Original Article

Edoxaban Exposure in Patients With Atrial Fibrillation and Estimated Creatinine Clearance Exceeding 100 mL/min

Clinical Pharmacology in Drug Development
2022, 11(5) 666–674

DOI: 10.1002/cpdd.1050

Ophelia Yin[1], Tarundeep Kakkar[1], Anil Duggal[1], Masakatsu Kotsuma[1], Minggao Shi[1], Hans Lanz[2], and Michael A. Grosso[1]

Abstract

Edoxaban 60 mg is approved for stroke prevention in patients with atrial fibrillation (AF) not fulfilling any dose-reduction criteria. As edoxaban is partially renally cleared (≈50%), this study compared pharmacokinetics (PK) and pharmacodynamics of edoxaban 60 mg once daily with edoxaban 75 mg once daily in patients with AF with high renal clearance (creatinine clearance > 100 mL/min) over 12 months. Primary PK and pharmacodynamics end points were plasma edoxaban exposure and anti–factor Xa (FXa) concentration. A population PK model estimated edoxaban exposure at steady state. Efficacy and safety outcomes included composites of stroke, transient ischemic attack, systemic embolism, and major and clinically relevant nonmajor bleeding. Of 607 patients, 303 and 304 were randomized to edoxaban 60 and 75 mg, respectively. Edoxaban 75 mg provided ≈25% higher exposure than 60 mg. This increase was accurately depicted in the population PK model; anti–factor Xa concentration correlated with edoxaban exposure. Rates of composite and individual outcomes were similarly low between doses. In conclusion, the 25% increase in edoxaban dose (60-75 mg) resulted in ≈25% exposure increase in the 75-mg group. Higher exposure was not associated with reduced stroke risk in patients with AF with high renal clearance.

Keywords

anticoagulants, atrial fibrillation, hemorrhage, pharmacokinetics, stroke

Direct oral anticoagulants (DOACs)—including dabigatran, apixaban, rivaroxaban, and edoxaban—are preferred over vitamin K antagonists for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF); unlike vitamin K antagonists, DOACs do not need routine anticoagulation monitoring.[1,2] Edoxaban 60 mg once daily—dose reduced to 30 mg once daily in patients meeting dose-reduction criteria—was approved for the prevention of stroke and systemic embolic events (SEEs) based on the results of the phase 3 Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) study.[3] In this study, edoxaban was noninferior to well-managed warfarin for the prevention of stroke/SEEs and was associated with less major bleeding and cardiovascular (CV)-related death.[3] Although warfarin (specifically S-warfarin) is mainly eliminated via CYP2C9-mediated metabolism with minimal contribution of renal clearance, edoxaban, like all other DOACs, is partially eliminated via the kidney, with ≈50% renal clearance (dabigatran 80% renally cleared, rivaroxaban 35%, and apixaban 27%).[4,5] Given the high renal clearance, it was postulated that edoxaban exposure may be lower in patients with high creatinine clearance (CrCL >100 mL/min); thus, efficacy could hypothetically be lower in this subpopulation.

The impact of renal function on response to edoxaban was explored in subgroup analyses by Bohula

[1]Daiichi Sankyo Inc., Basking Ridge, New Jersey, USA
[2]Daiichi Sankyo Europe GmbH, Munich, Germany

Submitted for publication 1 September 2021; accepted 27 October 2021.

Corresponding Author:
Masakatsu Kotsuma, PhD, Daiichi Sankyo Inc., 211 Mount Airy Road, Basking Ridge, NJ 07920
(e-mail: mkotsuma@dsi.com)

[Correction added on 18 December 2021, after first online publication: In Table 3, the value in the row "Day 360" "Mean (SD)" and the column "Edoxaban 75 mg Once Daily (n = 292)" "Before Dosing" has been updated.]

et al of the ENGAGE AF-TIMI 48 study (ENGAGE AF).[6] It was noted that in patients with AF with CrCL > 95 mL/min, there was a trend toward decreased relative efficacy of edoxaban 60 mg once daily compared with warfarin (stroke/SEE hazard ratio 1.36; 95%CI, 0.88-2.10; $P = 0.17$), although the absolute event rate in the edoxaban 60-mg subgroup was low (1.1%/year).[6] However, it is important to note that in the ENGAGE AF study, patients in the warfarin treatment group with high CrCL had substantially lower ischemic stroke event rates than, and not consistent with, the published warfarin ischemic stroke event rates in this subpopulation in the other 3 major DOAC AF pivotal trials.[3,7–10] Thus, the observed unfavorable hazard ratio for the stroke event rate in ENGAGE AF in patients treated with edoxaban 60 mg once daily relative to warfarin in this limited select subgroup of patients with CrCL >95 mL/min appears driven by a surprisingly low event rate for the warfarin arm.[3]

To further characterize the impact of high CrCL on edoxaban exposure, this prospective study was conducted to compare the drug exposure of edoxaban 60 mg once daily vs edoxaban 75 mg once daily in patients with AF who were anticoagulant-naïve and had a CrCL >100 mL/min.

