

Modeling and Simulation of the Activity of Intrinsic Factor X Following Edoxaban Treatment

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Introduction

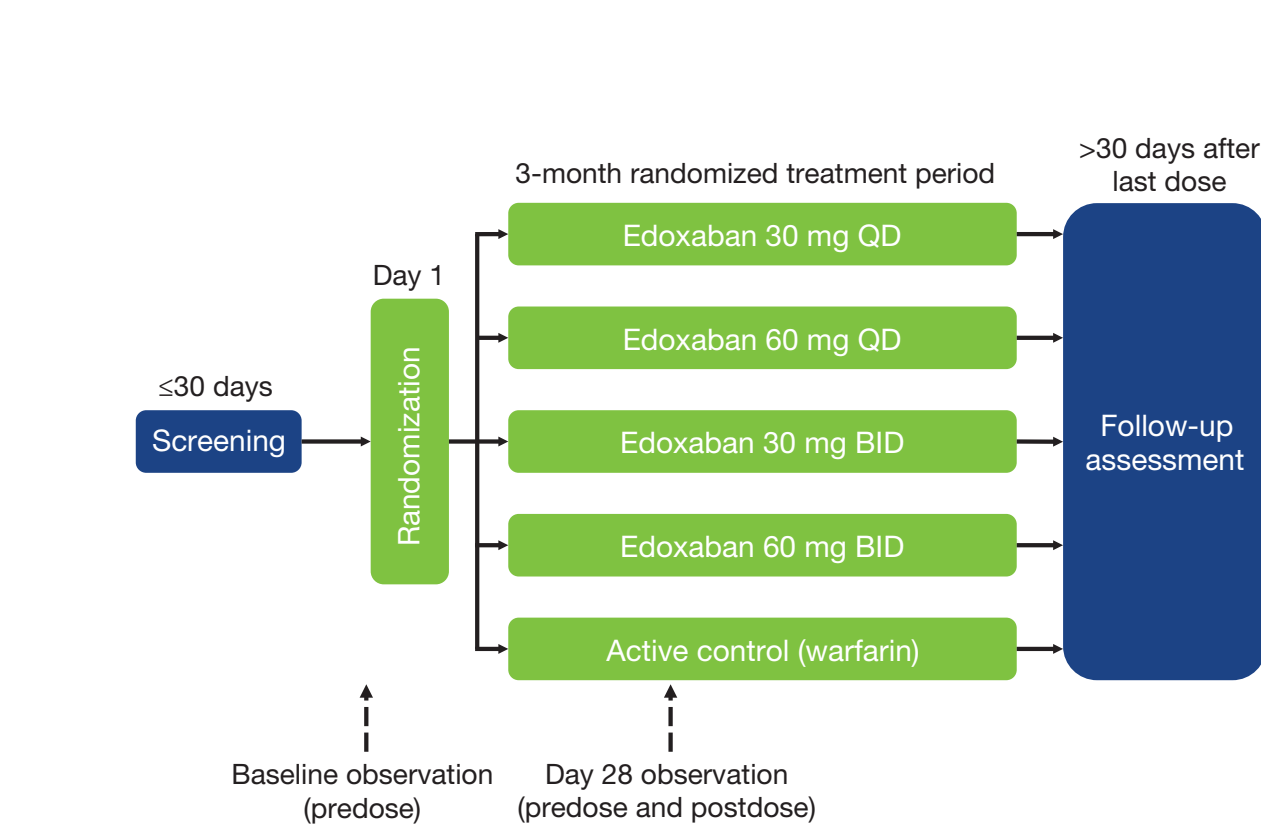
- Edoxaban is an oral anticoagulant, a direct factor Xa inhibitor, evaluated for the prevention of stroke in patients with atrial fibrillation (AF)¹ and the treatment and prevention of venous thromboembolism recurrence²
- A phase 2 study, PRT018,³ evaluated the safety of the 4 dosing regimens of edoxaban (30 mg once daily [QD], 60 mg QD, 30 mg twice daily [BID], and 60 mg BID) compared with the warfarin active control (Figure 1) in patients with non-valvular AF. The activity of intrinsic factor X (iFXa) data was obtained from the 585 edoxaban-treated patients through the two-stage chromogenic method (Biogenic, Tokyo, Japan)
- The observed bleeding rate from the PRT018 study was higher in the 30-mg BID group than the 60-mg QD group (12.7 % vs. 7.3 %), despite the same daily dose of 60 mg.³ Therefore, mechanistic insight into such difference in bleeding risk is warranted

Objectives

- To describe the population pharmacokinetics (PopPK) of edoxaban, a direct factor Xa inhibitor
- To describe the relationship between the PK of edoxaban and iFXa
- To identify significant predictors for the observed bleeding from a Phase 2 study

