

1 **Supplemental Materials**

2 **Paper title: Association between Dabigatran versus Warfarin and Risk of Osteoporotic Fractures among Patients with Nonvalvular**
3 **Atrial Fibrillation**

4 **No. of supplemental tables: 4**

5 **No. of supplemental figures: 3**

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16 **eTable 1. International Classification of Diseases codes, Ninth Revision,**
 17 **Clinical Modification (ICD-9-CM) codes used in the study**

ICD-9-CM	Descriptions
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Valvular heart diseases/replacement or hyperthyroidism	
242	Thyrotoxicosis with or without goitre
394.0	Mitral stenosis
Valvular heart surgery (procedure codes)	
35.20	Open and other replacement of unspecified heart valve
35.22	Open and other replacement of aortic valve
35.24	Open and other replacement of mitral valve
35.26	Open and other replacement of pulmonary valve
35.28	Open and other replacement of tricuspid valve
Transient atrial fibrillation	
Cardiac surgery (procedure codes)	
00.5	Other cardiovascular procedures
35	Operations on valves and septa of heart
36	Operations on vessels of heart
37	Other operations on heart and pericardium
Pericarditis	
391	Rheumatic fever with heart involvement
393	Chronic rheumatic pericarditis
420	Acute pericarditis
423.2	Constrictive pericarditis
036.41	Meningococcal pericarditis
074.21	Coxsackie pericarditis
093.81	Syphilitic pericarditis
098.83	Gonococcal pericarditis
Myocarditis	
130.3	
391.2	Acute rheumatic myocarditis
398.0	Rheumatic myocarditis
422	Acute myocarditis
429.0	Myocarditis, unspecified
032.82	Diphtheritic myocarditis
036.43	Meningococcal myocarditis
074.23	Coxsackie myocarditis
093.82	Syphilitic myocarditis
Pulmonary embolism	
415.1	Pulmonary embolism and infarction

19 **eTable 1. International Classification of Diseases codes, Ninth Revision,**
 20 **Clinical Modification (ICD-9-CM) codes used in the study (continued)**

ICD-9-CM	Descriptions
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
437.2	Hypertensive encephalopathy
Diabetes	
250	Diabetes mellitus
Ischaemic stroke	
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease

22 **eTable 1. International Classification of Diseases codes, Ninth Revision,**
 23 **Clinical Modification (ICD-9-CM) codes used in the study (continued)**

ICD-9-CM	Descriptions
Transient ischaemic attack	
435	Transient cerebral ischemia
Systemic embolism	
444	Arterial embolism and thrombosis
445	Atheroembolism
Vascular disease	
410-414	Ischemic heart disease
443.8	Other specified peripheral vascular diseases
443.9	Peripheral vascular disease, unspecified
Chronic Obstructive Pulmonary Disease	
490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified
506.4	Respiratory conditions due to chemical fumes and vapors
Liver disease	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
456.2	Esophageal varices in diseases classified elsewhere
571.2	Alcoholic cirrhosis of liver
571.4	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
Chronic Kidney Disease	
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
582	Chronic glomerulonephritis
585	Chronic kidney disease (ckd)
590.0	Chronic pyelonephritis

25 **eTable 1. International Classification of Diseases codes, Ninth Revision,**
 26 **Clinical Modification (ICD-9-CM) codes used in the study (continued)**

ICD-9-CM	Descriptions
Rheumatoid arthritis and other inflammatory polyarthropathies	
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
725	Polymyalgia rheumatica
Bone tumour	
170	Malignant neoplasm of bone and articular cartilage
Epilepsy/seizure	
333.2	Myoclonus
345	Epilepsy and recurrent seizures
780.33	Post traumatic seizures
780.39	Other convulsions
Osteoporosis	
733.0	Osteoporosis
Fractures	
805	Fracture of vertebral column without mention of spinal cord injury
812	Fracture of humerus
813	Fracture of radius and ulna
814	Fracture of carpal bone(s)
820	Fracture of neck of femur
History of falls	
781.2	Abnormality of gait
781.3	Lack of coordination
781.99	Other symptoms involving nervous and musculoskeletal systems
V15.88	History of fall
E880-E888	Accidental Falls