Methods

Study Design

This was a prospective, randomized, double-blind study with evaluation of end points by an independent clinical event committee. Patients were randomized (1:1) via an interactive web/voice response system to receive either edoxaban 75 mg once daily or edoxaban 60 mg once daily. Patients in both arms were treated for up to 12 months with a 2- to 4-week follow-up period. Treatment interruptions were discouraged but could occur due to an adverse event (AE) or other medical reasons. No edoxaban dose reductions were allowed in the study, and no patients who met standard labeling criteria for edoxaban dose reduction were enrolled.

The on-treatment period was defined as the time during which patients were taking the study drug through up to 3 days after their last dose. The overall study period was the time from the date of the first dose of the study drug to the follow-up visit. For patients without a follow-up visit, the overall study period was defined as the final dose plus 28 days. A summary of the study design is presented in Figure 1.

The protocol and all study documents were approved by the appropriate institutional review boards and independent ethics committees. The full list of study sites, the majority of which were in eastern Europe, and their corresponding approval committee is in Table S1. This study was conducted in accordance with the Good Clinical Practice standards for drugs and the ethical principles specified in the Declaration of Helsinki. Informed consent was obtained from all patients before enrollment.

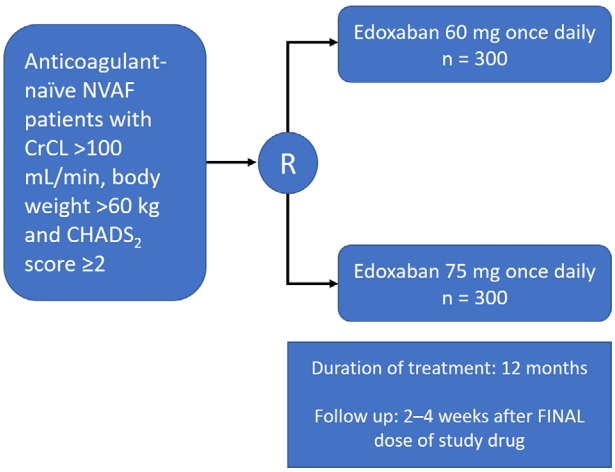

Figure 1. Study design. The goal was to randomize ≈600 patients (300 per treatment arm—edoxaban 60 mg once daily or edoxaban 75 mg once daily) with a treatment duration of 12 months. $CHADS_2$ indicates stroke risk stratification scheme for patients with atrial fibrillation (congestive heart failure, hypertension, age, diabetes, and previous stroke); CrCL, creatinine clearance; NVAF, nonvalvular atrial fibrillation; R, randomization.

Patient Population

Patients were required to have a diagnosis of nonvalvular AF documented by any electrical tracing within the prior 12 months and a CrCL >100 mL/min (calculated by the Cockcroft-Gault formula),[11] and patients were required to be anticoagulant-naïve (defined as having received no dose of any oral anticoagulants for 30 days before randomization) with a stroke risk stratification scheme for patients with atrial fibrillation ($CHADS_2$) score of ≥2. Patients with an indication for an edoxaban dose reduction (body weight <60 kg, CrCL <50 mL/min, or the use of concomitant P-glycoprotein inhibitors) were excluded. Additional exclusion criteria included concomitant medication use such as nonstudy anticoagulants, or chronic oral, or parenteral nonaspirin/nonsteroidal anti-inflammatory drugs for ≥4 days/week. A complete list of exclusion criteria is summarized in Table S2.

