Prospective Surveillance Pilot of Rivaroxaban Safety within the US Food and Drug Administration Sentinel System

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Workgroup

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- Many thanks are due to Data Partners who provided data used in the analysis

Funding and Disclosures

- Funding: This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006I
- Conflict of interest statements:
  - JJG reports a research grant from Novartis Pharmaceuticals
  - JJN receives industry funding for a FDA post-marketing requirement contract (through inVentiv Health) to assess factors associated with opioid-related adverse events
  - Other investigators report no conflicts

Background: Rivaroxaban in A Fib

- ROCKET-AF[1] compared rivaroxaban with warfarin for stroke prevention in non-valvular atrial fibrillation
- Compared with warfarin, rivaroxaban had:
  - Similar effect on ischemic stroke
    - HR 0.94 (95% CI 0.75-1.17)
  - Decreased risk of intracranial hemorrhage
    - HR 0.67 (95% CI 0.47, 0.93)
  - Increased risk of major gastrointestinal bleeding
    - HR 1.61 (95% CI 1.30, 1.99)

Study Goal

- Test a sequential, propensity-score matched approach by examining the safety of rivaroxaban (Xarelto®) vs. warfarin among patients with atrial fibrillation in the drug's early uptake period

Background: Sequential Monitoring Using Propensity Score Matching

- Sequential methods have been commonly applied in randomized trials
- General challenges of sequential monitoring in observational settings have been explored[2]
- Less is known about sequential implementation of propensity score matching (PSM) in a setting such as Sentinel

Study Design (1/2)

- New user, parallel cohort design
  - Cohort Identification and Descriptive Analysis (CIDA) tool in combination with the PSM tool[3]

Study Design (2/2)

- Inclusion criteria
  - Age ≥ 21 years
  - Initiated rivaroxaban or warfarin November 1, 2011 or after
  - Nonvalvular AF
- Exclusion criteria
  - Less than 183 days continuous prior enrollment
  - Prior use of rivaroxaban, warfarin, or other non-vitamin K anticoagulants
  - Dialysis, history of kidney transplant, valve disease, knee/hip replacement

Outcomes

- Outcomes of Interest
  - Gastrointestinal bleeding
  - Ischemic Stroke
  - Intracranial hemorrhage*
- Definitions
  - Inpatient care setting
  - Sequential testing: Primary and non-secondary position ICD9 diagnosis codes
  - End of surveillance: Primary position ICD9 diagnosis codes

*ICD9 Codes include both hemorrhagic stroke (430, 431) and other intracranial hemorrhage (432, 852.0X, 852.2X, 852.4X, 853.0)

Exposure and Follow-up

- Follow-up began the day after first dispensing (index) date
- 7-day gap in days supply allowed between two claims
- Censored at
  - Occurrence of outcome event
  - Treatment discontinuation
  - Initiation of another anticoagulant
  - Death or disenrollment from the health plan
  - End of available data

Propensity Score Matching (1/2)

- Variable ratio propensity score (PS) matching (each new rivaroxaban user matched to up to 10 new warfarin users)[4]
- Using nearest neighbor algorithm, matching caliper 0.05
- PS estimation and matching within Data Partner

Propensity Score Matching (2/2)

- 70+ confounders:
  - Age, sex, year of index date
  - Combined comorbidity score
  - Health service utilization variables (counts of encounters by setting, number of drugs)
  - Procedures and diagnoses: risk factors for bleeding, ischemic stroke
  - Medications: oral cardiovascular agents, medications that increase bleeding risk, interacting medications

Statistical Analysis

- Cox regression stratified by Data Partner and matched set to estimate hazard ratio
- Sequential testing
  - Group sequential design, multiple looks, flat boundary
  - Initial threshold for signal (5 looks): Wald z-score > 2.37 (P<0.018)
  - Revised signaling threshold (2 looks): Wald z-score >2.06 (P<0.039)
    - To reflect change of number of looks and amount of information at each look
    - Delay due to tool refinements
- End-of-surveillance analysis (one-time estimation)
  - Included only diagnosis codes in primary position

