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Research Article

Poor Correlation of Rivaroxaban Concentration with the Routine Coagulation Screening Test in Chinese Patients with Atrial Fibrillation

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Aims. The aim of this study is to assess the relationship between rivaroxaban plasma concentration quantified by the gold standard and anticoagulant activities measured by routine coagulation assays in Chinese atrial fibrillation (AF) patients. Whether the normal results of these tests were reliable to rule out clinically relevant rivaroxaban levels at various thresholds was also explored. The effect of clinical drug-drug interactions (DDIs) on the exposure and anticoagulant effect of rivaroxaban were further evaluated. *Methods*. 116 patients receiving rivaroxaban for the management of nonvalvular AF were recruited. Rivaroxaban concentrations and coagulation tests were measured by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and a blood coagulation analyzer, respectively. *Results*. The correlation of trough concentration (C_{trough}) and prothrombin time (PT) or international normalized ratio (INR) was moderate with Spearman's correlation coefficient of 0.495 and 0.506, respectively. A normal PT/INR was unable to rule out C_{trough} levels of >30 ng/mL and >50 ng/mL, but the negative predictive value reached 100% to exclude C_{trough} of >100 ng/mL. C_{trough} showed a small correlation with activated partial thromboplastin time (aPTT) (Spearman's correlation coefficient: 0.241) and no correlation with thrombin time (TT) (Spearman's correlation coefficient: 0.074). Neither aPTT nor TT accurately predicted C_{trough} at any concentration. Peak concentration (C_{peak}) did not correlate with any coagulation parameters. The presence of digoxin and febuxostat significantly increased rivaroxaban C_{trough} by 2.18 fold and prolonged PT and INR by 44.16% and 43.60%, respectively. *Conclusions*. Normal routine coagulation assays were insufficient to monitor therapy with rivaroxaban. Poor correlations between rivaroxaban concentration and routine coagulation assays were observed in Chinese AF patients. The use of digoxin/febuxostat alone had no effect on rivaroxaban concentrations; however, combined strong breast cancer resistance protein inhibitor (febuxostat) and P-glycoprotein probe (digoxin) in patients with renal impairment is likely to cause clinically significant DDI with rivaroxaban. More studies are needed to establish routine therapeutic drug monitoring of rivaroxaban in clinical practice.

1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, affects 1.8% of Chinese adults [1]. AF is associated with an increased risk of myocardial infarction, all-cause mortality, heart failure, and ischemic stroke [2, 3]. The initiation of direct oral anticoagulants (DOACs) such as rivaroxaban is now recommended as the first drug of choice as an alternative or in preference to vitamin K antagonists (VKAs) in the guidelines for AF management [4, 5].

Rivaroxaban (Xarelto), a direct factor Xa inhibitor, has been approved by the China Food and Drug Administration

for the prevention of stroke and systemic embolism in patients with nonvalvular AF in 2015. It potently inhibits prothrombinase activity and endogenous factor Xa activity with IC_{50s} of 2.1 ± 0.4 nM and 21 ± 1 nM, respectively [6, 7]. Rivaroxaban is rapidly absorbed with an absolute bioavailability of about 80–100% for the 10 mg dosage. The maximal plasma concentration (C_{max}) is achieved at 2–4 h post-dose. Approximately, two-thirds of rivaroxaban is metabolized and one-third of the dose is excreted as an unchanged drug in the urine [8]. Cytochrome P450 (CYP) 3A4/5, CYP2J2, and non-CYP-associated hydrolysis are responsible for 18%, 14%, and 14% of total rivaroxaban elimination, respectively. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are also involved in the disposition of rivaroxaban [9].

The clinical use of rivaroxaban is generally safe and effective despite the risk of bleeding. Routine monitoring of coagulation or frequent dose adjustment is not required. However, the evaluation of rivaroxaban exposure and anticoagulant effect may help clinicians in ensuring adherence, switching between different anticoagulant therapies, in patients with compromised renal or hepatic function, in the presence of drug-drug interaction (DDI), as well as in emergencies such as bleeding, urgent procedures, antidote requirement, or an acute stroke [5, 10].

A surgically relevant rivaroxaban plasma concentration was less than 50 ng/mL [11]. Anti-Xa activity correlated well with rivaroxaban plasma concentrations in a range between 50 and 200 ng/mL [12]. However, these assays systematically overestimated rivaroxaban concentration. Ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) has been considered as the gold standard to quantitatively assess the concentration of rivaroxaban. However, it usually requires highly skilled personnel and has a long turnaround time and is not readily available to smaller medical institutions. Point-of-care tests are not yet available for Chinese patients receiving DOACs. Therefore, routine coagulation screening tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and thrombin time (TT) remain widely used in emergencies or urgent clinical scenarios to determine the presence, absence, supratherapeutic, or subtherapeutic of the anticoagulation effect.

