Received: 10 March 2023 | Revised: 19 July 2023 | Accepted: 9 August 2023

DOI: 10.1002/psp4.13032

ARTICLE

Population pharmacokinetics of apixaban in a real-life hospitalized population from the OptimAT study

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Abstract

This study aimed to characterize apixaban pharmacokinetics (PKs) and its variability in a real-world clinical setting of hospitalized patients using a population PK (PopPK) approach. Model-based simulations helped to identify factors that affect apixaban exposure and their clinical significance. A classic stepwise strategy was applied to determine the best PopPK model for describing typical apixaban PKs in hospitalized patients from the OptimAT study ($n = 100$) and evaluating the associated variability and influencing factors. Apixaban exposure under specific conditions was assessed using the final model. A two-compartment model with first-order absorption and elimination best described the data. The developed PopPK model revealed a major role of renal function and a minor role of P-glycoprotein phenotypic (P-gp) activity in explaining apixaban variability. The final model indicated that a patient with stage 4 chronic kidney disease (creatinine clearance [CLcr] = 15–29 mL/min) would have a 45% higher drug exposure than a patient with normal renal function (CLcr >90 mL/min), with a further 12% increase if the patient was also a poor metabolizer of P-gp. A high interindividual variability in apixaban PKs was observed in a real-life setting, which was partially explained by renal function and by P-gp phenotypic activity. Target apixaban concentrations are reached under standard dosage regimens, but overexposure can rapidly occur in the presence of cumulative factors warranting the development of a predictive tool for tailoring apixaban exposure and its clinical utility in at-risk patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Apixaban pharmacokinetics (PKs) is highly variable and may lead to suboptimal concentration and toxicity. Several factors have been shown to influence

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apixaban PKs, but their cumulative impact and clinical significance on its exposure is limited.

WHAT QUESTION DID THIS STUDY ADDRESS?

Which factors influence apixaban PKs and its variability in a real-world clinical setting of hospitalized patients, and what is the clinical significance of these factors?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Renal function and P-gp activity are the main factors affecting apixaban concentration in our cohort of hospitalized patients. Reduced P-gp activity, along with moderate to severe renal impairment, increases the risk of reaching at-risk apixaban concentrations, and dosage reduction is recommended. The study's results challenge the current recommendation for standardized periprocedural management of anticoagulants in patients with renal impairment.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

A priori adjustment of dosage regimen according to moderate and severe renal function and monitoring of apixaban plasma concentrations might be beneficial in specific situations, such as periprocedural management of polymorbid and/or polymedicated patients.

INTRODUCTION

Apixaban is a selective, direct, and reversible inhibitor of the coagulation factor Xa and is approved worldwide for multiple indications, including thromboprophylaxis after knee or hip replacement surgery, secondary treatment of deep vein thrombosis and pulmonary embolism, and reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).[1–3]

The pharmacokinetic (PK) profile of apixaban is described by an oral bioavailability of ~50%, a dose-proportional increase in exposure across the therapeutic dose interval (2.5–10 mg), a total clearance of 3.3 L/h, and a volume of distribution of ~21 L at steady-state.[1,4] Multiple pathways are involved in the plasma elimination of apixaban, including metabolism by cytochrome P450 3A4 (CYP3A4), biliary, renal, and direct intestinal excretion.[5,6] Renal clearance following intravenous administration accounts for ~30% of the total systemic clearance in healthy patients.[4] Apixaban is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein.[6] Only a small portion, about 5%, is eliminated through the bile.[7]

Two phase III trials evaluating apixaban in patients with NVAF demonstrated a significantly improved benefit–risk profile compared to anti-vitamin K therapy.[2] A dose-modification strategy based on advanced age, low body weight, and reduced renal function was designed to minimize the potential for higher exposure in populations at inherently higher bleeding risk.[8,9] Although the results of clinical studies have indicated that each factor individually has limited effect on apixaban exposure, the combinations of two or more intrinsic factors may increase apixaban exposure to a much greater extent.[10–13] In addition, when apixaban is used in real-world conditions and in populations outside the rigorous setting of clinical trials, a larger interpatient variability in plasma concentrations is expected with growing evidence correlating higher apixaban exposures and hemorrhages.[14–18] The monitoring of apixaban plasma concentrations is not performed routinely but might be beneficial in specific situations, although based on expected populational concentration ranges as a "therapeutic" window has not yet been established.[19] Concentration monitoring may be considered to better individualize apixaban dosage in at-risk situations, such as off-label doses, extreme-weight patients, drug–drug interactions, decreased renal function, high bleeding risk patients, or for adherence monitoring.[19] Another at-risk situation is the periprocedural management of anticoagulation, for which current international guidelines have defined a standardized management approach based on a few nonrandomized and observational studies.[20–22] Such recommendations may not be suitable for very high-risk bleeding procedures, polymorbid and/or polymedicated patients, and patients with renal insufficiency.[21,23] Clinicians must thus rely on an empirical clinical judgment to anticipate when most of the drug will be cleared from the blood to minimize the risk of periprocedural bleeding without enhancing the risk of thromboembolism. Models aiming at better predicting

drug concentrations may be beneficial to reduce the risk of adverse drug events in selected patients and procedures at higher bleeding risk.

