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Effectiveness and safety of edoxaban in patients with atrial fibrillation: data from the Danish nationwide cohort

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Abstract

Aim: Edoxaban treatment for stroke prevention in atrial fibrillation (AF) has mainly been investigated in randomized controlled trials, and data reflecting clinical practice are limited. We ascertained the clinical effectiveness and safety of edoxaban 30mg and 60mg once daily among Danish patients with AF.

Methods and results: This was an observational study based on Danish nationwide registries collecting information for administrative purposes. From June 2016 through November 2018 we identified 3,405 patients initiating edoxaban. After exclusions, 2,285 AF patients were followed for the effectiveness outcome of thromboembolism (ischemic stroke and/or systemic embolism) and bleeding outcomes (composite of major bleeding, gastrointestinal bleeding, and intracranial hemorrhage), as well as bleeding requiring hospitalization. Population mean age was 75 years and 43% were female; 643 patients received the 30mg edoxaban dosage regimen and 1,642 initiated 60mg edoxaban. During follow-up, we observed 41 thromboembolic events and 89 bleeding events of which 40 events required hospitalization. Among patients with 30mg edoxaban the rate (per 100 person-years) of thromboembolism was 2.07 versus 1.62 for 60mg edoxaban. Rates of bleeding were similar for the two dosages at approximately 3.85. Bleeding requiring hospitalization occurred at a rate of 1.74 for 30mg edoxaban and 1.69 with 60mg edoxaban.

Conclusion: In this nationwide cohort of Caucasian AF patients treated with edoxaban for stroke prevention, the clinical effectiveness and safety was in line with data from the ENGAGE AF-TIMI 48 trial. Studies investigating comparative effectiveness and safety for edoxaban in comparison with other choices of antithrombotic treatment options are needed.

Keywords: Edoxaban, atrial fibrillation, anticoagulant treatment, stroke

Introduction

Stroke prevention is central to the clinical management of patients with nonvalvular atrial fibrillation (AF).[1] Four different non-vitamin K antagonist oral anticoagulants (NOACs) have shown non-inferiority or superiority in randomized clinical trials for efficacy when compared to warfarin, but with an appealing safety profile largely driven by lower risk of intracerebral haemorrhage.[2] Since the market entry of NOACs, the prescribing physicians now have a range of treatment options where individual patient characteristics can be factored into the treatment choice(s), as reflected in recent guidelines.[3–5]

Despite similar indications for stroke prevention in AF, the NOACs have drug-drug differences including different degree of elimination through renal excretion, volume of distribution, hepatic metabolism, cytochrome P-450 enzymatic system, once daily vs twice daily dosing, and indications for dose reductions. Given the availability of different NOACs, prescribers should be able to fit the drug to the patient characteristics allowing targeted/individualized effective stroke prevention in patients with AF.[3]

Edoxaban is a factor Xa-inhibitor similar to apixaban and rivaroxaban, and received indication for stroke prevention in AF in Denmark in June 2016 – approximately four years after the other agents in this class of drugs. Edoxaban is prescribed once daily in 60mg, while dose reduction to 30mg once daily is needed in patients with one or more of the three following characteristics: a creatinine clearance between 15-50mL/min; bodyweight ≤60kg; concurrent use of certain P-glycoprotein inhibitors. Previous observations from Denmark have indicated a niche use, e.g. the majority of patients being experienced oral anticoagulant users (either with warfarin or another NOAC).[6,7] Additionally, edoxaban users had higher prevalence of prior bleeding events, and more often chronic kidney failure compared with users of other NOAC agents.

Published studies evaluating effectiveness and safety of edoxaban in AF patients have mostly investigated Asian populations or very small Caucasian populations.[8–11] Currently, there is a paucity of evidence on data reflecting clinical practice in Caucasian AF patients. Therefore, we aimed to assess the effectiveness and safety of edoxaban in a mainly Caucasian population using data from the well-validated Danish nationwide registries.

Methods

This was an observational cohort study based on data from the Danish nationwide administrative registries holding quality data available for epidemiological research. This study was approved by the Danish Data Protection Agency (ref. Northern Region of Denmark, 509-00006). Ethics approval is not required for registry-based studies in Denmark, and Danish data legislation only allows access to data by authorized researchers in Danish public health research.