Study Objectives and Assessments

The primary pharmacokinetic (PK) parameters were the minimum and average edoxaban plasma concentrations at steady state; anti-factor Xa (FXa) activity was the primary pharmacodynamic (PD) parameter. PK/PD samples were collected before dosing, 1 to 2 hours after dosing, and 4 to 8 hours after dosing on days 30, 90, and 360 in the lithium heparin

tube (for PK) and the sodium citrate tubes (for PD). Edoxaban plasma concentration was analyzed using a validated liquid chromatographic–tandem mass spectrometric method in Q2 Solutions (Ithaca, New York).[12] Anti-FXa levels were measured at Medpace Research Laboratory (Cincinnati, Ohio) using a commercially available anti-FXa activity assay (STA-Liquid Anti-Xa; Diagnostica Stago, Asnières sur Seine, France) with an edoxaban-specific setup using the STA-Edoxaban Calibrator and STA-Edoxaban Control on the STA-R analyzer (Diagnostica Stago).[13]

To account for variability in PK parameters due to sample collection within time windows rather than at precise time points in the treatment arms, edoxaban steady-state PK values were estimated by applying a previously developed population PK (popPK) model for edoxaban that used pooled data from 13 phase 1 studies along with the phase 3 study.[14] This popPK model included body weight, race (Asian vs non-Asian), health status (healthy patients vs patients with nonvalvular AF), CrCL (mL/min), and P-glycoprotein inhibitor as covariates on relevant PK parameters. Model-estimated steady-state concentrations were used to make precise and adequate comparisons of PK exposure parameters between the 2 doses.

Clinical efficacy and safety outcomes events were tabulated and reported. Efficacy outcomes included the composite of stroke, transient ischemic attack (TIA), and SEEs; the composite of ischemic stroke, TIA, and SEEs; and the composite of stroke and/or TIA, SEEs, myocardial infarction, CV death, and major bleeding. Secondary safety outcomes included the incidence of major (including intracranial) and clinically relevant nonmajor (CRNM) bleeding, and all bleeding events that were categorized as major, CRNM, or nuisance bleeding; AEs of special interest included combined elevations of aminotransferases and bilirubin (alanine or aspartate aminotransferase $\geq$3 times the upper limit of normal and total bilirubin $\geq$2 times the upper limit of normal). All investigator-reported clinical outcome events were adjudicated by an independent panel of experts without knowledge of the study treatment. The adjudicated bleeding events were defined as major bleeding, CRNM bleeding, nuisance bleeding, or no bleeding event, based on International Society on Thrombosis and Haemostasis classification.

Statistical Analysis

Continuous data were summarized with descriptive statistics. Categorical data were summarized with frequency counts and percentages. The percentages were calculated based on the total number of patients in each treatment group and analysis category.

The safety analysis set included all patients who were randomized and who received at least 1 dose of the study drug. The PK analysis set (PKAS) included all patients in the safety analysis set who received edoxaban and had at least 1 postdose PK concentration measurement. The PD analysis set included all patients in the safety analysis set who had at least 1 predose PD assessment and at least 1 postdose PD assessment. The modified intent-to-treat (mITT) analysis set included all randomized patients who received at least 1 dose of the study drug.

Results

Patient Disposition and Demographics

Overall, 607 patients were randomized to edoxaban 60 mg once daily or edoxaban 75 mg once daily (303 in the edoxaban 60 mg once-daily arm and 304 in the edoxaban 75 mg once-daily arm). The majority of randomized patients (98.2% [596/607]) completed the study, with similar proportions of completing patients in both treatment groups. Eleven patients withdrew from the study (10 due to death; 1 patient withdrew from the study after 173 days). No patients were lost to follow-up.

The demographics and baseline clinical characteristics were well balanced between treatment arms (Table 1). The demographics and baseline characteristics were predominately younger (median age, 61), more likely men (72%), with higher body mass index (median, 34.6) and more extensive medical history of congestive heart failure, hypertension, and diabetes mellitus (Table 1) than the overall AF population in ENGAGE AF-TIMI 48.[3] Of note, the demographics and baseline characteristics of patients in this study were similar to the patients with high CrCL enrolled in ENGAGE AF-TIMI 48 (Table S4). Five patients had an initial CrCL $>$ 100 mL/min via local lab measurement at randomization but were subsequently found to have CrCL $<$ 100 mL/min via central lab measurement (Table 1); the CrCL for these patients ranged from 92 to 100 mL/min. Of these 5 patients, 1 received edoxaban 60 mg once daily, and 4 received edoxaban 75 mg once daily. None experienced a stroke, bleeding event, or serious AE during the study.

Pharmacokinetic End Points

The PKAS included 298 patients randomly assigned to edoxaban 60 mg once daily and 297 patients randomly assigned to edoxaban 75 mg once daily. Figure S1 shows the observed edoxaban plasma concentrations before dosing, 1 to 2 hours after dosing, and 4 to 8 hours after dosing on days 30, 90, and 360 of the on-treatment periods for both treatment arms. As expected, the resulting measured actual plasma concentrations showed large variability, partly due to noise from different sampling times within the specified collection window.

