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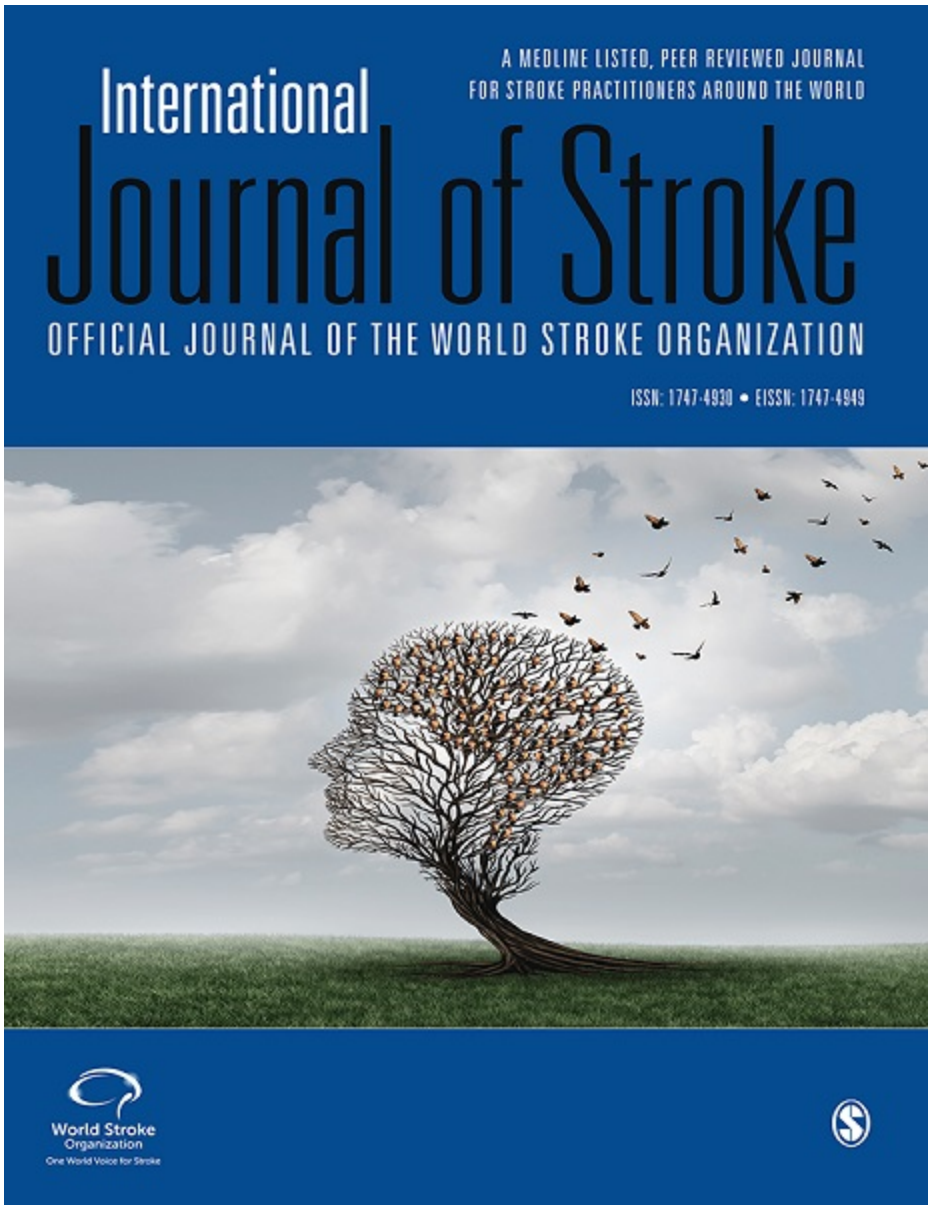

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Comparative effectiveness and safety of edoxaban vs warfarin in patients with atrial fibrillation: A nationwide cohort study

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Abstract (294 words)

Background and purpose: The effectiveness and safety of edoxaban 60 mg and 30 mg for stroke prevention compared with warfarin in patients with atrial fibrillation (AF) has not been well-described in a nationwide cohort of Caucasian patients treated in standard clinical practice.

