Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement

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Summary

Rivaroxaban (Xarelto®) is an oral, direct factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. The aim was to compare the population pharmacokinetics (PK) and pharmacodynamics (PD) of twice-daily (bid) and once-daily (od) rivaroxaban in patients undergoing total hip replacement (THR). Blood samples were collected from patients enrolled in two phase IIb, dose-ranging studies undertaken to investigate rivaroxaban for thromboprophylaxis after THR. A sparse sampling technique was used and the samples were pooled for PK and PD analysis, which used non-linear mixed effect modelling. Rivaroxaban PK (samples from 758 patients) were well described by an oral, one-compartment model; age and renal function influenced clearance, and body surface area affected volume of distribution. When comparing the same total daily doses, maximum plasma concentrations of rivaroxaban were higher and minimum plasma concentrations were lower with od dosing, compared with bid dosing; however, the 90% intervals overlapped. The area under the plasma concentration–time curve was 18–30% higher in the od than in the bid study. Prothrombin time in seconds (samples from 1181 patients) correlated with rivaroxaban plasma concentrations in a linear fashion in both studies. In conclusion, the PK and PD of rivaroxaban were predictable when given either bid or od. These findings, along with the suggested efficacy and safety of rivaroxaban in the phase II studies, relative to enoxaparin, supported the selection of a convenient, once-daily 10 mg rivaroxaban dose for investigation in phase III studies.

Keywords

Factor Xa, pharmacodynamics, population pharmacokinetics, rivaroxaban, total hip replacement

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Introduction

Major orthopaedic surgery, such as total hip replacement (THR) and total knee replacement (TKR), is associated with a significant increase in the risk of developing venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE) (1). As a result, prophylactic anticoagulant therapy is recommended in these patients and has become the standard of care (1, 2).

Traditionally, thromboprophylaxis in patients undergoing THR or TKR comprises either low-molecular-weight heparins (LMWHs; including enoxaparin) or vitamin K antagonists (including warfarin). LMWHs are the standard European prophylactic therapy in patients undergoing major orthopaedic surgery and were developed to overcome the pharmacokinetic limitations of unfractionated heparin. Enoxaparin has a short half-life (4–5 hours); however, anticoagulant effects are still observed 24 hours after administration, permitting a once-daily (od) dosing regimen (3). A major shortcoming of the LMWHs is that they require subcutaneous administration, limiting their utility in the outpatient setting (4). Warfarin has a slow onset of action (3–4 days), a narrow therapeutic window, unpredictable pharmacology and numerous food and drug interactions, which make fre-

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Table 1: Demographics of patients from the twice-daily (bid) and once-daily (od) studies providing pooled data for population pharmacokinetic analysis. Median values and range are shown. Gender demographics: 302 (40%) male, 456 (60%) female.

	bid study (n=362)		od study (n=396)		Pooled population (n=758)	
Age (years)	66	(26–86)	65	(27–93)	66	(26–93)
Weight (kg)	76	(45–120)	74	(45–120)	75	(45–120)
Height (cm)	166	(140–201)	167	(146–197)	167	(140–201)
Body surface area (m^2)	1.86	(1.34–2.43)	1.83	(1.37–2.41)	1.84	(1.34–2.43)
Creatinine clearance (ml/min)	95.5	(33.3–208)	80.7	(18.8–203)	88.1	(18.8–208)
Serum albumin (g/dl)	3.3	(1.8–4.5)	4.5	(2.7–5.3)	3.4	(1.7–5.4)
Haematocrit (%)	34	(21.6–50.9)	40	(23.6–53.0)	37.3	(21.6–53.0)

quent monitoring necessary (5). As such, there is a need for an oral anticoagulant with a rapid onset of action, predictable pharmacokinetics (PK) and pharmacodynamics (PD) and a low propensity for food and drug interactions (4).

Rivaroxaban (Xarelto®, Bayer HealthCare AG) is a novel, oral, direct Factor Xa (FXa) inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. Results of phase I clinical studies showed that rivaroxaban was well tolerated in healthy human subjects, with predictable, dose-proportional PK and PD up to total daily doses of 60 mg (6). The PK and PD of rivaroxaban were not affected to a clinically relevant degree by differences in age, gender or body weight (7, 8).

Four phase II studies in patients undergoing THR or TKR were performed to investigate the efficacy and safety of rivaroxaban. Male patients over the age of 18 and post-menopausal female patients scheduled for elective THR or TKR were enrolled in these studies. Exclusion criteria included any bleeding disorder, current use of drugs that may affect study outcome such as anticoagulants, platelet aggregation inhibitors (e.g. acetylsalicylic acid, clopidogrel or dipyridamole), or any other drug influencing coagulation (except non-steroidal anti-inflammatory drugs [NSAIDs] with a half-life of <17 hours), and severe liver or renal impairment (9). An open-label, dose-ranging study in patients undergoing THR demonstrated proof of principle for both twice-daily (bid) and od rivaroxaban dosing (9). Two phase IIb dose-finding studies in patients undergoing THR or TKR were then undertaken with bid rivaroxaban. Both of these studies investigated rivaroxaban total daily doses of 5–60 mg and demonstrated that a four-fold total daily dose range of rivaroxaban 5–20 mg had good efficacy and safety for the prevention of VTE after major orthopaedic surgery (10, 11). A further phase IIb study was performed with od rivaroxaban (5–40 mg) in patients

Table 2: Rivaroxaban population estimates for the final structural pharmacokinetic (one-compartment) model.

