New (direct) oral anticoagulants: from the laboratory point of view

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HRZZ Croatian Science Foundation

IP-2016-06-8208 LAB-NOAC

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Introduction

- Basic pharmacological facts about NOAC (DOAC) drugs
- Clinical conditions that require measurement of NOACs

- **What do we need to know about laboratory assessment of NOACs:**
- effect on screening coagulation tests
- quantitative methods/assays for measuring NOACs concentration – including key preanalytical, analytical and postanalytical factors
- impact of NOACs on other specialized haemostasis assays

Research project approved and funded by Croatian Science Foundation

New oral anticoagulants: relationship between drug concentration and anticoagulant effect

LAB-NOAC; IP-206-06-8208

- **Project duration: 4 years (2017 – 2021)**
- **Principal investigator: Ph.D. Sandra Margetić, Research Associate**
- **Home institution of the project implementation: University Hospital Center Sestre milosrdnice Zagreb, Croatia**
- **Multidisciplinary team (10): specialists in laboratory medicine, cardiologists and neurologists**

New oral anticoagulants: relationship between drug concentration and anticoagulant effect

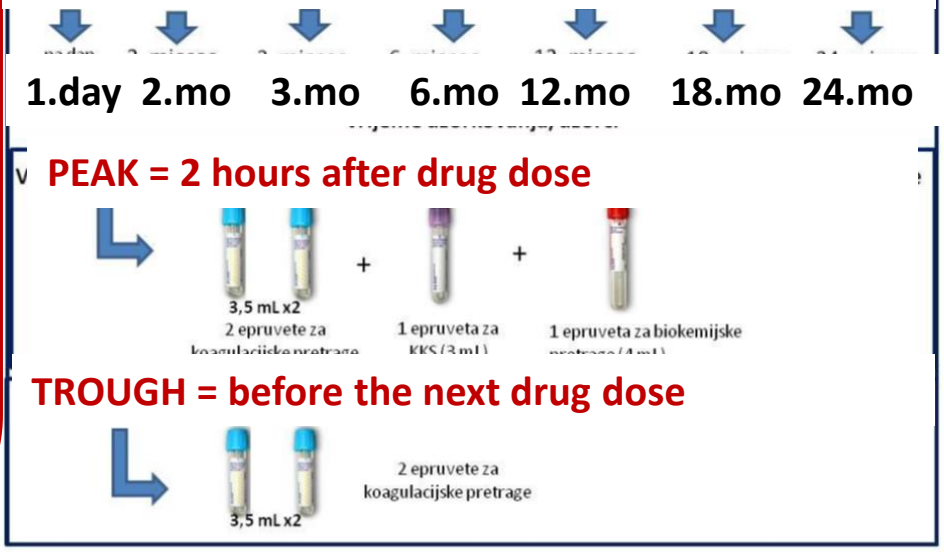
AIM: to examine relationship between peak and trough NOAC conc. **(DABI, RIVA, API)** and

- efficacy of treatment
- anticoagulant effects
- incidence of adverse events (bleeding, thrombosis)
- demographic factors (age, gender)
- pathophysiological factors (renal and liver function, BMI)
- interactions with other drugs