Methods: We used Danish nationwide registries to identify patients with AF during June 2016 and November 2018 who were treated with edoxaban or warfarin and computed rates per 100 person-years of thromboembolic, all-cause mortality, and bleeding events using an inverse probability of treatment weighting approach to account for baseline confounding. We used weighted pooled logistic regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) comparing events between edoxaban 60 mg and warfarin users; edoxaban 30 mg was not included in formal comparisons.

Results: We identified 6451 AF patients, mean age was 72 years and 40% were females. A total of 1772 patients were treated with edoxaban 60 mg, 537 with edoxaban 30 mg, and 4142 with warfarin. The median CHA_2DS_2-VASc score was similar between warfarin and edoxaban 60 mg with a score of 3 (interquartile range [IQR] 2-4). In the inverse probability of treatment-weighted pseudo-population, the thromboembolic event rate for edoxaban 60 mg was 0.95 and 1.0 for warfarin, corresponding weighted HR of 1.00 (95% confidence intervals [CI] 0.59, 1.71). Edoxaban 60 mg users were associated with lower rates of all-cause mortality (3.93) compared to warfarin (6.04), with a HR of 0.64 (95% CI 0.47 to 0.88). The event rates for bleeding were 3.36 and 3.14, respectively; HR 1.09 (95% CI 0.77, 1.57)

Conclusion: Edoxaban 60 mg is a safe and effective treatment compared with warfarin for stroke prevention in routine clinical care for white European patients with AF, with non-significantly different risks for stroke and clinically relevant bleeding, but lower all-cause mortality.

Non-standard Abbreviations and Acronyms

AF: Atrial fibrillation

OAC: Oral anticoagulant

DOAC: Direct oral anticoagulants

CI: Confidence intervals

CHA_2DS_2-VASc: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Sex category

eGFR: estimated glomerular filtration rate

HAS-BLED: Hypertension, Abnormal liver or renal function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol

IQR: Interquartile range

SD: Standard deviation

HR: Hazard ratio

RR: Relative risk

LVD: Left ventricular dysfunction

NSAID: Nonsteroidal anti-inflammatory drugs

INTRODUCTION

Atrial fibrillation (AF) affects more than 44 million individuals worldwide [1], and patients with AF are at several-fold increased risk of stroke compared with individuals without AF [1]. Oral anticoagulant (OAC) therapy is effective for reducing the risk of stroke [2].

The direct oral anticoagulants (DOACs) continuously replace vitamin K-antagonists for stroke prevention in AF [3–7]. Despite similar indications, the individual DOACs have important differences including renal excretion and liver metabolism, once daily vs twice daily dosing, and indications for dose reductions [8].

Edoxaban was marketed in Denmark in June 2016, which was up to four years later than other DOACs. In the ENGAGE AF-TIMI 48 trial, the two edoxaban one daily dose regimes (30 mg and 60 mg) was noninferior compared with warfarin (dose adjusted) for prevention of stroke or systemic embolism, and was additionally associated with significantly lower bleeding rates [9]. Meta-analyses of randomized controlled trials have shown similar results [10–12]. Observational studies evaluating the effectiveness and safety of edoxaban in standard clinical practice compared with warfarin have been conducted primarily in Asian AF populations [13,14], with limited data from Europe.

We therefore used Danish nationwide registries to compare the effectiveness and safety of edoxaban with warfarin for stroke prevention in a cohort of patients with AF.

METHODS

This was an observational cohort study based on registry data of Danish residents who claimed a prescription of warfarin or edoxaban between June 2016 and November 2018. Please see supplemental Table 1 and supplemental methods for details on data sources.

Study population and exposure

Individuals with a record of claiming a prescription of edoxaban or warfarin for stroke prevention after AF diagnosis between June 2016 through December 2018 was considered for inclusion. Individuals were screened for a hospital diagnosis (inpatient or outpatient) of AF before the first prescription claim or up to 30 days after. Patients with a record of mitral stenosis or heart valve replacement were excluded. Similarly, patients with an estimated glomerular filtration rate (eGFR; using the Chronic Kidney Disease Epidemiology Collaboration formula) <15 ml/min/1.73m^2, dialysis treatment, or chronic kidney disease were excluded. Patients identified as receiving continuous warfarin treatment at the time of study start were excluded. Finally, we excluded patients with a record of an outcome event within the first month after first OAC prescription to ensure that outcomes would occur under the studied treatment exposure. The index date was therefore defined at the time of treatment initiation, while outcome analyses commenced 30 days after first prescription claim.

