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Effect of extremes of body weight on drug level in patient treated with standard dose of rivaroxaban for venous thromboembolism; real life experience

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Venous thromboembolism (VTE) is a leading cause of morbidity and mortality worldwide. Appropriate anticoagulation is crucial in the treatment and prevention of recurrent VTE. Overdosing of an anticoagulant could result in life-threatening bleeding while under-dosing could result in lack of efficacy leading to recurrence of thrombosis. It is possible that "extremes in body weight" [EBW] (<50 kg or >120 kg) may alter the exposure profile of an anticoagulant and its benefit: risk ratio. Monitoring of anticoagulant intensity of direct acting oral anticoagulants (DOACs) is not routinely required due to their predictable anticoagulant effects but assessment of drug levels may be useful in some situations including EBW as recommended by both International Society for Thrombosis and Haemostasis (ISTH) [1] and the British Committee for Standards in Haematology (BCSH) guidelines [2].

Patients with EBW, both very low and very high, are underrepresented in clinical trials and in preclinical dose-finding studies. The mean weight was around 84 kg; with the majority of participants in phase III clinical studies weighing between 60 and 100 kg [3]. Sub-analysis of EINSTEIN DVT and PE studies in which weight was categorised into three groups as 50 kg, 50–100 kg and >100 kg, found no association between body weight and the risk of recurrent VTE and similar rates of recurrent VTE by treatment group (2.3% on rivaroxaban vs 2.0% on VKA in patients >100 kg) [4]. However, none of the phase III trials with DOACs reported the patients with body mass index (BMI) >40 kg/m^2 or their clinical outcome. The guidance from the SSC of the ISTH on use of DOACs in obese patients 2016 [3], recommended against the use of DOACs in patients with BMI >40 kg/m2 or the weight > 120 kg due to limited clinical data in this group of patients.

We assessed the effect of EBW on rivaroxaban levels and clinical outcome with standard dose of rivaroxaban (15 mg BD for three weeks followed by 20 mg once daily) in the treatment of venous thromboembolism (VTE) in a routine clinical practice. The study was untaken as a part service evaluation project in a tertiary haemostasis and thrombosis centre in UK and approved by the trust clinical effectiveness unit.

An unselected group of 219 patients with VTE (53% deep vein thrombosis [DVT], 41% pulmonary embolism [PE] and 6% PE and DVT: 51% male, 49% female, mean age 59 years) were studied. Rivaroxaban levels were measured in blood samples taken 2–4 h from the last dose of rivaroxaban in patients on rivaroxaban 20 mg daily after an initial 3 weeks of 15 mg twice daily over a 15 month period at routine clinic appointments. Patients were divided into three groups based on weight (<50 kg: $n = 20$, 50-120 kg: $n = 135$ and >120 kg: $n = 45$). Patients for whom weight was unavailable or levels not taken within 2–4 h after the last dose were excluded and 167 patients were available for analysis (<50 kg: $n = 18$, 50-120 kg: $n = 105$ and >120 kg: $n = 44$). All patients were on rivaroxaban 20 mg OD and had a calculated creatinine clearance (CrCl) of >50 mL/min by Cockcroft Gault formula except four and two patients had CrCl 30–50 mL/min with weight 50–120 kg and >120 kg respectively. All patients had ALT <1.5 of upper normal limit. Baseline characteristics of the 167 patients are shown in Table 1. Bleeding episodes and recurrent VTE rates during follow-up period of 12–18 months (median 14 months) were collected from our VTE database, case notes and electronic records. All patients were counselled about the lack of evidence for rivaroxaban when used at EBW during their first visit at the thrombosis service following the diagnosis of VTE and made an informed decision to receive rivaroxaban mainly due to convenience and not wanting to have regular blood tests for INR monitoring if they had to have a VKA. It is the standard practice in our thrombosis centre to review all patients with VTE presenting to the trust within 48–72 h of diagnosis at the nurse lead VTE clinic.

