

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. ICD-9-CM Codes for Stroke/SE and Major Bleeding

Diagnosis	ICD-9 Diagnosis and Procedure Codes
Hemorrhagic Stroke	430.xx-432.xx
	Cases were excluded if traumatic brain injury (ICD-9: 800-804, 850-854) was present during hospitalization.
Ischemic Stroke	433.x1, 434.x1, 436
Systemic Embolism	444.x, 445.x
Major Gastrointestinal Bleeding	456.0, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
	Procedure Code: 44.43
Major Intracranial Hemorrhage	430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0x,
Major Other Hemorrhage	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11
	Procedure codes: 99.04

eTable 2. Baseline Characteristics and Outcomes for Prematched Apixaban, Dabigatran, Rivaroxaban, and Warfarin Patients

	Warfarin (N = 145,063)		Apixaban (N = 89,296)			Dabigatran (N = 28,317)			Rivaroxaban (N = 118,378)		
	N/Mean	%/SD	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*
Age	78.4	8.4	77.9	8.7	5.94	76.3	8.7	24.70	76.7	8.9	19.65
18-54	1,166	0.8%	1,068	1.2%	3.94	487	1.7%	8.21	2,135	1.8%	8.82
55-64	4,735	3.3%	3,851	4.3%	5.49	1,615	5.7%	11.81	6,567	5.5%	11.14
65-74	38,094	26.3%	24,347	27.3%	2.27	8,859	31.3%	11.12	35,295	29.8%	7.92
75-79	34,312	23.7%	20,920	23.4%	0.53	7,258	25.6%	4.59	28,976	24.5%	1.93
≥80	66,756	46.0%	39,110	43.8%	4.47	10,098	35.7%	21.19	45,405	38.4%	15.56
Gender											
Male	74,062	51.1%	43,719	49.0%	4.19	15,003	53.0%	3.86	60,781	51.3%	0.58
Female	71,001	48.9%	45,577	51.0%	4.19	13,314	47.0%	3.86	57,597	48.7%	0.58
U.S. Geographic Region											
Northeast	27,043	18.6%	15,060	16.9%	4.65	5,340	18.9%	0.55	20,739	17.5%	2.92
Midwest	44,641	30.8%	18,991	21.3%	21.79	6,358	22.5%	18.91	26,903	22.7%	18.25
South	47,108	32.5%	41,082	46.0%	27.98	11,464	40.5%	16.70	50,094	42.3%	20.45
West	25,915	17.9%	14,008	15.7%	5.83	5,060	17.9%	0.01	20,275	17.1%	1.94
Other	356	0.2%	155	0.2%	1.57	95	0.3%	1.67	367	0.3%	1.23
Baseline Comorbidity											
Deyo-Charlson Comorbidity Index	3.6	2.9	3.2	2.7	14.51	3.0	2.6	24.90	3.0	2.6	21.99
CHA₂DS₂-VASc Score	4.3	1.5	4.2	1.5	10.75	4.0	1.5	22.17	4.0	1.5	20.97
0	411	0.3%	507	0.6%	4.37	243	0.9%	7.64	1,024	0.9%	7.70
1	1,831	1.3%	1,743	2.0%	5.49	835	2.9%	11.77	3,346	2.8%	11.07
2	11,690	8.1%	8,702	9.7%	5.93	3,146	11.1%	10.38	13,421	11.3%	11.10
3	29,975	20.7%	19,475	21.8%	2.80	6,672	23.6%	6.99	27,348	23.1%	5.90
4+	101,156	69.7%	58,869	65.9%	8.16	17,421	61.5%	17.35	73,239	61.9%	16.63
HAS-BLED Score[†]	3.4	1.3	3.3	1.2	3.96	3.2	1.2	15.56	3.3	1.2	11.15