The study population was stratified according to first treatment claim, i.e. warfarin, edoxaban 60 mg, or edoxaban 30 mg. Patients claiming a prescription were assumed in continuous treatment throughout follow-up.

Comorbidities and comedications

We obtained information from the Danish registries on history of comorbidities at index date. Use of medication within 365 days before index. We combined covariate information into modified

HAS-BLED scores (the L component of labile INR values was not included) as a measure of baseline bleeding risk, and CHA_2DS_2-VASc scores to ascertain the risk of stroke in individuals. The Danish National Laboratory Registry was used to categorize renal function measured by (eGFR); the most recent available measurement was included in this characterization: the median time from index date to most recent measurement was 7 days, interquartile range (IQR) 2 to 39 days.

Endpoints and follow-up

The study cohort was followed in the registries for up to two years. Only hospital-based primary diagnoses were included for outcome analyses to increase the validity of the coded diagnoses. The primary effectiveness outcome of thromboembolism was comprised by a composite of ischemic stroke, unspecified stroke, and systemic embolism. The safety outcomes were a composite endpoint of clinically relevant bleedings events leading to hospital contact, including intracranial bleeding, gastrointestinal bleeding, and major bleeding in other anatomic sites. All-cause mortality was investigated as an independent endpoint, since some of the studied outcomes may be fatal and therefore not recorded with diagnosis code at the hospital. All patients were followed from the index date to ascertain thromboembolism or bleeding events, with censoring at emigration, death (if not the outcome), or 31 December 2018, whichever came first.

Statistical analysis

Descriptive characteristics at the index date were provided as proportions for discrete variables and means and standard deviations (SD) for continuous variables. We calculated event rates as the number of events divided by person-time stratified by treatment exposure group.

Because of the non-randomized study design, differences in prognostic factors between exposure groups may bias the comparative treatment effectiveness and safety estimates. The analytic approach to establish comparative cohorts was based on an inverse probability treatment weighting

approach, as done previously [15]. The weights were obtained using boosted regression trees including the following covariates to predict treatment exposure groups: 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).

When inspecting the propensity scores for sufficient overlap, we observed poor overlap for edoxaban 30 mg vs the other two treatment alternatives. Post-hoc, we therefore decided not to include edoxaban 30 mg in the formal comparative effectiveness and safety analyses. However, to allow for comparison of warfarin vs edoxaban 30mg, we conducted an unplanned propensity score matched analysis. Specifically, we estimated the average treatment effect among the edoxaban 30mg treated patients vs a matched group of warfarin users (control). Additional details and results are reported in supplemental materials.

The comparative effectiveness and safety analysis of edoxaban 60 mg vs. warfarin was based on the intention to treat approach, and contrasts between exposure groups were estimated by means of weighted pooled logistic regression models [16]. The calculated weights were applied to ascertain the average treatment effect in the population and reported as hazard ratios (HRs) with warfarin being the reference. In detail, we fit weighted pooled logistic regressions including a categorical variable for treatment groups, and months of follow-up as a linear and a quadratic term. The survival curves depict the hypothetical situation had the entire population received warfarin treatment and had the entire population received edoxaban 60 mg [17]. Please see supplemental information for additional details on the modelling approach and description on sensitivity analyses.

RESULTS

We identified a total of 16960 patients who initiated edoxaban or warfarin during 2016 through November 2018. After applying exclusion criteria, 6451 were eligible for the study: 4142 were treated with warfarin, 1772 with edoxaban 60 mg, and 537 with edoxaban 30 mg (see supplemental Figure 1). The population mean age was 72 years and 40% were females. The baseline characteristics from the unweighted cohort are shown in Table 1. The median CHA_2DS_2-VASc score was similar between warfarin and edoxaban 60 mg with a score of 3 (IQR 1-3), but higher among edoxaban 30 mg, median score of 4 (IQR 3-6). The eGFR was markedly lower among edoxaban 30 mg users, with a mean eGFR of 53.3 ml/min/1.73m^2 After applying IPTW, the baseline differences in the pseudo-population were minor when comparing warfarin and edoxaban 60 mg, and absolute standardized differences were less than 0.1 for all measured covariates.

