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Fixed dose rivaroxaban can be used in extremes of bodyweight: a population pharmacokinetic analysis

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Abstract

Background

Emerging safety and efficacy data for rivaroxaban suggest traditional therapy and rivaroxaban are comparable in the morbidly obese. However, real-world data that indicate pharmacokinetic (PK) parameters are comparable at the extremes of body size are lacking. The International Society of Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) suggests avoiding the use of DOACs in patients weighing >120kg or with a BMI >40kg/m^2 and gives no recommendation on the use of DOACs in those <50kg.

Objectives

To generate a population PK model to understand the influence of bodyweight on rivaroxaban exposure from clinical practice data.

Method

Rivaroxaban plasma concentrations and patient characteristics were collated between 2013 and 2018 at King's College Hospital anticoagulation clinic. A population PK model was developed using a non-linear mixed effects approach and then used to simulate rivaroxaban concentrations at the extremes of bodyweight.

Results

A robust population PK model derived from 913 patients weighing between 39kg and 172kg was developed. The model included data from n=86 >120kg, n=74 BMI >40kg/m^2 and n=30 <50kg. A one-compartment model with between-subject variability on clearance and a proportional error model best described the data. Creatinine clearance calculated by Cockcroft-Gault, with lean bodyweight as the weight descriptor in this equation, was the most significant covariate influencing rivaroxaban exposure.

Conclusions

Our work demonstrates rivaroxaban can be used at extremes of bodyweight provided renal function is satisfactory. We recommend that the ISTH SSC revises the current guidance with respect to rivaroxaban at extremes of body size.

Essentials

- Evidence to support the use of rivaroxaban at extremes of body weight is limited.
- A population pharmacokinetic model for rivaroxaban was derived from clinic practice data.
- Renal function is the most important factor to be considered when prescribing rivaroxaban.
- Rivaroxaban can be used at extremes of bodyweight provided renal function is satisfactory.

Keywords

Anticoagulants

Body weight

Drug Monitoring

Pharmacokinetics

Rivaroxaban

Introduction

The direct oral anticoagulants (DOACs) are increasingly prescribed for the prevention and treatment of venous thromboembolism (VTE) and for stroke prophylaxis in the context of atrial fibrillation (AF).[1] DOACs are at least as safe and effective as vitamin K antagonists for these indications, both in controlled phase III studies and post-marketing real-world studies.[2-5] However, a commonly encountered question in clinical practice is whether DOACs are safe and effective in those at the extremes of weight: <50kg and >120kg. The clinical trials of these agents did not have sufficiently large numbers of patients in the extremes of weight categories to be able to conclude that this would be the case.

Evidence from traditional anticoagulants suggests that bodyweight does impact on the dose required.[6] For example, low-molecular-weight heparin is dosed on a IU/kg basis for the acute management of VTE [7-9] and it is widely recognised that the maintenance dose of warfarin is higher in those of a higher bodyweight.[10,11] It is therefore intuitive to expect the same to be true for the DOACs.

Rivaroxaban was the first DOAC to be licensed in the European Union for treatment of VTE and the first factor Xa inhibitor to be licensed for the prevention of stroke in AF. Despite its widespread use clinicians have been cautious when prescribing rivaroxaban in patients at extremes of bodyweight, due to concern that these patients may have appreciable differences in their pharmacokinetic parameters which may impact on overall drug exposure and clinical outcomes.[12] The manufacturer of rivaroxaban states, 'in patients who are at the extremes of weight, only a small influence of weight on patients' rivaroxaban plasma concentrations (<25%) is observed and no dose adjustment is necessary'.[13] However, these recommendations are based on either small pharmacokinetic studies or work derived from the phase III clinical trials for rivaroxaban, with insufficient numbers of patients at the extremes of weight to allay clinicians' concerns.

In 2016 the International Society of Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) published guidance, and made the following recommendations [12] : (i)to use

appropriate standard dosing of DOACs in patients up to 40 kg/m^2 or weight <120kg for VTE prevention and treatment and prevention of ischemic stroke and systemic arterial embolism in AF, (ii)not to use DOACs in patients with a BMI >40 kg/m^2 or weight >120 kg due to limited data and available pharmacokinetic/ pharmacodynamic (PK/PD) evidence suggesting decreased drug exposure, peak concentration, and shorter elimination half- lives with increasing weight, and (iii)if DOACs are used in patients with a BMI >40 kg/m^2 or weight >120 kg, then to check a drug- specific peak and trough level. If the drug level is reported back within the expected range, continuation of the DOAC seems reasonable. No guidance is provided for patients with weight <50 kg.

