

Supplementary Material

Supplementary Table S1: ICD-9-CM Codes Major hemorrhage

Diagnosis	ICD-9 Diagnosis and Procedure Codes
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

ICD-9-CM: International Classification of Disease, 9th Revision, Clinical Modification.

Supplementary Table S2: Univariate analysis of each candidate predictor with major bleeding risk: descriptive statistics, incidence density rate, and univariate sHRs for the association between each variable and major bleeding

Variable	Number of patients	Number of events	Person years	Events per 1000 person years	Sub-distribution hazard ratio and 95% CI
Age categories, years					
<65	2122	24	3450.76	7.0	Ref.
65-74	6392	127	11525.81	11.0	1.60[1.03,2.47]
≥75	19541	511	33063.75	15.5	2.03[1.35,3.06]
Sex					
Male	13483	388	22600.18	17.2	Ref.
Female	14572	274	25440.14	10.8	0.63[0.54,0.74]
Smoking					
No	17564	394	30599.83	12.9	Ref.
Yes	10491	268	17440.50	15.4	1.18[1.01,1.38]
Alcohol abuse					
No	27809	653	47714.91	13.7	Ref.
Yes	246	9	325.42	27.7	1.86[0.96,3.62]
BMI (per 1 unit increase), kg/m ²	28055			.	0.99[0.97,1.00]
Hypertension					
No	2773	34	4420.61	7.7	Ref.
Yes	25282	628	43619.71	14.4	1.85[1.31,2.62]
Congestive heart failure					
No	18919	424	34156.62	12.4	Ref.
Yes	9136	238	13883.71	17.1	1.21[1.03,1.41]
Diabetes Mellitus					
No	15064	321	26311.20	12.2	Ref.
Yes	12991	341	21729.12	15.7	1.25[1.08,1.46]
COPD					
No	23836	557	41838.51	13.3	Ref.
Yes	4219	105	6201.81	16.9	1.14[0.93,1.41]
Active cancer					
No	26944	628	46414.12	13.5	Ref.
Yes	1111	34	1626.21	20.9	1.37[0.97,1.93]
Prior major bleeding, any					
No	15730	312	27632.08	11.3	Ref.
Yes	12325	350	20408.25	17.1	1.47[1.26,1.71]
Prior major GI bleeding					
No	19801	416	34192.02	12.2	Ref.
Yes	8254	246	13848.31	17.8	1.45[1.24,1.70]
Prior major intracranial bleeding					
No	22227	495	38756.66	12.8	Ref.
Yes	5828	167	9283.66	18.0	1.32[1.11,1.57]
GI disease, any					
No	21374	467	36805.37	12.7	Ref.
Yes	6681	195	11234.95	17.4	1.33[1.12,1.57]
Peptic ulcer					
No	23388	533	40075.02	13.3	Ref.
Yes	4667	129	7965.30	16.2	1.19[0.98,1.44]
Crohn's disease					
No	27953	658	47892.41	13.7	Ref.
Yes	102	4	147.92	27.0	1.80[0.68,4.78]
Ulcerative colitis					
No	27899	655	47791.27	13.7	Ref.