Risk of thromboembolism

During follow-up, we observed a total of 89 thromboembolic events: 60 among warfarin users, 21 for edoxaban 60 mg, and 8 among edoxaban 30 mg (Table 2). The corresponding crude (unweighted) event rates per 100 person-years were 0.97, 1.25, and 1.66, respectively.

In the IPTW pseudo-population, event rates were 1.0 for warfarin and 0.95 for edoxaban 60 mg. The median follow-up time was 10 months (IQR 5-16) for warfarin and 7 months (IQR 4-12) for edoxaban 60 mg. The comparative effectiveness analysis comparing warfarin with edoxaban 60 mg showed a similar risk for thromboembolism with a HR of 1.00 (95% confidence intervals [CI] 0.59 to 1.71). Figure 1 shows the standardized survival curves free from thromboembolic events representing what would have occurred had the entire population received either of the two treatment options.

All-cause mortality

All-cause mortality was the most common outcome in the study population with an overall rate of 6.69 (total of 560 deaths). All-cause mortality was markedly higher among edoxaban 30 mg users with a rate of 19.54, while it was 6.45 for warfarin, and 3.86 for edoxaban 60 mg.

Comparative analyses showed that edoxaban 60 mg had a lower risk compared to warfarin, HR of 0.65 (95% CI 0.47 to 0.88) (Table 2). Of note, the risk of all-cause mortality visualized in Figure 2 showed the two curves separating early, but also that the absolute risk of events differed little despite the statistically significant HR. Analyzing the composite outcome of all-cause mortality and thromboembolism resulted in a HR of 0.71 (95% CI 0.54 to 0.95).

Risk of bleeding

We observed a total of 256 clinically relevant bleeding events during two years of follow-up: 188 events among warfarin users, 55 for edoxaban 60 mg, and 13 for edoxaban 30 mg. The event rates for bleeding outcomes were 3.12 for warfarin, 3.33 for edoxaban 60 mg, and 2.71 for edoxaban 30 mg (Table 2). Intracranial bleeding events were rare with event rates below 0.40, and the event rate for gastrointestinal bleeding was 1.27 (see Supplemental Table 2).

In the weighted cohort of warfarin vs edoxaban 60 mg, the event rates for bleeding were 3.14 and 3.36, respectively. The HR from the comparative safety analysis was 1.09 (95% CI 0.77 to 1.57). Figure 3 shows the standardized bleeding free survival curves for both treatment options.

Subgroup analyses

Detailed results from all subgroup analyses are presented in Supplemental Table 3. Among OAC naïve patients, the risk of thromboembolism mirrored the main analysis with a HR of 0.99 (95% CI 0.47 to 2.08) and similarly for the bleeding outcome with a HR of 1.10 (95% CI 0.71 to 1.71), and all-cause mortality, HR of 0.58 (95% CI 0.37 to 0.89).

Among patients age 75 years or older, the mean age was 82 years (SD 5.0) among warfarin users and 81 years (SD 5.0) among edoxaban 60 mg users. The HRs for thromboembolism and all-cause mortality was similar to the main analysis, and the (non-significant) HR for bleeding was 1.42 (95% CI 0.89 to 2.28).

Restriction to patients at very high stroke risk, i.e. a CHA_2DS_2-VASc score of 4 or higher, there was a non-significant higher hazard for thromboembolism among edoxaban 60 mg users: HR of 1.22 (95% CI 0.66 to 2.26), while HRs for all-cause mortality and bleeding were similar as reported in the main analysis.

In the subgroup of patients with some degree of affected renal function, the mean eGFR was 66.2 ml/min/1.73m^2 (SD 17.1) among warfarin users, and 71.5 ml/min/1.73m^2 (SD 11.98) among edoxaban 60 mg users. The relative risk of comparative outcomes was similar to that of the main analysis.

