SUPPLEMENTAL MATERIAL

Table 1. Definition of exposures, covariates and outcomes

Diagnoses	**ICD-9-CM codes**	**ICD-10-CM codes**
Atrial fibrillation/flutter	427.3 (includes 427.31 and 427.32)	I48.91, I48.92
Mitral stenosis; history of valve surgery (exclusion criteria)	394.0, 394.2, 396.0, 396.1, 396.8, 746.5, V43.3	I05.0, I05.8, I05.9, I08.0, I34.2, Z95.2, Z95.4
Ischemic stroke	433.x1, 434.x (except subcode: x0), 436	
Systemic embolism	444.x	I74.x
Major bleeding	Major bleeding is defined as a bleeding event with (i) a critical site code (intracranial, retroperitoneal, intraspinal, intra-ocular, pericardial, or intraarticular), (ii) a transfusion of blood products, or (iii) death, as described in Cunningham et al. Critical site code: 430, 431, 432, 363.6, 376.32, 377.42, 379.23, 719.1, 729.92, 423.0, 800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x, 803.7x, 803.8x, 804.2x, 804.3x, 804.7x, 804.8x, 852.x, 853.x Transfusion: a) ICD-9 PRC: 99.02, 99.03, 99.04, 99.05, 99.06, 99.07, 99.08, b) CPT 36430, c) HCPC: P9010, P9011, P9012, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031-P9040, P9043, P9044, P9051 – P9060, P9070-P9072, d) Revenue Center Codes: 0380-0392, 0399, e) Additional Value Codes: 37, 38, 39	Major bleeding is defined as a bleeding event with (i) a critical site code (intracranial, retroperitoneal, intraspinal, intra-ocular, pericardial, or intraarticular), (ii) a transfusion of blood products, or (iii) death, as described in Cunningham et al. Critical site code: I60.x, I61.x, I62.x, H31.309, H05.239, H47.029, H43.1x, M79.81, M25.00 Transfusion: PCS: 3023, 3024, 3028, b) CPT 36430, c) HCPC P9010, P9011, P9012, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031-P9040, P9043, P9044, P9051 – P9060, P9070-P9072, d) Revenue Center Codes: 0380-0392, 0399, e) Additional Value Codes: 37, 38, 39
Gastrointestinal bleeding	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, 535.71, 537.83, 537.84, 456.0, 456.20,	K92.0, K92.1, K92.2, K29.01, K62.5, K31.811, K31.82, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K29.x1, K22.11, K25.0, K25.2,

	530.21, 530.7, 530.82, 578.0, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x	K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K55.21
Intracranial bleed	430, 431, 432, 800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x, 803.7x, 803.8x, 804.2x, 804.3x, 804.7x, 804.8x, 852.x, 853.x	I60.x, I61.x, I62.x
Death	USRDS collects death information from several sources, including the CMS Medicare EDB, CMS forms 2746 and 2728, the OPTN transplant follow-up form, CROWNWeb database, inpatient claims, and, where allowed by regulation, the Social Security Death Master File.	
Procedures	**ICD-9-CM codes**	**ICD-10-PCS codes**
Any valve surgery (exclusion criteria)	35.00, 35.01, 35.02, 35.03, 35.04, 35.10, 35.11, 35.12, 35.13, 35.14, 35.20, 35.21, 35.22, 35.23, 35.24, 35.25, 35.26, 35.27, 35.28, 35.96, 35.99, 35.0x, 35.1x, 35.2x	02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, 02RH37Z, 02RH38Z, 02RH3JZ, 02RH3KZ, 027F0ZZ, 02NF0ZZ, 02QF0ZZ, 027G0ZZ, 02NG0ZZ, 02QG0ZZ, 02QF0ZZ, 02QF3ZZ, 02QF4ZZ, 027H0ZZ, 02NH0ZZ, 02QH0ZZ, 02QH3ZZ, 02QH4ZZ, 027J0ZZ, 02NJ0ZZ, 02QJ0ZZ, 02QJ3ZZ, 02QJ4ZZ, 02RF07Z, 02RF08Z, 02RF0KZ, 02RF0JZ, 02RG07Z, 02RG08Z, 02RG0KZ, 02RG0JZ, 02RH07Z, 02RH08Z, 02RH0KZ, 02RH0JZ, 02RJ07Z, 02RJ08Z, 02RJ0KZ, 02RJ0JZ, 02UF0JZ, 02UF07Z, 02UF0KZ, 02UF47Z, 02UF4KZ, 02UF37Z, 02UF38Z, 02UF3JZ, 02UG37Z, 02UG3KZ, 02UH37Z, 02UG0JZ, 02UH0JZ, 02UJ0JZ, 02BK0ZZ, 027F3ZZ, 027G3ZZ, 027H3ZZ, 027J3ZZ, 02UG3JZ, 02RF37H, 02RF38H, 02RG3JH, 02RG3KH, 02RH38H, 02RH3KH, 024F07J, 024F08J, 024F0JJ, 024F0KJ, 024G072, 024G082, 024J072, 024J082, 024J0J2, 024J0K2, 02QF0ZJ, 02QG0ZE, 02QG3ZE, 02QG4ZE, 02QJ0ZG, 02QJ3ZG, 02QJ4ZG, 02UF0JJ,

		02UF0KJ, 02UF37J, 02UF38J, 02UF3JJ, 02UF4KJ, 02UG07E, 02UG08E, 02UG0JE, 02UG0KE, 02UG3JE, 02UG3KE, 02UJ0JG, 02UJ0KG, X2RF032, X2RF332, X2RF432

Based on previous studies[1,2]

