ORIGINAL ARTICLE

Model-Based Exposure–Response Analysis of Apixaban to Quantify Bleeding Risk in Special Populations of Subjects Undergoing Orthopedic Surgery

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Population pharmacokinetic (PK) and exposure–response analyses of apixaban were performed using data from phase I–III studies to predict bleeding risks for patients receiving apixaban 2.5 mg b.i.d. after total knee or hip replacement (TKR, THR) surgery (N = 5,510). Renal function, age, gender, and body weight impacted apixaban exposure. Bleeding risk increased as a function of exposure. Predicted bleeding frequencies for TKR and THR populations at risk for high apixaban exposure (female, age > 75 years, calculated creatinine clearance (cCrCL) < 30 ml/min, body weight < 50 kg) (6.85 and 10.3%, respectively) were comparable to the reference population (male/female, age 65–75 years, cCrCL ≥ 80 ml/min, body weight 65–85 kg) (6.18 and 9.32%, respectively). A 100% increase in apixaban exposure is expected to raise bleeding frequencies to 7.25% (TKR) and 10.9% (THR), whereas a 200% increase would raise them to 8.49 and 12.7%. Coexistence of combined patient risk factors or doubling of exposure is not likely to result in a substantial, clinically relevant increase in bleeding risk with 2.5 mg b.i.d. apixaban.
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e136; doi:10.1038/psp.2014.34; published online 17 September 2014

Venous thromboembolism (VTE) is a serious and potentially fatal complication after total knee or hip replacement (TKR or THR) surgery. Therefore, routine thromboprophylaxis with unfractionated heparin, low-molecular-weight heparin, or a vitamin K antagonist is generally recommended for subjects undergoing orthopedic surgery.[1] These agents have a long history of efficacy in the hospital setting, although drawbacks have limited their use in the outpatient setting. For example, unfractionated/low-molecular-weight heparins need to be administered as subcutaneous daily (or more frequent) injections and carry a risk of thrombocytopenia.[2–4] Vitamin K antagonists have high PK variability, significant food–drug interactions, and a narrow therapeutic window requiring frequent visits for laboratory monitoring and dose adjustment.[5–8] Thus, new anticoagulants with improved efficacy, lower bleeding risk, and more convenient formulations are needed to overcome the shortcomings of traditional agents and improve patient care.

Apixaban is an orally bioavailable, highly selective, reversible factor Xa inhibitor that exerts antithrombotic and anticoagulant effects by decreasing the generation of thrombin from prothrombin.[9–11] Apixaban has an oral bioavailability of ~50% and reaches a peak plasma concentration ~3h after oral administration.[9,12–15] It is eliminated via multiple pathways, including hepatic metabolism, biliary and intestinal excretion, and renal elimination.[14,16,17] The bioavailability of apixaban is not significantly affected by food.[9] The potential for co-medications to impact the exposure of apixaban is limited. Studies conducted in healthy subjects observed only a twofold increase in exposure (area under the concentration–time curve) after coadministration with ketoconazole, a strong inhibitor of both cytochrome P3A4 and P-glycoprotein, and a 50% decrease in exposure after coadministration with rifampin, a strong inducer of both cytochrome P3A4 and P-glycoprotein.[12]

In clinical studies of apixaban in the patient population, apixaban 2.5 mg twice daily (b.i.d.) was superior to enoxaparin 40 mg once daily (q.d.) for VTE prevention in subjects after TKR and THR, without an increase in the risk of bleeding.[18,19] Compared with enoxaparin 30 mg b.i.d., apixaban was similar in efficacy with reduced bleeding.[20] Therefore, apixaban provides a therapeutic advantage relative to current standards of care and is approved in several countries for the prevention of VTE after elective TKR or THR.

The objectives of the present analysis were to use a model-based approach to (i) characterize the relationship between apixaban dose and exposure (i.e., population PK) in subjects after TKR (12 days of treatment) and THR (35 days of treatment), (ii) identify covariates that may significantly impact exposure, and (iii) quantify the relationship between apixaban exposure and bleeding risk in the target population. This allowed for an evaluation of the potential need for dose adjustment in subpopulations that might be expected to have an increased risk for bleeding due to an increase in apixaban exposure.

RESULTS
Population pharmacokinetic model development
The apixaban population pharmacokinetic (PK) was described by a two-compartment disposition model with first-order absorption and elimination. Several covariate effects were identified as statistically significant in the population PK model (**Figure 1**). Apixaban clearance seemed to decrease in elderly and female subjects, and immediately after surgery. Apixaban clearance seemed to return to within 10% of pre-treatment by the fourth day after surgery. The central volume of distribution of apixaban seemed to increase with increasing body weight and decrease with decreasing hematocrit.

