Remedial dosing regimens for delayed or missed rivaroxaban doses in patients with non-valvular atrial fibrillation based on Monte Carlo simulation

Running head: remedial dosing regimens of rivaroxaban

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Abstract

Background: Rivaroxaban is an oral anticoagulant used widely for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). During long-term anticoagulant therapy, delayed or missed doses are common. However, a lack of practical instructions on remedial methods has created a barrier to maximise the benefit of the medications. This study aimed to explore appropriate remedial dosing regimens for non-adherent rivaroxaban-treated patients.

Methods: Monte Carlo simulation based on a previously established rivaroxaban population pharmacokinetic/pharmacodynamic (PK/PD) model for patients with NVAF was employed to design remedial dosing regimens. The proposed regimens were compared with remedial strategies in the European Heart Rhythm Association (EHRA) guide by assessing deviation time in terms of drug concentration, factor Xa activity, and prothrombin time under various scenarios of non-adherence.

Results: The proposed remedial dosing regimens were dependent on delay duration. The missed dose should be taken immediately when the delay does not exceed 6 h; a half dose is advisable when the delay is between 6-20 h. A missed dose should be skipped if less than 4 h remains before the next dose. Age or renal function does not significantly influence remedial dosing regimens. The proposed regimens resulted in shorter deviation time than that of the EHRA guide in most non-adherence scenarios.

Conclusion: EHRA guide may not provide optimal remedial strategies for rivaroxaban-treated non-adherent patients based on simulation. PK/PD and simulation

provide valid evidence on the remedial dosing regimen of rivaroxaban for patients with NVAF, which could help to minimise the risk of bleeding and thromboembolism.

Keywords: adherence, modelling and simulation, pharmacokinetic-pharmacodynamic, anticoagulants, medication safety

What is already known about this subject:

Delayed or missed rivaroxaban is common in stroke prevention for patients with non-valvular atrial fibrillation and may increase thrombosis risk.

Current remedial dosing strategies recommended by package insert and European Heart Rhythm Association guide lack of supporting evidence.

What this study adds:

Proposed remedial dosing strategy is related to delay duration, but not related to age and renal function.

Newly proposed remedial dosing strategies based on Monte Carlo simulation may provide better solutions than current practice in most non-adherence scenarios.

1 Introduction

Rivaroxaban is one of the most commonly used non-vitamin K oral anticoagulants (NOACs) and was the first oral direct factor Xa (FXa) inhibitor approved for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) [1-5]. More than two-thirds of rivaroxaban doses are excreted by the kidney as metabolites or unchanged drugs[6, 7]; therefore, dose adjustment based on renal function is required in patients with moderate renal impairment (creatinine clearance, CrCl, 30–49 mL/min) [2] to achieve consistent efficacy and safety, when compared with the case in individuals with normal renal function [8].

Patients with NVAF receiving anticoagulant therapy usually require long-term therapy; however, adherence to NOACs, including rivaroxaban, decreases over time. In a large retrospective study, adherence to rivaroxaban was 68% three months after treatment initiation and decreased to 50% after twelve months of treatment [9]. Additionally, a considerable proportion of NVAF patients are elderly patients (> 70 years) [10, 11]. Delayed or missed doses, which represents a major form of non-adherence in clinical practice, is common in this population of elderly patients [12, 13]. As a class of drugs with fast on/fast off characteristics [14], low adherence to NOACs is associated with an increasing risk of mortality and stroke [15-17]. For example, a 10% decrease in dabigatran adherence, another NOAC, results in a 13% increase in all-cause mortality and stroke [18]. Therefore, appropriate remedial dosing to keep patients in appropriate therapeutic range after delayed or missed rivaroxaban

dose is necessary, to minimise the occurrence of thromboembolic events, and to avoid the unintentional overdose. Developing an appropriate remedial regimen is essential for the prevention of overdose-related bleeding events and underdose-related thromboembolic events caused by inappropriate remedial dosing. By providing scenario-specific instructions, patients can maximise the benefit and minimise the risk associated with rivaroxaban therapy.

Several resources provide general recommendations for patients who experience a delayed or missed dose. The package inserts from the United States Food and Drug Administration (US FDA) states that 'the patient should take the missed rivaroxaban dose immediately. The dose should not be doubled within the same day to make up for a missed dose' [2]. Similar recommendations are found in patient information leaflets [19] and consumer medicine information [20]. Furthermore, the 2018 European Heart Rhythm Association (EHRA) practical guide on the use of NOACs in patients with atrial fibrillation recommends that 'for NOACs with a once-a-day dosing regimen, a delayed dose can be taken up until 12 h after the scheduled intake. After this time point, the dose should be skipped, and the next scheduled dose should be taken' [21]. However, these recommendations are not supported by solid evidence from clinical studies or by extrapolation from pharmacokinetic/pharmacodynamic (PK/PD) analyses. It is also uncertain whether the recommendation can be applied to patients with impaired renal function.