Description	Mean estimate	RSE (%)[a]
First-order absorption rate		
on study day 2 for mixed population 1 (h^{-1})	0.047	24.2
on study days 3/4 for mixed population 1 (h^{-1})	0.222	9.4
on study day ≤4 for mixed population 2 (h^{-1})	1.07	11.0
on study day >4 (for all patients) (h^{-1})	1.49	10.0
Percentage of mixed population 1 (for first-order absorption rate) on study days ≤4	55.0	6.7
Relative bioavailability factor in relation to 2.5 mg bid treatment (with F = 1 per definition) for 5 mg and 10 mg treatment	0.877	4.5
for 20 mg treatment	0.791	5.8
Clearance (l/h)[b]		
on study day 2	5.46	8.7
on study days 3/4	6.91	4.3
on study days >4	7.51	4.1
Inter-individual variability in clearance (%CV)[c]	38.2	10.0
Volume of distribution (l)[b]	58.2	4.9
Inter-individual variability in volume of distribution (%CV)[c]	32.4	23.0
Proportional residual error (%)	52.6	3.0

bid, twice daily; CV, coefficient of variation; F, bioavailability; RSE, relative standard error.
[a]Relative standard error, expressed as a percentage of the estimate. [b]The bioavailability (F) of rivaroxaban is currently unknown; therefore, the clearance (CL) and volume of distribution (Vd) were modelled as CL/F and V/F, respectively. [c]Coefficient of variation, calculated as the square root of the variance (which is approximately equivalent to the %CV).

undergoing THR. In this study, rivaroxaban 10 mg od had the optimal combination of efficacy and safety, relative to enoxaparin 40 mg od, suggesting that this dose should be investigated further (12). In three phase III studies (part of the RECORD programme), rivaroxaban (10 mg od) has been shown to have superior efficacy and a similar safety profile to enoxaparin in patients undergoing THR and TKR (13–15).

The aim of this analysis was to compare the PK and PD of bid and od rivaroxaban for the prevention of VTE in patients undergoing THR and to investigate the influence of patient demographic characteristics on the PK and PD of rivaroxaban in this patient population.

Methods

Study design and patients

Data were pooled from two phase IIb, double-blind, dose-ranging studies investigating rivaroxaban in patients undergoing elective THR using either bid or od dosing regimens (11, 12). Rivaroxaban was administered in total daily doses of 5, 10, 20, 40 or 60 mg in the bid study, and 5, 10, 20, 30 or 40 mg in the od study. The first dose of rivaroxaban was given 6-8 hours after wound closure, then bid (12 ± 1 hours) or od (24 ± 2 hours) thereafter for 8 ± 2 days, with food. For the present study, only total daily doses of 5–20 mg were studied because they were demonstrated to compare favourably with enoxaparin in the clinical studies (11).

The study population comprised male patients aged 18 years or older and post-menopausal female patients undergoing THR. Patients were excluded from the studies if their body weight was less than 45 kg or they had severely impaired liver or renal function (creatinine clearance [CrCL] <30 ml/minute).

Pharmacokinetic and pharmacodynamic sampling

All patients underwent major orthopaedic surgery and, therefore, it was unreasonable to expect them to also undergo full PK and PD profiling. As a result, a sparse sampling technique was employed in both studies, and population modelling was used to generate full PK profiles of rivaroxaban.

Blood samples for PK and PD analyses were collected from all randomized patients using a sparse sampling schedule optimized for the bid dosing regimen (16). Briefly, blood samples were taken from patients receiving bid dosing 1 ± 0.5, 3 ± 1 and 6 ± 1 hours after administration on the day after surgery (day two, if the day of surgery is day one). When rivaroxaban reached a steady state (day five or six), blood samples were taken 1 ± 0.5, 3 ± 1 and 6 ± 1 hours after administration and in the time interval between eight hours post-administration and the next dose. The sampling schedule for patients receiving od dosing began 2–4 hours after the first administration of rivaroxaban on the day of surgery (day 1). On day 2 or 3, blood samples were taken from 4 hours up to 0.5 hours before the evening rivaroxaban administration, and then 1 ± 0.5, 3 ± 1 and 12 ± 2 hours after dosing. Further samples were taken when rivaroxaban reached steady state (day four, five or six), again from four hours up to 0.5 hours before the evening dose and 3±1 hours after dosing. The final blood sample was taken 12 ± 2 hours after the last rivaroxaban dose on day 9 ± 2 of the study.

