Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Dose Optimization of Rivaroxaban in Elderly Chinese Patients with Non-Valvular Atrial Fibrillation: Analysis of Populations Pharmacokinetics and Exposure-Response Relationships

Tian-yu Li[1], Xin Liu[2], Lian Tang[1,3], Wei Cai[4], Jun Zhang[4], Ya Su[5], Chao Yu[6], Bi-jue Liu[2], Lin-feng Jiang[7], Chun Liu[1,3], Yan-xia Yu[1,3]

[1]Department of Pharmacy, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, People's Republic of China; [2]Department of Clinical Pharmacy, School of Pharmaceutical Science, Fudan University, Shanghai, People's Republic of China; [3]Gusu School, Nanjing Medical University, Suzhou, People's Republic of China; [4]Department of Cardiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, People's Republic of China; [5]Department of Pharmacy, Taizhou Hospital of Traditional Chinese Medicine, Taizhou, People's Republic of China; [6]Department of Pharmacy, Ruijin Hospital Wuxi Branch, Shanghai Jiao Tong University School of Medicine, Wuxi, People's Republic of China; [7]College of Pharmacy, Nanjing Medical University, Nanjing, People's Republic of China

Correspondence: Chun Liu; Yan-xia Yu, Email liuchun83@163.com; yuyxsz@163.com

Purpose: This study aimed to develop a population pharmacokinetic (PopPK) model in elderly Chinese patient with NVAF, characterize the pharmacokinetic variability, identify relevant covariates affecting rivaroxaban disposition, and explore the exposure-response relationship.

Patients and Methods: A prospective observational study was conducted with rivaroxaban plasma samples collected and analyzed. A PopPK model was developed using the nonlinear mixed-effects modeling approach. Monte Carlo simulations were employed to explore the correlation between significant covariates and estimated drug exposure. $AUC_{24,ss}$ derived from the PopPK analysis, was computed to evaluate exposure-response relationships.

Results: Ninety-three elderly Chinese NVAF patients contributed 256 plasma concentrations were well described by a one-compartment PopPK model. Creatinine clearance (CrCL) and concomitant use of amiodarone were identified as significantly influencing clearance (CL). The simulation results revealed the following: (1) For patients with normal or mildly impaired renal function (CrCL ≥50 mL/min), both a 20 mg once-daily dosage without amiodarone and a 10 mg with amiodarone were acceptable; (2) For those with moderate to severe renal impairment (CrCL 15–49 mL/min), a 10 mg once-daily dosage was appropriate regardless of amiodarone coadministration; (3) Although a 15 mg once-daily dosage was generally suitable from the pharmacokinetic standpoint, concomitant use of amiodarone significantly increased bleeding risk in patients (RR = 8.00, p = 0.039); (4) $AUC_{24,ss}$ was significantly decreased in patients with thromboembolic events compared to those without such events ($p < 0.0001$), with 2840 ng·h/mL identified as the optimal cut-off value (p = 0.023).

Conclusion: For elderly Chinese NVAF patients, a reduced-dose rivaroxaban regimen, specifically 10 mg once daily with amiodarone, is recommended for all patients regardless of renal function, whereas 15 mg once daily is a more optimal option for those not taking amiodarone. Based on the risk-benefit assessment, maintaining $AUC_{24,ss}$ above 2840 ng·h/mL does not yield additional clinical benefit.

Keywords: rivaroxaban, elderly Chinese patients, population pharmacokinetic, exposure-response analysis, drug–drug interactions, atrial fibrillation

Received: 28 August 2025
Accepted: 21 November 2025
Published: 3 December 2025

Introduction

Nonvalvular atrial fibrillation (NVAF), the most prevalent cardiac arrhythmia, affects over 10% of the elderly population, which represents an escalating epidemic and constitutes an urgent global health concern.[1] While warfarin was historically the sole oral anticoagulant for long-term NVAF management, meta-analyses demonstrate that direct oral anticoagulants (DOACs) exhibit superior efficacy and safety profiles versus warfarin in NVAF patients.[2] Consequently, current evidence-based clinical practice guidelines[3,4] endorse DOACs as first-line anticoagulant therapy for NVAF.

Rivaroxaban is the most commonly prescribed DOACs among patients in the US with NVAF.[5] Rivaroxaban is a selective factor Xa inhibitor, quickly absorbed, reaching peak plasma concentration within 2–4 hours.[6,7] Rivaroxaban is cleared through a dual system. Approximately 65% of rivaroxaban is removed via metabolic transformation by cytochrome P450 enzymes (CYP3A4, CYP2J2) by the liver.[8,9] Approximately, 35% of rivaroxaban is eliminated as unchanged active drug in the urine, primarily via active renal secretion.[10] The approved dosages of rivaroxaban for NVAF are 20 mg and 15 mg administered once daily in patients with normal renal function (creatinine clearance ≥50 mL/min) and moderately impaired renal function (creatinine clearance 15–49 mL/min).[3,4] Pharmacokinetic studies indicate that standard dosage during anticoagulant therapy is more likely to be associated with elevated rivaroxaban exposure and an increased bleeding risk in Asian versus Caucasian populations.[11,12] Critically, there is currently a lack of systematic research on the dose optimization for Chinese patients with NVAF.

In addition, it is still uncertain whether results from pivotal clinical trials are fully generalizable to all older adult populations in the real world. The elder patients are characterized by the presence of multiple comorbidities and polypharmacy, potentially altering both rivaroxaban exposure and effect.[13,14] Thus, the management of the elder patients receiving rivaroxaban treatment may be challenging even though several meta-analysis provided reassuring limited data regarding the clinical benefit-risk balance of rivaroxaban.[15,16] Rivaroxaban exposure was shown to significantly attribute to age and renal function. In patients with renal impairment, a decline in CrCL directly translates to a reduction in the renal clearance of rivaroxaban. The impaired glomerular filtration and tubular secretion mechanisms diminish the capacity to excrete the unchanged drug. The elderly population showed elevated systemic exposure, with mean AUC values 41% greater than those observed in younger individuals.[17] A decline in renal glomerular filtration also occurs with aging, which elevates plasma concentration and prolongs elimination half-life.[12,18,19]

The elderly subjects exhibited high interindividual variabilities of rivaroxaban exposure.[13,20,21] Drug–drug interactions (DDIs) frequently occur in the older adults due to coexistence of multiple diseases and polypharmacy. Concomitant use of medications such as dronedarone and verapamil has been reported to significantly increase rivaroxaban plasma levels and potentiate its anticoagulant effect in elderly patients with NVAF.[18,22,23] These findings underscore the need for dose optimization in the Chinese population, especially likely in frail, more physically restricted elderly individuals with complex medication regimens. To address this gap, a rivaroxaban PopPK model based on the Chinese population in the elderly people with NVAF is necessary to determine whether this discrepancy stems from concomitant medications.

This study aimed to develop a PopPK model of rivaroxaban in elderly Chinese patients with NVAF, quantitatively assessing the impact of routine physiological parameters and other potential variables, and establish optimal individualized rivaroxaban dosing regimens via Monte Carlo simulations and exposure-response analyses.

Materials and Methods

Study Design

A prospective, single-center clinical study was conducted at Suzhou Municipal Hospital, affiliated with Nanjing Medical University, China. From January 2021 to March 2022, 93 DOAC-eligible patients with NVAF who met the diagnostic criteria in 2021 European Heart Rhythm Association (EHRA) Guidelines[4] were randomly recruited. These patients had been continuously taking rivaroxaban for a minimum of 4 weeks. Patients were excluded if they exhibited at least one of the following: (1) age <65 years; (2) coagulation disorders; (3) gastrointestinal or metabolic disorders; (4) moderate or severe hepatic insufficiency (Child-Pugh classification B or C[24]); (5) severe renal insufficiency (estimated creatinine clearance [CrCL] <15 mL/min, calculated using the Cockcroft-Gault equation[25]); (6) spontaneous bleeding tendency; (7) concurrent use of other anticoagulants; (8) concomitant therapy with strong CYP3A4 or P-glycoprotein (P-gp) inhibitors. This study was

approved by the Ethics Committee of Suzhou Municipal Hospital (K-2021-GSKY20210405). Informed consent was obtained from all individual participants included in the study according to the principles of the Declaration of Helsinki.