Although human studies are ideal for assessing the proposed remedial regimen, prospective clinical research is unethical, and post-marketing adherence data are usually inadequate to explore the effects of non-adherence and to investigate appropriate remedial doses [22]. Monte Carlo simulations based on established population PK/PD models provide a practical approach to overcome this problem and have been successfully applied to antiepileptic, antipsychotic, and immunosuppressive agents [23]. Therefore, this study aimed to (i) assess the effect of delayed dose on the PK/PD of rivaroxaban and (ii) explore appropriate remedial dosing regimens by Monte Carlo simulation for patients with NVAF receiving rivaroxaban.

2 Materials and methods

2.1 Patients and dosing regimens

Adult patients (aged 55 or 75 years old) with various levels of creatinine clearance (CrCl, calculated by the Cockcroft-Gault formula [24]) were simulated, including patients with normal and moderately impaired renal function (CrCl 80 and 40 mL/min, respectively). The demographic characteristics of patients with NVAF were collected from epidemiologic reports [10, 11, 25]. As indicated on the US FDA label [2] and as recommended in the 2018 EHRA guide [21], patients with CrCl ≥50 mL/min received rivaroxaban 20 mg every 24 h (q24h), and those with CrCl 30–49 mL/min received 15 mg q24h. It was assumed that patients took rivaroxaban with food at the same time every day. Demographic information and simulated dosing regimens for typical patients are listed in Table 1.

2.2 Remedial dosing regimen assessment

For patients with NVAF taking rivaroxaban 20 or 15 mg daily, various scenarios were investigated in which doses were delayed from 1 to 24 h after the scheduled time (Figure 1).

2.2.1 Population PK/PD model and simulation

A previously published population PK/PD analysis of rivaroxaban was used in our study[26]. The study cohorts were obtained from a subset of patients in the largest multinational phase III ROCKET AF trial (Rivaroxaban once daily Oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) [27]. A total of 161 NVAF patients with time-matched PK and PD samples were included in this population PK/PD analysis. These included 136 patients with normal or mildly impaired renal function (CrCl≥50 mL/min) receiving 20 mg daily, and 25 patients with moderate renal impairment (CrCl 30–49 mL/min) receiving 15 mg daily. Detailed demographic and dosing regimen information is listed in Supplementary Table 1. Blood samples were used to determine rivaroxaban concentration, FXa activity, and prothrombin time (PT).

In this analysis, population PK was depicted by a one-compartment model with first-order absorption and elimination. The PK model was parameterised by the absorption rate constant (k_a), apparent clearance (CL/F), and apparent volume of distribution (V/F). The time-concentration relationship is described in Eq. 1.

$$C_p = \frac{k_a \cdot F \cdot DOSE}{V \cdot \left(k_a - \frac{CL}{V}\right)} \cdot \left[\left(\frac{1 - e^{\frac{-CL}{V} \cdot n \cdot \tau}}{1 - e^{\frac{-CL}{V} \cdot \tau}} \cdot e^{\frac{-CL}{V} \cdot t} \right) - \left(\frac{1 - e^{-k_a \cdot n \cdot \tau}}{1 - e^{-k_a \cdot \tau}} \cdot e^{-k_a \cdot t} \right) \right] \text{ (Eq.1)}$$

This equation comprised bioavailability (F), dose (DOSE; mg), apparent volume of distribution (V; L), number of doses administered (n), dosing interval (τ; h), time after the last dose (t; h), and concentration at time t (C_p; mg/L). Age and serum creatinine (SCr; mg/dL) affected CL/F (Eq 2.), while age and lean body mass (LBM) influenced V/F (Eq 3.).

$$\text{CL/F (L/h)} = 6.1 \cdot (1 - 0.011 \cdot [\text{age} - 65] - 0.194 \cdot [\text{SCr} - 1.09]) \text{ (Eq. 2)}$$

$$\text{V/F (L)} = 79.7 \cdot (1 - 0.00133 \cdot [\text{age} - 65] + 0.0118 \cdot [\text{LBM} - 57.5]) \text{ (Eq. 3)}$$

PD markers, including FXa activity and PT, were modelled to correlate with rivaroxaban concentration. FXa activity was negatively correlated with the concentration of rivaroxaban, with a direct inhibitory maximum-effect (E_{max}) relationship, as described by Eq 4.

$$FXa = E_0 \cdot \left(1 - \frac{E_{max} \cdot C_p}{EC_{50} + C_p}\right) \text{ (Eq.4)}$$

where, E_0 represents baseline FXa activity, E_{max} represents the relative maximum level of inhibition, and EC_{50} represents the concentration of rivaroxaban resulting in 50% of maximum inhibition.