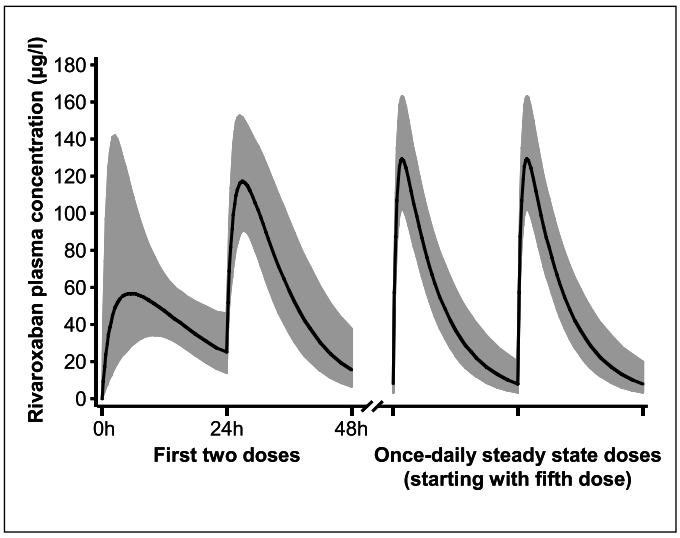

Figure 1: Predicted rivaroxaban plasma concentration–time curves in patients receiving rivaroxaban 10 mg once daily. Line, geometric mean; shading, standard deviation.

Pharmacokinetic and pharmacodynamic investigations

Rivaroxaban plasma concentrations were determined using a validated and selective chromatographic assay with mass spectrometric detection (LC-MS/MS) (8).

Prothrombin time (PT; in seconds) was determined at a central laboratory according to standard clinical procedures. PT in blood samples taken from patients in the bid study was analysed using freeze-dried thromboplastin from rabbit brain (Sta Neoplastine®, Diagnostica Stago, Asnières, France) with an international sensitivity index (ISI) of 1.8. PT in blood samples collected from patients in the od study was determined using recombinant human thromboplastin (Innovin®, Dade Behring, Marburg, Germany) with an ISI of 1.0.

Population pharmacokinetics/pharmacodynamics modelling

The population PK analysis was performed using data pooled from patients receiving rivaroxaban in both the bid and od studies. The PK analysis was restricted to the 5, 10 and 20 mg total daily dose groups, which had been previously identified for further investigation based on their efficacy and safety outcomes (10, 11). The assessment of how rivaroxaban plasma concentrations correlated with PT was conducted separately for each study, using data from all rivaroxaban dose groups.

The non-linear mixed-effects population modelling approach used in this study was similar to that used in the modelling of population PK and PD from phase I studies of rivaroxaban (16). The analysis was performed using NONMEM Version V level 1.1 (GloboMax LLC, Hanover, MD, USA), running on a validated Linux server farm environment (Linux SuSE Enterprise Server 8; Fortran compiler G77 version 3.2.2), as described previously (16). This modelling technique allows the estimation of population means for the PK and PK/PD models and quantifies both inter-individual and inter-occasion variability (IIV and IOV, respectively) in these parameters, as well as residual (unexplained) variability. The first-order conditional esti-