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30 **eTable 1. International Classification of Diseases codes, Ninth Revision,**
 31 **Clinical Modification (ICD-9-CM) codes used in the study (continued)**

ICD-9-CM	Descriptions
Motor vehicle accidents	
E800-E807	Railway Accidents
E810-E819	Motor Vehicle Traffic Accidents
E820-E825	Motor Vehicle Nontraffic Accidents
E826-E829	Other Road Vehicle Accidents
E830-E831	Water Transport Accidents
E840-E845	Air And Space Transport Accidents
E846-E848	Vehicle Accidents, Not Elsewhere Classifiable
Accidental falls from height	
E880	Accidental fall on or from stairs or steps
E881	Accidental fall on or from ladders or scaffolding
E882	Accidental fall from or out of building or other structure
E883	Accidental fall into hole or other opening in surface
E884.0	Accidental fall from playground equipment
E884.1	Accidental fall from cliff

32 **eTable 2. Baseline patient characteristics for the analysis with 5% trimming of propensity score**

	Before propensity-score matching			After propensity-score matching		
	Dabigatran	Warfarin	Standardized difference ^a	Dabigatran	Warfarin	Standardized difference ^a
N	3298	6981		2799	4207	
Age, mean ± SD	74.3 ± 10.1	72.1 ± 11.7	0.20	73.6 ± 9.9	72.9 ± 10.6	0.07
Female	1685 (51.1)	3227 (46.2)	0.10	1364 (48.7)	2008 (47.7)	0.02
Baseline medical conditions						
CHADS ₂ , mean ± SD	2.1 ± 1.5	2.1 ± 1.6	0.02	2.0 ± 1.5	2.0 ± 1.6	0.02
CHA ₂ DS ₂ -VASc, mean ± SD	3.4 ± 2.2	3.3 ± 2.2	0.04	3.2 ± 2.2	3.2 ± 2.2	0.02
Congestive heart failure	689 (20.9)	2205 (31.6)	-0.24	589 (21.0)	1052 (25.0)	-0.09
Prior ischemic stroke/transient ischemic attack	1116 (33.8)	2073 (29.7)	0.09	863 (30.8)	1217 (28.9)	0.04
Chronic Obstructive Pulmonary Disease	274 (8.3)	581 (8.3)	<0.001	222 (7.9)	353 (8.4)	-0.02
Diabetes mellitus	997 (30.2)	1982 (28.4)	0.04	786 (28.1)	1144 (27.2)	0.02
History of falls	518 (15.7)	931 (13.3)	0.07	410 (14.6)	593 (14.1)	0.02
History of fractures	237 (7.2)	446 (6.4)	0.03	198 (7.1)	279 (6.6)	0.02
Liver disease	16 (0.5)	44 (0.6)	-0.02	12 (0.4)	27 (0.6)	-0.03
Osteoporosis	40 (1.2)	69 (1.0)	0.02	28 (1.0)	39 (0.9)	0.01
Rheumatoid arthritis and other inflammatory polyarthropathies	14 (0.4)	45 (0.6)	-0.03	12 (0.4)	18 (0.4)	<0.001
Chronic kidney disease	94 (2.9)	536 (7.7)	-0.22	31 (1.1)	72 (1.7)	-0.05
Baseline medication use						
ACE inhibitor or ARB	1552 (47.1)	3332 (47.7)	-0.01	1264 (45.2)	1940 (46.1)	-0.02
Beta-blocker	2011 (61.0)	4028 (57.7)	0.07	1649 (58.9)	2428 (57.7)	0.02
Bisphosphonates	43 (1.3)	54 (0.8)	0.05	15 (0.5)	25 (0.6)	-0.01
Systemic glucocorticoid	213 (6.5)	583 (8.4)	-0.07	188 (6.7)	314 (7.5)	-0.03
Antidepressants	128 (3.9)	224 (3.2)	0.04	95 (3.4)	127 (3.0)	0.02