However, there is an ongoing debate on the usefulness of routine coagulation assay to evaluate DOACs. Although studies have reported that rivaroxaban prolonged PT and aPTT and elevated INR in patients, routine test itself suffers from large variability, considerably due to different responsiveness to increasing concentrations, limited specificity, as well as sensitivity [13–16]. The Chinese were found to have less prothrombotic calibrated automated thrombogram parameters, longer aPTT, as well as lower protein C and S levels than Caucasians [17]. Furthermore, real-life data on rivaroxaban's effect on routine coagulation parameters in Chinese patients is scarce. The aim of our study was to assess the relationship between rivaroxaban plasma concentration quantified by UPLC-MS/MS and anticoagulant activity measured by routine coagulation screening tests in a real clinical setting. Whether the normal results of these tests were reliable to rule out clinically relevant rivaroxaban levels at various thresholds were also explored. Then, the study determined whether concomitant medication or the presence of transporter/metabolism-related DDI had a clinically significant impact on the exposure and anticoagulant effect of rivaroxaban in Chinese AF patients.

2. Materials and Methods

2.1. Design. This was a single-center, prospective, observational study.

2.2. Ethical Statement. The study protocol was reviewed and approved by the medical ethics committee of the second affiliated hospital of Nanchang University ((2017) no. 099). This study was in accordance with the requirements of the Declaration of Helsinki of the World Medical Association. Written and informed consent was obtained from each patient or the family.

2.3. Patients and Treatment. The inclusion criteria were patients over 18 years of age receiving rivaroxaban for the management of nonvalvular AF, as well as collection of blood samples at trough and peak concentrations. In this case, the included patients were inpatients. The dosages of rivaroxaban (10–20 mg/day) and concomitant drugs were prescribed at the discretion of the attending physician based on both clinical characteristics and renal function.

At baseline, patient's demographic data (age, sex, and body weight (bw)); hematologic tests, including hemoglobin (HGB), platelets (PLT), hematocrit (HCT), renal function tests, including serum creatine (Cre) and glomerular filtration rate (eGFR) using a simplified modification of diet in renal disease (MDRD) formula, and liver function tests, including liver enzymes, bilirubin (BIL), total protein (TP), and albumin (ALB); comorbidities, and concomitant medications were obtained (Supplemental Table 1).

2.4. Blood Sampling and Processing. Blood sampling was performed at least 3 days after initiating rivaroxaban for AF. A venous blood sample was collected in blood collection tubes with sodium citrate just before (trough, 24 ± 2 h after last pill intake) and 2 h (peak, 2–2.5 h after last pill intake) after rivaroxaban administration. Plasma samples were obtained by centrifugation and all samples were stored at −80°C until analysis by UPLC-MS/MS.

2.5. Quantification of Rivaroxaban Plasma Concentrations in Patients. Biological sample preparation and analysis were performed according to our previously established method with minor modifications [18]. A Shimadzu LC-30AD liquid chromatography system (Shimadzu, Kyoto, Japan) coupled with API 4000 triple quadruple tandem mass spectrometer (Applied Biosystems/Sciex, Framingham, MA, USA) was used. In brief, multiple reaction monitoring in positive mode was applied. Ion transitions at m/z 436.1⟶m/z 145.1 for

rivaroxaban and m/z 440.2⟶m/z 145.0 for d4-rivaroxaban (internal standard) were used for the UPLC-MS/MS analysis, respectively. The optimized MS/MS parameters were as follows: dwell time, 100 ms; ion spray voltage, 5.5 kV; curtain gas, gas 1 and gas 2 (all nitrogen): 172.4 kPa, 448.2 kPa, and 379.2 kPa, respectively; source temperature, 450°C; declustering potential, 95 V for rivaroxaban and 120 V for d4-rivaroxaban; and collision energy, 40 eV for rivaroxaban and 43 eV for d4-rivaroxaban. The chromatographic separation was performed with a Thermo Hypersil Gold C18 analytical column (column size: 2.1 × 100 mm, 1.9 μm, and no. 25002-102130) at 40°C. The mobile phase consisted of water (A) and acetonitrile (B) containing 0.1% (v/v) of formic acid and 5 mmol/L of ammonium acetate. The flow rate was 0.4 mL/min and the mobile phase was programmed to linearity change as follows: 10% (B) at 0–0.4 min, 10%–80% (B) at 0.4–0.8 min, 80% (B) at 0.8–2.0 min, 80%–10% (B) at 2.0-2.1 min, and 10% (B) at 2.1–3 min. The injection volume was 5 μL.

2.6. Coagulation Screening Test. Thromborel S, Dade Actin FSL Activated PTT reagent, and Test Thrombin reagent (Siemens Healthcare Diagnostics, Marburg, Germany) were used in the measurement of PT, aPTT, and TT by Sysmex CS-5100 Automated Blood Coagulation Analyzer, respectively. The INR was calculated through the manufacturer's international sensitivity index.

2.7. Sample Size. The sample size calculation was 116 patients, which was based upon the need to recruit in a timely fashion and the expectation that this sample size would provide reasonable estimates of the correlation between the rivaroxaban level and the coagulation screening test (assuming correlation coefficient = 0.24, significance level = 0.95, power = 0.80, and 10% loss during the study) (R, ver. 4.1.0, R Foundation for Statistical Computing).

2.8. Statistical Analysis. Categorical data were reported as frequency (n) and percent (%) and numerical data as mean and standard deviation (SD). Plasma concentration of rivaroxaban (C_{trough} and C_{peak}) and aPTT were logarithmically transformed and PT and INR were reciprocally transformed to fit a normal distribution.