	Warfarin (N = 145,063)		Apixaban (N = 89,296)			Dabigatran (N = 28,317)			Rivaroxaban (N = 118,378)		
	N/Mean	%/SD	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*
0	152	0.1%	172	0.2%	2.28	108	0.4%	5.62	388	0.3%	4.80
1	7,925	5.5%	4,323	4.8%	2.81	1,494	5.3%	0.83	6,417	5.4%	0.19
2	27,750	19.1%	17,369	19.5%	0.81	6,222	22.0%	7.04	24,207	20.4%	3.31
3+	109,236	75.3%	67,432	75.5%	0.49	20,493	72.4%	6.68	87,366	73.8%	3.44
Bleeding history*	36,115	24.9%	19,564	21.9%	7.06	5,802	20.5%	10.54	25,796	21.8%	7.34
Congestive heart failure*	52,537	36.2%	27,111	30.4%	12.45	7,885	27.8%	18.01	33,056	27.9%	17.84
Diabetes mellitus*	59,524	41.0%	33,000	37.0%	8.37	10,776	38.1%	6.09	43,266	36.5%	9.21
Hypertension*	128,409	88.5%	79,956	89.5%	3.27	25,257	89.2%	2.14	105,191	88.9%	1.08
Renal disease*	47,637	32.8%	24,054	26.9%	12.92	5,999	21.2%	26.47	26,730	22.6%	23.07
Liver disease*	8,340	5.7%	5,024	5.6%	0.53	1,494	5.3%	2.07	6,948	5.9%	0.51
Myocardial infarction*	17,632	12.2%	8,988	10.1%	6.65	2,389	8.4%	12.26	11,170	9.4%	8.77
Dyspepsia or stomach discomfort*	31,328	21.6%	19,521	21.9%	0.64	5,758	20.3%	3.10	25,457	21.5%	0.22
Non-stroke/SE peripheral vascular disease*	82,688	57.0%	50,214	56.2%	1.55	15,077	53.2%	7.56	63,611	53.7%	6.57
Stroke/SE*	23,595	16.3%	12,127	13.6%	7.54	3,558	12.6%	10.55	14,756	12.5%	10.85
Transient ischemic attack*	11,979	8.3%	7,562	8.5%	0.76	2,299	8.1%	0.51	9,374	7.9%	1.24
Anemia and coagulation defects*	51,995	35.8%	27,557	30.9%	10.58	7,903	27.9%	17.09	34,680	29.3%	14.00
Alcoholism*	3,262	2.2%	1,909	2.1%	0.76	752	2.7%	2.63	3,281	2.8%	3.34
Peripheral artery disease	35,361	24.4%	19,707	22.1%	5.47	5,637	19.9%	10.78	24,941	21.1%	7.90
Coronary artery disease	71,255	49.1%	43,812	49.1%	0.11	13,069	46.2%	5.94	54,806	46.3%	5.65
Baseline Medication Use[‡]											