Methods

FIGURE 1. Schematic diagram of the phase 2 PRT018 study design



FXa = factor Xa; QD = once daily; BID = twice daily

- A PopPK model of edoxaban was established using 13 phase 1 and 5 phase 2 studies, including 11,444 PK samples from 1,624 subjects. The phase 1 study data with dense sampling facilitated the modeling of the sparse phase 2 study data, which contained the pharmacodynamic (PD) biomarker of interest, iFXa, and the key adverse event from anticoagulation treatment, bleeding. Individual *post hoc* concentration values were used to model the iFXa data
- The iFXa data from 585 patients in the PRT018 study were modeled using various PK/PD models. The final PK/PD model was determined by taking into consideration model performance, physiological plausibility, and other factors
- For both the PopPK and PK/PD models of edoxaban, the first-order conditional estimation with interaction (FOCEI) estimation as implemented in NONMEM 7.2 was used to obtain estimates of the model parameters and the variance-covariance matrix
- Logistic regression analysis was then employed to find the best predictor for the incidence of the observed bleeding event, followed by the ordered categorical regression analysis with respect to severity of bleeds
- Summary of the demographic information from the PopPK and PD datasets are shown in Table 1

TABLE 1. Demographic summary of the PopPK and PD datasets

Category	PopPK Dataset	PD Dataset
N	1624	585
Sex		
Male	1239 (76.3)	369 (63.1)
Female	385 (23.7)	216 (36.9)
Race		
White	940 (57.9)	571 (97.6)
Asian	569 (35.0)	-
Black	97 (6.0)	1 (0.2)
Native	2 (0.1)	-
Other	16 (1.0)	13 (2.2)
Age (yr)	56.2 ± 18.4 [18, 88]	65.2 ± 8.5 [41, 85]
Weight (kg)	77.6 ± 17.1 [40.0, 165.3]	88.3 ± 18.2 [42.0, 165.3]
Height (cm)	169.6 ± 10.0 [112.0, 201.0]	170.6 ± 9.6 [112.0, 196.0]
BMI	26.9 ± 5.0 [15.9, 56.0]	30.3 ± 5.4 [18.1, 56.0]
Creatinine clearance (mL/min)	91.5 ± 33.3 [14.1, 246.8]	88.4 ± 29.9 [32.1, 246.8]

Shown are count (percentage) for categorical variables (sex, race), and mean ± standard deviation [minimum, maximum] for continuous variables (age, weight, height, BMI, creatinine clearance). Patients included in the logistic regression analysis dataset are the same as the PD dataset.

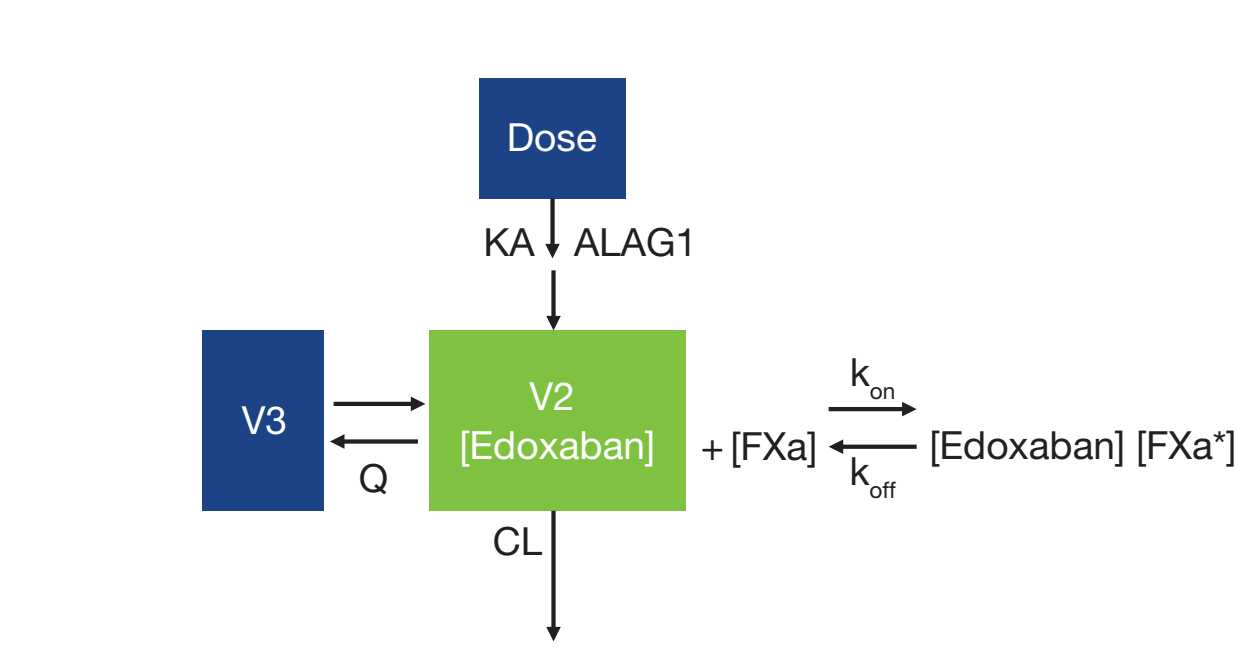
BMI = body mass index; PopPK = population pharmacokinetics; PD = pharmacodynamics

