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

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26

1 **Abstract**

2 **Background**

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

9 **Objectives**

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

12 **Method**

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

17 **Results**

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

24 **Conclusions**

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

4

5

6 **Essentials**

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

11

12

13 **Keywords**

14 Anticoagulants

15 Body weight

16 Drug Monitoring

17 Pharmacokinetics

18 Rivaroxaban

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## 1 **Introduction**

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

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

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

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

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

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

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

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

## 1 **Methods**

### 2 **Study Population**

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

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

## 1 **Ethics**

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

6

## 7 **Assaying the Rivaroxaban Plasma Concentration**

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

16

## 17 **Population Pharmacokinetic Modelling**

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

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

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

7

### 8 **Rivaroxaban Population Pharmacokinetic Model Building**

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

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

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

23

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

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

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

19 NONMEM version 7.4.2 was used for modelling and simulation, using both the first-order conditional  
20 estimation with interaction and the Laplacian estimation method (when M3 method applied to ULOQ  
21 data).[31] Perl Speaks NONMEM (version 4·8·1) (PsN), and R Studio (version 3.6.0) were used for  
22 graphical analysis, model diagnostics and for statistical summaries.[32,33] PKNCA (version  
23 0·9·1) was used to generate and describe simulation data.[30]

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## 1 Results

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

6

**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 <sup>2</sup> (mean [SD])*	29.67 [7.01]	
BMI, kg/m <sup>2</sup> 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
<hr/>			
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<sup>2</sup>, 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

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

5

## 6 **Pharmacokinetic Model Development**

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

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

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

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1 **Table 2. Univariate covariate analysis**

Model	Covariate	Covariate Relationship	$\Delta$ OBV
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

$\Delta$ OBV 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

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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.

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

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1 **Final Model**

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

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

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

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

Parameter	Model Estimate		1000 Bootstrap	
	Estimates	95% CI	Median	2.5th-97.5 <sup>th</sup> 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 <sup>-1</sup> )	0.707	0.552 – 0.862	0.704	0.556 – 0.858
Shape $\lambda$	-1.830	-3.133 – -0.527	-1.707	-2.929 - -0.730
FACRCLLBW	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
$\omega_{CL}$ , % 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;  $\omega_{CL}$  between subject variability on rivaroxaban clearance; Shape  $\lambda$ , Lambda - Box-Cox transformation parameter. The shrinkage values of interindividual variability and residual variability are shown in parentheses.

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## 1 **Simulation**

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

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

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

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## 1 **Discussion**

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

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

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

16 Emerging outcome data are encouraging for rivaroxaban use in morbidly obese patients. The Dresden  
17 NOAC registry investigated the impact of BMI on cardiovascular rates, major bleeding and all-cause  
18 mortality with no association between high BMI and DOAC efficacy or safety.[37] On a larger scale,  
19 a retrospective US database analysis revealed no difference in VTE recurrence between a 1:1  
20 propensity matched, morbidly obese cohort of patients prescribed rivaroxaban or warfarin.

21 Interestingly, contrary to ISTH recommendations, <1% of those rivaroxaban patients had an anti-Xa  
22 level drawn.[16] Similarly in the US, Peterson and colleagues reported the safety and efficacy of  
23 rivaroxaban prescribed for a 1:1 propensity matched, morbidly obese cohort of patients with AF,  
24 again reporting a comparable rate of ischaemic stroke or systemic embolism as those treated with  
25 warfarin.[17]

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

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

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

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

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

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

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

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

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

11 To conclusively answer the question of whether rivaroxaban is as safe and as effective as warfarin  
12 across indications at extremes of bodyweight, a large randomised control trial would be required.  
13 However, conducting a prospective analysis of patients weighing <50kg or >120kg, or with a BMI  
14 >40kg/m<sup>2</sup> would be challenging. The low event rate for VTE recurrence and major bleeding would  
15 mean large numbers of patients would be required and ultimately they represent small subgroups of  
16 the population as a whole.[46]

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

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

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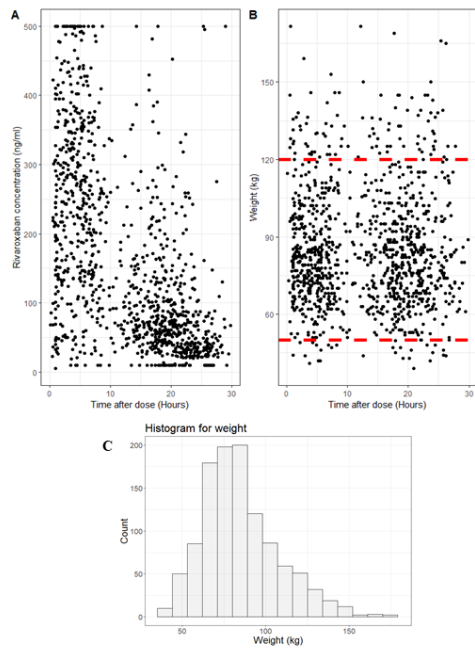
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22  
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24

1 **Figures**

2

3 Figure 1:

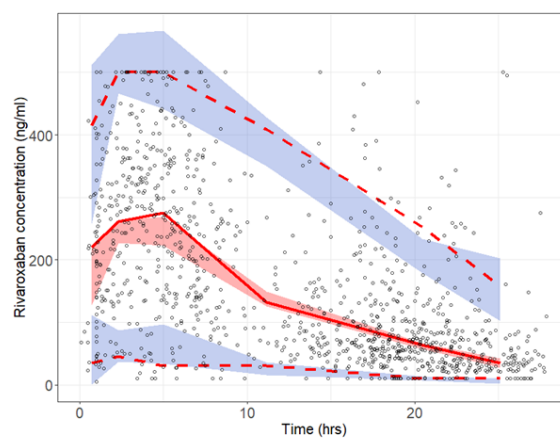


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7 Figure 2:



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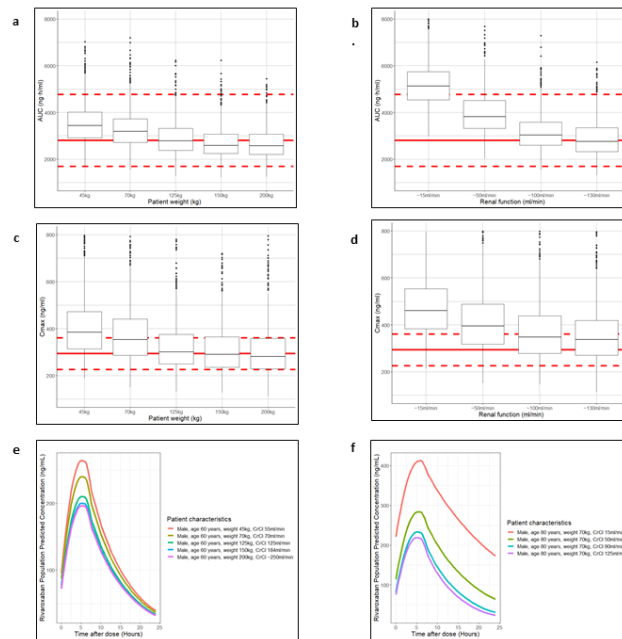
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1 Figure 3:

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

2

3 Figure 4:



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