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ARTICLE

Apixaban and rivaroxaban's physiologically-based pharmacokinetic model validation in hospitalized patients: A first step for larger use of a priori modeling approach at bed side

Jean Terrier[1,2,3,†] | **Frédéric Gaspar**[4,5,6,7,†] | **Pauline Gosselin**[1] | **Olivier Raboud**[4,5,6,7] | **Camille Lenoir**[3] | **Victoria Rollason**[3] | **Chantal Csajka**[5,6,7] | **Caroline Samer**[3,5] | **Pierre Fontana**[2,8] | **Youssef Daali**[2,3,‡] | **Jean-Luc Reny**[1,2,‡] | **for the OptimAT study group**

[1]Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland

[2]Geneva Platelet Group, Faculty of Medicine, University of Geneva, Geneva, Switzerland

[3]Clinical Pharmacology and Toxicology Service, Anesthesiology, Pharmacology and Intensive Care Department, Geneva University Hospitals, Geneva, Switzerland

[4]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[5]School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland

[6]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Lausanne, Switzerland

[7]Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Abstract

When used in real-world conditions, substantial interindividual variations in direct oral anticoagulant (DOAC) plasma concentrations are observed for a given dose, leading to a risk of over- or under-exposure and clinically significant adverse events. Physiologically-based pharmacokinetic (PBPK) models could help physicians to tailor DOAC prescriptions in vulnerable patient populations, such as those in the hospital setting. The present study aims to validate prospectively PBPK models for rivaroxaban and apixaban in a large cohort of elderly, polymorbid, and hospitalized patients. In using a model of geriatric population integrating appropriate physiological parameters into models first optimized with healthy volunteer data, observed plasma concentration collected in hospitalized patients on apixaban ($n = 100$) and rivaroxaban ($n = 100$) were adequately predicted (ratio predicted/observed area under the concentration curve for a dosing interval [AUC_{tau}] = 0.97 [0.96–0.99] geometric mean, 90% confidence interval, ratio predicted/observed AUC_{tau} = 1.03 [1.02–1.05]) for apixaban and rivaroxaban, respectively. Validation of the present PBPK models for rivaroxaban and apixaban in in-patients represent an additional step toward the feasibility of bedside use.

[†]These authors should be considered co-first authors.

[‡]These authors should be considered co-last authors.

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[8]Division of Angiology and Haemostasis, Geneva University Hospitals, Geneva, Switzerland

Correspondence
Jean Terrier, Clinical Pharmacology and Toxicology Service, Anesthesiology, Pharmacology and Intensive Care Department, Geneva University Hospitals, 4 Rue Gabrielle Perret-Gentil, 1205 Geneva, Switzerland.
Email: jean.terrier@hcuge.ch

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Direct oral anticoagulant (DOAC) significant variability in pharmacokinetics requires dose adjustment in high-risk situations frequently encountered in hospitalized populations. Physiologically-based pharmacokinetic (PBPK) could help clinicians predict DOAC plasma concentrations that are associated with clinical events and adjust the dose.

WHAT QUESTION DID THIS STUDY ADDRESS?

How PBPK modeling applied to a real-world population of vulnerable hospitalized patients can predict DOAC pharmacokinetics (PKs).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study represents a proof-of-concept of the use and validation of PBPK models associated to specific physiological parameters of geriatric populations in real-life hospital settings.

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

The present study serves as a basis for future apixaban's, and rivaroxaban's PK studies based on PBPK models in real-life setting and strengthen the role of PBPK in model-informed precision dosing.

INTRODUCTION

Physiologically-based pharmacokinetic modeling (PBPK) is now well-established, guiding early phase clinical trials and is officially used by government agencies to assist with drug registration's requirements.[1] Although its use remains mainly limited to pharmaceutical companies, there is also growing enthusiasm for this tool to be integrated into the clinical setting.[2] Indeed, this bottom-up approach in its purest form could help physicians prescribe drugs such as direct oral anticoagulants (DOACs) in vulnerable populations, including children, the elderly, or polymedicated patients.[3] There is increasing evidence that shows promising results in various areas, such as psychiatry, oncology, or pediatrics.[4–7] However, PBPK has not yet gained the full attention of other fields, such as that of cardiovascular disease, which could benefit from PBPK to predict over- and under-dosing of DOACs, both of which are associated with clinical events. When DOACs were compared to vitamin K antagonists, the fact that blood monitoring was not required proved to be a significant advantage. However, when DOACs are used in the real world, outside the strict guidelines of clinical trials, there is significant interindividual variation in the dose-concentration response relationship.[8] Thus, simulating DOACs' plasma exposure could prove valuable for patients, as it is linked to clinical events, including bleeding, more frequently seen in patients with higher DOAC levels.[9] This is particularly true in the presence of cumulative risk factors (e.g., drug–drug interaction [DDI], renal insufficiency, extremes in weight, and variations in genetically influenced drug metabolism and transport) that are difficult to study in classic pivotal clinical trials where polymorbid and polymedicated patients are not generally represented.[10,11] PBPK tools have the ability to predict complex DDIs and are useful for adjusting doses or choosing the appropriate molecule in individuals not falling into standard patient groups. Several PBPK models have been developed and validated in healthy individuals for DOACs,[12–18] although there is no formal and prospective validation of PBPK in vulnerable hospitalized patients. Among the developed PBPK models for DOACs, several have specifically focused on DDIs and complex DDIs,[14,16,18] one on renal function impact on plasma exposure[12] and one on food impact on rivaroxaban exposure.[13] Two models explored the change in DOACs exposure in the elderly but no formal validation on observed data have been performed.[14,15] The primary objective of the OpimAT study (NCT03477331) was precisely designed to fill in this gap and validate PBPK models prospectively in a clinical setting for several antithrombotic drugs. In the following, we present the validation of PBPK models for apixaban and rivaroxaban in patients hospitalized in a tertiary hospital.

