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**

The study was funded by the Croatian Science Foundation as part of the research project IP-2016-06-8208, LAB-NOAC.

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.

CONTACT INFORMATION

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The authors have nothing to disclose

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INTRODUCTION

FVIII and D-dimer coagulation markers

- increasingly evaluated in prediction models to stratify risk for thrombotic recurrence and associated clinical decision making on anticoagulation withdrawal

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Prediction models for assessment risk of thrombotic recurrence

- ✓ When the balance between the benefit and risk of long term anticoagulation not clear
- ✓ Approach targeted on an individual basis
- ✓ Lack of a single reliable predictive indicator
- ✓ Clinical factors alone and laboratory markers alone do not provide high discriminatory power
- Combination of both clinical and laboratory markers can increase discriminatory power
- ✓ Coagulation assays (DD, FVIII) reflect the overall prothrombotic phenotype – thus representing a promising additional tool in assessing risk for recurrent VTE
- ✓ Most studies examining laboratory markers have been conducted on non-anticoagulated patients (3-4 weeks after anticoag. cessation) - prediction models mostly rely on measurements after anticoagulant therapy withdrawal
- ✓ The risk of VTE recurrence can be high within the first month after anticoagulation withdrawal
- ✓ Efforts to develop new prediction models without stopping anticoagulant treatment (ideally the risk should be assessed during therapy)

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Unresolved issues and chalenges in applying these coagulation markers into clinical practice for thrombotic risk assessment –
- can affect result interpretation and comparison in clinical settings

D-dimer and FVIII

- Nonspecific: increase with age, during pregnancy, malignancy and inflammation) (D-dimer)
- A lack of standardization (D-dimer)
- Different methods = different reagent sensitivity (FVIII)
- Unknown optimal timing of FVIII measurement
- Not well defined cut-off values (FVIII activity: >150% or >200%, age adjusted cut-offs for D-dimer not evaluated in prediciton models yet etc.)

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INTRODUCTION

FVIII and D-dimer assays

Whether are there differences in DD and FVIII levels between **trough vs. peak** DOAC plasma conc.?

D-dimer and FVIII for risk stratification in patients during therapy with DOACs (before anticoagulant withdrawal)

- **Effect of DOAC plasma concentration on DD and FVIII values**

The optimal timing of blood sampling related to the last DOAC drug dose (trough *vs.* peak)

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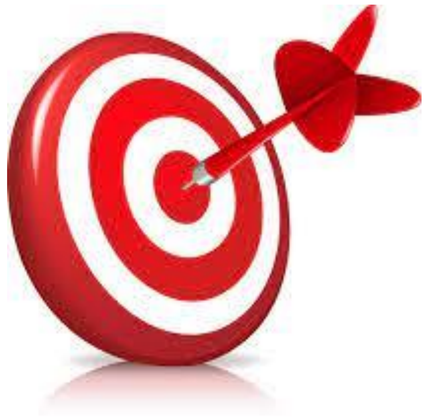
AIM



- To assess the impact of DOAC plasma concentrations on FVIII and D-dimer levels
- To define optimal time of blood sampling for DD and FVIII measurements in relation to the last DOAC dose (at peak or trough DOAC concentration)

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MATERIALS AND METHODS

Subjects:

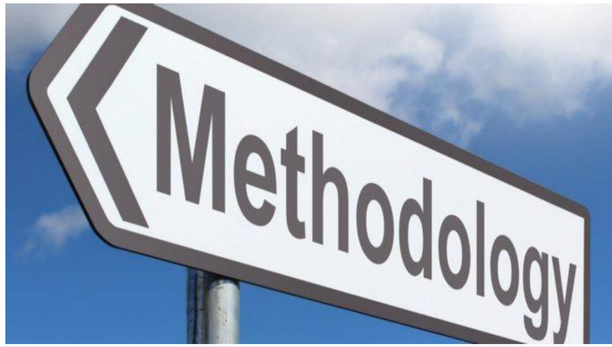
- patients on DOACs (VTE, CVI, NVAF)
- **rivaroxaban (n=32), apixaban (n=24) and dabigatran (n=28)**
- outpatients during regular control clinical examination
- time of blood sampling: at **trough** DOAC plasma levels (**before the next drug dose)**
  at **peak** DOAC plasma levels (**two hours after drug intake)**

Methods:

D-dimer: quantitative immunoturbidimetric assay (Innovance D dimer)
FVIII acitivity: APTT-based coagulometric method (Actin FS/FVIII deficient plasma)
Rivaroxaban and apixaban: chromogenic anti-FXa assay with drug specific calibrators
Dabigatran: chromogenic Innovance DTI assay
All assays from Siemens Healthineers, Germany on BCSXP analyzer (Siemens Healthineers)

Statistical analysis:

- descriptive statistics (median and 95%CI, interquartile range)
- testing of statistically significant difference: Wilcoxon and Friedman tests



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RESULTS

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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 DOAC conc. Median (95%CI) IQR	D-dimer (mg/L FEU) at TROUGH DOAC conc. Median (95%CI) IQR	FVIII (%) at PEAK DOAC conc. Median (95%CI) IQR	FVIII (%) at TROUGH DOAC conc. Median (95%CI) IQR
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P	**<0.001**		**0.909**		**0.850**	
P*			**0.008**	**0.001**	**0.026**	**0.001**

What do the study results mean for the clinical practice?

whether the same limit values for all drugs can be used for risk assessment at all

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CONCLUSION

- **Plasma concentration of DOACs (trough vs. peak) affects FVIII values: significantly higher FVIII at trough DOAC levels**
  Blood sampling for FVIII measurement should be performed at trough DOAC levels exclusively (for risk assessment it is mandatory to know FVIII levels not affected by DOAC conc.)

- **Plasma concentration of DOACs does not affect D-dimer values: no difference between trough and peak DOAC concentrations**
  D-dimer can be measured at both trough or peak DOAC levels in circulation

- **FVIII levels were significantly lower at both trough and peak DOAC concentrations in patients treated with dabigatran compared to those on rivaroxaban and apixaban**
- **DD and FVIII levels were significantly higher in patients taking apixaban compared with the other two DOACs – is it correct to use the same cut-off values for D-dimer and FVIII for all DOAC drugs to stratify risk for thrombotic recurrence?**

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