The Relationship of Renal Function to Outcome: A Post hoc Analysis from the **EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion Of Atrial Fibrillation (ENSURE-AF) study**

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The Relationship of Renal Function to Outcome: A Post hoc Analysis from the **E**doxaba**N** versus warfarin in subject**S** **U**nde**R**going cardiov**E**rsion Of **A**trial **F**ibrillation (ENSURE-AF) study

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Abstract

Background: The ENSURE-AF study (NCT 02072434) of anticoagulation for electrical cardioversion in non-valvular atrial fibrillation (NVAF) showed comparable low rates of bleeding and thromboembolism between the edoxaban and the enoxaparin–warfarin treatment arms. This post hoc analysis investigated the relationship between renal function and clinical outcomes.

Methods: ENSURE-AF was a multicenter, PROBE evaluation trial of edoxaban 60 mg, or dose reduced to 30 mg/day for weight ≤60 kg, CrCl (creatinine clearance; Cockroft-Gault) ≤50 ml/min, or concomitant P-glycoprotein [P-gp] inhibitors) compared with therapeutically monitored enoxaparin–warfarin in 2,199 NVAF patients undergoing electrical cardioversion. Efficacy and safety outcomes and time in therapeutic range (TiTR) in the warfarin arm were analyzed in relation to CrCl in prespecified ranges ≥15 and ≤30; >30 and ≤50; >50 and <80 and ≥80 ml/min, and an exploratory ≥95 ml/min analysis.

Results: 1,095 subjects were randomized to edoxaban and 1,104 to enoxaparin–warfarin. Mean age was 64.3±10 and 64.2±11 years. Mean TiTR was progressively lower with reducing CrCl strata, being 66.8% in those with CrCl >30 to ≤50, compared to 71.8% in those with CrCl ≥80. The Odds Ratios for the primary efficacy and safety endpoints were comparable for the different predefined renal function strata; given the small numbers the 95% CI included 1.0. In the subset of those with CrCl ≥95, the Odds Ratios showed consistency with the other CrCl strata. When CrCl was assessed as a continuous variable, there was a non-significant trend towards higher major or clinically relevant non-major bleeding with reducing CrCl levels, with no significant differences between the 2 treatment arms. When we assessed CrCl at baseline compared to end of treatment, there were no significant differences in CrCl change between the edoxaban and enoxaparin–warfarin arms. The proportions with worsening of renal function (defined as a decrease of >20% from baseline) were similar in the 2 treatment arms.

Conclusion: Given the small number of events in ENSURE-AF, no effect of renal (dys)function was demonstrated in comparing edoxaban to enoxaparin–warfarin for cardioversion; efficacy and safety of edoxaban remained consistent even in patients with normal or supranormal renal function.

Key words: cardioversion, oral anticoagulant, renal function, stroke, thromboembolism

Introduction

The availability of the nonvitamin K antagonist oral anticoagulants (NOACs) has transformed the landscape for the prevention of atrial fibrillation (AF)-related stroke. Nonetheless, all of the NOACs have a degree of renal excretion, ranging from the highest being for dabigatran (80% renal excreted) to 50% for edoxaban to 33% for rivaroxaban and 27% for apixaban.[1] In contrast, warfarin is eliminated principally through hepatic metabolism and is not directly renally excreted.[2]

Patients with AF and impaired renal function are at high risk of stroke, thromboembolism, myocardial infarction, death and serious bleeding.[3] In patients with supranormal renal function, with eGFR >95ml/min some concern has been expressed for less efficacy in ischemic stroke prevention, seen in a post hoc subgroup exploratory analyses for edoxaban by the United States FDA.[4,5]

The ENSURE-AF study (ClinicalTrials.gov Identifier: NCT02072434) of anticoagulation for electrical cardioversion in non-valvular atrial fibrillation (NVAF) showed comparable low rates of bleeding and thromboembolism between the edoxaban and the enoxaparin–warfarin treatment arms.[6] In this post hoc analysis from ENSURE-AF we investigated the relationship between renal function and blinded adjudicated outcomes.