The aims of this study are to describe the population PK (PopPK) of apixaban in a cohort of hospitalized patients and to quantify the impact of intrinsic/extrinsic factors on apixaban concentration and variability. Model-based simulations of apixaban concentrations will help evaluating drug exposure under specific conditions potentially affecting it, as well as the delay between the last apixaban intake and the target plasma concentration of 50 ng/mL, defined as the security threshold usually accepted for most of the extracranial procedures and used in the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study.[23]

METHODS

Study population

Samples and data used for the analyses were obtained from a population of hospitalized patients admitted to the Geneva University Hospitals from January 2018 to November 2019 with a prescription of apixaban and enrolled in the "Antithrombotics' Therapeutic Optimization in Hospitalized Patients Using Physiologically- and Population-based Pharmacokinetic Modelling, (OptimAT) study," a single-center prospective observational study (NCT03477331, clinicaltrials.gov). Each participant underwent 1 day of multiple finger prick sampling with dried blood spot (DBS) after the administration of their morning dose of apixaban for every hospitalization. Scheduled sampling times were predose (0) and 0.5, 1, 2, 3, 4, 6, and 8 h postdrug intake. The exact sampling times, date and time of the evening dose prior to blood sampling, and date of therapy start were recorded. An independent group of patients under apixaban enrolled in the direct anticoagulant pharmacogenetic (DAPHNE) study (NCT03112525) was used for external model validation.[24] Briefly, the DAPHNE study aimed to assess the impact of cytochrome activity and relevant polymorphisms on rivaroxaban/apixaban dosing or treatment efficacy in a hospital setting.

Analytical method

Apixaban concentrations in whole blood were quantified using a fully validated liquid chromatography with tandem mass spectrometry method.[24] The DBS–plasma relationship reported by Foerster et al., namely $Conc_{plasma} = Conc_{DBS} \times 1.46 + 13.84$, was used to determine apixaban concentrations in plasma.[25]

Phenotyping

CYP3A4/5 and P-gp activities were assessed using the Geneva cocktail method.[26] The CYP3A4/5 enzymes and P-gp activities were quantified based on the midazolam metabolite/drug concentration ratio at 2 h and the fexofenadine area under the curve from 2 to 6 h (AUC_{2-6}), respectively. Continuous values of CYP3A4/A5 and P-gp activities within pre-identified metabolic categories were used for the simulations. According to Bosilkovska et al.,[26] CYP3A4/5 ratios (mean ± SD) of 75.3 ± 17.5 correspond to poor metabolizers (PMs), 27.0 ± 14.8 to normal metabolizers (NMs), and 13.8 ± 4.0 to ultra-rapid metabolizers (UMs). Regarding P-gp activities, AUC_{2-6} concentrations (mean ± SD) of 285.5 ± 67.1, 100.1 ± 47.5, and 50.4 ± 15.3 mg·h/L characterize reduced PM, normal NM, and increased UM P-gp activity, respectively.[26]

Population pharmacokinetic analysis

The PopPK analysis was performed using the stochastic approximation expectation maximization algorithm of the nonlinear mixed-effects modeling program MONOLIX.[27] Patients were assumed to be at steady-state unless therapy started earlier than a week from the study inclusion. In that case, dosage regimen was explicitly informed in the dataset. One occasion refers to one hospitalization, with six patients being hospitalized twice. A classic stepwise approach was pursued for the final model identification. R version 4.2.1 (Rstudio version 1.4.1717) was used for data management, statistical analyses, and graphical outputs.

Base model

Multicompartment models with linear elimination and a variety of absorption types (i.e., simple first-order processes, zero-order processes, simultaneous and sequential combinations, and coupled or not with lag-time) were compared to find the best description of the data. A log-normal distribution was assumed for all PK parameters, with interindividual and interoccasion variability (IIV and IOV, respectively) sequentially tested on all PK parameters and retained in case of statistical significance. The residual unexplained variability (RUV) was described

by comparing the additive, proportional, or mixed error models.

Covariate model

The relationships among PK parameters and available plausible demographic (i.e., body weight, age, and gender), environmental (i.e., smoking status), and laboratory (i.e., alanine aminotransferase, aspartate aminotransferase [AST], bilirubin, albumin, gamma-glutamyl transferase, phosphatase, creatinine clearance [CLcr; Cockcroft and Gault equation], and urea) factors in addition to the CYP3A4/5 and P-gp phenotypic activities were graphically explored to detect possible associations. No drug–drug interactions were evaluated as they are quantitatively integrated within the CYP3A4/5 and P-gp phenotypic activities. Forward addition followed by backward deletion steps were subsequently pursued to identify statistically significant covariates using either Equations 1 or 2:

$$\mathrm{Par}_i = \mathrm{Par}_{\mathrm{pop}} \left(\frac{\mathrm{Cov}}{\mathrm{Cov}_{\mathrm{weight}}} \right)^{\beta} e^{\eta_i} \quad (1)$$

where Par_i and η_i are the individual i PK parameter and corresponding IIV element, respectively; β is the parameter capturing the continuous covariate Cov effect on the population parameter $\mathrm{Par}_{\mathrm{pop}}$, $\mathrm{Cov}_{\mathrm{weight}}$ is Cov weighted mean or typical value in case of body weight (70 kg) and CLcr (100 mL/min);

$$\mathrm{Par}_i = \mathrm{Par}_{\mathrm{pop}} e^{\sum_j \beta_j \mathrm{Cov}_j} e^{\eta_i} \quad (2)$$

where β_j is the parameter for Cov_j, j the component of the categorical covariate Cov, relative to the reference category, and the remaining terms are as previously defined.

Missing values in continuous covariates were imputed using the corresponding median values, whereas missing values in categorical covariates were treated as a separate category.