Normalized concentrations were used for dose correction, thus reducing variation. The correlation between rivaroxaban concentration and coagulation parameters was evaluated using Spearman's rank correlation coefficient. Spearman's coefficient absolute values were interpreted as follows: between 0.1 and 0.3 as a small correlation, greater than or equal to 0.3 and less than 0.6 as a moderate correlation, and greater than or equal to 0.6 as a strong correlation. The entire range of C_{trough} in patients was subdivided into 5 groups according to the cutoff values for surgical procedures [11, 19–22]: ≤5 ng/mL (low concentration without a potent systemic anticoagulation effect), 5–30 ng/mL (clinically relevant concentration for surgery with a high bleeding risk), 30–50 ng/mL (clinically relevant concentration without increasing bleeding risk in general patients), 50–100 ng/mL (clinically relevant concentration warranting antidote administration in patients with serious bleeding or requiring an urgent intervention associated with a high risk of bleeding), and >100 ng/mL (extremely high concentration with a potent systemic anticoagulation effect and preclusion of intravenous thrombolysis). These concentrations were then plotted (y-axis) against the corresponding coagulation parameters (x-axis), and the results were compared with the upper limit of the reference interval. Statistical analysis was performed using SPSS ver. 22.0 (IBM, Chicago, IL, USA). Nonparametric Kruskal–Wallis one-way analysis was used in those data that were not normally distributed. After testing for homogeneity of variance, statistical analysis was performed with one-way ANOVA followed by LSD or Dunnett's T3 post hoc test, which was used to compare rivaroxaban concentrations and coagulation parameters between patient groups receiving rivaroxaban and co-medications. Chi-square statistics were used to compare categorical data. A two-tailed probability (p) of less than 0.05 was statistically significant. Figures were designed using software (R, ver. 4.1.0, R Foundation for Statistical Computing, and SPSS ver. 22.0, IBM).

3. Results

3.1. Patient Characteristics. A total of 116 patients were enrolled and 232 blood samples were tested. Baseline patient characteristics are shown in Supplemental Table 1. 48.3% of the patients were male and 51.7% were female, with an average age of 68.0 ± 12.5 years. Renal function was mildly impaired with a mean eGFR of 77.9 ± 23.1 mL/min and a mean Cre level of 86.5 ± 32.2 μM. Of the 116 patients in this study, 7 (6.0%) received the rivaroxaban dose of 10 mg qd, 17 (14.7%) received the rivaroxaban dose of 15 mg qd, and 92 (79.3%) received the standard dose of rivaroxaban (20 mg qd).

On comparison of patient characteristics on admission, four factors indicated substantial differences (Supplemental Table 1). Dose and eGFR in the febuxostat group were lower than those of the rivaroxaban alone group ($p = 0.005$ and $p = 0.048$, respectively). Body weight (bw) in the digoxin group was higher than that of the rivaroxaban alone group ($p = 0.005$). HCT in the digoxin plus febuxostat group and statin group was lower than that of the rivaroxaban alone group ($p = 0.001$ and $p = 0.012$, respectively). Subgroup analysis of concomitant medication was performed according to the influence of drug metabolism enzymes and transporters on the pharmacokinetics of rivaroxaban (Supplemental Table 1).

3.2. Relationship of Rivaroxaban Plasma Concentration vs. Routine Coagulation Parameters. The correlation of rivaroxaban C_{trough} and PT was moderate (spearman's correlation coefficient 0.495, $p < 0.001$, Table 1, and Supplemental Figure 1A). A normal PT was unable to rule out rivaroxaban C_{trough} levels of >30 and >50 ng/mL (negative predictive value (NPV): 79.5% and 95% confidence intervals (CI):

68.1–87.7%; NPV: 97.3% and 95% CI: 89.6–99.5%, respectively). NPV reached 100% (95% CI: 93.8–100%) for C_{trough} of > 100 ng/mL (Table 2, Figure 1). Similarly, the correlation of rivaroxaban C_{trough} with INR was moderate (Spearman's correlation coefficient: 0.506, $p < 0.001$, Table 1, and Supplemental Figure 1B). A normal INR was unable to rule out rivaroxaban C_{trough} levels of >30 and >50 ng/mL (NPV: 76.7% and 95% CI: 66.2–84.9%; NPV: 97.7% and 95% CI: 91.1–99.6%, respectively). NPV reached 100% (95% CI: 94.7–100%) for C_{trough} of > 100 ng/mL (Table 2, Figure 1). The aPTT showed a small correlation with C_{trough} (Spearman's correlation coefficient: 0.241, $p = 0.009$, Table 1, and Supplemental Figure 1C). However, there was no correlation between C_{trough} and TT (Spearman's correlation coefficient: 0.074, $p = 0.431$, Table 1, and Supplemental Figure 1D). The aPTT and TT were unable to accurately predict rivaroxaban C_{trough} at any concentration (Table 2 and Figure 1). C_{peak} did not correlate with any routine coagulation parameters (Table 1).

3.3. Rivaroxaban Plasma Concentration in the Presence of Drug Interactions. The accuracy (bias, %) or precision (CV, %) in the assay of rivaroxaban, based on quality control (QC) samples that spanned the calibration range, was <15% (Table 2).