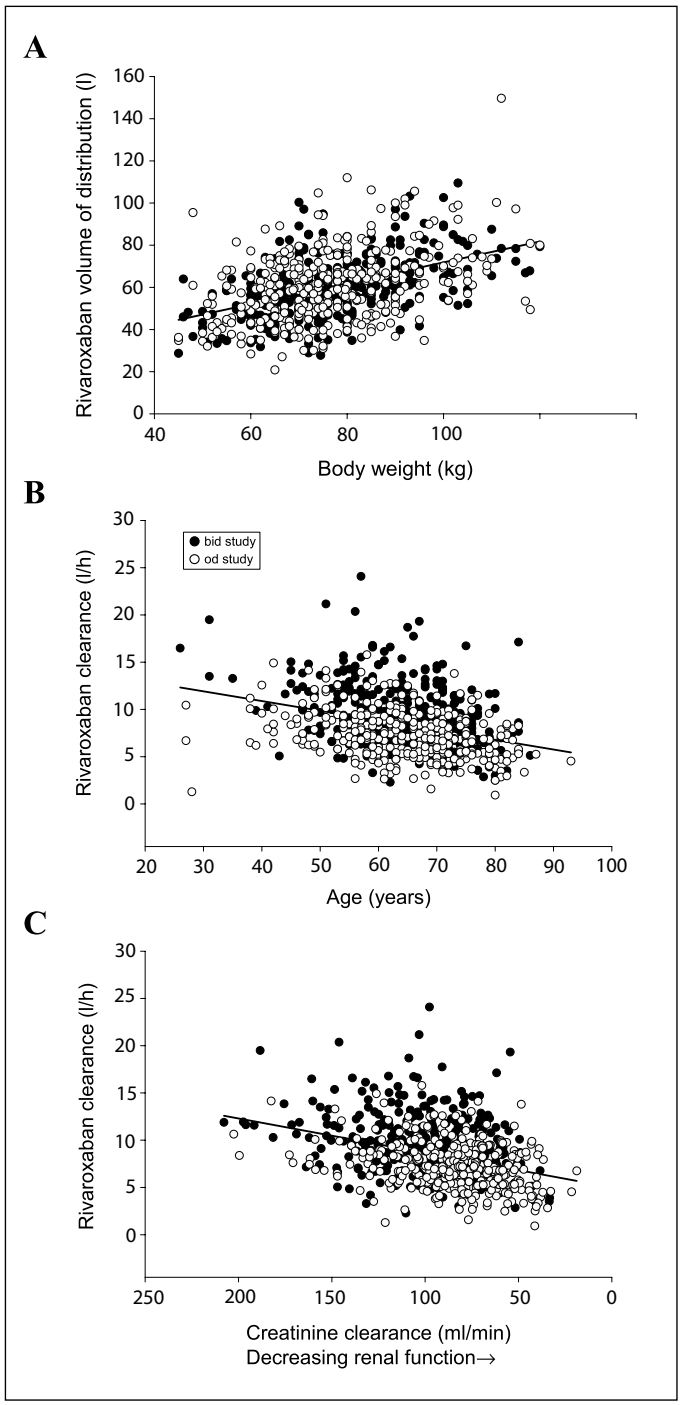

Figure 2: Relationship between rivaroxaban and demographic factors with regression lines of model approximates in the pooled twice-daily and once-daily studies. A) Rivaroxaban volume of distribution versus body weight, B) rivaroxaban clearance versus patient age, C) rivaroxaban clearance versus calculated creatinine clearance.

mation algorithm with interaction (FOCE with η-ε interaction) was used for all analyses. Additional statistics and graphs were generated using S-Plus version 5.1 (Insightful Corp., Seattle, WA, USA) or SAS version 8.2 software (SAS Institute Inc., Cary, NC, USA).

In addition to scientific plausibility based on all previous project knowledge, model evaluation included graphical inspection of basic goodness-of-fit plots, the objective function value (OFV) and the precision of parameter estimates. The main tool used for selection between models was their difference in the OFV: model components were incorporated into the model if the likelihood ratio (LR) test showed significance at a level of p=0.01 (change in OFV >6.63); model components remained in the model when, after backwards stripping from the full model, the LR test showed significance at a critical level of p=0.001 (change in OFV >10.8) (17).

Due to the sparse sampling approach, an oral, one-compartment model was used as PK model, parameterized in terms of apparent oral clearance (CL/F), volume of distribution (Vd/F) and a first-order absorption rate constant (k_a). The structural PK/PD models tested for the PT and FXa activity were direct-effect linear intercept or general maximum effect models (16). Exponential models described in previous population PK/PD studies of rivaroxaban were used to account for IIV in structural parameters (17).

A stepwise model-building procedure used in previous population PK/PD studies of rivaroxaban, including forward inclusion and backward deletion at respective increasing significance levels of p<0.01 and p<0.001, was used to identify covariate–parameter relationships. The potential influence of the prospectively defined covariates was implemented as present/absent (categorical) or as local linear functions (continuous variables), with only the parameter resulting in the most significant change in the OFV being kept in cases of closely related covariates (e.g. weight, body surface area [BSA] and lean body mass [LBM]) (17). Predefined covariates investigated for the influence on both PK and PK/PD structural models were the effect of time (day post-surgery), dosage, food status and the patient covariates of age, body weight, height, BSA, LBM, body fat, gender, serum creatinine concentration, creatinine clearance (calculated according to the Cockcroft–Gault formula [18]), serum albumin, haematocrit, haemoglobin and selected concomitant medications (including benzodiazepines, diuretics, NSAIDs, opioids and drugs that accelerate gastrointestinal passage). The final PK model was used to estimate full PK profiles over the course of the study for all patients, allowing the calculation of specific exposure parameters, such as the maximum and minimum plasma concentrations (C_{max} and C_{trough}, respectively) within the dosing interval and the area under the plasma concentration–time curve over 24 hours ($AUC_{0–24}$), for each patient; descriptive statistics were then calculated. In addition, simulations were performed to study the influence of specific patient covariates on rivaroxaban exposure and for validation purposes (17).

Results

Patients and samples

In total, 758 patients from the rivaroxaban 5–20 mg total daily dose groups provided 5743 samples for the pooled PK analysis (362 patients from the bid study and 396 patients from the od study). Patient demographics were similar in both study populations, allowing the pooling of PK data (Table 1). A total of 4849 PT measurements were obtained from all 516 eligible patients in