Table 1. Demographic and Baseline Clinical Characteristics (mITT Analysis Set)

	Edoxaban 60 mg Once Daily (n = 303)	Edoxaban 75 mg Once Daily (n = 303)	Overall (N = 606)
Age, y			
Mean (SD)	60.9 (8.1)	60.4 (8.4)	60.6 (8.2)
Median (min-max)	61.0 (32-80)	61.0 (32-82)	61.0 (32-82)
<65, n (%)	195 (64.4)	201 (66.3)	396 (65.3)
65 to <75, n (%)	97 (32.0)	91 (30.0)	188 (31.0)
≥75, n (%)	11 (3.6)	11 (3.6)	22 (3.6)
Male, n (%)	215 (71.0)	221 (72.9)	436 (71.9)
BMI, kg/m^2			
Mean (SD)	35.4 (5.8)	35.3 (6.4)	35.4 (6.1)
Median (min-max)	35.1 (23.2-55.2)	34.4 (22.0-58.3)	34.6 (22.0-58.3)
<30, n (%)	47 (15.5)	55 (18.2)	102 (16.8)
≥30 to <35, n (%)	102 (33.7)	113 (37.3)	215 (35.5)
≥35, n (%)	154 (50.8)	133 (43.9)	287 (47.4)
CrCL, mL/min			
Mean (SD)	128.7 (24.2)	129.4 (28.0)	129.0 (26.2)
Median (min-max)	123.4 (100.0-250.8)	122.3 (92.0-295.8)	122.5 (92.0-295.8)
≤100, n (%)	1 (0.3)	4 (1.3)	5 (0.8)
>100 to ≤120, n (%)	134 (44.2)	137 (45.2)	271 (44.7)
>120, n (%)	168 (55.4)	162 (53.5)	330 (54.5)
Atrial fibrillation type, n (%)			
Paroxysmal	122 (40.3)	134 (44.2)	256 (42.2)
Persistent	87 (28.7)	82 (27.1)	169 (27.9)
Permanent	94 (31.0)	87 (28.7)	181 (29.9)
$CHADS_2$			
Mean (SD)	2.5 (0.8)	2.5 (0.8)	2.5 (0.8)
Median (min-max)	2.0 (2.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)
<2, n (%)	0	1 (0.3)	1 (0.2)
2, 3, n (%)	268 (88.4)	270 (89.1)	538 (88.8)
>3, n (%)	35 (11.6)	32 (10.6)	67 (11.1)
Medical history, n (%)			
Congestive heart failure	231 (76.2)	231 (76.2)	462 (76.2)
Hypertension	300 (99.0)	299 (98.7)	599 (98.8)
Diabetes	112 (37.0)	130 (42.9)	242 (39.9)
Ischemic/embolic stroke	30 (9.9)	24 (7.9)	54 (8.9)

BMI, body mass index; $CHADS_2$, stroke risk stratification scheme for patients with atrial fibrillation (congestive heart failure, hypertension, age, diabetes, previous stroke); CrCL, creatinine clearance; mITT, modified intent-to-treat; SD, standard deviation.

The popPK model adequately described the observed steady-state concentrations during the on-treatment period among patients included in the PKAS (Figure S2). The model-estimated steady-state edoxaban exposure was ≈25% higher in patients receiving 75 mg once daily, as compared with patients receiving 60 mg once daily (Table 2). The average edoxaban concentration at steady state was 74.8 ng/mL in the 60-mg group and 93.2 ng/mL in the 75-mg group (Table 2).

Anti-FXa

The mean predose concentrations of anti-FXa in patients in the PD analysis set during days 30, 90, and 360 of the on-treatment period ranged from 23.1 to 28.0 ng/mL in the edoxaban 60-mg once-daily arm and 33.4 to 35.9 ng/mL in the edoxaban 75-mg once-daily arm. Anti-FXa levels for edoxaban 60 mg once daily and 75 mg once daily at days 30, 90, and 360 are provided in Table 3. Figure 2 illustrates the linear correlation between anti-FXa activity and edoxaban concentration.

A post hoc analysis was also performed to exclude the patients who had measurable anti-FXa at baseline (likely due to concomitant heparin use). With this exclusion, the change in anti-FXa levels also remained consistent with the increase in dose.