Model selection and evaluation

The difference in the importance sampling objective function values of nested models (ΔOFV, approximation of a χ^2 distribution) was used for model selection. A level of significance of 0.05 was chosen for base model development and for both forward and backward deletion covariate analysis steps. The corrected Bayesian information criterion (ΔBICc) was used for non-nested models retaining the candidate instead of the reference model if ΔBICc was less than −2.[28] Additional tools for model selection and evaluation were the visual inspection of the goodness-of-fit (GOF) plots (observed vs. individual predicted concentrations; observed vs. population predicted concentrations; individual weighted residuals vs. time after dose; and normalized prediction distribution errors) and the precision and plausibility of the parameter estimates. Prediction-corrected visual prediction checks (pcVPCs) further allowed final model evaluation through comparisons of the observed versus model-based ($n = 500$) percentiles standardized over the changing independent variables.[29]

Nonparametric bootstrap as implemented in the Rsmlx package was used to assess the final model reliability, estimating the PK parameters and variabilities on each resampled dataset ($n = 1000$), and comparing the original parameters with the bootstrap median and 95th-percentile confidence interval ($\mathrm{CI}_{95\%}$). The external model validation on DAPHNE data was assessed through calculations of the mean prediction error (MPE) and the root mean squared prediction error, that is, bias and precision, between observed and predicted concentrations.[30]

Model-based simulations

The final model was used to simulate 1000 virtual subjects per stage of chronic kidney disease (CKD) and P-gp activity level. The CKD stages were as follows: stage 1 (CLcr >90 mL/min), stage 2 (CLcr = 60–89 mL/min), stage 3 (CLcr = 30–59 mL/min), stage 4 (CLcr = 15–29 mL/min), and stage 5 (CLcr <15 mL/min). P-gp activity was defined based on AUC_{2-6} in PM, NM, and UM patients.

A uniform distribution in the studied range was assumed for all covariates. Model-based steady-state apixaban minimal concentrations (C_{min}) were retrieved for each simulated group of patients under the three available dosage regimens (2.5, 5, or 10 mg b.i.d.) and compared with the expected safe C_{min} range under standard dosage regimen and the cutoff concentration associated with a clinically significant 20% increased bleeding risk (i.e., 230 ng/mL).[19,31] Last, the pre-operative stopping time to reach plasma concentrations below 50 ng/mL for the three dosage regimens and the different renal function/P-gp conditions was evaluated.

RESULTS

The 100 patients treated by apixaban included in the OptimAT study provided 825 samples, including those of six rehospitalizations. A median of eight samples per individual (range = 7–8) was available. Patients received apixaban

TABLE 1 Study population characteristics.

Variables	OptimAT study ($n=100$)		DAPHNE study ($n=63$)	
	Median [min–max] or % of participants	Percent of missing values	Median [min–max] or % of participants	Percent of missing values
Demographics				
Age (years)	77 [51–94]	0.0	80 [50–97]	0.0
Body weight (kg)	75 [44–126]	1.0	74.5 [58–120]	0.0
Height (cm)	170 [150–185]	1.0	170 [151–193]	0.0
BMI (kg/m^2)	26 [17–46]	1.0	25 [15–44]	0.0
Female (%)	42%	0.0	32%	0.0
Laboratory measurements				
Creatinine clearance (mL/min)[a]	57.2 [23–136]	1.0	89 [40–378]	1.59
Bilirubin (μmol/L)	8 [2.9–37]	2.0	9 [3–63]	4.76
Urea (mmol/L)	7.3 [1.1–37.7]	1.0	NA	3.17
AST (U/L)	21 [9–286]	3.0	23 [9–96]	3.17
ALT (U/L)	22 [5–424]	3.0	23 [6–144]	3.17
Gamma-glutamyl transferase (U/L)	41 [6–662]	3.0	66 [10–548]	3.17
Alkaline phosphatase (U/L)	69 [14–295]	3.0	74 [13–529]	4.76
Albumin (g/L)	37 [24–62]	1.0	NA	4.76
Drug indication				
Atrial fibrillation (%)	89%	0.0	79%	0.0
Venous thromboembolism (%)	11%	0.0	21%	0.0
Phenotype				
CYP3A4/5 PM, NM, UM (%)	19, 78, 3	0.0	43, 57, 0	0.0
P-gp PM, NM, UM (%)	47, 51, 2	0.0	30, 68, 2	0.0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NA, not available; NM, normal metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer.

[a]According to CG equation.

dosages of 2.5 mg b.i.d. ($n=40$), 5 mg b.i.d. ($n=56$), or 10 mg b.i.d. ($n=4$). Table 1 summarizes the characteristics of the patients included in the model building (OptimAT study) and validation (DAPHNE study) steps.

Base model

The use of IOV instead of IIV on apparent clearance (CL) in a one-compartment model with linear absorption and elimination markedly improved data description ($\Delta OFV=-110$, $p<0.01$), which was further enhanced by the addition of IIV on the apparent volume of distribution (V_c, $\Delta OFV=-95$, $p<0.01$) and absorption rate constant (k_a, $\Delta OFV=-64.5$, $p<0.01$). A two-compartment model with additional IIV on both apparent intercompartment clearance (Q) and peripheral volume of distribution (V_p) provided a better fit of the data ($\Delta OFV=-77$, $p<0.01$) and allowed discarding IIV on V_c ($\Delta OFV=1.7$, $p>0.05$). The inclusion of lag-time and associated IIV in addition to k_a (Tlag, $\Delta OFV=-104$, $p<0.01$) captured the apixaban absorption process more adequately than the sequential and simultaneous first- and zero-order absorption models ($\Delta BIC>22$). No significant changes were observed using IOV on the PK parameters in addition to CL ($\Delta OFV > -1.1$, $p>0.05$). A three-compartment model did not improve the description of the data ($\Delta OFV=3.5$, $p>0.05$). The proportional error model adequately captured the RUV.