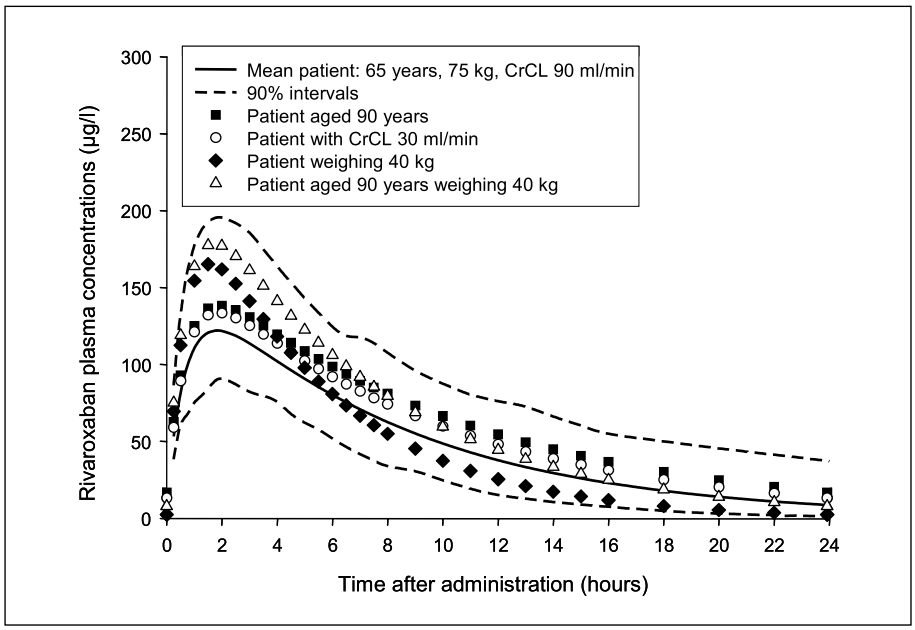

Figure 3: Simulations of rivaroxaban plasma concentrations in typical patients who are elderly, have moderate-to-severe renal impairment (assessed via calculated creatinine clearance), have low body weight, and are elderly with low body weight receiving rivaroxaban 10 mg once daily, in comparison to the estimated exposure range of the overall population (mean with 90% interval). CrCL, creatinine clearance.

the bid study and 5618 PT measurements were obtained from all 665 eligible patients in the od study.

Rivaroxaban pharmacokinetic model

Pharmacokinetics of rivaroxaban

An oral, one-compartment model with parameters described in terms of first-order absorption rate constant, Vd/F and CL/F was found to describe the PK of rivaroxaban well, with both bid and od dosing, in patients undergoing THR (Table 2). Rivaroxaban mean CL/F was 5.5 l/h on the day after surgery, increasing to 7.5 l/h at steady state; rivaroxaban Vd/F was 58 l.

The PK of rivaroxaban were more variable on the first two post-operative days than at steady state with both bid and od dosing, especially in the absorption phase (Fig. 1), as reflected in the variability of the absorption rate constant. The IIV for rivaroxaban CL/F was 38.2% and was not affected by the study day after day 2; the IIV for rivaroxaban Vd/F of distribution was 32.4%. Overall residual variability of the model was moderate (52.6%).

Influence of demographic factors on the pharmacokinetics of rivaroxaban

Rivaroxaban volume of distribution was affected by body weight (expressed as BSA in the final model). Rivaroxaban CL was affected by the study day, age, renal function, serum albumin and haematocrit (Fig. 2 and Table 3). However, the average influence of these factors was within the variability of the studied patient population. Gender did not affect the PK of rivaroxaban.

Simulations of rivaroxaban plasma concentration–time profiles after a 10 mg od dose were performed to represent typical patients with extreme demographic characteristics (aged 90

Table 3: Influence of demographic factors on the pharmacokinetics of rivaroxaban in patients undergoing elective total hip replacement (N=758).

	Affected PK parameter	Effect	Example*
Study day	CL	Mean CL of 5.46 l/h on the first post-operative day, increasing to 7.51 l/h at steady state	Not applicable
Age	CL	Decrease of 1.0% per year older than the median of 66 years (and vice versa)	Approximately 24% higher exposure in a 90-year-old patient
Renal function	CL	Decrease of 0.3% per 1 ml/min less than the median calculated creatinine clearance of 88.1 ml/min (and vice versa)	Approximately 17% higher exposure in a moderately renally impaired patient with a calculated creatinine clearance of 30 ml/min
Serum albumin	CL	Decrease of 2.2% per 0.1 g/dl less than the median of 3.4 g/dl (and vice versa)	Approximately 31% higher exposure in a patient with a serum albumin concentration of 2 g/dl
Haematocrit	CL	Decrease of 1.2% per 1% haematocrit less than the median of 37.3% (and vice versa)	Approximately 15% higher exposure in a patient with a haematocrit of 25%
Body weight†	Vd	Decrease of 6.4% per 0.1 m^2 below the median body surface area of 1.84 m^2 (and vice versa)	Approximately 32% higher exposure in a patient with a body surface area of 1.3 m^2

CL, clearance; Vd, volume of distribution. *Based on min/max values in the study population. †Expressed as body surface area.