Real-world clinic population data have focused on outcomes, with most emerging data focused on high bodyweight. EINSTEIN and Xalia investigators comparing rivaroxaban and enoxaparin/warfarin found no difference between treatment arms in the rate of VTE recurrence amongst obese patients.[14,15] This has also been observed in prospective registry data and large retrospective data from the United States (US).[16-18]

Conversely, outcome data for patients <50kg are limited to a subgroup analysis of the so-called fragile patients of the EINSTEIN pooled data and observational studies.[15,19] Reflecting current practice, the Registro Informatizado Enfermedad Trombo Embólica (RIETE) registry has described a tendency toward traditional anticoagulation therapies in this subgroup.[19]

Barsam and colleagues have previously derived a population PK model from 101 clinic patients, which suggested that bodyweight on its own was not a significant predictor of rivaroxaban PK. However, the work was limited by the number of samples from patients in the extremes of weight categories.[20] We now present a full population PK model developed from a large number of patients attending our anticoagulation clinics. The aim was to develop a population PK model which would address the question of whether bodyweight matters when rivaroxaban is prescribed at fixed doses.

Methods

Study Population

Data were collected from King's College Hospital Foundation NHS Trust, in South East London. Comprising two main sites, the hospital cares for an ethnically diverse, inner-city population, as well as an older adult population of Northern European descent. DOAC use began in the anticoagulation clinics during the summer of 2012, when dabigatran became available, followed by rivaroxaban in early 2013. In order to confirm the applicability of fixed dosing to all patients and gain a better understanding of the possible factors influencing drug exposure, it was standard practice locally to measure a DOAC plasma concentration during the early years of DOAC prescribing. For the purpose of this study we have retrospectively assimilated the plasma concentration data for patients prescribed rivaroxaban between June 1, 2013 – September 21, 2018. The patients included in this study were attending the anticoagulation clinic as part of routine follow up, predominantly for the prevention of stroke due to AF and the acute treatment and secondary prevention of VTE. Case notes were reviewed, with patient characteristics (age, weight, height, indication for anticoagulation, history of heart failure) and laboratory results (creatinine, bilirubin, albumin, rivaroxaban plasma concentration) collated for analysis. Creatinine clearance (CRCL) was calculated for each patient using the Cockcroft-Gault (CG) equation.[21] For the purposes of this study, this was computed using both total bodyweight and lean bodyweight in order to understand which weight descriptor was optimal (Calculations described in the Supplemental Material).[22] All subjects were eligible if they had a rivaroxaban sample drawn and a patient reported time of last dose recorded on their blood test form and/or electronic DAWN® record (anticoagulation software system).[23] Sample times for the rivaroxaban plasma concentrations were not pre-specified.

One hundred and one (11%) patients have been previously described by our group, from which an early PK model was developed and are also included in this dataset.[20] The data for these patients were collected specifically for the research being undertaken between June 1, 2013- April 30, 2014 from our hospital for patients prescribed rivaroxaban for VTE treatment and primary prevention following orthopaedic surgery.[20]

Ethics

Since rivaroxaban samples were collected as standard of care, no ethical approval was required. Samples from Barsam's study were collected with ethical approval by the London Harrow Ethics Committee, REC reference number: 12/LO/1951 as well as the King's College Hospital Research and Development Department.[20]

Assaying the Rivaroxaban Plasma Concentration

An anti-Xa activity assay (Diagnostica Stago, Asnières-sur-Seine, France), was used to characterise the rivaroxaban plasma concentration. Following sample collection, it was centrifuged in a Rotina 420 R centrifuge (Hettich Zentrifugen), double spun for 7 minutes at 2500 g and frozen within 1 hour of sample collection. The samples were stored at −40°C until analysed on the STA-R evolution analyser (Diagnostica Stago) in the laboratory at King's College Hospital within 4 weeks. The lower and upper limits of quantification (LLOQ/ULOQ) for this assay were 20ng/mL and 500ng/mL, respectively. This anti-Xa assay has previously been shown to correlate well when the same samples were assayed using turbulent flow liquid chromatography with high-resolution mass spectrometry.[24]

