Direct Oral Anticoagulant Concentrations in Obese and High Body Weight Patients: A Cohort Study

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Background

- The preferred option for the management of venous thromboembolism (VTE) and the prevention of stroke in patients with atrial fibrillation (AF) is the use of direct oral anticoagulants (DOACs) due to their favorable risk–benefit profile when compared with vitamin K antagonists (VKAs).
- However, there is uncertainty whether obesity affects DOAC levels and whether there are variations in the levels by type of DOAC and clinical indication.
- The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) in its guidance statements issued in 2016 recommended against use of DOAC in patients with morbid obesity with a body mass index (BMI) 40 kg/m2 or high body weight weighing more than 120 kg.
- If used, the current view is to check DOAC levels and continue if the level is within the expected range, or change to VKA if the level is found to be below the expected range.

AIM of the study

- To investigate the relationship between factor Xa (FXa) inhibitor concentrations, body weight, and renal function, and compare them in high body weight patients from unselected populations.

Methods

- Consecutive patients in two United Kingdom centers, weighing $\geq$120 kg receiving 5 mg twice daily apixaban or 20 mg once daily rivaroxaban for AF or VTE were prospectively included.
- Peak or trough concentrations were measured using specific chromogenic assays, expressed in mean or median (5th–95th percentiles).
- On-therapy range was the interval from the 5th percentile trough concentration to the 95th percentile peak concentration.

Results

- 100 patients were included; 31% were women.
- Median body weight was 139 kg, and 84% had BMI $\geq$ 40 kg/m2.
- There was a wide interindividual variability both at peak and trough.
- There was no linear relationship between FXa inhibitor concentrations at peak or trough and body weight or BMI, and creatinine clearance.
- Apixaban troughs in AF and rivaroxaban peaks in VTE were lower than in unselected populations.
- However, only two trough concentrations were below the expected range, and 109/116 were within the on-therapy range.

Table 2 Factor Xa inhibitor concentration ranges according to DOAC type, indication, and peak or trough measurement

	AF cohort $n = 63$		VTE cohort $n = 53$	
Concentrations (ng/mL)	**Peak**	**Trough**	**Peak**	**Trough**
Apixaban concentrations	$n = 11$ 176 [102–373]	$n = 14$ 65 [39–119][a]	$n = 8$ 96 [88–199]	$n = 4$ 62 [21–116]
Expected apixaban concentrations	171 [91–321]	103 [41–230]	132 [59–302]	63 [22–177]
Rivaroxaban concentrations	$n = 22$ 214 [61–672]	$n = 16$ 59 [14–148]	$n = 36$ 220 [99–474][a]	$n = 5$ 98 [20–299]
Expected rivaroxaban concentrations	249 [184–343]	44 [12–137]	270 [189–419]	26 [6–87]

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICSH, International Council for Standardization in Haematology; VTE, venous thromboembolism.

Note: The expected values obtained in unselected body weight populations published in the ICSH recommendations were also presented.[9] Apixaban concentrations are expressed in median [5th–95th], rivaroxaban concentrations are expressed in mean [5th–95th], as published in the ICSH recommendations.[9]

[a] $p < 0.05$ for comparison between measured and expected concentrations.