METHODS

Study design

The study was a prospective observational pharmacokinetic (PK) study in a cohort of hospitalized patients taking rivaroxaban ($n = 100$) or apixaban ($n = 100$) where regular

capillary blood samples were taken throughout a single day. The primary objective was to validate a PBPK model for three DOACs (rivaroxaban, apixaban, and dabigatran).

The study protocol was approved by the regional research ethics Committee of the Canton of Geneva (CCER no. 2017-00225). The OptimAT study aims to validate PBPK models for antithrombotic therapy and is registered in the US National Institutes of Health Clinical Trials Registry (NCT03477331). Written informed consent was obtained from all patients prior to initiation of any study procedure. This clinical trial was carried out in compliance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

Selection and recruitment procedures

Inclusion criteria were patients greater than 18 years old, admitted to Geneva University Hospitals having received the same dose of a DOAC (dabigatran, rivaroxaban, and apixaban) for at least 72 h (to ensure that concentrations obtained were at a steady-state). Potential candidates were automatically identified by the institutional electronic health record software. Patients with a reduced life span (<6 months) or hospitalized in intensive care units were excluded from the study. Recruitment of participants on dabigatran was quickly abandoned because of the rapid decrease of its prescription in Switzerland in favor of apixaban and rivaroxaban. Patients treated with edoxaban were not included because this drug had only recently been accepted on the Swiss market at the time that the study began. Research staff invited identified patients respecting inclusion and exclusion criteria to participate in the study.

Observed concentrations and PK parameters

Multiple capillary blood samples were collected from patients using dried blood spots (DBS) to obtain observed PK parameters (Figure S1). Patients' apixaban and rivaroxaban's whole blood concentrations were obtained at: 0, 0.5, 1, 2, 3, 4, 6, and 8 h post-dosage. The determination of blood concentrations was achieved using a previously described, fully validated liquid-chromatography tandem mass spectrometry method.[19] The observed area under the concentration curve for a dosing interval (AUC_{tau}; [time intervals were defined as follows: 0–12 h for apixaban 5 mg b.i.d. and rivaroxaban 15 mg b.i.d., 0–24 h for rivaroxaban 20 mg q.d.) and other classic PK parameters (maximum plasma concentration [C_{max}], time to C_{max} [T_{max}], minimum plasma concentration [C_{min}], and terminal half-life [$t_{1/2}$]) were calculated by noncompartmental analysis using PKanalix, Lixoft, version 21 (Antony, France). AUC_{tau} was obtained by calculating the AUC in a plot of blood concentration versus time using the log-trapezoidal rule. PK parameters were normalized to 5 mg b.i.d. and 20 mg q.d. for apixaban and rivaroxaban, respectively, to facilitate comparison with simulated data. Because concentrations were measured in whole blood, the DBS-plasma relationship reported in the Foerster et al.[20] study, was used for the conversion of apixaban and rivaroxaban blood to plasma concentrations.

PBPK models development: Generalities

The absorption, distribution, metabolism, and excretion (ADME) simulator SimCYP version 21 software (Certara, SimCYP Ltd.) was used as the platform for PBPK simulation. The workflow for model development and verification is described in Figure S2. Our first aim in this analysis was to optimize previously developed models for rivaroxaban and apixaban in healthy volunteers using the Simcyp population "Sim Healthy Volunteers." The SimCYP geriatric population "Sim GeriatricNEC" was also used to assess the model's performance in the OptimAT study population. The GeriatricNEC physiological model is a submodel of the Simcyp Population-based Simulator, designed to simulate drug PK in the elderly. It includes a set of physiological and anatomic parameters specific to this population, accounting for changes in organ size, blood flow, enzyme activity, renal function, liver function, and transporter function.[21] The model, for example, adjusts renal clearance based on age and glomerular filtration rate, and accounts for changes in hepatic blood flow, enzyme activity, protein binding, cytochrome P450 (CYP) enzyme activity, and drug transporter expression and activity.

PBPK model development: Rivaroxaban

The literature review revealed 11 individual PBPK models for rivaroxaban (Table S1), with the majority of these models utilizing input parameters from Cheong et al.[17] Consequently, this model served as our foundational model, from which we initiated optimization in using observed data obtained from phase I studies in healthy adult volunteers[22] and by gathering information from the literature and other models to complete missing input parameters (some models featured additional "in vitro" experiments). The mean fold error (MFE) of PK parameters AUC_{tau}, C_{max}, T_{max}, and $t_{1/2}$ were utilized to assess