Population Pharmacokinetic Modelling

Population PK modelling uses data from all subjects simultaneously to characterise the concentration time-course of a drug for both the population and the individual subjects. Central tendency is used to estimate population PK parameters. The approach is recommended by both the US Food and Drug Administration and the European Medicines Agency during the drug development process and also works well in a clinical environment, where the data can be sparse.[25,26] Population PK modelling combines a mathematical and statistical approach to characterise a complex biological system. A mathematical model is used to generate population estimates for parameters such as apparent volume of distribution (Vd/F) and apparent clearance (CL/F). These estimated population values are termed the fixed effects. A statistical model describes the random effects. The statistical model aims to

describe the variance between and within individuals and to estimate residual unexplained variability (the error model). A covariate analysis is then executed to explain between-subject variability.

Population PK is commonly utilised by the pharmaceutical industry to determine optimal dosing of drugs and is also used by researchers in the clinical setting. For example, population PK analysis has previously provided compelling evidence that enoxaparin could be administered once daily during the ante-natal period for the treatment of VTE.[27]

Rivaroxaban Population Pharmacokinetic Model Building

To develop a base model, rivaroxaban plasma concentration data were explored by applying one-and two-compartment models, with a first order input parameter. On review of the literature, two compartmental models have been described in healthy volunteers and in the paediatric setting, but they have not been successfully replicated from more sparse data.[28]

Competing base models were assessed by statistical improvements in the fit of the model according to the objective function value (OFV) (computed as minus twice the log-likelihood of the data), goodness of fit plots, assessment of the precision of the parameter estimates and residual variability. Initially a first order conditional estimation with interaction method was used. The importance of sampling method was included to review the standard errors for the precision of parameter estimates. Using these criteria, a base model was identified.

A proportion of the observed rivaroxaban concentrations was reported as ULOQ and LLOQ (46 samples, 4.2% ULOQ and 28 samples, 2.5% LLOQ). Observations reported as ULOQ were accounted for using Beal's M3 likelihood estimation and observations reported as LLOQ were fixed to half the LLOQ (10ng/mL) (M5 method).[29]

Only covariates with mechanistic meaning were considered for analysis; age, gender, total bodyweight (TBW), lean bodyweight (LBW), creatinine, albumin, bilirubin, creatinine clearance

TBW (CRCLTBW), creatinine clearance LBW (CRCLLBW), diagnosis of AF and a diagnosis of heart failure.[21,22] Covariates were initially plotted against the PK parameters random effects to identify relevant trends. Selected covariates were then added in a univariate stepwise approach to the base model. Covariates were retained if a decrease in the objective function value of >6.64 ($p<0.01$) was seen. A backwards elimination was then executed, whereby all covariates that had been identified as significant were added to the base model and removed singularly to evaluate their continued relevance. The covariate was considered to have continued relevance if the increase in objective function was greater than >10.83 ($p< 0.001$). A nonparametric 1000 replicate bootstrap procedure was carried out on both the base and final covariate models. To evaluate the final model, a visual predictive check (VPC) was generated. The VPC shows the 5^{th}, 50^{th} and 95^{th} prediction intervals, simulated from the final model parameter estimates, overlaid with the 5^{th},50^{th} and 95^{th} percentiles from the observed data. A well-performing model would see the simulated data superimposed on the observed data.

Finally, a 1000-replicate simulation was performed from the final model to estimate rivaroxaban concentration-time profiles based on patients at extremes of bodyweight and for those with varying degrees of renal impairment. Simulation data were then used to estimate area under the curve (AUC) and maximum concentration (Cmax) using PKNCA in R.[30] AUC and Cmax derived from the model were compared with those described in the literature.

NONMEM version 7.4.2 was used for modelling and simulation, using both the first-order conditional estimation with interaction and the Laplacian estimation method (when M3 method applied to ULOQ data).[31] Perl Speaks NONMEM (version 4·8·1) (PsN), and R Studio (version 3.6.0) were used for graphical analysis, model diagnostics and for statistical summaries.[32,33] PKNCA (version 0·9·1)was used to generate and describe simulation data.[30]

Results

A total of 913 patients contributed 1108 rivaroxaban plasma concentrations, 193 (17%) from the previous Barsam model and 915 (83%) samples from routine care in the anticoagulation clinic. The mean number of samples per patient was 1.21 (range 1-6). The characteristics of the 913 patients are outlined in Table 1.