The presence of digoxin and febuxostat significantly increased rivaroxaban C_{trough} by 2.18 fold ($p = 0.037$) (Table 3). Although concomitant use of statin, amiodarone, and febuxostat increased rivaroxaban C_{trough} by 7.3%, 79.9%, and 22.2%, respectively, and increased normalized C_{trough} (defined as C_{trough}/daily dose) by 11.3%, 79.8%, and 66.9%, respectively, they failed to elicit significant changes (Table 3).

Rivaroxaban C_{peak} was significantly higher than C_{trough} ($p < 0.001$). There were no significant differences in rivaroxaban C_{peak} (Table 3) among various groups.

3.4. Coagulation Parameters in Patients in the Presence of Drug Interactions. The presence of digoxin and febuxostat significantly prolonged PT by 44.16% ($p = 0.001$) and INR by 43.60%, respectively ($p = 0.001$ and Table 3). Concomitant use of digoxin or febuxostat increased PT and INR by 7.21% and 6.17% and 7.34% and 6.32% respectively, while they missed statistical significance (Table 3). There were no significant differences in aPTT and TT among these groups. The quality controls of coagulation screening tests are shown in Supplemental Table 3.

4. Discussion

As a potent DOAC with predictable pharmacokinetic and pharmacodynamic profiles, rivaroxaban is widely indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF [8, 9]. There is an ongoing debate regarding the quantitative laboratory monitoring of DOACs [13, 15, 16, 23]. However, given the complexities in real-life clinical practice, assessment of DOACs' anticoagulant activity by a fast and reliable assay could be helpful in decision-making, especially under urgent clinical situations. Despite the development of specific anti-Xa, anti-IIa, and LC-MS/MS assays for DOACs, [16, 24] routine coagulation screening test (PT, INR, aPTT, and TT) remains the most readily available method.

The PT test measures the activity of clotting factors I, II, V, VII, and X and the INR is a mathematical standardization of the PT. The aPTT is a measure of the activity and presence of factors II, V, and VIII-XII. Dose-dependent effects on PT and aPTT have been observed for rivaroxaban [25, 26]. In healthy Chinese volunteers, there was a strong correlation between rivaroxaban plasma concentrations and prolongation of PT ($r = 0.931$, a median prolongation of 1.51 times baseline) [27]. In this study, we noticed a maximum of 1.43–1.47 folds increase in PT. Li et al. found PT and aPTT correlated with the plasma concentration of rivaroxaban in Chinese patients with deep venous thrombosis ($r = 0.827$ and $r = 0.807$, respectively) [28]. However, we observed a statistically significant (but moderate) correlation of PT and INR with rivaroxaban C_{trough}. The difference between recruited study population (deep venous thrombosis vs. AF), sample size (39 vs. 116), concomitant medication (unknown vs. Supplemental Table 1), and used PT reagents (unknown vs. Thromborel S) could be the complicating factors. Normal PT was unreliable to exclude rivaroxaban plasma levels of >30 ng/mL and >50 ng/mL, but the NPV reached 100% to rule out C_{trough} of > 100 ng/mL. Thus, the PT provided some quantitative information on rivaroxaban exposure and anticoagulant effects, which was in accordance with the findings of Jabet et al. [29]. It is suggested each clinical center establishes its own institutional interdisciplinary standard operating procedure or performs a dose-response study for better data interpretation. Generally, the INR is used for VKA assessment and is not a viable option for the evaluation of factor Xa inhibitory activity. However, we found the NPV of a normal INR was 100% (46.3%–100%) to exclude rivaroxaban of >100 ng/mL, suggesting that INR must be applied with caution in the clinic. Similarly, Ofek et al. reported that INR was significantly elevated in patients receiving rivaroxaban and apixaban therapies [14]. Normal aPTT was not able to rule out rivaroxaban level at any thresholds. In addition, limited sensitivity, variability in reagents, and paradoxical response at low concentrations make aPTT not suitable for measuring rivaroxaban blood concentrations. Clinicians should be aware that the prolongation of PT/INR or aPTT may be due to other factors other than the presence of rivaroxaban, such as compromised liver function, antibiotic use, vitamin K deficiency, and lupus anticoagulant. The TT measured thrombin activity in plasma. It showed no correlation with rivaroxaban C_{trough} and cannot be used for any meaningful evaluation of rivaroxaban. Moreover, the mechanism of factor Xa inhibition with rivaroxaban also makes the TT an undesirable assay. Overall, we confirmed that routine coagulation assays were not sufficient to exclude a clinically relevant rivaroxaban plasma concentration [29–31].

For patients taking DOACs, surgical procedures were sometimes unavoidable, especially in the presence of ischemic or hemorrhagic strokes. The lower limit of

Table 1: The correlation of rivaroxaban plasma concentration and routine coagulation parameters.