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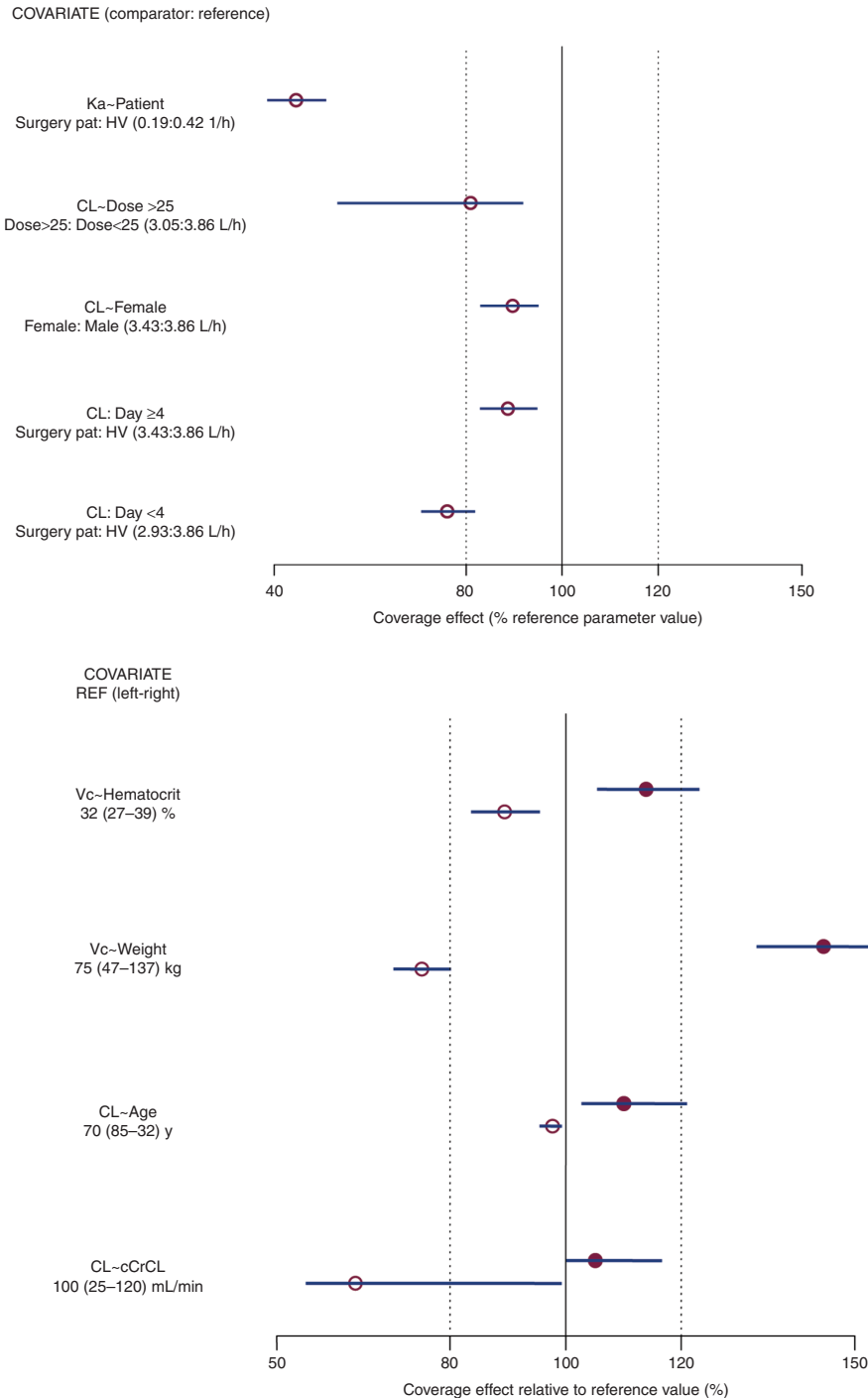
Figure 1 Effects of covariates in the population pharmacokinetic model. (**a**) The effect of categorical covariates on CL and Ka; (**b**) the effect of continuous covariates on CL and Vc. Open circles represent point estimates of the parameter estimate for the comparator relative to the parameter estimate for the reference on the percentage scale, and error bars represent 95% confidence intervals of effect obtained from 500 bootstrap replications; solid vertical line represents the covariate effect at the reference value of the covariate; dotted vertical lines represent the indicators of ±20% covariate effect. For continuous covariate effects, the parameter estimates for the comparator at the lower and upper bounds of the covariate are compared with the parameter estimate at the reference value for the covariate. For example, CL in a subject with cCrCL of 25 ml/min is ~35% lower than CL at the reference cCrCL (100 ml/min). cCrCL, calculated creatinine clearance; CL, clearance; HV, healthy volunteer; Ka, absorption rate constant; pat, patient; Vc, volume of distribution for central compartment.