Methods

ENSURE-AF was a multicenter, PROBE evaluation trial of edoxaban 60 mg once daily or dose adjusted 30 mg/day if weight ≤60 kg, CrCl (creatinine clearance) ≤50 ml/min, and/or concomitant use of P-glycoprotein (P-gp) inhibitors compared with therapeutically monitored enoxaparin–warfarin in 2,199 patients with NVAF of at least 48 hours and no longer than 12 months undergoing electrical cardioversion.[7]

By protocol and as published previously,[6,7] patients were stratified according to cardioversion approach (TEE or non-TEE) as determined by the local investigator. In the TEE-guided stratum, both the TEE and cardioversion had to be performed

within three days of randomization. Patients in the warfarin arm with INR <2 started treatment with a minimum of one dose each of enoxaparin and warfarin before cardioversion and these drugs were continued until INR ≥2 was obtained. After a therapeutic range was achieved, patients were to discontinue enoxaparin and continue warfarin until end of treatment (day 28 following the procedure). Patients randomized to the edoxaban arm had to start treatment at least two hours prior to electrical cardioversion. The next dose of edoxaban was taken the day after cardioversion and then continued on a 24-hour cycle until day 28 post cardioversion. Patients with thrombi on TEE had a choice of completing 28 days of study treatment without cardioversion or being discontinued from the study. All patients were followed up for safety for another 30 days after completing or discontinuing the treatment.

In all patients in the non-TEE-guided stratum, electrical cardioversion was performed at a minimum of 21 days following the start of treatment. Patients in the enoxaparin–warfarin arm received anticoagulation for a minimum of 21 days from the day of randomization. Patients with an INR <2 at randomization received enoxaparin and daily warfarin until the INR was ≥2·0. At that time, enoxaparin was discontinued and warfarin continued for the duration of the study. In the edoxaban arm, patients received edoxaban for a minimum of 21 days before cardioversion followed by the procedure and an additional 28 days of treatment. All patients in the non-TEE guided strategy were followed for safety for 30 days after completing treatment.

Patients were also stratified according to prior experience in taking anticoagulants at the time of randomization (i.e. anticoagulant-experienced or anticoagulant-naïve); and selected edoxaban dose (60 mg QD or reduced 30 mg QD dose).

Briefly, categorical evaluation based on renal function was assessed at baseline and at the end of treatment, as per the clinical trial protocol. The central laboratory (Quintiles Q^2 Solutions) evaluated the CrCl based on Cockcroft-Gault formula to determine renal function. Estimation of CrCl for males: = (140 – age [years]) x (body

weight [kg]) / (72 x serum creatinine [mg/dL]); estimation for females = CrCl = 0.85 x (140 – age [years]) x (body weight [kg]) / (72 x serum creatinine [mg/dL]. All clinical events, both for efficacy and safety were evaluated by a blinded adjudication committee composed of cardiologist/hematologist.[7]

The primary efficacy analysis was comparing the occurrence of a composite endpoint of stroke, systemic embolic event (SEE), myocardial infarction (MI), and cardiovascular death (CVD) between the edoxaban group and the enoxaparin–warfarin group from randomization to end of follow-up and was performed on the intention-to-treat population, all individuals who were enrolled into the study and randomly assigned.

The primary safety endpoint of the trial was the composite of major + clinically relevant non-major (CRNM) bleeding which occurred during the on treatment period, defined as the time period the patient was taking study medication plus up to 3 days after the last dose for that time period. Any bleeding was defined as the composite of major + CRNM + minor bleeding from time of first administration of study drug to end of treatment +3 days. Patients were followed for 28 days on study drug after cardioversion plus another 30 days to assess safety on an investigator-prescribed standard of care.

Efficacy and safety outcomes and time in therapeutic range (TiTR) in the warfarin arm were analyzed in relation to CrCl in prespecified ranges ≥15 and ≤30; >30 and ≤50; >50 and <80 and ≥80 ml/min, and an exploratory ≥95 ml/min analysis). The same outcome parameters were also assessed with CrCl as a continuous variable.

Statistical methods

Time in therapeutic range (TiTR) for a patient is defined as the percent of time sustained in international normalized ratio (INR) therapeutic range (2.0 ≥ INR ≤ 3.0),

from the first date of achieving 2.0 ≥ INR ≤ 3.0 during the on-treatment period. Mean TiTR was shown for all renal function strata. Demographic and baseline characteristics were summarized by treatment group and renal function stratum. Descriptive statistics were presented for the baseline CrCl and the change from baseline to end of treatment. The difference of the change from baseline between two treatment groups was assessed using an ANOVA model. Frequency and percentage of patients with worsening renal function at the end of treatment were presented and compared using Chi-square test. The associations of CrCl strata with other binary variables and ordinal variables were evaluated by Cochran-Armitage trend test and Spearman correlation coefficient, respectively. Breslow-Day-Tarone test was performed to assess homogeneity of odds ratio across CrCL strata.