Patient demographics and clinical data were collected. Rivaroxaban was administered at fixed dosage of 10, 15, and 20 mg once daily. Clinicians independently determined whether and how to adjust the dosage regimen based on individual patient characteristics.

Rivaroxaban Quantification

For each subjects, at least five continuous administrations of the rivaroxaban were conducted before sampling. Blood samples were collected 0.5 hours before the next dose (trough concentration) and 3 ± 1 hours after administration (peak concentration), in accordance with previous studies.[12,19] For each patient, dosing and sampling times were documented. Collected blood samples (2.5 mL) were centrifuged at 2000 rpm for 10 min at 20 °C within 4 hours of collection. All samples were stored at −80 °C and analyzed within three months. The concentrations of rivaroxaban were then measured by a validated Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method.[26]

Population Pharmacokinetic Analysis and Model Evaluation

The Phoenix NLME program (version 8.3, Pharsight, Mountain View, CA, USA) with the method of first-order conditional estimation-extended least square method (FOCE-ELS) was used to develop the rivaroxaban PopPK model. Both one- and two-compartment models with first-order elimination were evaluated to characterize the concentration-time profiles. Inter-individual variability was described using an exponential error model. Residual variability of PK parameters was assessed through comparison of additive, proportional, and combined (additive + proportional) error models. Model selection criteria was based on the precision of parameter estimates (standard error), goodness-of-fit diagnostics, and the likelihood ratio test (−2LL).

The stepwise covariate modeling (SCM) approach was employed to test the covariate model in this analysis. Covariates evaluated included demographic factors (eg, gender, age, weight), laboratory test results (eg, total bilirubin [TBIL], creatinine clearance [CrCL]), comorbidities (eg, diabetes, hyperlipidemia), and concomitant medications (eg, amiodarone, atorvastatin). Potential covariates affecting the pharmacokinetic parameters were incorporated into the final model by a stepwise forward inclusion with an objective function value (OFV) decrease of at least 3.84 points ($p < 0.05$) followed by backward elimination approach with an OFV increase of at least 6.64 points ($p < 0.01$).

Model performance was assessed through convergence criteria, OFV, Akaike information criterion (AIC), parameter precision, goodness-of-fit (GOF) plots, visual predictive checks (VPC), and nonparametric bootstrap analysis. The VPC option of Phoenix NLME was fully utilized to complete the VPC of the final model. The model would be reliable if the values of the observed dependent variable concentration were distributed between the 95th and 5th percentile prediction intervals.

Dosage Regimen Simulations

Monte Carlo simulations were performed to evaluate three rivaroxaban dosing regimens (10, 15, and 20 mg once daily) in a virtual population of 1000 subjects by RStudio version 4.4.2 (Boston, Massachusetts, USA) based on the established final PopPK model. The area under the concentration-time curve over 24 h at a steady state ($AUC_{24,ss}$) was selected as the primary exposure metric, as mentioned in previous studies.[11] The 5th and 95th percentile ranges of $AUC_{24,ss}$ (1860–5434 ng·h/mL) in DOAC-eligible NVAF patients were used as the typical exposure range, consistent with prior research.[9] To evaluate covariate effects, simulations were stratified by renal function categories (CrCL: 15–29, 30–49, 50–69, 70–89, 90–110 mL/min) and concomitant amiodarone use. The probability of target attainment (PTA) was calculated for each regimen by calculating the proportion of simulated $AUC_{24,ss}$ within the therapeutic range. Dosing regimens achieving PTA ≥90% were considered optimal for clinical recommendation.

Hemorrhagic Risk Evaluation

During the 180-day follow-up period, all hemorrhagic events were systematically documented and classified according to International Society on Thrombosis and Hemostasis (ISTH) criteria.[18] Major bleeding was identified based on at least

one of the following criteria: hemoglobin decrease ≥2 g/dL; transfusion requirement of ≥2 units of whole blood or packed red cells; Bleeding in critical anatomical sites (intracranial, intraspinal, intraocular, pericardial, intra-articular, or retroperitoneal, or intramuscular bleeding related to compartment syndrome). Clinically relevant non-major bleeding (CRNMB) was defined as any bleeding event associated with medical or physician intervention or impacting daily activities due to pain, mainly including epistaxis, cutaneous hematoma formation, gingival bleeding, and gastrointestinal bleeding.

Exposure-Response Analysis

Data from elderly patients with NVAF who received rivaroxaban were included in the exposure-efficacy and exposure-safety analyses. Individual $AUC_{24,ss}$ was computed from the final model using empirical Bayes (post hoc) estimates and used as the exposure metric in the analyses. Only rivaroxaban-treated patients for whom exposure data could be computed from the popPK model were included.

For exposure-efficacy analyses, incidence of thromboembolic events was used as the most prevalent and typical metric to assess efficacy outcomes, whereas the hemorrhagic risk was used for the exposure-safety analysis. Thromboembolic events included stroke, thrombotic myocardial Infarction (MI), transient ischemic attack (TIA) and embolism-induced mortality.[27] Several mathematical models were evaluated to determine the best model to describe potential underlying relationships between the $AUC_{24,ss}$ and incidence of thromboembolic events based on the PopPK model. Receiver operator curve (ROC) was considered to the best exposure-efficacy model. Youden's Index computed by ROC was used as a cut-off value of $AUC_{24,ss}$ for determining the efficacy of anticoagulant therapy. The relationships between rivaroxaban exposures and the efficacy endpoint and safety outcomes were explored graphically using histograms and box plots.

To mitigate potential confounding effects on bleeding risk assessment, patients receiving concomitant antiplatelet therapy (aspirin or clopidogrel) were excluded from both the exposure-efficacy and exposure-safety analyses. This refinement ensured that the subsequent analyses of thromboembolic events and hemorrhagic risk would primarily reflect the pharmacological activity of rivaroxaban rather than being influenced by additional platelet aggregation inhibitors.

Statistical Analysis

All data were analyzed using SPSS 26.0 (IBM, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (first quartile–third quartile), while categorical variables were expressed as count (percentage). Comparisons of descriptive statistics between groups for continuous variables were analyzed using the independent samples *t*-test and the Mann–Whitney *U*-test (when data were not normally distributed). Pearson's chi-squared test or Fisher's exact test was used for categorical variables. The relative risk (RR) of hemorrhage events was calculated with 95% confidence intervals. All statistical tests were two-tailed with p-value <0.05 considered statistically significant.

Results

Population Characteristics

Data from a total of 93 elderly Chinese DOAC-eligible NVAF patients were collected in this study, with 256 plasma concentration measurements available for PopPK modeling. The cohort demonstrated advanced age (mean: 79 years), with 24.7% (n = 23) being octogenarians (>85 years). Renal function varied substantially (CrCL ranged: 14.3–91.7 mL/min), with 73.1% (n = 68) presenting moderate-to-severe renal impairment (CrCL <50 mL/min). The population had elevated thromboembolic risk (median CHA2DS2-VASc score: 5) with moderate bleeding risk (median HAS-BLED score: 2). It was noteworthy that amiodarone was the most prevalent comedication, administered to 45 patients (48.4%). The standard dosing regimen for amiodarone was 200 mg qd for long-term rhythm control. Complete demographic and clinical characteristics were presented in Table 1.