Table 2. Baseline characteristics in the prognostic score matched cohorts

	Stroke/SE		Major bleeding		GI bleeding		Intracranial bleeding		Death	
Variable	**Apixaban (n=2,351)**	**Warfarin (n=7,053)**	**Apixaban (n=2,351)**	**Warfarin (n=7,053)**	**Apixaban (n=2,351)**	**Warfarin (n=7,053)**	**Apixaban (n=2,350)**	**Warfarin (n=7,050)**	**Apixaban (n=2,351)**	**Warfarin (n=7,053)**
Demographics										
Age (yrs)	68.87 (11.49)	68.04 (11.90)	68.87 (11.49)	68.21 (12.00)	68.87 (11.49)	68.27 (12.01)	68.87 (11.49)	68.55 (11.73)	68.87 (11.49)	68.14 (11.80)
Male	1280 (54.4)	3875 (54.9)	1280 (54.4)	3790 (53.7)	1280 (54.4)	3830 (54.3)	1280 (54.5)	3835 (54.4)	1280 (54.4)	3796 (53.8)
Race										
White	604 (25.7)	2103 (29.8)	604 (25.7)	2080 (29.5)	604 (25.7)	2033 (28.8)	604 (25.7)	1969 (27.9)	604 (25.7)	2138 (30.3)
Black	152 (6.5)	315 (4.5)	152 (6.5)	347 (4.9)	152 (6.5)	339 (4.8)	151 (6.4)	298 (4.2)	152 (6.5)	334 (4.7)
Other	1595 (67.8)	4635 (65.7)	1595 (67.8)	4626 (65.6)	1595 (67.8)	4681 (66.4)	1595 (67.9)	4783 (67.8)	1595 (67.8)	4581 (65.0)
Nephrology care										
Time on dialysis	656 (27.9)	1976 (28.0)	656 (27.9)	1941 (27.5)	656 (27.9)	2073 (29.4)	655 (27.9)	1981 (28.1)	656 (27.9)	2032 (28.8)
<1 year	240 (10.2)	831 (11.8)	240 (10.2)	831 (11.8)	240 (10.2)	796 (11.3)	240 (10.2)	841 (11.9)	240 (10.2)	802 (11.4)
1 to <2 years	256 (10.9)	791 (11.2)	256 (10.9)	773 (11.0)	256 (10.9)	752 (10.7)	256 (10.9)	782 (11.1)	256 (10.9)	757 (10.7)
2 to <3 years	1199 (51.0)	3455 (49.0)	1199 (51.0)	3508 (49.7)	1199 (51.0)	3432 (48.7)	1199 (51.0)	3446 (48.9)	1199 (51.0)	3462 (49.1)
≥3 years	416 (17.7)	1076 (15.3)	416 (17.7)	1031 (14.6)	416 (17.7)	1050 (14.9)	416 (17.7)	1075 (15.2)	416 (17.7)	1064 (15.1)
Private insurance	656 (27.9)	1976 (28.0)	656 (27.9)	1941 (27.5)	656 (27.9)	2073 (29.4)	655 (27.9)	1981 (28.1)	656 (27.9)	2032 (28.8)
Pre-ESRD nephrology care										
None	1012 (43.0)	3372 (47.8)	1012 (43.0)	3370 (47.8)	1012 (43.0)	3382 (48.0)	1011 (43.0)	3353 (47.6)	1012 (43.0)	3308 (46.9)
<6 months	283 (12.0)	806 (11.4)	283 (12.0)	790 (11.2)	283 (12.0)	765 (10.8)	283 (12.0)	779 (11.0)	283 (12.0)	770 (10.9)
6 to <12 months	422 (17.9)	1189 (16.9)	422 (17.9)	1184 (16.8)	422 (17.9)	1179 (16.7)	422 (18.0)	1183 (16.8)	422 (17.9)	1206 (17.1)
≥12 months	634 (27.0)	1686 (23.9)	634 (27.0)	1709 (24.2)	634 (27.0)	1727 (24.5)	634 (27.0)	1735 (24.6)	634 (27.0)	1769 (25.1)
Comorbidities										
Hypertension	2342 (99.6)	7015 (99.5)	2342 (99.6)	7018 (99.5)	2342 (99.6)	7029 (99.7)	2341 (99.6)	7028 (99.7)	2342 (99.6)	7025 (99.6)
Cerebrovascular event	778 (33.1)	2215 (31.4)	778 (33.1)	2368 (33.6)	778 (33.1)	2314 (32.8)	778 (33.1)	2529 (35.9)	778 (33.1)	2408 (34.1)
Diabetes	1773 (75.4)	5163 (73.2)	1773 (75.4)	5265 (74.6)	1773 (75.4)	5246 (74.4)	1772 (75.4)	5272 (74.8)	1773 (75.4)	5303 (75.2)
Congestive heart failure	1868 (79.5)	5372 (76.2)	1868 (79.5)	5470 (77.6)	1868 (79.5)	5489 (77.8)	1867 (79.4)	5503 (78.1)	1868 (79.5)	5505 (78.1)
SCD/VA	279 (11.9)	935 (13.3)	279 (11.9)	935 (13.3)	279 (11.9)	942 (13.4)	279 (11.9)	950 (13.5)	279 (11.9)	968 (13.7)
Peripheral arterial disease	1084 (46.1)	3070 (43.5)	1084 (46.1)	3242 (46.0)	1377 (58.6)	4396 (62.3)	1377 (58.6)	4407 (62.5)	1377 (58.6)	4359 (61.8)
Smoking	978 (41.6)	2736 (38.8)	978 (41.6)	2712 (38.5)	1084 (46.1)	3201 (45.4)	1084 (46.1)	3197 (45.3)	1084 (46.1)	3171 (45.0)