Table 1. Patient characteristics and indications for anticoagulation (n=913)

Patient Characteristic	N	%
Gender (%)		
Female	391	42.8
Male	522	57.2
Age (mean [SD])*	67.03 [15.00]	
Weight (kg) (mean [SD])*	85.75 [23.07]	
Weight (kg)		
<50	30	3.3
50-100	668	73.2
100-120	129	14.1
>120	86	9.4
Lean body weight, kg (mean [SD])	55.80 [13.10]	
Creatinine (umol/L) (mean [SD])	86.73 [27.57]	
BMI, kg/m^2 (mean [SD])*	29.67 [7.01]	
BMI, kg/m^2 categories (%)		

Underweight	<18.5	19	2.1
Normal	18.5-25	231	25.3
Overweight	25-30	282	30.9
Obese (Class I)	30-35	185	20.3
Obese (Class II)	35-40	122	13.4
Obese (Class III)	>40	74	8.1
CRCLTBW, ml/min (mean [SD])*		91.47 [43.81]	
CRCLTBW, ml/min (%)			
<30		20	2.2
30-50		132	14.5
50-90		358	39.2
>90		403	44.1
CRCLLBW, ml/min (mean [SD])		59.51 [26.71]	
CRCLLBW, ml/min (%)			
<30		128	14.0
30-50		255	27.9
50-90		399	43.7
>90		131	14.3
Indication for anticoagulation (%)			
Atrial Fibrillation		629	68.9
	20mg once daily	476	75.6
	15mg once daily	151	24
	Other†	2	0.3
VTE		267	29.2
	15mg twice daily	71	26.6
	20mg once daily	171	64.0
	15mg once daily	15	5.6

	10mg once daily	7	2.6
	Other†	3	1.1
Other‡		17	1.9
	20mg once daily	11	64.7
	15mg once daily	5	29.4
	10mg once daily	1	5.9

Abbreviations: BMI, Body mass index, CRCLLBW, Creatinine clearance calculated using lean bodyweight; CRCLTBW, Creatinine clearance calculated using total bodyweight; LBW, lean bodyweight; SD, standard deviation; TBW, total bodyweight; VTE, venous thromboembolism * Patient characteristic range; Age 19-96 years, weight 39-172kg, body mass index 16-56 kg/m^2, and creatinine clearance 16- 259ml/min. †Alternative doses, 30mg once daily (x1) and 10mg twice daily (x4) ‡ Other indications for anticoagulation – Left ventricular thrombus, cardioembolic stroke of unknown aetiology

Figure 1a describes the breadth of samples in relation to the time after dose and Figure 1b illustrates the range of rivaroxaban samples taken from patients according to bodyweight, with those falling outside the ISTH SSC guideline range highlighted. Figure 1c illustrates the frequency distribution of total bodyweight.

Pharmacokinetic Model Development

One- and two-compartment models with different inter-individual variability and residual unexplained variability were evaluated. A one-compartment model parameterised in terms of CL/F, Vd/F and a first-order absorption rate constant (Ka) with inter-individual variability on CL/F and a proportional error model, was the best performing base model. The estimation of CL/F was not normally distributed and so a Box-Cox transformation was applied. Dose was explored on relative bioavailability (F) as previously described in the literature, [28,34] although this did not improve the fit of the model to the data and caused model instability.

The results from the 1000 bootstrap procedure demonstrated that the median and confidence interval estimates were in alignment with estimates derived from the base model (Supplemental Material).

Following the development of the base model, a covariate analysis was conducted. Gender, age, TBW, LBW, albumin, bilirubin, creatinine, creatinine clearance, calculated with the CG equation using TBW and LBW, the diagnosis of AF or a documented diagnosis of heart failure were explored on CL/F. Additionally, gender, age, TBW, LBW, albumin, and the diagnosis of AF or a documented diagnosis of heart failure were explored on Vd/F (Table 2).