the various models tested. We examined different values for the unbound fraction in plasma[22] and the permeability coefficient[13,15,22,23] as found in multiple published models. However, the values chosen for the final model are identical to those used in the Cheong et al. model as best fits the MFE values for all PK parameters. Another significant difference among the published PBPK models was the estimation of the distribution model. In the Cheong et al. model,[17] a whole-body PBPK model was applied to describe the distribution of rivaroxaban, where the tissue-to-plasma distribution equilibrium ratios were calculated via mechanistic tissue composition equations developed by Rodgers and Rowland.[24] The volume of distribution at steady-state was predicted to be 0.2 L/kg, which is lower than the observed in vivo volume of distribution at steady-state of ~0.62 L/kg.[25] Despite an adjustment made with a tissue/plasma partition coefficient scalar (applied to all tissues), the Cheong et al. model poorly predicted the elimination phase of rivaroxaban (with an MFE for the average $t_{1/2}$ time being 0.28, 0.33, and 0.47 for 10, 20, and 30 mg, respectively, compared to observed data in healthy volunteers[25]). The value used by Grillo et al.,[12] which is closer to the observed value in vivo (volume of distribution at steady-state of 0.66 L/kg), improved the prediction for $t_{1/2}$ (MFE of 0.79–0.87; Figure S3). Although the predictions for AUC_{tau} and C_{max} were slightly less accurate, the significant improvement in $t_{1/2}$ resulted in maintaining this change in the model. Furthermore, the advanced dissolution, absorption and metabolism model was used for the prediction of oral absorption, and the parameters related to the intestinal P-gp efflux transporter were obtained from the data of Cheong et al. The intrinsic clearances of CYP3A4 and CYP2J2 were calculated using a retrograde model with fraction metabolized (fm) CYP3A4 of 0.37 and fm CYP2J2 of 0.29, as found in all published models. The effects of renal transporters, such as P-gp and OAT3, were also incorporated using the renal mechanistic model in Simcyp software.

The final model for rivaroxaban accurately predicted PK parameters in healthy volunteers in two states: fasting and fed after a single dose of rivaroxaban 10 mg, 15 mg, and 20 mg (Table S2). The input parameters are detailed in Table 1.[4,12,17,25,26]

PBPK model development: Apixaban

The literature review identified two different PBPK models for apixaban.[16,18] One of the models did not provide enough information to reproduce the results in a healthy population.[16] We were, however, able to reproduce Otsuka et al.'s model validation in a healthy population as originally presented and this model was therefore used unchanged for simulation in the OptimAT population. The input parameters for apixaban's final PBPK model are shown in Table 2.[26–30]

PBPK simulations in the OptimAT population

The parameters for the simulated clinical trial were the following: apixaban 5 mg b.i.d., rivaroxaban 20 mg q.d., and rivaroxaban 15 mg b.i.d. taken in the morning (fasting state) with an intake duration of 72 h after the first dose to ensure steady-state as designed in the observational study. We simulated 10 trials of 100 participants per molecule.

Statistical analysis

Performance of the final models were assessed by the MFE, which equals the ratio of observed over predicted PK parameters expressed in percentage, with the following formula:

$$\text{MFE} = \frac{\text{PK Parameters, (mean, predicted)}}{\text{PK Parameters, (mean, observed)}}$$

Validation was accepted if the predicted 95% confidence interval (CI) around the mean of the AUC_{tau} is included within the equivalence margins set at 20% for this study (MFE: 0.8–1.25). A 20% error is clinically acceptable when considering the risk change for DOACs' clinical events.[9] The number of subjects was based on a previous model used to assess the observed and simulated AUC_{tau} in 19 human volunteers taking the $P2Y_{12}$ inhibitor ticagrelor.[31] The mean of individual differences between observed and model-predicted AUC_{tau} was 3% (CI: −15 to 21%) of the measured AUC_{tau} with an SD of 39%. Considering an equivalence margin of 20% for the difference expressed in percentage of the measured AUC_{tau} and assuming conservatively a true mean difference of 3% and an SD of 43%, the number of subjects needed for the study power to be 90% is 69 with a risk of type 1 error of 0.05 (2-sided).[32] Due to potential variations in the calculation of the number of subjects for the other antithrombotic drugs of interest and for dropouts, the number of needed subjects was set to 100 per drug of interest.

RESULTS

Observed data

One hundred patients per molecule were successfully recruited as originally planned between January 2018

TABLE 1 Input parameters for rivaroxaban's final PBPK model.

Parameter	Value	Method/ References
Molecular weight (g/mol)	435.88	CAS ID: 366789-02-8
log P	1.5	[25]
Compound type	Neutral	–
B/P	0.71	[12]
fu	0.065	[12]
Main plasma-binding protein	Human serum albumin	–
Absorption model	**ADAM model**	
fu_{gut}	0.21	Predicted
$P_{eff,man}$ (10^{-4} cm/s)	3.020492	Predicted
Permeability Assay	Caco-2	[26]
Apical pH: Basolateral pH	7.4:7.4	
Activity	Passive	
$P_{appA:B}$ (10^{-6} cm/s)	21.8	
Scalar	1.284077	Predicted
Solubility pH Type	Intrinsic	
Transporter	ABCB1 (P-gp/ MDR1)	
J_{max} (pmol/min)	37.83	[17]
K_m (μM)	9.416	[17]
$f_{u,inc}$	1	Predicted
Insert growth area of the Transwell (cm^2)	0.33	[4]
System	MDCK	[4]
RAF/REF	1.5	
Distribution model	**Full PBPK model**	
V_{SS} (L/kg)	0.66	Predicted—Method 1
Elimination model		
Enzyme	CYP3A4	Predicted in Simcyp
Pathway	Pathway 1	
CL_{int} (μL/min/pmol)	0.06353705	
Enzyme	CYP2J2	Predicted in Simcyp
Pathway	Pathway 1	
CL_{int} (μL/min/pmol)	5.685421	
CL_{int} (HLM) (μL/ min/mg protein)	7.998799	Predicted in Simcyp using the retrograde calculator