Hypothyroidism	90 (3.8)	114 (1.6)	90 (3.8)	124 (1.8)	978 (41.6)	2685 (38.1)	977 (41.6)	2745 (38.9)	978 (41.6)	2706 (38.4)
Liver disease	221 (9.4)	725 (10.3)	221 (9.4)	750 (10.6)	90 (3.8)	131 (1.9)	90 (3.8)	121 (1.7)	90 (3.8)	123 (1.7)
Obesity	590 (25.1)	1513 (21.5)	590 (25.1)	1497 (21.2)	221 (9.4)	689 (9.8)	221 (9.4)	725 (10.3)	221 (9.4)	730 (10.4)
Venous thromboembolism	279 (11.9)	1271 (18.0)	279 (11.9)	1325 (18.8)	590 (25.1)	1530 (21.7)	590 (25.1)	1499 (21.3)	590 (25.1)	1509 (21.4)
Cancer	330 (14.0)	1086 (15.4)	330 (14.0)	1020 (14.5)	279 (11.9)	1339 (19.0)	279 (11.9)	1266 (18.0)	279 (11.9)	1336 (18.9)
Anemia	2334 (99.3)	6999 (99.2)	2334 (99.3)	7002 (99.3)	330 (14.0)	1076 (15.3)	330 (14.0)	1133 (16.1)	330 (14.0)	1068 (15.1)
Myocardial infarction	632 (26.9)	1844 (26.1)	632 (26.9)	1925 (27.3)	2334 (99.3)	7005 (99.3)	2333 (99.3)	6994 (99.2)	2334 (99.3)	6993 (99.1)
Sleep apnea	550 (23.4)	1466 (20.8)	550 (23.4)	1479 (21.0)	632 (26.9)	1870 (26.5)	632 (26.9)	1981 (28.1)	632 (26.9)	1898 (26.9)
Prior major bleeding	217 (9.2)	710 (10.1)	217 (9.2)	768 (10.9)	550 (23.4)	1458 (20.7)	550 (23.4)	1509 (21.4)	550 (23.4)	1462 (20.7)
Prior GI bleeding	249 (10.6)	839 (11.9)	249 (10.6)	884 (12.5)	217 (9.2)	711 (10.1)	217 (9.2)	782 (11.1)	217 (9.2)	718 (10.2)
CHA_2DS_2VASc score, mean	5.27 (1.77)	5.14 (1.78)	5.27 (1.77)	5.26 (1.79)	249 (10.6)	819 (11.6)	249 (10.6)	861 (12.2)	249 (10.6)	792 (11.2)
Baseline medications										
Statin	553 (23.5)	1699 (24.1)	553 (23.5)	1648 (23.4)	553 (23.5)	1664 (23.6)	552 (23.5)	1697 (24.1)	553 (23.5)	1706 (24.2)
Non-statin lipid lowering	44 (1.9)	186 (2.6)	44 (1.9)	193 (2.7)	44 (1.9)	193 (2.7)	44 (1.9)	189 (2.7)	44 (1.9)	198 (2.8)
ACEi	213 (9.1)	904 (12.8)	213 (9.1)	895 (12.7)	213 (9.1)	907 (12.9)	212 (9.0)	878 (12.5)	213 (9.1)	933 (13.2)
Angiotensin receptor blocker	156 (6.6)	405 (5.7)	156 (6.6)	392 (5.6)	156 (6.6)	369 (5.2)	156 (6.6)	402 (5.7)	156 (6.6)	400 (5.7)
Beta-blocker	925 (39.3)	3013 (42.7)	925 (39.3)	2930 (41.5)	925 (39.3)	2958 (41.9)	924 (39.3)	2942 (41.7)	925 (39.3)	2939 (41.7)
Calcium channel blocker	530 (22.5)	1651 (23.4)	530 (22.5)	1624 (23.0)	530 (22.5)	1633 (23.2)	530 (22.6)	1645 (23.3)	530 (22.5)	1593 (22.6)
Diuretic	214 (9.1)	628 (8.9)	214 (9.1)	656 (9.3)	214 (9.1)	614 (8.7)	214 (9.1)	669 (9.5)	214 (9.1)	626 (8.9)
Other antihypertensive	332 (14.1)	1036 (14.7)	332 (14.1)	1014 (14.4)	332 (14.1)	1002 (14.2)	331 (14.1)	932 (13.2)	332 (14.1)	1038 (14.7)
Antiarrhythmics	538 (22.9)	1512 (21.4)	538 (22.9)	1485 (21.1)	538 (22.9)	1587 (22.5)	538 (22.9)	1585 (22.5)	538 (22.9)	1503 (21.3)
Antianginal vasodilator	206 (8.8)	623 (8.8)	206 (8.8)	671 (9.5)	206 (8.8)	641 (9.1)	206 (8.8)	726 (10.3)	206 (8.8)	630 (8.9)
Antiplatelet	154 (6.6)	493 (7.0)	154 (6.6)	522 (7.4)	154 (6.6)	533 (7.6)	154 (6.6)	552 (7.8)	154 (6.6)	565 (8.0)
NSAIDs	32 (1.4)	98 (1.4)	32 (1.4)	108 (1.5)	32 (1.4)	106 (1.5)	32 (1.4)	94 (1.3)	32 (1.4)	115 (1.6)
Insulin	283 (12.0)	888 (12.6)	283 (12.0)	964 (13.7)	283 (12.0)	933 (13.2)	283 (12.0)	987 (14.0)	283 (12.0)	932 (13.2)
Non-insulin diabetes drug	126 (5.4)	358 (5.1)	126 (5.4)	370 (5.2)	126 (5.4)	353 (5.0)	125 (5.3)	342 (4.9)	126 (5.4)	352 (5.0)
Proton pump inhibitor	408 (17.4)	1405 (19.9)	408 (17.4)	1368 (19.4)	408 (17.4)	1362 (19.3)	408 (17.4)	1450 (20.6)	408 (17.4)	1378 (19.5)
Antidepressant	307 (13.1)	1082 (15.3)	307 (13.1)	1054 (14.9)	307 (13.1)	1082 (15.3)	307 (13.1)	1078 (15.3)	307 (13.1)	1088 (15.4)

Categorical variables are shown as n (%). Continuous variables are shown as mean (standard deviation). None of the listed variables had a standardized mean difference >0.2 between the apixaban and warfarin groups. Abbreviations: ESRD, end-stage renal disease; SE, systemic embolism; SCD/VA, sudden cardiac death/ventricular arrhythmia; ACEi, angiotensin converting enzyme inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs

Table 3. Baseline characteristics of the warfarin group in the study years 2010-2012 and 2013-2015 (prognostic score matched warfarin cohort for the "death" outcome)

Variable	**Overall (n=7,053)**	**2010-2012 (n=3,131)**	**2013-2015 (n=3,922)**
Demographics			
Age (yrs)	68.14 (11.80)	68.00 (11.91)	68.25 (11.70)
Male	3796 (53.8)	1603 (51.2)	2193 (55.9)
Race			
White	2138 (30.3)	988 (31.6)	1150 (29.3)
Black	334 (4.7)	140 (4.5)	194 (4.9)
Other	4581 (65.0)	2003 (64.0)	2578 (65.7)
Nephrology care			
Time on dialysis			
<1 year	2032 (28.8)	810 (25.9)	1222 (31.2)
1 to <2 years	802 (11.4)	372 (11.9)	430 (11.0)
2 to <3 years	757 (10.7)	344 (11.0)	413 (10.5)
≥3 years	3462 (49.1)	1605 (51.3)	1857 (47.3)
Private insurance	1064 (15.1)	434 (13.9)	630 (16.1)
Pre-ESRD nephrology care			
None	3308 (46.9)	1612 (51.5)	1696 (43.2)
<6 months	770 (10.9)	314 (10.0)	456 (11.6)
6 to <12 months	1206 (17.1)	518 (16.5)	688 (17.5)
≥12 months	1769 (25.1)	687 (21.9)	1082 (27.6)
Comorbidities			
Hypertension	7025 (99.6)	3117 (99.6)	3908 (99.6)
Cerebrovascular event	2408 (34.1)	1095 (35.0)	1313 (33.5)
Diabetes	5303 (75.2)	2376 (75.9)	2927 (74.6)
Congestive heart failure	5505 (78.1)	2483 (79.3)	3022 (77.1)
SCD/VA	968 (13.7)	435 (13.9)	533 (13.6)
Peripheral arterial disease	3171 45.0)	1399 (44.7)	1772 (45.2)
Smoking*	2706 (38.4)	966 (30.9)	1740 (44.4)
Hypothyroidism	123 (1.7)	29 (0.9)	94 (2.4)
Liver disease	730 (10.4)	331 (10.6)	399 (10.2)
Obesity	1509 (21.4)	541 (17.3)	968 (24.7)
Venous thromboembolism	1336 (18.9)	648 (20.7)	688 (17.5)
Cancer	1068 (15.1)	460 (14.7)	608 (15.5)
Anemia	6993 (99.1)	3107 (99.2)	3886 (99.1)
Myocardial infarction	1898 (26.9)	818 (26.1)	1080 (27.5)
Sleep apnea	1462 (20.7)	575 (18.4)	887 (22.6)
Prior major bleeding	718 (10.2)	333 (10.6)	385 (9.8)
Prior gastrointestinal bleeding	792 (11.2)	389 (12.4)	403 (10.3)