33 Values are expressed as frequency (%) unless otherwise specified. Abbreviations: SD, standard deviation; CHADS₂, congestive heart failure, hypertension, age ≥75 years,
34 diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism (doubled); CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years (doubled),
35 diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); CHA₂DS₂-VASc score
36 ranges from 0-9, where a higher score indicates a higher risk for stroke; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
37 ^aStandardized difference is the difference in mean or proportion of covariates in dabigatran group versus warfarin group divided by the pooled standard deviation; standardized
38 difference <0.2 indicates a negligible difference in covariates between treatment groups.

39 **eTable 3. Baseline patient characteristics for the post-hoc analysis for dabigatran versus non-treated patients**

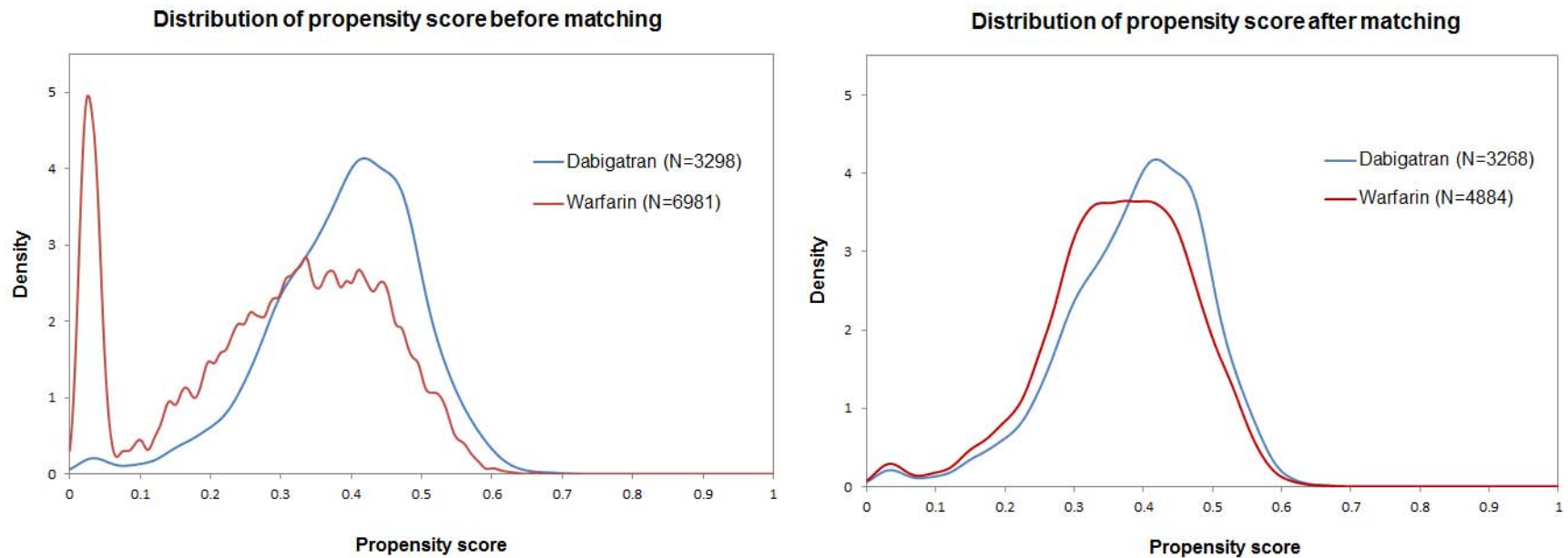
	Before propensity-score matching			After propensity-score matching		
	Dabigatran	Non-treated	Standardized difference ^a	Dabigatran	Non-treated	Standardized difference ^a
N	3298	30 900		2829	5556	
Age, mean ± SD	74.3 ± 10.1	78.4 ± 12.6	-0.37	74.2 ± 10.1	74.5 ± 13.4	-0.02
Female	1685 (51.1)	15902 (51.5)	-0.01	1462 (51.7)	2913 (52.4)	-0.02
Baseline medical conditions						