TABLE 1 (Continued)

Mechanistic kidney model		
$CL_{PD,basal}$ (mL/min/ million proximal tubular cells)	1.09E-05	[17]
$CL_{PD,apical}$ (mL/min/ million proximal tubular cells)	1.09E-05	[17]
$fu_{kidney,cell}$	0.3788975	Predicted in Simcyp
fu_{urine}	1	
Transporter	SLC22A8 (OAT3)	
Function	Uptake	
$CL_{int,T}$ (μL/min/ million cells)	43	Scaled using sensitivity analysis
Transporter	**ABCB1 (P-gp/MDR1)**	
Function	Efflux	
J_{max} (pmol/min/ million cells)	80.921	[17]
K_m (μM)	9.416	[17]
RAF/REF	4	

Note: References refer to the original source where the inputs were found.

Abbreviations: ADAM, advanced dissolution, absorption and metabolism; B/P, blood to plasma partition ratio; CL_{int}, in vitro intrinsic clearance; $CL_{int,T}$, in vitro transporter-mediated intrinsic clearance; CL_{PD}, passive diffusion clearance; f_u, fraction unbound in plasma; $f_{u,gut}$, fraction unbound in the enterocytes; $f_{u,inc}$, fraction unbound in the in vitro incubation; $f_{u,kidney,cell}$, fraction unbound in the kidney cell; $f_{u,inc}$, fraction unbound in the urine; HLM, human liver microsome; J_{max}, maximum rate of transporter-mediated efflux or uptake; K_m, Michaelis–Menten constant; K_p, tissue to plasma partition coefficient; log P, common logarithm of the octanol: water partition coefficient; MDCK, Madin Darby Canine Kidney cell line; $P_{appA:B}$, apparent passive permeability; PBPK, physiologically-based pharmacokinetic; $P_{eff,man}$, human jejunum effective permeability; RAF/REF, Relative activity/ expression factor; V_{ss}, volume of distribution at steady state.

and November 2019. The study flowchart is shown in Figure 1. Seven hundred forty-seven and 1270 patients were screened for apixaban and rivaroxaban, respectively. The three main reasons for patients' exclusion were inability to obtain consent (e.g., due to cognitive impairment), discharge from the hospital before blood sampling, and discharge before the molecule reached steady-state (Tables S3 and S4). In addition, the main reason for patients' exclusion on rivaroxaban was treatment taken in the evening, disallowing daytime blood sampling. Table 3 summarizes clinical and demographic characteristics of the apixaban and rivaroxaban populations. Patients taking apixaban were on average slightly older (77 vs. 74 years), had a higher proportion

TABLE 2 Input parameters for final apixaban's PBPK model.

Parameter	Value	Method/References
Molecular weight (g/mol)	459.5	[27]
log P	1.6	[28]
Compound type	Neutral	[28]
B/P	0.9	[27]
fu	0.1	[27]
Main plasma binding protein	Human serum albumin	[27]
Absorption model	**ADAM model**	
Formulation	Solution	Assumed because administration of oral tablet resulted in comparable exposure to that of oral solution administration[29]
fu_{gut}	0.158	Predicted with Simcyp built-in module
P_{app} (10^{-6} cm/s)		
LLC-PK1 cell passive permeability	6.0	[30]
Scalar	1	Assumed
$P_{eff,man}$ (10^{-4} cm/s)	1.286	Predicted
$P_{eff,man}$ (10^{-4} cm/s) Colon	0.514	Predicted
$P_{eff,man}$ (10^{-4} cm/s) Colon	0.206	Predicted
Distribution model	**Full PBPK model**	
V_{SS} (L/kg)	0.31	Predicted—Method 2
K_p scalar	1	
Elimination Model		
CL_{iv} (L/h)	3.3	
CL_R (L/h)	1.0725	Calculated from CL_{iv} and elimination ratio of unchanged drug into urine
CL_{add} (L/h)	0.9735	Calculated from CL_{iv} and unrecovered ratio of dosed radioactivity
$CL_{int,CYP3A4}$ (mL/min/pmol)	0.0112	Retrograde calculation from CL_{iv}
$f_{u,mic}$	1	Assumed
$CL_{int,HLM}$ (μL/min/mg protein)	1.957	Retrograde calculation from CL_{iv}
$f_{u,mic}$	1	Assumed
Transporter	**ABCB1 (P-gp/MDR1)**	
CL_{int}, p-gp in intestine (μL/min)	1.39	Estimated from in vitro P-gp facilitated transport velocity
		[30]
$f_{u,inc}$	1	Assumed
RAF/REF for intestinal P-gp	15	Optimized in the current analysis. See text for the details

Note: References refer to the original source where the inputs were found.