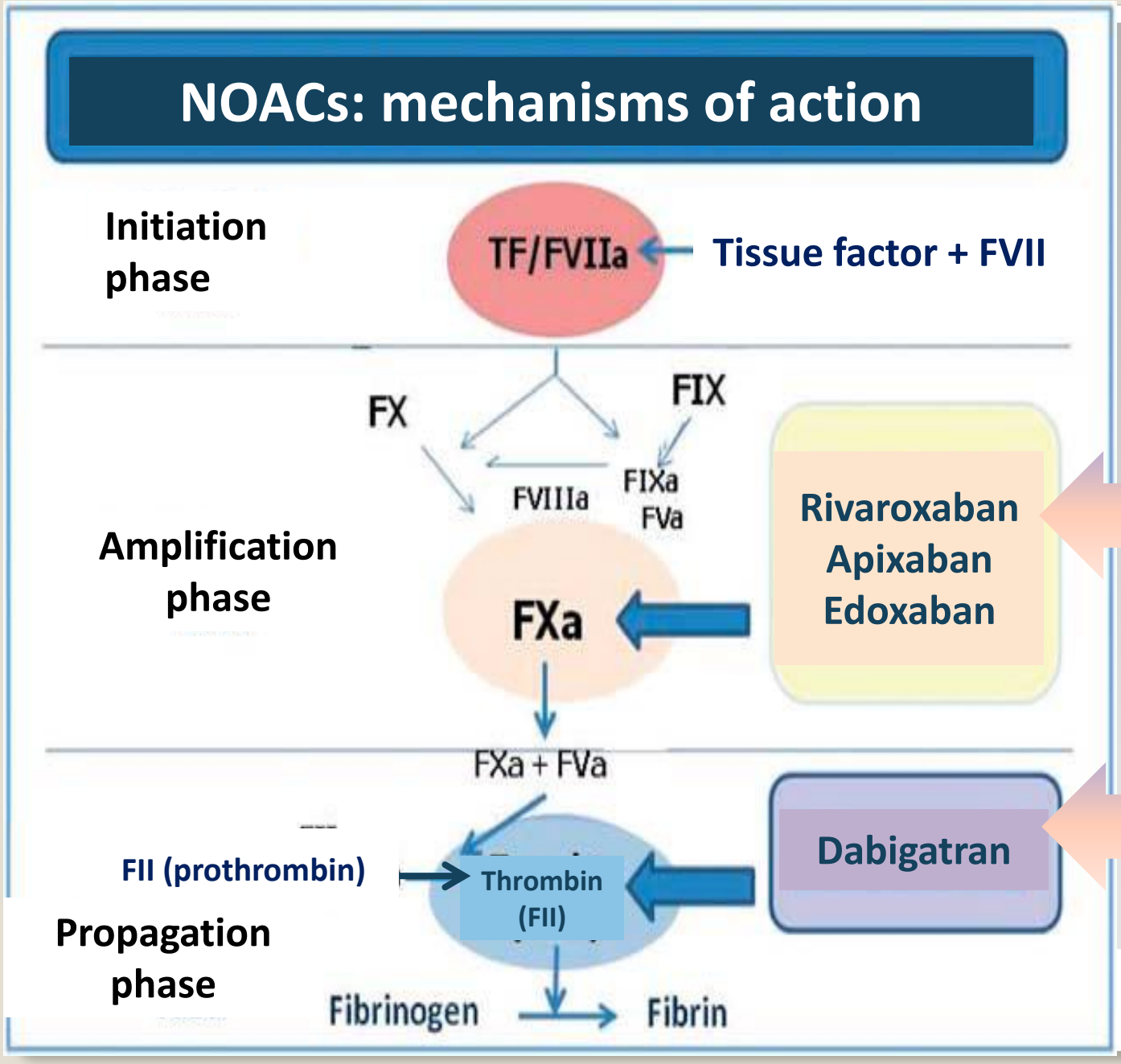
in different clinical indications approved for NOACs
(NVAF, prevention and treatment of VTE)

Patient follow up: 24 months
NOAC conc: peak and trough – at defined intervals

7 time points for blood sampling during 1-24 months of overall patient follow-up



NOACs: mechanisms of action

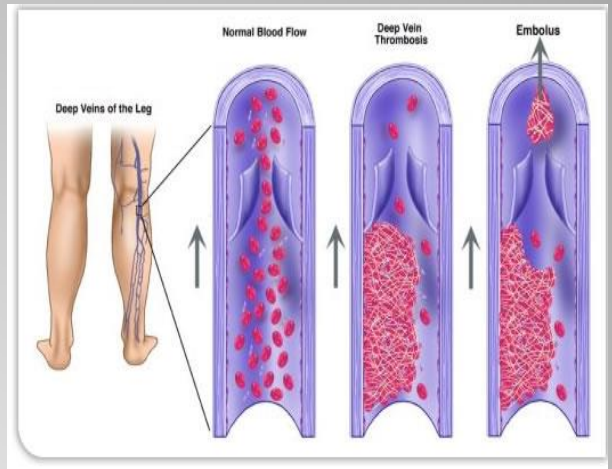


Direct inhibitors of FXa

Direct thrombin inhibitor (FIIa)