	Warfarin (N = 145,063)		Apixaban (N = 89,296)			Dabigatran (N = 28,317)			Rivaroxaban (N = 118,378)		
	N/Mean	%/SD	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*	N/Mean	%/SD	STD*
ACE/ARB	87,985	60.7%	56,335	63.1%	5.01	17,870	63.1%	5.05	73,542	62.1%	3.02
Amiodarone	16,934	11.7%	11,443	12.8%	3.48	3,210	11.3%	1.06	13,745	11.6%	0.19
Beta blockers	87,932	60.6%	55,389	62.0%	2.90	16,983	60.0%	1.31	72,248	61.0%	0.85
H2-receptor antagonist	11,388	7.9%	6,621	7.4%	1.64	1,987	7.0%	3.18	8,539	7.2%	2.41
Proton pump inhibitor	47,072	32.4%	30,924	34.6%	4.62	8,983	31.7%	1.56	39,373	33.3%	1.73
Statins	89,181	61.5%	56,740	63.5%	4.26	17,132	60.5%	2.00	72,192	61.0%	1.01
Anti-platelets	31,348	21.6%	21,768	24.4%	6.58	6,006	21.2%	0.98	26,752	22.6%	2.38
NSAIDS	32,333	22.3%	24,546	27.5%	12.05	8,235	29.1%	15.59	34,996	29.6%	16.66
Dose of the Index Prescription											
Standard Dose§			64,131	71.8%		22,613	79.9%		80,835	68.3%	
Lower Dose			25,165	28.2%		5,704	20.1%		37,543	31.7%	
Follow-up Time (in days)	240.8	219.4	188.3	169.6	26.75	232.7	230.7	3.58	230.6	217.6	4.68
Median	157		127			129					
Outcomes											
Stroke/SE	2,243	1.6%	681	0.8%	7.34	305	1.1%	4.12	1,232	1.0%	4.47
Hemorrhagic Stroke	599	0.4%	122	0.1%	5.28	34	0.1%	5.68	256	0.2%	3.51
Ischemic Stroke	1,552	1.1%	542	0.6%	5.08	256	0.9%	1.68	910	0.8%	3.16
SE	114	0.1%	22	0.0%	2.38	15	0.1%	1.00	76	0.1%	0.54
Major Bleeding	6,630	4.6%	1,910	2.1%	13.53	774	2.7%	9.81	4,778	1.1%	2.63
GI Bleeding	3,235	2.2%	935	1.1%	9.33	467	1.7%	4.21	2,710	4.0%	0.40
ICH	1,042	0.7%	260	0.3%	6.03	84	0.3%	5.94	463	2.3%	4.41
Other sites	2,768	1.9%	827	0.9%	8.32	283	1.0%	7.60	1,999	0.4%	1.65

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CHA₂DS₂-VASC: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 – 74 years, sex category; GI: gastrointestinal; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs or alcohol; ICH: intracranial hemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; SD: standard deviation; SE: systemic embolism; STD: standardized difference.

Std Difference=100|actual std diff|. Std Difference greater than 10 is considered significant. Warfarin was the reference.

[†]as the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

[‡]Based on non-oral anticoagulant prescriptions on the index date.

[§]Standard dose: 5mg Apixaban, 150mg Dabigatran, 20 mg Rivaroxaban.

^{||}Lower dose: 2.5mg Apixaban, 75 mg Dabigatran, 10 mg Rivaroxaban, 15mg Rivaroxaban.

eTable 3. Hazard Ratios of Stroke/SE and Major Bleeding in the Low-Dose Population

	Hazard Ratio (95% CI)	p-value
Apixaban vs Warfarin		
Stroke/SE	0.64 (0.53-0.77)	<.001
Major Bleeding	0.60 (0.55-0.67)	<.001
Dabigatran vs Warfarin		
Stroke/SE	1.05 (0.80-1.37)	0.72
Major Bleeding	0.93 (0.78-1.11)	0.43
Rivaroxaban vs Warfarin		
Stroke/SE	0.84 (0.73-0.97)	0.02
Major Bleeding	1.15 (1.07-1.25)	<0.001
Apixaban vs Dabigatran		
Stroke/SE	0.61 (0.41-0.91)	0.02
Major Bleeding	0.77 (0.60-0.99)	0.04
Apixaban vs Rivaroxaban		
Stroke/SE	0.75 (0.60-0.94)	0.01
Major Bleeding	0.54 (0.47-0.61)	<0.001
Dabigatran vs Rivaroxaban		
Stroke/SE	1.34 (0.94-1.91)	0.11
Major Bleeding	0.71 (0.58-0.86)	<0.001