PT was positively correlated with rivaroxaban concentration in a near-linear relationship, as described by Eq 5.

$$PT = PT_0 + slope \cdot C_p^{1 - exponent \cdot C_p} \text{ (Eq.5)}$$

PT_0 represents baseline PT, slope represents the per unit difference in CrCl (mL/min) to the median CrCl (76 mL/min), and the exponent represents the parameter describing the decline linearly with increasing C_p. CrCl was found to affect both PT_0 and the exponent, which is expressed by Eq.6 and Eq.7.

$$PT_0=11.4\cdot(1-0.000192\cdot[CrCl-76]) \quad \text{(Eq.6)}$$

$$Exponent=0.0000551\cdot(1+0.0174\cdot[CrCl-76]) \quad \text{(Eq.7)}$$

All PK/PD parameter estimates employed in the Monte Carlo simulation are listed in Table 2.

Monte Carlo simulations were performed with NONMEM software (version 7.4; Icon Incorporation, PA, USA) using the $SIMULATION block. Output profiles were processed using the R package (version 3.5.3, https://www.r-project.org/). A total of 5000 virtual patients were simulated to depict the PK/PD profiles under each non-adherence scenario. Virtual patients were assumed to have already received multiple doses of rivaroxaban and have reached steady state. Patients were also assumed to obtain expected level of anticoagulation without any unexpected drug-related adverse effects.

2.2.2 Remedial dosing regimens

Based on previous research and clinical practice [23], six strategies, as well as recommendations included in the EHRA guide, were assessed when the dose was delayed or missed. Graphic remedial strategies are shown in Figure 2, and details are below as follows:

Strategy A: skip the delayed dose, administer the regular dose at the next scheduled dosing time, and then resume the regular dosing regimen.

Strategy B: administer the regular dose immediately, followed by a regular dose at the next scheduled dosing time, and then resume the regular dosing regimen.

Strategy C: administer a half dose immediately followed by a regular dose at the next scheduled dosing time, and then resume the regular dosing regimen.

Strategy D: administer a regular dose immediately followed by a half dose at the next scheduled dosing time, and then resume the regular dosing regimen.

Strategy E: administer one and a half regular doses immediately, skip the next scheduled dose, and then resume the regular dosing regimen.

Strategy F: administer a double dose, skip a dose at the next scheduled dosing time, and then resume the regular dosing regimen;

EHRA guide: administer the delayed dose if less than 12 h late; otherwise, skip the delayed or missed dose and administer the next scheduled dose.

2.2.3 Index for evaluating remedial regimens

Currently, there is no widely accepted therapeutic range of rivaroxaban concentrations, FXa activity, or PT. Therefore, the on-therapy range, defined as the 'interval delineated by the 5^{th} percentile trough concentration and the 95^{th} percentile peak concentration' at the steady state of a given dose [28, 29], was used in this study. Considering the differences in patient demographics, we estimated the on-therapy range for each typical patient at steady state by Monte Carlo simulation. To assess the

196 effect of a delayed or missed dose, we defined the percentage of individuals outside
197 the on-therapy range as those whose concentration or PD marker levels were not
198 within the on-therapy range. The percentages of individuals outside the on-therapy
199 range under all non-adherence scenarios described above were estimated to evaluate
200 the effect of non-adherence over time.
201 Deviation time, defined as the duration when simulated rivaroxaban concentration,
202 FXa activity or PT were outside the on-therapy range, was chosen as the index to
203 evaluate the remedial regimen. It was calculated by adding each deviation time when
204 simulated data is higher than the upper limit and lower than the lower limit of on-
205 therapy range. The two aspects of deviation time may represent higher risk of
206 bleeding and thromboembolic events, respectively. It was assumed that patients
207 adherent to rivaroxaban had reached expected anticoagulant effects within the on-
208 therapy range. Therefore, when the rivaroxaban dose was delayed or missed, optimal
209 remedial dosing could help patients to restore the rivaroxaban concentration, FXa
210 activity, or PT to the on-therapy range as soon as possible to minimise the deviation
211 time.
212 Two remedial dosing regimens with deviation times of less than 2 h were assumed to
213 be equivalent. If there were discrepancies among recommendations for rivaroxaban
214 concentration, FXa activity, or PT, those based on FXa activity were prioritised. This
215 was because quantification of FXa activity is considered as a more specific biomarker

for NOACs, which is recommended by the International Society on Thrombosis and Haemostasis American College of Chest Physicians guidelines [30, 31].