Approved clinical indications for NOACs

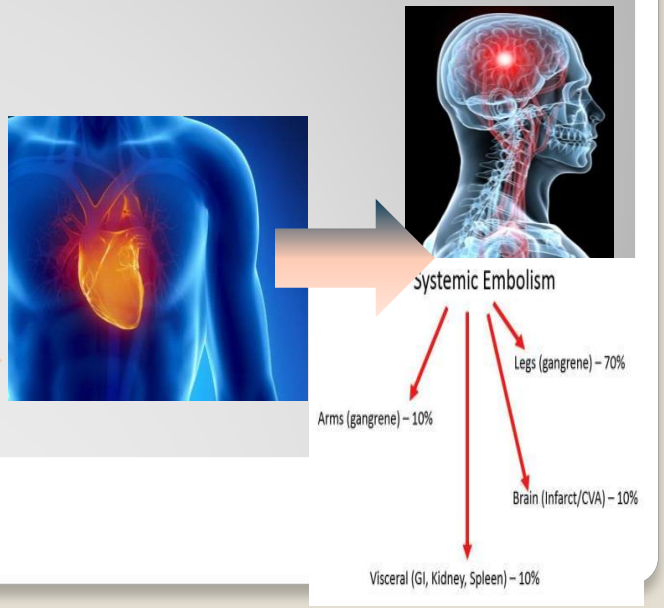
1. **Prevention of VTE in adult patients following orthopedic surgery**
   (total hip or knee replacement)



2. **Prevention and treatment of VTE (DVT/PE)**

(but not for all patients yet: some populations and/or indications clinical trials are still ongoing: VTE in cancer, pediatric population, antiphospholipid syndrome)

3. **Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)**



Basic pharmacological properties of NOACs

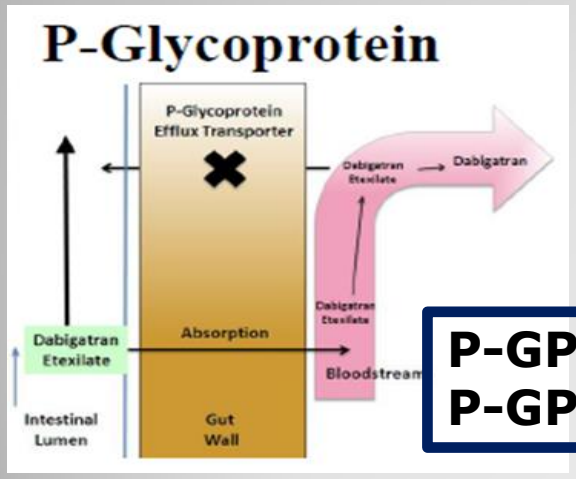
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	yes	no	no	no
Dosage	**Fixed: 150 (110) mg twice daily**	**Fixed: 20(15) mg once daily**	**Fixed: 5(2) mg twice daily**	**Fixed: 60(30) mg twice daily**
Bioavailability (%)	7	80	50	60
Half-life (h)	**12-14***	**5-13**	**12**	**10-14**
Peak conc. (h)	**1.5 - 3**	**2 - 3**	**1-3**	**1 - 2**
Primary clearance	**80% renal**	**67% renal**	**56% faecal**	**50% renal**
Protein binding	35%	92%	87%	55%
Intake with or without food	without	**With****	without	without

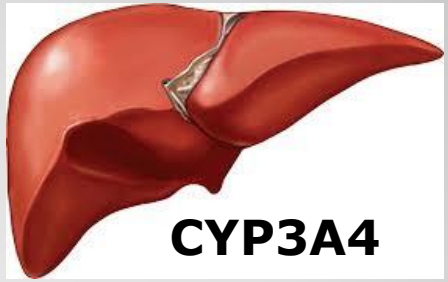
*** half life is prolonged up to 24 h in patients with impaired renal function and in older patients (>70 yrs)**

**** food enhances absorption**

Interactions of NOACs with other drugs: anti-fungal, antibiotics, antiarhythmics, antihypertensives, anti-convulsant

Lijek	Dabigratan	Rivaroxaban	Apixaban	Edoxaban
Significant interactions with other drugs	Inhibitors/ inductors of P-glycoprotein (P-GP)	Inhibitors/ inductors of P-GP and CYP3A4	Inhibitors/ Inductors of P-GP and CYP3A4	Inhibitors/ Inductors of P-GP CYP3A4 (<10%)





P-GP and CYP3A4 inhibitors: increase NOAC level
P-GP and CYP3A4 inductors: decrease NOAC evel

P-GP inhibitors: azithromycin, erythromicin, ketoconazole, quinidine, verapamil
P-GP inductors: rifampicin
Combined P-GP i CYP3A4 inhibitors: ketoconazole, ritonavir, clarithromycin, erythromicin
Combined P-GP i CYP3A4 inductors: rifampicin, carbamazepine, phenytoin

NOACs and laboratory diagnostics

Clinical 353–36 *Tripodi A. Clin Chem 2013;59:353-62.* Review

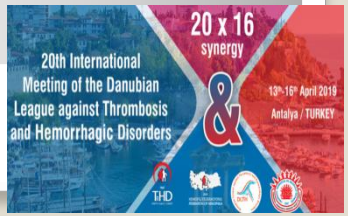
The Laboratory and the New Oral Anticoagulants