Adjudicated Efficacy Outcomes

In the mITT population during the on-treatment period, the incidence of the composite end point of stroke,

Table 2. Population Pharmacokinetic Parameters Estimates for Edoxaban at Steady State by Dose (Pharmacokinetic Analysis Set)

	Edoxaban 60 mg Once Daily (n = 298)		Edoxaban 75 mg Once Daily (n = 297)
C_{av} (ng/mL)			
Mean (SD)	74.8 (13.3)		93.2 (16.2)
Median (min-max)	74.5 (44.5-121)		92.4 (55.5-146)
Geometric mean/CV (%)	73.7/17.8		91.8/17.8
Ratio of means edoxaban 75/60 mg (95%CI)		1.25 (1.2-1.3)	
P value		<.0001	
C_{max}, ng/mL			
Mean (SD)	214 (51.1)		269 (62.4)
Median (min-max)	211 (124-429)		261 (144-496)
Geometric mean/CV (%)	209/23.7		262/23.2
Ratio of means edoxaban 75/60 mg (95%CI)		1.25 (1.2-1.3)	
P value		<.0001	
C_{min}, ng/mL			
Mean (SD)	18.2 (5.2)		22.5 (6.5)
Median (min-max)	17.8 (4.8-33.9)		22.1 (8.7-42.4)
Geometric mean/CV (%)	17.4/30.6		21.6/30.5
Ratio of means edoxaban 75/60 mg (95%CI)		1.24 (1.2-1.3)	
P value		<.0001	

C_{av}, average plasma concentration of edoxaban at steady state; C_{max}, maximum (peak) concentration of drug in blood plasma (applied to extravascular drug administration); C_{min}, minimum observed (or could infer lowest effective) concentration of edoxaban in blood plasma; CV, coefficient of variation; min, minimum; max, maximum; SD, standard deviation.

TIA, and SEEs was 0.7% (2/303) in the edoxaban 60-mg once-daily arm vs 1.0% (3/303) in the edoxaban 75-mg arm (odds ratio, 1.51; 95%CI, 0.2-18.1; $P = 1.000$; Table 4). All events were stroke events; there were no reported TIA or SEE events. In the edoxaban 60-mg once-daily group, two patients experienced an ischemic stroke; in the 75-mg once-daily group, 1 patient experienced an ischemic stroke and 2 experienced a hemorrhagic stroke (1 fatal). No other patients in the mITT population experienced an event during the overall study period. The annual event rate of the composite end point was <1% during the study.

Adjudicated Safety Outcomes

Clinically relevant bleeding (major and/or CRNM bleeding) during the on-treatment period occurred in 21 patients (3.5%) overall, with 11 patients (3.6%) in the edoxaban 60-mg once-daily arm and 10 (3.3%) in the edoxaban 75-mg once-daily arm (odds ratio, 0.9; 95%CI, 0.3-2.4; $P = 1.000$). In the edoxaban 60-mg once-daily arm, two patients (0.7%) experienced a major bleeding event (1 event of intraocular bleeding and 1 intramuscular). There were no fatal bleeding events in the edoxaban 60-mg once-daily arm. Nine patients (3.0%) experienced a CRNM bleeding event in the edoxaban 60-mg once-daily arm. In the edoxaban 75-mg once-daily group, 3 patients (1.0%) experienced a major bleeding event (2 experienced intracranial bleeds [1 fatal], and 1 experienced an upper gastrointestinal bleed). Seven patients (2.3%) experienced CRNM bleeding in the edoxaban 75-mg once-daily arm. A summary of safety data related to bleeding is presented in Table 4. No patient in either treatment group had more than one confirmed on-treatment major bleeding event.

The PK data of edoxaban was examined for patients with adjudicated and confirmed stroke or bleeding outcome events, and no consistent relationship between exposure and outcome events was observed (Table 5). The exposures in patients with outcome events were within the expected range (between the 5th and 95th percentiles) and were not different from the exposure range observed in all patients.