The population PK model was evaluated using both visual and quantitative predictive checks. The quantitative predictive check was conducted by comparing the 10th, 50th, and 90th percentiles of observed trough plasma concentration with corresponding statistics calculated from simulated data using the final model. Results for both TKR and THR subjects
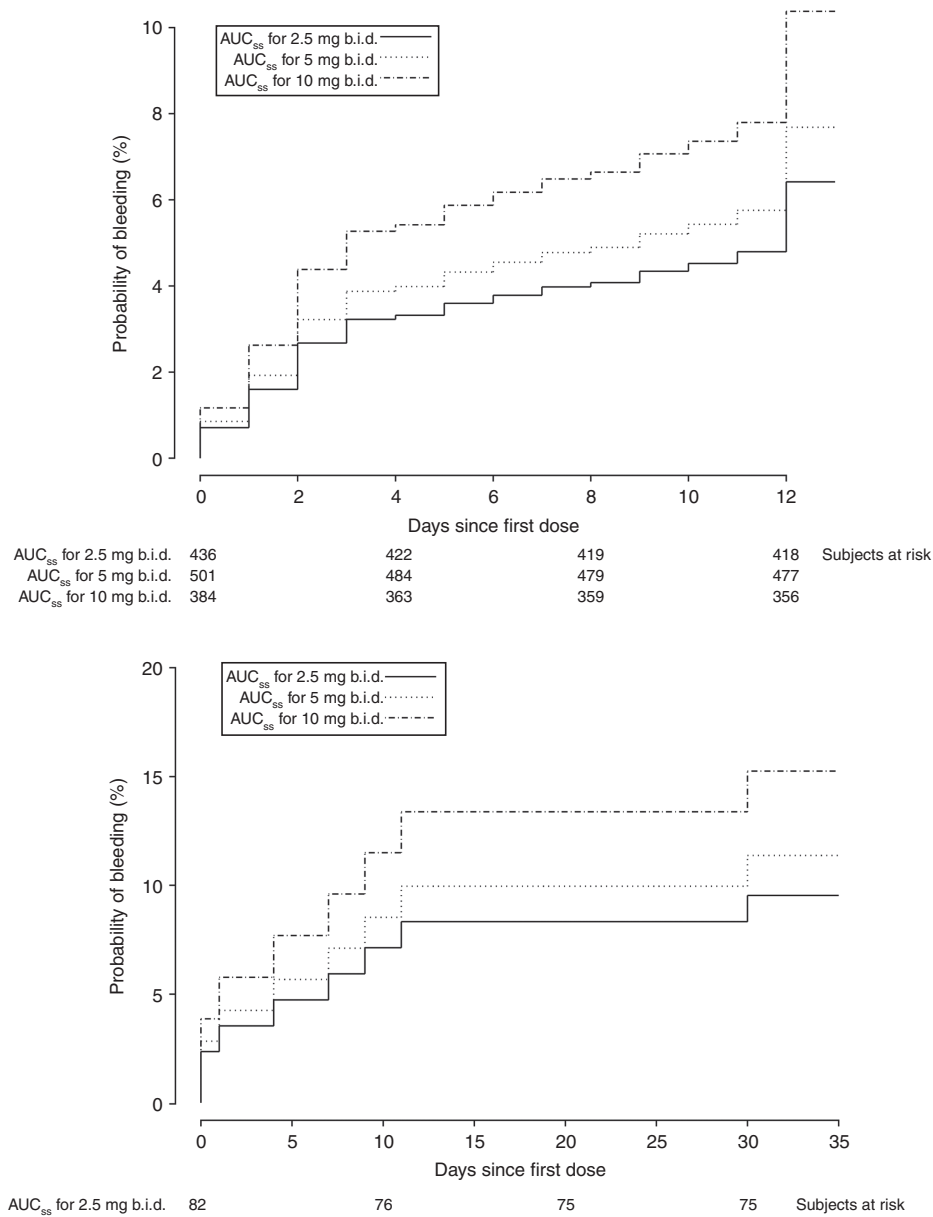
Figure 2 Exposure–response relationship vs. time for bleeding (including major bleeding, minor bleeding, potentially significant nonovert bleeding, clinically relevant nonmajor bleeding, and fatal bleeding) in TKR (ADVANCE 2, upper panel) and THR (ADVANCE 3, lower panel) populations. The different curves in the plot represent the probability of a bleed as a function of exposure over time for the 2.5-, 5-, and 20-mg b.i.d. dosages of apixaban. The observed bleeding event data are depicted at the bottom of each figure as the number of subjects at risk on days 0, 4, 8, and 12 for the range of exposures covered by the different dosages of apixaban in TKR subjects (upper panel) and on days 0, 10, 20, and 30 for the range of exposures covered by the 2.5-mg b.i.d. dosage in THR subjects (lower panel). AUC_{ss}, area under plasma concentration–time curve at steady state; b.i.d., twice daily; THR, total hip replacement; TKR, total knee replacement.

demonstrated that the model was able to predict the range of exposures in both of these populations. More detailed information on population PK model development and diagnostic evaluations can be found in the **Supplementary Material**.

Exposure–bleeding analysis

Figure 2 is a Kaplan–Meier plot that shows the observed relationship between apixaban exposure and the probability of a bleeding event as a function of time, after 12 days of treatment for TKR subjects and after 35 days of treatment for THR subjects. A Cox proportional hazards model was used

to characterize the relationship of apixaban exposure level and duration with bleeding risk. Of the covariates evaluated in the model (gender, dosing regimen, surgery type, and area under the concentration–time curve (AUC) at steady state (AUC_{ss})), only apixaban daily AUC_{ss} was found to be a significant predictor of bleeding risk. Bleeding risk was stratified by surgery type (TKR vs. THR). The interaction of surgery type with apixaban AUC_{ss} was evaluated, but not found to be statistically significant. This indicates that bleeding risk will be similar between the two populations for a similar level and duration of apixaban exposure. More detailed information

on development of the exposure–bleeding model can be found in the **Supplementary Material**. The point estimates (and 95% confidence intervals) for predicted bleeding after 12 days of treatment in TKR subjects as a function of apixaban exposure were 6.2% (4.4–8.7%), 7.4% (5.3–10%), and 10% (7.1–14%) for the 2.5-, 5-, and 10-mg b.i.d. dosages, respectively. The point estimates (and 95% confidence intervals) for predicted bleeding at day 35 in THR subjects as a function of apixaban exposure were 9.5% (4.8–18%), 11% (5.8–22%), and 15% (7.8–28%) for the 2.5-, 5-, and 10-mg b.i.d. dosages, respectively. The exposure–bleeding relationship seems to be relatively shallow (**Figure 3**). The observed rates of bleeding for each of the total daily doses (5, 10, and 20 mg/d) are shown in **Figure 3**, as are the observed rates for the 2.5-mg b.i.d. dosage in the phase III TKR and THR studies. The 95% confidence intervals for the model predictions seem to capture the observed bleeding rates for the 2.5-mg b.i.d. dosage in those studies (**Figure 3**).