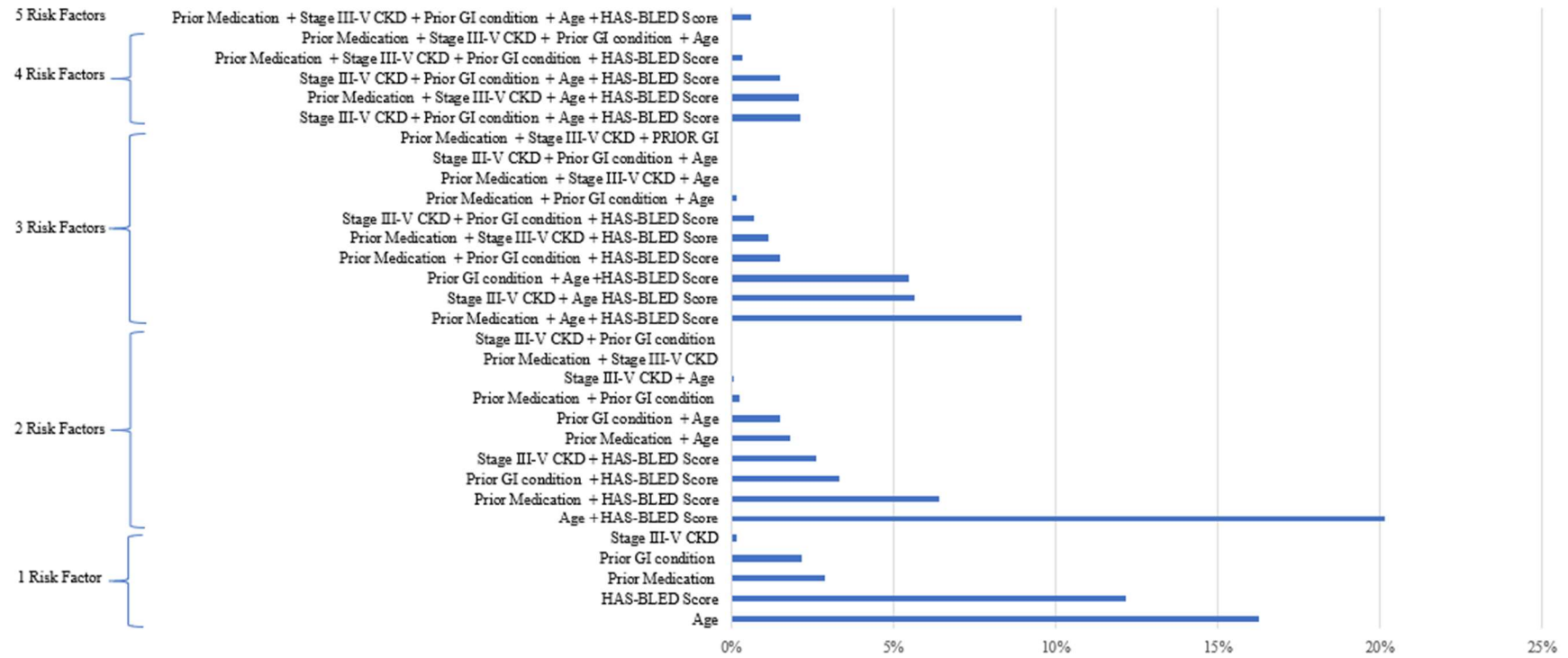
CI: confidence interval; SE: systemic embolism

eTable 4. Hazard Ratios of Stroke/SE and Major Bleeding in the Standard-Dose Population

	Hazard Ratio (95% CI)	p-value
Apixaban vs Warfarin		
Stroke/SE	0.56 (0.49-0.64)	<0.001
Major Bleeding	0.61 (0.56-0.66)	<0.001
Dabigatran vs Warfarin		
Stroke/SE	0.68 (0.56-0.83)	<0.001
Major Bleeding	0.76 (0.67-0.85)	<0.001
Rivaroxaban vs Warfarin		
Stroke/SE	0.79 (0.70-0.88)	<0.001
Major Bleeding	1.11 (1.05-1.18)	<0.001
Apixaban vs Dabigatran		
Stroke/SE	0.80 (0.64-1.01)	0.06
Major Bleeding	0.78 (0.66-0.93)	0.005
Apixaban vs Rivaroxaban		
Stroke/SE	0.79 (0.68-0.92)	0.003
Major Bleeding	0.52 (0.48-0.56)	<0.001
Dabigatran vs Rivaroxaban		
Stroke/SE	0.90 (0.74-1.10)	0.29
Major Bleeding	0.66 (0.58-0.76)	<0.001