Sensitivity analyses

Overall, the obtained results remained robust when analyzed in different analytic approaches. When restricting the outcome of bleeding events to primary diagnoses leading to hospitalization, the number of events were lower in the two exposure groups, but the HR was consistent with the main analysis: HR of 1.06 (95% CI 0.77 to 1.47). Examining competing risk of death on the outcome of thromboembolism did not change our treatment effectiveness estimates [data not shown]. In the exploratory analysis, risk factors strongly associated with all-cause mortality were heart failure and a cancer diagnosis within the last three years. When performing an additional post-hoc analysis restricting the population to patients without these clinical characteristics, this did not materially change the HR point estimate for all-cause mortality comparing warfarin and edoxaban 60 mg, HR of 0.73 (95% CI 0.48 to 1.10). The formal comparative outcome analyses between edoxaban 30mg

vs warfarin using propensity score matching are reported in supplemental materials: supplemental Figure 2 displays the propensity score overlap after matching, and supplemental Table 4 summaries patient characteristics in the matched cohort. The propensity score match HR of thromboembolism was 1.25 (95% CI 0.43 to 2.96); HR for bleeding was 0.57 (95% CI 0.28 to 1.15); and all-cause mortality HR was 1.33 (95% CI 0.96 to 1.83), please see supplemental Figure 3-5 for standardized survival curves for each outcome.

DISCUSSION

In this large, nationwide comparative effectiveness and safety study of edoxaban vs. warfarin for stroke prevention in Danish routine clinical care for patients with AF, we found that edoxaban 60 mg was a safe and effective treatment compared with warfarin, with non-significantly different risks for stroke and clinically relevant bleeding, but lower all-cause mortality and the composite outcome of 'all-cause mortality and thromboembolism'. This was evident irrespective of various sensitivity analyses.

The observed thromboembolic event rates and relative risks are largely comparable with previous studies documenting comparable effectiveness of edoxaban for stroke prevention in AF [9,10,12]. For example, a meta-analysis of randomized trials demonstrated similar relative risk for stroke (relative risk (RR) =1.00, 95% CI: 0.90-1.11), systemic embolic events (RR=1.00, 95% CI: 0.67 to 1.49), and adverse bleeding events (RR= 1.00, 95% CI: 0.91 to 1.0) [12]. Bleeding rates per 100 person-years in our study were also similar at 3.36 for edoxaban 60 mg and 3.14 for warfarin. Bleeding associated with edoxaban in standard clinical practice has been shown to mainly consist of minor or clinical relevant non major bleeding [18]. We also demonstrated similar bleeding risks in our

sensitivity analysis restricted to bleeding events leading to hospitalization, HR of 1.06 (95% CI 0.77 to 1.47) compared with the relative risk of 0.90 (95% CI 0.82 to 0.98) in the ENGAGE-AF-TIMI 48 trial comparing edoxaban with warfarin [19].

In the present study, we show a significant reduction in all-cause mortality and the composite of 'all-cause mortality and thromboembolism'. In the historical randomized trials, warfarin reduced all-cause mortality by 26% compared to placebo/control and in the meta-analysis by Ruff et al. of the randomized trials, DOACs were associated with 10% lower mortality compared to those allocated to warfarin [20,21]. In the randomized trials, outcome events are adjudicated by an events committee and cerebral scanning or post-mortems used to confirm a stroke diagnosis. In data obtained from routine clinical practice, there is rarely adjudication of events, nor mandatory postmortems, so some deaths could be due to (undiagnosed) fatal strokes.

Rates of intracranial hemorrhage was generally low in both edoxaban and warfarin treated patients. In the randomized trials, there was a clear class-effect of DOACs with significant reduction in intracranial hemorrhage compared with warfarin [21], an observation supported by numerous studies based on data from routine clinical practice [22,23]. Hence, the low risk of clinically relevant bleeding or intracranial hemorrhage, and our reduction of the composite of 'all-cause mortality and thromboembolism' supports the beneficial effectiveness and safety profile of edoxaban.

Our data are generally consistent with real world data from Asia, showing better effectiveness and safety with edoxaban compared to warfarin as well as improved safety compared to some DOACs [24].

Strengths and Limitations

Our study was based on a large, nationwide cohort of patients with AF and a prescription for edoxaban or warfarin who were treated in a uniformly organized healthcare system. Our ability to

identify patients in these registries, in a national setting with free access to health care, and to track individuals enabled unselected patient inclusion and complete follow-up [25].