Model-based simulations

Simulations from the population PK and exposure–bleeding models were used to predict changes in exposure and bleeding risk in the TKR and THR subpopulations potentially at risk for higher apixaban exposures and bleeding (**Table 1**). The model predicted that subjects with mild, moderate, and severe renal impairment would be expected to have median exposures that are ~19, 43, and 62% higher, respectively, than for subjects with normal renal function. The effects of other covariates were smaller when compared with calculated creatinine clearance (cCrCL, calculated using Cockroft-Gault equation), but would be expected to have a combined (although not additive) effect on apixaban exposure. For example, the model predicted that older age (>75 years) alone, lower weight (<50 kg) alone, and female gender alone

would increase apixaban total exposure by ~22, 33, and 9%, respectively, relative to a reference population (defined as age 65–75 years, cCrCL ≥ 80 ml/min, weight 65–85 kg). For a subject with all these factors combined (female, age > 75 years, cCrCL < 30 ml/min, weight < 50 kg), the exposure was expected to be only ~64% higher than for a reference population (**Table 1**).

Bleeding risk over the treatment period is expected to increase with an increase in apixaban exposure, which is affected by several covariates, as described above. The effect of covariate combinations that increase apixaban exposure (female gender, age > 75 years, cCrCL < 30 ml/min, and body weight < 50 kg) would be expected to increase bleeding risk by 11% (**Table 1**). Increases in apixaban exposure of 100% would be expected to increase bleeding risk by 18% relative to a reference population and represents the change in exposure that might be encountered in the presence of a strong inhibitor of cytochrome P3A4 and P-glycoprotein. A 200% increase in apixaban exposure would be expected to increase bleeding risk by 39%; however, such increased exposures were not seen during any clinical trials.

DISCUSSION

A population PK model was developed to characterize the relationship between apixaban dose and plasma exposure in TKR and THR subjects. Covariates were identified that explain some of the variability in the PK of apixaban. For a 30-year-old man not having surgery and with a cCrCL of 80 ml/min, the predicted renal and nonrenal component of apparent plasma clearance of apixaban (CL_R/F) and CL_{NR}/F would be 1.19 and 3.10 l/h, respectively, such that renal clearance would account for ~28% of total plasma apixaban
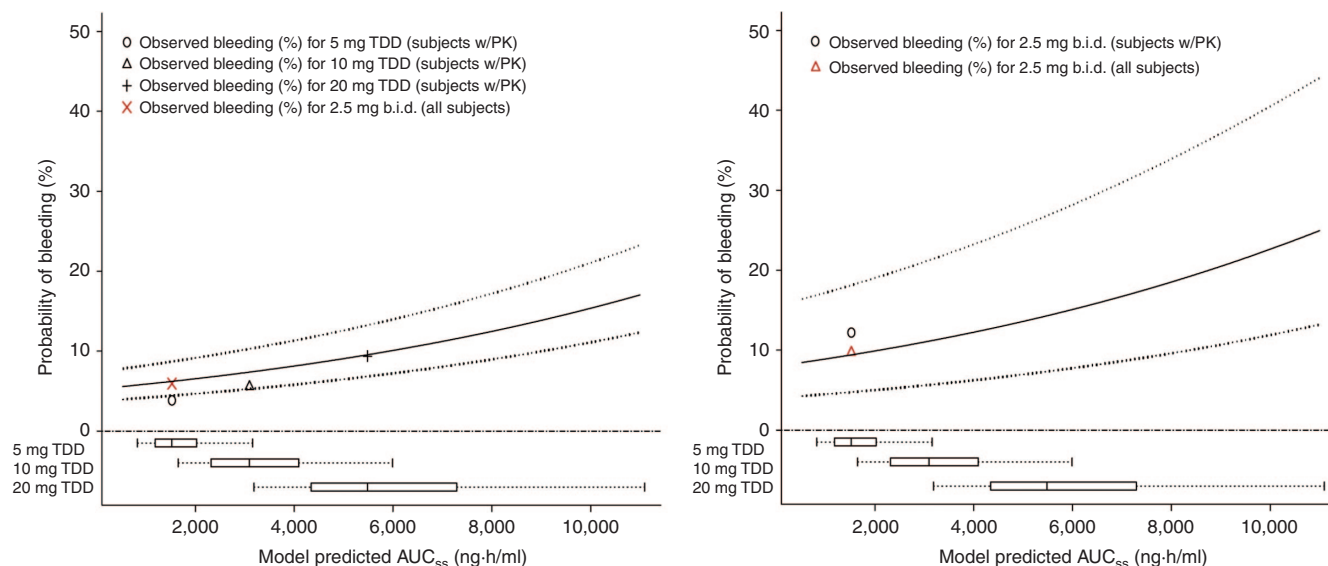
Figure 3 Exposure–response relationship for bleeding (including major bleeding, minor bleeding, potentially significant nonovert bleeding, clinically relevant nonmajor bleeding, and fatal bleeding) in TKR (ADVANCE 2, left panel) and THR (ADVANCE 3, right panel) subjects. Solid line represents the median bleeding probability and dotted lines represent the 95% confidence intervals. Observed bleeding (%) in "subjects w/PK" indicates the subjects in the E-R analysis dataset, whereas "all subjects" indicates the observed rate from the overall ADVANCE 2 and 3 populations, respectively. AUC_{ss}, area under plasma concentration–time curve at steady state; b.i.d., twice daily; TDD, total daily dose; THR, total hip replacement; TKR, total knee replacement.