Armando Tripodi[1,2*]

Concluding Remarks

A statement that laboratory monitoring is not needed for patients on NOAs may be seen at the beginning of a review article or heard at a conference on NOAs. Although true, this concept has been emphasized to such an extent that it is misleading and potentially dangerous, because clinicians might be falsely reassured that laboratory testing is never needed when dealing with NOAs. On the contrary, the accumulating evidence indicates that this statement is an oversimplification. An interesting and paradigmatic case report published re-

Although it is generally accepted that NOACs do not need routine coagulation monitoring, the results of clinical experiences dispute the fact that the treatment with NOACs completely excludes the need for laboratory diagnostics.



Journal of Thrombosis and Haemostasis, 11: 756–760 DOI: 10.1111/jth.12149

OFFICIAL COMMUNICATION OF THE SSC

Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

Measuring of NOACs anticoagulant effect or plasma drug levels is required in certain clinical conditions

Baglin T et al. J Thromb Haemost 2013;11:756-60

Cambridge, UK;
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acting drugs. However, there will be clinical circumstances in specific patients when measurement of the anticoagulant effect of an ODI will be required. Such clinical scenarios may include the following:

1 Bleeding;
2 Before surgery or an invasive procedure when the patient has taken the drug in the previous 24 h, or longer if creatinine clearance (CrCl) is < 50 mL min^{-1};
3 Identification of subtherapeutic or supratherapeutic levels in patients taking other drugs that are known to significantly affect pharmacokinetics;
4 Identification of subtherapeutic or supratherapeutic levels in patients at the extremes of body weight;
5 Patients with deteriorating renal function;
6 Perioperative management;
7 Reversal of anticoagulation;
8 Suspicion of overdose;
9 Assessment of compliance in patients suffering thrombotic events while on treatment (although this application may be limited by the short half-life of ODIs).

Clinical conditions in which NOACs assessment should be performed:

- **before urgent surgery or invasive procedures**
- **adverse events (bleeding or thrombosis) during th.**
- **making decision on thrombolytic therapy in stroke patients**
- **suspicion of overdose**
- **need for reversal of anticoagulation**
- **patients with severe impaired renal function**
- **in patients taking other drugs known to affect pharmacokinetics of NOACs**
- **patients with extreme of body weight (<50kg and >110kg)**

International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants

Robert C. Gosselin[1] Dorothy M. Adcock[2] Shannon M. Bates[3] Jonathan Douxfils[4] Emmanuel J. Favaloro[5] Isabelle Gouin-Thibault[6] Cecilia Guillermo[7] Yohko Kawai[8] Edelgard Lindhoff-Last[9] Steve Kitchen[10]

Gosselin et al. Thromb Haemost 2018;118:437–50.

Abstract

This guidance document was prepared on behalf of the International Council for Standardization in Haematology (ICSH) for providing haemostasis-related guidance documents for clinical laboratories. This inaugural coagulation ICSH document was developed by an ad hoc committee, comprised of international clinical and laboratory direct acting oral anticoagulant (DOAC) experts. The committee developed consensus recommendations for laboratory measurement of DOACs (dabigatran, rivaroxaban, apixaban and edoxaban), which would be germane for laboratories assessing DOAC anticoagulation. This guidance document addresses all phases of laboratory DOAC measurements, including pre-analytical (e.g. preferred time sample collection, preferred sample type, sample stability), analytical (gold standard method, screening and quantifying methods) and post analytical (e.g. reporting units, quality assurance). The committee addressed the use and limitations of screening tests such as prothrombin time, activated partial thromboplastin time as well as viscoelastic measurements of clotting blood and point of care methods. Additionally, the committee provided recommendations for the proper validation or verification of performance of laboratory assays prior to implementation for clinical use, and external quality assurance to provide continuous assessment of testing and reporting method.