Data sources and study population

We used the Danish nationwide registries that continuously collect data for administrative purposes. In this study, four registries were cross-linked using a unique identifier to obtain demographic and clinical characteristics of incident edoxaban users. Specifically, we used the Danish National Patient Register that contains discharge diagnoses for hospital admissions defined in terms of International Classification of Diseases revision 10 [ICD-10].[12] The Danish National Prescription Registry records purchase date, Anatomical Therapeutic Chemical [ATC] classification code, and package details for prescription purchases.[13] The Danish Civil Registration System holds information on sex, date of birth, vital and emigration status.[14] The Danish National Laboratory Registry accumulating clinical biochemical and immunological measurements since 2013 based on the international NPU coding (Nomenclature for Properties and Units).[15] The data coverage for this registry was approximately 80% for all laboratory measurements claimed in Denmark (data from the Middle Region of Denmark are currently not available).

Patients with AF considered for inclusion were incident edoxaban users from July 1st 2016 through November 1st 2018. In details, we identified all individuals claiming an edoxaban (ATC: B01AF03) prescription in the designated period, and characterized the patient at the date of first purchase (baseline

date). We excluded patients with migration status within the last year to allow for sufficient lookback period. Additional exclusion criteria were: i) prior venous thromboembolism (VTE) defined as one diagnosis within one year, or two or more VTE diagnoses using full lookback period; ii) no hospital AF diagnosis before baseline or up to 30 days after edoxaban initiation; iii) use of edoxaban dosage not approved for the AF indication (i.e. other dosages than 30mg/60mg), see supplemental Figure 1 for study population flowchart.

Demographics and clinical characteristics

Baseline comorbidities were ascertained from hospital diagnoses using the full lookback period available; baseline medication use was ascertained from prescription claims within the year before edoxaban initiation. Both primary and secondary discharge codes in either in-hospital or ambulatory settings were extracted (codes from emergency wards were not considered due to poor positive predictive values). Concurrent medication use was defined by at least one claimed prescription within the last year prior to baseline. Medication for nearly all chronic diseases are subsidized in Denmark, hence virtually any medical treatment involving general practice is covered by data captured in the Danish National Prescription Registry. The individual CHA_2DS_2-VASc score was calculated using information on comorbidities using complete hospital records history; concomitant medication during the preceding year was obtained at baseline, as done previously.[16] Data on kidney function were obtained by records in the Danish National Laboratory Registry to derive the individual estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[17] We included one record of kidney function between three months before and up to seven days after baseline. If more than one measurement was available, we used the measurement closest to

the baseline date. Cut-off values for eGFR were defined as 15-29mL/min/1.72m^2, 30-49mL/min/1.72m^2, and >49mL/min/1.72m^2, or 'missing' if data was not available.

Follow-up and outcomes

Patients were followed up in the Danish National Patient Registry. The primary effectiveness outcome of thromboembolism was comprised by a composite outcome of ischemic stroke and systemic embolism. For this outcome, we only considered hospital record codes at the primary position (i.e. the reason for hospital contact) to increase the validity of the coding.[18,19] The safety outcomes were a composite of all bleedings including intracranial bleeding, gastrointestinal bleeding, and major bleeding in other anatomic sites (supplemental Table 1). The safety outcomes were based on hospital records of the codes in both the primary and secondary position. To allow for a thorough clinical perspective of the safety outcome, we also investigated the primary safety outcome in conjunction with hospitalization ('bleeding requiring hospitalization'). All-cause mortality was investigated as an independent endpoint, and stratified according to patient's status on cancer diagnosis within three years before initiation of edoxaban treatment, realizing that cancer (whether active or cured) is associated with mortality.

Statistics

We provided descriptive characteristics at the time of first prescription claim as proportions for discrete variables and means and standard deviations (SD) for continuous variables and stratified by exposure to 30mg edoxaban or 60mg edoxaban. For outcome analyses, we used time-to-event data to examine the associated risk of outcomes under edoxaban treatment. These were calculated based on the time from first prescription claim until the outcome of interest, or an administrative censoring event death (if not the endpoint of interest), emigration, end of study, whichever came first. We calculated crude event

rates per 100 person-years according to strength of first edoxaban prescription claim. In addition, the development of outcome risk over time was depicted using the cumulative incidence curve for one-year follow-up, based on the Aalen-Johansen estimator taking competing risk of death into the consideration for the absolute risk calculations. Two subgroup outcome analyses were undertaken to examine patients according to: i) status on prior oral anticoagulant use, categorized as 'OAC experienced' and 'OAC naïve'; and ii) according to age <75 years or ≥75 years. Additionally, baseline characteristics of the 23.4% of the identified patients initiating edoxaban (in both dosages) without a hospital record of AF (see Supplemental Figure 1) was also provided to allow for thorough evaluation on how edoxaban has been prescribed in Denmark (disregarding accuracy of AF coding in the hospital). Point estimates were reported with 95% confidence intervals (CIs). Analyses were performed using STATA/MP (v. 15.1).