CI: confidence interval; SE: systemic embolism.

eFigure 1. Patient Risk Factors for GI Bleeding

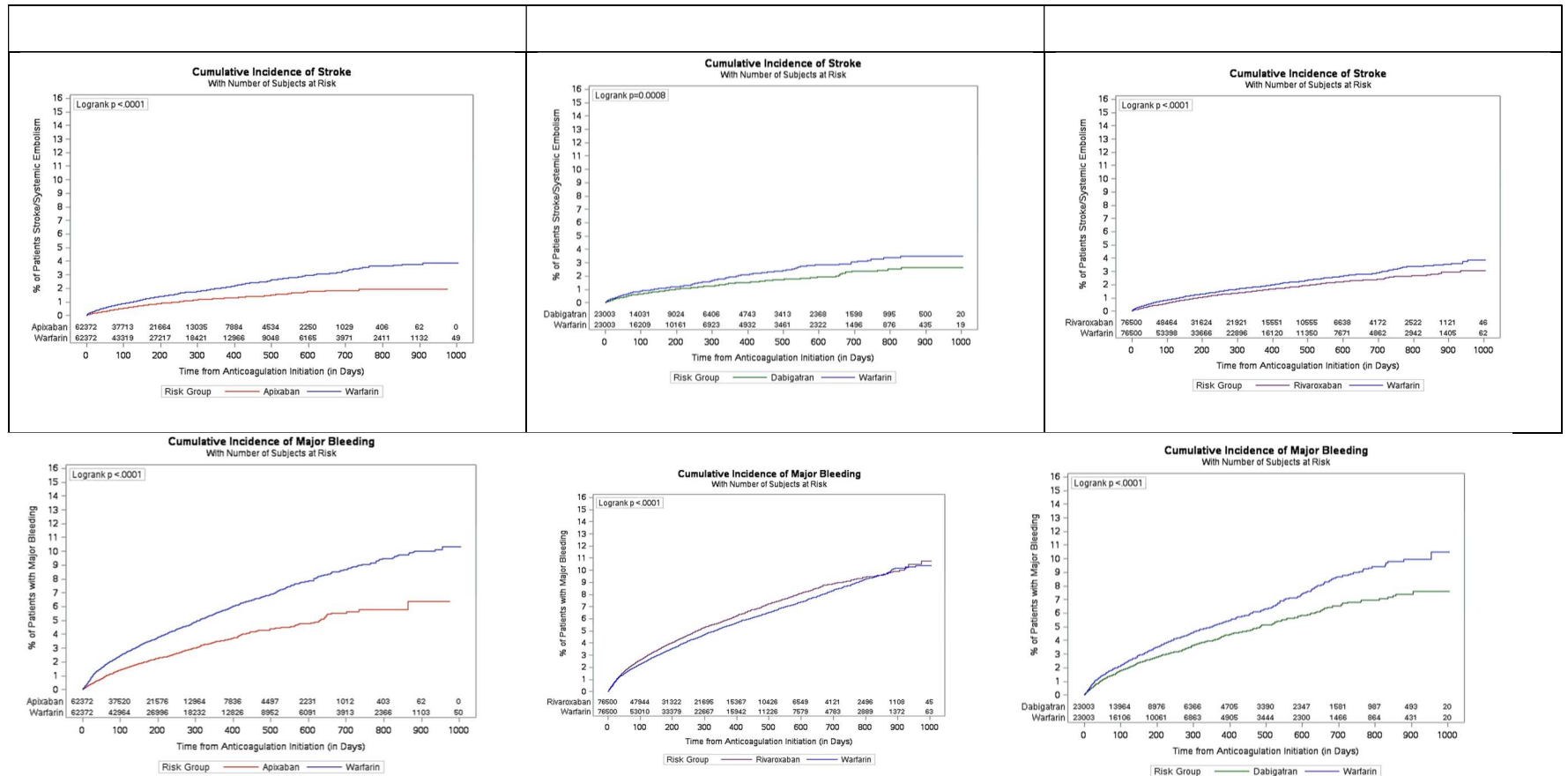


Five risk factors that predispose patients for high risk of GI bleeding were identified: aged ≥ 75 years, HAS-BLED score ≥ 3 , prior GI conditions, prior corticosteroid, antiplatelet, or