2.2.4 Sensitivity analysis

A sensitivity analysis was applied to identify parameters that had a substantial influence on model output, and to determine the extent that these important parameters contributed to the overall variability in model output [32]. Therefore, dosing intervals and demographic characteristics (age and lean body weight) were included in the sensitivity analysis to investigate their influence on the remedial dosing regimens.

Irregular dosing intervals of 22–26 h (18:00, 16:00, and 18:00) and 26–22 h (18:00, 20:00, and 18:00) were assessed considering situations where patients took rivaroxaban at different times every day. Moreover, considering the demographics of the modelling population, patients with different ages and body weights (expressed as LBM in population analysis) were also investigated (Supplementary Table 2). Furthermore, the criterion used to judge the equality of the two strategies was also examined from 1 to 3 h, to investigate whether it had an influence on the remedial dosing recommendations.

3 Results

3.1 Effect of delayed or missed doses of rivaroxaban on PK/PD

The results from the Monte Carlo simulation showed that the effect of a delayed dose was related to the delay time. With an increasing delay time, the risk of a patient being outside the on-therapy range was also increased considering both the PK and PD (Figure 3). For example, among patients with CrCl of 80 mL/min who took rivaroxaban 20 mg q24h, 12.6% and 47.9% patients were outside the on-therapy range based on rivaroxaban concentration when the dose was delayed for 6 h and 24 h, respectively.

The effect of delayed dose was not significantly affected by age or renal function. (Figure 3). For example, among elderly patients with normal and impaired renal function, the percentage of those who were outside the on-therapy concentration range was 22.6% and 20.4% when the dose was delayed for 12 h, respectively, representing a relative difference less than 15%. Moreover, the difference in the percentages of patients who were outside of the FXa activity (8.6 vs. 8.26%) or PT on-therapy (10.2 vs. 10.1%) range were also less than 15%.

In addition, the impact of the delayed dose on the PK/PD was very similar when the delay time was less than 3 h. However, the percentage of patient falling outside the on-therapy range increased as the delay time increased (Figure 3). Considering rivaroxaban concentration, this percentage increased approximately linearly with time. The percentage changed considering FXa activity and PT were close also increased with delay time but with a smaller slope. For example, for adult patients receiving a 20 mg q24h dose delayed for 2 h, the percentages of those outside the on-

therapy range were 6.9, 6.5, and 6.4% for rivaroxaban concentration, FXa activity, and PT, respectively. These percentages were 23.4, 7.6, and 9.3%, respectively, when dosing was delayed for 12 h, with a greater difference between rivaroxaban concentration and PD markers compared with that at 2 h.

3.2 Remedial dosing regimens

The remedial dosing recommendations following a delayed rivaroxaban dose are summarised in Table 3. Figure 4a–c shows the concentration, FXa activity, and PT profiles for fully adherent elderly patients with normal renal function (aged 75 years, CrCl 80 mL/min, receiving 20 mg q24h). In general, remedial dosing recommendations are related to delayed time. Considering FXa activity, a regular dose of rivaroxaban could be taken immediately when the delay doesn`t exceed 6 h. Figure 4d–f showed the concentration, FXa activity, and PT profiles following a delay of 6 h under optimal remedial regimens. When the delay exceeds 6 h but is less than 20 h, it is advisable to remedy a half dose either by taking a half dose immediately followed by a regular dose at the next scheduled time, or by taking a regular dose immediately followed by a half dose at the next scheduled dosing time. When the delay exceeds 20 h, it is recommended to skip the delayed dose and take a regular dose at the next scheduled dosing time. When a dose is missed, it is advisable to take a regular dose at the scheduled dosing time.

Recommendations based on rivaroxaban concentration and FXa or PT levels were the same among almost all scenarios, except for scenarios where the delay time was 4–6 h. Under this scenario, recommendations based on FXa activity may supported taking a regular dose immediately, while recommendations based on concentration and PT preferred taking a half dose. Based on pre-established criteria where FXa activity was preferred, recommendations based on FXa activity were selected.

Additionally, age and renal function did not affect remedial dosing regimens. For example, for adult patients with normal renal function, a half dose (10 mg) is recommended when the dose is delayed by 5–20 h, based on rivaroxaban concentration, FXa activity, and PT. For elderly patients with impaired renal function taking a lower daily dose, a half dose (7.5 mg) is also recommended when the delay was 6–22 h.

Because recommendations from the EHRA did not consider splitting rivaroxaban tablets, this represented a missed opportunity to provide a more personalised remedial strategy. Based on the present results, our recommendation is consistent with that of the EHRA only when the delay was less than 6 h, or it was less than 4 h before the next dose. Recommendations from the EHRA guide may not be optimised. A comparison of the deviation time between the EHRA guide and our proposed remedial strategy is shown in Figure 5. Deviation times under different strategies are listed in Supplementary Table 3–6, which can provide supportive information to balance the risk of thromboembolism and bleeding.