Results

PopPK and PK/PD Modeling Analysis Results

- A two-compartment PK model with first order absorption with lag time adequately described the PopPK of edoxaban in the 18 studies. Systemic clearance (CL) was parameterized as a power function of creatinine clearance, and volumes (V2, V3) were parameterized as power functions of weight. Separate residual error terms were used for healthy volunteers (σ_1), PRT018 patients (σ_2), and all the other patients (σ_3)
- Several PK/PD models (equilibrium model, binding model, and indirect response model) were fit to the iFXa data from the phase 2 PRT018 study. The equilibrium model (Figure 2, OBJ: 6759) was chosen as the final model with the consideration of model performance and parsimony, though the binding model (OBJ: 6695) showed numerically better fit. Indirect response model (OBJ: 6693) performed similarly to the binding model
- Model parameters from the final PopPK and PK/PD models are shown in Table 2, and the goodness-of-fit plots are shown in Figure 3

FIGURE 2. PK/PD model for the iFXa



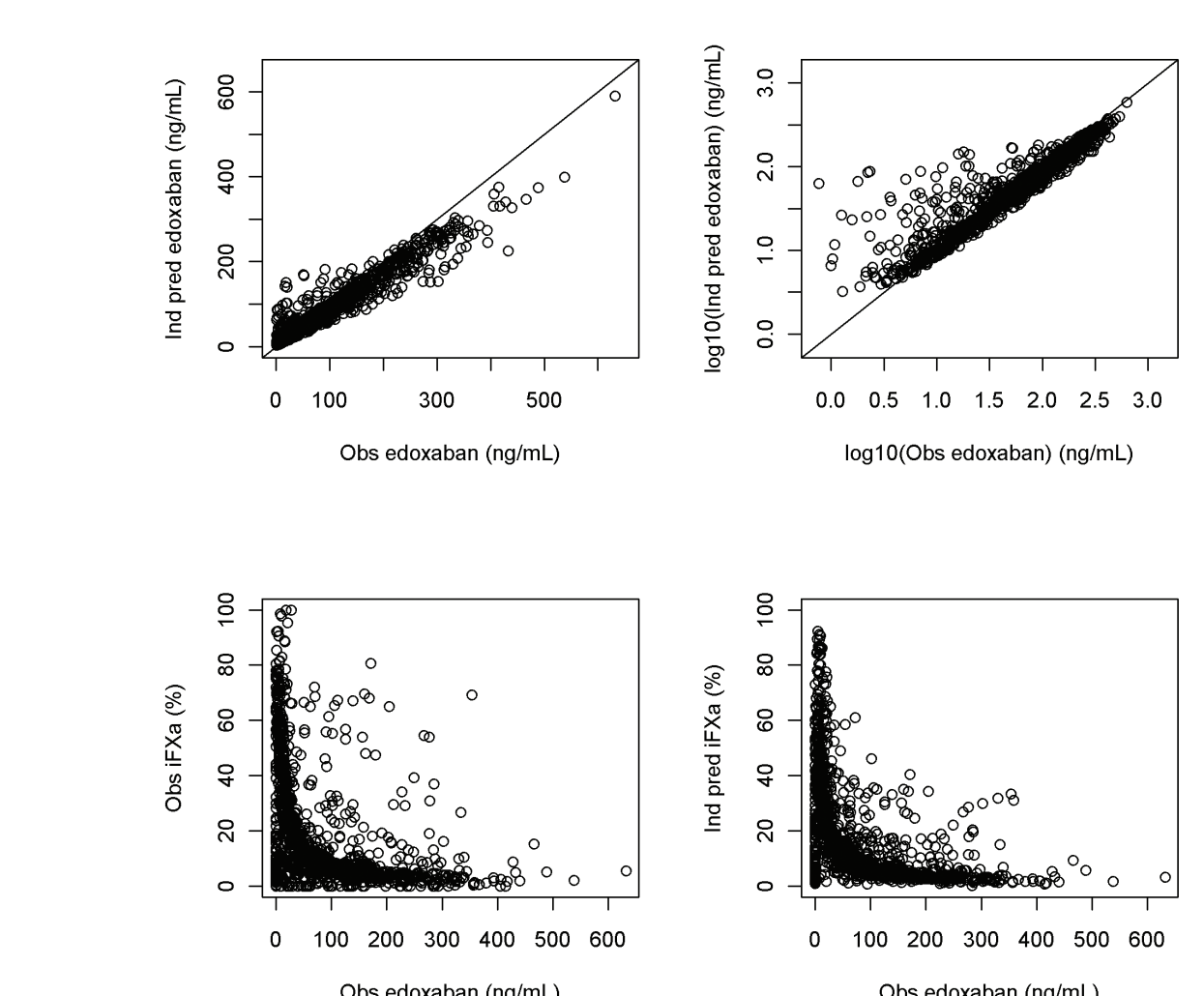
ALAG1 = absorption lag time; KA = absorption rate constant; CL = systemic clearance; FXa = free, active factor X; FXa* = bound, inactive factor X; iFXa = activity of intrinsic factor X; k_{on} = association rate constant; k_{off} = dissociation rate constant; K_D (equilibrium dissociation constant) = k_{off}/k_{on} ; PK = pharmacokinetics; PD = pharmacodynamics; Q = intercompartmental clearance; V2 = distribution volume of the central compartment; V3 = distribution volume of the peripheral compartment