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Results

1,095 subjects were randomized to edoxaban and 1,104 to enoxaparin–warfarin. Mean age was 64.3±10 and 64.2±11 years, respectively, and overall mean CHA_2DS_2-VASc score was 2.6. Patient demography and clinical features are summarized in Table 1 in relation to CrCl strata. Mean age and the proportion of females progressively increased as CrCl decreased (P<0.0001 for both variables). The proportions of paroxysmal and persistent AF were fairly similar across all CrCl strata. More comorbidities, such as heart failure, were generally more common in those with low CrCl (≤50), leading to a higher stroke risk, as reflected by higher mean CHA_2DS_2-VASc score. Higher mean HAS-BLED score was evident in those with CrCl ≤50.

Efficacy and safety endpoints in relation to renal function strata and treatment allocation are shown in Table 2. Mean TiTR was progressively lower with reducing CrCl strata, being 66.8% in those with CrCl >30 to ≤50, compared to 71.8% in those with CrCl ≥80 although this trend was not statistically significant (*P*=0.199).

The Odds Ratios for the primary efficacy and safety endpoints were comparable for the different predefined (≥15 to ≤30, >30 to ≤50, >50 to <80, ≥80) renal function strata; given the small numbers the 95% CI included 1.0. In the subset of those with CrCl ≥95, the Odds Ratios showed consistency with the other CrCl strata.

When CrCl was assessed as a continuous variable, there was a nonstatistically significant trend towards higher events in the efficacy analysis (composite of stroke, SEE, MI, and CVD) and in the safety analysis (major + CRNM bleeding) with reducing CrCl levels (Figure 1 and Figure 2), with no significant differences between the 2 treatment arms.

When we assessed CrCl at baseline compared to end of treatment, there were no significant differences in CrCl change between the edoxaban and enoxaparin–warfarin arms. The proportions with worsening of renal function (defined as a decrease of >20% from baseline) were similar in the 2 treatment arms (Table 3).

Discussion

In this ancillary analysis from ENSURE-AF, our principal findings are the following: (i) as renal function declines, mean age and comorbidities were higher, and mean TiTR was progressively lower with reducing CrCl strata; (ii) the Odds Ratios for the primary efficacy and safety endpoints were comparable for the different predefined renal function strata, with non-significant trends; and (iii) in the subset of those with CrCl ≥95, the Odds Ratios showed consistency with the other CrCl strata, in relation to efficacy versus safety.

Patients with AF and renal impairment represent a high risk group of patients, with a greater risk of stroke, myocardial infarction, death and serious bleeding[3]. As expected, we noted an increase in age and comorbidities, as well as stroke risk, with decreasing CrCl levels. Interestingly we also observed a small trend towards slightly less good anticoagulation control (but TiTR was still high, ≥68%) at lower CrCl strata, as was seen in other studies showing poorer anticoagulation control with renal impairment.[8-11]

Nonetheless, the efficacy and safety of edoxaban compared to enoxaparin–warfarin remained consistent, irrespective of CrCl strata. Even in the subset of those with CrCl ≥95, the Odds Ratios showed consistency with the other CrCl strata, with no signal for decreased efficacy and/or safety.

When CrCl was assessed as a continuous variable, there was a non-significant trend towards higher major or CRNM bleeding with reducing CrCl levels (as expected, and consistent with other studies),[12] with no significant differences between the 2 treatment arms, and the apparent wide confidence intervals, given the low event rates. This observation of higher event rates with lower CrCl is generally consistent with findings from other Phase 3 NOAC trials, notwithstanding the low event rates in these patients.[12,13] The higher event rates in patients with low CrCl may be associated with other comorbidities and perhaps reduced therapeutic control due to increased exposure for renally dependent anti -FXa clearance.

When we assessed CrCl at baseline compared to end of treatment, we observed no significant differences in CrCl change between the edoxaban and enoxaparin–warfarin arms. The proportion of patients with worsening renal function (defined as a decrease of >20% from baseline) were also similar in the 2 treatment arms. In the RE-LY trial, a post hoc analysis showed that renal function decline was worse on warfarin compared to dabigatran[14]; however, our smaller sample size and shorter follow-up in the present study precludes similar conclusions.

Limitations

This is pre-specified and exploratory ancillary analysis to the ENSURE-AF trial, with consideration of the robust sample size; our observations are limited by the low event rates for the primary efficacy and safety endpoints. We also had shorter follow-up period compared to the Phase 3 NOAC trials, such that we were unable to fully assess the longer term impact on renal function of edoxaban compared to enoxaparin–warfarin.