Treatment-Emergent AEs

Treatment-emergent AEs (TEAEs) occurred in 244 patients (40.3%) during the on-treatment period. The most common TEAE was AF, which was reported by 11 patients (3.6%) in the 60-mg once-daily group and 14 (4.6%) in the 75-mg once-daily group. During the overall study period, there were seven reported deaths: 2 patients receiving edoxaban 60 mg once daily and 5 patients receiving 75 mg once daily. Five of the deaths

Table 3. Anti-FXa (ng/mL) Measures at Days 30, 60, and 360 in Patients Receiving Edoxaban 60 mg Once Daily or Edoxaban 75 mg Once Daily

	Edoxaban 60 mg Once Daily (n = 292)			Edoxaban 75 mg Once Daily (n = 292)		
	Before Dosing	1-2 h After Dosing	4-8 h After Dosing	Before Dosing	1-2 h After Dosing	4-8 h After Dosing
Day 30						
N	284	280	280	284	291	292
Mean (SD)	28 (58)	201 (109)	161 (63)	33 (58)	233 (122)	191 (73)
Median (min-max)	0 (0-400)	205 (0-400)	145 (27-400)	22 (0-397)	251 (0-400)	181 (0-400)
Day 90						
N	281	281	283	273	280	277
Mean (SD)	23 (47)	180 (107)	157 (67)	33 (59)	229 (120)	184 (79)
Median (min-max)	0 (0-375)	173 (0-400)	144 (0-363)	22 (0-386)	234 (0-400)	174 (0-400)
Day 360						
N	276	277	279	269	269	267
Mean (SD)	26 (55)	181 (111)	147 (77)	36 (59)	215 (126)	184 (95)
Median (min-max)	0 (0-399)	166 (0-400)	139 (0-400)	23 (0-387)	215 (0-400)	177 (0-400)

FXa, factor Xa; min-minimum; max, maximum; SD, standard deviation.

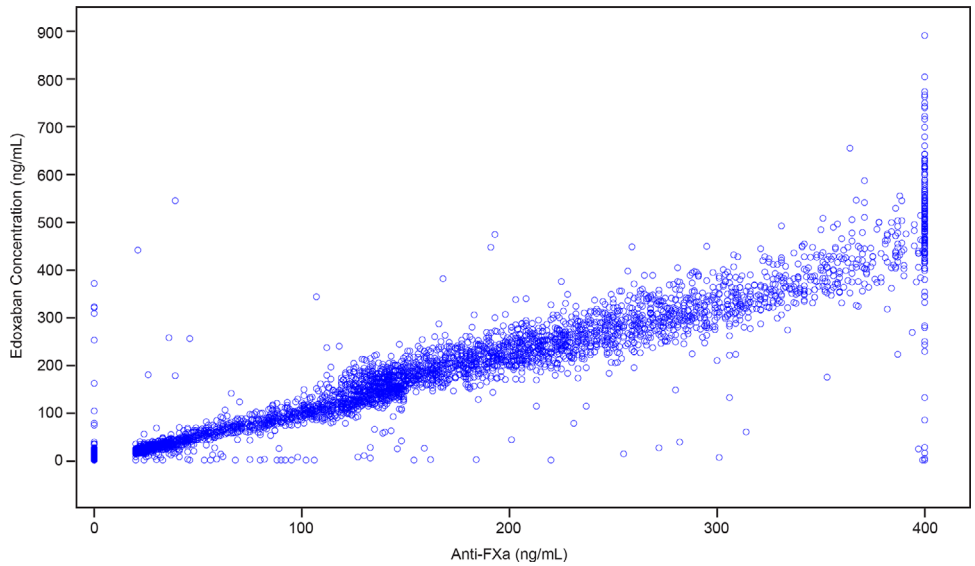

Figure 2. Scatterplot of edoxaban concentration versus anti-FXa in the PD analysis set. Anti-FXa values greater than the upper limit of quantification (400 ng/mL) were reported as 400 ng/mL, and anti-FXa values less than the lower limit of quantification (20 ng/mL) were reported as 0 ng/mL. FXa indicates factor Xa; PD, pharmacodynamics.

were adjudicated as due to CV disease and not associated with a stroke or bleeding event within 30 days of death; 1 death was due to urosepsis and adjudicated as unrelated to the study medication. One death (edoxaban 75 mg once daily) was due to hemorrhagic stroke (Table 4). No other TEAE occurred in >3% of patients in either arm of the study. A summary of TEAEs is presented in Table S3.