Parameters	Correlation	PT	INR	aPTT	TT
C_{trough}	Spearman's correlation coefficient	0.495	0.506	0.241	0.074
	Significance (p value)	<0.001	<0.001	0.009	0.431
C_{peak}	Spearman's correlation coefficient	0.023	0.027	−0.073	−0.075
	Significance (p value)	0.807	0.773	0.436	0.425
Normalized C_{trough}	Spearman's correlation coefficient	0.454	0.465	0.212	0.115
	Significance (p value)	<0.001	<0.001	0.026	0.229
Normalized C_{peak}	Spearman's correlation coefficient	0.011	0.015	−0.068	−0.075
	Significance (p value)	0.912	0.878	0.476	0.430

PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time; C_{trough}, trough concentration; C_{peak}, peak concentration. Normalized concentrations were used for dose correction, thus reducing variation.

quantification for most anti-Xa assays was set at 20 ng/mL–30 ng/mL, therefore this concentration was considered to be clinically safe and was accepted as C_{trough} cutoff values in many clinical centers. A preoperative rivaroxaban concentration of less than 30 ng/mL was recommended for surgery with high bleeding risk, while an empirical cutoff value of 50 ng/mL has been adopted by the University Hospital of Zurich [11, 19, 20]. However, definite clinical thresholds for DOACs in Chinese AF patients have not been established yet. In this study, most of the patients (89.5%) were found to have rivaroxaban C_{trough} of < 50 ng/mL, suggesting a remote likelihood of antidote requirement. In case of surgery such as AF ablation, additional intervention is likely to be unnecessary in patients (64.7%) with a C_{trough} of < 30 ng/mL. However, we should keep in mind that plasma concentration alone may not provide clinicians with sufficient information for decision-making. When interpreting drug concentrations, it is important to consider the timing of the last dose relative to blood sampling and other factors.

Large interindividual variability exists in rivaroxaban exposure in real-life patients, causing broad ranges of C_{trough} and C_{peak} [15, 32]. A higher-than-expected interindividual variabilities were observed (Supplemental Table 4). This large variation could result in less predictable pharmacokinetics and pharmacodynamics of rivaroxaban in a real-world clinical setting. In another aspect, it may diminish the effect of comedications on the disposition of rivaroxaban. Both intrinsic (i.e., age, renal impairment, body weight, or genetics) and extrinsic (i.e., comorbidity or comedications and environment) factors may also have an impact on the pharmacokinetics of rivaroxaban [33]. Rivaroxaban absorption was dependent on the site of drug release in the gastrointestinal tract [34]. Delay in rivaroxaban absorption is likely to result in interpatient variability as seen in this study. In addition, rivaroxaban is a substrate of ATP-binding cassette transporter of subfamily B, members 1 (ABCB1 and P-gp) and ATP-binding cassette transporter of subfamily G, members 2 (ABCG2 and BCRP), [32] which might play a role on rivaroxaban's disposition. No clinically relevant effect of age on rivaroxaban pharmacokinetics and pharmacodynamics was observed in healthy, older adults [35]. It is well established that systemic rivaroxaban concentrations or exposures increased as the renal function declined [36]. Rivaroxaban labeling also recommended dose adjustment for renally impaired patients according to the degree of impairment. Body weight has little influence on the pharmacokinetics or pharmacodynamics of rivaroxaban in healthy subjects, in patients for prevention or treatment of venous thromboembolism, and in Thai patients with nonvalvular AF [33, 37, 38]. A previous study reported that the risk of major bleeding for patients receiving 20 mg qd rivaroxaban was 5.3% and increased with increasing exposure (AUC_{ss} or $C_{max,ss}$) [39, 40]. In the current study, the maximum C_{peak} was 708 ng/mL which is significantly high and could lead to potential bleeding risk. The C_{trough} for the same patient was as high as 94.9 ng/mL (Supplemental Table 4). However, we did not observe any bleeding events. An increased risk does not mean a bleeding event. Zhang et al. failed to identify a statistically significant association between exposure and the risk of major bleeding [40]. A shallow exposure-response relationship with no clear threshold for acceleration of bleeding risk has been found in patients receiving rivaroxaban for nonvalvular AF, for venous thromboembolism prophylaxis after hip/knee replacement surgery, and for acute coronary syndrome [40–42]. However, carefully examining the signs or symptoms of blood loss and promptly evaluating the risk of bleeding in patients with clinically relevant increases in exposure due to intrinsic and extrinsic factors would potentially bring clinical benefits.

The presence of polypharmacy has increased the risk of DDIs and associated adverse effects. In this study, 91.4% of AF patients received polypharmacotherapy. It is important that clinicians must be aware of the potential for DDI between rivaroxaban and specific drugs and must take measures to prevent it. As a substrate of CYP3A4/5, CYP2J2, P-gp, and BCRP, rivaroxaban is likely to act as a victim of metabolism and transporter-related DDI. Digoxin is a known P-gp probe and amiodarone is a moderate P-gp inhibitor. Both drugs were commonly prescribed in AF patients for cardiac rhythm control [43]. Consistent with previous reports, 0.125 mg of digoxin once daily has no effect on rivaroxaban concentrations. Steffel et al. reported a minor effect of amiodarone on rivaroxaban plasma concentration [5]. We observed a statistically insignificant increase in rivaroxaban C_{trough} (79.9%) and normalized C_{trough} (79.8%), respectively. In patients without any renal impairment, it seems no precautions are necessary when on concomitant use of amiodarone, as the change in exposure is unlikely to affect the bleeding risk. In

Table 2: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of routine coagulation parameters for the detection of rivaroxaban lever greater than 4 different concentrations (5, 30, 50, or 100 ng/mL).

