SUPPLEMENTAL INFORMATION

Comparative effectiveness and safety of edoxaban vs warfarin in patients with atrial fibrillation: A nationwide cohort study

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Supplemental Figure 5: Standardized event free survival curves of bleeding outcome

Supplemental methods

Setting and data sources

The Danish National Health Service provides tax-supported health care to the entire population [1]. Nationwide registries track vital status, diagnoses, and procedures for all residents. Data can be linked across registries using the unique civil registration number assigned to all Danish residents at birth or upon immigration. Migration, sex, and vital status are tracked by the Civil Registration System (CRS) [2]. The Danish National Patient Registry covers all Danish hospitals and records all clinical inpatient discharge diagnoses since 1977 and diagnoses made at outpatient clinic visits since 1995 [3]. The Danish National Prescription Database records information on prescription claims from outpatient pharmacies since 2004 using the Anatomical Therapeutic Chemical (ATC) Classification System [4]. The Danish National Laboratory Registry has recorded clinical, biochemical and immunological measurements since 2013 based on the international Nomenclature for Properties and Units coding [5]. (See applied diagnoses and ATC codes in Supplemental Table 1).

Modelling approach

Data were arranged accordingly such that each patient-month was represented by a single row (maximum of 24 per individual, corresponding to 2 years). The pooled logistic regression models estimated the average treatment effect under the strong assumption of no unmeasured confounding. Risk of outcomes were assessed through the models by including an additional interaction term between exposure variables and time. This allowed for construction of standardized outcome-free survival curves within exposure groups.

Sensitivity analyses

We conducted the following sensitivity analyses to assess the robustness of our results: 1) The cohort was restricted in various subgroup analyses, including i) OAC naïve patients defined as no prescription claim of any anticoagulant treatment within the last year; ii) age 75 years or older; iii) affected renal function defined as an eGFR <90 ml/min/1.73m2 ; iv) 'very high' stroke risk defined as a CHA2DS2-VASc score of 4 or higher. 2) Since stroke in some cases can be fatal and therefore not recorded as a stroke, we investigated competing risk of death by keeping person-time in the analytic dataset after death was recorded (i.e. death did not prompt administrative censoring) [6]. 3) To allow for a thorough evaluation of the safety outcome, we restricted the bleeding events to those events leading to hospitalization. 4) All-cause mortality and thromboembolic events was examined as a composite outcome. 5) Last, the all-cause mortality outcome was explored post-hoc to examine clinical characteristics associated with the mortality difference in the two treatment groups.

Ethics

The study was performed in compliance with the General Data Protection Regulation, by the North Denmark Region's record of processing activities (project no. 2017-40). No ethics approval or informed consent were needed according to Danish law for studies that does not involve patient contact.

Additional analyses

To allow for comparisons between edoxaban 30mg and warfarin, a post-hoc decision was made to contrast outcomes for the two treatment alternatives using a propensity score matching approach. This necessitated a change in the original research question of interest, i.e. what would be the expected

outcomes had the entire population receive (e.g.) edoxaban 60mg vs edoxaban 30mg vs warfarin – to the question, among those who received edoxaban 30mg what would have happened if they was changed to warfarin treatment. In details, the estimand was changed from the original average treatment effect in the population (ATE) to the average treatment effect among the treated (ATT).[7] The following covariates were included to established a propensity score matched cohort, where patients receiving edoxaban 30mg was considered the treated and warfarin users the untreated: sex, age (continuous), eGFR (continuous), ischemic heart disease, previous intracerebral bleeding, heart failure, diabetes, hypertension, prior thromboembolic event, vascular disease, use of statin or aspirin within the last year, a cancer diagnosis within last three years, and OAC experience status (binary). A 1:1 matching was selected with a (mahalanobis distance) caliper of 0.1 and no replacement after a match. After matching, a total of 456 edoxaban 30mg users were matched with 456 warfarin users; see supplemental Figure 2 for plots of the propensity score distribution, and supplemental Table 4 for baseline characteristics. Supplemental Figure 3-5 displays the outcome analyses for thromboembolism, bleeding outcome, and all-cause mortality.