Table 1 Predicted bleeding probability (%) for apixaban 2.5-mg b.i.d. dosage in TKR (ADVANCE 2) and THR (ADVANCE 3) subpopulations

Subject type	Change in exposure (%)[a]	TKR (95% CI)[b,c]	THR (95% CI)[b,d]	Hazard ratio[e] (95% CI)
Reference subject (male/female, age 65–75 years, cCrCL ≥ 80 ml/min, body weight 65–85 kg)	0	6.18 (4.41–8.65)	9.32 (4.72–18.0)	Ref.
Severe renal impairment (cCrCL ≥15–<30 ml/min)	57.6	6.79 (4.84–9.48)	10.1 (5.14–19.5)	1.10 (1.00–1.17)
Moderate renal impairment (cCrCL ≥30–<50 ml/min)	38.4	6.58 (4.69–9.19)	9.87 (5.00–19.0)	1.06 (1.00–1.11)
Mild renal impairment (cCrCL ≥50–<80 ml/min)	14.6	6.33 (4.51–8.85)	9.51 (4.82–18.3)	1.02 (1.00–1.04)
Normal renal function (cCrCL ≥80 ml/min)	–4.64	6.14 (4.47–8.71)	9.21 (4.66–17.8)	0.991 (0.985–1.00)
Low exposure (male, age <65 years, cCrCL ≥80 ml/min, body weight >120 kg)	–18.5	6.00 (4.28–8.40)	9.04 (4.57–17.5)	0.969 (0.949–0.999)
High exposure (female, age >75 years, cCrCL <30 ml/min, body weight <50 kg)	63.6	6.85 (4.89–9.57)	10.3 (5.23–19.8)	1.11 (1.00–1.19)
Twofold increase in apixaban exposure	100	7.25 (5.18–10.1)	10.9 (5.52–20.8)	1.18 (1.01–1.31)
Threefold increase in apixaban exposure	200	8.49 (6.07–11.8)	12.7 (6.46–24.0)	1.39 (1.01–1.72)

Bleeding probabilities are for predicted median apixaban exposures in the TKR and THR special populations. Bleeding events include major bleeding, minor bleeding, potentially significant nonovert bleeding, clinically relevant nonmajor bleeding, and fatal bleeding.

AUC_{ss}, area under plasma concentration–time curve at steady state; b.i.d., twice daily; cCrCL, calculated creatinine clearance; CI, confidence interval; THR, total hip replacement; TKR, total knee replacement.

[a]Change in exposure (daily AUC_{ss}) relative to the reference subject. [b]CIs represent the uncertainty in the prediction from exposure–response model for bleeding only. [c]Bleeding probability after 12 days of apixaban treatment. [d]Bleeding probability after 35 days of apixaban treatment. [e]Hazard ratio relative to reference subject for 2.5-mg b.i.d. dosage of apixaban.

CL/F. This prediction is consistent with estimates in healthy subjects, based on noncompartmental analysis.[13] The population PK model suggests there is a reduction in total plasma CL/F of 24% in the 3 days immediately after wound closure in TKR and THR subjects. The reduced clearance in the days after surgery may arise from the reduced blood flow to the liver, kidney, and gastrointestinal tract after surgery.[21] Apixaban volume of distribution was found to correlate with mean postsurgery hematocrit in TKR and THR subjects. This association may be linked to changes in hemodynamics after surgery[22]; however, subjects with a low mean hematocrit (27%) would not be expected to have a reduction in volume of distribution (<20% decrease) that would be associated with a clinically meaningful change in peak or trough plasma apixaban concentrations.

A previous exploratory exposure–response analysis based on a phase II clinical study in TKR subjects identified gender and AUC_{ss} as significant predictors of bleeding[23]; however, of the variables tested in the current exposure–response analysis, only daily AUC_{ss} was a significant predictor of bleeding. In phase III studies, the observed frequency of postsurgery bleeding events for all apixaban-treated TKR and THR subjects was 5.9 and 9.8%,[24] respectively, which is similar to the model-predicted frequency of any bleeding (6.2 and 9.3%, respectively) in the reference population (**Table 1**). This suggests that, even though only a subset of the TKR and THR subjects was available for development of the exposure–bleeding model, it is representative of the overall target population.