CHA_2DS_2VASc score, mean	5.27 (1.77)	5.33 (1.79)	5.22 (1.76)
Baseline medications			
Statin	1706 (24.2)	722 (23.1)	984 (25.1)
Non-statin lipid lowering	198 (2.8)	101 (3.2)	97 (2.5)
ACEi	933 (13.2)	443 (14.1)	490 (12.5)
Angiotensin receptor blocker	400 (5.7)	177 (5.7)	223 (5.7)
Beta-blocker	2939 (41.7)	1252 (40.0)	1687 (43.0)
Calcium channel blocker	1593 (22.6)	689 (22.0)	904 (23.0)
Diuretic	626 (8.9)	265 (8.5)	361 (9.2)
Other antihypertensive	1038 (14.7)	465 (14.9)	573 (14.6)
Antiarrhythmics	1503 (21.3)	700 (22.4)	803 (20.5)
Antianginal vasodilator	630 (8.9)	277 (8.8)	353 (9.0)
Antiplatelet	565 (8.0)	269 (8.6)	296 (7.5)
NSAIDs	115 (1.6)	58 (1.9)	57 (1.5)
Insulin	932 (13.2)	455 (14.5)	477 (12.2)
Non-insulin diabetes drug	352 (5.0)	176 (5.6)	176 (4.5)
Proton pump inhibitor	1378 (19.5)	596 (19.0)	782 (19.9)
Antidepressant	1088 (15.4)	485 (15.5)	603 (15.4)

Categorical variables are shown as n (%). Continuous variables are shown as mean (standard deviation).

* Standardized mean difference >0.2 between the 2 groups.

Abbreviations: ESRD, end-stage renal disease; SCD/VA, sudden cardiac death/ventricular arrhythmia; ACEi, angiotensin converting enzyme inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardized mean difference

Table 4. Event rates in the warfarin group in the study years 2010-2012 and 2013-2015 (in prognostic score matched cohorts)

Outcome	**Overall**	**2010-2012**	**2013-2015**
Stroke/SE	11.8	11.8	11.9
Major bleeding	22.9	22.9	22.8
GI bleeding	23.4	22.7	24
Intracranial bleeding	3.5	3.3	3.6
Death	24.9	25.6	24.2

Event rates shown per 100 patient-years.
Abbreviations: SE, systemic embolism; GI, gastrointestinal

Table 5. Comparison of unmatched apixaban and warfarin groups based on multivariate Cox regression model including anticoagulant drug exposure as one of the predictor variables

Outcome	**HR (95% CI) for apixaban vs warfarin**		**P_{int}**
	Main analysis	**Multivariate Cox regression analysis**	
Stroke/SE	0.88 (0.69-1.12)	0.95 (0.75-1.19)	0.65
Major bleeding	0.72 (0.59-0.87)	0.68 (0.57-0.81)	0.67
GI bleeding	0.86 (0.72-1.02)	0.89 (0.75-1.05)	0.78
Intracranial bleeding	0.79 (0.49-1.26)	0.77 (0.49-1.20)	0.94
Death	0.85 (0.71-1.01)	0.86 (0.73-1.01)	0.92

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, systemic embolism; GI, gastrointestinal; CVA, cerebrovascular accident; P_{int}, P-for-interaction

Table 6. Sensitivity analysis excluding apixaban patients who were originally prescribed warfarin and then switched to apixaban

Outcome	**HR (95% CI) for apixaban vs warfarin**		**P_{int}**
	Main analysis	**Sensitivity analysis**	
Stroke/SE	0.88 (0.69-1.12)	0.97 (0.73-1.28)	0.61
Major bleeding	0.72 (0.59-0.87)	0.65 (0.52-0.81)	0.50
GI bleeding	0.86 (0.72-1.02)	0.91 (0.74-1.12)	0.68
Intracranial bleeding	0.79 (0.49-1.26)	0.67 (0.38-1.19)	0.66
Death	0.85 (0.71-1.01)	0.81 (0.66-1.00)	0.73

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, systemic embolism; GI, gastrointestinal; CVA, cerebrovascular accident; P_{int}, P-for-interaction