Venous blood was collected into 0.109 M trisodium citrate in the proportion 9:1 (Vacutainer Plus, Becton Dickinson, Franklyn lakes USA), centrifuged at 2000 *g* for 10 min at room temperature and processed within 2 h of collection for PT/Activated Partial Thromboplastin Time (APTT) or anti Xa levels if required immediately or stored deep frozen at −70 °C for up to 6 weeks prior to analysis. All patients had been on rivaroxaban 20 mg daily at least for a week (range 1–3 weeks) following standard 15 mg twice daily for 3 weeks before they had the blood samples taken 2–4 h from the last dose of rivaroxaban in routine clinic visits.

PT was determined using Innovin thromboplastin (Siemens, Marburg, Germany). APTT was determined using Actin FS (Siemens, Marburg Germany). Both PT and APTT were performed using Sysmex CS series analysers (Sysmex, Kobe Japan). PT and APTT results were expressed as prothrombin time ratio (PTR) = PT patient/PT normal and APTT ratio = APTT patient/APTT normal respectively. Geometric mean normal PT was 10.5 s and APTT was 24 s with Innovin and Actin FS respectively were established using samples from 25 healthy normal subjects. Anti Xa activity was determined using the Biophen DiXal assay (Hyphen, Neuville-sur-Oise, France). Assays were performed using Sysmex CA series analysers and were calibrated using rivaroxaban specific calibrators (Hyphen, Neuville-sur-Oise, France).

Data analysis was performed using GraphPad Prism® version 6 (GraphPad Software, Inc. La Jolla, USA). Results were reported as median or mean based on the distribution of results with 95% confidence interval (CI). Multiple group comparisons were performed using Kruskal-Wallis ANOVA and paired comparisons using Mann-Whitney '*U*' test after adjusting the significant *p*-values by Bonferroni correction. Fisher's exact test (FET) was used to study associations. A p value of <0.05 was considered significant.

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Table 1
Baseline characteristics of study population.

Characteristics		<50 kg ($N = 18$)	50-120 kg ($N = 105$)	>120 kg ($N = 44$)
Age (years) mean (SD)		58.3 ± 21.4	63.4 ± 16.4	50.4 ± 10.6
Sex	Male	10 (66)	63 (60)	28 (64)
N (%)	Female	8 (44)	42 (40)	16 (36)
BMI(kg/m^2)		17.9	30.5	42.4
Mean (95% CI)		(17.5–18.4)	(29.4–31.7)	(41.1–43.8)
Type of thrombosis (%)				
DVT alone		10 (56)	57 (54)	20 (45)
PE alone		5 (28)	39 (37)	10 (23)
DVT + PE		3 (17)	9 (9)	14 (32)
CrCL (mL/min)		67.1 (57.2 to 77.6)	65.1 (55.2 to 80.6)	63.4 (52.8 to 90.7)
Mean (95% CI)				
ALT (IU/L)		18.2 (16.6 to 22.1)	21.2 (18.6 to 24.1)	19.6 (17.4 to 22.2)
Mean (95% CI)				

SD = standard deviation; BMI = Body mass index; CI = confidence interval CrCL = creatinine clearance; DVT = deep vein thrombosis; PE = pulmonary embolism; and VTE = venous thromboembolism.

Mean weight [range] (kg) in the three groups were 43 [38–49], 86 [50–120)] and 135 [121–186]. BMI of each weight category is shown in Fig. 1A. Patients with weight < 50 kg had significantly higher rivaroxaban levels (ng/mL) (median [95% confidence interval] 460 [380–601]) compared to patients with weight 50–120 kg: 308 [308–381] and >120 kg: 281 [242–327], ($p = 0.001$) (Fig. 1B). Furthermore, 5/18 (27.7%) patients with weight < 50 kg had rivaroxaban levels ≥ 700 ng/mL. There was no significant difference in the rivaroxaban levels between patients with weight 50–120 kg and >120 kg. PT ratio (mean normal 10.5 s) was significantly higher in patients with weight < 50 kg (mean [95% CI]: 1.34 [1.30–1.41]) compared to patients with weight 50–120 kg: 1.20 [1.15–1.24] and >120 kg: 1.19 [1.15–1.23], $p < 0.0001$ (Fig. 1C). APTT ratios (mean normal 24 s) showed a similar pattern of results: weight < 50 kg (mean [95% CI]: 1.63 [1.51–1.74]) compared to patients with weight 50–120 kg: 1.35 [1.31–1.51] and > 120 kg: 1.29 [1.23–1.48], $p < 0.0001$ (Fig. 1D). PT and APTT reagents differ in their sensitivities to rivaroxaban. Reagents that we used in this study to measured PT; Innovin is one of the least sensitive thromboplastin reagents to rivaroxaban compared to other commonly used thromboplastin reagents; Actin FS is one of the more-sensitive APTT reagents to rivaoroxan that is used more commonly in routine laboratories [5].

