Replicating the findings of a Medicare study on stroke and bleeding risk in patients using NOACs for atrial fibrillation in the Sentinel System

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Background and Objective

- A recent FDA study in Medicare [1] concluded that among older patients (aged ≥65 years) with nonvalvular atrial fibrillation (NVAF) rivaroxaban had a less favorable benefit-harm profile compared to other nonvitamin K oral anticoagulants (NOACs).
- However, limited data exist on the benefit-harm profile of rivaroxaban compared to other NOACs in younger users aged <65 years. We wanted to study the comparative safety and effectiveness of individual NOACs in younger users in the Sentinel system.
- The analytic approach (inverse probability of treatment weighting with a pooled NOAC group as the reference for weighting) used in the Medicare study was not a capability of the Sentinel modular programs at the time.
- Objective: As a prelude to studying the comparative safety and effectiveness of individual NOACs in younger users within the Sentinel System, we sought to use Sentinel modular programs to replicate the findings of a previous FDA study in Medicare that compared the safety and effectiveness of individual NOACs in older patients in Sentinel, to compare the analytic approaches.

Methods

- Retrospective new user cohort study among standard dose NOAC users with NVAF, aged ≥ 65 years between October 19, 2010 to September 30, 2015 in the Sentinel Medicare DP only
- Identified new initiators of standard dose apixaban, dabigatran, rivaroxaban, with a diagnosis of NVAF in the previous 183 days
- Outcomes included: inpatient principal diagnosis for major extracranial bleeding (MEB), gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), or thromboembolic stroke - defined using previously validated algorithms based on *ICD-9-CM* diagnosis codes
- Three pairwise comparisons: Rivaroxaban vs. Dabigatran, Rivaroxaban vs. Apixaban, Dabigatran vs. Apixaban
- For each pairwise comparison:
  - Propensity score matching to estimate average treatment effects on individual NOACs
- Cox proportional hazards regression to estimate the hazard ratios (HR) and 95 % confidence intervals (95% CI) for each outcome