The base model typical PopPK parameters estimates with their associated IIV or IOV values were as follows: $T_{lag}=0.2$ h (IIV 95%), $k_a=0.6\,h^{-1}$ (IIV 67%), CL = 2.6 L/h (IOV 43%), $V_c=19.1$ L, $Q=17.4$ L/h (IIV 50%), and $V_p=57.4$ L (IIV 64%).

Covariate analyses

Univariable analyses revealed significant associations between CL and CLcr (ΔOFV = −34, $p < 0.01$), age (ΔOFV = −20, $p < 0.01$), P-gp AUC_{2-6} (ΔOFV = −15, $p < 0.01$), urea (ΔOFV = −12, $p < 0.01$), smoking status (ΔOFV = −10, $p < 0.01$), albumin (ΔOFV = −8.8, $p < 0.01$), AST (ΔOFV = −5.8, $p < 0.05$), and body weight (ΔOFV = −4.6, $p < 0.05$). Moreover, gender and age affected both V_p (ΔOFV < −4.0, $p < 0.05$) and Q (ΔOFV < −5.5, $p < 0.02$), with the latter also associated with body weight (ΔOFV = −6.0, $p < 0.05$). Neither CYP3A4/5 phenotype (ΔOFV = 2.8, $p = 0.08$) nor any of the other tested covariates (ΔOFV > −3.7, $p > 0.05$) showed any influence on apixaban PK. Multivariable analyses and backward deletion steps retained only CLcr and P-gp in the final model, with the inclusion of P-gp AUC_{2-6} in addition to CLcr (ΔOFV = −4.3, $p = 0.04$) providing a slight improvement of data description. CLcr explained 41% of the initial variance of apixaban CL, and P-gp AUC_{2-6} explained a further 17%. The final model indicated that a typical P-gp NM patient (AUC_{2-6} = 100.1 mg h/L) with stage 4 CKD (mean CLcr = 22 mL/min) would have 45% lower CL compared to a patient with the same P-gp phenotype and stage 1 CKD (mean CLcr = 100 mL/min). In addition, the CL of a patient with normal renal function would be reduced by 16% and increased by 12% in P-gp PM (AUC_{2-6} = 285.5 mg h/L) and UM (AUC_{2-6} = 50.4 mg h/L) versus NM, respectively. Apixaban half-lives estimated by the final model in a typical P-gp NM patient with normal renal function were 0.70 h (α) and 17 h (β); terminal half-lives would be increased up to 33 h on average in a patient with stage 3 CKD and 52 h with stage 4 CKD. Table 2 shows the final model PK parameters with their bootstrap estimations, whereas Figure S1 shows the GOF plots.

TABLE 2 Final model PopPK parameters with their bootstrap evaluations.

Parameters	Final model Estimate (RSE %)	Bootstrap ($n = 1000$) Median ($CI_{95\%}$)
T_{lag} (h)	0.16 (19)	0.18 (0.07–0.28)
k_a (h^{-1})	0.82 (11)	0.92 (0.54–1.87)
CL (L/h)	3.2 (6)	3.1 (2.4–3.6)
$\beta_{P\text{-}gp}$	−0.17 (32)	−0.21 (−0.44 to −0.05)
β_{CLcr}	0.47 (19)	0.47 (0.22–0.74)
V_c (L)	27 (8)	29 (18–44)
Q (L/h)	16 (12)	14 (8.0–27)
V_p (L)	51 (12)	56 (25–118)
IIV_{Tlag} (CV%)	108 (13)	100 (56–162)
IIV_{ka} (CV%)	58 (11)	58 (36–76)
IIV_Q (CV%)	65 (15)	67 (44–363)
IIV_{Vp} (CV%)	88 (8)	83 (36–131)
IOV_{CL} (CV%)	30 (9)	32 (20–51)
Proportional error model (CV%)	8.4 (3)	8.4 (7.5–9.4)

Note: Final model equation: $CL_{occ,i} = CL\left(\frac{CLcr}{100}\right)^{\beta_{CLcr}}\left(\frac{AUC_{2-6}}{205}\right)^{\beta_{PgP}} e^{IOV_{CL_{occ,i}}}$

Abbreviations: $CI_{95\%}$, bootstrap 95th-percentile confidence interval; CL, typical drug clearance; CLcr, creatinine clearance; $CL_{occ,i}$, CL of the individual i at occasion occ; CV, coefficient of variation; IIV, interindividual variability; IOV_{CL}, interoccasion variability clearance; k_a, first-order absorption rate; PopPK, population pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; T_{lag}, lag-time; V_c and V_p, central and peripheral volumes of distribution, respectively; β_{cov}, the effect of the covariate cov.

Model evaluation

The bootstrap procedure showed that PK parameter estimates lie within the $CI_{95\%}$ and are close to the bootstrap median estimates (weighted difference < 20%). The pcVPCs confirmed the adequate model performances (Figure 1). The model developed on the OptimAT data predicts the DAPHNE data with an insignificant bias (MPE [$CI_{95\%}$] = 0% (−1% to 1%)) and a precision of 11%, for the external validation of the model.