Variable	Number of patients	Number of events	Person years	Events per 1000 person years	Sub-distribution hazard ratio and 95% CI
Yes	156	7	249.06	28.1	2.01[0.95,4.27]
Diverticulosis					
No	26795	619	46022.95	13.4	Ref.
Yes	1260	43	2017.38	21.3	1.49[1.09,2.04]
GI Surgery					
No	26574	620	45722.56	13.6	Ref.
Yes	1481	42	2317.76	18.1	1.27[0.93,1.74]
Fall risk factor, any					
No	17021	357	30951.55	11.5	Ref.
Yes	11034	305	17088.78	17.8	1.36[1.17,1.59]
Fall					
No	21045	477	37445.48	12.7	Ref.
Yes	7010	185	10594.84	17.5	1.21[1.03,1.44]
Gait problem					
No	23105	511	40240.42	12.7	Ref.
Yes	4950	151	7799.90	19.4	1.40[1.17,1.68]
Hip Fracture					
No	26232	621	45401.01	13.7	Ref.
Yes	1823	41	2639.31	15.5	0.98[0.71,1.34]
Dementia					
No	25373	588	44295.35	13.3	Ref.
Yes	2682	74	3744.97	19.8	1.22[0.96,1.56]
Parkinson's disease					
No	27199	627	46711.11	13.4	Ref.
Yes	856	35	1329.21	26.3	1.80[1.28,2.53]
Liver disease					
No	26968	633	46397.56	13.6	Ref.
Yes	1087	29	1642.76	17.7	1.17[0.81,1.70]
eGFR categories, ml/min					
≥90	4439	69	7762.63	8.9	Ref.
89-60	8781	188	16009.98	11.7	1.31[0.99,1.73]
59-30	12778	340	21634.43	15.7	1.62[1.25,2.10]
≤29	2057	65	2633.28	24.7	2.07[1.48,2.91]
Serum total cholesterol categories, mg/dL					
<160	14877	404	26091.00	15.5	Ref.
160-199	8829	181	15191.82	11.9	0.78[0.65,0.93]
200-239	3227	62	5117.54	12.1	0.77[0.59,1.00]
≥240	1065	14	1563.56	9.0	0.55[0.32,0.93]
Serum LDL-C categories, mg/dL:					
<70	8028	.	14341.78	.	Ref.
70-99	11045	231	19646.34	16.1	0.83[0.69,0.99]
100-129	5781	258	9292.29	13.1	0.73[0.59,0.92]
130-159	2201	112	3370.86	12.1	0.71[0.51,0.99]
≥160	817	40	1149.17	11.9	0.84[0.52,1.38]
Serum platelets count					
Normal/Mild thrombocytopenia (≥100 x10 ⁹ /μL)	27703	645	47548.23	13.6	Ref.
Moderate/severe thrombocytopenia (<99 x10 ⁹ /μL)	343	17	476.38	35.7	2.28[1.40,3.70]
Anemia					
No	16050	304	29549.58	10.3	Ref.
Yes	12005	358	18490.75	19.4	1.67[1.44,1.95]

Variable	Number of patients	Number of events	Person years	Events per 1000 person years	Sub-distribution hazard ratio and 95% CI
HAS-BLED score					
≤1	1231	13	1986.0	6.5	Ref.
2	5761	85	10623.1	8.0	1.23[0.69,2.21]
3	12011	293	20657.4	14.2	2.07[1.19,3.61]
≥4	9052	271	14773.8	18.3	2.56[1.47,4.46]
CHA ₂ DS ₂ -VASc score					
≤1	489	3	702.93	4.3	Ref.
2	1494	17	2609.61	6.5	1.59[0.47,5.38]
3	3872	70	7101.73	9.9	2.40[0.76,7.57]
4	6500	133	11706.26	11.4	2.67[0.86,8.34]
5	6504	169	11428.01	14.8	3.36[1.08,10.46]
6	4825	141	8071.12	17.5	3.81[1.22,11.90]
7	2764	91	4275.21	21.3	4.39[1.40,13.78]
≥8	1607	38	2145.47	17.7	3.30[1.02,10.64]
Concurrent antiplatelet therapy					
No	26235	595	45147.65	13.2	Ref.
Yes	1820	67	2892.68	23.2	1.73[1.35,2.23]
Proton pump inhibitor					
No	14141	311	24616.81	12.6	Ref.
Yes	13914	351	23423.52	15.0	1.15[0.99,1.34]
Moderate CYP3A4/Pgp inhibitor therapy					
No	22039	534	37946.05	14.1	Ref.
Yes	6016	128	10094.27	12.7	0.89[0.74,1.08]
Strong CYP3A4/Pgp inhibitor therapy					
No	27715	656	47391.75	13.8	Ref.
Yes	340	6	648.57	9.3	0.70[0.31,1.55]