Abbreviations: ADAM, advanced dissolution, absorption and metabolism; B/P ratio, blood to plasma concentration ratio; CL_{add}, additional systemic clearance; $CL_{int,CYP3A4}$, intrinsic clearance of CYP3A4 mediated metabolism; $CL_{int,HLM}$, intrinsic clearance in human liver microsome; CL_{int},P-gp, intrinsic clearance of P-gp mediated transport; CL_{iv}, total systemic clearance after intravenous dosing; CL_R, renal clearance; f_u, fraction of unbound drug in plasma; $f_{u,gut}$, fraction of unbound drug in enterocytes; $f_{u,inc}$, fraction of unbound drug in the in vitro incubation; $f_{u,mic}$, fraction of unbound drug in the in vitro microsomal incubation; HLM, human liver microsome; HSA, human serum albumin; K_p, tissue to plasma partition coefficient; log P, logarithm of the octanol–water partition coefficient; P_{app}, apparent passive permeability; PBPK, physiologically-based pharmacokinetic; $P_{eff,man}$, in vivo permeability; P-gp, P-glycoprotein; RAF/REF, relative activity factor/relative expression factor; V_{ss}, volume of distribution at steady-state.

of women (42 vs. 34%), had reduced renal function (56.5 vs. 72.3 mL/min according to CG equation), and were more prone to take a DOAC for atrial fibrillation (AF) than for venous thromboembolism (VTE; 89 vs. 70%). Reasons for admission were similar between the two groups, with the exception of VTE, which was more common in rivaroxaban users. Patients on rivaroxaban for VTE were younger (69 vs. 75 years old, median) had better renal function (66.5 vs. 81.6 mL/min according CG equation), were heavier (87.3 vs. 75.2 kg), and have fewer comedications (10 vs. 12; Table S5).

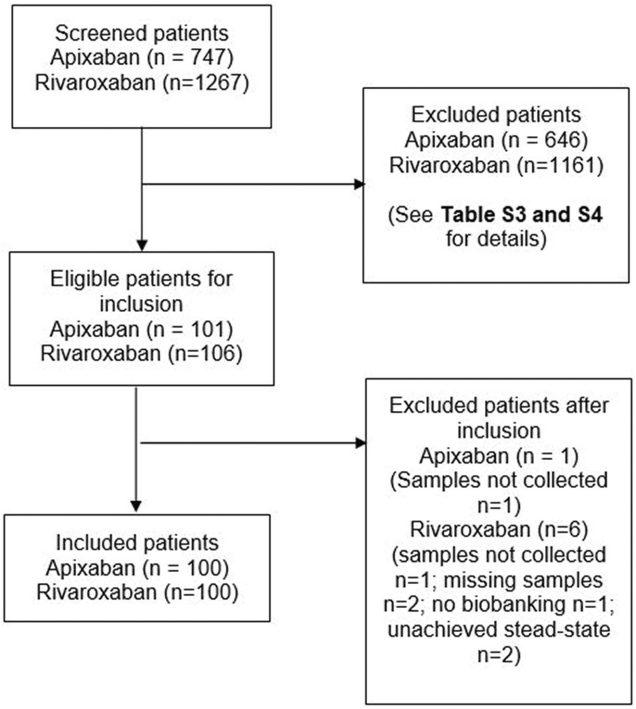

FIGURE 1 Flow-chart of the study.

The individual PK profiles observed for both molecules showed a high interindividual variability (Figure 2). Mean values (±SD) for C_{max} and C_{min} were 155.3 (±60.3) ng/mL and 88.4 (±38.1) ng/mL for apixaban (normalized to 5 mg b.i.d.), 153.1 (±53.0) ng/mL, and 44.5 (±24.8) ng/mL for rivaroxaban normalized to 20 mg q.d., 149.0 (±56.8) ng/mL and 69.1 (±31.5) ng/mL for rivaroxaban 15 mg b.i.d., respectively.

Apixaban's PBPK model: Validation in the OptimAT study population

A sensitivity analysis was performed for the apixaban model by changing the activity factor/relative expression factor (RAF/REF) of intestinal P-gp, as previously done by Ostuka et al. (Figure S4). In our case, a RAF/REF of 15 allowed to achieve the best predictions for the main PK parameters. The observed PK parameters from the OptimAT population were largely underpredicted by the model using the physiological model of a healthy population (Table 4). The P/O ratio for AUC_{tau} was neither within the predetermined interval nor within the classical 0.5- to two-fold ratio. The use of the physiological model in the geriatric population largely

TABLE 3 Clinical and demographic characteristics of the population.

Characteristics	Apixaban ($n = 100$)	Rivaroxaban ($n = 100$)
Age (years) (median, IQR)	77 (71–83)	74 (66–81)
Female (%)	42	36
Ethnicity (%)	White (97), African (1), Hispanic (1), Asian (1)	White (96), African (1), Hispanic (1), Asian (2)
Weight (median, IQR)	74.7 (60.3–89.2)	80.6 (70.0–91.8)
Height (median, IQR)	170 (163–175)	173 (166–180)
Creatinine clearance[a] (mL/min) (median, IQR)	56.5 (46.5–71.7)	72.3 (55.4–96.6)
Reason for admission	Acute decompensated heart failure (35), acute respiratory decompensation (6), acute infection (12), acute coronary syndrome (10), ischemic stroke (2), VTE (4), decline in physical function (2), loss of consciousness (1), hemorrhage (1), others (27)	Acute decompensated heart failure (25), acute respiratory decompensation (7), acute infection (18), acute coronary syndrome (6), ischemic stroke (1), VTE (19), decline in physical function (1), loss of consciousness (1), others (22)
Drug indication (%)	AF (89), VTE (11)	AF (64), VTE (36)
Dosage (%)	5 mg b.i.d. (56), 2.5 mg b.i.d. (40). 10 mg b.i.d. (4)	10 mg q.d. (4), 15 mg q.d. (14), 20 mg q.d. (59), 15 mg b.i.d. (23)
Comedications (n, %)	0–4 (2) 5–9 (29) >10 (69)	0–4 (6) 5–9 (33) >10 (61)

Abbreviations: AF, atrial fibrillation; IQR, interquartile range; VTE, venous thromboembolism.