Results

A total of 3,405 subjects initiating edoxaban from June 2016 through November 2018 were identified. After excluding patients who were not considered using edoxaban for stroke prevention in AF, 2,285 patients (43% females; mean age 75 years) were eligible for the study (Supplemental Figure 1).

Baseline characteristics

Demographic and clinical characterization of patients initiating edoxaban 30mg (N = 643) or 60mg (N = 1,642) is provided in Table 1. Patients initiating the 30mg dosage of edoxaban were more often female (56.6% vs 38.2% for 60mg edoxaban) and were older (mean age 80.5 years vs 73.0 years). The mean CHA_2DS_2-VASc score was higher among those using 30mg edoxaban (4.2 vs 3.2 points) as reflected by the comorbidity profile and medication use, including: heart failure (41.4% vs 24.5%); vascular disease (24.7% vs 17.1%); ischemic heart disease (35.1% vs 25.0%); and a higher proportion of previous bleeding episodes associated with hospital contact (26.4% vs 17.4%). The 30mg edoxaban initiators had a lower mean eGFR (53.8 mL/min vs 72.0 mL/min), were more often OAC experienced (65.3% vs 56.3%), most frequently shifting from warfarin treatment (41.5%). Among 30mg and 60mg edoxaban users, 10.1% and 9.6% used P-gp inhibitors at baseline, and 8.7% and 0.4% had an eGFR<30 at the time of initiation of edoxaban treatment. Additionally, 17.9% and 9.7%, respectively, may have had at least one indication for reduced dose edoxaban (based on baseline use of P-gp inhibitors or eGFR<30). The overall median time of follow-up was 0.95 (IQR: 0.55 to 1.52) years. Approximately 21% of the patients only claimed a single prescription of edoxaban during the follow-up period.

Almost one-fourth (23.5%) had a hospital diagnosis of cancer with a median time since last hospital record of cancer of 3.5 years, and 17.5% had a cancer diagnosis within three years prior to edoxaban

initiation. The anatomical site of the cancer varied little by edoxaban dosage, expect for gastrointestinal cancer (11.6% with 30mg vs 17%) and lung cancer (9.9% vs 5.2%).

Main outcome analyses

For the effectiveness outcome of thromboembolism, we observed a total of 41 events that primarily were ischemic strokes. The cumulative incidence curves (Figure 1) show that the risk of thromboembolism occurred uniformly during the first year after treatment imitation. The corresponding event rates for 30mg edoxaban was 2.07 (per 100 person-years) and 1.62 for 60mg edoxaban users (Table 2). A total of 89 bleeding events was identified; only a few gastrointestinal or intracranial bleeding episodes were observed, while the remaining bleeding events were in other anatomical positions. The event rate of the safety outcome was very similar among those using 30mg edoxaban and 60mg with a rate of 3.87 and 3.85, respectively. As expected, event rates for bleeding leading to hospitalization were markedly lower than the overall rate of bleeding: for patients using 30mg edoxaban the rate was 1.74 vs 1.69 for those using 60mg edoxaban. The rate of all-cause mortality was markedly higher among edoxaban 30mg users: 16.48 per 100 person-years vs 6.27 among 60mg users. Importantly, the relative high all-cause mortality rate was largely driven by patients with a cancer diagnosis within the last three years and advanced age (Table 2 and Table 3). The mortality rate in these subgroups were 24.25 for 30mg users and 13.50 among 60mg users.

Subgroup analyses

Supplemental Table 2 describes the characteristics of 940 OAC naïve and 1345 OAC experienced edoxaban initiators. When analyzing the effectiveness outcome stratified by OAC experience, the rate of thromboembolism was 2.02 among OAC naïve vs 1.56 among OAC experienced; the events were distributed uniformly throughout the follow-up (Figure 2 and Table 3). Bleeding rates also differed

little when stratifying the cohort based on OAC experienced and OAC naïve (4.00 vs 3.76). Rates for bleeding leading to hospitalization were lower than the overall rate of bleeding: 1.92 for OAC naïve and 1.56 for OAC experienced. All-cause mortality were generally similar in the two strata.

Supplemental Table 3 presents baseline characteristics for patients stratified by age <75 years or age 75 years or older. Thromboembolic complications occurred at a similar rate in the two groups: 1.69 and 1.79, respectively. Bleeding rates were lowest for patients aged <75 years (2.61) and was almost twice as high in the elderly subgroup (5.00). Similarly, rates for bleeding requiring hospitalization were lowest for patients at age <75 and higher among the elderly: 1.16 and 2.21, respectively. Not surprisingly, all-cause mortality was also highest among the elderly (rate of 14.31 vs 3.18 among patients aged <75 years).