Supplementary Table S3: Harrell Concordance statistic of the 9-predictor model, in comparison with other models

Model	Concordance Statistic	Standard Error	95% Confidence Interval
9-predictors	0.6416	0.0110	[0.620,0.663]
Full (all variables)	0.6465	0.0109	[0.625,0.668]
HAS-BLED	0.5702	0.0104	[0.550,0.591]
ATRIA	0.5980	0.0111	[0.576,0.620]
ORBIT	0.6047	0.0114	[0.582,0.627]
CHA ₂ DS ₂ -VASc	0.5635	0.0112	[0.542,0.585]

Supplementary Table S4: Major bleeding by 1-year prediction: ROC statistics of the 9-predictor model in comparison with other models

ROC Model	ROC Association Statistics			AUC-ROC Contrast		
	Area under the Curve	Standard Error	95% CI	Contrast Estimate	Standard Error	p-value
9-predictors	0.6579	0.014	[0.630,0.686]	Ref.		
Full (all variables)	0.6605	0.014	[0.633,0.688]	0.00258	0.006	0.6430
HAS-BLED	0.5765	0.013	[0.551,0.602]	-0.0814	0.013	<.0001
ATRIA	0.6162	0.014	[0.588,0.644]	-0.0417	0.012	0.0007
ORBIT	0.6263	0.015	[0.598,0.655]	-0.0316	0.011	0.0044
CHA ₂ DS ₂ -VASc	0.5723	0.015	[0.544,0.601]	-0.0856	0.018	<.0001

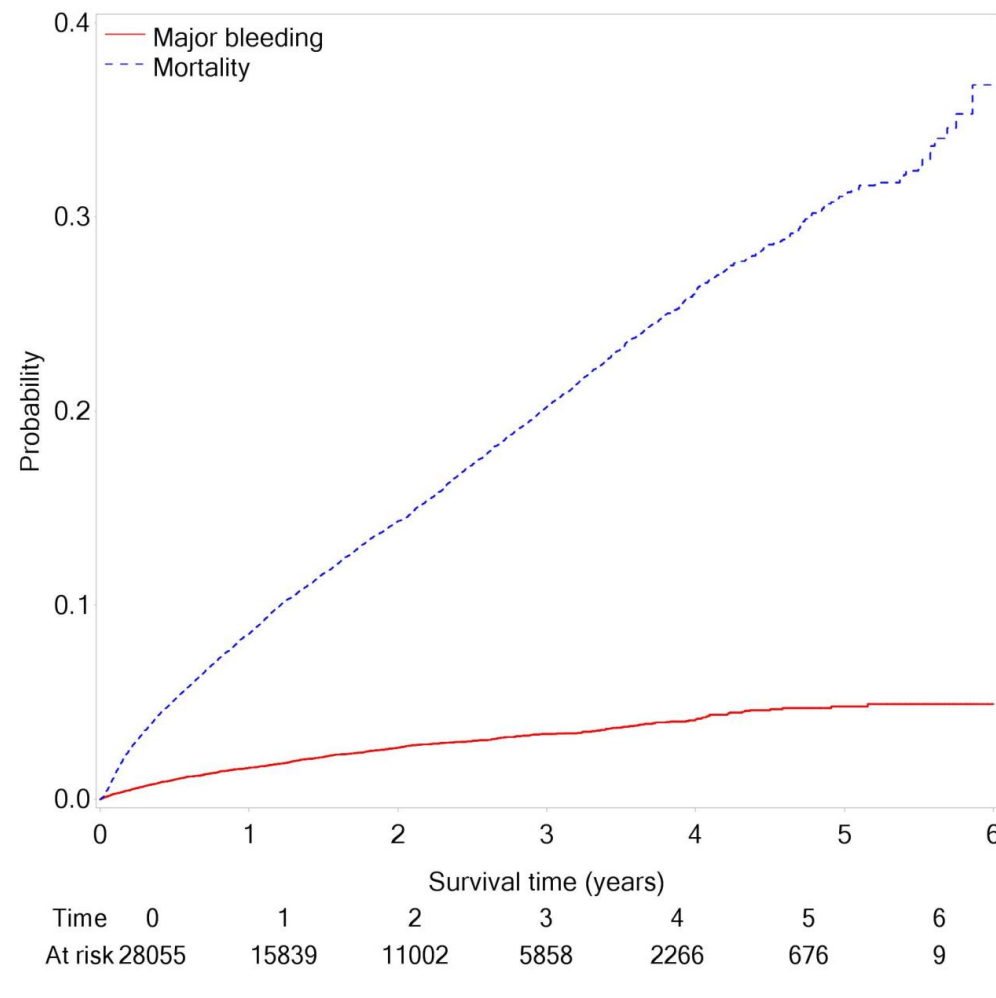
Supplementary Table S5: Points-based risk scoring system: predicted 1-year major bleeding cumulative incidence, along with number of observed events in the cohort