Model-based simulations

Figure 2 compares the simulated C_{min} as a function of the CKD stage and P-gp activity in patients receiving apixaban dosages of 2.5, 5, and 10 mg b.i.d. with the reference 5th and 95th percentile of C_{min} reported by the manufacturer[32] and the threshold of 230 ng/mL associated with a 20% increased risk of bleeding suggested by Bhagirath et al.[33] Under similar dosage regimens, patients with stage 3 CKD would have a median C_{min} 65%–80% higher than patients with a normal renal function, independently of their P-gp activities. This increase reaches up to 200%–250% in patients suffering from stage 5 CKD stage 5. A 20%–35% difference in C_{min} is expected between P-gp PM and UM patients at all dosage regimens and CKD stages combined. P-gp activity seems to influence less overall apixaban exposure than renal function, but the accumulation of both factors puts the patient at higher risk of overexposure and bleeding.

The simulated time intervals between treatment discontinuation and the target of 50 ng/mL stratified according to dose, CKD stage, and P-gp activity are presented in Table 3. Figure 3 shows, as an example, the simulated concentration-time profiles of apixaban in patients on apixaban 5 mg b.i.d. (a) with stage 1 CKD and normal renal function and (b) with stage 4 CKD and decreased P-gp activity (patient with multiple risk factors).

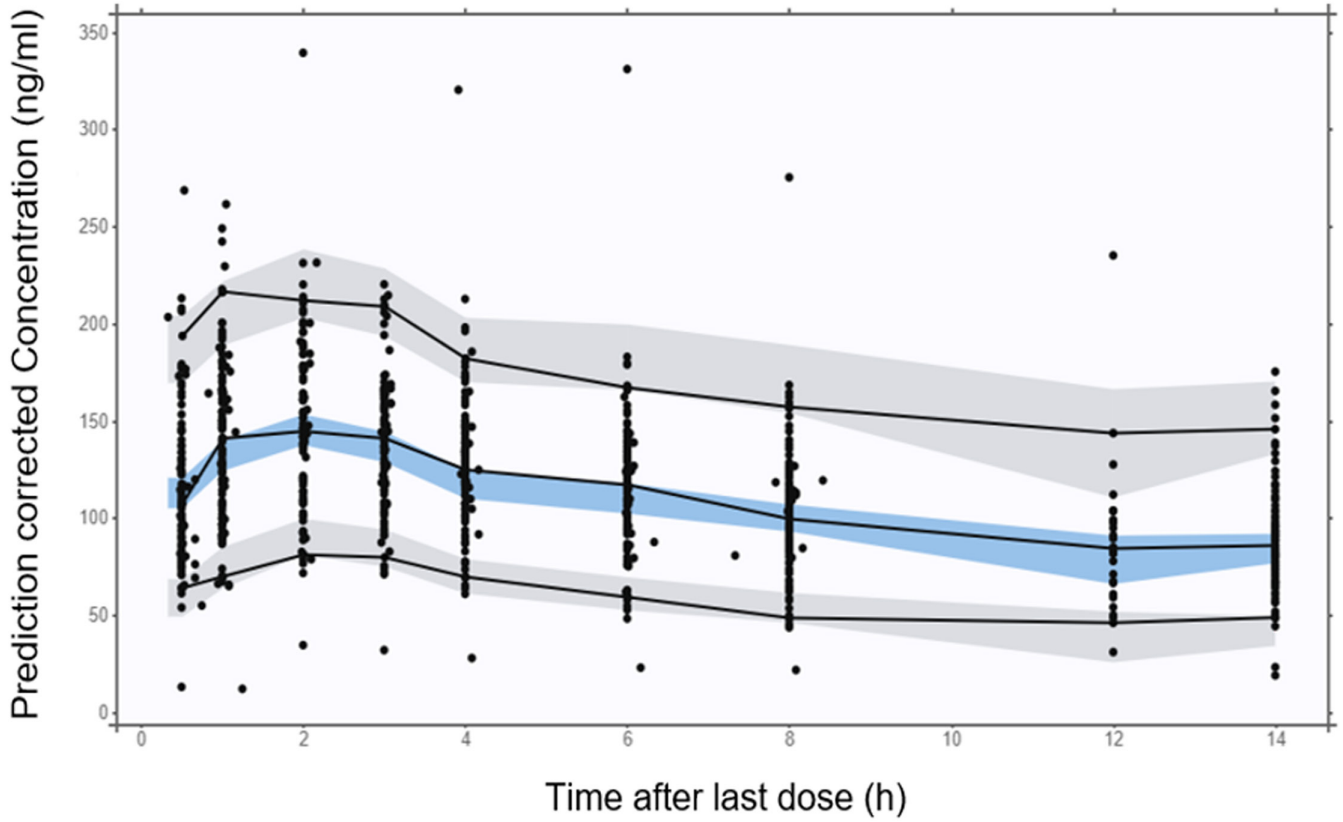

FIGURE 1 Prediction-corrected visual predictive checks. Dots represent the prediction-corrected observations and black lines link the corresponding medians and 5th and 95th percentiles. The shaded areas are the 90% confidence intervals around the model-based prediction-corrected median and 5th and 95th percentiles.

DISCUSSION

This study developed for the first time a PopPK model of apixaban based on data collected in a real-world population of hospitalized patients to quantify concentration variability and sources of variability. Renal function and P-gp activity were identified as explaining 58% of the important interpatient variability in apixaban concentration, the former having the greatest influence.