Reference

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7. Mccaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat. Med.* 2013;32:3388–3414.

Supplemental Table 1: ICD10 codes and ATC-codes

	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
Clinical characteristics		
Congestive heart failure	I11.0 I13.0 I13.2 I42.0 I50	CO3C
Left ventricular dysfunction	I50.1 I50.9	
Hypertension		See specified definition*
Diabetes mellitus	E10.0 E10.1 E10.9 E11.0 E11.1 E11.9	A10
Ischemic stroke	I63 I64	
Systemic embolism	I74	
Transient ischemic attack	G45	
Aortic plaque	I70.0	
Peripheral arterial disease	I70.2-I70.9 I71 I73.9 I74	
Myocardial infarction	I21-I23	
Chronic kidney disease	I12 I13 N00-N05 N07 N11 N14 N17-N19 Q61	
Liver disease	B15.0 B16.0 B16.2 B19.0 K70.4 K72 K76.6 I85	
Major bleeding	D62 J492 H356 H431 N02 R04 R31 G951A H052A H313 H450 I312	
Intracranial bleeding	I60 I61 I62 I690 I691 I692	
Gastrointestinal bleeding	K250 K252 K254 K260 K262 K264 K270 K272 K274 K280 K282 K290 K921 K922 I850 I864A K228F K284 K298A K625 K638B K638C K661 K838F K868G	
Alcohol intake	E22.4 E52.9A F10 G31.2 G62.1 G72.1 I42.6 K29.2 K70 K86.0 L27.8A O35.4M T51 Z71.4 Z72.1	
Atrial fibrillation	I48	

Alcohol abuse	E244 E529A F10 G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	
Cancer diagnosis	C	
CPD	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J67 J684 J701 J703 J841 J920 J921 J982 J983	
Ischemic heart disease	I20 I21 I22 I23 I24 I25	
CABG procedure	KFNA KFNC KFND KFNE	
PCI procedure	KFNG	
Medication information		
Dabigatran		B01AE07
Rivaroxaban		B01AE07
Apixaban		B01AF02
Edoxaban		B01AF03
Warfarin		B01AA03
Aspirin		B01AC06
Clopidogrel		
Beta-blockers		C07
Calcium channel blockers		C07F C08 C09BB C09DB
Renin-angiotensin system inhibitors (ACEi/ARBs)		C09
Loop diuretics		C03C
Statin		C10
NSAID		M01AA M01AB M01AC M01AE M01AG M01AH M01AX01
Non-loop diuretics		C02DA C02L C03A C03B C03D C03EA C03X C07C C07D C08G C09BA C09DA C09XA52

PGP inhibitors		J02AB02 J02AC02 L04AD02 L04AD01 C08DA01 C01BD01 J01FA09
CYP-PGP inhibitors		J02AB02 J02AC02 J05AE10 J05AE08 J05AR14 J05AR15 J02AC01
Proton-pump inhibitors		A02BC
Vasodilators		C02DB C02DD C02DG C04 C05
Calcium		C07F C08 C09BB C09DB
Estimated glomerular filtration rate**	DNK35301; DNK35302; NPU04998	

*We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:
I. Alpha adrenergic blockers (C02A, C02B, C02C)
II. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)
III. Vasodilators (C02DB, C02DD, C02DG, C04, C05)
IV. Beta blockers (C07)
V. Calcium channel blockers (C07F, C08, C09BB, C09DB)
VI. Renin-angiotensin system inhibitors (C09).

