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.

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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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.
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. The change in exposure that might be encountered in the presence of a strong inhibitor of cytochrome P450 would be captured using CYP3A4 and P-glycoprotein, and 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/F) and Clrenal/F would be 1.19 and 3.10 l/h, respectively, such that renal clearance would account for ~28% of total plasma apixaban exposure. The 95% confidence intervals for the model predictions 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 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).
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 CL/F. This prediction is consistent with estimates in healthy subjects, based on noncompartamental analysis.\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsubscript{ss} as significant predictors of bleeding\textsuperscript{23}; however, of the variables tested in the current exposure–response analysis, only daily AUC\textsubscript{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\%,\textsuperscript{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)).\textsuperscript{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.\textsuperscript{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.\textsuperscript{26} The bleeding frequency reported in this meta-analysis for apixaban was similar to that reported for the current study.

### 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 (%)\textsuperscript{a} | TKR (95\% CI)\textsuperscript{b,c} | THR (95\% CI)\textsuperscript{b,c} | Hazard ratio\textsuperscript{a} (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.

\textsuperscript{a}Change in exposure (daily AUC\textsubscript{ss}) relative to the reference subject. \textsuperscript{b}CIs represent the uncertainty in the prediction from exposure–response model for bleeding only. \textsuperscript{c}Bleeding probability after 12 days of apixaban treatment. \textsuperscript{d}Bleeding probability after 35 days of apixaban treatment. \textsuperscript{e}Hazard ratio relative to reference subject for 2.5-mg b.i.d. dosage of apixaban.
Table 2 Summary of studies and data used for population pharmacokinetic and exposure–bleeding analyses

| Study type       | Doses                          | Target population          | Treatment duration | No. of subjectsa | PK observations (no. of subjects) | Bleeding eventsb (no. of subjects) |
|------------------|--------------------------------|-----------------------------|--------------------|------------------|-----------------------------------|-----------------------------------|
| Phase I studies  |                                |                             |                    |                  |                                   |                                   |
| Multiple doses   | 2.5–25 mg b.i.d., 10–25 mg q.d.| Healthy                     | 7 days             | 36               | 1,052 (36)                       | None                              |
| Single dose      | 2.5, 10, 25, 50 mg              | Healthy Caucasian and Japanese | Single dose       | 24               | 1,440 (24)                       | None                              |
| Age and gender   | 20 mg                          | Healthy                     | Single dose        | 79               | 1,121 (79)                       | None                              |
| Multiple doses   | 2.5, 5, 10 mg b.i.d.            | Healthy Japanese            | 7 days             | 24               | 639 (18)                         | None                              |
| Multiple doses   | 10 mg single dose, then 10 mg b.i.d. | Healthy Chinese          | Single dose, then 6 days | 12              | 356 (12)                         | None                              |
| Body weight      | 10 mg                          | Healthy                     | Single dose        | 55               | 693 (55)                         | None                              |
| Renal impairment | 10 mg                          | Healthy and renally impaired | Single dose        | 32               | 523 (32)                         | None                              |
| Phase II VTEp studies |                           |                             |                    |                  |                                   |                                   |
| Dose response    | 5, 10, 20 mg q.d.               | Advanced cancer              | 12 weeks           | 96               | 267 (87)                         | 6 (96)a                           |
| APROPOS29 dose response | 2.5, 5, 10 mg b.i.d.; 5, 10, 20 mg q.d. | TKRf                      | 12 days            | 916              | 4,645 (853)                      | 53 (853)                          |
| Phase III VTEp studies |                           |                             |                    |                  |                                   |                                   |
| ADVANCE-2:19 confirmatory | 2.5 mg b.i.d.                  | TKRf                       | 12 days            | 1528             | 49 (6)                           | 1 (6)                             |
| ADVANCE-3:19 confirmatory | 2.5 mg b.i.d.                  | THRf                       | 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.

aNumber of subjects randomized to apixaban. bBleeding 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. cOther treatment: placebo q.d. dOther treatment: warfarin: 5 mg q.d. titrated to INR of 1.8 to 3.0; enoxaparin: 30 mg b.i.d. subcutaneously. eOther treatment: enoxaparin 40 mg q.d. subcutaneously.