Table 7. Results of subgroup analyses in matched apixaban and warfarin cohorts

Subgroup	**HR (95% CI) for apixaban vs warfarin**									
	Stroke/SE	**P_{int}**	**Major bleeding**	**P_{int}**	**GI bleeding**	**P_{int}**	**Intracranial bleeding**	**P_{int}**	**Death**	**P_{int}**
Age										
<75 years	0.96 (0.72-1.29)	0.27	0.70 (0.55-0.89)	0.77	0.79 (0.62-1.00)	0.31	0.93 (0.52-1.67)	0.37	0.74 (0.58-0.94)	0.13
≥75 years	0.72 (0.47-1.10)		0.74 (0.55-0.99)		0.95 (0.73-1.23)		0.59 (0.26-1.31)		0.97 (0.75-1.24)	
Sex										
Male	0.89 (0.63-1.26)	0.89	0.70 (0.54-0.90)	0.77	0.73 (0.56-0.95)	0.08	1.03 (0.58-1.81)	0.16	0.73 (0.57-0.93)	0.08
Female	0.86 (0.62-1.21)		0.74 (0.56-0.98)		1.00 (0.79-1.27)		0.49 (0.21-1.15)		0.99 (0.78-1.27)	
Diabetes										
Yes	0.89 (0.68-1.16)	0.71	0.73 (0.59-0.91)	0.67	0.92 (0.76-1.13)	0.13	0.86 (0.51-1.45)	0.53	0.82 (0.68-1.00)	0.51
No	0.79 (0.44-1.40)		0.66 (0.44-0.99)		0.66 (0.45-0.97)		0.59 (0.21-1.68)		0.94 (0.66-1.35)	
Prior CVA										
Yes	0.76 (0.53-1.08)	0.31	0.84 (0.63-1.12)	0.16	1.00 (0.76-1.30)	0.15	0.72 (0.34-1.53)	0.74	0.88 (0.66-1.16)	0.75
No	0.98 (0.70-1.37)		0.64 (0.50-0.82)		0.77 (0.61-0.97)		0.85 (0.46-1.54)		0.83 (0.67-1.04)	
Prior major bleeding										
Yes	1.41 (0.80-2.50)	0.08	0.89 (0.57-1.39)	0.34	1.06 (0.70-1.59)	0.29	1.27 (0.42-3.84)	0.37	1.05 (0.67-1.65)	0.41
No	0.80 (0.61-1.05)		0.70 (0.57-0.86)		0.83 (0.68-1.01)		0.73 (0.44-1.23)		0.82 (0.68-0.99)	
Obesity										
Yes	0.93 (0.61-1.43)	0.67	0.65 (0.43-0.99)	0.59	0.78 (0.54-1.14)	0.54	0.40 (0.12-1.34)	0.21	0.83 (0.58-1.20)	0.91
No	0.83 (0.62-1.12)		0.74 (0.60-0.92)		0.89 (0.73-1.08)		0.93 (0.56-1.55)		0.85 (0.70-1.04)	
Dialysis modality										
Hemodialysis	0.85 (0.66-1.09)	0.36	0.73 (0.60-0.88)	0.50	0.84 (0.70-1.00)	0.30	0.84 (0.52-1.34)	n/a*	0.83 (0.70-1.00)	0.62
Peritoneal dialysis	1.26 (0.57-2.82)		0.54 (0.23-1.29)		1.19 (0.63-2.26)		n/a*		0.98 (0.52-1.83)	
Interacting drugs†										
Group 1	0.97 (0.51-1.83)	0.71	0.94 (0.63-1.40)	0.31	1.07 (0.74-1.54)	0.27	0.84 (0.29-2.47)	0.97	1.22 (0.85-1.76)	0.07
Group 2	1.02 (0.61-1.69)		0.73 (0.48-1.13)		0.67 (0.43-1.04)		0.86 (0.33-2.26)		0.67 (0.44-1.02)	
None	0.81 (0.60-1.10)		0.65 (0.50-0.83)		0.85 (0.68-1.07)		0.75 (0.40-1.39)		0.80 (0.64-1.00)	

HR and 95% CIs were obtained from univariable Cox regression analyses with anticoagulant drug exposure as the only predictor variable.
*too few events in this subgroup precluding effect estimate calculation

†Patients were categorized into 3 groups depending on whether they had concomitant prescriptions at time 0 for medications that have been recently shown to (i) increase bleeding risks with DOACs (amiodarone, fluconazole, rifampin, phenytoin) (Group 1); (ii) decrease bleeding risks (atorvastatin, digoxin, erythromycin, clarithromycin) (Group 2); or (iii) none of these medications[3].
Abbreviations: HR, hazard ratio; CI, confidence interval; SE, systemic embolism; GI, gastrointestinal; CVA, cerebrovascular accident; P_{int}, P-for-interaction

Table 8. Baseline characteristics of patients prescribed apixaban 5 mg and apixaban 2.5 mg

Variable	**Overall (n=2,351)**	**Apixaban 5 mg (n=1,034)**	**Apixaban 2.5 mg (n=1,317)**
Demographics			
Age (yrs)*	68.87 (11.49)	65.16 (10.14)	71.79 (11.65)
Male	1,280 (54.4)	616 (59.6)	664 (50.4)
Race			
White	1,595 (67.8)	696 (67.3)	899 (68.3)
Black	604 (25.7)	290 (28.0)	314 (23.8)
Other	152 (6.5)	48 (4.6)	104 (7.9)
Nephrology care			
Dialysis modality			
Hemodialysis	2,216 (94.3)	977 (94.5)	1239 (94.1)
Peritoneal dialysis	135 (5.7)	57 (5.5)	78 (5.9)
Time on dialysis			
<1 year	656 (27.9)	252 (24.4)	404 (30.7)
1 to <2 years	240 (10.2)	111 (10.7)	129 (9.8)
2 to <3 years	256 (10.9)	107 (10.3)	149 (11.3)
≥3 years	1,199 (51.0)	564 (54.5)	635 (48.2)
Private insurance	416 (17.7)	193 (18.7)	223 (16.9)
Pre-ESRD nephrology care			
None	1,012 (43.0)	464 (44.9)	548 (41.6)
<6 months	283 (12.0)	114 (11.0)	169 (12.8)
6 to <12 months	422 (17.9)	182 (17.6)	240 (18.2)
≥12 months	634 (27.0)	274 (26.5)	360 (27.3)
Comorbidities			
Hypertension	2,342 (99.6)	1,032 (99.8)	1,310 (99.5)
Cerebrovascular event	778 (33.1)	312 (30.2)	466 (35.4)
Diabetes	1,773 (75.4)	815 (78.8)	958 (72.7)
Congestive heart failure	1,868 (79.5)	815 (78.8)	1,053 (80.0)
SCD/VA	279 (11.9)	135 (13.1)	144 (10.9)
Peripheral arterial disease	1,084 (46.1)	476 (46.0)	608 (46.2)
Smoking	978 (41.6)	469 (45.4)	509 (38.6)
Hypothyroidism	90 (3.8)	40 (3.9)	50 (3.8)
Liver disease	221 (9.4)	96 (9.3)	125 (9.5)
Obesity*	590 (25.1)	336 (32.5)	254 (19.3)
Venous thromboembolism	279 (11.9)	123 (11.9)	156 (11.8)
Cancer	330 (14.0)	120 (11.6)	210 (15.9)
Anemia	2,334 (99.3)	1,025 (99.1)	1,309 (99.4)
Myocardial infarction	632 (26.9)	302 (29.2)	330 (25.1)