Conclusion

In conclusion, given the small number of events in ENSURE-AF, no apparent effect of renal (dys)function was demonstrated on clinical outcomes when comparing edoxaban to enoxaparin–warfarin for cardioversion; the efficacy and safety of edoxaban remained consistent even in patients with normal or supranormal renal function.

Disclosures

GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi Sankyo, and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo. NA-S is employed by Covance, which received funding from Daiichi Sankyo for the management of the study. MDE has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Medtronic, Merck, Pfizer, Portola, and Sanofi, and as a speaker for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, and Pfizer. MB has nothing to disclose. AG has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer, and a speaker for Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi-Aventis.

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Table 1 Clinical Demography of Patients in Relation to Renal Function Strata

	(a) Edoxaban by CrCl					
	Total	**≥15 and ≤30 ml/min**	**>30 and ≤50 ml/min**	**>50 and <80 ml/min**	**≥80 ml/min**	**≥95 ml/min**
N	1095	10	73	304	643	459
Age, Mean (SD)	64.3 (10.34)	76.6 (10.54)	76.7 (8.26)	70.0 (7.52)	59.9 (9.03)	58.0 (8.89)
Sex, n (%)						
Male	721 (65.8)	4 (40.0)	38 (52.1)	157 (51.6)	484 (75.3)	358 (78.0)
Female	374 (34.2)	6 (60.0)	35 (47.9)	147 (48.4)	159 (24.7)	101 (22.0)
Atrial Fibrillation History n (%)						
Paroxysmal	208 (19.0)	2 (20.0)	18 (24.7)	60 (19.7)	111 (17.3)	82 (17.9)
Persistent	887 (81.0)	8 (80.0)	55 (75.3)	244 (80.3)	532 (82.7)	377 (82.1)
Medical History, n (%)						
Congestive heart failure	476 (43.5)	6 (60.0)	34 (46.6)	133 (43.8)	275 (42.8)	191 (41.6)
Coronary artery disease	181 (16.5)	3 (30.0)	24 (32.9)	57 (18.8)	88 (13.7)	64 (13.9)
Hypertension	850 (77.6)	8 (80.0)	60 (82.2)	241 (79.3)	485 (75.4)	337 (73.4)
Diabetes	218 (19.9)	2 (20.0)	20 (27.4)	63 (20.7)	118 (18.4)	91 (19.8)
Ischemic/embolic stroke or transient ischemic attack	68 (6.2)	2 (20.0)	11 (15.1)	29 (9.5)	23 (3.6)	16 (3.5)
Life-Threatening Bleed	3 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
CHA_2DS_2VASc, Mean (SD)	2.6 (1.49)	4.4 (1.26)	4.0 (1.53)	3.2 (1.45)	2.1 (1.25)	2.0 (1.20)
HAS-BLED, Mean (SD)	0.9 (0.78)	1.3 (0.82)	1.4 (0.67)	1.2 (0.71)	0.7 (0.73)	0.6 (0.74)

	(b) Warfarin by CrCl					
	Total	**≥15 and ≤30 ml/min**	**>30 and ≤50 ml/min**	**>50 and <80 ml/min**	**≥80 ml/min**	**≥95 ml/min**
N	1104	8	68	315	636	444
Age, Mean (SD)	64.2 (10.75)	79.5 (5.24)	75.7 (7.21)	70.4 (7.67)	59.6 (9.78)	57.2 (9.43)
Sex, n (%)						
Male	722 (65.4)	2 (25.0)	29 (42.6)	170 (54.0)	471 (74.1)	342 (77.0)
Female	382 (34.6)	6 (75.0)	39 (57.4)	145 (46.0)	165 (25.9)	102 (23.0)
Atrial Fibrillation History n (%)						
Paroxysmal	207 (18.8)	2 (25.0)	18 (26.5)	64 (20.3)	105 (16.5)	74 (16.7)
Persistent	890 (80.6)	6 (75.0)	50 (73.5)	251 (79.7)	529 (83.2)	368 (82.9)
Medical History, n (%)						
Congestive heart failure	484 (43.8)	3 (37.5)	34 (50.0)	133 (42.2)	280 (44.0)	212 (47.7)
Coronary artery disease	197 (17.8)	2 (25.0)	18 (26.5)	62 (19.7)	99 (15.6)	67 (15.1)
Hypertension	864 (78.3)	6 (75.0)	56 (82.4)	260 (82.5)	477 (75.0)	325 (73.2)
Diabetes	197 (17.8)	1 (12.5)	12 (17.6)	49 (15.6)	116 (18.2)	74 (16.7)
Ischemic/embolic stroke or transient ischemic attack	66 (6.0)	1 (12.5)	5 (7.4)	25 (7.9)	29 (4.6)	25 (5.6)
Life-Threatening Bleed	3 (0.3)	0	0	2 (0.6)	0	0
CHA_2DS_2VASc, Mean (SD)	2.6 (1.40)	4.4 (0.92)	3.9 (1.38)	3.2 (1.29)	2.2 (1.25)	2.0 (1.24)
HAS-BLED, Mean (SD)	0.9 (0.79)	1.9 (0.64)	1.4 (0.76)	1.2 (0.68)	0.7 (0.75)	0.6 (0.72)