3.3 Sensitivity analysis

Age, lean body weight and dosing intervals were included in the sensitivity analysis when the rivaroxaban dose was delayed for 3, 6, 12, and 24 h. Deviation time may vary slightly by age, body weight, and dosing intervals. However, these factors did not significantly impact remedial dosing regimens (Supplementary Figure 1). As for criterion for assessing the equality of two strategies, extending to 3 h or reducing to 1 h did not significantly change the remedial dosing recommendations, either (Supplementary Table 7).

4 Discussion

This was the first study to characterise the effects of delayed rivaroxaban dose on the PK/PD profiles and to investigate appropriate remedial dosing regimens for patients with NVAF under different scenarios. A few studies have estimated the rate of non-adherence of NOACs and explored the associated risk factors [12, 13, 15]. However, non-adherence is common, and very few studies have proposed solutions after doses are delayed or missed. Considering the high risk for thromboembolism resulting from non-adherence and the serious consequences resulting from inappropriate remedial and delayed doses, our study is the first to provide insight into remedial regimens for patients with NVAF following delayed or missed rivaroxaban doses.

Our study explored optimal remedial regimens based on Monte Carlo simulation from the perspective of both PK and PD, and considering both population level and individual variation. Handling delayed doses from the population PK perspective has been previously discussed for various diseases, such as epilepsy [33-36], schizophrenia [37, 38] and renal transplantation [39]. However, few studies have explored this with consideration of PD, or PK/PD [23]. The PD effect should also be considered for medicine acting via an indirect mechanism [40], such as rivaroxaban, since some studies demonstrated the association between PD effect of rivaroxaban (i.e. FXa activity, PT) and hemorrhagic events [41-43].

Given that no clearly defined therapeutic ranges have been established for rivaroxaban [28], an on-therapy range was adopted to describe appropriate maintained levels of concentration, FXa activity, and PT. The concept of an "on-therapy range" for NOACs was recognized by CHEST[44], and applied to latest clinical studies to indicate to drug level where most subjects will fall during treatment [45, 46]. Moreover, it has been used for antiepileptic drugs, and was thought to be appropriate for epilepsy management [34, 35]. Regarding rivaroxaban, the calculated PK on-therapy ranges based on simulated data are close to those estimated in clinical trials [47]. We hypothesised that patients taking the prescribed dose could obtain expected anticoagulation outcomes within the on-therapy range. It is reasonable to assume that a remedial strategy restoring drug concentrations to a previous range can minimise

negative outcomes associated with non-adherence, such as lower exposure, in addition to potential thromboembolic events.

Through population analysis and Monte Carlo simulation, our study provides remedial dosing recommendations that are more time-specific than those included in the EHRA guide. Recommendations from the EHRA are general for all NOACs, including rivaroxaban, apixaban, edoxaban, and dabigatran [21]. Our research optimises these recommendations from both PK and PD perspectives, suggesting that the cut-off point for remedying a full dose is not 12 h, as noted in the EHRA guide. Based on the concentration and PT, the cut-off point is approximately 3 h, while based on FXa activity, the cut-off is approximately 6 h. When the dose is delayed for less than the cut-off point, taking the delayed dose of rivaroxaban as soon as possible is recommended. However, when the delay exceeds the cut-off point, a half dose is advisable, to minimise the deviation time. When the dose is close to the next scheduled dose or is completely skipped, it is advisable to skip the missed dose and to continue with the regular dosing regimen at the next scheduled time.

It is also notable that doubling the dose of rivaroxaban after a missed dose (strategy F) is not recommended based on the drug package insert, the EHRA guide, and our research. In fact, even remedying a half dose (strategy E) is unnecessary. This is inconsistent with the findings of previous similar studies exploring remedial dosing strategies in simulations based on antiepileptic drugs [34-36] or immunosuppressants [39], which are taken every 12 or 24 h. Remedying no extra dose when missing a dose

may result in a deviation time that is below the lower limit of the on-therapy range, while remedying a half dose increases the deviation time above the upper limit of the on-therapy range. Furthermore, a double dose substantially increases the drug concentration to levels beyond the upper limit of the on-therapy range. This also leads to a much longer deviation time outside the on-therapy range.

The risk of bleeding or thromboembolism varies among patients with atrial fibrillation. The CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack [TIA], vascular disease, age 65–74 years, sex category) score is commonly used for the assessment of stroke risk [48]. The risk of stroke may differ for patients of the same age and with the same renal function, considering other factors included in the CHA2DS2-VASc scoring system.