TABLE 2. Final PopPK and PK/PD model parameters

Parameter	Mean	RSE (%)	BSV (%)	RSE (%)
PK Model				
CL (L/hr)	34.6	1.07	57.4	3.07
V2 (L)	240	2.05	68.8	4.60
Q (L/hr)	8.15	4.71	81.9	9.48
V3 (L)	116	4.46	71.2	7.87
KA (/hr)	3.13	9.94	128.1	19.50
ALAG1 (hr)	0.428	2.73	34.2	4.94
Exponent for (CLcr/100) on CL	0.450	4.44	-	-
Exponent for (WT/80) on V2 and V3	0.602	9.49	-	-
$\sigma_{1, pop}$ (% CV)	45.7	1.38	-	-
$\sigma_{2, pop}$ (% CV)	64.7	3.92	-	-
$\sigma_{3, pop}$ (% CV)	59.8	3.13	-	-
CORR _{CL-V2}	0.84	-	-	-
PD Model				
K_D	8.53	3.88	85.2	10.1
σ_{pop} (% CV)	54.3	5.73	-	-

ALAG1 = absorption lag time; BSV = between-subject variability; CL = clearance; CLcr = creatinine clearance; CORR = correlation; CV = coefficient of variation; KA = absorption rate constant; $\sigma_{1, pop}$ = proportional error for healthy subjects; $\sigma_{2, pop}$ = proportional error for the PRT018 study patients; $\sigma_{3, pop}$ = proportional error for all the other patients; PopPK = population pharmacokinetics; PD = pharmacodynamics; Q = intercompartmental clearance; RSE = relative standard error; V2 = central volume of distribution; V3 = peripheral volume.

FIGURE 3. Goodness-of-fit plots of the final PopPK and PK/PD model

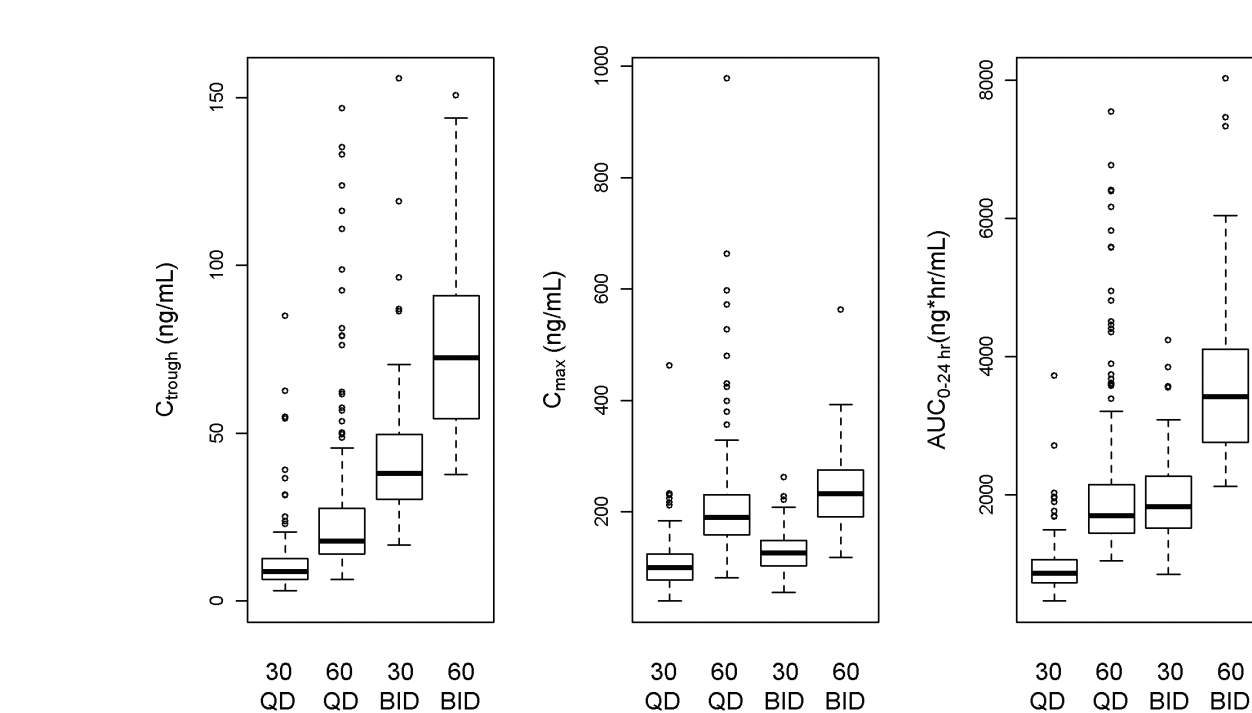


PopPK goodness-of-fit plot is shown only for the PRT018 study. iFXa = activity of intrinsic factor X; PopPK = population pharmacokinetics; PD = pharmacodynamics