Table 1 Demographic Characteristics

Characteristics	
Number of patients (male/female), n (%)	93 (50/43)
Number of rivaroxaban concentrations, n (%)	256
Age (year), mean ± SD	79 ± 7
Weight (kg), mean ± SD	61.4 ± 12.1
Height (cm), mean ± SD	162.3 ± 8.2
BMI (kg/m^2), mean ± SD	23.2 ± 3.7
TBIL (μmol/L), median (IQR)	16 (6–40)
PLT (10^9/L), mean ± SD	185 ± 57
ALB (g/L), mean ± SD	39.64 ± 5.34
AST (U/L), median (IQR)	23 (11–111)
ALT (U/L), median (IQR)	17 (3–130)
Cr (μmol/L), median (IQR)	92.0 (46.0–267.7)
CrCL (mL/min), median (IQR)	48.6 (14.3–91.7)
INR, median (IQR)	1.13 (0.86–4.38)
PT (s), median (IQR)	13.6 (10.0–48.0)
APTT (s), median (IQR)	29.3 (21.8–54.4)
CHA2DS2-VASc[a], median (IQR)	5 (1–9)
HAS-BLED[b], median (IQR)	2 (0–5)
Classification of AF[c], n (%)	
Paroxysmal	38 (40.9%)
Persistent	25 (26.9%)
Permanent	30 (32.3%)
Co-morbidities, n (%)	
Diabetes	27 (29.0%)
HyperLipoproteinemia	37 (39.8%)
Stroke	17 (18.3%)
Congestive Heart Failure	59 (63.4%)
Hypertension	80 (86.0%)
Concomitant medication, n (%)	
Amiodarone	45 (48.4%)
Atorvastatin	37 (39.8%)
Rosuvastatin	20 (21.5%)
Aspirin	12 (12.9%)
Clopidogrel	4 (4.3%)
PPI	23 (24.7%)
NSAIDs	3 (3.2%)

Notes: [a]CHA2DS2-VASc score: Congestive heart failure/left ventricular dysfunction (1 point); known hypertension (1 point); Age ≥75 (2 points); diabetes (1 point); history of stroke, TIA or TE event (2 points); vascular disease, coronary heart disease, peripheral artery disease or complex aortic plaque (1 point); female sex (1 point) and age >65 to <75 years (1 point). [b]HAS-BLED score: uncontrolled hypertension - > 160 mm Hg systolic- (1 point); abnormal renal/liver function (1 point for each); previous history of stroke (1 point); bleeding history or predisposition (anemia) (1 point); labile INR (1 point); elderly > 65 years (1 point); drug use-antiplatelet agents, non-steroidal anti-inflammatory drugs- and alcohol consumption (1 point each). [c]The classification of AF based on AF episode duration and temporal patterns proposed by 2019 AHA/ACC/HRS guideline for the management of AF[3] was adapted.

Abbreviations: BMI, body mass index; TBIL, total bilirubin; PLT, platelet; ALB, serum albumin; AST, aspartate aminotransferase; ALT, alanineaminotransferase; Cr, creatinine; CrCL, creatinine clearance; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drug.

https://doi.org/10.2147/DDDT.S563521

PopPK Model of Rivaroxaban

Due to limited plasma concentration data points during the absorption phase, the absorption rate constant (Ka) could not be reliably estimated and was therefore fixed to the reported value (0.821 h-1).[28,29] The results of the present study indicated that, among all the candidate pharmacokinetic models evaluated, the one compartment disposition model with first-order absorption and elimination fits the data best. An exponential model and an additive model were used to describe the interindividual variability and residual variability, respectively. The parameter estimation results of the base model are presented in Table 2.

Following forward inclusion and backward elimination, CrCL and co-administration of amiodarone were consequently identified as significant covariates affecting the apparent clearance of rivaroxaban (CL/F). However, none of the other covariates were found to significantly affect the deposition of rivaroxaban.

There was a drop in OFV of 17.14 in the final PopPK model compared to that in the base model. The parameter estimation results of the final model are presented in Table 2.

Where CL is the individual clearance, V is the individual volume of distribution, CrCL and amiodarone represents the individual creatinine clearance and amiodarone, ηCL is the normally distributed random effect with a mean of 0 and a variance of ω^2.

Model Evaluation

The GOF diagnostic plots (Figure 1) revealed no systematic bias in model predictions, with marked improvement over the base model as evidenced by reduced residual variability and improved agreement between observed and predicted values. Of note, GOF of the final model to the data had a certain degree of improvement compared with the base model. The pc-VPC plot (Figure 2) suggested that the majority of the observed values fell within the 95% prediction intervals, indicating that the final population model possessed satisfactory predictive performance. Moreover, the estimated parameter values from the final model were closely aligned with the median and within the 95% confidence interval of the non-parametric bootstrap (Table 2), indicating that the model was stable and reproducible.

Simulations and Dosing Regimen Optimization

Figure 3 displays the simulated $AUC_{24,ss}$ distributions across different dosage regimens, stratified by CrCL and amiodarone coadministration status. The PTA of simulated patients having $AUC_{24,ss}$ within rivaroxaban typical exposure ranges under various scenarios is summarized in Figure 4.

Table 2 Population PK Parameter Estimates in the Final Model and Bootstrap

Parameter (Unit)	Base Model Results	Final Model Results	Bootstrap Results	
	Estimate (RSE %)	Estimate (RSE %) [Shrinkage]	Median (RSE %)	95% CI
Structural model parameters				
tvKa	0.821, fixed	0.821, fixed	0.821, fixed	/
tvV(L)	30.703 (2.19)	30.714 (2.19)	30.712 (2.26)	29.389–32.056
tvCL (L/h)	4.165 (2.40)	4.501 (2.84)	4.492 (3.74)	4.165–4.830
dCLdCrCL	/	0.179 (18.61)	0.179 (27.08)	0.083–0.276
dCLamiodarone	/	−0.124 (30.51)	−0.123 (−37.63)	(−0.223)-(−0.041)
Inter-individual variability				
ω^2 CL (%)	/	3.6 [21]	3.6	/
ω^2 V (%)	/	3.3 [19]	3.1	/
Residual variability				
stdev0	17.430 (8.09)	18.025 (7.54)	17.807 (8.23)	14.770–20.745

Notes: the final PopPK model was as follows: CL (L/h) = 4.5 * (CrCL/47.4)^0.18 * exp(amiodarone * −0.12)*exp (ηCL).
Abbreviations: tv, typical population value; RSE, relative standard error; CV, coefficient of variation; 95% CI, 2.5th and 97.5th percentile of the ranked bootstrap parameter estimate; V, volume of distribution; CL, clearance; ω inter-individual variation; stdev0, standard deviation.