Sleep apnea*	550 (23.4)	296 (28.6)	254 (19.3)
Prior major bleeding	217 (9.2)	79 (7.6)	138 (10.5)
Prior gastrointestinal bleeding	249 (10.6)	94 (9.1)	155 (11.8)
CHA_2DS_2VASc score, mean*	5.27 (1.77)	4.92 (1.71)	5.54 (1.77)
Baseline medications			
Statin	553 (23.5)	250 (24.2)	303 (23.0)
Non-statin lipid lowering	44 (1.9)	20 (1.9)	24 (1.8)
ACEi	213 (9.1)	104 (10.1)	109 (8.3)
Angiotensin receptor blocker	156 (6.6)	64 (6.2)	92 (7.0)
Beta-blocker	925 (39.3)	413 (39.9)	512 (38.9)
Calcium channel blocker	530 (22.5)	231 (22.3)	299 (22.7)
Diuretic	214 (9.1)	80 (7.7)	134 (10.2)
Other antihypertensive	332 (14.1)	156 (15.1)	176 (13.4)
Antiarrhythmics	538 (22.9)	243 (23.5)	295 (22.4)
Antianginal vasodilator	206 (8.8)	94 (9.1)	112 (8.5)
Antiplatelet	154 (6.6)	65 (6.3)	89 (6.8)
NSAIDs	32 (1.4)	19 (1.8)	13 (1.0)
Insulin	283 (12.0)	134 (13.0)	149 (11.3)
Non-insulin diabetes drug	126 (5.4)	62 (6.0)	64 (4.9)
Proton pump inhibitor	408 (17.4)	172 (16.6)	236 (17.9)
Antidepressant	307 (13.1)	138 (13.3)	169 (12.8)

Categorical variables are shown as n (%). Continuous variables are shown as mean (standard deviation).

* Standardized mean difference >0.2 between the 2 groups.

Abbreviations: ESRD, end-stage renal disease; SCD/VA, sudden cardiac death/ventricular arrhythmia; ACEi, angiotensin converting enzyme inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardized mean difference

Table 9. Event rates in the matched dose-specific apixaban and warfarin cohorts

	Overall (n=4,136)	**Apixaban 5 mg (n=1,034)**	**Warfarin (n=3,102)**
Stroke/SE			
N events	186	26	160
Event rate per 100 PY	11.3	8.8	11.8
Major bleeding			
N events	355	54	301
Event rate per 100 PY	21.3	18.3	21.9
GI bleeding			
N events	346	70	276
Event rate per 100 PY	21.4	23.9	20.8
Intracranial bleeding*			
N events	61	7	54
Event rate per 100 PY	3.6	2.3	3.9
Death			
N events	358	48	310
Event rate per 100 PY	21.5	16.0	22.8
	Overall (n=5,268)	**Apixaban 2.5 mg (n=1,317)**	**Warfarin (n=3,951)**
Stroke/SE			
N events	268	55	213
Event rate per 100 PY	12.4	15.3	11.8
Major bleeding			
N events	499	75	424
Event rate per 100 PY	23.9	20.8	24.6
GI bleeding			
N events	491	85	406
Event rate per 100 PY	24.2	23.7	24.3
Intracranial bleeding			
N events	67	14	53
Event rate per 100 PY	3.2	3.8	3.0
Death			
N events	532	111	421
Event rate per 100 PY	25.5	29.9	24.6

*the matched cohorts for this outcome included 1,033 apixaban and 3,099 warfarin patients (n=4,132 total)

Abbreviations: SE, systemic embolism; PY, patient-years; GI, gastrointestinal

Table 10. Multivariate Cox regression analyses restricted to the apixaban patients and including the apixaban dose as a predictor variable

Outcome	**HR (95% CI) for apixaban 5 mg vs 2.5 mg**	**P-value**
Stroke/SE	0.61 (0.37-0.98)	0.04
Major bleeding	0.98 (0.68-1.42)	0.93
GI bleeding	1.17 (0.84-1.63)	0.37
Intracranial bleeding	0.65 (0.25-1.67)	0.37
Death	0.64 (0.45-0.92)	0.01

Model covariates: apixaban dose, age, sex, prior CVA, prior major bleeding.

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, systemic embolism; GI, gastrointestinal