METHODS

Study populations and data

Data for apixaban population PK and exposure–response analyses were obtained from 11 clinical studies (Table 2). 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. Intensive PK samples were collected for up to 72h 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 level of quantification of 1 ng/ml and calibration curves ranging from 1 to 1,000 ng/ml. 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.

\[
SBC = OFV + N_P \log(N_{obs})
\]

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, the effect of cCrCL on the CL/F of apixaban was incorporated into the base model. cCrCL was derived from Cockcroft-Gault equation. An EMAX model was used to describe the relationship between cCrCL and apixaban CL/F.
The population PK model was developed from previously reported work. \(^2\) As with the previously published analysis, daily AUC\(_{\text{ss}}\) 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:

\[
\lambda_{\text{surg}}(t) = \exp \left( \alpha + \beta_1 \text{AUC}_{\text{ss}} + \beta_2 \text{Reg} + \beta_3 \text{Sex} + \beta_4 \text{AUC}_{\text{ss}} \times \text{Reg} + \beta_5 \text{AUC}_{\text{ss}} \times \text{Sex} \right),
\]

where \(\lambda_{\text{surg}}\) is the frequency of the bleeding events as a function of time, apixaban exposure, and surgery type; \(\alpha\) is the baseline hazard function; \(\hat{\alpha}\) is the estimate of the effect of apixaban exposure (AUC\(_{\text{ss}}\)) on the rate of bleeding; \(\hat{\beta}_1\) is the estimate of the effect of dosing regimen (Reg) on the rate of bleeding; and \(\hat{\beta}_2\) is the estimate of the effect of gender (Sex) on the rate of bleeding. The interactions between AUC\(_{\text{ss}}\) and the other predictor variables were also included in the full model and are represented by the coefficients \(\hat{\beta}_4\) (AUC\(_{\text{ss}}\) \times Reg) and \(\hat{\beta}_5\) (AUC\(_{\text{ss}}\) \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\(_{\text{ss}}\) was also tested [\(\hat{\beta}_4\) (AUC\(_{\text{ss}}\) \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
translated 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.

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Conflict of interest. T.A.L., C.F., X.W., and F.L. are employees of Bristol-Myers Squibb. M.P. was an employee of Bristol-Myers Squibb at the time of research.

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. 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.

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.