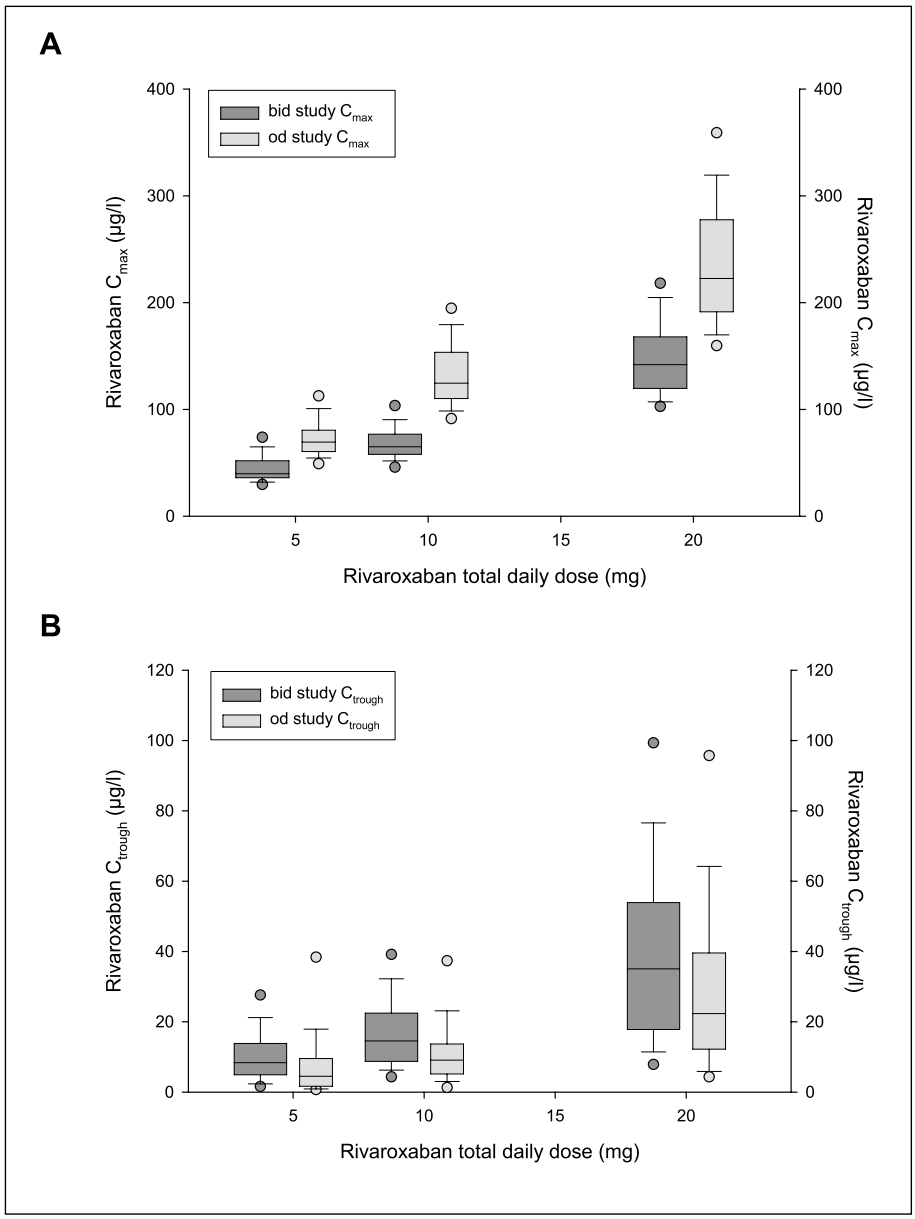

Figure 4: Box–whisker plots showing rivaroxaban A) maximum (C_{max}) and B) minimum (C_{trough}) plasma concentrations in the twice-daily and once-daily studies, with 25th and 75th percentiles (horizontal lines) and 5th and 95th percentiles (circles).

years; with moderate-to-severe renal impairment [CrCL of 30 ml/min]; underweight [40 kg]; and 90 years old and underweight) at the upper and lower limits of the studied population to provide further insights into the expected average influence of these covariates on rivaroxaban exposure. The predicted plasma concentrations of rivaroxaban 10 mg od for each typical 'extreme' individual in each of the four demographic groups were plotted for comparison alongside the plasma concentrations for the average population. Plasma concentration–time profiles for each simulated typical 'extreme' patient fell within the predicted 90% confidence intervals of the average patient in these studies (Fig. 3).

Pharmacokinetic parameters of rivaroxaban

The C_{max} and C_{trough} of rivaroxaban increased in a dose-dependent manner with both dosing regimens up to 20 mg (total daily doses). When total daily doses were compared, C_{max} was consistently higher, and C_{trough} consistently lower in patients receiving rivaroxaban od than in patients receiving rivaroxaban bid. However, the 90% intervals for C_{max} and C_{trough} overlapped between the two dosing regimens (Fig. 4).

The steady-state $AUC_{0–24}$ of rivaroxaban was higher in the od study than the bid study: after total daily doses of 5, 10 and 20 mg, the $AUC_{0–24}$ values with od dosing were 27%, 30% and 18% higher, respectively, compared with bid dosing (Table 4).

Pharmacokinetics / pharmacodynamics: Correlation between prothrombin time and rivaroxaban concentrations

In both studies, baseline PT was prolonged for two to three days after surgery in patients receiving rivaroxaban; this was also observed in patients receiving enoxaparin (which does not affect PT). As a result, model components describing recovery of clotting factors to pre-surgery levels over time were

factored into the baseline of the PD model, as described previously (17).

In the PK/PD models of both the bid and od study data, prolongation of PT correlated strongly with plasma rivaroxaban concentrations. This correlation followed a simple, linear intercept model. However, there was a difference in the gradient of the slope between the two studies; 3.2 seconds/(100 µg/l) in the bid study and 0.8 seconds/(100 µg/l) in the od study (Fig. 5).