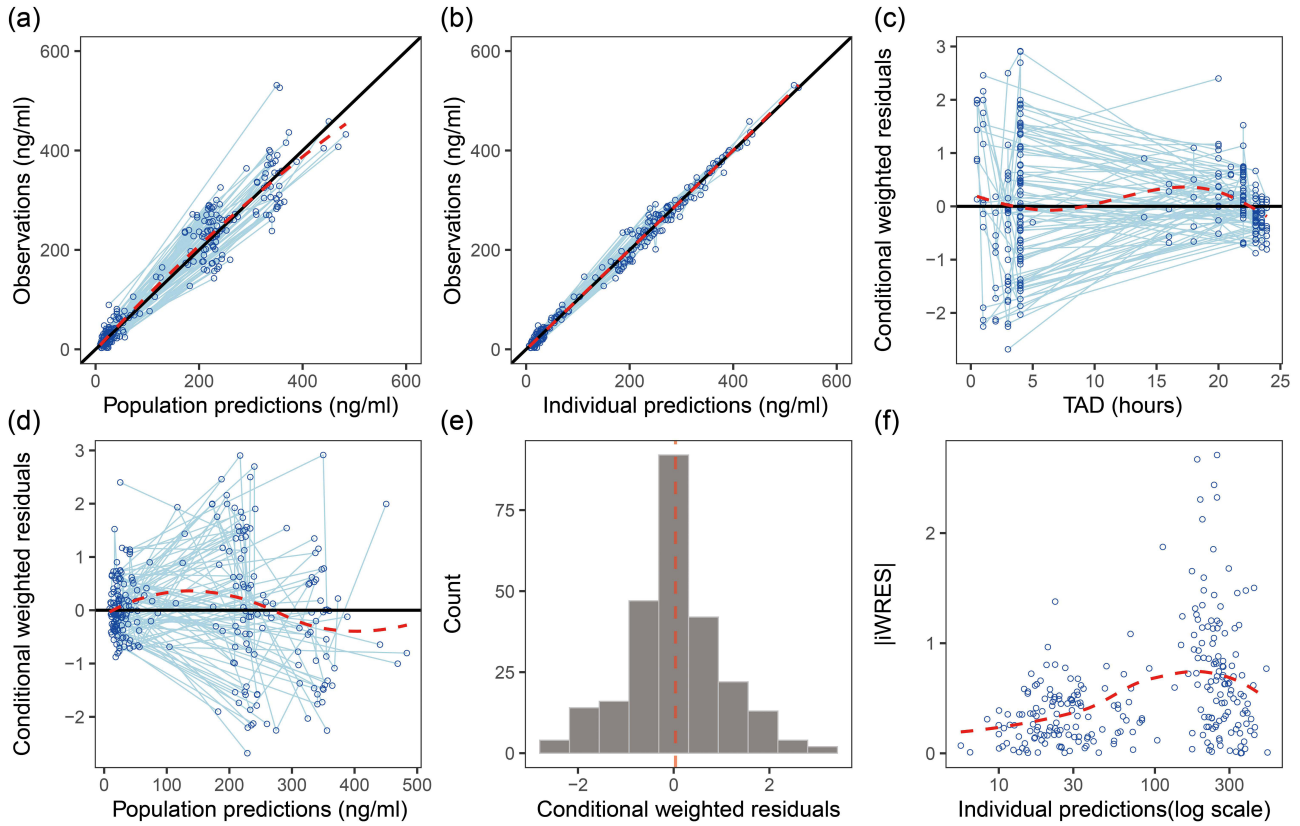

Figure 1 Goodness-of-fit plots for the final model.

Notes: (**a**) individual prediction (IPRED) versus observed dependent variable (DV) scatter plot; (**b**) population prediction (PRED) versus DV scatter plot; (**c**) corrected weighted residual (CWRES) versus time after last dose (TAD) scatter plot; (**d**) CWRES versus PRED scatter plot; (**e**) CWRES histogram; (**f**) |iWRES| versus log(IPRED) scatter plot.

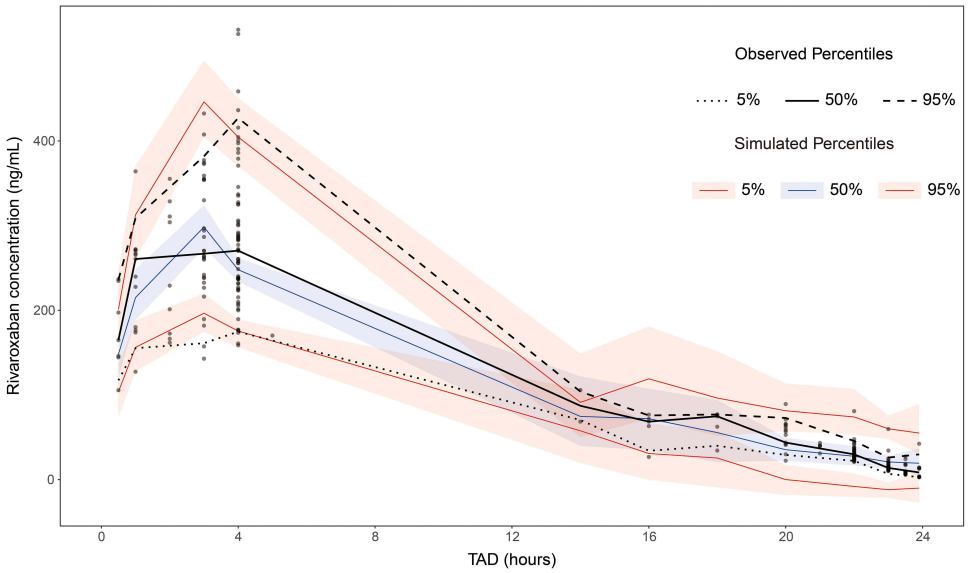

Figure 2 Prediction corrected-visual predictive check of the final model.

Notes: Black circles represent the observed rivaroxaban concentrations. Red or blue solid lines represent the 5th, 50th, and 95th percentiles of the Simulated concentrations and shaded areas represent the 90% CIs of the simulated 5th, 50th and 95th percentiles.

https://doi.org/10.2147/DDDT.S563521

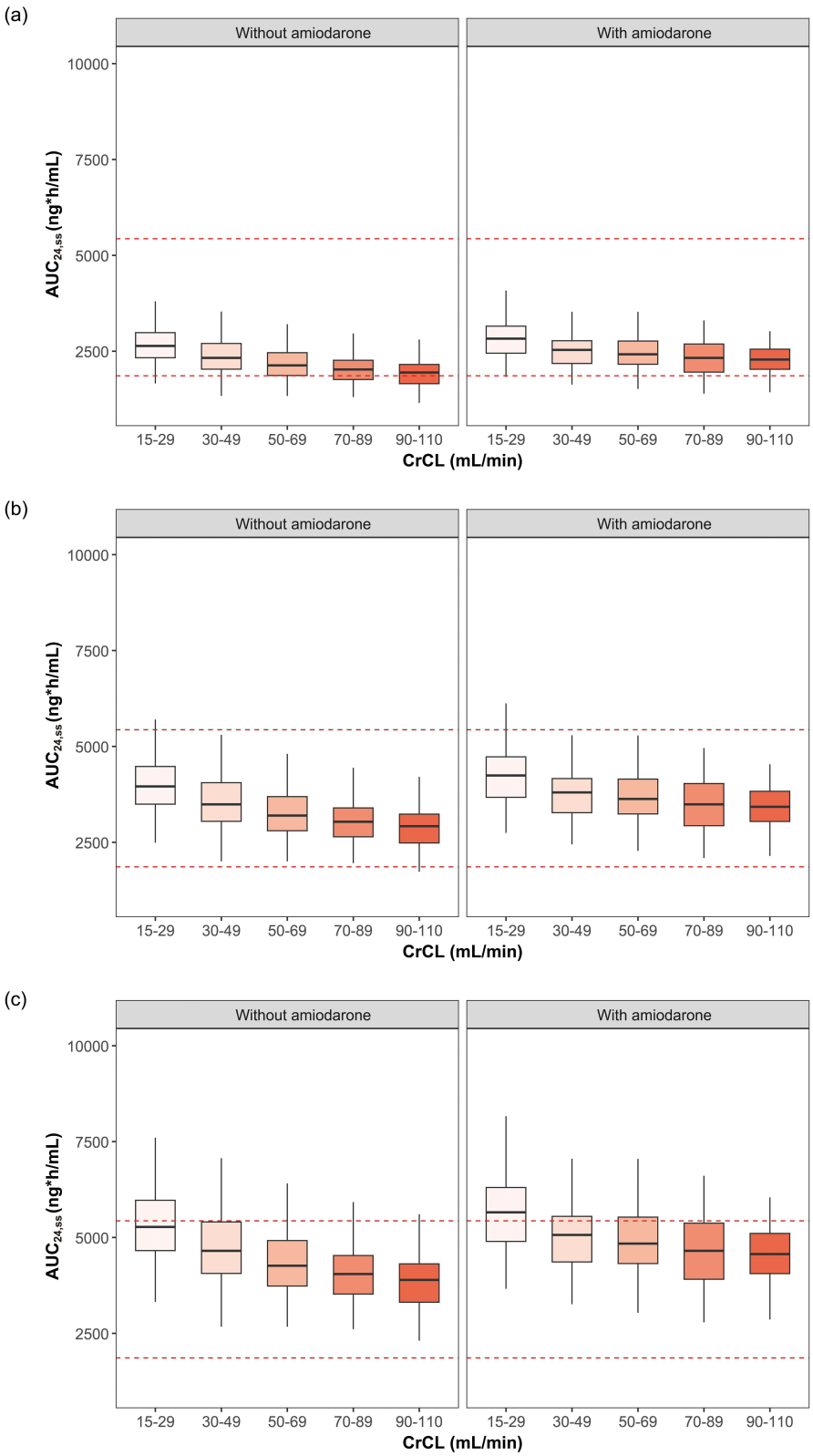

Figure 3 Simulated $AUC_{24,ss}$ of rivaroxban with different dosing regimes. The boxplots represent the predicted $AUC_{24,ss}$ stratified by creatinine clearance and whether combined with amiodarone.