Adherence to anticoagulant therapy, such as with rivaroxaban, is particularly important for patients with a high CHA2DS2-VASc score, given their high risk for stroke [38]. Also, in patients with a history of bleeding, it is important to avoid an inappropriate remedial strategy. Therefore, deviation times that exceed the upper limit of the on-therapy range and that were below the lower limit of the on-therapy range, representing the risk of bleeding and thromboembolism, respectively, are also listed in Supplementary Table 3–6. Therefore, clinicians can select the optimal remedial dose for individual patients based on deviation time and patient characteristics.

There are several limitations to this study. First, the simulated dosing regimen complied with that of the modelling population, who took 20 or 15 mg daily rivaroxaban based on renal function. Therefore, our recommendations may not apply to patients receiving other doses of rivaroxaban. Second, our recommendations were based on a 90% predicted interval of simulation data. Therefore, attention should be paid to special populations, such extremely obese patients or older patients, who were not included in our analysis.

In conclusion, this study assessed the effect of non-adherence to rivaroxaban and explored appropriate remedial dosing regimens for patients with NVAF considering the drug concentration, FXa, and PT. Comparison of deviation time between proposed remedial dosing regimens and the EHRA guide revealed that EHRA guide may not be optimal to deal with delayed or missed dose. Model-informed simulation may be an effective and executable way to solve clinical problems associated with delayed or missed doses. Further, this may help to reduce the risk of bleeding and thromboembolism for patients treated with oral anticoagulants. Clinicians should also balance the risk of bleeding and stroke and select appropriate remedial strategies based on the clinical situation of each patient.

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Conflict of Interest statement

The authors have no conflict of interest to disclose.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author contributions

Xiao-qin Liu: Conceptualization, Methodology, Formal analysis, Writing-original draft, Writing-review & editing, Visualization. **Yi-wei Yin**: Writing-original draft, Writing-review & editing, Visualization. **Chen-yu Wang**: Formal analysis, Data

curation, Visualization. **Zi-ran Li**: Formal analysis, Data curation. **Xiao Zhu**: Writing-review & editing. **Zheng Jiao**: Conceptualization, Methodology, Writing-original draft, Writing-review & editing, Supervision, Project administration.

Figure legends

Figure 1 Simulation scenarios for delayed or missed rivaroxaban doses for patients with non-valvular atrial fibrillation (NVAF) receiving 15 or 20 mg dose every 24 h.

Figure 2 Graphical representation of six remedial dosing regimens following a delayed or missed dose A round tablet represents an integrated rivaroxaban dose, and a half-round tablet represents a half rivaroxaban dose. Patients were assumed to take rivaroxaban at 18:00 daily and to have reached a steady state following a delayed or missed dose. [a] n represents the delayed time, whose range is from 1 to 24 h.

Figure 3 Percentage of patients with NVAF falling outside the on-therapy ranges versus time after the delayed or missed doses in terms of rivaroxaban concentration, FXa activity and PT. (a) Adult patients, 55 years old, CrCl 80 mL/min receiving 20 mg every 24 h (q24h). (b) Adult patients, 55 years old, CrCl 40 mL/min receiving 15 mg q24h. (c) Elderly patients, 75 years old, CrCl 80 mL/min receiving 20 mg q24h. (d) Elderly patients, 75 years old, CrCl 40 mL/min receiving 15 mg q24h. Simulated patients were assumed to take rivaroxaban doses regularly and to have reached steady state.

Figure 4 Pharmacokinetic (PK) and pharmacodynamic (PD) profiles under full adherence and optimal remedial regimens in terms of rivaroxaban concentration, FXa

activity and PT for elderly patient with CrCl 80 mL/min receiving rivaroxaban 20 mg every 24 h when the dose was delayed for 6 h. (a) Full adherence based on concentration, (b) FXa activity, and (c) PT. (d) optimal remedial regimens in terms of concentration, (e) FXa activity, and (f) PT when the dose was delayed for 6 h. Dark pink shadows represent the distribution of the range between the 5th percentile of the simulated trough concentration (FXa activity or PT) and 95th percentile of the simulated peak concentration (FXa activity or PT). Light pink shadows represent the distribution of the remaining simulated concentration (FXa activity or PT). Red solid lines represent the median of the simulated concentration (FXa activity or PT). Black dotted lines represent the on-therapy range calculated by the simulated concentration (FXa activity or PT). Black horizontal bold solid lines represent the deviation time.

Figure 5 Total deviation time from recommendations by the European Heart Rhythm Association (EHRA) guide and proposed remedial regimens. (a) Adult patients, 55 years old, CrCl 80 mL/min taking 20 mg every 24 h (q24h). (b) Adult patients, 55 years old, CrCl 40 mL/min taking 15 mg q24h. (c) Elderly patients, 75 years old, CrCl 80 mL/min taking 20 mg q24h. (d) Elderly patients, 75 years old, CrCl 40 mL/min taking 15 mg q24h. Simulated patients were assumed to take rivaroxaban doses regularly and to have reached steady state.