Due to the registry-based study design, we lacked information on drug adherence and persistence, quality of VKA treatment. Therefore, and by design, the study could not inform on outcomes based on an on-treatment analytic strategy. Our comparative analysis was based on weighted populations, which accounted only for observed imbalances between the treatment groups. For bleeding events, we used hospital diagnoses without specification of extent and severity of the bleeding events, and the validity of bleeding codes in the DNPR may vary with bleeding side and severity [26].

Conclusion

Edoxaban 60 mg is a safe and effective treatment compared with warfarin for stroke prevention in routine clinical care for Danish (mainly Caucasian) patients with AF, with non-significantly different risks for stroke and clinically relevant bleeding, but lower all-cause mortality and the composite of all-cause mortality and thromboembolism with edoxaban 60 mg.

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Disclosures

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lip has served as a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and Speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. Dr Nielsen has received consulting fees from Bayer and Daiichi-Sankyo, and grant support from Bristol-Myers Squibb/Pfizer and Daiichi-Sankyo. Dr Søgaard has received consultant fees from Bayer. Other authors report no conflicts.

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Table 1: Characteristics of patients with atrial fibrillation according to treatment regimen with warfarin (dose adjusted), edoxaban 60 mg, and edoxaban 30 mg.

Patient characteristics	Warfarin	Edoxaban 60 mg	Edoxaban 30 mg
No.	4142	1772	537
Women % (N)	38.1 (1577)	38.6 (684)	64.6 (347)
Age, mean (SD)	70.6 (12.0)	72.2 (9.5)	82.8 (8.2)
Ischemic stroke	9.0 (371)	10.4 (185)	16.0 (86)
Hypertension	55.7 (2309)	60.2 (1066)	67.6 (363)
Heart failure or LVD	26.8 (1108)	22.3 (396)	40.2 (216)
Diabetes	15.5 (640)	16.0 (284)	18.4 (99)
Ischemic heart disease	24.3 (1005)	22.9 (406)	31.3 (168)
Intracranial bleeding	0.9 (38)	1.0 (18)	1.1 (6)
Gastrointestinal bleeding	3.2 (134)	3.3 (58)	4.5 (24)
Median CHA_2DS_2-VASc score (IQR)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-5.0)
Score 0-2	43.3 (1795)	39.3 (696)	8.6 (46)
Score 3-5	47.8 (1979)	53.4 (946)	68.2 (366)
Score >5	8.9 (368)	7.3 (130)	23.3 (125)
Median HAS BLED	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (2.0-3.0)

score (IQR)			
Score 0-1	33.6 (1390)	26.7 (474)	18.2 (98)
Score 2-3	55.0 (2278)	62.8 (1113)	64.4 (346)
Score >3	11.4 (474)	10.4 (185)	17.3 (93)
Cancer (ever)	18.6 (772)	21.0 (373)	27.7 (149)
Cancer diagnosed within 3 years	9.8 (406)	9.7 (171)	12.1 (65)
Mean creatinine clearance, ml/min/1.73m^2 (SD)	72.2 (20.1)	75.5 (14.5)	53.3 (18.9)
Medication			
OAC naïve	69.6 (2883)	46.0 (815)	36.3 (195)
Warfarin	0	33.0 (584)	41.0 (220)
Apixaban	8.8 (364)	4.0 (70)	5.0 (27)
Dabigatran	6.4 (267)	6.4 (114)	6.0 (32)
Rivaroxaban	11.7 (485)	5.2 (93)	5.0 (27)
Aspirin	25.9 (1073)	19.9 (353)	22.0 (118)
Clopidogrel	9.1 (375)	7.6 (135)	9.9 (53)
Proton-pump inhibitors	29.5 (1222)	29.0 (513)	33.0 (177)

Beta blocker	67.3 (2786)	65.6 (1163)	70.0 (376)
Non-loop diuretic	33.0 (1366)	35.3 (625)	44.1 (237)
Calcium channel blocker	27.8 (1152)	31.7 (561)	33.0 (177)
Renin-angiotensin inhibitor	48.2 (1998)	51.6 (914)	55.1 (296)
NSAID	19.5 (809)	16.8 (298)	9.5 (51)

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

Table 2: Number of events, crude and inverse probability of treatment weighted event rates for studied outcomes.