Score points	Predicted 1-year (%)	Number of subjects in the risk category in the cohort	Number of observed events in the cohort
0	0.3	5	0
1	0.3	19	0
2	0.3	38	0
3	0.4	.	.
4	0.4	11	0
5	0.4	65	0
6	0.4	90	0
7	0.5	67	0
8	0.5	112	1
9	0.5	214	1
10	0.6	302	0
11	0.6	127	0
12	0.6	223	0
13	0.7	593	6
14	0.7	683	5
15	0.8	444	3
16	0.8	770	3
17	0.9	953	5
18	0.9	677	4
19	1	1090	5
20	1	1228	11
21	1.1	1147	6
22	1.1	936	10
23	1.2	1275	11
24	1.3	1540	18
25	1.4	1453	19
26	1.5	1653	29
27	1.6	927	8
28	1.7	1095	16
29	1.8	1370	15
30	1.9	1209	22
31	2	1119	18
32	2.1	1229	14
33	2.2	591	16
34	2.4	863	18
35	2.5	656	14
36	2.7	637	18
37	2.8	605	15
38	3	332	7
39	3.2	395	13
40	3.4	72	2

Score points	Predicted 1-year (%)	Number of subjects in the risk category in the cohort	Number of observed events in the cohort
41	3.6	547	19
42	3.8	72	3
43	4	177	2
44	4.3	70	3
45	4.6	35	2
46	4.8	37	0
47	5.1	9	2
48	5.4	30	4
49	5.8	2	0
50	6.1	19	1
51	6.5	.	.
52	6.9	11	1
53	7.3	3	0
54	7.7	.	.
55	8.2	.	.
56	8.7	.	.
57	9.2	1	0
58	9.7	.	.
59	10.3	1	1