Table 2 Efficacy and Safety Endpoints in Relation to Renal Function Strata, and Treatment Allocation

	Total by Treatment No. of events / Total No. (%)			
Primary efficacy endpoint* ITT Analysis Set Overall Treatment Period	**Edoxaban N=1095**	**Warfarin + Enoxaparin N=1104**	**OR (95% CI)**	***Mean TiTR with warfarin/ enoxaparin arm***
CrCl, ml/min				
≥15 and ≤30	0/10 (0.0)	0/8 (0.0)	-	
>30 and <50	0/73 (0.0)	2/68 (2.9)	0.38 (0, 3.22)	
≥50 and <80	2/304 (0.7)	5/315 (1.6)	0.41 (0.04, 2.53)	
≥80	2/643 (0.3)	3/636 (0.5)	0.66 (0.05, 5.77)	
≥95	0/459 (0.0)	2/444 (0.5)	0.40 (0, 3.36)	
Primary safety endpoint† Safety Analysis Set On Treatment Period	N=1067	N=1082		
CrCl, ml/min				
≥15 and ≤30	0/10 (0)	0/8 (0)	-	95.2
>30 and <50	2/70 (2.9)	1/67 (1.5)	1.94 (0.10, 116.23)	66.8
≥50 and <80	6/297 (2.0)	3/308 (1.0)	2.10 (0.44, 13.06)	68.9
≥80	5/630 (0.8)	6/631 (1.0)	0.83 (0.20, 3.30)	71.8
≥95	4/451 (0.9)	3/440 (0.7)	1.30 (0.22, 8.95)	73.8
Net clinical benefit‡ ITT Analysis Set Overall Treatment Period	N=1095	N=1104		
CrCl, ml/min				
≥15 and ≤30	0/10 (0)	0/8 (0)		

>30 and <50	0/73 (0)	2/68 (2.9)	0.38 (0, 3.22)	
≥50 and <80	3/304 (1.0)	7/315 (2.2)	0.44 (0.07, 1.95)	
≥80	4/643 (0.6)	6/636 (0.9)	0.66 (0.14, 2.79)	
≥95	2/459 (0.4)	3/444 (0.7)	0.64 (0.05, 5.65)	

*Composite of stroke, systemic embolic events (SEEs), myocardial infarction (MI) and cardiovascular (CV) death occurring between randomization until the end of study.
†Composite of major and clinically-relevant non-major bleeding, from the time of first administration of study drug to end of treatment +3 days.
‡Composite of stroke, SEE, MI, CV mortality, and major bleedings occurring between randomization until the end of study.
Median unbiased estimate is used for odds ratio.

Table 3: Summary of Renal Function (by eGFR); Safety Analysis Set

	Edoxaban N=1067	Enoxaparin/ Warfarin N=1082
Baseline		
n	1007	1014
Mean, ml/min	94.1	94.3
SD	35.81	34.72
Median, ml/min	90.0	90.0
Minimum, ml/min	20	23
Maximum, ml/min	313	264
End of Treatment		
n	983	955
Mean, ml/min	94.9	96.4
SD	36.67	36.20
Median, ml/min	90	91
Minimum, ml/min	22	17
Maximum, ml/min	318	296
Change from Baseline		
n	944	905
Mean*	0.9	1.7
SD	15.61	15.33
Median	0	1
Minimum	-85	-89
Maximum	108	91
Worsening n (%)		
Yes	55 (5.83)	44 (4.86)
No†	889 (94.17)	861 (95.14)

*P value 0.2159.
†P value 0.3571.
P-values for continuous variable and categorical variable are from ANOVA model with treatment as factor and Chi-square test, respectively.
End of treatment: Day 28 assessment is used if it is available (last data if multiple Day 28 assessments). Latest post-dose assessment is used if Day 28 is not available.
Worsening is defined as a decrease of greater than 20% from baseline.