Cohort Characteristics

Sentinel

	Unmatched			Matched[a]		
Selected Characteristics	N(%) Rivaroxaban	N(%) Warfarin	Standard-ized Difference	N(%) Rivaroxaban	N(%) Warfarin	Standard-ized Difference
	41,800	87,907		36,173	79,520	
Gender (F)	16,374 (39.2)	37,017 (42.1)	0.06	14,669 (40.6)	14,574 (40.3)	0.005
Age-mean (SD)	69.7 (10.7)	73.4 (10.6)	0.352	71.1 (10.4)	71.1 (10.7)	0
Combined Comorbidity Score - mean (SD)	2.4 (2.4)	3.2 (2.8)	0.313	2.5 (2.4)	2.5 (2.4)	0.007
Atrial fibrillation	36,581 (87.5)	77,568 (88.2)	0.022	31,630 (87.4)	31,866 (88.1)	0.02
Atrial flutter	7,627 (18.2)	12,454 (14.2)	0.111	5,994 (16.6)	6,008 (16.6)	0.001
GI bleed	1,507 (3.6)	4,841 (5.5)	0.091	1,393 (3.9)	1,426 (3.9)	0.005
Intracranial hemorrhage	231 (0.6)	1,152 (1.3)	0.079	224 (0.6)	239 (0.7)	0.005
Ischemic stroke	3,150 (7.5)	10,207 (11.6)	0.139	3,031 (8.4)	2,973 (8.2)	0.006
Hypertension	32,865 (78.6)	71,386 (81.2)	0.064	28,662 (79.2)	28,683 (79.3)	0.001
Hyperlipidemia	12,819 (30.7)	25,265 (28.7)	0.042	10,884 (30.1)	11,046 (30.5)	0.01
Heart failure or cardiomyopathy	15,110 (36.1)	39,359 (44.8)	0.176	13,781 (38.1)	13,940 (38.5)	0.009
Peripheral vascular disease	6,638 (15.9)	18,645 (21.2)	0.137	6,234 (17.2)	6,277 (17.4)	0.003
Diabetes	12,505 (29.9)	31,905 (36.3)	0.136	11,417 (31.6)	11,398 (31.5)	0.001
Venous thrombo-embolism	2,525 (6.0)	10,598 (12.1)	0.211	2,456 (6.8)	2,340 (6.5)	0.013
Walker use	886 (2.1)	3,126 (3.6)	0.087	844 (2.3)	807 (2.2)	0.007
Home oxygen	2,240 (5.4)	7,017 (8.0)	0.105	2,123 (5.9)	2,078 (5.7)	0.005

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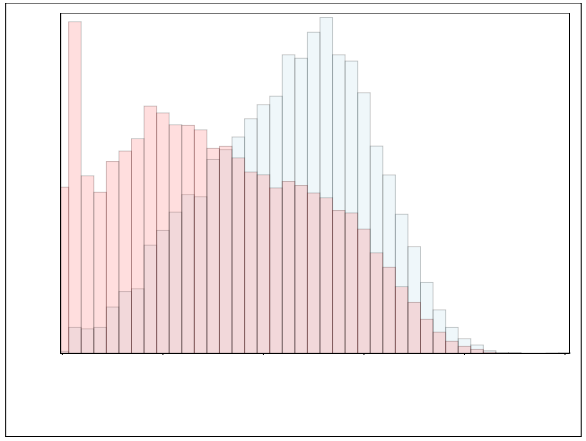
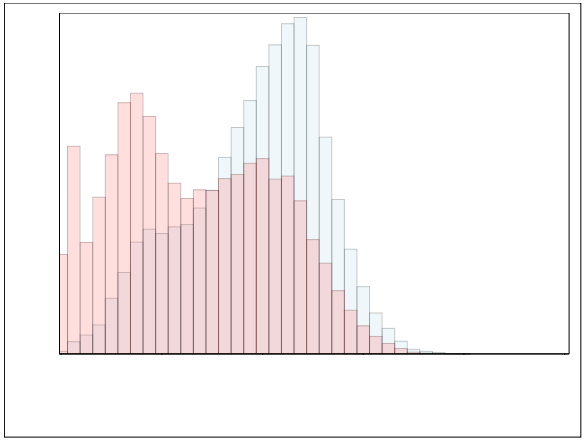
[a] weighted

Histograms of Propensity Scores, Unmatched Cohort, 4 Data Partners, Gastrointestinal Bleeding Analysis Cohort