Table 2. Univariate covariate analysis

Model	Covariate	Covariate Relationship	ΔOBV
1_002	$CL/F*(CRCLLBW/55)^{0.396}$	Power	-169.376
1_032	CRCLLBW on CL/F	Emax	-161.098
1_001	$CL/F*(CRCLTBW/84)^{0.353}$	Power	-143.138
1_032	$CL/F*(AGE/67)^{-0.524}$	Power	-99.572
1_011	$CL/F*(LBW/55)^{0.468}$	Power	-52.420
1_007	$CL/F*(AF)^{0.808}$	Proportional change	-44.510
1_012	$CL/F*(CR/82)^{-0.337}$	Power	-40.973
1_010	$CL/F*(TBW/84)^{0.331}$	Power	-32.310
1_008	$CL/F*(HF)^{0.804}$	Proportional change	-28.016
1_006	$CL/F*(SEX)^{0.873}$	Proportional change	-19.322
1_004	$CL/F*(ALBU/42)^{0.708}$	Power	-13.815
1_003	$CL/F*(BMI/29)^{0.153}$	Power	-5.481
1_005	$CL/F*(BILI/9)^{-0.1}$	Power	0.631
1_019	$Vd/F*(AGE/67)^{0.384}$	Power	-15.331
1_025	$Vd/F*(AF)^{1.2}$	Proportional change	-10.282
1_024	$Vd/F*(HF)^{1.19}$	Proportional change	-5.249
1_018	$Vd/F*(ALBU/42)^{—0.705}$	Power	-3.881
1_026	$Vd/F*(BILI/9)^{0.106}$	Power	-2.897
1_021	$Vd/F*(LBW/55)^{-0.085}$	Power	-0.534
1_020	$Vd/F*(TBW/84)^{-0.0739}$	Power	-0.506
1_022	$Vd/F*(BMI/29)^{-0.0141}$	Power	-0.021
1_023	$Vd/F*(SEX)^{0.994}$	Proportional change	-0.017

ΔOBV represents the change from the basemodel objective function value with the addition of a covariate. All models minimised successfully. Gender, a diagnosis of heart failure (HF) and a diagnosis of atrial fibrillation (AF) were modelled as proportional change, with 'female', the

presence of AF and HF as the factors=1. Abbreviations: AF, atrial fibrillation; ALBU, albumin; BILI, bilirubin; BMI, body mass index; CL/F, Apparent clearance, CRCLLBW, Creatinine clearance calculated using lean bodyweight; CRCLTBW Creatinine clearance calculated using total bodyweight, CR, creatinine; HF, heart failure; LBW, lean bodyweight, TBW, total bodyweight; Vd/F, Apparent volume of distribution.

The covariate which improved the performance of the model to the greatest extent was CRCLLBW. Age, creatinine, LBW, TBW and gender were not investigated further on CL/F as they are included within the CG equation, thus confounding their influence. In the literature, bodyweight had shown to be a significant covariate on Vd/F, so this was added in addition to CRCLLBW on CL/F and the objective function showed a marked improvement (ΔOBJ function -21.92).[28] Age and AF on Vd/F were found to improve the objective function during the univariate analysis. However, during the backwards elimination they were no longer found to be significant influential covariates and were not investigated further. CRCLLBW on CL/F and LBW on Vd/F were included as significant covariates in the final model.

Final Model

The final model described the observed data well. Goodness of fit plots (Supplemental Material), displaying observed and individual predicted rivaroxaban concentrations, showed a trend consistent with the line of unity at lower concentrations. However, there is a trend for underestimation at higher concentrations. This has been seen within the studies from industry and has been previously attributed to the selection of a one-compartment structural model which is required with such sparse data.[28,34,35]

A visual predictive check (VPC) for the final model is presented in Figure 2, with the shaded areas representing simulated data and the red lines representing the observed data. As described previously, we see an underestimation of the rivaroxaban concentration at high concentrations on the VPC around the median, but good agreement as plasma concentration decreases. The overall trend is well characterised by the model.

The final parameter estimates are shown with the 1000 replicate bootstrap in Table 3, and represented mathematically in Figure 3. A visual predictive check for stratified by weight <120kg and weight>120kg is displayed in the supplemental material.

Table 3 Parameter estimates from the Final Pharmacokinetic Model with Bootstrap Results

	Model Estimate		1000 Bootstrap	
Parameter	Estimates	95% CI	Median	2.5th-97.5th Percentile
CL/F (L/h)	5.57	5.34 - 5.82	5.54	5.33 – 5.80
Vd/F (L)	59.4	54.60 – 64.20	59.3	54.6 – 64.2
Ka (h^{-1})	0.707	0.552 – 0.862	0.704	0.556 – 0.858
Shape λ	-1.830	-3.133 – -0.527	-1.707	-2.929 - -0.730
FACCRCLLBW	0.446	0.390 – 0.502	0.449	0.388 - 0.503
FACLBW	0.519	0.319 - 0.719	0.560	0.313 - 0.725
ω_{CL}, % CV	23.02 (37.9)	18.64 - 26.69	23.34	19.42 – 26.13
Proportional error (%)	46.37 (15.6)	43.96 – 48.66	46.17	43.90 – 48.63
Objective function	-4561.424			