Reference

1. Misselwitz F, Berkowitz SD, Perzborn E. The discovery and development of rivaroxaban. Ann N Y Acad Sci. 2011;1222:64-75.

2. Food and Drug Administration. XARELTO® (insert package). [updated 2020 Mar; cited 2020 Sep 30]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202439s031,022406s035lbl.pdf.

3. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol. 2017;83(9):2096-106.

4. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010-2017. Pharmacotherapy. 2018;38(9):907-20.

5. Maggioni AP, Dondi L, Andreotti F, Pedrini A, Calabria S, Ronconi G, et al. Four-year trends in oral anticoagulant use and declining rates of ischemic stroke among 194,030 atrial fibrillation patients drawn from a sample of 12 million people. Am Heart J. 2020;220:12-9.

6. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53(1):1-16.

7. Kvasnicka T, Malikova I, Zenahlikova Z, Kettnerova K, Brzezkova R, Zima T, et al. Rivaroxaban - Metabolism, Pharmacologic Properties and Drug Interactions. Curr Drug Metab. 2017;18(7):636-42.

8. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32(19):2387-94.

9. Pham PN, Brown JD. Real-world adherence for direct oral anticoagulants in a newly diagnosed atrial fibrillation cohort: does the dosing interval matter? BMC Cardiovasc Disord. 2019;19(1):64.

10. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. Am Heart J. 2018;202:20-6.

11. Weber C, Hung J, Hickling S, Li I, McQuillan B, Briffa T. Drivers of hospitalisation trends for non-valvular atrial fibrillation in Western Australia, 2000-2013. Int J Cardiol. 2019;276:273-7.

12. Rodriguez-Bernal CL, Peiró S, Hurtado I, García-Sempere A, Sanfélix-Gimeno G. Primary Nonadherence to Oral Anticoagulants in Patients with Atrial Fibrillation: Real-World Data from a Population-Based Cohort. J Manag Care Spec Pharm. 2018;24(5):440-8.

13. Reading SR, Black MH, Singer DE, Go AS, Fang MC, Udaltsova N, et al. Risk factors for medication non-adherence among atrial fibrillation patients. BMC Cardiovasc Disord. 2019;19(1):38.

14. Moll S, Berkowitz JN, Miars CW. Elite athletes and anticoagulant therapy: an intermittent dosing strategy. Hematology Am Soc Hematol Educ Program. 2018;2018(1):412-7.

15. Deshpande CG, Kogut S, Laforge R, Willey C. Impact of medication adherence on risk of ischemic stroke, major bleeding and deep vein thrombosis in atrial fibrillation patients using novel oral anticoagulants. Curr Med Res Opin. 2018;34(7):1285-92.

16. Borne RT, O'Donnell C, Turakhia MP, Varosy PD, Jackevicius CA, Marzec LN, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. BMC Cardiovasc Disord. 2017;17(1):236.

17. Alberts MJ, Peacock WF, Fields LE, Bunz TJ, Nguyen E, Milentijevic D, et al. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. Int J Cardiol. 2016;215:11-3.

18. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63(4):321-8.

19. Electronic Medicines Compendium. Xarelto 20/15mg film-coated tablets (Package leaflet: Information for the user). [updated 2019 Jul; cited 2020 Sep 30]. https://www.medicines.org.uk/emc/files/pil.2793.pdf.

20. New Zealand Medicines and Medical Devices Safety Authority. XARELTO® (Consumer Medicine Information). [updated 2020 Jul 7; cited 2020 Sep 30]. https://www.medsafe.govt.nz/Consumers/CMI/x/Xarelto.pdf.

21. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330-93.

22. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace. 2015;17(4):514-23.

23. Gu JQ, Guo YP, Jiao Z, Ding JJ, Li GF. How to Handle Delayed or Missed Doses: A Population Pharmacokinetic Perspective. Eur J Drug Metab Pharmacokinet. 2020;45(2):163-72.

24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

25. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Nielsen JC, Sorensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. Int J Cardiol. 2016;225:30-6.

26. Girgis IG, Patel MR, Peters GR, Moore KT, Mahaffey KW, Nessel CC, 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):917-27.

27. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.

28. Cuker A, Siegal D. Monitoring and reversal of direct oral anticoagulants. Hematology Am Soc Hematol Educ Program. 2015;2015:117-24.

29. Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. Blood Rev. 2017;31(1):77-84.

30. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e44S-e88S.

31. Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring Oral Direct Inhibitors (ODIs) of thrombin and factor Xa: A recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2013;11(4):756-60.