Apixaban PK was best characterized by a two-compartment model with linear elimination and absorption coupled with lag-time. The predicted PK parameters are in good agreement with previous reports.[34–36] The estimated population clearance of 3.2 L/h is close to the value reported in the study by Byon et al.[34] The total volume of distribution of 78 L is slightly higher than previously reported (25–53 L). This difference may be due to the age range of our patients (51–94 years), with elderly patients in whom body fat percentage tends to increase, thereby increasing the volume of distribution of lipophilic drugs, such as apixaban (log$P$ = 2.23).[22] The average terminal half-life of 17 h is slightly higher than that reported for healthy patients (10–15 h), which might be explained by the decreased renal function and the increased volume of distribution in our study population. The only difference with previously published models is the presence of an absorption delay, which might be explained by the known slower absorption rate that can occur with age.[37]

Overall, the main covariate influencing apixaban elimination is CKD stage. These results confirm data from clinical trials, in which mild, moderate, and severe renal impairment were associated with higher estimated apixaban C_{min} values of ~16%, 29%, and 44%, respectively, compared to patients with a normal renal function.[10] Although apixaban has the lowest renal excretion of all direct oral anticoagulants (DOACs), a correlation between renal function and apixaban elimination has been reported in several studies.[35,36,38–40] In addition, low glomerular filtration rates have been associated with higher bleeding rates, warranting the use of adjusted doses in patients with a glomerular filtration rate of less than 60 mL/min.[41]

Our simulations indicate that 8% of patients with stage 3 CKD would exceed the threshold concentration of 230 ng/mL (associated with a 20% increased bleeding risk[33]) with a nonadjusted dosage of 5 mg b.i.d. Adjusting the apixaban dosage from 5 to 2.5 mg b.i.d. reduced the proportion to zero. Only 1.4% of patients with stage 4 CKD would exceed the 230 ng/mL threshold with the

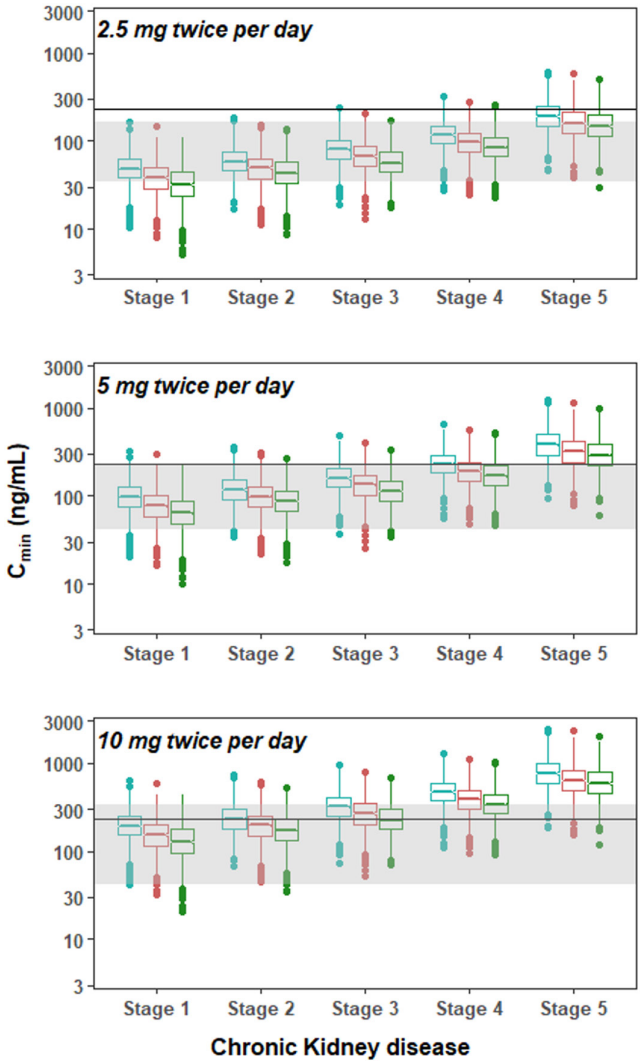

FIGURE 2 Model-based simulated steady-state apixaban minimal concentration (C_{min}) with variability after intake of 2.5, 5, and 10 mg b.i.d. as a function of chronic kidney disease stage and P-gp activity (poor metabolizer, light blue; normal metabolizer, light red; and ultra-rapid metabolizer, green). The gray surface represents the 5th and 95th percentiles of reported C_{min} in patients with atrial fibrillation for each apixaban dosage (34–162 ng/mL for 2.5 mg b.i.d.; 41–230 ng/mL for 5 mg b.i.d.; 41–335 and in patients with deep vein thrombosis and pulmonary embolism (DVT/PE) for 10 mg b.i.d.); the black line represents the limit associated with a 20% increased bleeding risk (C_{min} = 230 ng/mL).[33] Slightly different 5th and 95th percentiles (not presented) have been reported in different indications: 11–90 ng/mL for 2.5 mg b.i.d. in the prevention of DVT/PE after 6 months of therapeutic treatment; 23–109 ng/mL for 2.5 mg b.i.d. in the prevention in elective orthopedic surgery; 22–177 ng/mL for 5 mg b.i.d. in DVT/PE treatment.[32]