Discussion

This study was conducted to determine if a daily dose of edoxaban >60 mg would increase exposure among patients with CrCL >100 mL/min. Over a period of 12 months, 303 patients received edoxaban 60 mg once daily, and 304 received edoxaban 75 mg once daily. On day 30, 1 to 2 hours after dosing, the edoxaban concentration was 232 ng/mL in patients receiving the

Table 4. Adjudicated Clinical Outcome Events (on Treatment) by Dose

	Edoxaban 60 mg Once Daily (n = 303)	Edoxaban 75 mg Once Daily (n = 303)	Overall (N = 606)
Stroke, TIA, or SEE, n (%) – mITT	2 (0.7)	3 (1.0)	5 (0.8)
Ischemic stroke	2	1	3
Hemorrhagic stroke	0	2[a]	2
TIA or SEE	0	0	0
Patient exposure years	307	303	610
Annualized event rate, %	0.7	1.0	0.9
95% exact CI for annualized event rate, %	(0.1-2.4)	(0.2-2.9)	(0.3-1.9)
Odds ratio (95% exact CI): 75 mg vs 60 mg	1.51 (0.17-18.1)	1.00	
P value			
Major or CRNM bleeding, n (%) – SAS	11 (3.6)	10 (3.3)	21 (3.5)
Patient exposure years	292	287	579
Annualized event rate, %	3.8	3.5	3.6
95% exact CI for annualized event rate, %	(1.9-6.8)	(1.7-6.4)	(2.2-5.5)
Odds ratio (95% exact CI): 75 mg vs 60 mg	0.91 (0.34-2.39)	1.00	
P value			
Major bleeding, n (%) – SAS	2 (0.7)	3 (1.0)	5 (0.8)
Intracranial	0	2 (0.7)[a]	2 (0.3)
Upper gastrointestinal	0	1 (0.3)	1 (0.2)
Patient exposure years	293	289	582
Annualized event rate, %	0.7	1.0	0.9
95% exact CI for annualized event rate, %	(0.1-2.5)	(0.2-3.0)	(0.3-2.0)
Odds ratio (95% exact CI): 75 mg vs 60 mg	1.51 (0.17-18.1)	1.00	
P value			
Net clinical end point,[b] n (%) – mITT	5 (1.7)	8 (2.6)	13 (2.1)
Patient exposure years	293	288	581
Annualized event rate, %	1.7	2.8	2.2
95% exact CI for annualized event rate, %	(0.6-4.0)	(1.2-5.5)	(1.2-3.8)
Odds ratio (95% exact CI): 75 mg vs 60 mg	1.62 (0.46-6.35)		
P value	.577		

CRNM, clinically relevant nonmajor; MI, myocardial infarction; mITT, modified intent-to-treat; SAS, safety analysis set; SEE, systemic embolic event; TIA, transient ischemic attack.
[a] One fatal.
[b] Composite of stroke, TIA, SEE, MI, cardiovascular death, and major bleeding.

60-mg dose and 281 ng/mL in patients receiving the 75-mg dose. As expected, given the linear edoxaban dose proportionality, the edoxaban dose of 75 mg once daily provided an ≈25% increase in exposure compared with the edoxaban 60-mg once-daily dose. This 25% increase was also accurately depicted in the pop-PK model estimation of steady-state edoxaban concentration. There was also an increase in anti-FXa concentration between the 60- and 75-mg doses that correlated well with edoxaban concentration.

In ENGAGE AF-TIMI 48, patients with CrCL >95 mL/min showed a trend toward decreased efficacy relative to warfarin and had lower edoxaban trough concentrations relative to patients with lower CrCL.[6] Of note, the demographics of patients with high CrCL (>95 mL/min) in ENGAGE AF-TIMI 48 were similar to the patients enrolled in this study (Table S3).[6] Although the current study was not designed to compare clinical events between the 2 treatment arms with sufficient power, the total number of patients with clinical outcome events (stroke or bleeding) was low overall and similar between the 2 treatment arms. The observed increase in exposure with edoxaban 75 mg compared with 60 mg was not associated with a decrease in the risk of overall stroke.

In the current study, AF patients with high renal clearance receiving edoxaban 75 mg once daily (vs edoxaban 60 mg once daily) demonstrated dose proportional increases in edoxaban and anti-FXa concentrations. Despite the increase in exposure, there was no apparent additional clinical benefit of the higher edoxaban dose, as the rates of overall stroke were similar between treatment arms. Therefore, the results of this study continue to support that edoxaban 60 mg once daily provides

Table 5. C_{av}, C_{max}, and C_{min} for Edoxaban at Steady State in Patients With Adjudicated Stroke or Bleeding Events (Safety Analysis Set)