[a]according to Cockroft-Gault equation.

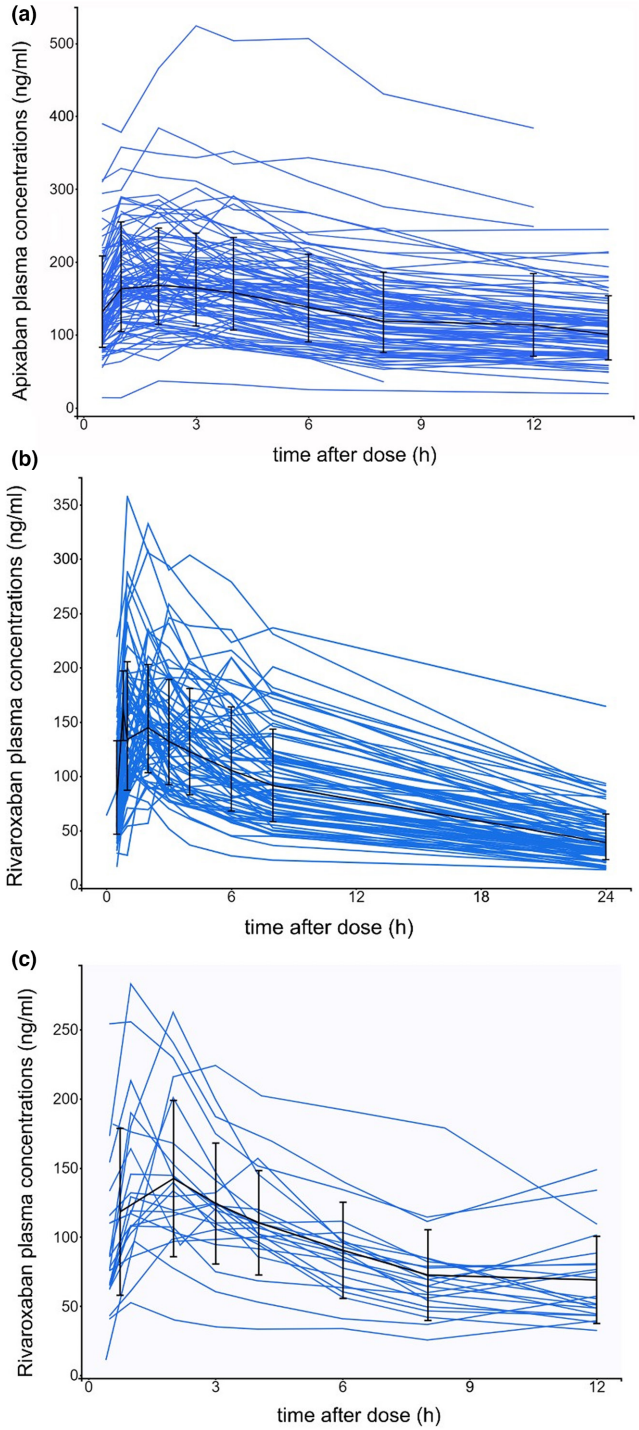

FIGURE 2 Individual observed pharmacokinetic profiles for: (a) apixaban (normalized to 5 mg b.i.d.); (b) rivaroxaban (normalized to 20 mg q.d.); (c) rivaroxaban 15 mg b.i.d. Black dots = mean ± SD.

improved the predictions in the OptimAT population for all PK parameters (Table 4 and Figure 3), 70 of 100 (70%) of the observed AUC_{tau} values were in the 5–95th percentiles (1000–2357 ng/mL), and 95% of the observed AUC_{tau} values were in the predicted AUC_{tau} range (667–4118 ng/mL; Figure S5).

Rivaroxaban's PBPK model: Validation in the OptimAT study population

As for the apixaban's model, the use of the physiological model in the geriatric population largely improved the predictions in the OptimAT population for all PK parameters (Table 4 and Figure 3).

Contrary to the healthy subject model predictions, a large overestimation of plasma exposure in patients receiving 15 mg rivaroxaban b.i.d. was observed with the geriatric model (Figure S6). For this latter 15 mg rivaroxaban b.i.d. group, the predefined criteria were satisfied using a healthy volunteer population-based model. The percentages of observed AUC_{tau} values within the 5–95th percentiles and the predicted range were 79% (1203–4075 ng/mL) and 93% (738–5819 ng/mL), respectively, for the 20 mg q.d. regimen (Figure S5). For the 15 mg b.i.d. regimen, the percentages were 63% (988–3400 ng/mL) in the 5–95th percentiles and 83% (619–4630 ng/mL) in the predicted range.