Notes: (**a**) rivaroxaban 10 mg qd. (**b**) rivaroxaban 15 mg qd. (**c**) rivaroxaban 20 mg qd. The dashed lines represent the 5th and 95th percentile ranges of the typical $AUC_{24,ss}$ (1860–5434 ng·h/mL) reported in patients with NVAF receiving 20 mg of rivaroxaban.

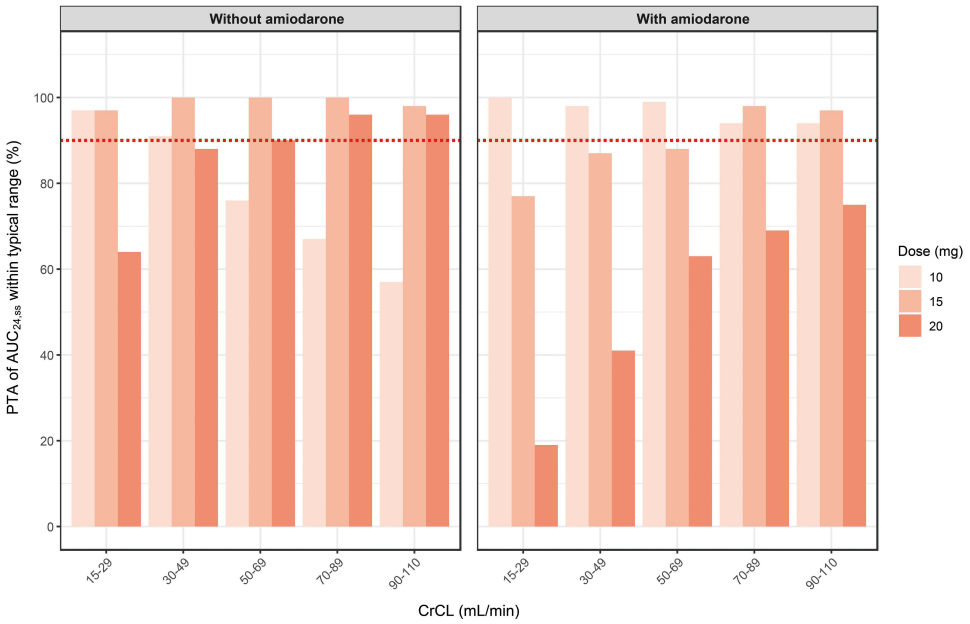

Figure 4 Simulated Probability of Attaining rivaroxaban $AUC_{24,ss}$ stratified by CrCL and whether combined with amiodarone in PopPK Study.

The optimal dosing recommendations were derived from Monte Carlo simulations based on a PopPK model. (1) Patients with preserved renal function (CrCL ≥ 50 mL/min): the 10 mg once daily dosing regimen is recommended in those with amiodarone administration (PTA > 90%), while the 20 mg once daily dosing regimen is also recommended for those without amiodarone administration (PTA ≥ 90%). (2) Patients with moderate to severe renal impairment (CrCL 15–49 mL/min): the 20 mg once daily dosing regimen is avoided regardless of amiodarone coadministration (PTA < 90%), whereas the 10 mg once daily dosing regimen is recommended. (3) The 15 mg once daily dosing regimen is suitable for the majority of scenarios, except for patients with CrCL 15–69 mL/min with receiving concomitant amiodarone.

Exposure-Response Results

Prior to the exposure-response analysis, 13 patients receiving concomitant antiplatelet therapy were excluded to mitigate potential confounding effects. Figure 5a displays $AUC_{24,ss}$ values across different rivaroxaban dosage regimens, while Figure 5b illustrates the corresponding $AUC_{24,ss}$ differences between subgroups stratified by amiodarone coadministration status. $AUC_{24,ss}$ exhibited a significant dose-dependent increase in elderly patients in Figure 5a ($p < 0.05$). Due to insufficient sample size (n = 3), the 20 mg once-daily group was excluded from exposure-response analyses. Notably, the geometric mean ratio of $AUC_{24,ss}$ for the 10 mg dose with versus without amiodarone subgroup was 1.17 ($p < 0.01$), and for the 15 mg dose was 1.25 ($p < 0.01$). Furthermore, the $AUC_{24,ss}$ difference between amiodarone subgroups demonstrated a progressive amplification with the increase in rivaroxaban-fixed doses (Figure 5b).

During the 180-day follow-up period, all reported bleeding events were classified as CRNMB, with no major bleeding events observed. In exposure-response analyses for safety, Figure 5c illustrated a significantly higher $AUC_{24,ss}$ among patients with bleeding events compared to those without bleeding events (3378 vs 2531 ng·h/mL, $p < 0.0001$). Subgroup analysis (Figure 5d) indicated no statistically significant increase in bleeding risk with 10 mg rivaroxaban once daily with amiodarone compared to 10 mg alone (RR = 4.11, $p > 0.050$). However, subjects receiving 15 mg once daily exhibited a significantly elevated risk (RR = 8.00, $p = 0.039$), representing a 1.9-fold higher relative risk than the 10 mg group.

Box plots depicting exposure-response analyses for efficacy are shown in Figure 5e, which demonstrated a significantly lower $AUC_{24,ss}$ among patients with thromboembolic events compared to those without thromboembolic events (2311 vs 2818 ng·h/mL, $p < 0.05$). Subsequently, ROC curve analysis identified 2840 ng·h/mL as a potential optimal cut-off value for rivaroxaban exposures to discern the presence of efficacy endpoints (AUC = 0.70, 95% CI:

https://doi.org/10.2147/DDDT.S563521

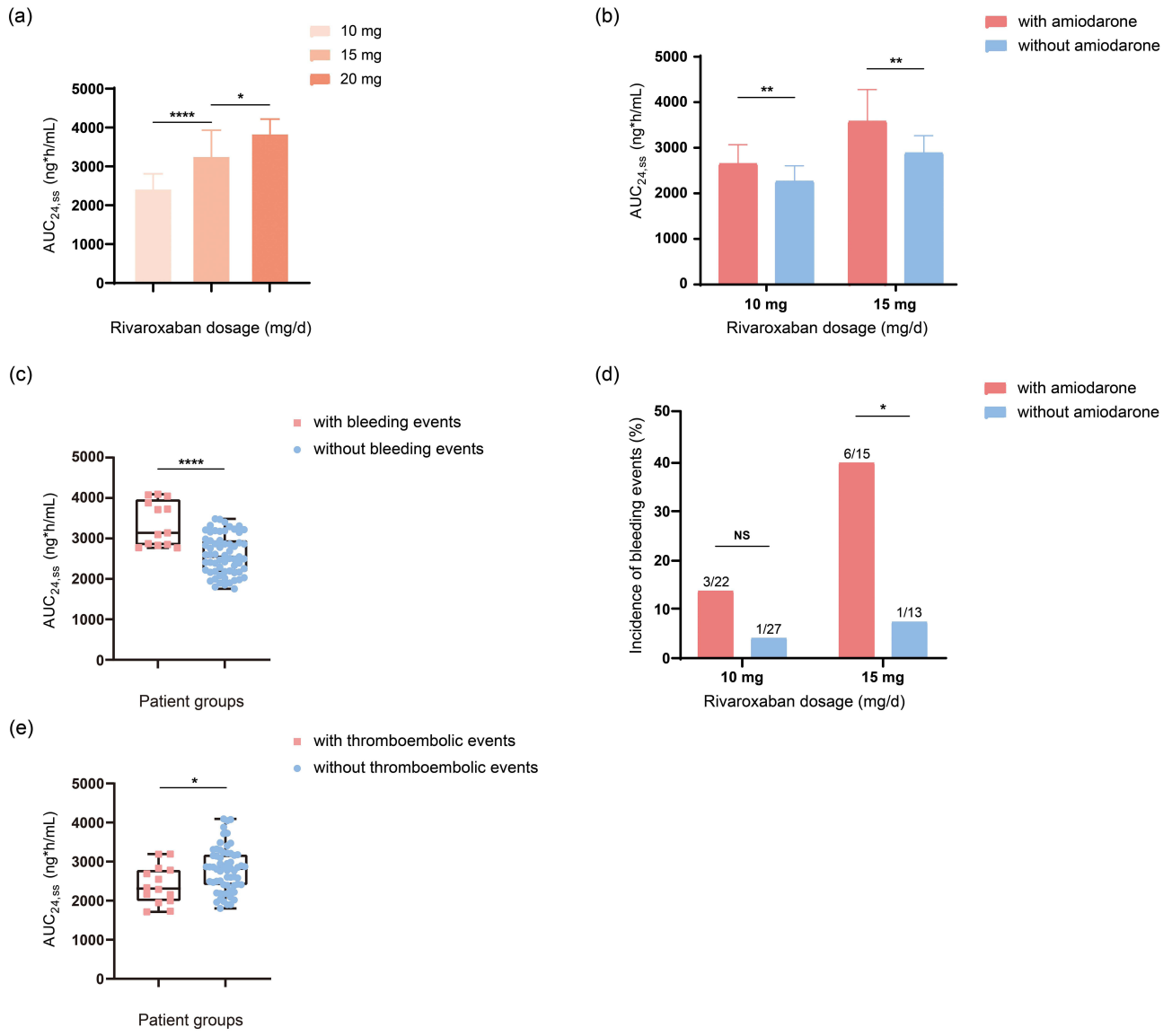

Figure 5 Model-based exposure-response analyses for efficacy and safety.
Notes: (**a**) comparison of $AUC_{24,ss}$ stratified by different daily rivaroxaban dosage; (**b**) comparison of $AUC_{24,ss}$ stratified by whether combined with amiodarone based on daily rivaroxaban dosage; (**c**) comparison of $AUC_{24,ss}$ based on occurrence of bleeding events; (**d**) comparison of hemorrhagic risk stratified by whether combined with amiodarone based on daily rivaroxaban dosage; (**e**) comparison of $AUC_{24,ss}$ based on occurrence of thromboembolic events. n = 80, NS (not significant) $p > 0.05$, *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

0.55–0.84, p = 0.023) presented in Figure 6. Of note, the median $AUC_{24,ss}$ in patients without thromboembolic events approached Youden's Index. Although limited data were available, our findings preliminarily associate $AUC_{24,ss}$ <2840 ng·h/mL with increased incidence of thromboembolic events.

Discussion

The present study has identified CrCL as the predominant determinant on CL/F of rivaroxaban, with CL increased by approximately 1.8% for every 10% elevation in CrCL. Of note, this is the first report in elderly Chinese patients with NVAF to reveal and quantitate amiodarone coadministration significantly influenced CL/F of rivaroxaban in PopPK modeling, with reduction in CL to 0.88-fold with concomitant amiodarone use. Moreover, $AUC_{24,ss}$ emerged as a robust predictor of both efficacy and safety outcomes.

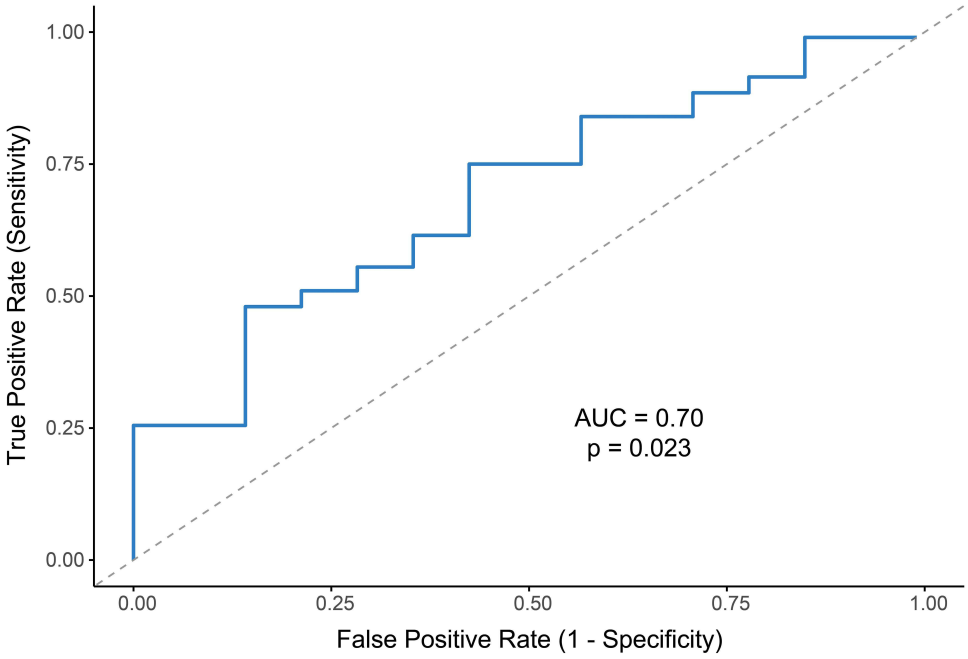

Figure 6 Model-based ROC curve for exposure-efficacy.

The apparent clearance CL/F in our elderly Chinese cohort was estimated at 4.50 L/h, representing a 19-26% reduction compared to reported values in Caucasians (5.58–6.10 L/h).[28,30] The findings aligns with observations reported in Thai (3.88–4.50 L/h)[12] and Japanese (4.72–4.73 L/h)[8,31] cohorts, but remains 11-22% lower than younger Chinese NVAF cohorts (5.03–5.79 L/h).[11,19] Notably, the estimated V/F in our study (30.7 L) was substantially reduced (24–40%) relative to literature reports (40.3–51.5 L), potentially reflecting age-related changes in body composition. The observed interethnic variability in pharmacokinetic parameters may be partially explained by genetic polymorphisms affecting rivaroxaban metabolism and transport. However, compared with other Chinese relative studies, the significantly lower CL/F in elderly Chinese patients taking the same dose of rivaroxaban, could be attributed to the higher proportion of elderly patients and reduced renal function. These age-related physiological changes, particularly diminished renal clearance and altered body composition, are well-established determinants of rivaroxaban disposition. The demographic characteristics in our elderly cohort were characterized by advanced age (mean 79 years) and reduced renal function (median CrCL 48.6 mL/min), which significantly differ from the other populations.[11,19,32] These findings suggest that conventional rivaroxaban dosing may necessitate adjustment in elderly patients with renal impairment to optimize therapeutic efficacy while minimizing the risk of adverse drug reactions.

In order to achieve a personalized-dosing regimen for rivaroxaban, it is imperative to understand the covariates that affect rivaroxaban disposition. From the available model repository, it has been shown that body weight, age, and renal function (CrCL/eGFR) are the most commonly observed influential covariates. Aligning with prior studies,[11,12,19,23,33] the present study has identified CrCL as the predominant determinant on CL/F of rivaroxaban. Of note, to the best of our knowledge, it is the first to incorporate amiodarone coadministration into influential covariates on CL/F based on PopPK modeling. However, this study did not detect any evidence of age-dependent effects on CL/F in contrast to previous findings,[23,33] potentially due to our cohort's restricted age distribution (66–94 years) and higher mean body weight (61.4 kg), which may have attenuated age-related metabolic decline. These findings provide valuable clinical insights into the factors that should be taken into account when personalizing rivaroxaban dosing, especially for the elderly population, particularly highlighting the need to consider renal function and concomitant medications. These results contribute to the growing evidence base for developing age-appropriate dosing strategies that balance therapeutic efficacy with safety in this vulnerable population.

https://doi.org/10.2147/DDDT.S563521

DDIs represent a critical consideration for the DOACs use in older adults, given the high prevalence of polypharmacy and multimorbidity in this population. Both CYP3A4 and P-gp play an important role in the PK profile of rivaroxaban by impairing their intestinal absorption or promoting elimination by the kidney.[18,34,35] Clinically relevant interactions occur with dual inhibitors of these pathways,[8,36] for instance, amiodarone coadministration elevates rivaroxaban exposure by approximately 50% (1.5-fold increase), potentially augmenting bleeding risk in vulnerable elderly patients.[37] A physiologically based PK study published in 2023[23] demonstrated that aging and DDIs increases exposure of rivaroxaban in older Chinese adults, but aging has no drastic impact on the extent of DDIs. This further supports the reliability of our results and moreover indirectly proves that amiodarone coadministration with rivaroxaban is an independent and significant covariate influencing CL/F. In the absence of complex polypharmacy, the clinical management of rivaroxaban in elderly Chinese patients can a priori align with the EHRA guidelines.[4] However, routine monitoring of bleeding risk is necessary when rivaroxaban is co-administered with amiodarone, particularly in patients with renal impairment.