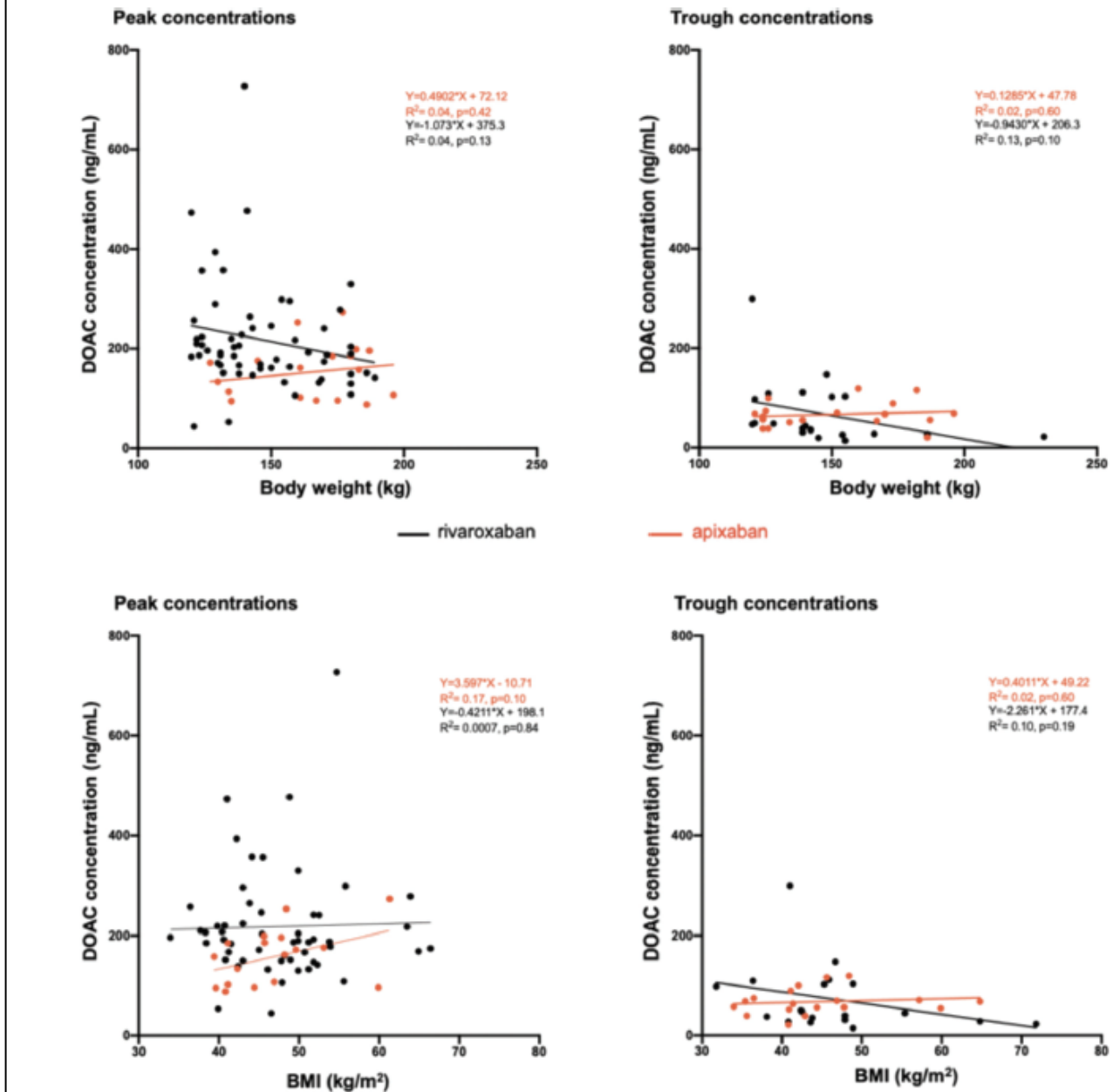

Fig. 1 Relationship between direct oral anticoagulant (DOAC) concentrations at peak or trough and body weight or body mass index (BMI). Black lines and dots for rivaroxaban; red lines and dots for apixaban. BMI, body mass index. $p < 0.05$ for significance.