Coagulation parameters	Performance	>5 ng/mL	>30 ng/mL	>50 ng/mL	>100 ng/mL
PT	Sensitivity	39.8 (30.4–49.9)	63.4 (46.9–77.4)	83.3 (50.9–97.1)	100.0 (46.3–100)
	Specificity	84.6 (53.7–97.3)	77.3 (65.9–85.9)	68.3 (58.3–76.9)	65.8 (56.1–74.3)
	PPV	95.3 (82.9–99.2)	60.5 (44.5–74.6)	23.3 (12.3–39.0)	11.6 (4.36–25.9)
	NPV	15.1 (8.12–25.8)	79.5 (68.1–87.7)	97.3 (89.6–99.5)	100.0 (93.8–100)
INR	Sensitivity	28.2 (20.0–38.0)	51.2 (35.4–66.8)	83.3 (50.9–97.1)	100.0 (46.3–100)
	Specificity	92.3 (62.1–99.6)	88.0 (78.0–94.0)	80.8 (71.6–87.6)	77.5 (68.4–84.6)
	PPV	96.7 (80.9–99.8)	70.0 (50.4–84.6)	33.3 (17.9–52.9)	16.7 (6.30–35.5)
	NPV	14.0 (7.72–23.5)	76.7 (66.2–84.9)	97.7 (91.1–99.6)	100.0 (94.7–100)
aPTT	Sensitivity	3.9 (1.25–10.2)	9.8 (3.17–24.1)	25.0 (6.69–57.2)	60.0 (17.0–92.7)
	Specificity	92.3 (62.1–99.6)	98.7 (91.8–99.9)	98.1 (92.5–99.7)	98.2 (93.0–99.7)
	PPV	80.0 (29.9–98.9)	80.0 (29.9–98.9)	60.0 (17.0–92.7)	60.0 (17.0–92.7)
	NPV	10.8 (5.96–18.5)	66.7 (57.0–75.2)	91.9 (84.8–96.0)	98.2 (93.0–99.7)
TT	Sensitivity	4.9 (1.80–11.5)	4.9 (0.849–17.8)	0.0 (0–30.1)	0.0 (0–53.7)
	Specificity	100.0 (71.7–100)	96.0 (88.0–99.0)	95.2 (88.6–98.2)	95.5 (89.3–98.3)
	PPV	100.0 (46.3–100)	40.0 (7.26–83.0)	0.0 (0–53.7)	0.0 (0–53.7)
	NPV	11.7 (6.63–19.5)	64.9 (55.2–73.5)	89.2 (81.5–94.0)	95.5 (89.3–98.3)

Data in parenthesis (brackets) means 95% confidence intervals (CI). The normal range of PT, INR, aPTT, and TT were 9–13 s, 0.8–1.2, 20–40 s, and 14–24 s, respectively. PPV, positive predictive value; NPV, negative predictive value; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time.