** Obtained from the Danish National Laboratory Registry

Supplemental Table 2: Number of events and event rates per 100 person-years for each component in the safety outcome

Outcome	Number of events	100 Person-years	Crude event rate
Gastrointestinal bleeding	105	82.92	1.27
Edoxaban 30mg	10	4.81	2.08
Edoxaban 60mg	20	16.71	1.20
Warfarin	75	61.40	1.22
Intracranial bleeding	32	83.62	0.38
Edoxaban 30mg	<5	-	0.41
Edoxaban 60mg	6	16.83	0.36
Warfarin	24	61.93	0.39
Bleeding in other anatomical sites	175	82.09	2.13
Edoxaban 30mg	7	4.81	1.45
Edoxaban 60mg	39	16.59	2.35
Warfarin	129	60.69	2.13

Supplemental Table 3: Subgroup analyses of comparative effectiveness and safety outcomes in inverse probability weighted populations

Subgroup analysis	Number of patients included	Hazard ratios (95% confidence interval)		
OAC naïve		Stroke	Bleeding	All-cause mortality
Edoxaban 60 mg	815	0.99 (0.47 to 2.08)	1.10 (0.71 to 1.71)	0.58 (0.37 to 0.89)
Warfarin	2883	Reference		
Age 75 years or older		Stroke	Bleeding	All-cause mortality
Edoxaban 60 mg	755	0.97 (0.48 to 1.97)	1.42 (0.89 to 2.28)	0.54 (0.36 to 0.82)
Warfarin	1655	Reference		
High risk of stroke		Stroke	Bleeding	All-cause mortality
Edoxaban 60 mg	680	1.22 (0.66 to 2.26)	0.98 (0.57 to 1.68)	0.57 (0.40 to 0.83)
Warfarin	1501	Reference		
Affected renal function		Stroke	Bleeding	All-cause mortality
Edoxaban 60 mg	1266	1.09 (0.60 to 1.97)	1.08 (0.74 to 1.59)	0.64 (0.45 to 0.90)
Warfarin	2498	Reference		

Supplemental Table 4: Characteristics of patients with atrial fibrillation according to treatment regimen with warfarin (dose adjusted) after propensity matching