Keywords

- direct oral anticoagulants
- laboratory measurement
- laboratory guidance
- recommendations

Guidance document containing consensus recommendations for laboratory measurements of NOACs including all phases:

- **pre-analytical** (sample collection and type, sample stability)
- **analytical** (gold standard, limitations of screening tests, quantitative methods for NOACs)
- **post analytical** (reporting units, quality assurance)

Effects of NOACs on screening coagulation test results

Assay	Direct inhibitor of thrombin	Direct inhibitors of FXa
PT	↑	↑↑
APTT	↑↑	↑
TT	↑↑↑	No
Fibrinogen	↓/No	No
D-dimer	No	No

depends on:

- particular NOAC drug (different effects on individual screening tests
- time of sampling in relation to the last drug intake (peak *vs* trough concentration)
- sensitivity of different commercial reagents for the same screening assay

Direct thrombin inhibitor (DTI): dabigatran

Impact on screening coagulation assays: PT, APTT, TT

- APTT is more sensitive test than PT
- different commercial reagents for APTT (PT) show very different sensitivity for DTI (remarkable between-reagent variability)
- results of APTT and PT within reference range do not exclude therapeutic concentration
- nonstandardized assays for DTI
- TT test = too sensitive (unmeasurable values ; TT > 150 s) at low concentrations
- normal thrombin time suggests very low (not clinically relevant) level of dabigatran in circulation

- specific quantitative methods should be used in all clinical situations intended for DTI measurement

DABIGATRAN, clinical indication: NVAF, dose 2x150 mg

DABIGA-TRAN ng/mL	Dabi (ng/mL) Median (95%CI) IQR Range	PT% Median (95%CI) IQR	APTT (s) Median (95%CI) IQR	APTT ratio Median (95%CI) IQR	TT (s) Median (95%CI) IQR
PEAK (n = 42)	165 (125 – 204) 102 – 249 14 - 415	53 (48 – 66) 46 – 77	45.5 (42 – 49) 39 - 52	1.6 (1.4 – 1.7) 1.4 – 1.8	>150 (37/42) (>150) >150
TROUGH (n = 42)	97 (61 – 120) 52 – 157 5 - 278	72 (59 – 77) 55 – 86	37.5 (34 – 42) 33 - 44	1.3 (1.2 – 1.4) 1.1 – 1.5	>150 (25/42) (122 - >150) 111 - >150
P	<0.001	0.012	<0.001	<0.001	0.024

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Peak = two hours after the last dose intake
Trough = before the next drug dose

Direct inhibitors of FXa: rivaroxaban, apixaban, edoxaban

Effect on screening coagulation assays: PT, APTT, TT

- PT is more sensitive test than APTT
- different commercial reagents show different sensitivity for FXa inhibitors (remarkable between-reagent variability)
- results of PT and APTT within reference range do not exclude therapeutic concentration
- TT test is not affected
- nonstandardized assays for inhibitors of FXa

- specific quantitative methods should be used in all clinical situations intended for measurement of FXa inhibitors

RIVAROXABAN, clinical indication NVAF; dose: 1x20 mg

RIVARO-XABAN ng/mL	Median (95%CI) IQR	Range (min – max)	PT (% akt.) Median (95%CI), IQR	APTT (s, ratio) Median (95%CI) IQR	Fib (g/L) Median (95%CI) IQR
PEAK (n= 35)	**189 (138 -240) 124 - 276**	**85 - 468**	**63 (55 – 67)**	**33 (30 – 39)** 28.5 – 40.0 **1.1 (1.0 – 1.3)** 1.0 – 1.4	**3.6 (3.2 – 3.9)** 3.1 – 4.0
TROUGH (n= 35)	**36 (23 –93) 15 - 109**	**1 - 311**	**85 (72 – 91)**	**29 (28 – 30)** 27 – 31 **1.0 (0.9 – 1.1)** 0.9 – 1.1	**3.6 3.1 – 4.0** 3.0 – 4.1
P	**< 0,001**		**0.001**	**0.003 (s) 0.021 (o)**	**0.883**

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Peak = two hours after the last dose intake
Trough = before the next drug dose

APIXABAN; clinical indication: NVAF; dose 2x5 mg

APIXABAN ng/mL	Median (95%CI) IQR, range	PT (% akt.) Median(95%CI) IQR	APTT (s, ratio) Median (95%CI) IQR	Fibrinogen (g/L) Median (95%CI) IQR
PEAK (n = 44)	180 (160 – 206) 142 – 224 60 - 385	87 (80 – 94) 74 – 96	27 (27 – 28) 26 – 29 0.95 (0.9 – 1.0) 0.9 – 1.0	3.5 (3.3 – 3.8) 3.1 – 4.4
TROUGH (n = 44)	89 (67 – 125) 56 – 135 10 - 238	91 (83 – 96) 81 – 102	26 (26 – 27) 25 – 28 0.90 (0.9 – 1.0) 0.9 – 1.0	3.6 (3.2 – 4.0) 3.2 – 4.9
P	**<0.001**	**0.150**	**0.103**	**0.511**

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Peak = two hours after the last dose intake
Trough = before the next drug dose

Screening coagulation tests and NOACs

not suitable for laboratory assessment of NOACs

but both laboratory experts and treating clinicians should thoroughly understand **the limitations of the widely available screening assays.**

Knowing the impact of NOACs on the results of screening coagulation assays is a precondition for correct result interpretation.