2.5 mg b.i.d. dosage. However, for patients with stage 5 CKD, the percentage of patients predicted to exceed the above-mentioned threshold was 19.5% despite dose adjustment to 2.5 mg b.i.d., supporting current recommendations not to use apixaban in patients with end stage CKD.[42] These results confirm the importance of carefully adjusting apixaban dosages to avoid overdose and bleeding risk. Recent data also demonstrate the importance of monitoring renal function in DOAC-treated patients with atrial fibrillation (AF).[43] Although the therapeutic range for apixaban remains unclear, recent data suggest that the expected C_{min} (34–230 ng/mL) is effective in identifying patients at risk of complications during DOAC therapy and should be targeted in clinical practice.[31]

In patients with AF with stage 3 CKD and either low body weight (≤60 kg) or an advanced age (≥80 years), apixaban should be used at a dose of 2.5 mg b.i.d. (instead of 5 mg b.i.d.).[32] Our study supports these recommendations, although no direct effect of weight or age was found in our model, these latter two variables are incorporated in CLcr to adapt the dose. Although some studies have reported minor effects of age[34,38,40] and sex[34,38] on apixaban exposure, the impact of renal function remains paramount in all studies. However, patients greater than 80 years of age should not be disregarded, as age, combined with renal function or weight, continues to be a crucial factor in the dosage adjustment of apixaban.[32] Moreover, we recognize that the risk of bleeding is multifactorial, and factors such as co-existing conditions significantly contribute to the condition.[19]

Currently, no dose adjustment is recommended for the prevention of venous thromboembolic events after major orthopedic surgery, nor for the treatment of venous thromboembolic disease. We show that a large proportion of patients (32%) on an intensive dosing regimen (10 mg b.i.d.) for the initial treatment of venous thromboembolic events will present concentrations above the margin of safety. Although the risk is offset by the short duration of treatment on this high regimen, this observation calls into question the lack of dose adjustment in this indication.

The modulation of CYP3A4 and P-gp phenotypic activity by genetic, clinical (inflammation), and environmental factors (co-administration of inhibitors or inducers) was expected to influence apixaban elimination. This study shows that apixaban exposure increased by only a small amount (~20%) when the P-gp phenotype PM was present, explaining additional 17% of the variability in clearance compared to renal function, whereas no effect of CYP3A4 phenotypes was found. Our study population could not assess the influence of CYP3A4/5 activity due to the low number of carriers of the PM or UM phenotype. Byon et al.[34] reported that strong/moderate inhibitors of both CYP3A4 and P-gp decreased apixaban clearance by 20%, which is in close agreement with the value found in our study for P-gp phenotype. Lenoir et al. did not observe any influence of CYP3A4/5 phenotype on apixaban in a population of patients comprising a large proportion of PM

TABLE 3 Pre-operative time required to reach the 50 ng/mL threshold after the last dosing in patients under 2.5, 5, and 10 mg b.i.d. according to renal function and P-gp activity.

CKD	P-gp activity	Time (h) (median ($PI_{90\%}$))		
		2.5 mg b.i.d.	5 mg b.i.d.	10 mg b.i.d.
Stage 1 (CLcr >90 mL/min)	PM	11 (3–44)	30 (11–95)	50 (20–152)
	NM	7 (2–28)	22 (8–72)	39 (16–127)
	UM	6 (2–22)	17 (7–63)	32 (14–114)
Stage 2 (CLcr = 60–89 mL/min)	PM	17 (5–58)	40 (15–121)	64 (25–196)
	NM	12 (3–48)	32 (11–99)	53 (21–163)
	UM	9 (3–34)	27 (9–81)	46 (18–138)
Stage 3 (CLcr = 30–59 mL/min)	PM	32 (8–101)	62 (22–189)	91 (33–240)
	NM	22 (6–72)	46 (17–145)	72 (27–221)
	UM	16 (4–57)	37 (14–121)	60 (24–194)
Stage 4 (CLcr = 15–29 mL/min)	PM	64 (21–165)	107 (38–240)	149 (54–240)
	NM	44 (12–138)	77 (27–240)	111 (40–240)
	UM	36 (10–110)	69 (25–198)	100 (36–240)

Abbreviations: $AUC_{2-6} = 285.5 \pm 67.1$ mg·h/L; $AUC_{2-6} = 100.1 \pm 47.5$ mg·h/L; $AUC_{2-6} = 50.4 \pm 15.3$ mg·h/L; CKD, chronic kidney disease; CLcr, creatinine clearance; NM, normal metabolizers; P-gp activity (mean ± SD): PM, poor metabolizers; $PI_{90\%}$, 90% prediction interval; UM, ultra-high metabolizers.;.

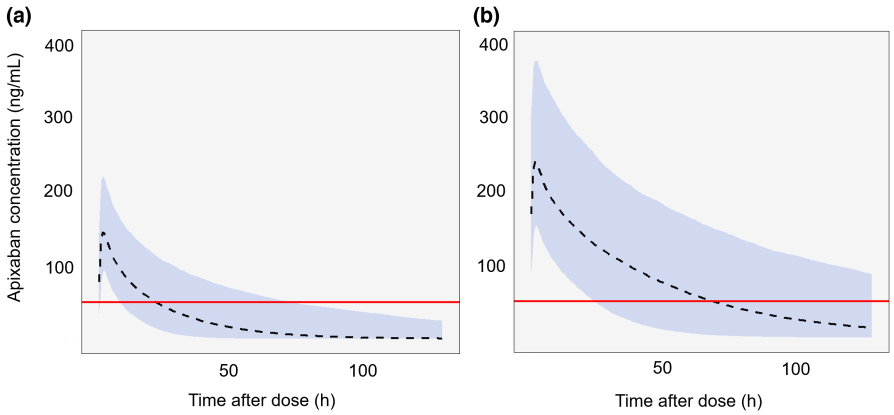

FIGURE 3 Median (black line) and 90% prediction interval (blue shaded surface) simulated concentration–time profiles at steady-state (5 mg b.i.d.) after the last drug intake (time 0) in (a) P-gp normal metabolizer and patients with stage 1 chronic kidney disease (CKD) and in (b) P-gp poor metabolizer and patients with stage 4 CKD. The red line represents the 50 ng/mL target concentration for most of the extracranial procedures.

phenotype for CYP3A4/5. Altogether these results question the influence of CYP3A4/5 in addition to P-gp activity on apixaban elimination in the absence of strong 3A4/5 inducer or inhibitor.