CHADS ₂ , mean ± SD	2.1 ± 1.5	1.9 ± 1.6	0.15	2.1 ± 1.5	2.2 ± 1.7	-0.02
CHA ₂ DS ₂ -VASc, mean ± SD	3.4 ± 2.2	3.2 ± 2.4	0.10	3.4 ± 2.2	3.5 ± 2.5	-0.03
Congestive heart failure	689 (20.9)	8021 (26.0)	-0.12	586 (20.7)	1107 (19.9)	0.02
Prior ischemic stroke/ transient ischemic attack	1116 (33.8)	5509 (17.8)	0.37	963 (34.0)	1789 (32.2)	0.04
Chronic Obstructive Pulmonary Disease	274 (8.3)	4363 (14.1)	-0.18	227 (8.0)	426 (7.7)	0.01
Diabetes mellitus	997 (30.2)	7680 (24.9)	0.12	871 (30.8)	1697 (30.5)	0.01
History of falls	518 (15.7)	7648 (24.8)	-0.23	431 (15.2)	866 (15.6)	-0.01
History of fractures	237 (7.2)	4113 (13.3)	-0.20	198 (7.0)	383 (6.9)	<0.001
Liver disease	16 (0.5)	341 (1.1)	-0.07	14 (0.5)	30 (0.5)	-0.01
Osteoporosis	40 (1.2)	629 (2.0)	-0.07	35 (1.2)	60 (1.1)	0.01
Rheumatoid arthritis and other inflammatory polyarthropathies	14 (0.4)	231 (0.7)	-0.04	12 (0.4)	28 (0.5)	-0.01
Chronic kidney disease	94 (2.9)	2994 (9.7)	-0.28	80 (2.8)	169 (3.0)	-0.01
Baseline medication use						
ACE inhibitor or ARB	1552 (47.1)	9044 (29.3)	0.37	1347 (47.6)	2626 (47.3)	0.01
Beta-blocker	2011 (61.0)	9710 (31.4)	0.62	1737 (61.4)	3398 (61.2)	0.00
Bisphosphonates	43 (1.3)	317 (1.0)	0.03	40 (1.4)	85 (1.5)	-0.01
Systemic glucocorticoid	213 (6.5)	2977 (9.6)	-0.12	185 (6.5)	374 (6.7)	-0.01
Antidepressants	128 (3.9)	1002 (3.2)	0.03	106 (3.7)	205 (3.7)	0.003