Laboratory assessment of NOACs

Screening coagulation assays: PT, APTT, TT

Only rough estimation of the relative intensity of anticoagulation

Should not be used for the quantitative measurement of NOAC concentrations.

QUANTITATIVE ASSAYS

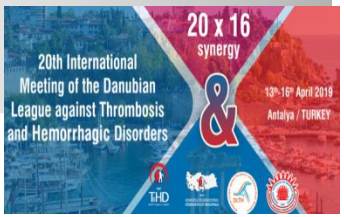
- **Direct: LC-MS/MS**
- **Indirect: coagulation assays based on clotting or chromogenic principles**

For the quantitative measurement of NOAC concentrations in plasma

QUANTITATIVE ASSAYS FOR NOACs

1. Liquid chromatography with tandem mass spectrometry (LC/MS-MS)

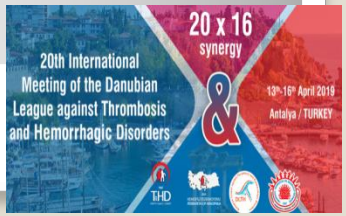
- *gold standard* method
- sample: serum or plasma (lithium heparin and EDTA anticoagulated)
- accurate measure of a wide range of NOAC conc. (5 – 500 ng/mL)
- not appropriate for widespread use in the clinical setting:
  - labour-intensive sample preparation steps
  - complexity of the technique
  - low instrument availability and high cost
- used for research purposes only



QUANTITATIVE ASSAYS FOR NOACs

2. Specific coagulation assays

- clotting and chromogenic measuring principles
- based on methods closely related to the anticoagulant targets and mechanism of action of particular NOAC drug
- standard calibration curve with drug specific calibrators
- accurate quantitative measurement of NOACs = reportable range up to 500 ng/mL – suitable for expected peak and trough concentrations in most patients



Direct thrombin inhibitor (DTI): dabigatran

Quantitative methods for measurement of DTI concentrations

Clotting methods

1. dTT - diluted thrombin time test
2. Ecarin clotting test (ECT)

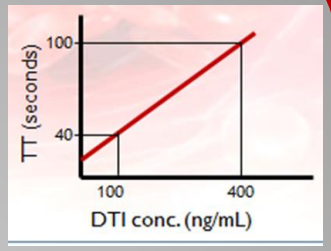
Chromogenic methods

1. Ecarin chromogenic assay (ECA)
2. Anti-FIIa assay

Clotting methods

Diluted thrombin time test (dTT)

Modification of standard TT test with plasma dilution (1:8 or 1:20) with normal plasma and using dabigatran standards to calculate dabigatran concentrations – linear relationship of dTT and DTI conc.



ECT (ecarin clotting test)

FII —ecarin→ meizothrombin —DTI→ FIIa

Chromo-genic methods

ECA (ecarin chromogenic assay)

FII —ecarin→ meizothrombin —DTI→ chrom. sups.- pNA → tripeptid + colour (405 nm)

Anti-FIIa assay

DTI + FIIa(s) → DTI - FIIa + FIIa(residual)

FIIa(res) + chrom. sup. for FIIa → tripeptid + colour (405 nm)

