

## APPENDIX A

**Selected Baseline Patient Characteristics, by Study Drug, Unmatched and Matched Cohorts<sup>a</sup>**

Selected Characteristics	Unmatched			Matched <sup>a</sup>		
	N(%) Rivaroxaban	N(%) Warfarin	Standardized Difference	N(%) Rivaroxaban	N(%) Warfarin	Standardized Difference
Number of Patients	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
Health Service Utilization Intensity: mean (SD)						

Selected Characteristics	Unmatched			Matched <sup>a</sup>		
	N(%) Rivaroxaban	N(%) Warfarin	Standardized Difference	N(%) Rivaroxaban	N(%) Warfarin	Standardized Difference
# Filled Rx	18.1 (14.8)	18.5 (15)	-0.029	18.1 (14.8)	18.3 (14.8)	-0.013
# inpatient hospital encounters	0.6 (0.8)	0.7 (0.9)	-0.178	0.6 (0.8)	0.6 (0.8)	0.011
# non-acute institutional encounters	0.2 (0.8)	0.4 (1)	-0.151	0.2 (0.9)	0.2 (0.8)	-0.004
# emergency room encounters	0.6 (1.1)	0.6 (1.3)	0.003	0.5 (1)	0.5 (1.2)	0.012
# ambulatory encounters	11.1 (9.6)	13.1 (11.5)	-0.192	11.5 (9.9)	11.6 (9.4)	-0.012

<sup>a</sup>Values for the matched cohort are weighted to incorporate the average values of all the matches in the matched set.

## APPENDIX B

### Propensity Score-Matched<sup>a</sup> End of Surveillance Cox Regression Analysis Comparing Rivaroxaban with Warfarin, by Health Outcome and Subgroup

Outcome/Subgroup	Hazard Ratio (95% CI) <sup>b</sup>
<b>Gastrointestinal Bleeding</b>	
Age Group:	
Patients age 21-65	0.88 ( 0.60, 1.30) *
Patients age 66 and over	1.49 ( 1.30, 1.71) *
Baseline History of Outcome Event:	
Patients without baseline gastrointestinal bleeding	1.52 ( 1.32, 1.76)
Patients with baseline gastrointestinal bleeding	1.36 ( 0.94, 1.95)
<b>Ischemic Stroke</b>	
Age Group:	
Patients age 21-65	1.09 (0.61, 1.96)
Patients age 66 and over	0.60 (0.45, 0.79)
Baseline History of Outcome Event:	
Patients without baseline ischemic stroke	0.68 (0.49, 0.93)
Patients with baseline ischemic stroke	0.61 (0.40, 0.94)
<b>Intracranial Hemorrhage</b>	
Age Group:	
Patients age 21-65	0.61 ( 0.20, 1.88)
Patients age 66 and over	0.77 ( 0.54, 1.10)
Baseline History of Outcome Event:	
Patients without baseline intracranial hemorrhage	0.66 ( 0.46, 0.94)
Patients with baseline intracranial hemorrhage	6.47 ( 0.87, 48.19)

<sup>a</sup> Monitoring period started November 1, 2011 for all data partners, but the end date varied among Data partners: April 30, 2014, December 31, 2014, March 31, 2015, and April 30, 2015. Matching caliper for this analysis was 0.01

<sup>b</sup>Hazard Ratio 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.

\* The null hypothesis that the two age subgroups differ by chance alone was rejected (Chi-square [1 degree of freedom] = 13.7, p = .0002)

## APPENDIX C

### Inpatient diagnosis codes for defining outcome events

Outcome Event	ICD-9-CM Codes <sup>a</sup>
Ischemic stroke <sup>b</sup>	433.x1, 434.x1, 436
Intracranial hemorrhage <sup>c</sup>	<p><u>Hemorrhagic stroke</u>: 430 (subarachnoid), 431 (intracerebral)</p> <p><u>Other intracranial hemorrhage</u>: 432.0 (nontraumatic extradural), 432.1 (subdural), 432.9 (unspecified ICH), 852.0x (subarachnoid after injury*), 852.2x (subdural after injury*), 852.4x (extradural after injury*), 853.0 (other and unspecified ICH after injury*)</p> <p>*="without mention of open intracranial wound"</p>
Gastrointestinal bleeding <sup>d</sup>	<p><u>Gastroduodenal site</u>: 531.0x, 531.1x, 531.2x, 531.4x, 531.6x, 532.0x, 532.1x, 532.2x, 532.4x, 532.6x, 533.0x, 533.1x, 533.2x, 533.4x, 533.6x, 534.0x, 534.1x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 537.84</p> <p><u>Esophageal site</u>: 456.0, 456.20, 530.21, 530.7, 530.82</p> <p><u>Upper gastrointestinal unspecified</u>: 578.0</p> <p><u>Lower gastrointestinal site</u>: 455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 569.86</p> <p><u>Unspecified gastrointestinal site</u>: 578.x</p>

<sup>a</sup> The position designation for discharge diagnosis codes in the Mini-Sentinel Common Data Model can be coded as primary, secondary, unable to classify, or missing.