Outcome	Number of events	100 Person-years	Crude event rate	IPT weighted event rate	Hazard ratio (95% CI)
Thromboembolism	89	83.13	1.07		
Edoxaban 60 mg	21	16.75	1.25	0.95	1.00 (0.59 to 1.71)
Warfarin	60	61.55	0.97	1.00	Reference
Bleeding	256	81.64	3.14		
Edoxaban 60 mg	55	16.50	3.33	3.36	1.09 (0.77 to 1.57)
Warfarin	188	60.34	3.12	3.14	Reference
All-cause mortality	560	83.72	6.69		
Edoxaban 60 mg	65	16.85	3.86	3.93	0.64 (0.47 to 0.88)
Warfarin	400	62.00	6.45	6.04	Reference

IPT: Inverse probability treatment. CI: Confidence intervals.

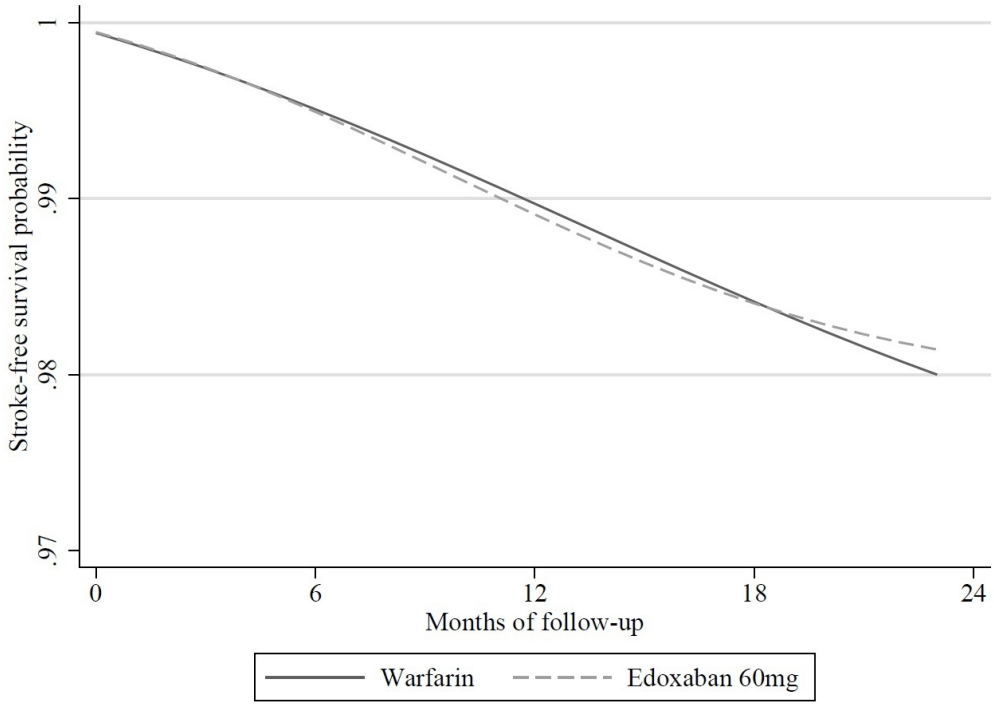

Figure 1: Standardized event free survival curves of thromboembolism

332x233mm (96 x 96 DPI)