Demographic and clinical characteristics for patients with no hospital AF diagnosis (excluded from main analyses) were generally alike the study population, apart from these patients more frequently being OAC naïve (74.9%), see supplemental Table 4.

Discussion

In this large observational study of a mainly Caucasian population of Danish AF patients initiating edoxaban, our principal findings were the following: i) edoxaban 60mg was more often used than 30mg, and the latter group had a more severe comorbidity profile; ii) thromboembolic events were generally rare and the rate ranged 1.6 to 2.1 (per 100 person-years) for 60mg and 30mg edoxaban, respectively. The overall bleeding events was observed at a rate of 3.8, while bleeding events requiring hospital admission was markedly lower with a rate of approximately 1.7; iii) all-cause mortality rates were high and mainly driven by patients of advanced age and patients with a cancer diagnosis within the last three year prior to edoxaban initiation. These observed rates of effectiveness and safety outcomes were comparable with what has been reported previously for other NOAC agents using data from the Danish nationwide registries.[20,21]

Stroke prevention with edoxaban became available in Denmark in June 2016 following the results from the ENGAGE AF-TIMI 48 trial published in 2013.[22] This study was a three-arm randomized controlled trial designed to evaluate the long-term efficacy of edoxaban 60mg vs edoxaban 30mg vs warfarin (dose adjusted). In a population of 21,105 patients with AF, the study showed that edoxaban in both dose regimens was noninferior to warfarin in stroke prevention, but with significantly lower bleeding outcomes among patients randomized to edoxaban. While this was a multinational trial, the proportion of patients from Western Europe was 3,229 (15.3%).

In the ETNA-AF-Europe registry including 13,638 AF patients receiving edoxaban for stroke prevention, the mean age was 73.6 years.[23] In comparison with our study, the patients in the ETNA-AF-Europe registry were more often hypertensive (63.2% vs 76.9%), but with markedly fewer with prior ischemic stroke (19.1% vs 5.9%) and heart failure (29.2% vs 5.8%). Additionally, the study

population of this observational study were generally older than in the ENGAGE AF-TIMI 48 trial (72 years vs 75 years). Conversely, patients in the current study were less likely to have heart failure (29% vs 56%), diabetes (18% vs 36%), and prior stroke (19% vs 28%). Importantly, inclusion in the randomized trial required a $CHADS_2$ score ≥2, while the summary of product characteristics recommends at least one 'qualifying risk factor' including age ≥75 years, stroke or transient ischemic attack, heart failure, diabetes, or hypertension requiring treatment for recommending edoxaban treatment for stroke prevention in AF. These inclusion criteria formed a specific high-risk population of stroke in the ENGAGE AF-TIMI 48 trial, while the SMPC recommendations open for inclusion of patients with a lower stroke risk. On the other hand, the proportion of patients developing cancer during the ENGAGE AF-TIMI 48 trial period was relatively low (5.5%)[24], which was likely related to the exclusion criteria of cancer in the trial. In our study, the proportion of patients with recent cancer was more than three-fold higher.

In the current study thromboembolic events occurred at a rate of 1.62 for 60mg edoxaban users and 2.07 for 30mg edoxaban users. Based on these data, it is not possible to untangle if the higher rates for the lower dose edoxaban were related to a lower effectiveness because of the lower dose, or associated with the difference in thromboembolic risk and CHA_2DS_2-VASc score profile (4.2 vs 3.2). Notwithstanding this finding, the reported event rates of thromboembolism was very similar to what was observed in the composite 'stroke' outcome in the ENGAGE AF-TIME 48 trial: the rate was 1.49 for 60mg edoxaban and 1.91 for the lower dose.[22] This is reassuring and our data adds to the current evidence that edoxaban is an effective treatment for stroke prevention in Caucasians.

The bleeding rates in any anatomical position was observed at a rate of 3.85 and was similar for the two dosages. In the randomized controlled trial, the major bleeding rates (defined according to the

International Society on Thrombosis and Haemostasis) were 2.75 for 60mg edoxaban and 1.61 for 30mg edoxaban; however, for the outcome of 'clinically relevant nonmajor bleeding', the rates were 8.67 and 6.60, respectively.[22] In general, bleeding outcome data obtained from a randomized controlled trial are difficult to compare with outcome data from observational studies, since patients treated in everyday clinical practice are not monitored according to a defined trial protocol (including adjudicative event registration). However, to provide clinical perspective, we also calculated event rates for bleeding outcomes requiring hospitalization. These rates were approximately 50% lower than the primary (composite) bleeding outcome, and suggests that many of the observed bleeding events were less severe and did not require hospitalization. In a post-hoc analysis of the ENGAGE AF-TIMI 48 trial data, Aisenberg et al. reported that the occurrence of gastrointestinal bleeding was likely to be associated with the edoxaban dose.[25] We were not able to replicate this finding, which may be related to very few observations of gastrointestinal bleeding events in our cohort.