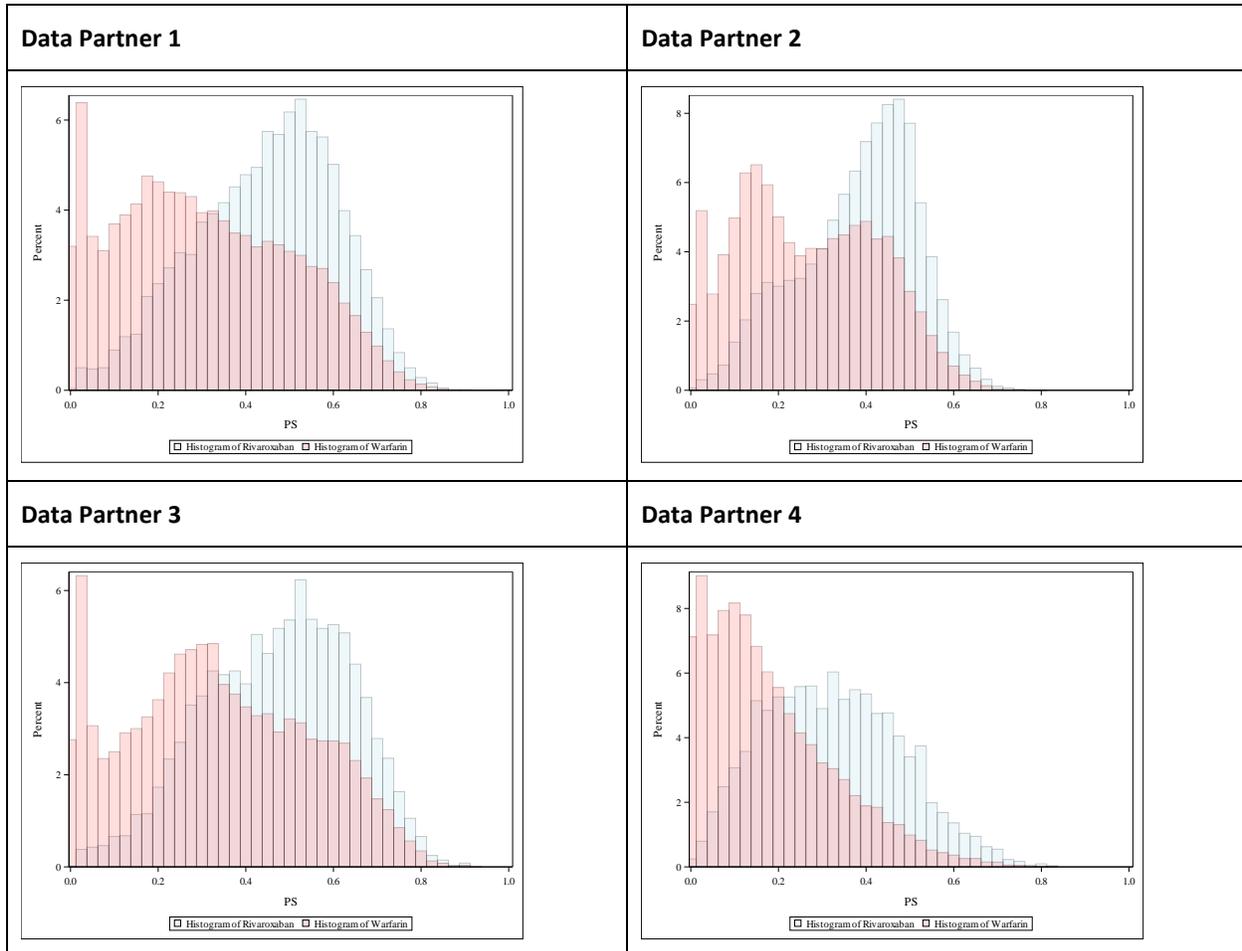
<sup>b</sup> For ischemic stroke, Tirschwell et al found a positive predictive value (PPV) of 90% and sensitivity of 86% for the codes in this algorithm when evaluated across all hospital discharge diagnoses. Primary position discharge diagnoses had a PPV of 88% and sensitivity of 74%. The inclusion and exclusion terms for ICD-9-CM code 436 changed in 2004, likely reducing its specificity for stroke. The PPV for the algorithm without code 436 was 95.5% using any position hospital diagnoses.<sup>30</sup>