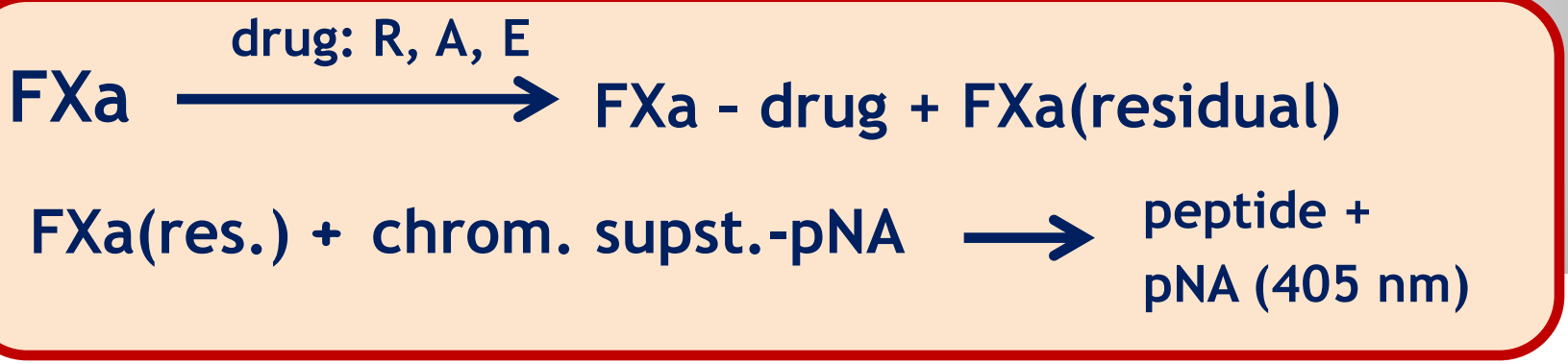
Direct inhibitors of FXa: rivaroxaban, apixaban, edoxaban

Quantitative assays are based on chromogenic measuring principle

Anti-FXa

also for monitoring of heparins (LMWH)

using drug specific calibrators for standard calibration curve



Potential application of chromogenic anti-FXa assay calibrated with LMWH measurement in patients treated with rivaroxaban and apixaban: possibilities and limitations.

Drug peak and trough concentration (ng/mL)				Heparin anti-Xa activity (IU/mL)	
	N	Median and IQR	P	Median and IQR	P
Apixaban peak	30	**157** 119 – 224	0.745	**0.80** 0.68 – 0.95	0.011
Rivaroxaban peak	30	**150** 122 – 200		**0.59** 0.52 – 0.72	
Apixaban trough	23	**48** 44 – 58	<0.001	**0.14** 0.11 -0.26	0.099
Rivaroxaban trough	31	**19.7** 12– 37		**0.11** 0.00 – 0.23	

LMWH-calibrated anti-FXa activity assay has a discriminating power between peak and trough concentrations of both rivaroxaban and apixaban

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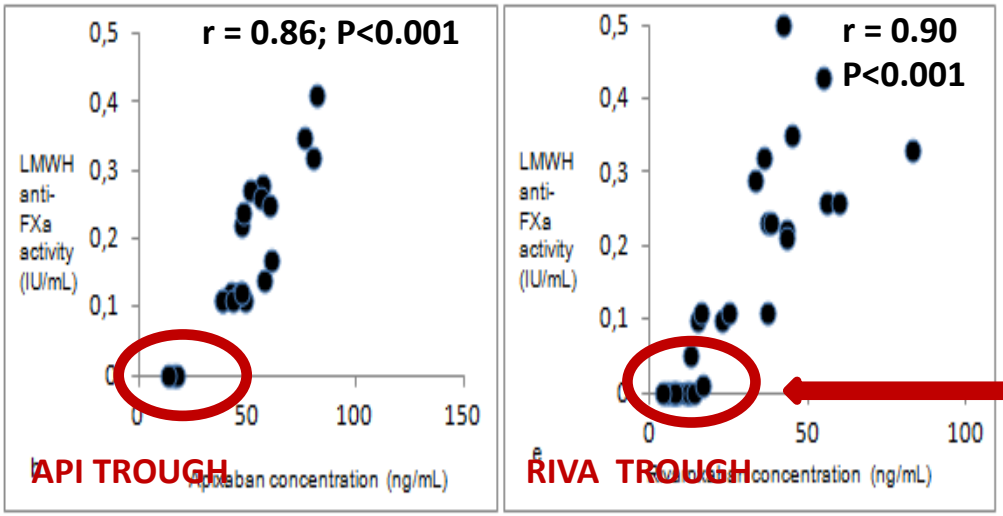
Potential application of chromogenic anti-FXa assay calibrated with LMWH measurement in patients treated with rivaroxaban and apixaban: possibilities and limitations



Measurement range for LMWH anti-FXa activity (0.05 – 1.26 IU/mL) was equivalent to concentrations of 30 - 300 ng/mL for both drugs

Value of 0.05 IU/mL (LLQ) corresponded to the conc. below 30 ng/mL for both drugs

Conc. of both drugs > 300 ng/mL can not be quantified

LMWH anti-FXa assay can be used in emergent clinical conditions for excluding the presence of clinically relevant concentrations (30 ng/mL) of rivaroxaban and apixaban but is not appropriate for quantitative determination of these drugs in terms of an interchangeable method