40 Values are expressed as frequency (%) unless otherwise specified. Abbreviations: SD, standard deviation; CHADS₂, congestive heart failure, hypertension, age ≥75 years,
41 diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism (doubled); CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years (doubled),
42 diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); CHA₂DS₂-VASc score
43 ranges from 0-9, where a higher score indicates a higher risk for stroke; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
44 ^aStandardized difference is the difference in mean or proportion of covariates in dabigatran group versus warfarin group divided by the pooled standard deviation; standardized
45 difference <0.2 indicates a negligible difference in covariates between treatment groups.

46 **eTable 4. Results for the post-hoc analysis for dabigatran versus non-treated patients**

	Dabigatran			Non-treated			Dabigatran vs. Non-treated		
	N	No. of cases/py	incidence per 100 py	N	No. of cases/py	incidence per 100 py	ARD (95% CI)	IRR (95% CI)	p
Before PS matching	3298	34/4594	0.7	30 900	1368/78 732	1.7	-0.98 (-0.68 to -1.18)	0.43 (0.30 to 0.60)	<.001
After PS matching	2829	32/4314	0.7	5556	173/13 078	1.3	-0.62 (-0.25 to -0.87)	0.52 (0.33 to 0.81)	.002

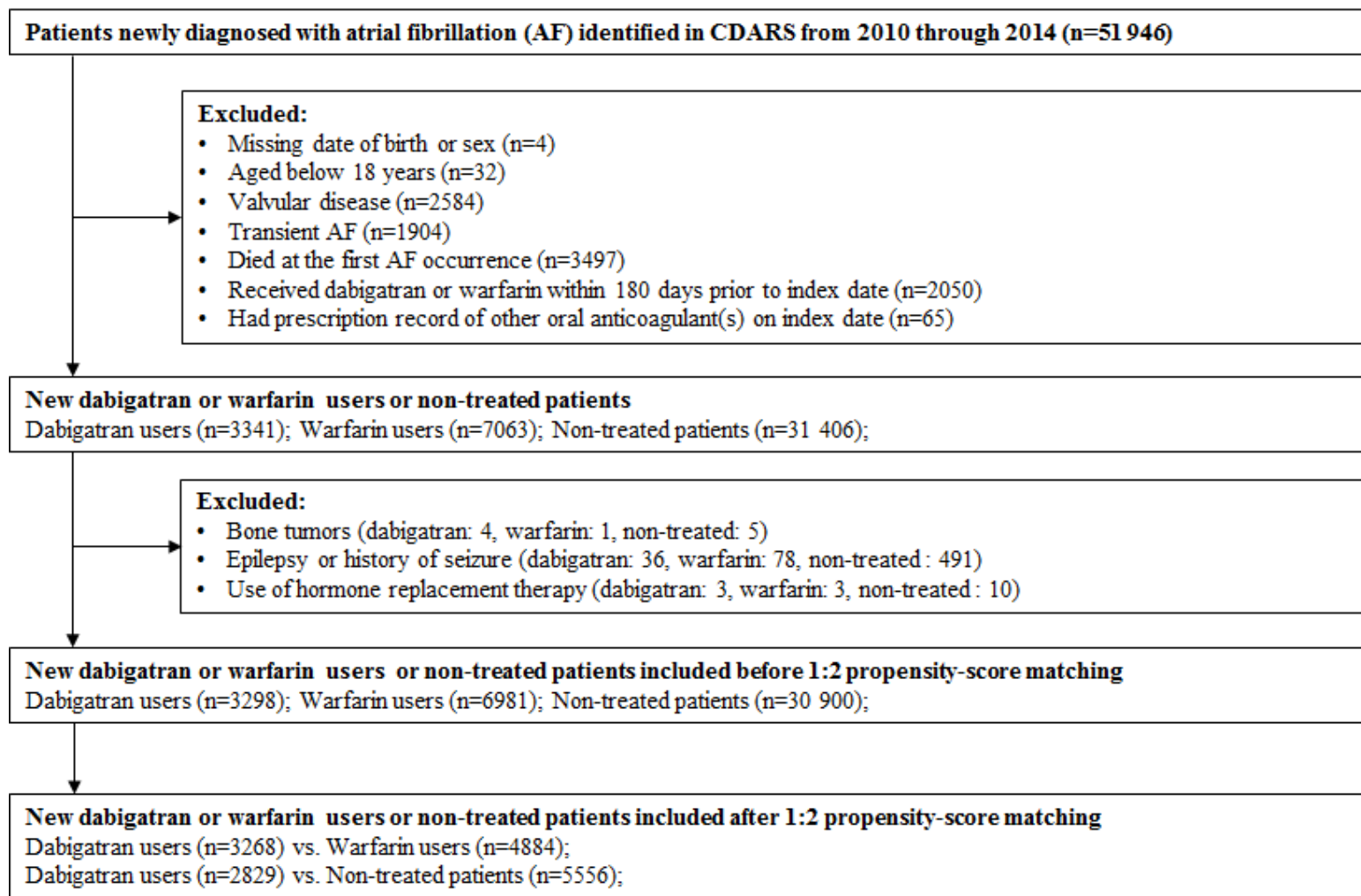
47 Abbreviations: py: person-years; ARD: absolute risk difference per 100 person-years; IRR, incidence rate ratio; CI, confidence interval; PS, propensity score.