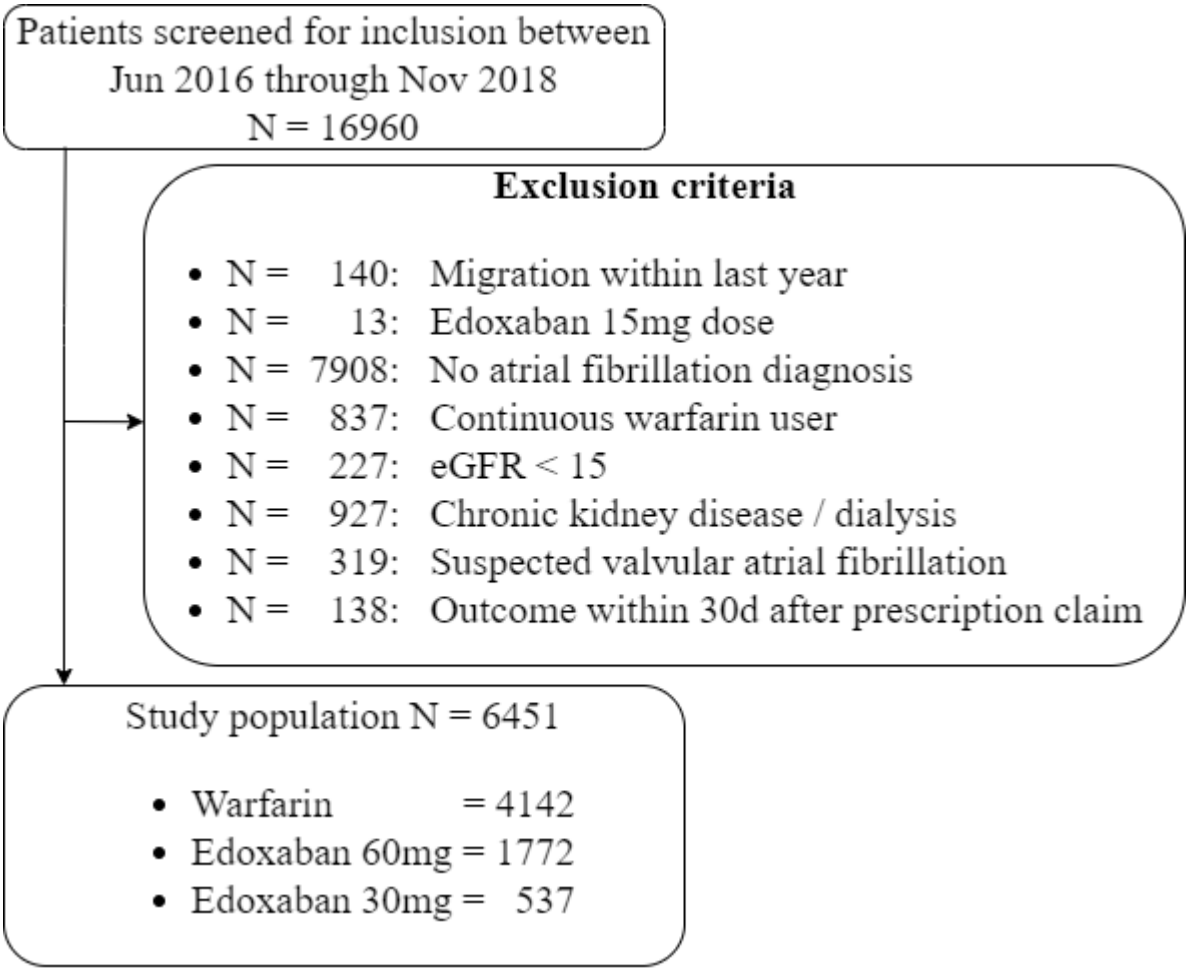
Patient characteristics	Warfarin	Edoxaban 30 mg
No.	456	456
Women % (N)	64.3 (293)	62.1 (283)
Age, mean (SD)	82.0 (8.7)	81.6 (8.1)
Ischemic stroke	13.6 (62)	14.3 (65)
Hypertension	66.9 (305)	67.1 (306)
Heart failure or LVD	37.3 (170)	37.9 (173)
Diabetes	19.1 (87)	18.4 (84)
Ischemic heart disease	27.2 (124)	30.3 (138)
Intracranial bleeding	- (<5)	1.1 (5)
Gastrointestinal bleeding	6.1 (28)	3.7 (17)
Median CHA_2DS_2-VASc score (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Score 0-2	11.4 (52)	9.9 (45)
Score 3-5	66.0 (301)	69.3 (316)
Score >5	22.6 (103)	20.8 (95)

Median HAS BLED score (IQR)	3.0 (2.0-3.0)	2.0 (2.0-3.0)
Score 0-1	16.0 (73)	20.0 (91)
Score 2-3	66.0 (301)	62.3 (284)
Score >3	18.0 (82)	17.8 (81)
Cancer (ever)	25.2 (115)	28.9 (132)
Cancer diagnosed within 3 years	11.4 (52)	12.7 (58)
Mean creatinine clearance, ml/min/1.73m^2 (SD)	56.5 (20.1)	55.5 (19.2)
Medication		
OAC naïve	44.7 (204)	41.4 (189)
Warfarin	0.0 (0)	37.7 (172)
Apixaban	24.6 (112)	8.1 (37)
Dabigatran	9.6 (44)	7.0 (32)
Rivaroxaban	24.1 (110)	10.1 (46)
Aspirin	25.4 (116)	23.2 (106)