Recently, observational studies evaluating the comparative effectiveness and safety of edoxaban (and other NOACs) vs warfarin have emerged. Lee et al. studied a population of Korean patients treated with edoxaban, who were free from stroke (ischemic and hemorrhagic) and gastrointestinal bleeding at baseline.[8] During a relative short median follow-up period, they reported ischemic stroke rates at 4.06 and 2.34 for patients treated with 30mg and 60mg edoxaban, respectively. Hospitalization for major bleeding events were highest for the lower dose of edoxaban (3.19 vs 1.62 for 60mg edoxaban). When the population was matched to a warfarin treated population using a calculated propensity score, they observed a lower risk for patients treated with edoxaban in comparison with warfarin for all six studied clinical outcomes. The data from the Korean nationwide cohort suggests that the burden from AF in

terms of risk for clinical outcomes are higher among ethnic Asian patients, which has also been observed in other epidemiological investigations in Asian populations.[10,26,27]

Limitations

We used a nationwide cohort of all residents in Denmark who claimed a prescription for edoxaban to identify a cohort of patients receiving edoxaban for stroke prevention in AF. However, 24% of the identified edoxaban users did not have a clear indication for the treatment, i.e. no VTE or AF diagnose records, which are the two indications for edoxaban treatment in Denmark. Whether or not these patients have been diagnosed with AF or VTE at the general practitioner only, and therefore not captured in the Danish National Patient Registry, is unclear. Nevertheless, the validity and coding accuracy of the applied registers have been validated previously, and have sufficiently high qualities to be used for epidemiological research.[19,28,29] We did not have access to bodyweight in data, which is one of the dose reduction criteria for edoxaban. In addition, we used eGFR to ascertain the status of renal function of the studied patients. We note that the dose reduction criteria for edoxaban in relation to kidney function should be based on creatinine clearance derived from serum creatinine. The assessment of outcomes were based on an intention-to-treat approach, hence adherence to edoxaban treatment during follow-up was not factored into the analyses. The proportion of patients claiming only a single prescription of edoxaban warrants further studies on adherence and treatment persistence. We did not include a treatment comparator in our study, thus the results do not allow for comparative effectiveness and safety inference between edoxaban and other OAC treatment options. However, the observed event rates were in line with what was observed in the ENGAGE AF-TIMI 48 trial.

Conclusion

In this nationwide cohort of AF patients receiving edoxaban treatment for stroke prevention we observed clinical effectiveness and safety similar to what have been reported for other NOACs in Denmark. Edoxaban treatment in AF has been effective and safe in this Caucasian population. Additional studies are warranted to specifically assess comparative effectiveness and safety for edoxaban in comparison with other choices of antithrombotic treatment options.

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Conflicts of Interests

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 Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim and received speaking fees from Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, MSD, and AstraZeneca. Dr Nielsen has received speaking fees from Boehringer Ingelheim, consulting fees from Bayer and Daiichi-Sankyo, and grant support from Bristol-Myers Squibb/Pfizer and Daiichi-Sankyo. Dr Skjøth has received consulting fees from Bayer. The other authors report no conflicts.

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List of table and figures

Table 1: Patient characteristics according to initial edoxaban dosage prescription

Characteristics, % (N)	**60mg edoxaban**	**30mg edoxaban**	**All**	**P-value**
Number	1642	643	2285	
Demographics				
Females	38.2 (627)	56.6 (365)	43.4 (991)	<0.01
Mean age (SD)	73.0 (9.4)	80.5 (10.0)	75.1 (10.2)	<0.01
Age <65	15.8 (260)	6.4 (41)	13.2 (301)	<0.01 (diff)
Age 65-69	15.2 (249)	5.4 (35)	12.4 (284)	
Age 70-74	23.2 (381)	12.4 (80)	20.2 (461)	
Age 75-79	21.7 (357)	16.3 (105)	20.2 (462)	
Age 80-84	13.9 (228)	19.6 (126)	15.5 (354)	
Age 85-89	7.3 (120)	24.1 (155)	12.0 (275)	
Age ≥90	2.9 (47)	6.4 (41)	6.5 (148)	
Clinical characteristics				
AF diagnosed within 30 days after treatment initiation	5.4 (89)	2.3 (15)	4.6 (104)	<0.01
Median years since AF diagnosis (IQR)	2.7 (0.1-8.2)	3.5 (0.3-8.4)	3.1 (0.1-8.2)	0.03
Mean eGFR (SD) mL/min/1.73m^2	72.0 (14.2)	53.8 (19.9)	66.7 (18.0)	<0.01
eGFR >49 /1.73m^2	71.6 (1175)	40.9 (263)	62.9 (1438)	<0.01 (diff)
eGFR 30-49 /1.73m^2	4.4 (73)	29.5 (190)	11.5 (263)	
eGFR 15-29 /1.73m^2	0.4 (7)	8.7 (56)	2.8 (63)	