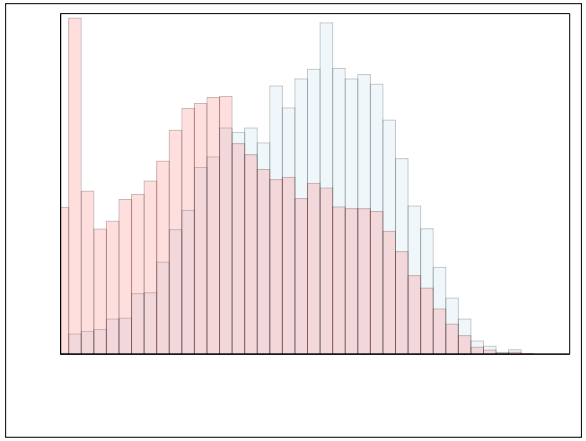
Data Partner 1



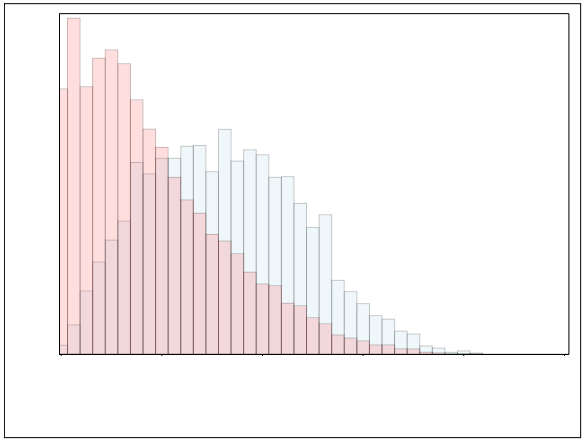
Data Partner 2



Data Partner 3



Data Partner 4



Histograms of Propensity Scores, Propensity Score-Matched Cohort, 4 Data Partners, Gastrointestinal Bleeding Analysis Cohort

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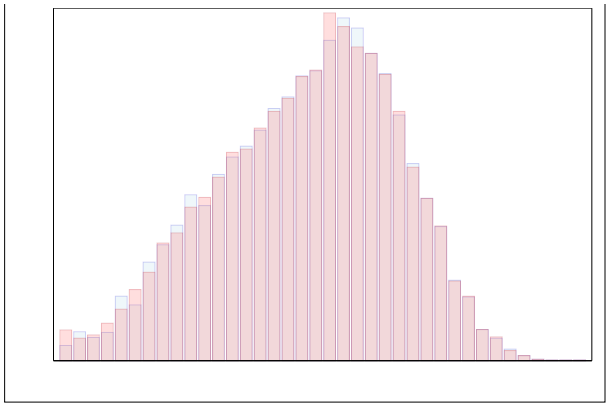

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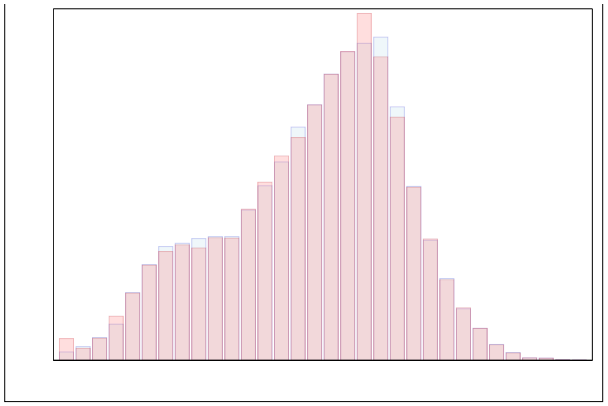