DISCUSSION

The present prospective study allowed the validation of PBPK models for apixaban and rivaroxaban in a large cohort of hospitalized, elderly, and polymorbid patients. The physiological model of a geriatric population was particularly relevant as we were able to achieve the predefined criteria traditionally used for bioequivalence for patients on apixaban and rivaroxaban. The healthy volunteer population, however, performed better for rivaroxaban 15 mg b.i.d. The latter result may be mainly explained by the demographic characteristics of this population, being exclusively VTE patients, which according to present and published data, is a younger population with fewer comorbidities than patients with AF.[33,34]

Traditionally, PBPK has been used in the pre-market phases of drug development because of its a priori approach, which is particularly useful when clinical data is lacking.[35] The present study indicates that this approach is of interest to clinicians in daily practice, including vulnerable patients. Our validated models for DOACs in real life settings will be of particular interest to assess the risk for under- and over-dosing that are proxies for clinical events in patients with AF.[9]

Although different in approach and complexity, published PBPK models for rivaroxaban share similar physicochemical parameters. Despite the growing number of PBPK models for rivaroxaban, none have been yet validated in hospitalized patients. This highlights the need for further validation of these models by clinicians. Having been optimized, prior to study analyses and using a proper

TABLE 4 Comparison between observed and predicted PK parameters for the final apixaban's and rivaroxaban's model.

DOAC (dosage)	Population	AUC_{tau} (ng/mL·h) (geometric mean, IC 90%)	C_{max} (ng/mL) (geometric mean, IC 90%)	C_{min} (ng/mL) (geometric mean, IC 90%)	$t_{1/2}$ (h) (geometric mean, IC 90%)
Apixaban (5 mg b.i.d.)	OptimAT (observed)	1591.8 (1488.75–1701.99)	182.95 (172.09–265.40)	122.43 (109.33–135.54)	13.42 (8.61–20.91)
	Healthy volunteers (predicted)	1032.06 (1018.08–1046.23)	120.47 (118.91–122.06)	50.38 (27.87–78.96)	6.92 (6.82–7.03)
	Ratio P/O	0.65 (0.64–0.66)	0.66 (0.65–0.67)	0.41 (0.40–0.42)	0.52 (0.51–0.52)
	Geriatric (predicted)	1547.6 (1526.59–1568.91)	160.73 (158.62–162.87)	100.23 (56.19–159.97)	11.95 (11.7–11.21)
	Ratio P/O	0.97 (0.96–0.99)	0.88 (0.87–0.89)	0.81 (0.80–0.82)	0.89 (0.87–0.91)
Rivaroxaban (20 mg q.d.)	OptimAT (observed)	1963.47 (1799.53-2127.41)	167.61 (157.25–177.97)	44.48 (35.97–52.99)	13.59 (12.02–15.63)
	Healthy volunteers (predicted)	1183.02 (1115.20–1254.96)	98.86 (94.48–103.43)	15.03 (6.25–35.75)	8.10 (7.88–8.22)
	Ratio P/O	0.60 (0.59–0.61)	0.59 (0.58–0.60)	0.34 (0.33–0.36)	0.57 (0.56–0.57)
	Geriatric (predicted)	2026.54 (1907.76–2152.71)	139.02 (132.60–145.77)	40.03 (14.65–94.66)	13.51 (13.02–14.01)
	Ratio P/O	1.03 (1.02–1.05)	0.83 (0.82–0.84)	0.90 (0.89–0.91)	0.99 (0.98–1.01)
Rivaroxaban (15 mg b.i.d.)	OptimAT (observed)	1049.99 (912.15–1187.33)	148.38 (127.22–169.54)	69.11 (63.21–75.01)	11.18 (9.33–13.94)
	Healthy volunteers (predicted)	983.37(926.80–1043.40)	110.01 (106.00–117.37	44.26 (18.47–96)	6.75 (6.44–7.08)
	Ratio P/O	0.94 (0.93–0.95)	0.74 (0.73–0.75)	0.64 (0.63–0.65)	0.60 (0.59–0.61)
	Geriatric (predicted)	1807.80 (1592.76–1796.28)	171.26 (162.16–180.87)	97.08 (46.23–224.62)	11.54 (10.82–12.31)
	Ratio P/O	1.72 (1.71–1.73)	1.15 (1.14–1.16)	1.40 (1.39–1.41)	1.03 (1.02–1.04)

Abbreviations: AUC_{tau}, area under the concentration curve for a dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; DOAC, direct oral anticoagulant; IC, inhibitory concentration; PK, pharmacokinetic; P/O, predicted/observed; $t_{½}$, terminal half-life.