Bleeding risk was also evaluated in subpopulations in which apixaban exposure could be altered by renal function, age, gender, and body weight as well as the combination of these factors. Although severe renal impairment alone would be expected to increase apixaban exposure by 58%, because of the shallow exposure–response relationship, this increase in exposure would not be expected to markedly increase the risk of bleeding in the TKR or THR target population. The combination of other intrinsic factors with renal impairment (e.g., age, body weight) does not seem to significantly increase apixaban exposure for the subpopulation. This is likely because of the high correlation of age and body weight with cCrCL. Results of the simulations suggest that for the apixaban 2.5-mg b.i.d. dosage, bleeding risk would be 6.85 and 10.3% in patients with combined risk factors (female gender, age > 75 years, cCrCL < 30 ml/min, body weight < 50 kg) after TKR and THR, respectively. Although higher than in typical subjects treated with this apixaban dose, this bleeding risk is similar to that observed in an overall population of subjects treated with enoxaparin 40 mg q.d. (6.8% (TKR) and 11.0% (THR)).[24] Furthermore, a pooled statistical analysis of major venous thromboembolism (VTE) and bleeding using multivariate logistic regression yielded no convincing evidence that age, weight, gender, or creatinine clearance individually influenced the balance of benefit to risk for apixaban vs. enoxaparin, which is consistent with the findings of the current analysis.[25]

The relationship between apixaban exposure and efficacy was explored, but a statistically significant relationship could not be detected. This is likely because of a shallow exposure–response relationship (The slope of the exposure–response relationship for VTE was estimated to be 0.0499 ± 0.0578 ml/μg/h) and the low rate of VTE events; however, a recently published, model-based meta-analysis of different anticoagulant treatments for VTE prevention demonstrated a reduction in VTE events and an increase in bleeding events as a function of the dose of factor Xa inhibitors.[26] The bleeding frequency reported in this meta-analysis for apixaban was similar to that reported for the current study.

In conclusion, the use of a model-based approach facilitated integration of PK and bleeding data from clinical trials of apixaban in a manner that permitted prediction of bleeding risk in clinically relevant scenarios and subpopulations of

Table 2 Summary of studies and data used for population pharmacokinetic and exposure–bleeding analyses

Study type	Doses	Target population	Treatment duration	No. of subjects[a]	PK observations (no. of subjects)	Bleeding events[b] (no. of subjects)
Phase I studies						
Multiple doses[14]	2.5–25 mg b.i.d., 10–25 mg q.d.	Healthy	7 days	36	1,052 (36)	None
Single dose[9]	2.5, 10, 25, 50 mg	Healthy Caucasian and Japanese	Single dose	24	1,440 (24)	None
Age and gender[28]	20 mg	Healthy	Single dose	79	1,121 (79)	None
Multiple doses[33]	2.5, 5, 10 mg b.i.d.	Healthy Japanese	7 days	24	639 (18)	None
Multiple doses[31]	10 mg single dose, then 10 mg b.i.d.	Healthy Chinese	Single dose, then 6 days	12	356 (12)	None
Body weight[32]	10 mg	Healthy	Single dose	55	693 (55)	None
Renal impairment[27]	10 mg	Healthy and renally impaired	Single dose	32	523 (32)	None
Phase II VTEp studies						
Dose response[30]	5, 10, 20 mg q.d.	Advanced cancer[c]	12 weeks	96	267 (87)	6 (96)[e]
APROPOS[29] dose response	2.5, 5, 10 mg b.i.d.; 5, 10, 20 mg q.d.	TKR[d]	12 days	916	4,645 (853)	53 (853)
Phase III VTEp studies						
ADVANCE-2[18] confirmatory	2.5 mg b.i.d.	TKR[f]	12 days	1528	49 (6)	1 (6)
ADVANCE-3[19] confirmatory	2.5 mg b.i.d.	THR[f]	35 days	2708	467 (82)	10 (82)

b.i.d., twice daily; INR, international normalized ratio; PK, pharmacokinetic; q.d., once daily; THR, total hip replacement; TKR, total knee replacement.
[a]Number of subjects randomized to apixaban. [b]Bleeding events refer to any bleeding, including major bleeding, minor bleeding, potentially significant nonovert bleeding, clinically relevant nonmajor bleeding, and fatal bleeding. The definition of major bleeding was adapted from the International Society on Thrombosis and Haemostasis (ISTH) definition. The Independent Central Adjudication Committee (ICAC) validated bleeding events according to guidelines using standardized criteria. [c]Other treatment: placebo q.d. [d]Other treatment: warfarin: 5 mg q.d. titrated to INR of 1.8 to 3.0; enoxaparin: 30 mg b.i.d. subcutaneously. [e]Bleeding event information was collected in this study but not used in the exposure–response analysis. [f]Other treatment: enoxaparin 40 mg q.d. subcutaneously.