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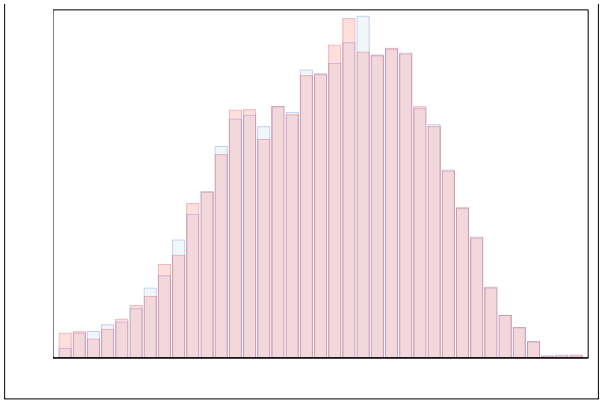
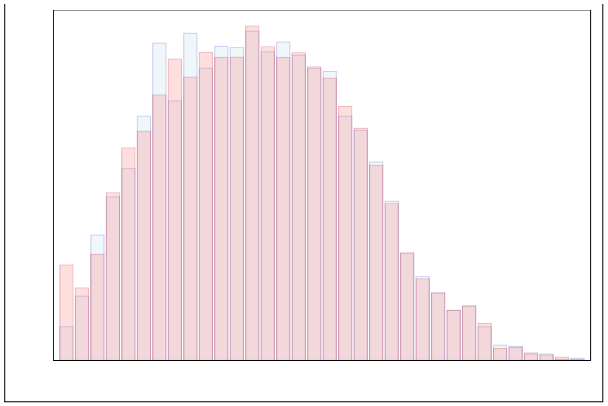


Data Partner 4



Sequential Analysis Results

Analysis Period/Outcome	Hazard Ratio	Wald p-value	Number of Events in Rivaroxaban New Users
First Look[A]			
Gastrointestinal Bleeding	1.19	.0625	167
Ischemic Stroke	0.65	.0036	54
Intracranial Hemorrhage	0.69	0.1434	21
Second Look[B]			
Gastrointestinal Bleeding	1.30	<.0001	738
Ischemic Stroke	0.81	NA	357
Intracranial Hemorrhage	0.73	.0159	86

[A] Monitoring period 11/1/2011-8/31/2013, 14,465 rivaroxaban new users

[B] Monitoring period 11/1/2011-4/30/2015, 36,126 rivaroxaban new users

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End-of-Surveillance Results (Specific Criteria for Outcomes[A])

Outcome/ Comparator	New Users	Person-Years at Risk	Events	Adjusted Incidence Rate per 1000 Person-Years[C]	Adjusted Hazard Ratio (95% CI)[B]
Gastrointestinal Bleeding					1.47 (1.29, 1.67)
Rivaroxaban	36,173	8,427	423	50.20	
Warfarin	79,520	15,384	651	34.82	
Ischemic Stroke					0.61 (0.47, 0.79)
Rivaroxaban	36,512	8,572	82	9.57	
Warfarin	80,180	15,672	268	17.10	
Intracranial Hemorrhage					0.71 (0.50, 1.01)
Rivaroxaban	36,171	8,502	46	5.41	
Warfarin	79,529	15,551	143	7.49	

[A] Outcome events required diagnosis codes in primary position. Monitoring period started Nov 1, 2011 for all data partners, but the end date varied among Data Partners: April 30, 2014, Dec 31, 2014, March 31, 2015, and April 30, 2015. Matching caliper for this analysis was 0.01.

[B] Hazard Ratios estimated by stratified Cox regression conditioned on Data Partner and PS matched set. Confidence intervals are nominal 95% intervals for the final hazard ratio estimates.

[C] Incidence rates adjusted for censoring in matched sets and variable ratio matching.

Subgroup Analysis

- By prior history of event
  - No significant variation
- By age groups
  - Only significant finding was for gastrointestinal bleeding

Subgroup	Adjusted HR for GI Bleeding (95% Confidence Interval)[A]
Patients under age 66	0.88 (0.60, 1.30)[B]
Patients age 66 and over	1.49 (1.30, 1.71)[B]

[A] Hazard Ratio estimated by stratified Cox regression. Confidence intervals are nominal 95% intervals.
[B] The null hypothesis that the two age subgroups differ by chance alone was rejected (Chi-square [1 degree of freedom] = 13.7, p = .0002).

Conclusion

- Sophisticated re-usable programming tools deployed against a common data model in a multi-site distributed database
  - Large heterogeneous patient populations
  - Complements cardiovascular outcomes trials
- No new concerns about rivaroxaban safety were raised
- Evidence of a lower risk of ischemic stroke in rivaroxaban users compared to warfarin users
  - Detected early
  - Persisted with additional monitoring and sensitivity analysis

References

1. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
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4. Wang SV, Schneeweiss S, Rassen JA. Optimal matching ratios in drug safety surveillance. Epidemiology (Cambridge, Mass) 2014;25:772-3.