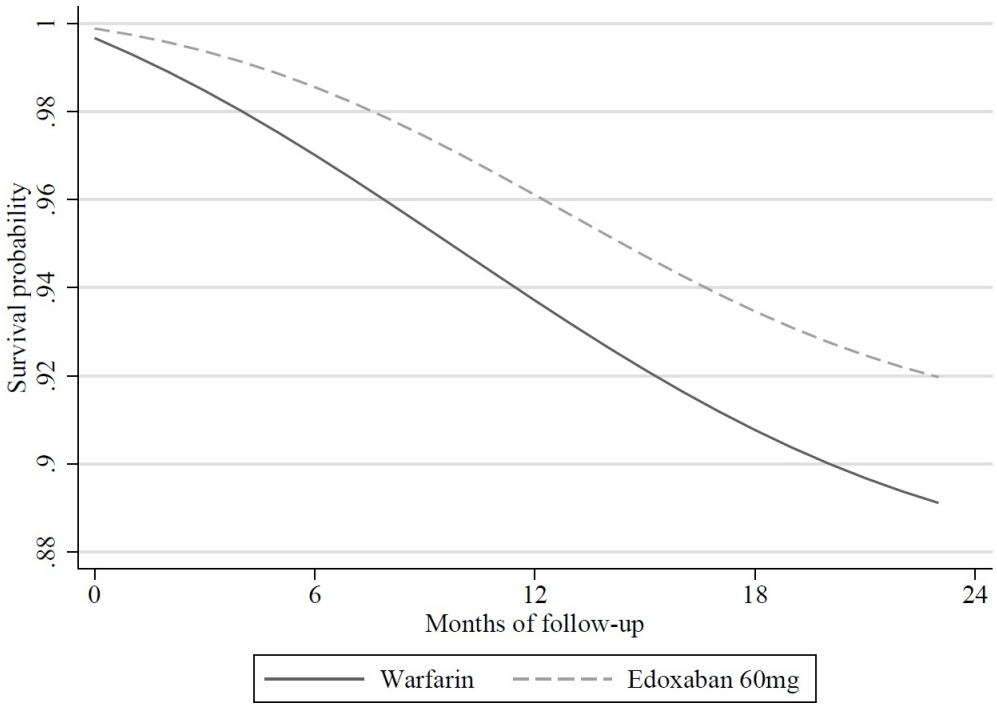

Figure 2: Standardized survival curves for all-cause mortality

330x233mm (96 x 96 DPI)

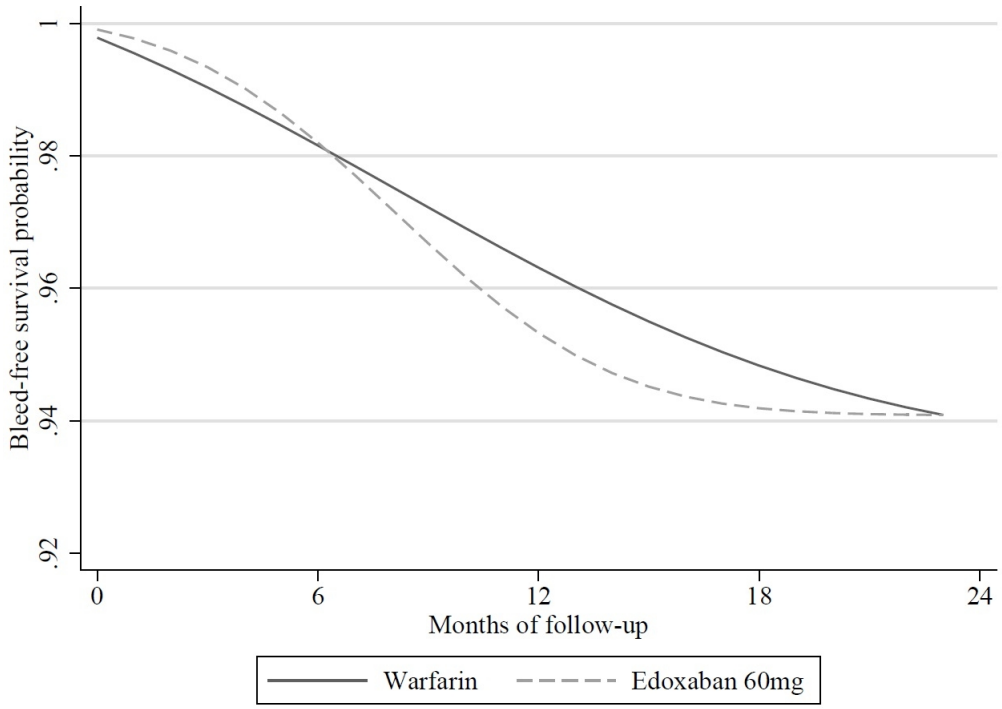

Figure 3: Standardized event free survival curves of bleeding outcome

330x235mm (96 x 96 DPI)