NSAID use, or presense of stage III, IV, or V CKD. Patients were required to have ≥ 1 risk factor, but could have multiple.

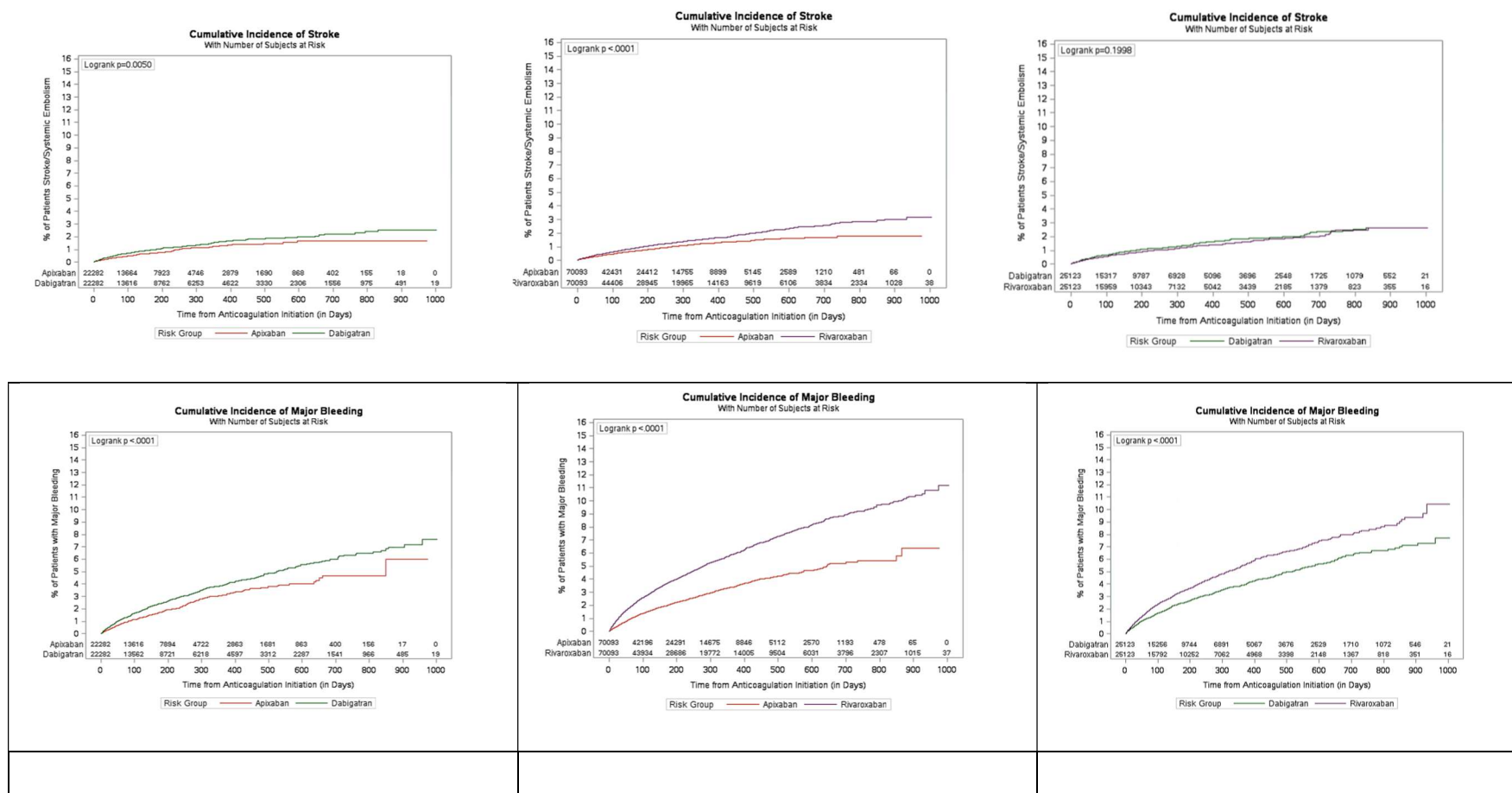
Percentage of patients with different combinations of risk factors are shown in Figure 2, in order of most to least number of risk factors.