eGFR missing	23.6 (387)	20.8 (134)	22.8 (521)	
Chronic kidney disease	3.7 (61)	14.2 (91)	6.7 (152)	<0.01
Mean CHA_2DS_2-VASc score (SD)	3.2 (1.7)	4.2 (1.7)	3.5 (1.7)	<0.01
0 risk factors (1 for females)	4.1 (67)	0.9 (6)	3.2 (73)	<0.01 (diff)
1 risk factor (2 for females)	15.7 (257)	6.4 (41)	13.0 (298)	
2-4 risk	58.2 (955)	50.9 (327)	56.1 (1282)	
>4 risk factors	22.1 (363)	41.8 (269)	27.7 (632)	
Mean HAS-BLED score (SD)	2.3 (1.1)	2.6 (1.2)	2.4 (1.1)	<0.01
Heart failure	24.5 (402)	41.4 (266)	29.2 (668)	<0.01
Hypertension	62.4 (1025)	65.2 (419)	63.2 (1444)	0.23
Diabetes	17.1 (281)	21.3 (137)	18.3 (418)	0.02
Stroke	17.7 (290)	22.9 (147)	19.1 (437)	<0.01
Vascular disease	17.1 (280)	24.7 (159)	19.2 (439)	<0.01
CPD	15.2 (250)	20.2 (130)	16.6 (380)	<0.01
Ischemic heart disease	25.0 (411)	35.1 (226)	27.9 (637)	<0.01
CABG procedure	3.7 (60)	5.3 (34)	4.1 (94)	0.08
PCI procedure	9.1 (149)	11.2 (72)	9.7 (221)	0.13
Liver disease	-- (<5)	-- (<5)	-- (<5)	-
Prior bleeding event	17.4 (286)	26.4 (170)	20.0 (456)	<0.01

Intracerebral hemorrhage	0.9 (14)	1.4 (9)	1.0 (23)	0.25
Gastrointestinal bleeding	2.2 (36)	4.5 (29)	2.8 (65)	<0.01
Major bleeding	13.9 (229)	19.8 (127)	15.6 (356)	<0.01
Alcohol abuse	5.3 (87)	3.4 (22)	4.8 (109)	0.06
Cancer history				
Cancer diagnosis	22.2 (365)	26.7 (172)	23.5 (537)	0.02
Cancer within 3 years	16.7 (275)	19.6 (126)	17.5 (401)	0.11
Median years with cancer (IQR)†	3.56 (1.11-8.04)	3.12 (0.59-9.80)	3.51 (0.88-8.65)	0.72
Breast	12.6 (46)	11.6 (20)	12.3 (66)	0.69
Gastrointestinal	17.0 (62)	11.6 (20)	15.3 (82)	0.44
Lung	5.2 (19)	9.9 (17)	6.7 (36)	0.01
Genitourinary	21.6 (79)	21.5 (37)	21.6 (116)	0.36
Gynecological	4.4 (16)	4.1 (7)	4.3 (23)	0.81
Hematological	7.9 (29)	7.6 (13)	7.8 (42)	0.68
Metastatic or other	31.2 (114)	33.7 (58)	32.0 (172)	0.09
Oral anticoagulant treatment				
OAC Naive	43.7 (717)	34.7 (223)	41.1 (940)	<0.01
OAC Experienced	56.3 (925)	65.3 (420)	58.9 (1345)	<0.01
Warfarin	34.8 (571)	41.5 (267)	36.7 (838)	<0.01
Dabigatran	6.3 (103)	7.0 (45)	6.5 (148)	0.80
Rivaroxaban	5.8 (96)	4.4 (28)	5.4 (124)	0.88