1. Geerts, W.H. et al.; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133, 3615–453S (2008).
2. Hirsh, J., Bauer, K.A., Donati, M.B., Gould, M., Samama, M.M. & Wolz, J.J.; American College of Chest Physicians. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133, 1415–169S (2008).
3. Martel, N., Lee, J. & Wells, P.S. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 106, 2710–2715 (2005).
4. Morris, T.A., Castrejón, S., Devendra, G. & Gamst, A.C. No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: a meta-analysis. Chest 132, 1131–1139 (2007).
5. Ansell, J., Hirsh, J., Hylek, E., Jacobson, A., Crowther, M. & Palareti, G.; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133, 160S–198S (2008).
6. Harris, J.E. Interaction of dietary factors with oral anticoagulants: review and applications. J. Am. Diet. Assoc. 95, 580–584 (1995).
7. Hawkins, D. Limitations of traditional anticoagulants. Pharmacotherapy 24, 62S–65S (2004).
8. Reinken, J.B. & Adang, A.E. Strategies and progress towards the ideal orally active thrombin inhibitor. Curr. Pharm. Des. 5, 1043–1075 (1999).
9. Frost, C. et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics and pharmacodynamics in healthy subjects. Br. J. Clin. Pharmacol. 75, 476–487 (2013).
10. Pinto, D.J. et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-4-aryl-5-[(1H-pyrrolo[2,3-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. J. Med. Chem. 50, 5339–5356 (2007).
11. Wong, P.C. et al. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antithrombotic studies. J. Thromb. Haemost. 6, 820–829 (2008).
12. Bristol-Myers Squibb. Eliquis® (apixaban tablets) Prescribing information. [http://packageinserts.bms.com/pijX_eliquis.pdf] (2013).
13. Frost, C. et al. Apixaban, a direct factor Xa inhibitor: single-dose pharmacokinetics and pharmacodynamics of an intravenous formulation [abstract 148]. J. Clin. Pharmacol. 48, 1132 (2008).
14. Frost, C. et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br. J. Clin. Pharmacol. 76, 776–786 (2013).
15. Vakkalagadda, B. et al. Effect of rifampin on the pharmacokinetics of apixaban, an oral direct inhibitor of factor Xa [abstract]. J. Clin. Pharmacol. 49, 1091–1130 (2009).
16. Zhang, D. et al. Investigating the enteroenteric recirculation of apixaban, a factor Xa inhibitor: administration of activated charcoal to bile duct-cannulated rats and dogs receiving an intravenous dose and use of drug transporter knockout rats. Drug Metab. Dispos. 41, 906–915 (2013).
17. Raghavan, N. et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab. Dispos. 37, 74–81 (2009).
18. Lassen, M.R., Raskob, G.E., Gallus, A., Pineo, G., Chen, D. & Hornick, P.; ADVANCE-2 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement. Arthritis Care Res. 68, 375–382 (2010).
19. Vettese, M.R., Gallus, A., Raskob, G.E., Pineo, G., Chen, D. & Ramirez, L.M.; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N. Engl. J. Med. 363, 2487–2498 (2010).
20. Lassen, M.R., Raskob, G.E., Gallus, A., Pineo, G., Chen, D. & Portman, R.J. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N. Engl. J. Med. 361, 594–604 (2009).
21. Kennedy, J.M. & Riji, A.M. Effects of surgery on the pharmacokinetic parameters of drugs. Clin. Pharmacokinet. 35, 293–312 (1998).
22. Grosfilam, J.M., Wright, E.A., Cleary, P.D. & Katz, J.N. Predictors of blood loss during total hip replacement surgery. Arthritis Care Res. 8, 167–173 (1995).
23. Leil, T.A., Fang, Y., Zhang, L., Paccaly, A., Mohan, P. & Pfister, M. Quantification of apixaban’s therapeutic utility in prevention of venous thromboembolism: selection of phase III trial dose. Clin. Pharmacol. Ther. 86, 375–382 (2010).
24. Bristol-Myers Squibb and Pfizer EERG. Eliquis® (apixaban tablets) Summary of product characteristics. [http://www.ema.europa.eu/ema/medicines/EPAR/Eliquis_-_Product_Information/human/002149/WC500107272.pdf].
25. Pineo, G.F. et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. J. Thromb. Haemost. 11, 444–451 (2013).
26. Mandema, J.W., Boyd, R.A. & DeCarlo, L.A. Therapeutic index of anticoagulants for prevention of venous thromboembolism following orthopedic surgery: a dose-response meta-analysis. Clin. Pharmacol. Ther. 90, 820–827 (2011).
27. Pineo, G.F. et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. J. Thromb. Haemost. 11, 444–451 (2013).
28. Chang, M. et al. Apixaban pharmacokinetics and pharmacodynamics in subjects with renal impairment. 2012 ACCP Annual Meeting (Abstract 13B812). Clin Pharmacol Drug Dev. 1, 185–186 (2012).
29. Frost, C., Nepal, S., Barrett, Y. & LaCreta, F. Effects of age and gender on the single-dose pharmacokinetics (PK) and pharmacodynamics (PD) of apixaban. J. Thromb. Haemost. 7, PP-MO-407 (2009).
30. Lassen, M.R., Davidson, B.L., Gallus, A., Pineo, G., Ansell, J. & Detchman, D. The efficacy and safety of apixaban versus enoxaparin in knee replacement surgery: a randomized trial. J. Thromb. Haemost. 5, 2368–2375 (2007).
31. Levine, M.N. et al. Randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. J. Thromb. Haemost. 10, 807–814 (2012).
32. Ou, Y. et al. Single- and multiple-dose pharmacokinetics, pharmacodynamics, and safety of apixaban in healthy Chinese subjects. Clin. Pharmacol. Ther. 8, 177–184 (2013).
33. Upadhyay, V.P. et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br. J. Clin. Pharmacol. 76, 908–916 (2013).
34. Yamahira, N. et al. A placebo-controlled, ascending multiple-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of apixaban in healthy Japanese subjects. (A637). Can. J. Clin. Pharmacol. 15, e420–e471 (2008).
35. Lavielle, M. & Mentré, F. Estimation of population pharmacokinetic parameters of saquinavir in HIV patients with the NONMEM software. J. Pharmacokin. Pharmacodyn. 34, 229–249 (2007).
36. Cockcroft, D.W. & Gault, M.H. Prediction of creatinine clearance from serum creatinine. Nephron 16, 31–41 (1976).
37. Yu, Z., Nepal, S., Bragat, A., Shenker, A. & Frost, C. Single dose apixaban pharmacokinetics and pharmacodynamics in healthy male Japanese and Caucasian subjects (A647). Can. J. Clin. Pharmacol. 15, e420–e471 (2008).
38. Glibanski, L. & Gastonguay, M.R. R/NONMEM Toolbox for simulation from posterior parameter (uncertainty) distributions (Abstract 958). PAG E 375, 807–815 (2010).
39. Yamasaki, H. et al. Apixaban pharmacokinetics and pharmacodynamics in subjects with renal impairment. Can. J. Clin. Pharmacol. 64, 776–786 (2015).
40. Cockcroft, D.W. & Gault, M.H. Prediction of creatinine clearance from serum creatinine. Nephron 16, 31–41 (1976).
41. Yu, Z., Nepal, S., Bragat, A., Shenker, A. & Frost, C. Single dose apixaban pharmacokinetics and pharmacodynamics in healthy male Japanese and Caucasian subjects (A647). Can. J. Clin. Pharmacol. 15, e420–e471 (2008).
42. Lavielle, M. & Mentré, F. Estimation of population pharmacokinetic parameters of saquinavir in HIV patients with the NONMEM software. J. Pharmacokin. Pharmacodyn. 34, 229–249 (2007).
43. Cockcroft, D.W. & Gault, M.H. Prediction of creatinine clearance from serum creatinine. Nephron 16, 31–41 (1976).