FVIII and D-dimer values at trough and peak concentrations of direct oral anticoagulants: important considerations for using these tests in assissting clinical decision for risk stratification scheme

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INTRODUCTION

FVIII and D-dimer are included in different prediction models to risk stratify for thrombotic recurrence or anticoagulation cessation. However, the optimal timing of their measurement related to the last drug dose is not sufficiently examined.

AIM

To determine FVIII and D-dimer levels at peak and trough plasma concentrations of direct oral anticoagulants (DOACs) in order to define optimal timing of blood drawing.

METHOD

Concentrations of rivaroxaban (n=32), Apixaban (n=24) and dabigatran (n=28), D dimer levels and FVIII activities were measured at trough (before the next drug dose) and peak (two hours after drug intake) DOAC levels in circulation of outpatients during their regular control Clinical examination. Rivaroxaban and apixaban were determined using specific chromogenic anti-Fxa assay, dabigatran with Innovance DTI assay, FVIII with APTT based coagulometric method (Actin FS/FVIII deficient plasma) and D dimer by quantitative immunoturbidimetric assay using monoclonal antibody (Innovance D dimer), all from Siemens Healthineers, Germany on BCSXP analyzer. Statistical analysis was done with Wilcoxon and Friedman tests.

RESULTS

In contrast to D-dimer, FVIII values were significantly higher at trough in comparison with peak dabigatran and rivaroxaban concentrations (P = 0.013 and 0.024), whereas for apixaban FVIII also showed a trend of higher values at trough, but without significant difference (P=0.850, Table 1).
Significantly higher values of both D-dimer and FVIII were measured at trough and peak drug levels of apixaban compared to dabigatran and rivaroxaban (Table 1, P*).

Table 1. Results of factor FVIII (FVIII) and D-dimer levels at peak and trough concentrations of DOACs.

DOAC drug	Peak drug conc. ng/mL Median (95%CI) IQR	Trough drug conc. ng/mL Median (95%CI) IQR	D-dimer (mg/L FEU) at peak conc. Median (95%CI) IQR	D-dimer (mg/L FEU) at trough conc. Median (95%CI) IQR	FVIII (%) at peak conc. Median (95%CI) IQR	FVIII (%) at trough conc. Median (95%CI) IQR
Dabigatran N=28	125 (92-132) 114-128	39 (17-47) 26-44	0.23 (0.17-0.36) 0.18-0.30	0.22 (0.17-0.39) 0.18-0.34	70 (58-128) 61-107	100 (87-119) 96-111
P	0.001		0.563		0.013	
Rivaroxaban N=32	238 (187-360) 201-337	21 (14-42) 14-39	0.22 (0.17-0.91) 0.17-0.64	0.29 (0.19-1.07) 0.20-0.82	122 (75-136) 83-131	159 (97-200) 115-191
P	0.001		0.203		0.024	
Apixaban N=24	179 (148-213) 140-208	97 (94-107) 98-111	0.60 (0.35-1.51) 0.30-1.50	0.58 (0.40-1.69) 0.39-1.60	147 (124-201) 120-201	173 (105-196) 101-201
P	<0.001		0.909		0.850	
P*			0.008	0.001	0.026	0.001

95%CI = 95% confidence interval; IQR = interquartile range; P< 0.05 was considered statistically significant
*P values for trough and peak values of D-dimer and FVIII levels in patients treated with apixaban compared with dabigatran and rivaroxaban

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CONCLUSIONS

Plasma concentration of DOACs significantly affects FVIII values, unlike D-dimer. These findings are important when using these tests in assissting clinical decisions related to risk stratification schemes for recurrent thrombotic event or anticoagulation cessation. For FVIII measurement blood drawing should be performed at trough DOAC levels exclusively, whereas D-dimer may be measured at both trough or peak drug levels in circulation.

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