<sup>c</sup> For intracranial hemorrhage, the PPV of the codes in the algorithm has been estimated as 75.5% when applied to primary and secondary discharge diagnoses. ICD-9 CM codes 430 and 431 in the primary position of hospital records have had PPVs ranging from 94% to 98% and 89% to 97%, respectively, for subarachnoid and intracranial hemorrhage.<sup>33</sup>

<sup>d</sup> The gastrointestinal bleeding algorithm combines codes from two published algorithms. Schelleman et al found a PPV of 91% for primary position, 81% for any position, and 71% for non-principal position inpatient codes for an algorithm that included most of codes in the algorithm utilized here.<sup>34</sup> Cunningham et al evaluated a more complex algorithm.<sup>35</sup> Based on their reporting of incidence and PPVs of individual codes, the codes added to the Schelleman algorithm have an estimated PPV of 71% for definite or probable bleeding. They comprised 26% of the gastrointestinal bleeding codes validated by Cunningham et al, suggesting that the PPV of the Sentinel combined algorithm for primary position codes is approximately 86%.

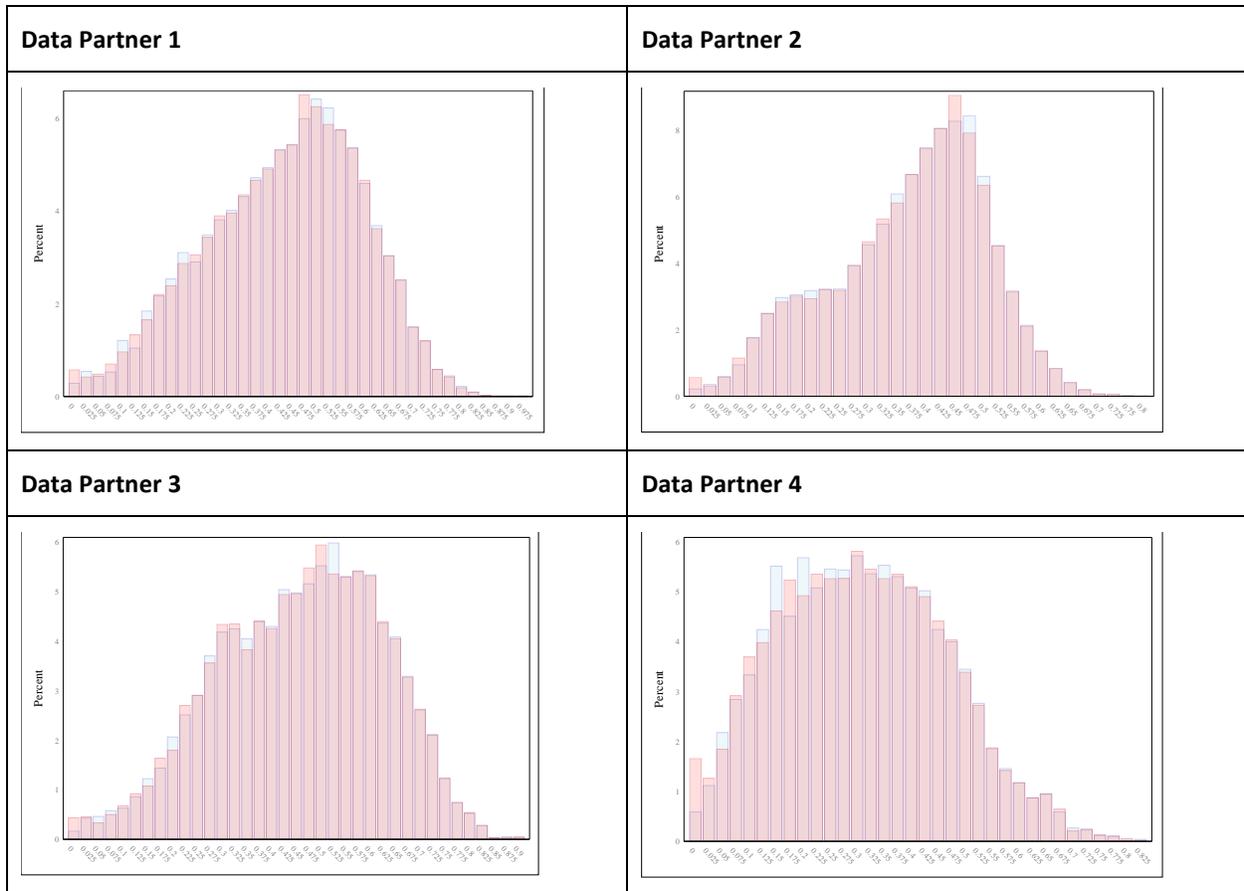
## APPENDIX D

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



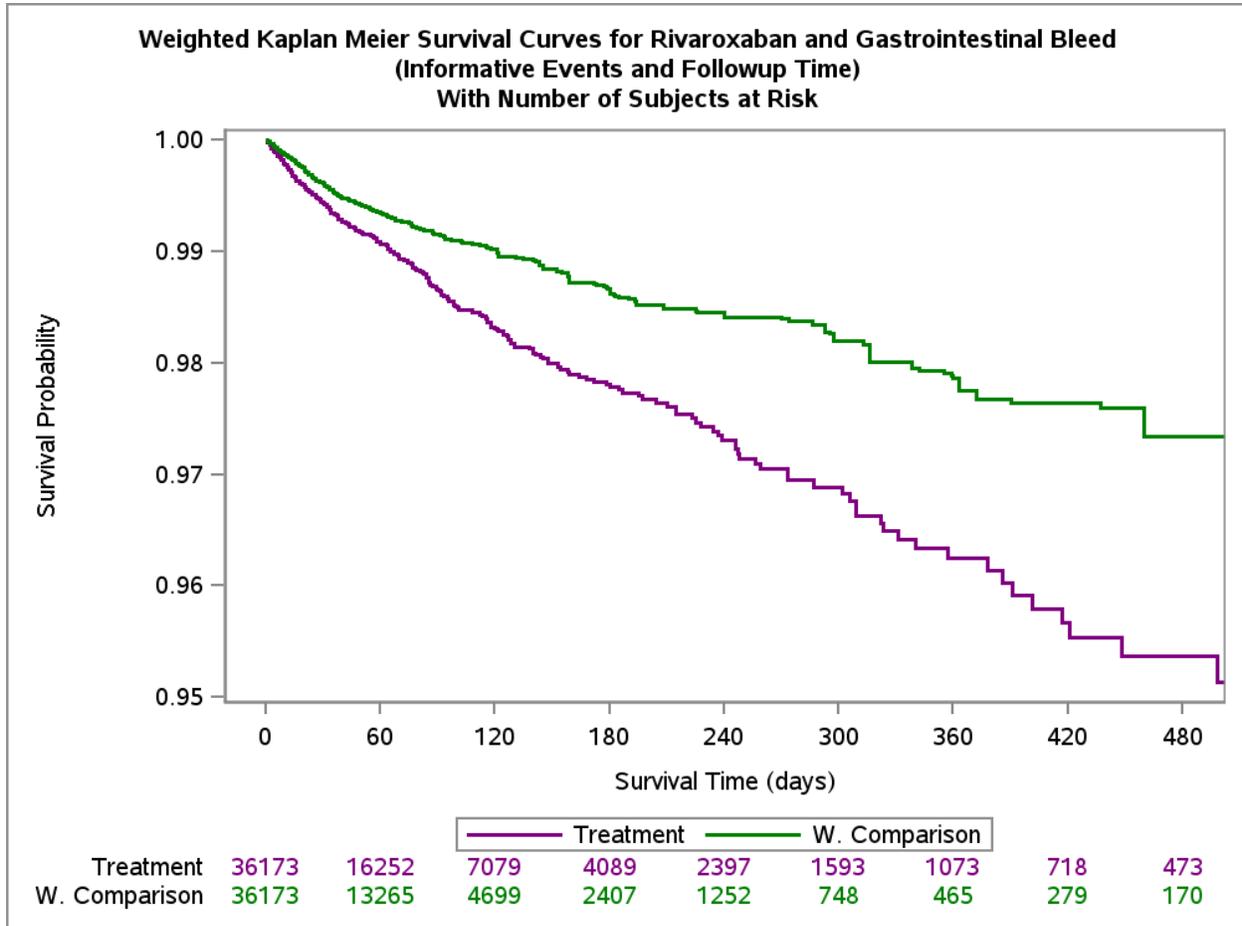