Apixaban	3.7 (60)	5.1 (33)	4.1 (93)	0.14
Dual NOAC	2.0 (33)	2.5 (16)	2.1 (49)	0.48
Both warfarin and NOAC	3.8 (62)	4.8 (31)	4.1 (93)	0.26
Other medications				
Aspirin	20.7 (340)	19.1 (123)	20.3 (463)	0.42
Beta-blocker	53.7 (882)	63.8 (410)	56.5 (1292)	<0.01
Clopidogrel	7.9 (130)	10.4 (67)	8.6 (197)	0.06
Renin-angiotensin system inhibitors (ACEi/ARBs)	51.0 (837)	52.4 (337)	51.4 (1174)	0.55
NSAID	15.9 (261)	10.1 (65)	14.3 (326)	<0.01
Statins	44.5 (730)	47.3 (304)	45.3 (1034)	0.23
Loop diuretics	24.3 (399)	46.8 (301)	30.6 (700)	<0.01
Non-loop diuretics	35.0 (574)	39.0 (251)	36.1 (825)	0.07
CYP-PGP inhibitors	1.9 (31)	4.4 (28)	2.6 (59)	<0.01
PGP inhibitors	9.6 (157)	10.1 (65)	9.7 (222)	0.70
Proton-pump inhibitors	28.9 (475)	35.8 (230)	30.9 (705)	<0.01
Vasodilators	4.4 (73)	6.4 (41)	5.0 (114)	0.07
Calcium	30.6 (502)	32.5 (209)	31.1 (711)	0.39
Proportion of patients with one edoxaban claim*	21.6 (355)	20.2 (130)	21.2 (485)	0.50

†At least one record of cancer diagnosis within the last three years. *The study inclusion event was the only observed prescription claim of edoxaban. "--" indicates masking due few cell numbers. SD: Standard deviation.

IQR: Interquartile range. AF: Atrial fibrillation. eGFR: Estimated glomerular filtration rate. CPD: Chronic pulmonary disease. CABG: Coronary artery bypass grafting. PCI: Percutaneous cardiac intervention. OAC: Oral anticoagulant treatment. NOAC: Non-vitamin k antagonist oral anticoagulants. ACE: Angiotensin converting enzyme. ARB: Angiotensin receptor blocker. NSAID: Non-steroidal anti-inflammatory drug. CYP-PGP: Cytochrome p450 and P-Glycoproteins.

Table 2: Absolute number of outcomes and event rate per 100 person-years – stratified according to initial dosage.

	60mg edoxaban		**30mg edoxaban**	
	Number of events	Event rate (95% CI)	Number of events	Event rate (95% CI)
Thromboembolism	28	1.62 (1.12 - 2.35)	13	2.07 (1.20 - 3.56)
Ischemic stroke	26	1.51 (1.03 - 2.21)	11	1.74 (0.97 - 2.35)
Systemic embolism	<5	0.12 (0.03 - 0.46)	<5	0.31 (0.08 - 1.26)
Bleeding events	65	3.85 (3.02 - 4.91)	24	3.87 (2.60 - 5.78)
Major bleeding	55	3.25 (2.49 - 4.23)	19	3.06 (1.95 - 4.80)
Gastrointestinal bleeding	<5	0.23 (0.09 - 0.61)	<5	0.47 (0.15 - 1.46)
Intracranial bleeding	7	0.40 (0.19 - 0.85)	<5	0.47 (0.15 - 1.46)
Bleeding requiring hospitalization	29	1.69 (1.17 - 2.43)	11	1.74 (0.97 - 3.15)
All-cause mortality	109	6.27 (5.19 - 7.56)	105	16.48 (13.61 - 19.95)
All-cause mortality among patients with recent cancer*	23	13.50 (8.97 - 20.31)	20	24.25 (15.64 - 37.59)

*Cancer diagnosis within three years

Table 3: Primary effectiveness and safety outcomes in subgroup analyses

	OAC experienced		**OAC naïve**	
	Number of events	Event rate (95% CI)	Number of events	Event rate (95% CI)
Thromboembolism	19	2.02 (1.29 - 3.17)	22	1.56 (1.03 - 2.37)
Bleeding events	37	4.00 (2.90 - 5.52)	52	3.76 (2.86 - 4.93)
Bleeding requiring hospitalization	18	1.92 (1.21 - 3.04)	22	1.56 (1.03 - 2.37)
All-cause mortality	77	8.11 (6.49 - 10.14)	137	9.60 (8.12 - 11.35)
All-cause mortality among patients with recent cancer*	15	17.23 (10.39 - 28.58)	28	16.88 (11.66 - 24.45)
	Age <75 years		**Age ≥75 years**	
	Number of events	Event rate (95% CI)	Number of events	Event rate (95% CI)
Thromboembolism	19	1.69 (1.08 - 2.66)	22	1.79 (1.18 - 2.71)
Bleeding events	29	2.61 (1.82 - 3.76)	60	5.00 (3.88 - 6.44)
Bleeding requiring hospitalization	13	1.16 (0.67 - 1.99)	27	2.21 (1.51 - 3.22)
All-cause mortality	36	3.18 (2.29 - 4.40)	178	14.31 (12.35 - 16.57)
All-cause mortality among patients with recent cancer*	5	5.48 (2.28 - 13.17)	38	23.50 (17.10 - 32.30)