PopPK and PK/PD Model Simulations

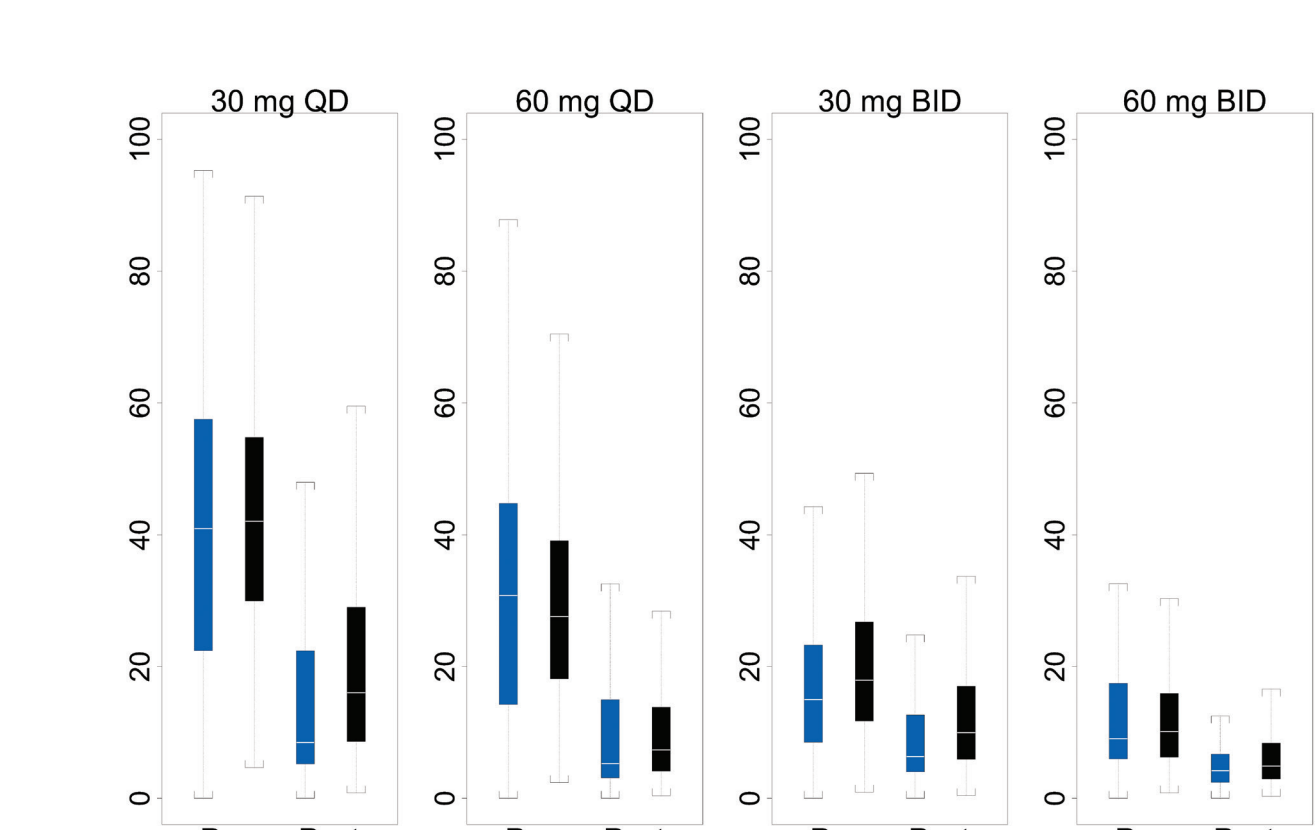
- Figure 4 shows the boxplots of PK exposure parameters (C_{trough} , C_{max} , AUC_{0-24hr}) and Figure 5 shows the boxplots of iFXa at predose and postdose for the 4 dose groups in the PRT018 study. The PK exposures show dose-strength-dependent and dosing-regimen-dependent trends. Similar trends can be observed in the boxplots of iFXa at predose. At postdose, iFXa differences are minimal because most of the FXa levels are well suppressed by edoxaban
- Figure 6 shows the edoxaban concentration profiles during a dosing cycle and the matching iFXa profiles, overlaid with the observed data. In general, the order of the observed bleeding events from the phase 2 study (Table 3, 30 mg QD < 60 mg QD < 30 mg BID < 60 mg BID) is
 - The same as the order of C_{trough}
 - The same as the order of the proportion of time that edoxaban concentration is maintained above a certain critical level
 - The same as the order of time duration that iFXa is maintained below a certain cutoff value ($T(iFXa \leq \alpha\%)$)
 - In the reverse order of Max iFXa, (ie, iFXa at predose)

FIGURE 4. Boxplots for the PK exposure parameters of the 4 dose groups in the PRT018 study