The large range in apixaban concentrations under standard dosage regimens reflects the large interpatient variability in apixaban PK, which raises concern. Few studies have examined the cumulative influence of risk factors[13] and our results show that in patients with both reduced P-gp activity and impaired renal function, the concentrations of apixaban falls above the security threshold (230 ng/mL) in ~17%, 53%, and 90% of those with stages 3, 4, and 5 CKD at dosages of 5 mg b.i.d. Our results also question the absence of a dose adaptation recommendation by the manufacturer when co-administered with P-gp inhibitors, as is the case for edoxaban.[7] Further research is necessary to determine the optimal management strategy for patients co-administering apixaban and P-gp inhibitors, especially in the presence of multiple risk factors as shown in our simulations.

The anticoagulation management in patients undergoing invasive procedures can be challenging, because interrupting anticoagulation for a procedure may increase the risk of thromboembolism and, at the same time, invasive procedures have been associated with an increased bleeding risk when anticoagulant(s) are administered. The current consensus for pre-operative management of apixaban is that a plasma concentration lower than 50 ng/

mL should be achieved to minimize the risk of bleeding during invasive procedures.[44] Yet, the time frame for withholding apixaban prior to surgery varies widely in the literature and differs according to the bleeding risk of the procedure. The PAUSE study[23] prospectively evaluated outcomes in 3007 individuals treated by a DOAC for AF who underwent an elective surgery or procedure, in whom a simple and standardized management approach for anticoagulant interruption was followed, independently of renal function; specifically, apixaban was discontinued for 2 full days after last dose before a high-bleeding-risk surgery or procedure and 1 day before a low-bleeding-risk procedure.[20] Our simulations support current guidelines in patients with normal renal function and P-gp activity. However, renal insufficiency and, to a greater extent, a combination with a decreased P-gp activity, strongly affects the time needed to reach such a target. Patients with stages 3 and 4 CKD require a two- and four-fold longer preoperative withdrawal time to reach the recommended level compared to patients with normal renal function; specifically, the median time to achieve the target concentration increases from 22 h in patients with normal renal function to 44 and 77 h (range 27–240 h) in those with stages 3 and 4 CKD, respectively, with a further increase to 107 h (range 38–240 h) in those with both stage 4 CKD and decreased P-gp activity. Defining the optimal stopping time in such a population is thus difficult considering the presence of one or several risk factors associated with the marked IIV in drug concentrations.

Model-based dosage individualization or prediction of the time needed to reach the safe concentration range for a given patient based on a single drug concentration measurement may be an attractive and efficient approach to reduce the risk of overexposure and toxicity, especially in high-risk patients. Bayesian therapeutic drug monitoring software could be used for such purposes. One main drawback is the lack of well-defined ranges associated with efficacy and toxicity, although safe concentrations, ranges, or targets have been proposed to lower the bleeding risk.[19] In addition, although the target threshold of 50 mg/mL is generally considered safe before an invasive procedure, other thresholds have been proposed.[45]

In conclusion, this work highlights an important IIV in apixaban concentrations in older patients treated under real-world conditions. Renal function and, to a lesser extent, P-gp activity are the two main factors affecting apixaban concentration and should be accounted for in dosage individualization. The present study shows that safe concentrations are reached under standard dosage regimens in most patients. However, at-risk concentrations are expected to be reached in patients with moderate to severe renal impairment (stages 3–5 CKD), especially in the presence of a reduced P-gp phenotypic activity for whom dosage reduction should be recommended. Our results also question the validity of the current recommendation for standardized periprocedural management of anticoagulants in patients suffering from renal impairment. In patients with CKD with factors influencing P-gp activity (e.g., comedications, inflammation, and genetic disposition), apixaban monitoring may be useful. A model-based predictive tool for better tailoring apixaban dosing and predicting discontinuation time before surgery represent an interesting way of minimizing the risk of both thrombosis and hemorrhage in high-risk situations.

AUTHOR CONTRIBUTIONS

F.G., J.T., P.G., P.F., Y.D., C.L., C.S., V.R., J.L.R., C.C., and M.G. wrote the manuscript. J.L.R., C.C., and M.G. designed the research. F.G., J.T., P.G., P.F., Y.D., C.L., C.S., V.R., J.L.R., C.C., and M.G. performed the research. F.G., J.T., S.V., P.G., J.L.R., C.C., and M.G. analyzed the data.

FUNDING INFORMATION

This study partially supported by the Schweizerischer Nationalfonds grant 407440_167381.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gaspar F, Terrier J, Favre S, et al. Population pharmacokinetics of apixaban in a real-life hospitalized population from the OptimAT study. *CPT Pharmacometrics Syst Pharmacol*. 2023;00:1-12. doi:10.1002/psp4.13032