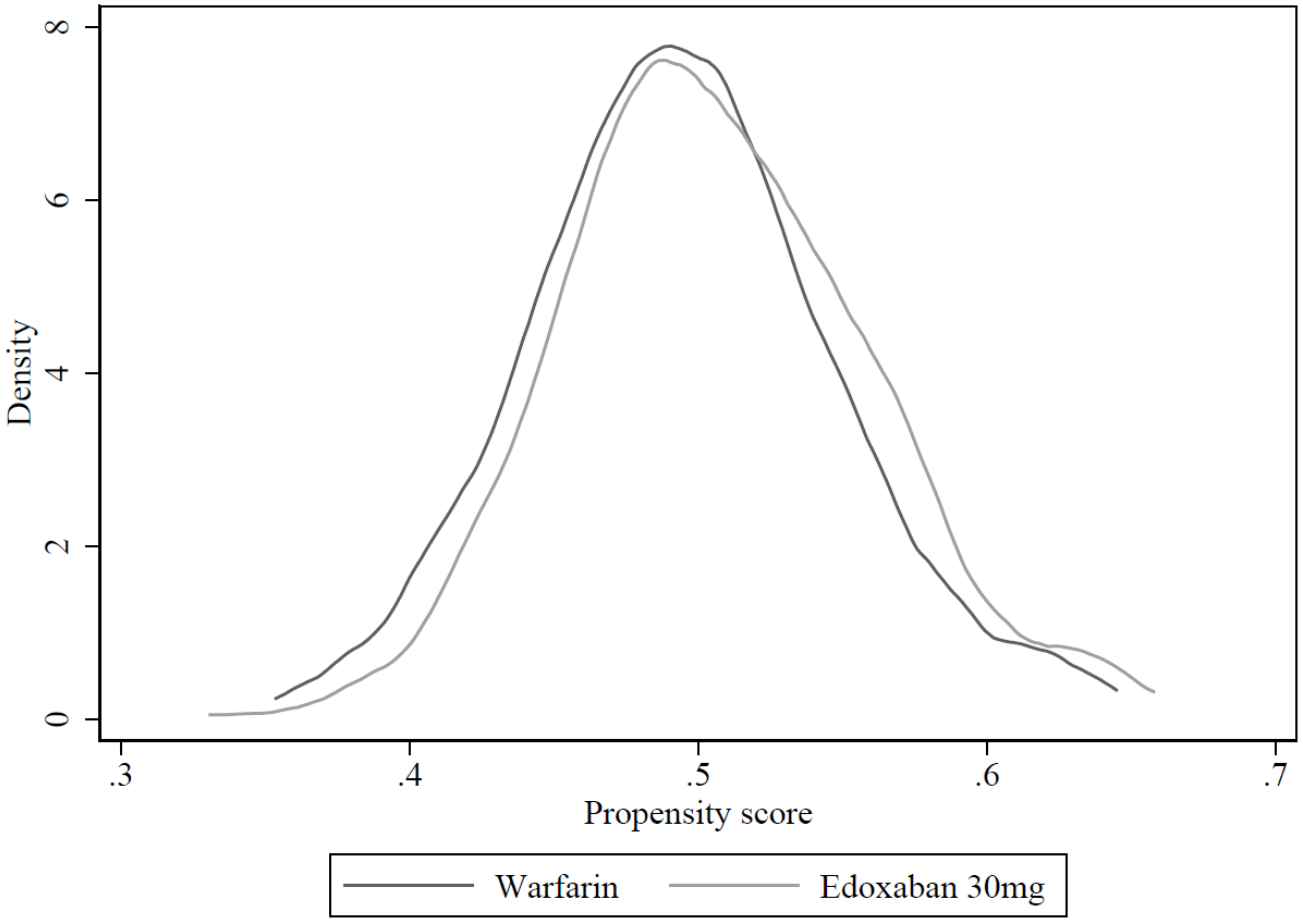
Clopidogrel	10.7 (49)	10.3 (47)
Proton-pump inhibitors	38.2 (174)	33.6 (153)
Beta blocker	68.4 (312)	70.0 (319)
Non-loop diuretic	44.5 (203)	44.7 (204)
Calcium channel blocker	35.3 (161)	33.8 (154)
Renin-angiotensin inhibitor	54.4 (248)	53.9 (246)
NSAID	16.9 (77)	9.4 (43)

SD: Standard deviation. IQR: Interquartile range. LVD: Left ventricular dysfunction. OAC: Oral anticoagulant. NSAID: Nonsteroidal anti-inflammatory drugs.