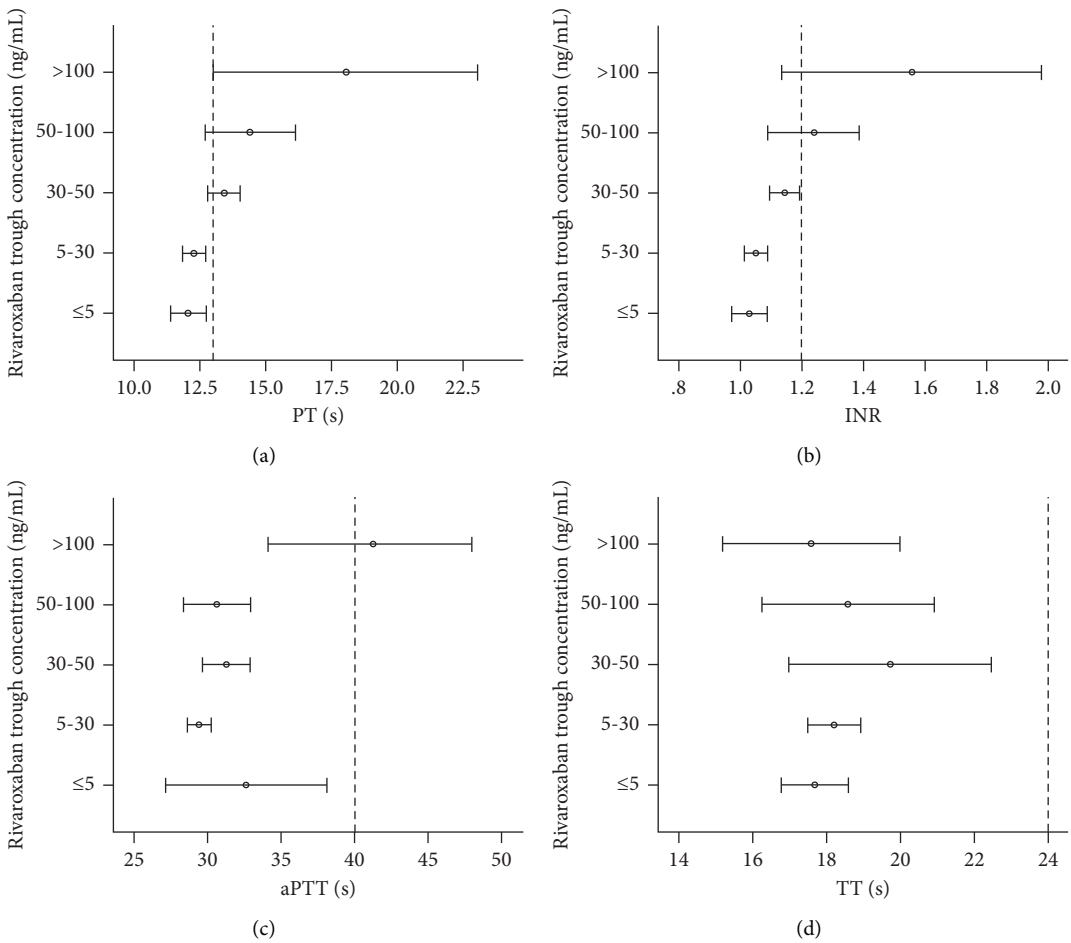

Figure 1: Mean and 95% confidence intervals (CI) of routine coagulation tests obtained for different arbitrary classes of rivaroxaban trough concentrations (C_{trough}). The normal range of prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and thrombin time (TT) were 9–13 s, 0.8–1.2, 20–40 s, and 14–24 s, respectively. The dotted lines represent the upper limit of the normal range: (a) PT, (b) INR, (c) aPTT, and (d) TT.

Table 3: Plasma concentration and coagulation parameters in patients after initiating rivaroxaban therapy.

Characteristic	Study population ($n = 116$)	Rivaroxaban alone ($n = 10$)	Amiodarone ($n = 11$)	Digoxin ($n = 9$)	Digoxin plus febuxostat ($n = 3$)	Febuxostat ($n = 6$)	Statin ($n = 19$)	Other medication with no major effect ($n = 50$)	Other medication with mixed effects ($n = 4$)	Benzbromarone	Glimepiride
C_{trough} (ng/mL)	31.3 ± 45.4	24.8 ± 14.6	44.6 ± 69.9	24.5 ± 21.4	78.8 ± 50.4*	30.3 ± 26.9	26.6 ± 34.7	21.2 ± 17.0	47.48 ± 48.12	40.3	204.6
C_{peak} (ng/mL)	189.0 ± 133.2###	186.6 ± 151.8	204.5 ± 89.8	170.6 ± 90.0	320.4 ± 235.1	195.1 ± 109.4	148.7 ± 156.9	170.2 ± 101.6	270.25 ± 157.89	327.5	533.5
Normalized C_{trough} (ng/mL/mg)	1.68 ± 2.29	1.24 ± 0.73	2.23 ± 3.49	1.48 ± 1.32	4.56 ± 1.91	2.07 ± 1.81	1.38 ± 1.72	1.12 ± 0.87	2.37 ± 2.41	2.34	10.23
Normalized C_{peak} (ng/mL/mg)	10.31 ± 7.31	9.33 ± 7.59	10.23 ± 4.49	9.57 ± 4.70	21.14 ± 14.37	13.92 ± 9.71	8.19 ± 8.41	9.17 ± 5.43	13.51 ± 7.89	17.91	26.68
PT (s)	12.93 ± 2.16	12.81 ± 1.44	12.89 ± 1.98	13.73 ± 1.89	18.47 ± 4.97**	13.60 ± 2.06	12.87 ± 2.14	12.22 ± 1.38	14.85 ± 3.32	11.95	14.9
INR	1.11 ± 0.18	1.09 ± 0.12	1.11 ± 0.17	1.17 ± 0.15	1.57 ± 0.43**	1.16 ± 0.17	1.11 ± 0.18	1.05 ± 0.12	1.27 ± 0.28	1.04	1.31
aPTT (s)	30.9 ± 5.1	31.9 ± 4.7	30.3 ± 4.5	30.6 ± 3.8	32.9 ± 4.1	31.0 ± 3.7	31.0 ± 4.2	30.1 ± 5.1	36.80 ± 9.63	26	36.6
TT (s)	18.52 ± 4.26	18.26 ± 1.89	17.79 ± 1.38	17.21 ± 1.79	18.40 ± 0.36	23.58 ± 15.72	18.15 ± 1.44	18.62 ± 3.33	17.43 ± 1.28	18.05	18.25

In this study, 1 received rivaroxaban and cimetidine (0.9%, dosage 20 mg, and CYP3A4 inhibition); 1 received rivaroxaban, celecoxib, and statin (0.9%, dosage 20 mg, CYP3A4, CYP2C9, P-gp, and BCRP competition); 1 received rivaroxaban, digoxin, and cimetidine (0.9%, dosage 20 mg, P-gp competition, and CYP3A4 inhibition); 1 received rivaroxaban and clarithromycin (0.9%, dosage 20 mg, and combined P-gp and CYP3A4 inhibition). Due to the mixed effect on drug metabolism enzyme and transporter, the plasma concentrations and coagulation parameters obtained from aforementioned patients were combined into one group (other medication with mixed effects). The details were summarized in Supplemental Table 6. PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time; C_{trough}, trough concentration; C_{peak}, peak concentration. Normalized concentrations were used for dose and body weight correction, thus reducing variation. *, $p < 0.05$ when compared with the rivaroxaban alone group. **, $p < 0.01$ when compared with the rivaroxaban alone group. ###, $p < 0.001$ when compared with C_{trough}. When patients were less than 3, statistic comparisons were not performed.