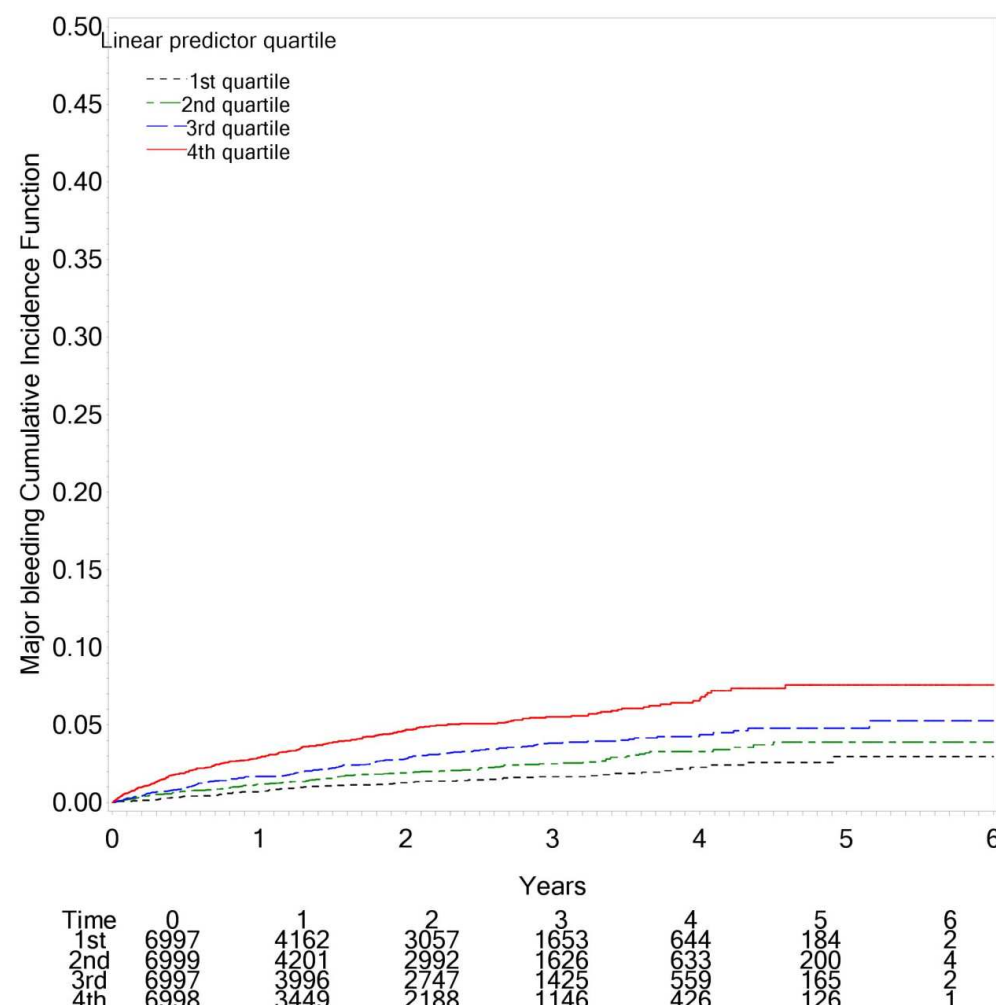
Supplementary Table S6: Baseline demographic and clinical characteristics of dabigatran and rivaroxaban cohorts

Characteristic	Dabigatran	Rivaroxaban
N	N= 5436	N= 14100
Age, mean (SD)	75.4(9.3)	76.6(9.1)
Age categories		
<65	738 [13.6%]	1552 [11.0%]
65-74	1690 [31.1%]	3891 [27.6%]
>=75	3008 [55.3%]	8657 [61.4%]
Sex-Male	2610 [48.0%]	6626 [47.0%]
BMI, mean (SD)	29.9(5.8)	30.0(5.9)
Hypertension	4755 [87.5%]	12643 [89.7%]
Prior major bleeding, any	3252 [59.8%]	8113 [57.5%]
Fall risk, any	1464 [26.9%]	3938 [27.9%]
eGFR, mean (SD), ml/min	75.3(31.5)	72.1(31.9)
eGFR categories, ml/min		
>=90	1398 [25.7%]	3216 [22.8%]
89-60	2116 [38.9%]	5200 [36.9%]
59-30	1806 [33.2%]	5217 [37.0%]
<=29	116 [2.1%]	467 [3.3%]
Serum total cholesterol categories, mg/dL		
<160	2796 [51.4%]	7207 [51.1%]
160-199	1788 [32.9%]	4773 [33.9%]
200-239	652 [12.0%]	1648 [11.7%]
>=240	200 [3.7%]	472 [3.3%]
Serum platelets count		
Normal/Mild thrombocytopenia ($\geq 100 \times 10^3/\mu\text{L}$)	5373 [98.8%]	13980 [99.1%]
Moderate/severe thrombocytopenia ($< 99 \times 10^3/\mu\text{L}$)	63 [1.2%]	120 [0.9%]
Anemia [Hb<13 g/dL (male), <12 g/dL (female)]	1834 [33.7%]	4977 [35.3%]
Concurrent antiplatelet therapy	377 [6.9%]	925 [6.6%]