Figure Legends

Figure 1. Efficacy Analysis Event Rate by CrCl at Baseline

CrCl = creatinine clearance.

Composite of stroke, systemic embolic events (SEEs), myocardial infarction (MI) and cardiovascular (CV) death occurring between randomization until the end of study.

Figure 2. Safety Analysis Event Rate by CrCl at Baseline

CrCl = creatinine clearance.

Composite of major and clinically-relevant non-major bleeding, from the time of first administration of study drug to end of treatment +3 days.

Figure 1

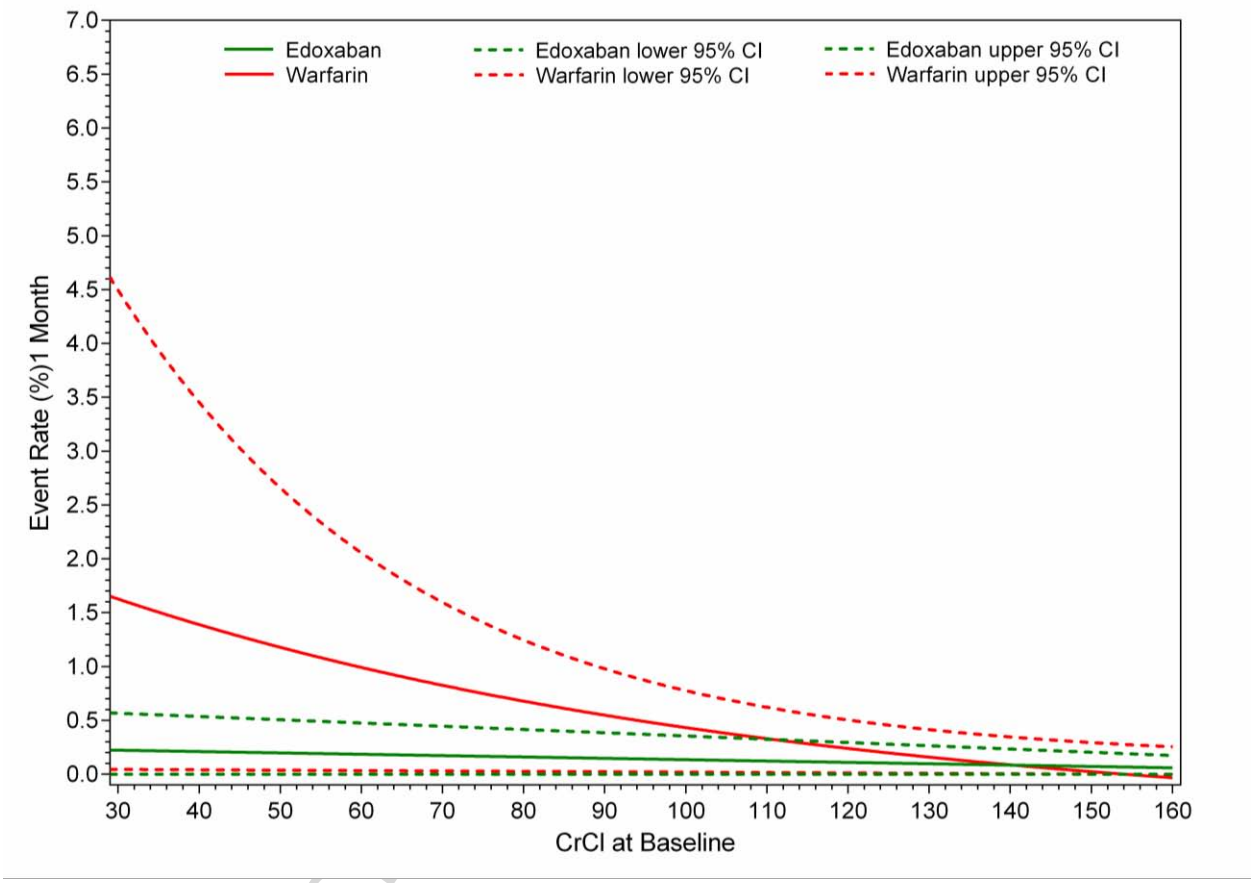

Figure 2