Abbreviations: CL/F, apparent clearance; CI, confidence interval, CV coefficient of variation; FACRCLLBW exponent on creatinine clearance calculated using lean bodyweight on CL/F; FACLBW exponent of LBW on Vd/F. Ka absorption rate constant; Vd/F, apparent volume of distribution; ω_{CL} between subject variability on rivaroxaban clearance; Shape λ, Lambda - Box-Cox transformation parameter. The shrinkage values of interindividual variability and residual variability are shown in parentheses.

Simulation

Using the final model population parameter estimates, simulations were generated. AUC and Cmax are presented in boxplots from the simulated data in Figures 4a-4d. The centre, lower edge and upper edge of the box represent the median, 25th and 75th percentiles. The geometric mean and range of the AUC and Cmax values described by the Einstein DVT phase II studies are plotted in red and dashed red lines respectively for comparison.[35]

The median AUC was 63% higher and the Cmax 35% higher in severe renal impairment, compared with patients with no renal impairment. The median AUC and Cmax were 18% and 19% lower respectively in simulated patients of 200kg and 16% and 17% lower in simulated patients of 150kg, compared with 70kg patients. The prediction intervals overlap across all bodyweights and are in keeping with those described in the literature from the Einstein DVT phase II data.[35]

Figure 4e describes the rivaroxaban concentration versus time profile for five patients at extremes of bodyweight with pre-specified mild or no renal impairment and Figure 4f graphically describes four patients with varying degrees of renal impairment.

Discussion

This is the largest cohort of real-world adult patients used to develop a population PK model for rivaroxaban. The results demonstrate that in real world clinical practice, rivaroxaban has a PK profile consistent with industry studies.[28,35,36]

The primary aim of our study was to address the question of whether bodyweight matters when rivaroxaban is prescribed at fixed doses. Current ISTH SSC recommendations caution against the use of rivaroxaban >120kg or BMI >40kg/m^2 due to limited efficacy and safety data and concern about inadequate exposure in this population.

The covariate analysis found CRCL, calculated using CG, with LBW as the weight descriptor in this equation, to be the most significant covariate. Notably, the univariate analysis did see a significant reduction of the objective function when bodyweight (LBW or TBW) was added as a covariate to CL/F. However, renal function was found to be the predominant covariate. Importantly, renal function is a composite covariate, combining creatinine, a weight descriptor, age and gender. Our data suggest that CRCL, calculated using CG as a combined covariate, is the single best predictor of rivaroxaban exposure.

Emerging outcome data are encouraging for rivaroxaban use in morbidly obese patients. The Dresden NOAC registry investigated the impact of BMI on cardiovascular rates, major bleeding and all-cause mortality with no association between high BMI and DOAC efficacy or safety.[37] On a larger scale, a retrospective US database analysis revealed no difference in VTE recurrence between a 1:1 propensity matched, morbidly obese cohort of patients prescribed rivaroxaban or warfarin. Interestingly, contrary to ISTH recommendations, <1% of those rivaroxaban patients had an anti-Xa level drawn.[16] Similarly in the US, Peterson and colleagues reported the safety and efficacy of rivaroxaban prescribed for a 1:1 propensity matched, morbidly obese cohort of patients with AF, again reporting a comparable rate of ischaemic stroke or systemic embolism as those treated with warfarin.[17]

Despite promising outcome data, the pharmacokinetics of rivaroxaban in obesity have not been fully described until now. Early PK studies in healthy volunteers have previously demonstrated that Cmax and AUC are unaffected by bodyweight over 120kg.[36] A large pooled PK model, derived across all indications from 4918 patients in industry-led studies, also showed that bodyweight alone had only a minor influence on rivaroxaban pharmacokinetics.[28] Barsam and colleagues presented an early population PK model which also signalled that weight alone was not a significant covariate. However, this study was limited by the small number of patients >100kg (n=17) or BMI >40kg/m^2 (n=6).[20]