Discussion

This pooled population analysis showed that the PK of rivaroxaban in patients undergoing THR were adequately described by an oral, one-compartment model when given either bid or od. PK parameters were affected by the dosing regimen; however, there were no significant differences between bid or od dosing regimens in terms of C_{max} or C_{trough}. With both the bid and od dosing regimens, rivaroxaban plasma concentrations correlated closely with PT in a simple, linear fashion.

An oral, one-compartment model with first-order elimination, generated using pooled data from the bid and od studies, was found to describe the PK of rivaroxaban well when given either bid or od, indicating that the PK of rivaroxaban were predictable. The model was influenced by study day, renal function, age, serum albumin levels, haematocrit and body weight. Although age-related decrease in renal function is the main factor for the exposure increase, age itself also affects rivaroxaban CL. This was to be expected for a drug that has a dual mode of excretion, with one-third of the active drug eliminated renally as unchanged drug and two-thirds metabolized by the liver (19). Indeed, age-related decline affects not only renal function (20), but also liver blood flow and liver activity (21). However, the average influence of these factors on the model was moderate and within the inherent inter-individual variability of the population.

The model was used to estimate rivaroxaban plasma concentration–time profiles for the different doses in both studies. These showed that plasma concentrations of rivaroxaban increased in a dose-dependent manner up to a dose of 20 mg, confirming the predictability of rivaroxaban PK observed in phase I studies (6, 22). Previous evaluations in patients undergoing THR and TKR have shown slight deviations from linearity at higher doses (23).

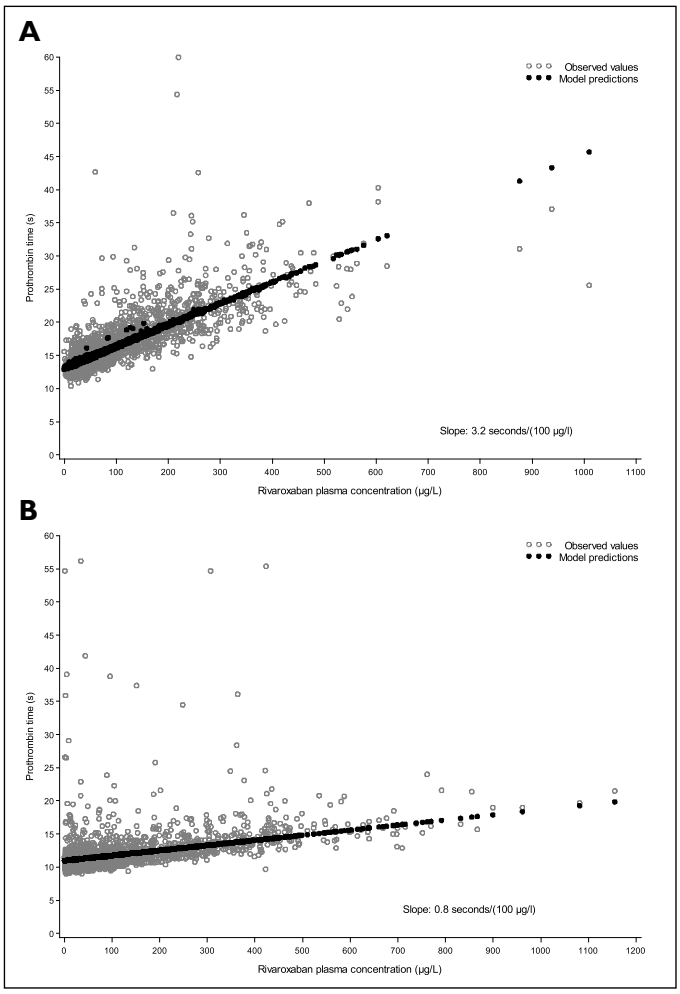

Figure 5: Correlation between rivaroxaban plasma concentration and prolongation of prothrombin time at steady state (3–4 days) in the twice-daily study (A), and in the once-daily study (B), employing different prothrombin time reagents in the assay.

Factors affecting the PK of rivaroxaban were as expected for an oral drug that undergoes a dual mode of elimination, i.e. biotransformation in the liver with no major or active circulating metabolites and renal excretion (19). Rivaroxaban clearance was

Table 4: Median predicted rivaroxaban pharmacokinetic parameters in patients undergoing total hip replacement after 5 days' rivaroxaban dosing, with 5/95 percentile range.

Parameter		Rivaroxaban total daily dose					
			5 mg		10 mg		20 mg
n, bid/od			114/118		114/135		109/131
C_{max}, µg/l	bid	39.8	(29.5–74.0)	64.9	(45.8–105.4)	141.9	(102.7–218.2)
	od	69.3	(49.0–112.9)	124.6	(91.4–195.5)	222.6	(159.6–359.8)
C_{trough}, µg/l	bid	8.4	(1.6–27.9)	14.6	(4.2–39.2)	35.1	(7.9–99.7)
	od	4.5	(0.7–38.8)	9.1	(1.3–37.6)	22.3	(4.3–95.7)
$AUC_{0–24}$, µg·h/l	bid	530.5	(303.6–1286.6)	902.1	(577.2–1636.8)	2009.8	(1138.8–3756.9)
	od	672.5	(372.5–1602.7)	1170.0	(771.5–2118.2)	2373.7	(1365.9–4857.5)