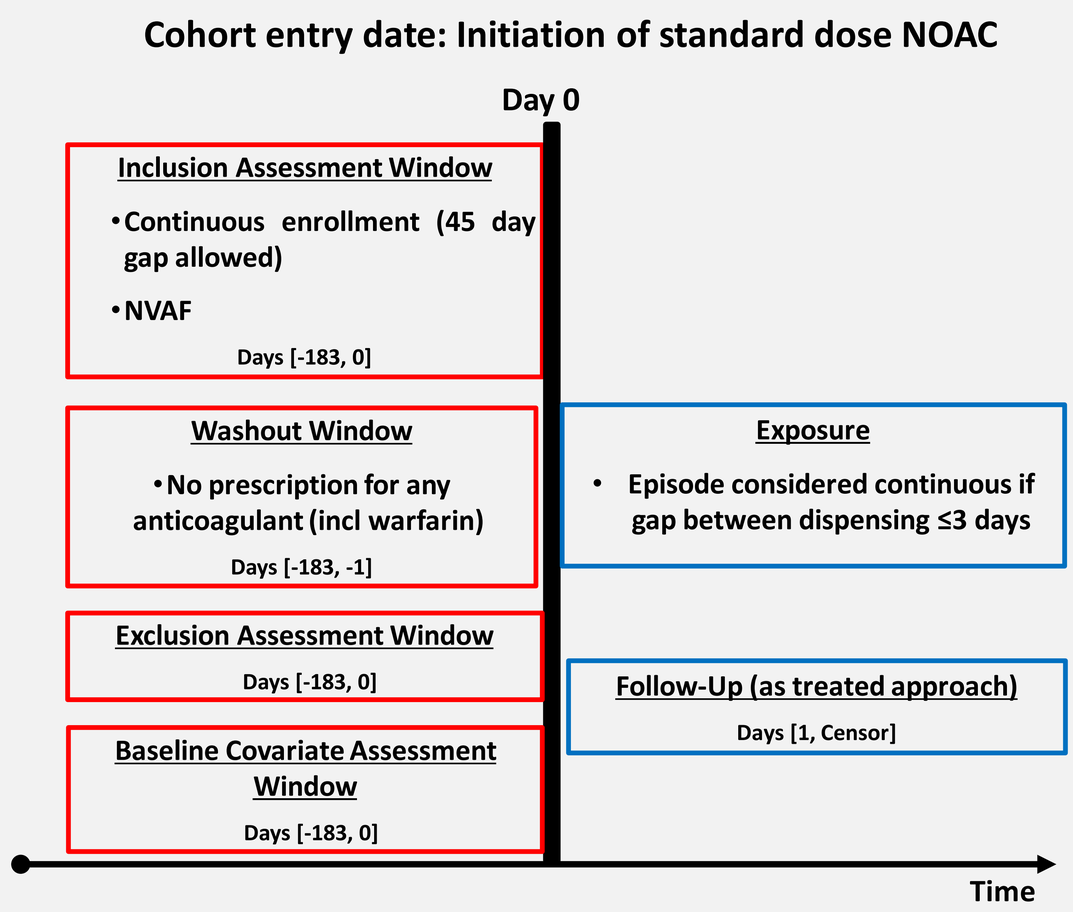

Figure 1: Study design diagram

Inclusion criteria

- Continuous enrollment (45 day gap allowed)
- NVAF diagnosis
- Age ≥65 years (day 0)

Exclusion criteria

- Dialysis, Kidney replacement, Deep vein thrombosis, Pulmonary embolism, Joint replacement, Mitral stenosis, Valve replacement or repair. (-183, -1)
- Institutional stay encounter, NOAC dispensing other than index NOAC (day 0)

Baseline Covariates

- Demographics
- Medical conditions and medication use
- Stroke and bleeding risk scores
- Health care utilization

Censoring Criteria

- Death, Query end date, Disenrollment, Any outcome event , End of exposure episode, Comparator drug dispensing, Low-dose of current exposure , Warfarin dispensing , Other NOAC dispensing, Kidney transplant or dialysis, Institutional stay encounter.

Results

- Overall, the risk estimates were largely similar in the Medicare and Sentinel studies
- No difference was seen in stroke risk with rivaroxaban compared with dabigatran use [Medicare HR (95% CI) 0.90 (0.76-1.06) and Sentinel 0.89 (0.74-1.07)]
- Similarly, rivaroxaban use was associated with a non statistically significant increased risk of ICH compared to apixaban in both studies-Medicare HR (95% CI) 1.21 (0.94-1.55) and Sentinel 1.28 (0.99, 1.67)
- Despite using a modified algorithm for identification of GI bleeding events in Sentinel (no transfusion, critical site involvement, or death required) the results were also largely similar:
  - HRs (95% CI) for MEB with rivaroxaban compared to apixaban in Medicare and Sentinel studies were 2.70 (2.38-3.05) and 2.29 (2.06-2.55)respectively
  - HRs (95% CI) for GIB was 2.83 (2.47-3.25) and 2.32 (2.07-2.59) respectively

Table 1: Adjusted hazard ratios (95% confidence intervals) for each NOAC pairwise comparison and thromboembolic stroke, intracranial hemorrhage, major extracranial (including major gastrointestinal) bleeding, and major GI bleeding in Medicare and Sentinel.

	HR (95%CI)			
	Thromboembolic stroke	Intracranial hemorrhage	Major extracranial bleed	Major GI bleed
Medicare study				
Rivaroxaban vs. Dabigatran	0.90 (0.76-1.06)	1.71 (1.35-2.17)	1.32 (1.21-1.45)	1.27 (1.16-1.40)
Rivaroxaban vs. Apixaban	1.02 (0.85-1.23)	1.21 (0.94-1.55)	2.70 (2.38-3.05)	2.83 (2.47-3.25)
Dabigatran vs. Apixaban	1.14 (0.94-1.37)	0.70 (0.53-0.94)	2.04 (1.78-2.32)	2.23 (1.93-2.58)
Sentinel Study				
Rivaroxaban vs. Dabigatran	0.89 (0.74-1.07)	1.67 (1.29-2.17)	1.21 (1.12-1.32)	1.17 (1.08- 1.28)
Rivaroxaban vs. Apixaban	1.00 (0.82-1.22)	1.28 (0.99-1.67)	2.29 (2.06-2.55)	2.32 (2.07-2.59)
Dabigatran vs. Apixaban	1.15(0.93-1.40)	0.75 (0.55-1.03)	1.96 (1.75-2.20)	2.04 (1.81-2.31)

Discussion and Conclusions

- We were able to successfully replicate the findings of a previous FDA Medicare study in the Sentinel Medicare data partner using a modified analytic approach.
- The individual propensity score matched analytic approach provided similar results to the combined IPTW analytic approach.
- Going forward we will use the Sentinel system to compare the safety and effectiveness of individual NOACs in users aged < 65 years.

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