Comparative Bleeding Risks Among NOAC Users With Nonvalvular Atrial Fibrillation Aged <65 Years in the Sentinel System

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- The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS or the U.S. Government
- **I have no conflicts of interest related to this presentation**

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- **Mention of a commercial product should not be construed as actual or implied endorsement**

Outline

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- Methods
- Discussion
- Strengths and limitations
- Conclusion

Background

- Randomized trials compared nonvitamin K antagonist oral anticoagulants (NOACs) to warfarin, but not the safety of individual NOACs against each other
- Head-to-head observational studies comparing NOAC safety limited by:
  - Inadequate adjustment of confounding
  - Inappropriate outcome ascertainment
  - Small study sizes
  - Prevalent user design
- FDA study using Medicare data concluded that among older patients (aged ≥65 years) with nonvalvular atrial fibrillation (NVAF), rivaroxaban had a less favorable benefit-harm profile compared to other NOACs. However, it remains unclear whether this less favorable benefit persists in younger users.

Graham et al. Am J Med. 2019 May;132(5):596-604

Objective: To evaluate, in the FDA Sentinel System, if rivaroxaban use is associated with higher bleeding risk compared to apixaban or dabigatran in patients <65 years with NVAF

Methods

Methods

- **Data source:** FDA Sentinel System https://www.sentinelinitiative.org/
  - Distributed database using Sentinel common data model
  - Five Sentinel data partners contributed to the analysis
    - Four nationally representative commercial insurance plans
    - One state Medicaid partner
  - Routinely refreshed, quality-checked data
    - Clear provenance

- 128.7 million members accruing new data
- 1.3 billion person-years of data
- 22.3 billion pharmacy dispensings
- 24 billion unique medical encounters
- 73.2 million members with ≥1 lab test result