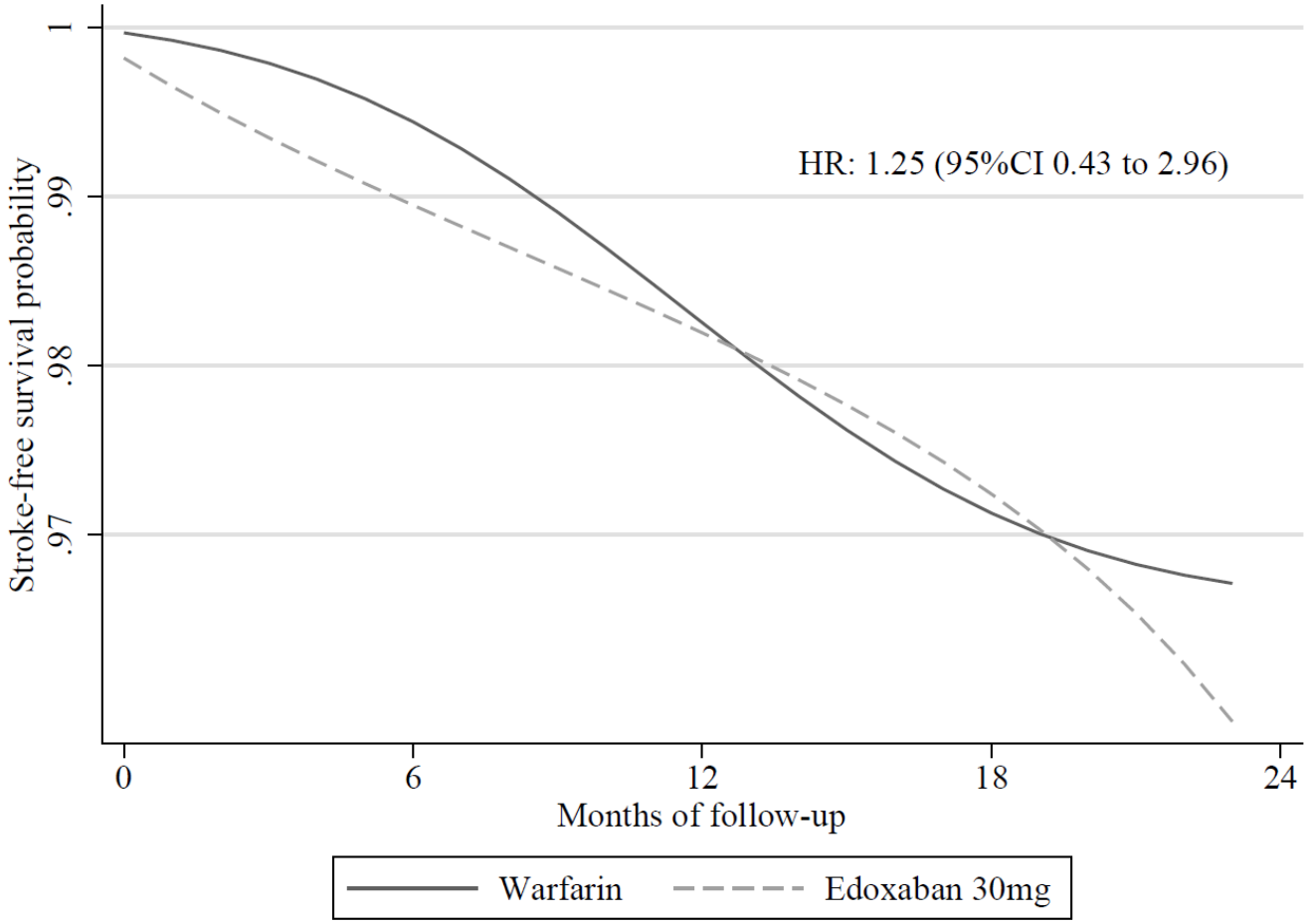
Figure 1: Flowchart of the study population