*Cancer diagnosis within three years

Figure 1

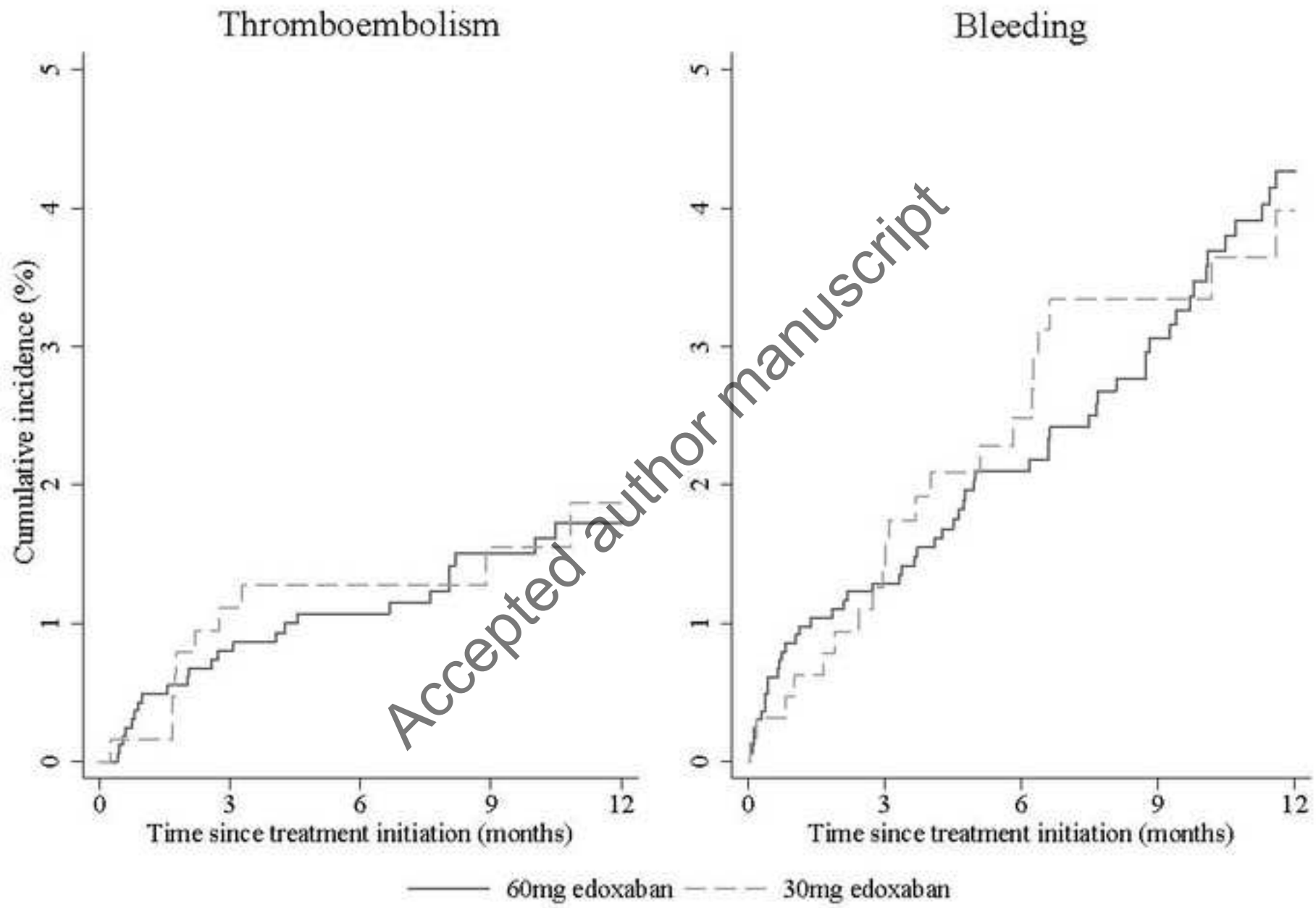

Figure 2