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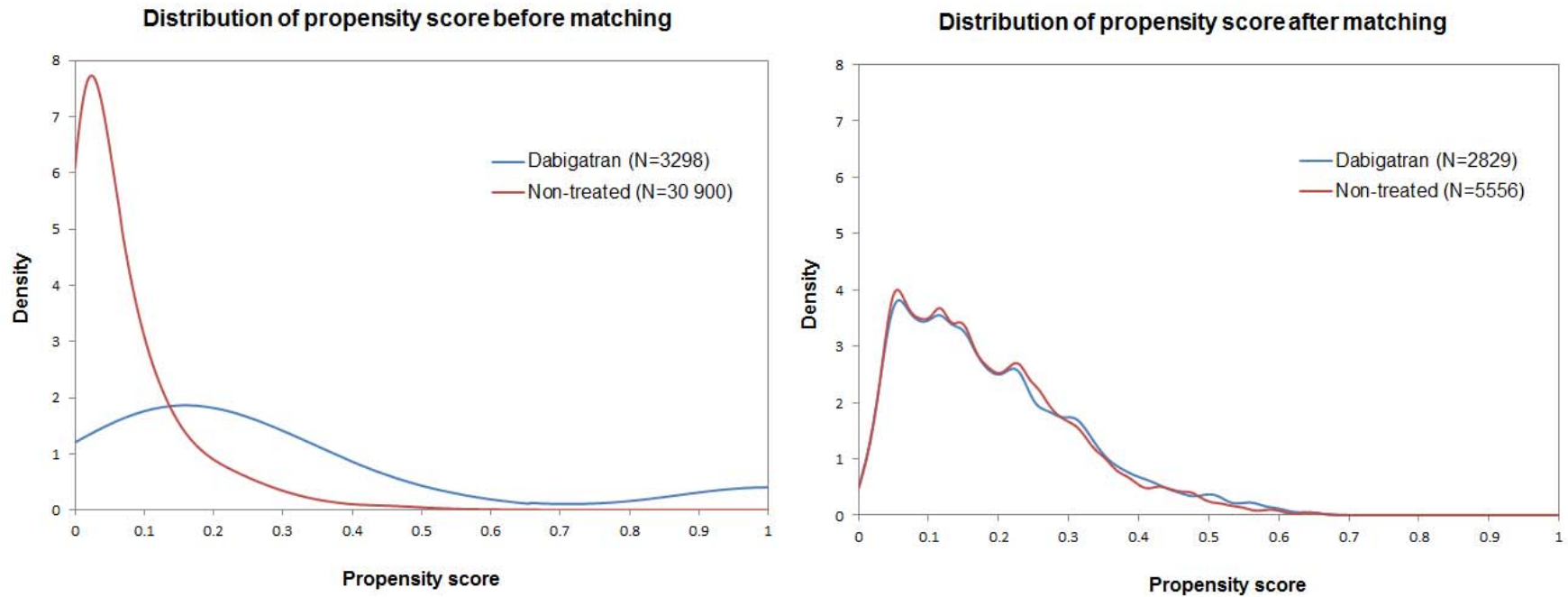
49 **eFigure 1. Distribution of propensity score before and after matching for dabigatran versus warfarin patients.** The curves
 50 illustrate the distribution of the probability of a patient receiving dabigatran conditional on the observed patient characteristics (i.e.
 51 propensity score). Such probability was calculated using logistic regression in which dabigatran treatment (yes/no) was the
 52 dependent variable and the observed patient characteristics were the covariates.

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55 eFigure 2. Selection of non-treated patients in the post-hoc analysis



56 **eFigure 3. Distribution of propensity score before and after matching in the post-hoc analysis for dabigatran versus non-**
 57 **treated patients.** The curves illustrate the distribution of the probability of a patient receiving dabigatran conditional on the
 58 observed patient characteristics (i.e. propensity score). Such probability was calculated using logistic regression in which
 59 dabigatran treatment (yes/no) was the dependent variable and the observed patient characteristics were the covariates.
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