TKR and THR subjects. The bleeding probability for apixaban 2.5 mg b.i.d. is expected to increase by less than 1% increase even in subjects whose apixaban exposure is potentially increased because of impaired renal function, low body weight, old age, and/or gender.[27]

METHODS
Study populations and data
Data for apixaban population PK and exposure–response analyses were obtained from 11 clinical studies (**Table 2**).[9,14,18,19,28–34] All available PK data from 11 studies have been used for population PK analysis. Exposure–bleeding analysis was conducted using data from one phase II study and two phase III studies. Because no VTE events occurred in the subset of subjects (*n* = 88) from the phase III studies contributing data to the population PK analysis, an exposure–efficacy analysis was not performed. An exploratory exposure–response analysis based on phase II data was previously reported.[23] Intensive PK samples were collected for up to 72 h postdose for the phase I studies, and sparse samples were collected for the phase II and III studies. Plasma apixaban concentration was quantified using a validated liquid chromatography–tandem mass spectrometry method, with a lower limit of quantification of 1 ng/ml and calibration curves ranging from 1 to 1,000 ng/ml.[17] Bleeding events included major bleeding, minor bleeding, potentially significant nonovert bleeding, clinically relevant nonmajor bleeding, and fatal bleeding (i.e., collectively called any bleeding, and hereafter, referred to as bleeding). Only events

that occurred after the first dose of apixaban were included. For individuals with more than one bleeding event, only the first recorded event was used.

Population PK analysis
The relationship of apixaban dose with exposure was characterized by a nonlinear mixed-effects ("population") compartmental model using NONMEM (version VI, level 1.1; GloboMax LLC, Hanover, MD). Before the evaluation of covariate effects, a parsimonious, base population PK model was selected using the Schwartz Bayesian Criterion to facilitate selection between hierarchical and nonhierarchical submodels[35]:

$$\text{SBC} = OFV + N_{P \cdot \log(Nobs)},$$

where *OFV*, objective function value, is equivalent to –2 log-likelihood of the data given in the model, *NP* is the number of parameters in the model, and *Nobs* is the number of observations in the dataset. In addition, diagnostic plots were evaluated to identify any trends in the base model predictions or residuals that indicate poor fit of the model to the data.

Alternative structural models were assessed to identify the one that could most appropriately describe the PKs of apixaban. Because renal elimination is known to account for approximately one third of apixaban clearance,[13,15] the effect of cCrCL on the CL/F of apixaban was incorporated into the base model. cCrCL was derived from Cockroft-Gault equation.[36] An E_MAX model was used to describe the relationship between cCrCL and apixaban CL/F:

$$CL_i / F = CL_{NR} / F + \frac{CL_{R,MAX} / F \times cCrCL^\gamma}{cCrCL_{50}^\gamma + cCrCL^\gamma},$$

$$cCrCL\left(\frac{mL}{min}\right) = \frac{(140 - Age) \times Body\ Weight(kg) \times [0.85\ if\ Female]}{72 \times Serum\ Creatinine\left(\frac{mg}{dL}\right)}$$

where CL_{NR}/F is the nonrenal component of apparent plasma clearance of apixaban, $CL_{R,MAX}/F$ is the maximal renal component of apparent plasma clearance of apixaban, $cCrCL_{50}$ is the value of cCrCL at which 50% of the maximum renal clearance of apixaban occurs, and $\tilde{a}$ is the shape parameter that describes the steepness of the relationship between cCrCL and renal clearance. Incorporation of this function to separate the renal and nonrenal components of total apparent plasma clearance of apixaban allows the estimation of the effects of covariates that may impact the nonrenal clearance of apixaban, but are highly correlated with cCrCL (e.g., age, body weight, and gender).

Given the dissolution rate-limited absorption of apixaban at doses >10 mg,[37] the loss of dose-proportional exposure as a function of dose was incorporated into the base model as a reduction in bioavailability of higher doses of apixaban relative to the 2.5 mg dose (F_{rel}) as a continuous function of dose using the following equation:

$$F_{rel,dose} = 1 - \frac{I_{MAX} \times Dose^\gamma}{ED_{50}^\gamma + Dose^\gamma}$$

where $F_{rel,dose}$ is the relative bioavailability of a given dose (*Dose*), I_{MAX} is the maximum reduction in relative bioavailability, ED_{50} is the dose at which half of the maximal reduction in $F_{rel,dose}$ is achieved, and $\tilde{a}$ is the shape parameter that controls the shape of the relationship between dose and $F_{rel,dose}$.

Once the base model was established, the full-covariate model was developed by incorporating all potentially significant covariates. The covariate–parameter relationships were screened both visually and statistically. The relationship between the typical value of a parameter (*PTV*) and a continuous covariate (*R*) was tested using the following relationship:

$$P_{TV} = P_1 \left(\frac{R}{R_{ref}}\right)^{p_2}$$

where *P*1 and *P*2 are fixed-effect parameters and *Rref* is a reference value of the covariate. The median value for the TKR and THR populations combined was used as the reference value for continuous covariates.

The proportional relationship between the typical value of a parameter (*PTV*) and a categorical covariate was tested using the following relationship:

$$P_{TV} = e^{P_i} \prod_{m=2}^{M} e^{P_m I_m}$$

where *Pm* (*m*=1, ..., M) are fixed-effect parameters and *Im* is an indicator variable where *Im*=1 for the *m*th category, and 0 otherwise.

The population PK model was developed from the full-covariate model by excluding nonsignificant covariate–parameter relationships to provide the most parsimonious model. A stepwise backward elimination procedure was used to retain only significant covariates as determined via Schwartz Bayesian Criterion in the model. Five hundred bootstrap replications of the original dataset and model estimation were generated to obtain robust confidence intervals for the final model parameter estimates. The final model was evaluated using both visual and quantitative predictive checks by comparing model-predicted values with observed data. Predictive checks were performed with 500 Monte Carlo-simulated datasets obtained from the population PK model, as described previously.[38]

Exposure–bleeding analysis

To model the relationship between apixaban exposure and bleeding events, a Cox proportional hazards time-to-event analysis was performed. This approach allows incorporation of the timing of the bleeding event, in addition to the degree of apixaban exposure, when characterizing the exposure–response relationship. Cox proportional hazards modeling was performed in Spotfire S-Plus (version 8.1 for Linux, Insightful Corporation, Seattle, WA).