CKD: chronic kidney disease; GI: gastrointestinal; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs or alcohol; NSAID: non-steroidal anti-inflammatory drug

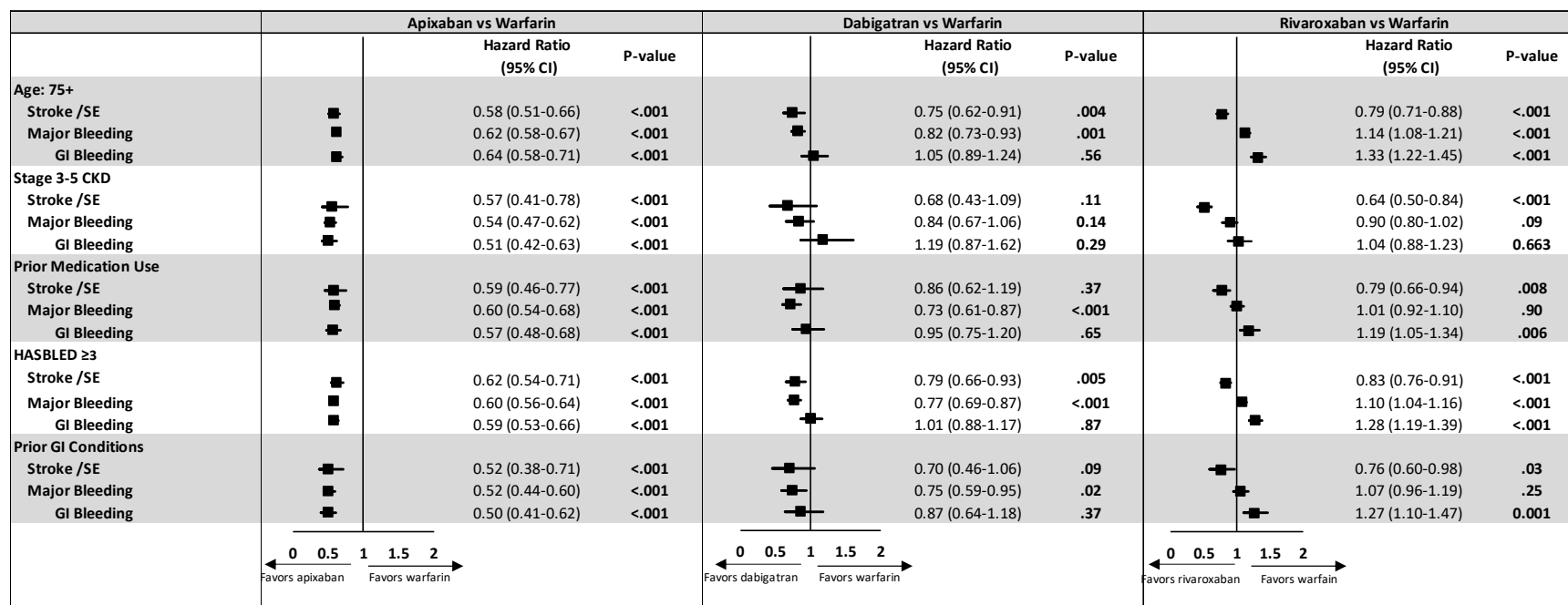
eFigure 2. Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC-Warfarin Propensity Score Matched Cohorts