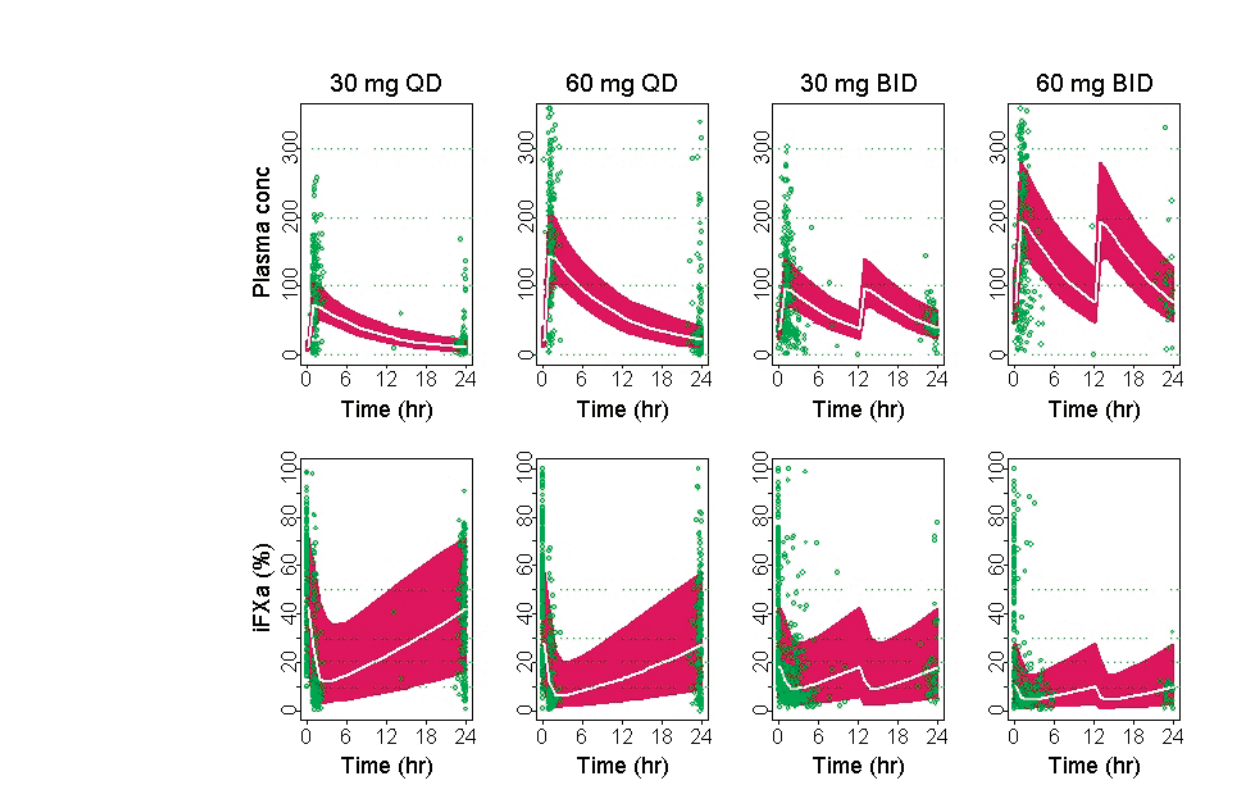
AUC_{0-24hr} = area under the concentration-time curve from 0 to 24 hours at steady state; BID = twice daily; C_{max} = peak plasma concentration; C_{trough} = trough plasma concentration; PK = pharmacokinetics; QD = once daily

FIGURE 5. Boxplots for the observed (blue) vs predicted (black) iFXa at predose and postdose for the 4 dose groups in the PRT018 study



BID = twice daily; QD = once daily

FIGURE 6. Edoxaban concentration and iFXa profiles overlaid with observed data



White line is the median line, shown with the 90% prediction interval. iFXa = activity of intrinsic factor X

TABLE 3. Summary of PK exposure parameters (mean ± standard deviation) and the observed bleeding events from the PRT018 study

Parameter	30 mg QD	60 mg QD	30 mg BID	60 mg BID
AUC_{0-24hr} (ng·hr/mL)	951 ± 397	2147 ± 1230	1916 ± 557	3630 ± 1098
C_{max} (ng/mL)	106.0 ± 47.4	212.5 ± 109.4	129.8 ± 36.5	238.0 ± 65.9
C_{trough} (ng/mL)	11.6 ± 10.5	33.3 ± 42.4	41.6 ± 17.9	80.4 ± 38.3
Mean iFXa (%)	26.6 ± 15.2	18.2 ± 13.2	12.4 ± 10.2	7.7 ± 7.8
Max iFXa (%)	46.6 ± 19.5	33.8 ± 20.3	19.3 ± 13.9	12.3 ± 10.7
Min iFXa (%)	10.3 ± 9.1	6.6 ± 6.3	7.6 ± 7.3	4.7 ± 5.8
Observed incidence of all bleeding events (% [n])	5.5 [13]	7.3 [17]	12.7 [31]	18.3 [33]