We present compelling evidence that high bodyweight has only a minor influence on rivaroxaban primary PK parameters (Figure 4a). Our population model includes 86 patients with weight >120kg and 76 with a BMI >40kg/m^2. The highest bodyweight reported in the study was 172kg, rendering our model well placed to answer the question of whether rivaroxaban PK is influenced by high bodyweight. Our findings strengthen the argument from early clinical studies in healthy volunteers, indication specific models, pooled industry data and the summary of product characteristics which recommend that no dose adjustment is necessary in this population.[28,35,36,38]

Increasingly, the question of bodyweight is also encountered for those with a low bodyweight. This is an important subgroup as we treat an increasingly ageing population, as well as more patients with cancer in light of new recommendations for the treatment of cancer associated VTE with DOACs.[39,40] As yet, there is no guidance for the management of patients with weight <50 kg.[12] The concern with low bodyweight is the risk of over anticoagulation. The Einstein investigators had only a small number of patients (n=167) weighing less than 50kg in their pooled analysis and were unable to draw meaningful conclusions on safety.[15] Whilst there is only limited outcome data in this subgroup for rivaroxaban, our study indicates that if renal function is good, then low bodyweight alone does not justify avoiding rivaroxaban. Our population model included 30 patients with a bodyweight <50kg, with the lowest bodyweight reported at 39kg. AUC values simulated from the model suggest that the median AUC is 10% higher in a patient weighing 45kg. Patient weight is accounted for within the CG equation and as such this calculation should be used to guide rivaroxaban dosing.

The most significant covariate driving rivaroxaban pharmacokinetics and exposure was CRCLLBW (Figure 4b). This is not surprising given one third of rivaroxaban is renally excreted as unchanged drug, whilst the remaining two thirds undergo metabolic degradation via cytochrome P450 (CYP)3A4, CYP2J2 and CYP-independent biotransformation processes. This further highlights the importance of assessing renal function at initiation and at regular intervals during therapy.

Consideration was given to the method for estimating renal function to be included in the covariate analysis. CG and estimated glomerular filtration rate (eGFR) were options from the data available. EGFR was found to be suboptimal in comparison with CG during a preliminary univariate analysis. For practical reasons, one method of estimating renal function was carried forward for the full covariate analysis. Consequently, and since it is the preferred method in industry, and clinical practice, CG was selected.

The selection of LBW rather than TBW in the CG calculation for renal function was based upon the results of the univariate covariate analysis. LBW improved the objective function by -169.376 compared with the use of TBW by -143.138. The limitations surrounding the use of CG at extremes of bodyweight has been highlighted for the DOACs previously.[41,42] The concern is that by calculating CG using TBW, renal function may be over-estimated in obese patients. A surrogate for TBW in the CG calculation is common for medications with a narrow therapeutic window such as gentamicin to avoid toxicity. However, no adjustments for weight were made in the calculation of renal function in the phase III studies for DOACs. Further research in this area is required.

Where there is concern about under and over anticoagulation, therapeutic drug monitoring (TDM) could be considered for rivaroxaban in view of its consistent PK profile. At extremes of bodyweight, the current ISTH recommendation for those prescribed rivaroxaban >40kg/m^2 or >120kg is for a peak and trough plasma concentration to assess adequate exposure.[12] In light of our findings we recommend, a rivaroxaban plasma concentration for those <50kg in whom there may be concern regarding accumulation and those >150kg in whom less data exists. A trough sample should be prioritised, since it is the clearance that is of interest. and assessed according to the expected range outlined by Gosselin and colleagues. [44], [45]

The limitations of this study are that most samples were collected during routine TDM as standard of care. Furthermore, all patients were assumed to have been adherent and followed dosing instructions (rivaroxaban should be taken with food) and therefore to have been at steady state at the time of the sample. The goodness of fit plots show a tendency to underestimate rivaroxaban concentrations at the higher concentrations, as has been described previously by Willmann and has been attributed to the sparse data and the use of a one-compartment rather than a two-compartment model.[28]

Importantly, these findings are limited only to rivaroxaban and cannot be extrapolated to the other DOACs in view of the heterogeneity of DOAC PK profiles. Given weight features in the dosing guidance for both apixaban (AF) and edoxaban (VTE and AF), further research to determine safety and efficacy for each of the DOACs at the extremes of bodyweight is required.