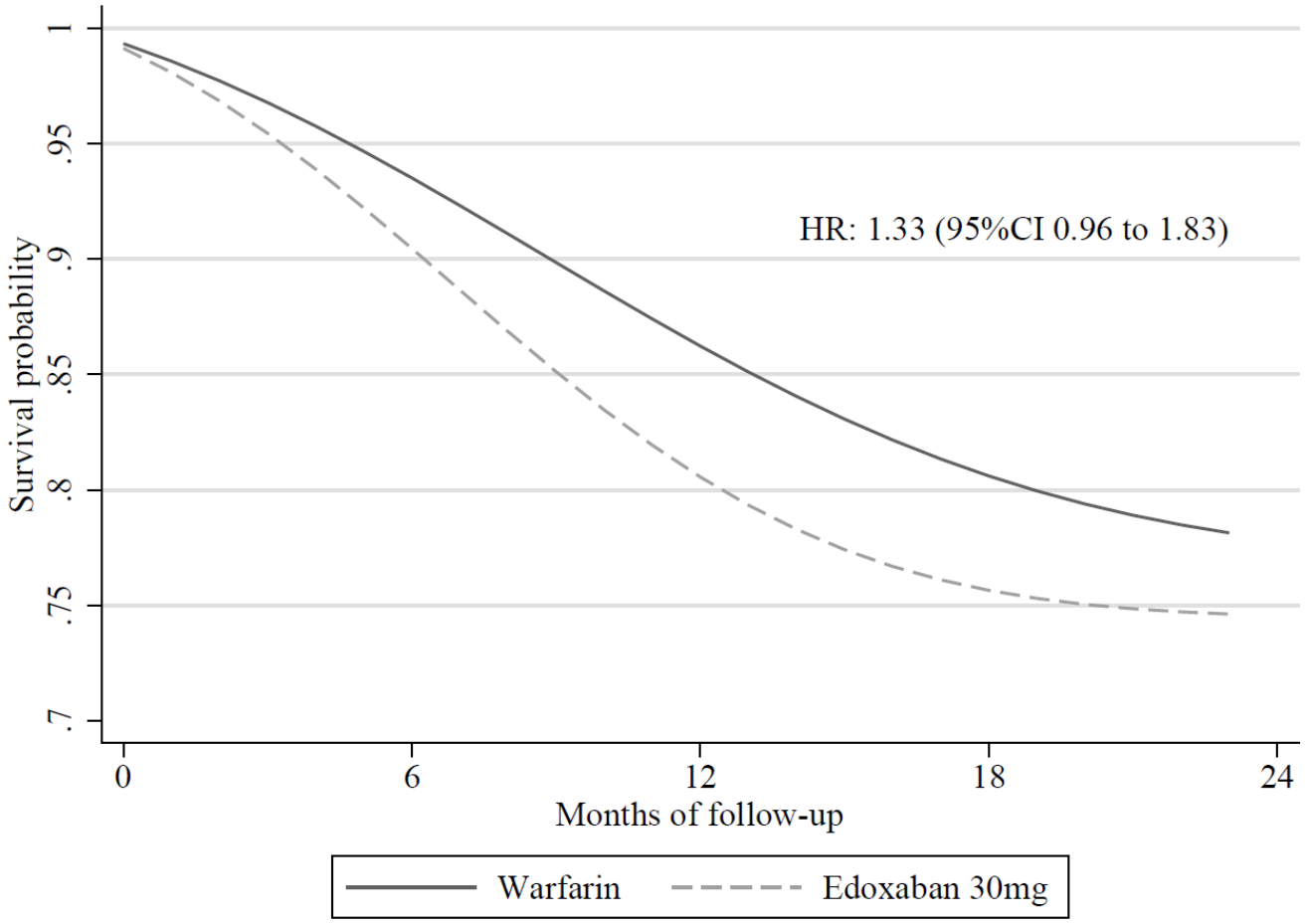
Supplemental Figure 2: Propensity score plot for edoxaban 30mg and warfarin users



Supplemental Figure 3: Standardized event free survival curves of thromboembolism after propensity score matching



Supplemental Figure 4: Standardized survival curves for all-cause mortality after propensity score matching



Supplemental Figure 5: Standardized event free survival curves of bleeding outcome after propensity score matching