AUC_{0-24hr} = area under the concentration-time curve from 0 to 24 hours at steady state; BID = twice daily; C_{max} = peak plasma concentration; C_{trough} = trough plasma concentration; iFXa = activity of intrinsic factor X; PK = pharmacokinetics; QD = once daily

Logistic Regression Analysis Results

- Various PK exposure parameters and iFXa parameters were tested on the incidence of bleeding event using logistic regression analysis
- Due to the collinearity among the covariates, one covariate each was tested using linear relationship to bleeding event in the logit domain
- Max iFXa showed the most significance (Table 4). However, other PK exposure parameters (C_{trough} and AUC_{0-24hr}) and most of the iFXa parameters (Avg iFXa, $T(iFXa \leq \alpha\%)$ with α values of 10, 15, 20, and 25) showed significance as well ($P < 0.01$)
- Figure 7 shows the model predictive check run result for the example of $T(iFXa \leq 15\%)^4$

TABLE 4. Univariate logistic regression analysis results for all bleeds from the PRT018 study

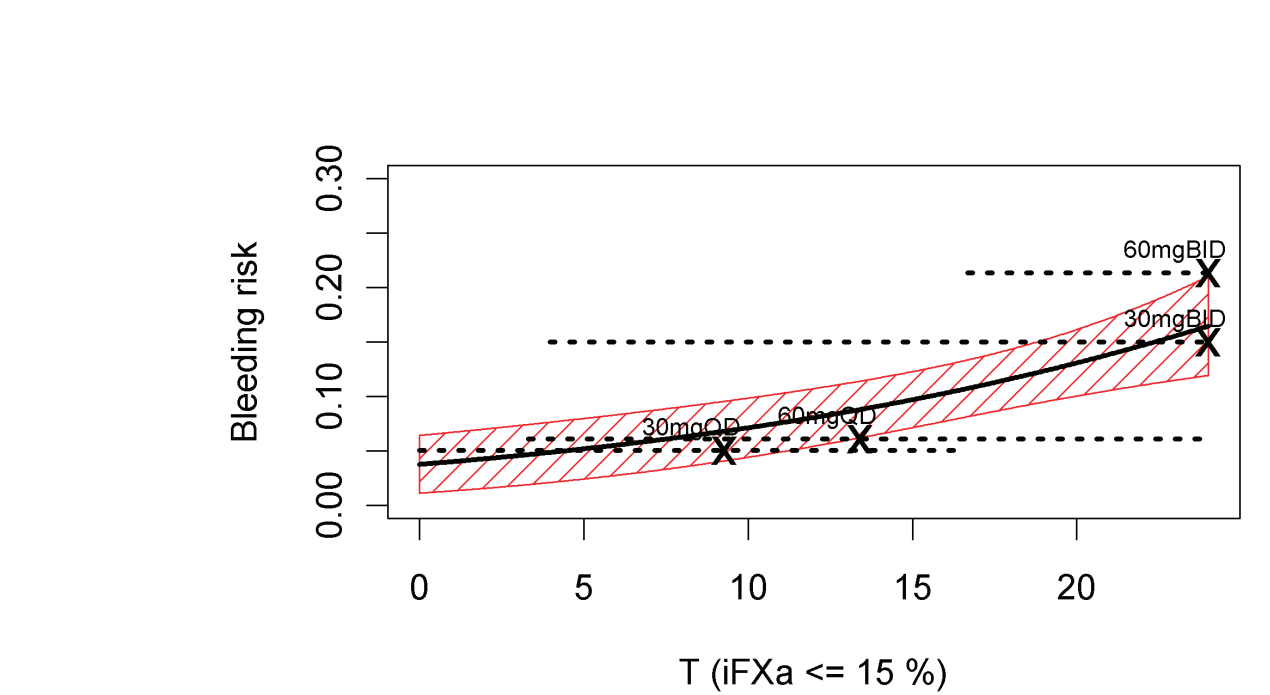
Covariate	Intercept	Slope	P-value
C_{max}	-2.52 (0.26)	0.0025 (0.0012)	0.0544
C_{trough}	-2.47 (0.19)	0.0087 (0.0028)	0.0035
AUC_{0-24hr}	-2.81 (0.26)	0.0003 (8.95E-05)	0.00063
Min iFXa	-5.17 (2.06)	-0.0330 (0.0219)	0.103
Max iFXa	-4.32 (0.67)	-0.0296 (0.0083)	7.02E-05
Avg iFXa	-5.51 (1.20)	-0.0340 (0.0137)	0.00089
$T(iFXa \leq 10\%)$	-2.80 (0.26)	0.0542 (0.0155)	0.00036
$T(iFXa \leq 15\%)$	-3.12 (0.35)	0.0622 (0.0176)	0.00015
$T(iFXa \leq 20\%)$	-3.37 (0.44)	0.0689 (0.0209)	0.00027
$T(iFXa \leq 25\%)$	-3.39 (0.51)	0.0655 (0.0238)	0.00214
$T(iFXa \leq 30\%)$	-3.35 (0.59)	0.0608 (0.0270)	0.012
$T(iFXa \leq 40\%)$	-3.37 (0.80)	0.0577 (0.0348)	0.0649