eFigure 3. Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC-NOAC Propensity Score Matched Cohorts



eFigure 4. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke/SE, Major Bleeding, and GI Bleeding for NOAC vs Warfarin Stratified by Risk Factor



CI: confidence interval; CKD: chronic kidney disease; GI: gastrointestinal; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs or alcohol; ICH: intracranial hemorrhage; NOAC: non-vitamin K antagonist oral anticoagulant; SE: systemic embolism.

eFigure 5. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke/SE, Major Bleeding, and GI Bleeding for NOAC Comparisons Stratified by Risk Factor

	Apixaban vs Dabigatran			Apixaban vs Rivaroxaban			Dabigatran vs Rivaroxaban		
		Hazard Ratio (95% CI)	P-value		Hazard Ratio (95% CI)	P-value		Hazard Ratio (95% CI)	P-value
Age: 75+									
Stroke /SE		0.75 (0.61-0.94)	.01		0.74 (0.66-0.84)	<.001		1.14 (0.92-1.41)	.22
Major Bleeding		0.74 (0.63-0.86)	<.001		0.54 (0.51-0.58)	<.001		0.73 (0.65-0.82)	<.001
GI Bleeding		0.64 (0.51-0.80)	<.001		0.47 (0.43-0.52)	<.001		0.77 (0.66-0.91)	.001
Stage 3-5 CKD									
Stroke /SE		0.85 (0.40-1.80)	.67		0.88 (0.64-1.20)	.42		1.09 (0.55-2.16)	.81
Major Bleeding		0.60 (0.42-0.85)	.005		0.65 (0.56-0.76)	<.001		1.15 (0.88-1.50)	.32
GI Bleeding		0.55 (0.36-0.84)	.005		0.58 (0.46-0.72)	<.001		1.32 (0.92-1.91)	.13
Prior Medication Use									
Stroke /SE		0.73 (0.50-1.06)	.10		0.80 (0.64-0.99)	.04		1.69 (1.20-2.36)	.002
Major Bleeding		0.81 (0.64-1.01)	.06		0.58 (0.52-0.65)	<.001		0.75 (0.63-0.89)	<.001
GI Bleeding		0.67 (0.49-0.92)	.01		0.49 (0.42-0.57)	<.001		0.84 (0.68-1.05)	.13
HASBLED ≥3									
Stroke /SE		0.75 (0.61-0.92)	.006		0.76 (0.68-0.85)	<.001		1.16 (0.97-1.40)	.11
Major Bleeding		0.75 (0.62-0.90)	.002		0.56 (0.52-0.60)	<.001		0.74 (0.67-0.82)	<.001
GI Bleeding		0.67 (0.54-0.85)	<.001		0.48 (0.44-0.53)	<.001		0.78 (0.69-0.90)	<.001
Prior GI Conditions									
Stroke /SE		0.54 (0.31-0.96)	.04		0.59 (0.44-0.80)	<.001		1.22 (0.78-1.90)	.39
Major Bleeding		0.76 (0.56-1.03)	.08		0.51 (0.45-0.59)	<.001		0.63 (0.50-0.78)	<.001
GI Bleeding		0.77 (0.51-1.16)	.21		0.48 (0.40-0.58)	<.001		0.61 (0.46-0.82)	<.001

CI: confidence interval; CKD: chronic kidney disease; GI: gastrointestinal; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs or alcohol; ICH: intracranial hemorrhage; NOAC: non-vitamin K antagonist oral anticoagulant; SE: systemic embolism.