.38 (0.14-1.05)**
Warfarin	14,172	2.88	
Age: 65-74 years			
Apixaban	17,804	4.30	**0.63 (0.39-1.03)**
Warfarin	17,804	5.50	
Age: 75+ years			
Apixaban	20,977	5.13	**0.52 (0.36-0.76)**
Warfarin	20,977	9.58	

Ischemic stroke	Number of New Users	Incidence Rate per 1,000 PY	Hazard Ratio (95% CI)
Age: 21-64 years			
Apixaban	14,172	1.44	**0.29 (0.13-0.68)**
Warfarin	14,172	4.80	
Age: 65-74 years			
Apixaban	17,804	4.96	**0.70 (0.46-1.07)**
Warfarin	17,804	6.71	
Age: 75+ years			
Apixaban	20,977	8.08	**0.57 (0.42-0.77)**
Warfarin	20,977	12.84	

Discussion and Conclusions

- Overall, among patients with NVAF in 7 Sentinel data partners, between 2012 and 2018, apixaban use was associated with a statistically significant decreased risk of GI bleeding, ICH and ischemic stroke compared to warfarin use.
- When analyses were stratified by age, the risk of GI bleeding and stroke were significantly reduced in apixaban users aged < 65 years. The risk of ICH was also reduced in younger apixaban users, but not significantly so. There were only 20 ICH events in this age-group (5 in apixaban users), giving reduced statistical power to show a significant reduction in risk.
- The favorable benefit risk profile for apixaban compared to warfarin for stroke prevention in NVAF, seen in older users in Medicare [1], appears to be consistent in younger users in Sentinel.

References: 1.Graham DJ, Baro E, Zhang R, et al. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *Am J Med* 2019;132(5):596-604 2. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64(7):749-759