A complete model development procedure to investigate all available covariate effects was not performed in the current analysis because this had been conducted in previously reported work.[23] As with the previously published analysis, daily AUC_{ss} was used as the exposure measure to predict bleeding risk. A full model approach was used in which all covariates were incorporated into the model simultaneously, as well as all potential interactions between the covariates and the exposure parameter. The equation for the full model, stratified by surgery type (THR vs. TKR), is shown below:

$$\lambda_{surg}(t) = \exp\begin{pmatrix} \alpha + \beta_1.AUC_{SS} + \beta_2.Reg + \beta_3.Sex + \\ \beta_4.AUC_{SS} \times Reg + \beta_5.AUC_{SS} \times Sex \\ + \beta_6.AUC_{SS} \times Surg \end{pmatrix},$$

where λ_{Surg} is the frequency of the bleeding events as a function of time, apixaban exposure, and surgery type; $\acute{a}$ is the baseline hazard function; $\hat{a}_1$ is the estimate of the effect of apixaban exposure (AUC_{ss}) on the rate of bleeding; $\hat{a}_2$ is the estimate of the effect of dosing regimen (*Reg*) on the rate of bleeding; and $\hat{a}_3$ is the estimate of the effect of gender (*Sex*) on the rate of bleeding. The interactions between AUC_{ss} and the other predictor variables were also included in the full model and are represented by the coefficients $\hat{a}_4$ ($AUC_{ss} \times Reg$) and $\hat{a}_5$ ($AUC_{ss} \times Sex$). Surgery type (THR vs. TKR) was used as a stratification variable to account for any potential differences between the two populations that are not related to the covariate effects of interest. Therefore, the interaction between the stratification variable and AUC_{ss} was also tested [$\hat{a}_6$ ($AUC_{ss} \times Surg$)].

A stepwise backward elimination was performed to obtain a final parsimonious model. Because hierarchical models were evaluated, model selection was based on the likelihood ratio test, with a critical *P* value of 0.01, which

translates to a change in –2 times the log-likelihood of 6.63 for 1 degree of freedom based on a chi-squared test. After arriving at the final model, alternate functional forms for incorporation of the effect of apixaban daily AUC_{ss} were tested; these included the log AUC_{ss}, the restricted cubic spline of AUC_{ss}, and the second-order polynomial transformation of AUC_{ss}.

Model evaluation was performed with a predictive check. The final model was evaluated by comparing the observed proportion of subjects achieving a safety event with the 95% prediction interval of the exposure–safety relationship. The 95% prediction interval was obtained from the variance–covariance matrix defined by 1,000 bootstrap replications of the final model.

Model-based simulations

To determine the range of apixaban exposure that may be expected in the TKR and THR populations, 500 trials of 10,000 subjects each treated with the 2.5-mg b.i.d. regimen were simulated using the population PK model. Each individual trial simulation was conducted with a new set of population parameters that were sampled from the variance–covariance matrix of the 500 bootstrap parameter estimates from the final model. In addition, a new set of covariates were produced for each trial by sampling from the means and variance–covariance matrix of the covariates in the phase III TKR and THR population samples.

To determine the exposures that may be expected in subpopulations of the TKR and THR population, 500 trials of 50,000 subjects each treated with the apixaban 2.5-mg b.i.d. regimen were simulated from the population PK model, as described above. Daily AUC_{ss} was calculated for each individual in each simulation using the individual plasma CL/F estimates.

To determine the bleeding risk in specific subpopulations relative to the reference population, the simulated daily AUC_{ss} (median, 5th and 95th percentiles) described above was used as input to the exposure–bleeding model to predict the range of bleeding probabilities to be expected in these populations. The reference population for clinical trial simulations was defined as male and female subjects 65–75 years of age with a cCrCL ≥80 ml/min and body weight of 65–85 kg. Confidence intervals were calculated for each estimated bleeding probability using the variance–covariance matrix derived from 1,000 bootstrap replications of the exposure–bleeding model.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Apixaban, an orally bioavailable, highly selective factor Xa inhibitor, exerts antithrombotic and anticoagulant effects by decreasing generation of thrombin from prothrombin.[9–11] Apixaban improves benefit/risk vs. enoxaparin for VTE prevention in subjects after TKR and THR.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Mathematical models developed based on integrated data from clinical trials of apixaban in patients and healthy subjects predict bleeding risk as a function of apixaban exposure in clinically relevant scenarios of VTE prevention with apixaban in TKR and THR.[18–20]

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ Bleeding probability for apixaban is expected to increase by less than 1% even in subjects whose apixaban exposure is potentially increased because of impaired renal function, low body weight, old age, and/or gender.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ This analysis supports the favorable benefit–risk profile of apixaban in prophylactic doses, and the recommendation that apixaban dose does not need to be adjusted routinely for bleeding reasons in VTE prevention patients with factors that may increase apixaban exposure.

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