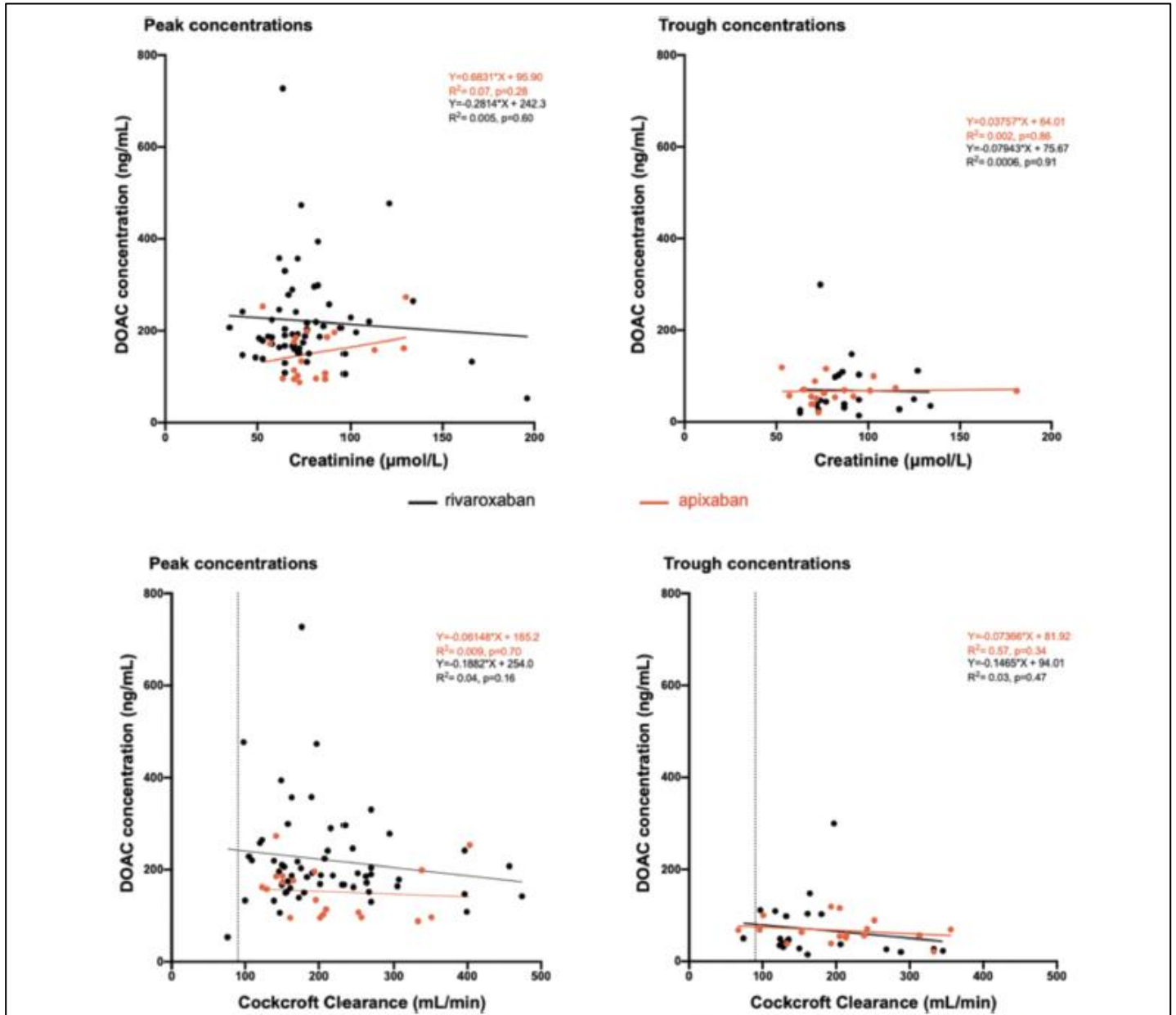

Fig. 2 Relationship between direct oral anticoagulant (DOAC) concentrations at peak or trough and creatinine level or Cockcroft clearance. Black lines and dots for rivaroxaban; red lines and dots for apixaban. $p < 0.05$ for significance. Dot line represents normal clearance (80 mL/min).

Conclusions

- There was no relationship between factor Xa inhibitor concentrations at peak or trough and body weight or BMI, and no relationship between factor Xa inhibitor concentrations at peak or trough and renal function.
- All trough values were within or just below the expected range obtained in unselected populations, and more than 95% of the factor Xa inhibitor concentrations were within the “on-therapy” range.
- These results suggest that high body weight and obesity per se are not sufficient to justify factor Xa inhibitor measurements and challenge current guidance.