Of note, the relatively high prevalence of amiodarone use in this study may reflect the specific clinical characteristics of our cohort (eg, advanced age, high heart failure burden), the substantial need for cardioversion within our patient population, and the rhythm control strategies preferred by the participating center. This selection bias, while clinically justified for patients requiring rhythm control, may limit the generalizability of our findings to AF populations where rate control with beta-blockers is the primary strategy. Consequently, the extrapolation of our results to all elderly NVAF patients should be made with caution. Furthermore, long-standing amiodarone intake usually leads to thyroid dysfunction. However, the absence of thyroid function monitoring in our study precluded an investigation of its potential role as an intermediary mechanism. This limitation should be addressed in future studies through the incorporation of specific thyroid indicators to fully delineate the integrated impact of amiodarone co-administration.

Given the limited availability of pharmacodynamic data for rivaroxaban, the evaluation of dose strategies was primarily confined to PK indices and clinical endpoints. The exposure simulation of rivaroxaban derived from the PopPK model assessed precision dosing regimens with particular consideration of renal function and amiodarone coadministration. Consistent with previous evidence, a population PK-PD analysis[11] demonstrated that 15 mg once daily in Chinese patients of rivaroxaban yielded a similar exposure to that observed in Caucasian patients taking 20 mg once daily. Additionally, a prospective multicenter study[19] based on a PopPK model indicated that 15 mg once daily may be appropriate as the principal rivaroxaban dosage for Chinese patients with NVAF. Furthermore, given that 15 mg has been approved in Japan as a standard daily dosage supported by well-established efficacy and safety profiles,[38–40] this finding reinforces the applicability of the reduced dose in ethnically similar Chinese populations. In our study, the once-daily 15 mg regimen demonstrates optimal versatility in maintaining therapeutic exposure across most clinical scenarios, except among amiodarone-treated patients with renal impairment. Taking into account the high prevalence of polypharmacy and multimorbidity in the elderly population, the once-daily 10 mg regimen emerges as a rational strategy to achieve optimal target exposure and safety, based on our findings. However, the limited number of patients receiving once-daily 20 mg rivaroxaban may constrain the robustness of Monte Carlo simulations in a relatively homogeneous elderly Chinese cohort.

This study pioneered the assessment of $AUC_{24,ss}$ relationships with efficacy and safety outcomes across amiodarone subgroups, with the incidence of thromboembolic events used as the efficacy endpoint. Rivaroxaban exposure has been linked to clinical outcomes and may help predict the benefit–risk profile.[27,41,42] In previous analyses, low-dose rivaroxaban was shown to provide a favorable benefit-risk profile, maximizing clinical activity while minimizing the risk of adverse reactions across various population-based covariates. Given the fixed-dose nature of rivaroxaban administration, a single dosage recommendation proves inadequate for heterogeneous populations, particularly elderly individuals suffering physiological decline and complex multimorbidity. Consequently, the $AUC_{24,ss}$ emerges as an essential and validated pharmacokinetic monitoring parameter for optimizing rivaroxaban therapy, yet underutilized in clinical outcomes prediction. Our ROC curve analysis showed that 2840 ng·h/mL of $AUC_{24,ss}$ might be an optimal exposure for determining the attainment of anticoagulant therapy of rivaroxaban in elderly Chinese patients with NVAF. Exposure-response analysis indicated that $AUC_{24,ss}$ exceeding 2840 ng·h/mL was not only failed to provide additional efficacy benefits, but was also likely to increase hemorrhagic risk instead. Overall, efficacy plateaued at lower

rivaroxaban exposure levels relative to the typical exposure range (1860–5434 ng·h/mL).[9] Further research employing more sophisticated statistical methods and larger sample sizes are warranted to validate this threshold and refine exposure cutoffs.

As established in prior research, a multivariate regression analysis derived from PopPK model revealed that elevated $AUC_{24,ss}$ was associated with an increased hemorrhagic risk (OR = 1.0006, $p < 0.0001$).[29] Similarly, rivaroxaban–amiodarone coadministration was associated with an increased incidence of bleeding events ($p = 0.041$; HR = 2.83, 95% CI: 1.05–7.66).[37] In our study, although differences in $AUC_{24,ss}$ across dosage regimens were statistically significant, but clinically modest, the hemorrhagic risk varied significantly between different rivaroxaban doses in subgroups with and without amiodarone. Specifically, the 15 mg dose combined with amiodarone conferred a 1.9-fold higher hemorrhagic risk compared to the 10 mg dose with amiodarone. That indicated the elevated $AUC_{24,ss}$ show a clear trend in assessing rivaroxaban-associated hemorrhagic risk, aligning with previous conclusions.[23,29] Our analysis further identified concomitant amiodarone use as an independent risk factor for bleeding. These findings underscore the necessity of incorporating hemorrhagic risk assessment into precision dosing strategies, especially for elderly patients with renal dysfunction and co-medication with amiodarone. Consequently, the 15 mg once-daily dose of rivaroxaban combined with amiodarone is clinically inappropriate for elderly Chinese patients. These findings are highly aligned with and support results of Monte Carlo simulations. This study was conducted at a single center and included few major bleeding events, which may limit the generalizability of the findings. Larger multicenter studies are needed to more accurately characterize bleeding risks and validate our observations, particularly with respect to concomitant rivaroxaban and amiodarone use.

Conclusion

In conclusion, a PopPK model of rivaroxaban was developed based on elderly Chinese patients with NVAF. Critical findings demonstrate that reduced-dose regimens optimize the efficacy–safety balance: 15 mg once daily is considered a superior option for patients not receiving amiodarone, whereas 10 mg once daily is recommended for those on amiodarone, irrespective of renal function. Concomitant amiodarone use was identified as an independent risk factor for clinically relevant non-major bleeding. From a pharmacokinetic perspective, exceeding the $AUC_{24,ss}$ threshold of 2840 ng·h/mL provided no additional anticoagulant efficacy; risk-benefit analysis confirmed that maintaining exposure above this level offers no clinical advantage. These data underscore the necessity of individualized dosing strategies based on comedication profiles rather than renal function alone in the elderly Chinese population, while validating $AUC_{24,ss}$ as a reliable exposure marker for therapeutic monitoring.

Acknowledgments

The work described in this paper has been funded by the Jiangsu Pharmaceutical Association-Ao Saikang Hospital Pharmaceutical Foundation (A202227) and Jiangsu Research Hospital Association Lean Drug Administration–Shiyao Specialized Scientific Research Foundation (JY202214).

Disclosure

The authors declare that they have no competing financial interests or personal relationships that could influence the work reported in this paper.