Figure 1. Flowchart of the cohort creation

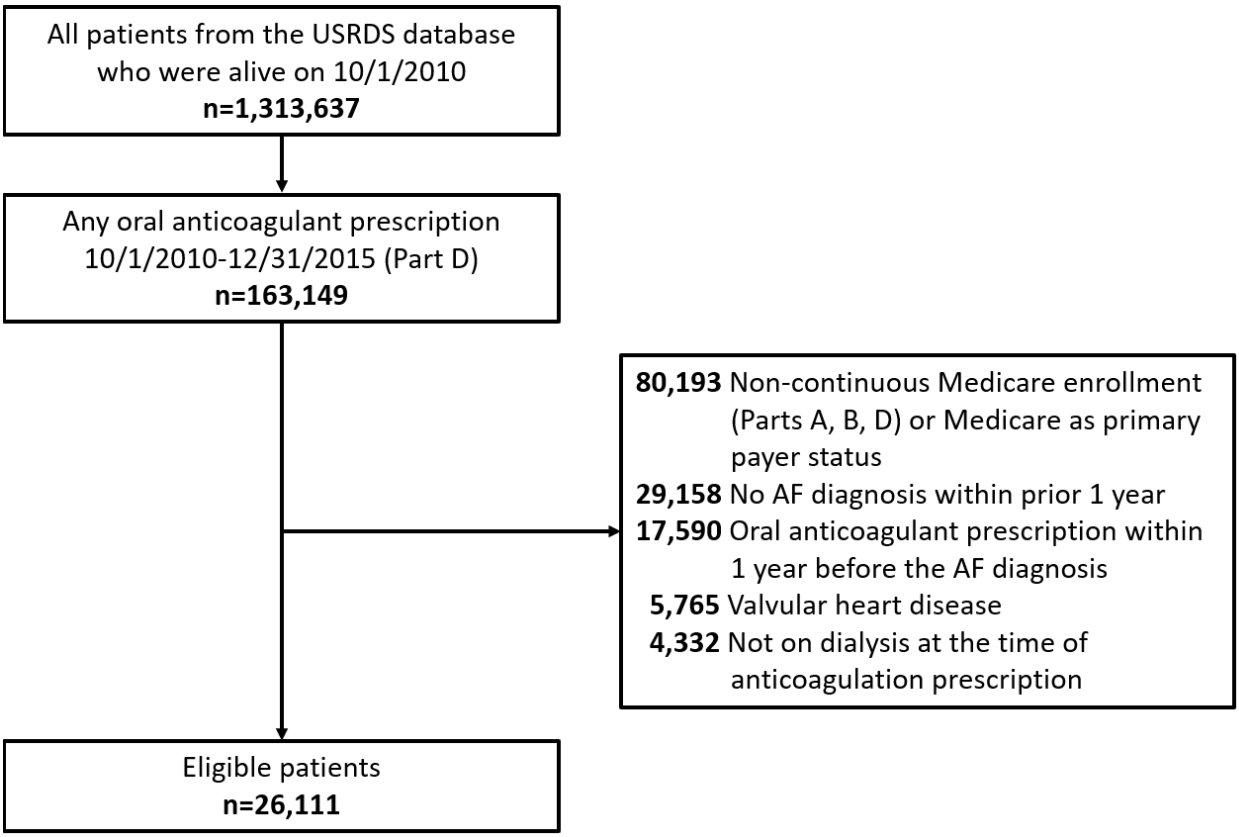
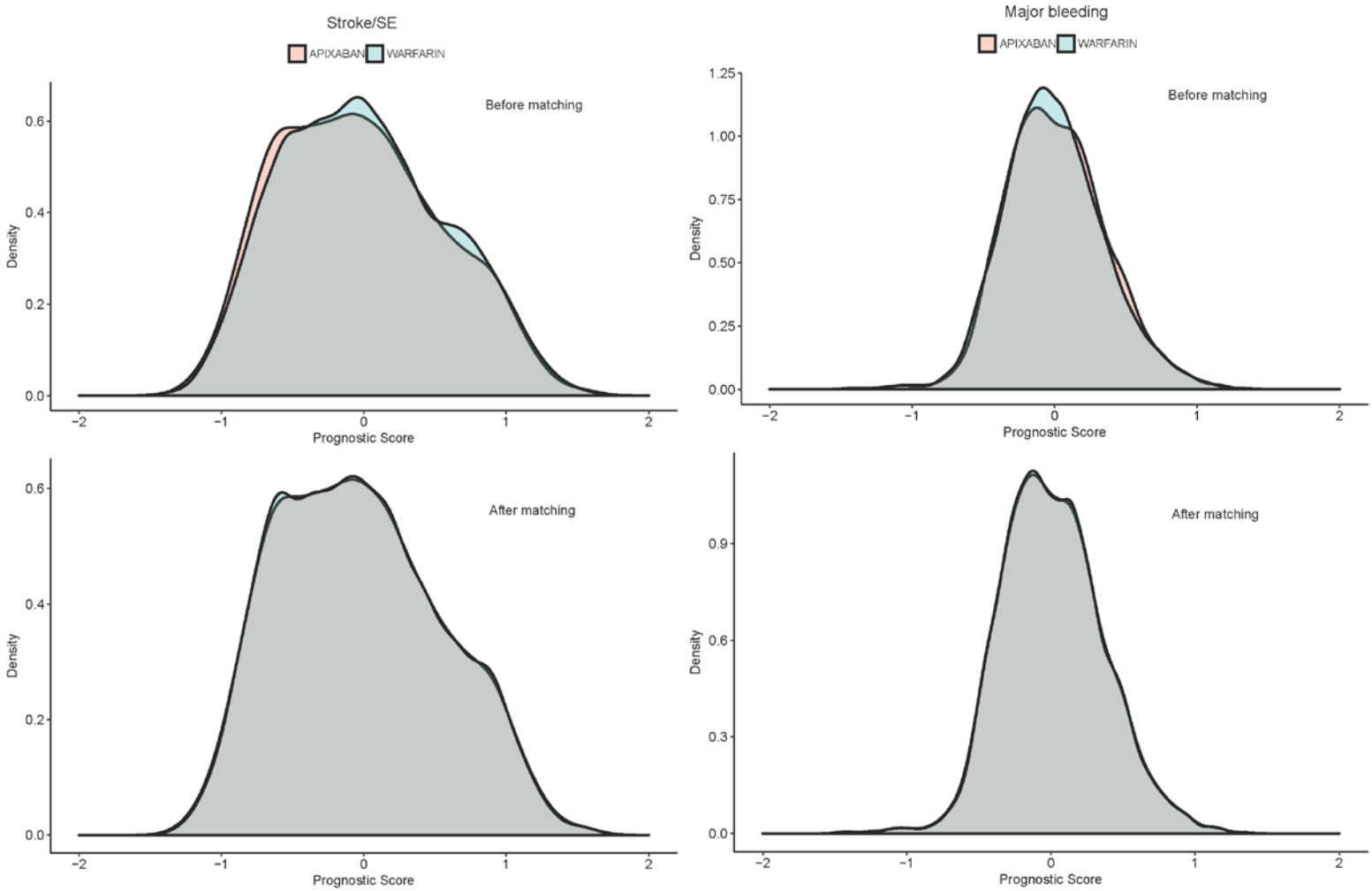
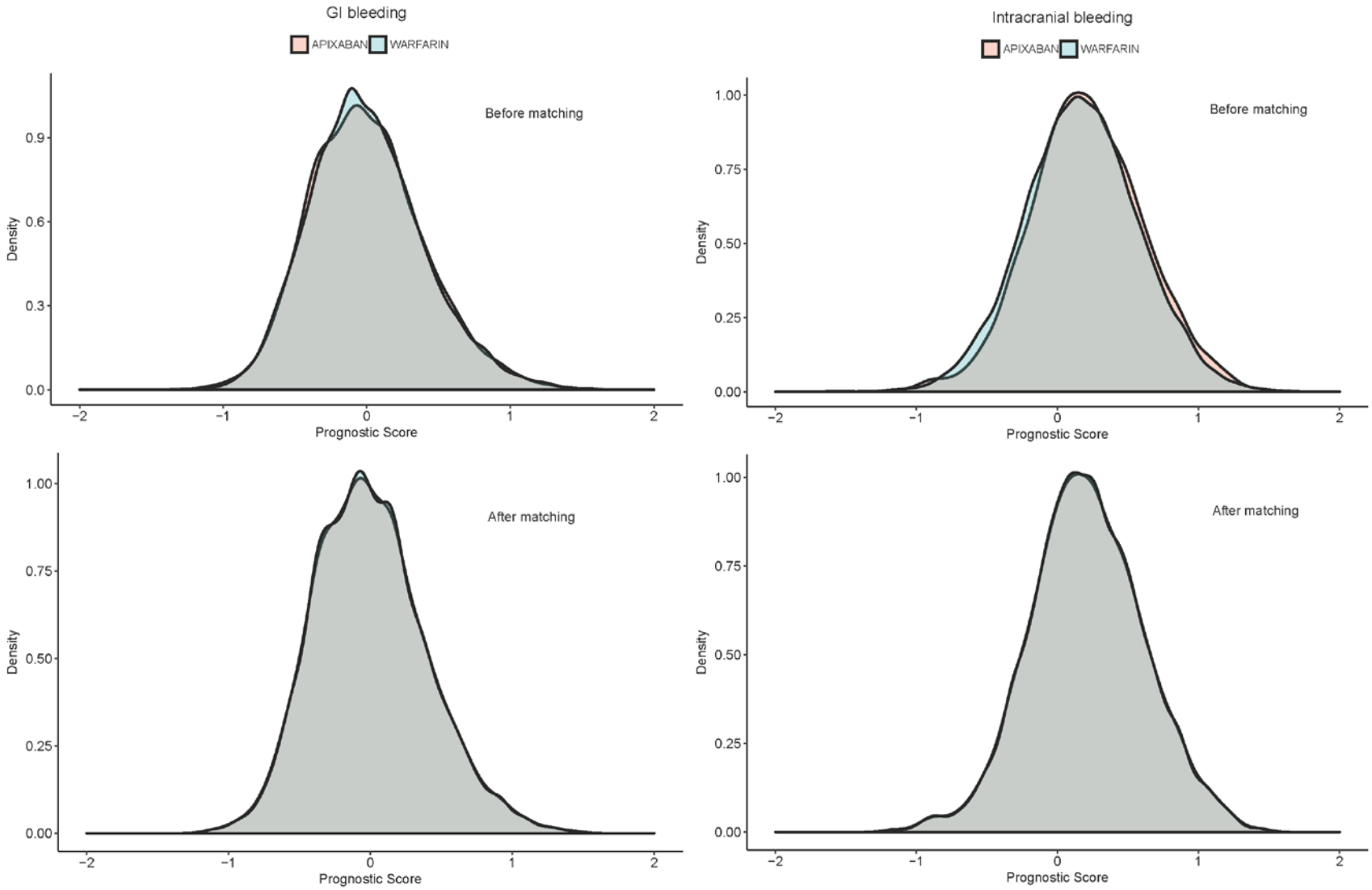
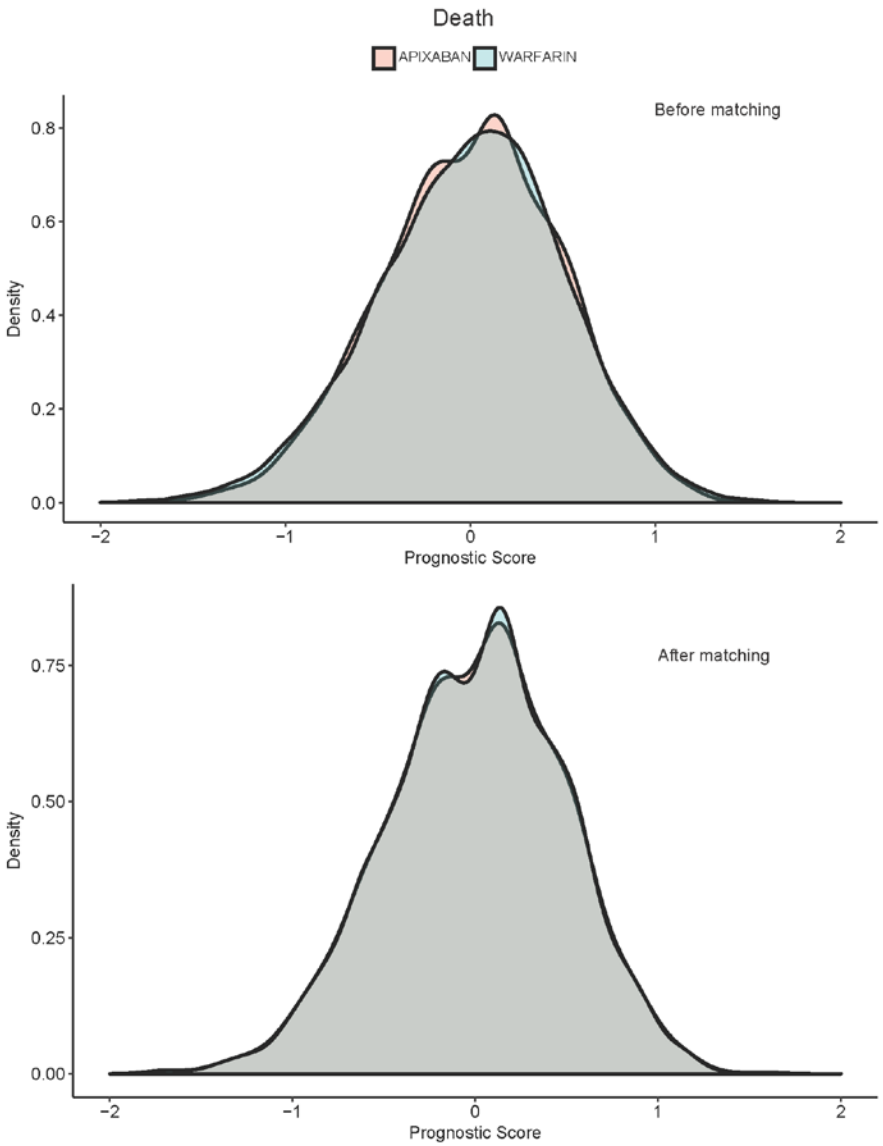


Figure 2. Distribution of prognostic scores for each outcome in the apixaban and warfarin cohorts before and after matching




GI bleeding
APIXABAN
WARFARIN
Before matching
After matching
Density
Prognostic Score
Intracranial bleeding
APIXABAN
WARFARIN
Before matching
After matching
Density
Prognostic Score


Death
APIXABAN
WARFARIN
Before matching
Density
0.0
0.2
0.4
0.6
0.8
−2
−1
0
1
2
Prognostic Score
After matching
Density
0.00
0.25
0.50
0.75
−2
−1
0
1
2
Prognostic Score

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