$AUC_{0–24}$, area under the plasma concentration–time curve over 24 hours at steady state; bid, twice daily; C_{max}, maximum plasma concentration; C_{trough}, minimum plasma concentration; od, once daily.

reduced with increasing age. This has been observed previously in healthy elderly subjects, and is partially due to reduced renal clearance (7), which is supported by the finding in this analysis that renal function affected rivaroxaban CL. Therefore, in this study, increased age and decreased renal clearance both led to a decrease in rivaroxaban CL. The effect of renal function has also been examined in a phase I study in otherwise healthy subjects: renal impairment delayed the elimination of rivaroxaban (resulting in an increase in AUC), but did not significantly increase the maximum effect of the drug (C_{max} was unchanged) (24). Serum albumin is the most abundant protein in mammalian blood; it is largely responsible for plasma osmotic pressure and carries many hormones and drugs (25). Rivaroxaban has been shown to bind to albumin (26); therefore, changes in serum albumin levels could be expected to influence the PK of rivaroxaban. Haematocrit is the percentage of red cells in the blood. A reduction in haematocrit is an indication of blood loss and, therefore, a decrease in blood volume, which may also influence the PK of rivaroxaban. Increases in body weight (referred to in this investigation as BSA) affected the volume of distribution of rivaroxaban, which is expected because larger individuals will have a larger body volume. However, the influences of all these factors were moderate and, on average, within the variability of the predicted population PK, indicating that fixed dosing of rivaroxaban may be possible with no restrictions for patient demographic factors.

Simulations showed that plasma concentrations of a 10 mg od dose of rivaroxaban in typical patients with 'extreme' demographic characteristics were within the variability range confidence interval of the average patient, suggesting that at this dose all these influencing factors should not lead to significant alterations in rivaroxaban exposure. For example, a simulation of an underweight 90-year-old patient was used to demonstrate the effects of age on clearance, and the decrease in BSA with reduced weight, resulting in a patient with both prolonged elimination and an increased C_{max} of rivaroxaban. These simulations of patients receiving rivaroxaban 10 mg od were similar to those of patients receiving rivaroxaban 5 mg bid (27), suggesting that either regimen could be used and that the same total daily dose may be suitable for all patients. Because of the convenience of once-daily dosing, rivaroxaban 10 mg od may be the preferred option.

The C_{max} of rivaroxaban increased dose dependently in both studies; however, it was consistently higher in the od study compared with the bid study for all doses. This was expected, due to the larger amount of rivaroxaban administered at time of intake in the od study compared with the bid study. The C_{trough} of rivaroxaban was lower in patients receiving the od regimen compared with patients receiving the bid regimen. This was also expected due to the longer time interval between doses. Although there were differences in the C_{max} and C_{trough} values between the bid and od dosing regimens, the 90% intervals overlapped, suggesting that od dosing of rivaroxaban should not carry a greater risk of VTE or bleeding than bid dosing. This was confirmed by the clinical results from the two phase IIb dose-ranging studies (11, 12). In the current study, the AUC was also 18–30% higher in patients receiving the od regimen than the bid regimen. This effect is likely to be a result of the sparse sampling schedule, which was optimized for bid dosing, or the slight demographic differences between the study populations.

Rivaroxaban plasma concentrations correlated in a linear fashion with PT (measured in seconds), as described previously (16, 17), further illustrating the predictability of the drug, and suggesting that this might be an appropriate test to measure rivaroxaban exposure, if necessary. However, the gradient of the slopes differed between the bid and od studies. This was likely to be due to the difference in the PT reagents used in the studies, which, in addition, had different ISI values. Furthermore, the effects of these targeted inhibitors on PT are different from those of non-specific vitamin K antagonists (28, 29), and potential consequences for direct FXa inhibitors such as rivaroxaban warrant further investigations.

The bid dose-ranging study of rivaroxaban suggested that a total daily dose range of 5–20 mg had similar efficacy and safety to enoxaparin, and the od rivaroxaban study identified a 10 mg od dose within this range as suitable for further investigation (11, 12). The current investigation demonstrated that, in addition to providing greater convenience, a 10 mg od dose should not put patients at an increased risk of either VTE or major bleeding compared with a 5 mg bid dose, supporting the selection of the 10 mg od dose for further investigation. Four phase III trials (the RECORD programme) have investigated rivaroxaban 10 mg od for thromboprophylaxis in patients undergoing major orthopaedic surgery, demonstrating the superior efficacy of this dose of rivaroxaban over enoxaparin 40 mg od (13–15).

In conclusion, the PK and PD of rivaroxaban were predictable and consistent in patients receiving it for VTE prevention after THR, whether administered bid or od. The influence of demographic factors on the PK of rivaroxaban was moderate and, on average, within the variability of the overall patient population. Simulations of typical patients with extreme demographics indicated that a fixed rivaroxaban 10 mg od dose should be possible in these patients and supported the selection of this convenient, fixed dosing regimen for further investigation in phase III clinical trials.

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