line with a previous study, coadministration of rivaroxaban with other substrates of CYP3A4, CYP2C9, P-gp, BCRP, or all (e.g., atorvastatin, simvastatin, rosuvastatin, and fluvastatin) does not significantly alter the plasma levels and routine coagulation test of rivaroxaban. Potent uricosuric agents, such as febuxostat and benzbromarone, were also identified as comedications with the frequency of 14.7% in AF patients receiving rivaroxaban. Febuxostat and benzbromarone were inhibitors of BCRP with IC_{50} values of 0.35 μM and 0.238 μM, respectively [44, 45]. At the dose of 40 mg febuxostat, the mechanistic static model predicted that the $(I_2)/IC_{50\,BCRP}$ and $(I_{max,u})/IC_{50\,BCRP}$ for febuxostat were approximately 1145.7 and 0.243 (>cutoff value 10 and 0.1), indicating a high likelihood of a potential DDI through BCRP inhibition (Supplemental Table 5). 50 mg of benzbromarone was also predicted to cause a potential DDI through BCRP inhibition ($(I_2)/IC_{50\,BCRP}$ ratios >10 and $(I_{max,u})/IC_{50\,BCRP}$ >0.1; Supplemental Table 5). Despite compromised renal function, the significant increase in rivaroxaban C_{trough}, prolonged PT, and INR after concomitant use of digoxin and febuxostat was a surprise (Table 3). The mechanism implicated is inhibition of BCRP in the gut, liver, and/or kidney, as well as in P-gp competition. It also suggests that patients taking concomitant BCRP inhibitors (such as febuxostat) and P-gp probes (such as digoxin) may be at high risk for super-therapeutic concentrations and subsequently, bleeding risk and thus can benefit from rivaroxaban concentration monitoring to prophylactically identify this risk. Dosage adjustment in certain patients could be a possible strategy.

This study has limitations. First, statistical analysis was limited by the small sample size and large variability. However, this allows us to perform an in-depth analysis of rivaroxaban at the individual level. Second, possible genetic polymorphisms, such as *ABCB1* and *ABCG2*, and their impacts on rivaroxaban exposures and coagulation parameters in each patient were not assessed. However, implementation of this evaluation should be better performed by a new study.

5. Conclusion

Normal routine coagulation assays were insufficient to monitor therapy with rivaroxaban. Poor correlations between rivaroxaban concentration and routine coagulation screening tests were observed in Chinese AF patients. The use of digoxin/febuxostat alone had no effect on rivaroxaban concentrations; however, combined strong BCRP inhibitor (febuxostat) and P-gp probe (digoxin) in patients with renal impairment is likely to cause clinically significant pharmacokinetic and pharmacodynamic DDI with rivaroxaban. More studies are needed to establish routine therapeutic drug monitoring of rivaroxaban in clinical practice.

Abbreviations

AF: Atrial fibrillation
DOACs: Direct oral anticoagulants
VKAs: Vitamin K antagonists
C_{max}: Maximal plasma concentration
CYP: Cytochrome P450
P-gp: P-glycoprotein
BCRP: Breast cancer resistance protein
DDI: Drug-drug interaction
UPLC-MS/MS: Ultra-performance liquid chromatography-tandem mass spectrometry
PT: Prothrombin time
aPTT: Activated partial thromboplastin time
INR: International normalized ratio
TT: Thrombin time
BW: Body weight
HGB: Hemoglobin
PLT: Platelets
HCT: Hematocrit
Cre: Serum creatine
eGFR: Glomerular filtration rate
MDRD: Modification of diet in renal disease
TBIL: Total bilirubin
DBIL: Direct bilirubin
TP: Total protein
ALB: Albumin
C_{trough}: Trough concentration
C_{peak}: Peak concentration
NPV: Negative predictive value
PPV: Positive predictive value
QC: Quality control
T_{max}: Time to reach maximal plasma concentration
ABCB1: ATP-binding cassette transporter of subfamily B, members 1
ABCG2: ATP-binding cassette transporter of subfamily G, members 2
AUC_{ss}: Area under the curve at steady-state
CI: Confidence intervals
SD: Standard deviation
CV: Coefficient of variation
I_2: Maximal theoretical gastrointestinal concentration
$I_{max,u}$: Unbound steady-state plasma peak concentration
IC_{50}: Half maximal inhibitory concentration.

Data Availability

The data used to support the findings of the study are available from the corresponding author upon request.

Consent

All patients were informed and signed the consent form.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplemental Table 1: patient characteristics. Supplemental Table 2: precision and accuracy of rivaroxaban quantification in patients' plasma by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Supplemental Table 3: quality control for coagulation screening tests. Supplemental Table 4: specific patient characteristics. Supplemental Table 5: summary of inhibitory properties and pharmacokinetic parameters of febuxostat and benzbromarone at clinically relevant doses. Supplemental Table 6: the plasma concentrations and coagulation parameters in other medication with the mixed effect group. Supplemental Figure 1: correlation of rivaroxaban trough concentration (C_{trough}) level and routine coagulation parameters: (A) prothrombin time (PT), (B) international normalized ratio (INR), (C) activated partial thromboplastin time (aPTT), and (D) thrombin time (TT). (*Supplementary Materials*)

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