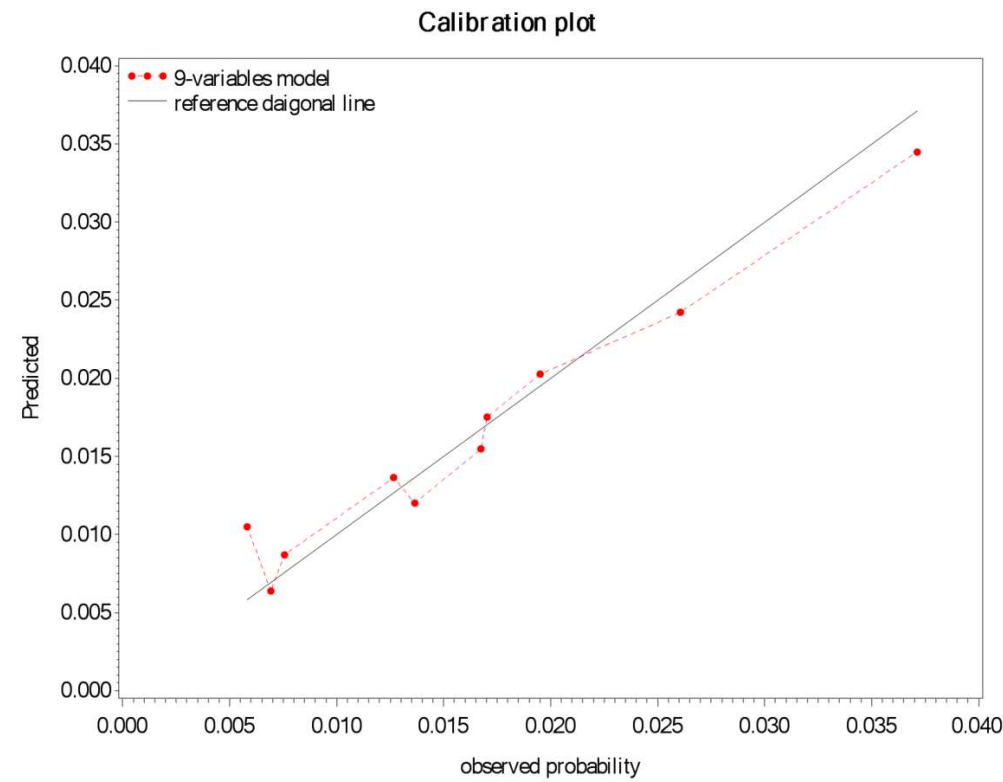
Supplementary Figure S1: Cumulative incidence function of major bleeding and overall mortality

Cumulative incidence functions of major bleeding (solid red line) and of all-cause mortality (dashed blue line) in the derivation cohort. 662 patients received a diagnosis a major bleeding event, and 3813 death events occurred among subjects who have not experienced major bleeding during follow up.

Supplementary Figure S2: Discrimination of the 9-predictors model: major bleeding Cumulative Incidence Function plot by quartiles of linear predictor (xbeta) estimated from the model



Discrimination of the 9-predictors model: Major bleeding Cumulative Incidence Function plot by quartiles of the linear predictor estimated from the model. Major bleeding cumulative incidence rates within 1-year were 0.74%, 1.2%, 1.7% in the first, second and third risk-quartiles, respectively, and 2.9% in the highest-risk quartile. Numbers of patients at risk are presented.

Supplementary Figure S3: Calibration plot for major bleeding risk by 1 year

Calibration plot of the 9-variables prediction model presenting the predicted probability of major bleeding to the observed probability of major bleeding, by 1 year, within the 10 deciles of predicted risk.