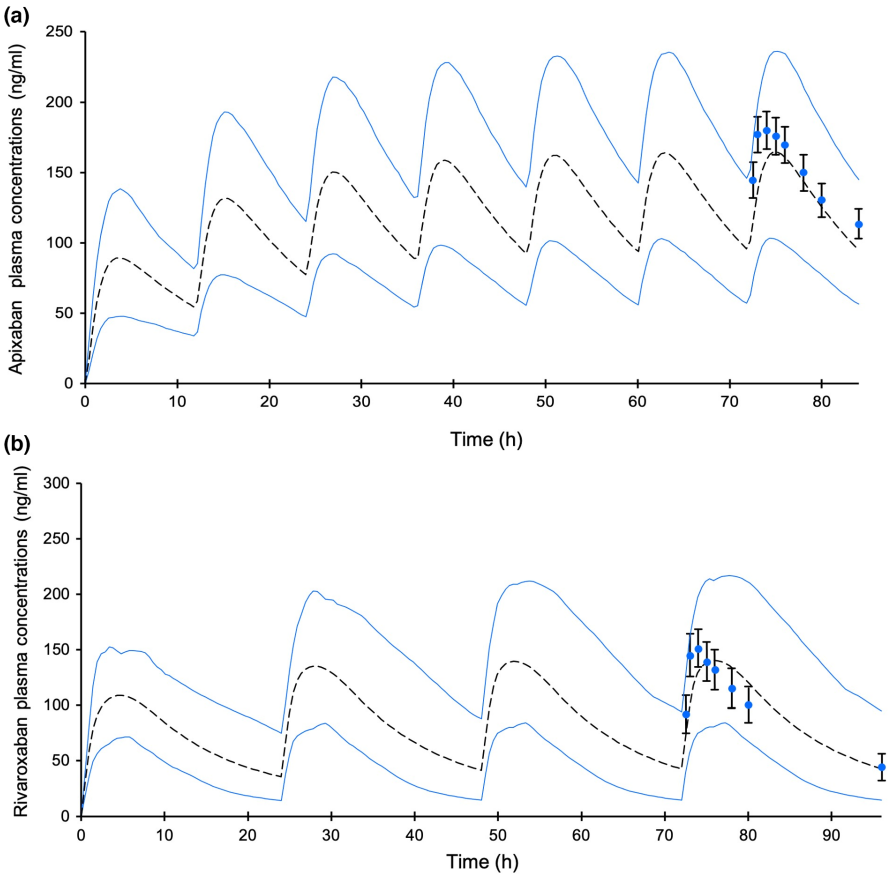

FIGURE 3 Observed (blue dots = mean ± SD) versus predicted pharmacokinetic profiles (dashed black line = mean predicted concentration) and continuous blue lines (5th and 95th percentiles of prediction) for: (a) apixaban (normalized to 5 mg b.i.d.); (b) rivaroxaban (normalized to 20 mg q.d.).

distribution volume from independent data in a healthy population, the Cheong et al.[21] model for rivaroxaban was accurate in predicting the PK parameters of hospitalized patients using a geriatric population. Our study supports the need for the integration of appropriate physiological parameters into PBPK models for them to be applied in clinical settings. Similarly, the apixaban model published by Ostuka et al. and validated in healthy volunteers,[18] was remarkably accurate in our geriatric population. The only parameter needing to be optimized, in a post hoc sensitivity analysis, was the RAF/REF scale factor for P-gp intestinal clearance. In our case, the scale factor used was lower, meaning a loss of P-gp abundance in our elderly population, which is consistent with data found in literature.[36]

Interindividual variabilities were well covered by the predictions for both molecules despite the large range of renal function in our population and the presence of several interacting drugs in ~25% of study patients. The interindividual variability was generated by the Monte-Carlo approach in Simcyp based on the known population variability for each parameter.[7] Thus, the range of predicted AUC_{tau} encompasses the large majority of observed AUC_{tau}, giving the clinicians the possibility of accounting for the true variability observed in the population.

In recent years, several studies have shown that PBPK models can be useful for personalized medicine in the elderly. The geriatric population is rarely included in the premarketing phases of drug development and PBPK could help to enable individualized dosing regimens and drug therapy guidance in elderly patients.[21] Several studies have highlighted the potential of such an approach in various fields, such as parenteral drug administration[37] or in determining appropriate dosing recommendations in this population.[38,39]

Limitations of the present study include the overprediction of PK parameters observed in the VTE population on rivaroxaban 15 mg b.i.d. Indeed, the VTE population in our cohort tends to be younger and has a better renal function, as previously observed in literature.[33,34] It is worth noting that the geriatric population available in Simcyp includes a demographic lower limit of 65 years, which may alter the prediction of PK parameters in younger patients of this specific VTE group taking rivaroxaban 15 mg. For this population, we therefore recommend using the healthy volunteer population instead. In addition, no demographic or biological parameters were set for our population, which could have improved our prediction.[7,40] Our primary goal was to test the a priori "intact" physiological model of the geriatric population.

The main strength of our study is its prospective design. OptimAT is the first study, to our knowledge, that was designed to validate PBPK models in hospitalized

patients. The rigorous design enabled comprehensive and high-quality data collection that was prespecified and planned for PK studies.

In conclusion, the validation of the present PBPK models for rivaroxaban and apixaban in a cohort of hospitalized patients represents an additional step toward the use of model-informed precision dosing at the bedside. The contribution of the physiological data from a specific geriatric population plays a major role in this study. The combination of the present models and the geriatric physiological data could therefore serve as a basis for future apixaban and rivaroxaban PK (e.g., dose adaptation in complex DDI) studies based on PBPK, in real-life setting. The next step is to validate a more individualized approach using virtual twin PBPK modeling on a large scale and in integrating individual parameters, including demographics, physiological factors, and CYP450 phenotypic activities.[7]

AUTHOR CONTRIBUTIONS

All the authors wrote the manuscript. J.T., F.G., P.F., C.C., Y.D., and J.L.R. designed the research. J.T., P.G., and C.L. performed the research. J.T., F.G., and O.R. analyzed the data. Y.D. contributed new reagents/analytical tools. The OptimAT study group includes all the authors, Christophe Combescure, Monia Guidi, and Fabienne Doffey Lazeyras.

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ORCID

Jean Terrier https://orcid.org/0000-0002-5878-4878
Frédéric Gaspar https://orcid.org/0000-0002-0225-7294
Camille Lenoir https://orcid.org/0000-0001-6506-8629
Pierre Fontana https://orcid.org/0000-0003-1546-0774

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