AUC_{0-24hr} = area under the concentration-time curve from 0 to 24 hours at steady state; C_{max} = peak plasma concentration; C_{trough} = trough plasma concentration; iFXa = activity of intrinsic factor X; T = time

Ordered Categorical Regression Analysis Result

- Bleeding data from the PRT018 study were organized as ordered categorical data of 0: no bleeds, 1: minor bleeds, 2: clinically relevant bleeds, and 3: major bleeds
- First, an incidence model was fit to the binary data of 0: no bleeds vs >0: bleeds. Since all PK exposure measures and iFXa parameters are correlated, the most significant parameter was chosen from the first stage of model building. These were then not considered in the later stages. From the 1st stage, Max iFXa was selected as the most significant factor ($P < 0.01$). Effect of country (2: East Europe [N=532] vs. 0 [EU, North America] or 3 [South America] [N=53]) was chosen to be the significant covariate from the second stage ($P < 0.01$). The significant country effect may indicate the impact of different methods of assessing the severity of bleeds depending on the geographical location, or might be due to something else that is unknown behind the country coding
- To further investigate the significant factors affecting the severity of bleeds, a subset dataset was created using only the patients who experienced bleeding. Then the ordered categorical model was fit to such event data. $T(iFXa \leq 20\%)$ was selected as the most significant factor ($P < 0.05$), whereas none of the PK parameters showed significance. The role of $T(iFXa \leq 20\%)$ in determining the severity of bleeds may imply a threshold mechanism of iFXa in producing anticoagulant effect. Also, disease status might be an important factor (CHADS₂ score with P -value of 0.05)
- To summarize, PK exposures (C_{trough} , AUC_{0-24hr}) affect the occurrence of bleeding, but iFXa determines the severity of bleeds as well as the incidence

FIGURE 7. Observed versus simulated bleeding risk



The x-axis values are the $T(iFXa \leq 15\%)$ in hours during a dosing period of one day. The y-axis values are the bleeding risk in probability. The horizontal dotted lines are the individual values of $T(iFXa \leq 15\%)$ in each dose group; 'x' sign shows the median value, and the extent of the line shows 80% range. The y-axis values of the 'x' sign are the observed bleeding risk for each dose group in the logistic regression analysis dataset (0.05, 0.06, 0.15, and 0.21 for 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID from the total N=585, respectively). The black solid line and the shaded interval are the median line and the 90% prediction interval of bleeding risk from the logistic regression model, respectively. BID = twice daily; iFXa = activity of intrinsic factor X; QD = once-daily; T = time

TABLE 5. Ordered categorical regression analysis result

Incidence Model (N=585)	P-value	Categorical Model (N=64)	P-value
1st stage		1st stage	
BASE		BASE	
C_{max}	0.0568	C_{max}	0.548
C_{trough}	0.00351	C_{trough}	0.386
AUC_{0-24hr}	0.00632	AUC_{0-24hr}	0.44
Min iFXa	0.103	Min iFXa	0.254
Max iFXa	7.03E-05	Max iFXa	0.0616
Mean iFXa	0.000893	Mean iFXa	0.097
$T(iFXa \leq 10\%)$	0.000363	$T(iFXa \leq 10\%)$	0.096
$T(iFXa \leq 15\%)$	0.000151	$T(iFXa \leq 15\%)$	0.0462
$T(iFXa \leq 20\%)$	0.000271	$T(iFXa \leq 20\%)$	0.0387
$T(iFXa \leq 25\%)$	0.00214	$T(iFXa \leq 25\%)$	0.0685
$T(iFXa \leq 30\%)$	0.012	$T(iFXa \leq 30\%)$	0.154
$T(iFXa \leq 40\%)$	0.065	$T(iFXa \leq 40\%)$	0.37
2nd stage		2nd stage	
Max iFXa		iFXa $\leq 20\%$	
CTRY = 2 (2 vs 0,3)	0.00142	CTRY = 2 (2 vs 0,3)	0.17
CHADS ₂ -2 (2 vs 3,4,5,6)	0.287	CHADS ₂ >2 (2 vs 3,4,5,6)	0.05

C_{trough} = trough plasma concentration; CTRY = country (0 = Europe, North America; 1 = Asia/Japan, 2 = East Europe, 3 = South America); CHADS₂: CHADS₂ score; iFXa = activity of intrinsic factor X; T = time

Conclusions

- The established PopPK and PK/PD models of edoxaban have good predictability with respect to the observed data
- The activity of intrinsic factor X (iFXa), as a combination of the extent (Max iFXa) and the duration ($T(iFXa \leq \alpha\%)$) of suppression, may provide a biological explanation for the greater bleeding risk observed from 30 mg BID compared with 60 mg QD, despite the same total daily dose
- The 30 mg QD and 60 mg QD regimens showed less and similar bleeding risk than the warfarin control treatment (5.5% and 7.3%, respectively, vs. 8.0%), and were successfully adopted in the phase 3 trials^{1,2}

References

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Acknowledgments

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