Methods cont'd

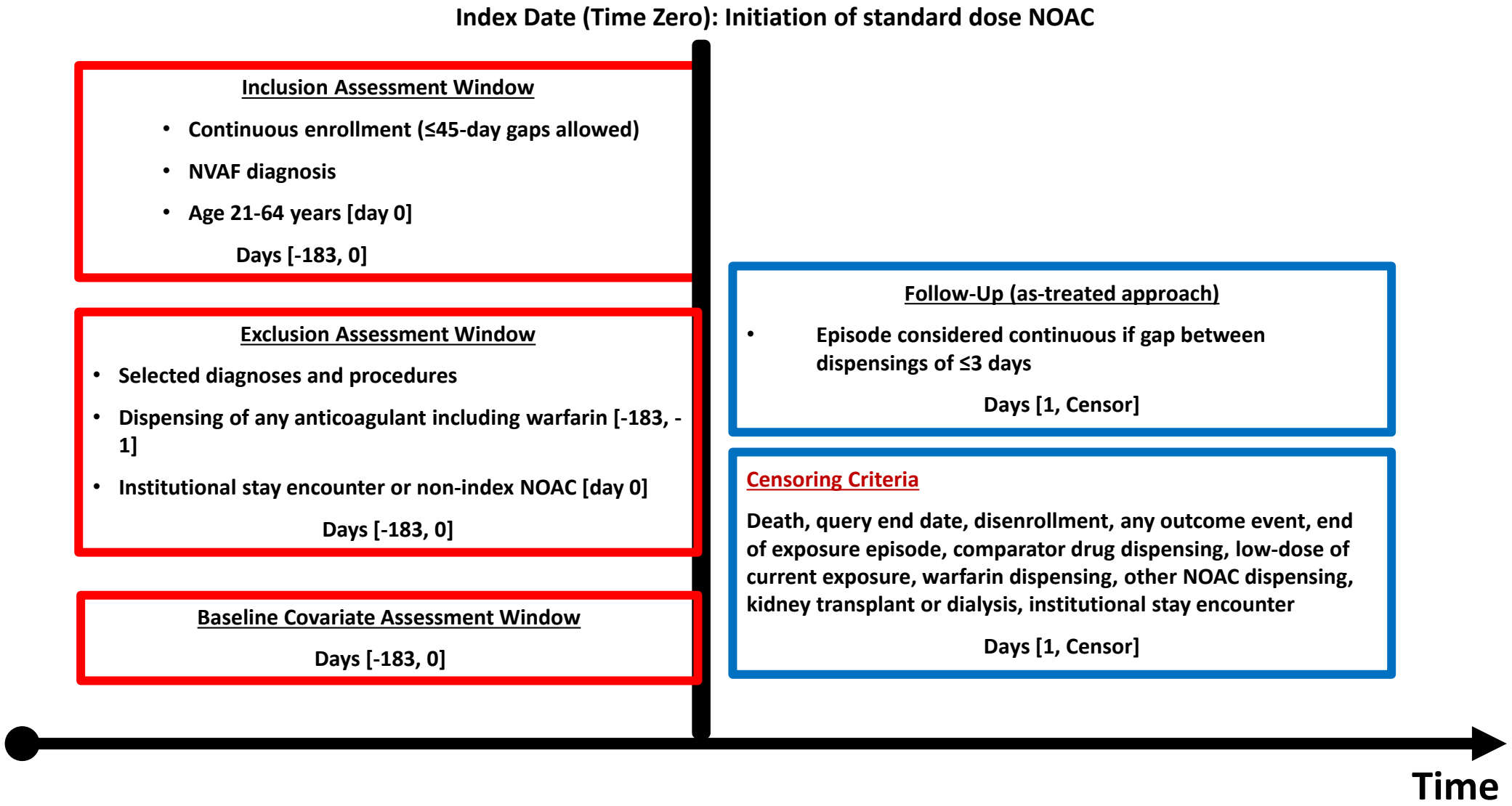
- **Study Design:** Retrospective new user cohort study
- **Study population and period:** Standard dose NOAC users with NVAF, aged 21-64 years between October 19, 2010, to February 28, 2022
- Continuous enrollment for ≥183 days
  - *Inclusion criterion: NVAF diagnosis 183 days prior to initiation of NOAC (index date)*
  - ***Exclusion criteria:*** *Dialysis, kidney replacement, deep vein thrombosis, pulmonary embolism, joint replacement, mitral stenosis, valve replacement or repair, other anticoagulant dispensing, institutional stay encounter (index date only)*
- **Exposure:** New initiators of standard dose apixaban, dabigatran, rivaroxaban, with a diagnosis of NVAF in the previous 183 days
  - **Three pairwise NOAC-NOAC comparisons:**
    - **Rivaroxaban vs. Dabigatran, Rivaroxaban vs. Apixaban, Dabigatran vs. Apixaban**

Methods (cont'd)

- **Baseline Covariates**
  - Demographic factors, medical conditions and medication use, stroke and bleeding risk scores, health care utilization
- **Analysis**
  - Inverse probability of treatment weighting with stabilized average treatment effect weights were applied separately for each pairwise comparison.
  - Cox proportional-hazards regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for outcomes: **intracranial hemorrhage (ICH), major extracranial bleeding (MEB), and GI bleeding (GIB)**
  - Subgroup analyses by age, sex, CHA2DS2-VASc score, and HAS-BLED score
- **Outcomes**
  - Defined using previously validated algorithms based on *ICD-9-CM* diagnosis codes

Cunningham et al, Pharmacoepidemiol Drug Saf. 2011 Jun; 20(6): 560–566.

Study Design Diagram



Results

Results

Select demographics and event rates after IPTW:

	Rivaroxaban vs. Apixaban		Rivaroxaban vs. Dabigatran		Dabigatran vs. Apixaban	
	Rivaroxaban	**Apixaban**	**Rivaroxaban**	**Dabigatran**	**Dabigatran**	**Apixaban**
New users (n)	57,965	96,013	57,127	19,679	18,882	96,132
Mean age (SD)	56.6 (7.2)	56.7 (7.3)	56.3 (7.4)	56.2 (7.4)	56.6 (7.1)	56.8 (7.2)
Female (%)	16,208 (28.0)	26,985 (28.1)	14,310 (25)	4,821 (24.5)	5,190 (27.5)	27,288 (28.4)
Outcome events MEB (n)	224	204	188	38	39	206
Weighted Incidence Rate per 1,000 Person Years	11.6	6.4	9.9	7.3	7.8	6.4
Outcome events GI bleed (n)	191	174	157	34	37	174
Weighted Incidence Rate per 1,000 Person Years	10.0	5.4	8.3	6.6	7.2	5.4
Outcome events ICH (n)	34	35	29	7	8	37
Weighted Incidence Rate per 1,000 Person Years	1.8	1.1	1.5	1.4	1.7	1.2