To conclusively answer the question of whether rivaroxaban is as safe and as effective as warfarin across indications at extremes of bodyweight, a large randomised control trial would be required. However, conducting a prospective analysis of patients weighing <50kg or >120kg, or with a BMI >40kg/m^2 would be challenging. The low event rate for VTE recurrence and major bleeding would mean large numbers of patients would be required and ultimately they represent small subgroups of the population as a whole.[46]

Our findings provide further compelling evidence that weight alone is not the most significant factor influencing rivaroxaban pharmacokinetics. Indeed, at our centre we use rivaroxaban for the acute treatment of VTE in patients weighing >120kg and weighing <50kg and suggest the ISTH SSC reviews its guidance with respect to rivaroxaban**.**

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Authorship contributions

VS, JPP, SD, EG, AG, VSc, RB, AB, SW, JBA, RP, SB, BV, JC, LNR, RKP, RA collected the data. JPP designed the study. VS, BG, JPP developed the PK model described. VS drafted the manuscript, which was critically reviewed by all authors.

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Figures

Figure 1:

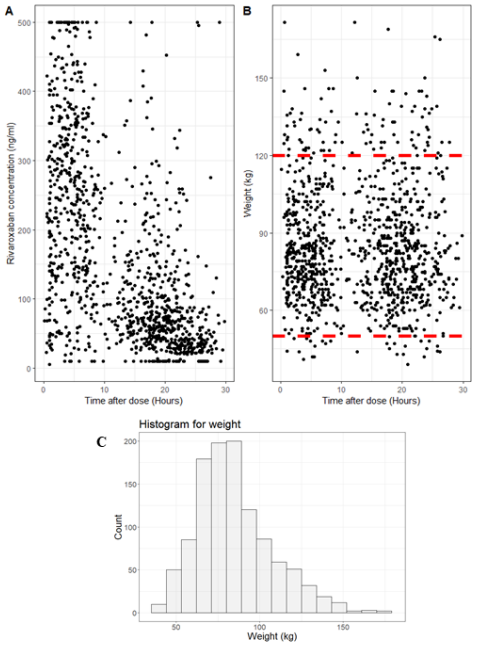
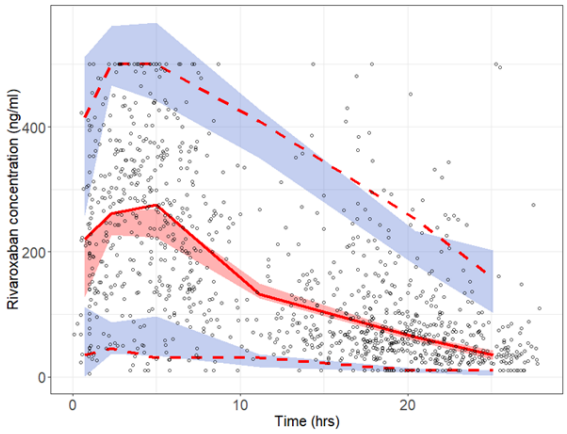


Figure 2:

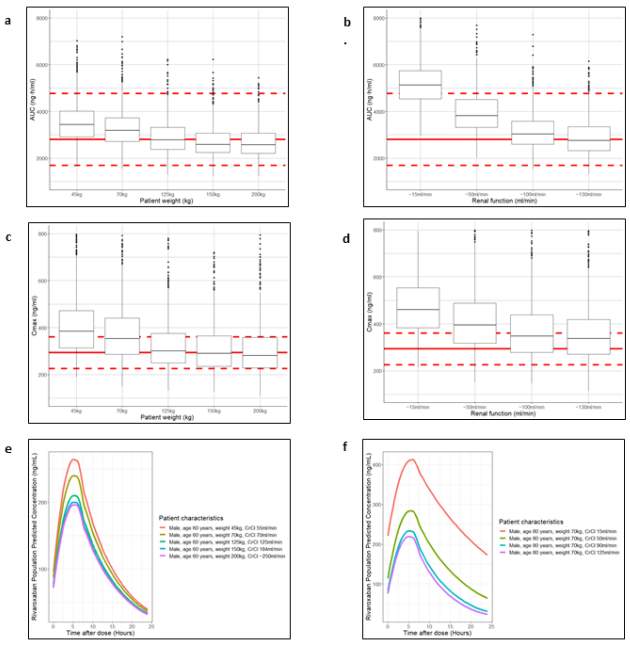


1 Figure 3:

$$CL/F = POPCL \times \left(\frac{CRCLLBW}{55}\right)^{0.446} \qquad Vd/F = POPV \times \left(\frac{LBW}{55}\right)^{0.519}$$

2

3 Figure 4:



4