References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014;129(8):837–847. doi:10.1161/CIRCULATIONAHA.113.005119
2. Carnicelli AP, Hong H, Connolly SJ, et al. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation*. 2022;145(4):242–255. doi:10.1161/CIRCULATIONAHA.121.056355
3. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. 2019;140(2):e125–e151. doi:10.1161/CIR.0000000000000665

4. Steffel J, Collins R, Antz M, et al. 2021 European heart rhythm association practical guide on the use of non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation. *Europace*. 2021;23(10):1612–1676. doi:10.1093/europace/euab065
5. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128(12):1300–5.e2. doi:10.1016/j.amjmed.2015.05.044
6. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther*. 2005;78(4):412–421. doi:10.1016/j.clpt.2005.06.011
7. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366(1):9–19. doi:10.1056/NEJMoa1112277
8. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. *Br J Clin Pharmacol*. 2013;76(3):455–466. doi:10.1111/bcp.12075
9. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet*. 2014;53(1):1–16. doi:10.1007/s40262-013-0100-7
10. Weinz C, Schwarz T, Kubitza D, Mueck W, Lang D. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos*. 2009;37(5):1056–1064. doi:10.1124/dmd.108.025569
11. Liu X-Q, Zhang Y-F, Ding H-Y, et al. Population pharmacokinetic and pharmacodynamic analysis of rivaroxaban in Chinese patients with non-valvular atrial fibrillation. *Acta Pharmacol Sin*. 2022;43(10):2723–2734. doi:10.1038/s41401-022-00892-9
12. Singkham N, Phrommintikul A, Pacharasupa P, et al. Population pharmacokinetics and dose optimization based on renal function of rivaroxaban in Thai patients with non-valvular atrial fibrillation. *Pharmaceutics*. 2022;14(8):1744. doi:10.3390/pharmaceutics14081744
13. Jiang J, Hu Y, Zhang J, et al. Safety, pharmacokinetics and pharmacodynamics of single doses of rivaroxaban - an oral, direct factor Xa inhibitor - in elderly Chinese subjects. *Thromb Haemost*. 2010;103(1):234–241. doi:10.1160/TH09-03-0196
14. Edwina AE, Dia N, Dreesen E, et al. Insights into the pharmacokinetics and pharmacodynamics of direct oral anticoagulants in older adults with atrial fibrillation: a structured narrative review. *Clin Pharmacokinet*. 2023;62(3):351–373. doi:10.1007/s40262-023-01222-w
15. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation*. 2015;132(3):194–204. doi:10.1161/CIRCULATIONAHA.114.013267
16. Mitchell A, Watson MC, Welsh T, McGrogan A. Effectiveness and safety of direct oral anticoagulants versus vitamin k antagonists for people aged 75 years and over with atrial fibrillation: a systematic review and meta-analyses of observational studies. *J Clin Med*. 2019;8(4):554. doi:10.3390/jcm8040554
17. Kubitza D, Becka M, Roth A, Mueck W. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban--an oral, direct Factor Xa inhibitor. *J Clin Pharmacol*. 2013;53(3):249–255. doi:10.1002/jcph.5
18. Ajam T, Cumpian TL, Tilkens BL, et al. Non-vitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation: safety issues in the elderly. *Expert Rev Clin Pharmacol*. 2020;13(12):1309–1327. doi:10.1080/17512433.2020.1842191
19. Zhang F, Chen X, Wu T, et al. Population pharmacokinetics of rivaroxaban in chinese patients with non-valvular atrial fibrillation: a prospective multicenter study. *Clin Pharmacokinet*. 2022;61(6):881–893. doi:10.1007/s40262-022-01108-3
20. Testa S, Tripodi A, Legnani C, et al. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: results observed in four anticoagulation clinics. *Thromb Res*. 2016;137:178–183. doi:10.1016/j.thromres.2015.12.001
21. Gulilat M, Tang A, Gryn SE, et al. Interpatient variation in rivaroxaban and apixaban plasma concentrations in routine care. *Can J Cardiol*. 2017;33(8):1036–1043. doi:10.1016/j.cjca.2017.04.008
22. Wiggins BS, Dixon DL, Neyens RR, Page RL, Gluckman TJ. Select Drug-drug interactions with direct oral anticoagulants: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(11):1341–1350. doi:10.1016/j.jacc.2019.12.068
23. Sia JEV, Lai X, Wu X, et al. Physiologically-based pharmacokinetic modeling to predict drug-drug interactions of dabigatran etexilate and rivaroxaban in the Chinese older adults. *Eur J Pharm Sci*. 2023;182:106376. doi:10.1016/j.ejps.2023.106376
24. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646–649. doi:10.1002/bjs.1800600817
25. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41. doi:10.1159/000180580
26. Gosselin RC, Adcock DM, Bates SM, et al. International council for standardization in haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. *Thromb Haemost*. 2018;118(3):437–450. doi:10.1055/s-0038-1627480
27. Perreault S, Dragomir A, Côté R, et al. Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: a propensity score-matched cohort study. *Pharmacotherapy*. 2021;41(4):379–393. doi:10.1002/phar.2509
28. Willmann S, Zhang L, Frede M, et al. Integrated population pharmacokinetic analysis of rivaroxaban across multiple patient populations. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(5):309–320. doi:10.1002/psp4.12288
29. Zhang D, Chen W, Qin W, et al. Population pharmacokinetics and hemorrhagic risk analysis of rivaroxaban in elderly Chinese patients with nonvalvular atrial fibrillation. *J Clin Pharmacol*. 2023;63(1):66–76. doi:10.1002/jcph.2145
30. Girgis IG, Patel MR, Peters GR, et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with non-valvular atrial fibrillation: results from ROCKET AF. *J Clin Pharmacol*. 2014;54(8):917–927. doi:10.1002/jcph.288
31. Tanigawa T, Kaneko M, Hashizume K, et al. Model-based dose selection for Phase III rivaroxaban study in Japanese patients with non-valvular atrial fibrillation. *Drug Metab Pharmacokinet*. 2013;28(1):59–70. doi:10.2133/dmpk.DMPK-12-RG-034
32. Zhao N, Liu Z, Xie Q, et al. A combined pharmacometrics analysis of biomarker distribution under treatment with standard- or low-dose rivaroxaban in real-world chinese patients with nonvalvular atrial fibrillation. *Front Pharmacol*. 2022;13:814724. doi:10.3389/fphar.2022.814724
33. Xu R, Ge W, Jiang Q. Application of physiologically based pharmacokinetic modeling to the prediction of drug-drug and drug-disease interactions for rivaroxaban. *Eur J Clin Pharmacol*. 2018;74(6):755–765. doi:10.1007/s00228-018-2430-8
34. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. *Can J Cardiol*. 2013;29(7 Suppl):S24–S33. doi:10.1016/j.cjca.2013.04.002
35. Wolking S, Schaeffeler E, Lerche H, Schwab M, Nies AT. Impact of genetic polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on drug disposition and potential clinical implications: update of the literature. *Clin Pharmacokinet*. 2015;54(7):709–735. doi:10.1007/s40262-015-0267-1

36. Terrier J, Gaspar F, Fontana P, et al. Drug-drug interactions with direct oral anticoagulants: practical recommendations for clinicians. *Am J Med*. 2021;134(8):939–942. doi:10.1016/j.amjmed.2021.04.003
37. Ding H, Wang Z, Wang J, et al. Co-administration of amiodarone increases bleeding by affecting rivaroxaban pharmacokinetics in patients with atrial fibrillation. *Pharmaceutics*. 2024;16(8):1006. doi:10.3390/pharmaceutics16081006
38. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. *Circ J*. 2012;76(9):2104–2111. doi:10.1253/circj.CJ-12-0454
39. Lee H-F, Chan Y-H, Tu H-T, et al. The effectiveness and safety of low-dose rivaroxaban in Asians with non-valvular atrial fibrillation. *Int J Cardiol*. 2018;261:78–83. doi:10.1016/j.ijcard.2018.03.063
40. Chan Y-H, Lee H-F, Wang C-L, et al. Comparisons of rivaroxaban following different dosage criteria (ROCKET AF or J-ROCKET AF Trials) in Asian patients with atrial fibrillation. *J Am Heart Assoc*. 2019;8(21):e013053. doi:10.1161/JAHA.119.013053
41. Rahme E, Godin R, Nedjar H, Dasgupta K, Tagalakis V. Dose specific effectiveness and safety of DOACs in patients with non-valvular atrial fibrillation: a Canadian retrospective cohort study. *Thromb Res*. 2021;203:121–130. doi:10.1016/j.thromres.2021.05.005
42. Kröll D, Nett PC, Rommers N, et al. Efficacy and safety of rivaroxaban for postoperative thromboprophylaxis in patients after bariatric surgery: a randomized clinical trial. *JAMA Network Open*. 2023;6(5):e2315241. doi:10.1001/jamanetworkopen.2023.15241