During the 12–18 (median 14) months follow-up periods, overall clinically relevant and major bleeding rates as per ISTH criteria [6]

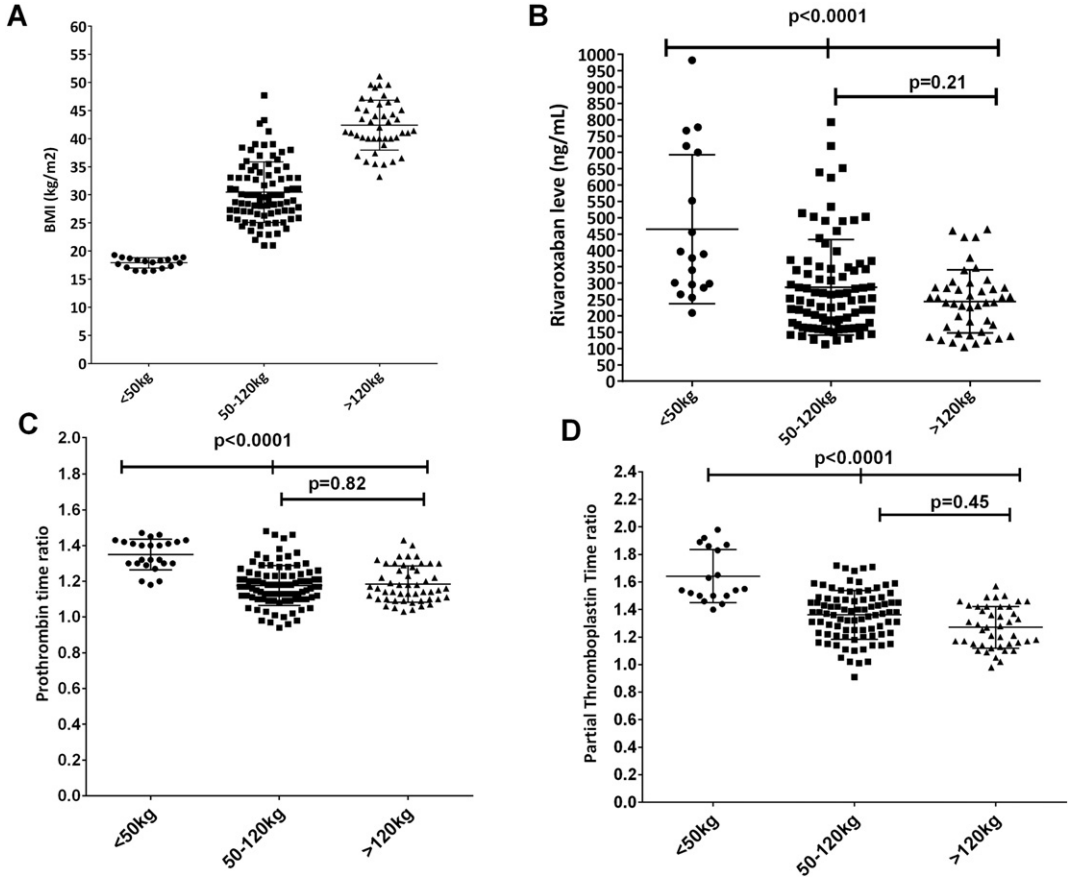

Fig. 1. Body mass index [BMI](A), Rivaroxaban levels (B), Prothrombin time ratio (C) and activated partial thromboplastin time ratio (D) in each patient weight category.