ID	Dose (mg)	Event	C_{av}, ng/mL	C_{max}, ng/mL	C_{min} ng/mL
Patient 1	60	Intramuscular bleeding	65.9	169	17.8
Patient 2	60	Ischemic stroke	66.7	186	16.1
Patient 3	60	Ischemic stroke	68.9	198	14.9
Patient 4	60	Eye (intraocular) bleeding	87.8	237	23.5
Patient 5	75	GI bleeding	102	263	29.2
Patient 6	75	Ischemic stroke	93.3	368	11.2
Patient 7	75	Hemorrhagic stroke/ICH	72.3	215	15.1
Patient 8	75	Hemorrhagic stroke/ICH	104	266	29.6
All patients	60	Mean (n = 298)	74.8	214	18.2
All patients	60	Median (n = 298)	74.5	211	17.8
All patients	75	Mean (n = 297)	93.2	269	22.5
All patients	75	Median (n = 297)	92.4	261	22.1

C_{av}, average plasma concentration of edoxaban at steady state; C_{max}, maximum concentration in plasma; C_{min}, minimum concentration in plasma; GI, gastrointestinal; ICH, intracranial hemorrhage.

appropriate stroke prevention for patients with AF with high renal clearance (CrCL > 100 mL/min).

The current study is not without limitations. As noted previously, this study was not designed to compare clinical events between the 2 treatment arms with sufficient power, given the low incidence of stroke and bleeding events in this subpopulation of patients with AF treated with FXa inhibitors. Accordingly, analysis of stroke, embolism, and other events served to support the exposure analyses. Additionally, renal function may have been more adequately described by formulas other than the Cockcroft-Gault formula, although this is a commonly used and accepted method.[15] Other methods for estimation of renal clearance, such as the Chronic Kidney Disease Epidemiology Collaboration and the Modification of Diet in Renal Disease equations that consider a number of demographic factors in various configurations, may have provided further insight into renal function.[16]

Conclusions

This study confirmed that edoxaban exposure was ≈25% higher in patients with AF with high renal clearance (CrCL > 100 mL/min) who received edoxaban 75 mg once daily compared with patients who received edoxaban 60 mg once daily. The increases in anti-FXa levels were also in line with the increase in dose. The risk of overall stroke and major/clinically relevant bleeding was similar in both treatment arms. Additionally, the exposures in patients with outcome events were within the expected range (between the 5th and 95th percentiles) and were not different from the exposure range observed in all patients. The results of this study continue to support that edoxaban 60 mg once daily provides appropriate stroke prevention for patients with AF with high renal clearance (CrCL > 100 mL/min).

Acknowledgments

This study was sponsored by Daiichi Sankyo. Writing and editorial support was provided by Margaret Van Horn, PhD, and Lauren Hanlon, PhD, of AlphaBioCom, LLC and was funded by Daiichi Sankyo.

Conflicts of Interest

All authors are/were employees of Daiichi Sankyo, Inc. at the time of manuscript development and creation.

Funding

This study was funded by Daiichi Sankyo.

Author Contribution

All authors contributed to the study concept and design. OY, TK, AD, MK, MS, and MG performed material preparation, data collection, and analysis. OY, TK, AD, HL, and MG contributed to writing the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation

developed in collaboration with EACTS. *Rev Esp Cardiol (Engl Ed)*. 2017;70(1):50.
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104-132.
3. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
4. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace*. 2018;20(8):1231-1242.
5. Vranckx P, Valgimigli M, Heidbuchel H. The significance of drug-drug and drug-food interactions of oral anticoagulation. *Arrhythm Electrophysiol Rev*. 2018;7(1):55-61.
6. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation*. 2016;134(1):24-36.
7. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33(22):2821-2830.
8. Del-Carpio Munoz F, Yao X, Abraham NS, et al. Dabigatran versus warfarin in relation to renal function in patients with atrial fibrillation. *J Am Coll Cardiol*. 2016;68(1):129-131.
9. Fordyce CB, Hellkamp AS, Lokhnygina Y, et al. On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from ROCKET AF. *Circulation*. 2016;134(1):37-47.
10. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
12. He L, Gajee R, Mangaraj R, Waldron MP, Brown KS. Validation and clinical application of dried blood spot assay for quantitative assessment of edoxaban in healthy adults. *Bioanalysis*. 2020;12(6):393-407.
13. He L, Kochan J, Lin M, Vandell A, Brown K, Depasse F. Determination of edoxaban equivalent concentrations in human plasma by an automated anti-factor Xa chromogenic assay. *Thromb Res*. 2017;155:121-127.
14. Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure-response analysis in patients with non-valvular atrial fibrillation. *Eur J Clin Pharmacol*. 2014;70(11):1339-1351.
15. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol*. 2010;5(6):1003-1009.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

Supplemental Information

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