Results (cont'd)

- **Increased risk of GI bleed and MEB when rivaroxaban compared to apixaban use**
- **Suggested increased risk of all outcomes when rivaroxaban compared to dabigatran use, and when comparing dabigatran to apixaban, but not statistically significant**

Outcome	Rivaroxaban vs. Apixaban	Rivaroxaban vs. Dabigatran	Dabigatran vs. Apixaban
	HR 95%CI	HR 95%CI	HR 95%CI
Gastrointestinal Bleed	1.92 (1.54, 2.39)	1.32 (0.89, 1.96)	1.34 (0.88, 2.05)
Major extracranial bleed	1.91 (1.56, 2.34)	1.42 (0.98, 2.07)	1.22 (0.82, 1.81)
Intracranial hemorrhage	1.63 (0.99, 2.70)	1.18 (0.52, 2.67)	1.43 (0.58, 3.52)

- **Results in the subgroups aligned with main analysis**

Results (cont'd)

Compared to previous FDA study in Medicare recipients aged over 65 years.

Outcome	Sentinel System Rivaroxaban vs. Apixaban (≤65 years)	Graham et al.* Rivaroxaban vs. Apixaban (≥65 years)	Sentinel System Rivaroxaban vs. Dabigatran (≤65 years)	Graham et al.* Rivaroxaban vs. Dabigatran (≥65 years)	Sentinel System Dabigatran vs. Apixaban (≤65 years)	Graham et al.* Dabigatran vs. Apixaban (≥65 years)
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
GI Bleeding	1.92 (1.54, 2.39)	2.83 (2.47, 3.25)	1.32 (0.89, 1.96)	1.27 (1.16, 1.40)	1.34 (0.88, 2.05)	2.23 (1.93, 2.58)
Major extracranial bleeding	1.91 (1.56, 2.34)	2.70 (2.38, 3.05)	1.42 (0.98, 2.07)	1.32 (1.21, 1.45)	1.22 (0.82, 1.81)	2.04 (1.78, 2.32)
Intracranial hemorrhage	1.63 (0.99, 2.70)	1.21 (0.94, 1.55)	1.18 (0.52, 2.67)	1.71 (1.35, 2.17)	1.43 (0.58, 3.52)	0.70 (0.53, 0.94)

**Am J Med. 2019 May;132(5):596-604*

Discussion

- **Aligned with findings from previous FDA studies, rivaroxaban use was associated with significantly increased risks of gastrointestinal bleeding and major extracranial bleeding compared to apixaban**
  - Non-significant increased risk of intracranial hemorrhage
  - Non-significant increased risks of these outcomes for rivaroxaban compared with dabigatran
- **Smaller numbers of bleeding outcomes in NOAC users aged less than 65 years compared to previous studies in older adults**
  - May have affected statistical power
- **Pharmacologic rationale:**
  - NOACs half-life of about 12 hours
  - Dabigatran and apixaban are dosed twice daily, rivaroxaban is dosed once daily
  - Rivaroxaban once daily might increase risk of bleeding
  - Concern raised at FDA advisory committee meeting convened prior to rivaroxaban's approval

Strengths and limitations

- Largest study to date to compare safety of NOACs to each other in those <65 years old
- ATE weights used for balancing characteristics in pairwise comparisons preserved sample size
- Bleeding events are typically less common in younger ages (approx. 80% of patients with AF are over 65 years)
- Included only initiators of standard-dose NOACs
  - Effects may differ in patients treated with lower doses
- First-time users of anticoagulant for stroke prevention in NVAF
  - Results might differ in patient switching from warfarin

Conclusion

- **Among patients less than 65 years old—treated with standard-dose NOACs for NVAF in the Sentinel System and with similar baseline characteristics—rivaroxaban use was associated with a less favorable benefit-harm profile than apixaban**
- **These findings largely align with findings on bleeding risk in NOAC users from previous FDA studies in older adults**

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