## APPENDIX E

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



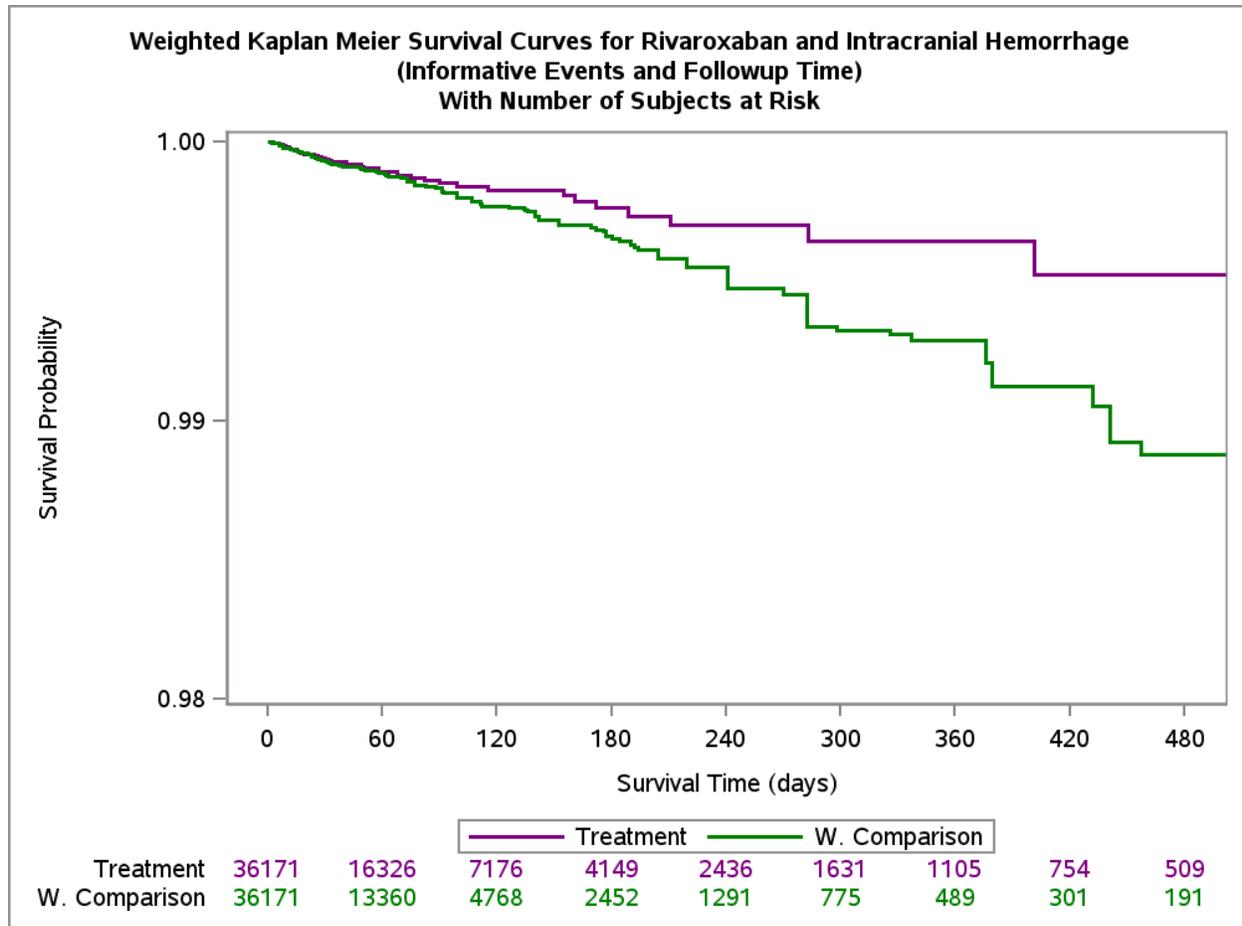
## APPENDIX F

### Weighted Kaplan Meier Survival Curves for Rivaroxaban and Gastrointestinal Bleed (Informative Events and Follow-up Time) with Number of Subjects at Risk



## APPENDIX G

### Weighted Kaplan Meier Survival Curves for Rivaroxaban and Intracranial Hemorrhage (Informative Events and Follow-up Time) with Number of Subjects at Risk



## APPENDIX H

### Weighted Kaplan Meier Survival Curves for Rivaroxaban and Ischemic Stroke (Informative Events and Follow-up Time) with Number of Subjects at Risk