566 32. Zhang XY, Trame MN, Lesko LJ, Schmidt S. Sobol Sensitivity Analysis: A Tool
567 to Guide the Development and Evaluation of Systems Pharmacology Models. CPT
568 Pharmacometrics Syst Pharmacol. 2015;4(2):69-79.
569 33. Wang CY, Jiao Z, Ding JJ, Yu EQ, Zhu GX. Remedial dosing recommendations
570 for delayed or missed doses of valproic acid in patients with epilepsy based on Monte
571 Carlo simulations. Epilepsy Behav. 2020;111:107265.
572 34. Yu EQ, Jiao Z, Wang CY, Ding JJ, Zhang XH. Remedial dosing
573 recommendations for delayed or missed doses of lamotrigine in pediatric patients with
574 epilepsy using Monte Carlo simulations. Epilepsy Behav. 2019;96:132-40.
575 35. Ding JJ, Zhang YJ, Jiao Z, Wang Y. The effect of poor compliance on the
576 pharmacokinetics of carbamazepine and its epoxide metabolite using Monte Carlo
577 simulation. Acta Pharmacol Sin. 2012;33(11):1431-40.
578 36. Dutta S, Reed RC. Effect of delayed and/or missed enteric-coated divalproex
579 doses on valproic acid concentrations: simulation and dose replacement
580 recommendations for the clinician. J Clin Pharm Ther. 2006;31(4):321-9.
581 37. Magnusson MO, Samtani MN, Plan EL, Jonsson EN, Rossenu S, Vermeulen A,
582 et al. Dosing and Switching Strategies for Paliperidone Palmitate 3-Month
583 Formulation in Patients with Schizophrenia Based on Population Pharmacokinetic
584 Modeling and Simulation, and Clinical Trial Data. CNS Drugs. 2017;31(4):273-88.
585 38. Hard ML, Wehr AY, Sadler BM, Mills RJ, von Moltke L. Population
586 Pharmacokinetic Analysis and Model-Based Simulations of Aripiprazole for a 1-Day

Initiation Regimen for the Long-Acting Antipsychotic Aripiprazole Lauroxil. Eur J Drug Metab Pharmacokinet. 2018;43(4):461-9.

39. Saint-Marcoux F, Woillard JB, Monchaud C, Friedl J, Bocquentin F, Essig M, et al. How to handle missed or delayed doses of tacrolimus in renal transplant recipients? A pharmacokinetic investigation. Pharmacol Res. 2015;100:281-7.

40. Whitlon DS, Sadowski JA, Suttie JW. Mechanism of coumarin action: significance of vitamin K epoxide reductase inhibition. Biochemistry. 1978;17(8):1371-7.

41. Sakaguchi T, Osanai H, Murase Y, Ishii H, Nakashima Y, Asano H, et al. Monitoring of anti-Xa activity and factors related to bleeding events: A study in Japanese patients with nonvalvular atrial fibrillation receiving rivaroxaban. J Cardiol. 2017;70(3):244-9.

42. Wada S, Toyoda K, Sato S, Matsuki T, Okata T, Kumamoto M, et al. Anti-Xa Activity and Event Risk in Patients With Direct Factor Xa Inhibitors Initiated Early After Stroke. Circ J. 2018;82(11):2872-9.

43. Nakano Y, Kondo T, Osanai H, Murase Y, Nakashima Y, Asano H, et al. Clinical usefulness of measuring prothrombin time and soluble fibrin levels in Japanese patients with atrial fibrillation receiving rivaroxaban. J Cardiol. 2015;65(3):185-90.

44. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants: A Systematic Review. Chest. 2017;151(1):127-38.

45. Hirota N, Suzuki S, Yamasaki M, Matsumoto N, Ajiki K, Kasao M, et al. Analysis of bioMARKer Distribution and Individual Reproducibility Under Rivaroxaban Treatment in Japanese Patients with Non-Valvular Atrial Fibrillation (R-MARK Study, CVI ARO2). Int Heart J. 2020;61(4):695-704.

46. Martin AC, Thomas W, Mahir Z, Crowley MP, Dowling T, Breen K, et al. Direct Oral Anticoagulant Concentrations in Obese and High Body Weight Patients: A Cohort Study. Thromb Haemost. 2020 Aug 30. Doi: 10.1055/s-0040-1715834.

47. Siguret V, Abdoul J, Delavenne X, Curis E, Carlo A, Blanchard A, et al. Rivaroxaban pharmacodynamics in healthy volunteers evaluated with thrombin generation and the active protein C system: Modeling and assessing interindividual variability. J Thromb Haemost. 2019;17(10):1670-82.

48. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., 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-e51.