Important characteristics of available quantitative methods for NOACs

- Reagent stability after reconstitution:
  8 weeks (2 months) at 2 – 8°C
- Reportable range of quantitation ~ 20 - 500 ng/mL (adequate for both peak and trough conc.)
- Emergency testing possible (TAT 60 min)
- IQC: Internal quality control: two levels (low and high)
- EQC: External quality control providers (ECAT, UKNEQAS...)
- Assays can be implemented on almost any automated coagulation analyzer

Important preanalytical factors of quantitative coagulation assays for NOACs

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- Blood sampling: 3,2% sodium-citrate
- Analytical sample: platelet poor plasma (PPP)

Sample stability

Drug	Room temp. (h)	5°C	-20°C
Dabigatran	24 h	24 h	min. 30 days
Rivaroksaban	8 h	48 h	min. 30 days
Apiksaban	8 h	48 h	min. 30 days

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Important preanalytical factors

Time of sampling

- **Non urgent clinical situations: determination of TROUGH concentration is recommended:**
  - **lower inter-individual variability of trough *vs* peak conc.**
  - **better correlation with adverse events: bleeding, thrombosis**

- **Urgent clinical situations:**
  - **sampling to obtain trough conc. usually not applicable (sampling at any time usually must be performed)**

Knowing the time of sampling in relation to the last drug intake is crucial for the proper interpretation of results!

Postanalytical phase: result reporting

- **reporting unit: ng/mL**
- **therapeutic ranges are not defined, but published expected trough (or peak) plasma levels correlating with dose should be reported with the test result**

Consensus Document 43

International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants

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	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE
Dose	150 mg bid	150 mg bid	20 mg qd	20 mg qd	5 mg bid	5 mg bid	60 mg qd	60 mg qd
Peak concentration, ng/mL	175[a] (117–275)	175[a] (117–275)	249[b] (184–343)	270[b] (189–419)	171[c] (91–321)	132[c] (59–302)	170[d] (125–245)	234[e] (149–317)
Trough concentration, ng/mL	91[a] (61–143)	60[a] (39–95)	44[b] (12–137)	26[b] (6–87)	103[c] (41–230)	63[c] (22–177)	36[e] (19–62)	19[e] (10–39)

Abbreviations: bid, twice daily; IQR, interquartile range; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; qd, once daily; VTE, venous thromboembolism.

Notes: Other approved indications for DOACs include secondary prevention of PE/VTE, and post hip and knee replacement, which may have alternative dosing strategies. Additionally, changes in doses may occur after initiation phase of DOAC treatment. Consultation of regional DOAC labeling information is required before interpreting or using these peak and trough DOAC concentration data.

[a]Mean (25th–75th percentile).

[b]Mean (5th–95th percentile).

[c]Median (5th–95th percentile).

[d]Median (1.5 x IQR).

[e]Median (IQR).

Clinical indication: NVAF, recommended dosing

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DABIGATRAN ng/mL	Median (95%CI)	IQR	Range (min – max)	Published expected values
Peak (n = 42)	165 (125 – 204)	102 - 249	14 - 415	175 (117 – 275)
Trough (n = 42)	97 (61 – 120)	52 - 157	5 - 278	91 (61 – 143)

RIVAROXBAN ng/mL	Median (95%CI)	IQR	Range (min – max)	Expected values
Peak (n= 35)	189 (138 -240)	124 - 276	85 - 468	249 (184 - 343)
Trough (n= 35)	36 (23 – 93)	15 - 109	1 - 311	44 (12 – 137)

APIXABAN ng/mL	Median (95%CI)	IQR	Range (min – max)	Expected values
Peak (n= 44)	180 (160 – 206)	142 - 224	60 - 385	171 (91 - 321)
Trough (n= 44)	89 (67 – 125)	56 - 135	10 - 238	103 (41 – 230)

Impact of NOACs on specialized haemostasis testing – thrombophilia testing

Assay	Direct inhibitor of thrombin	Direct inhibitors of FXa
Protein C coagulom.	↑ (FN)	↑ (FN)
Protein C chromogenic	No	No
Protien S coagulom.	↑ (FN)	↑ (FN)
Lupus anticoagulant	↑ (FP)	↑↑ (FP)
APCR	↑ (FN)	↑ (FN)
Antithrombin based on FIIa m.	↑ (FN)	No
Antithrombin based on FXa m.	No	↑ (FN)
FVIII	↓ (FN)	↓ (FN)

Most of assays for thrombophilia should not be performed in patients on NOACs due to the impact of NOACs in terms of FN or FP test results !!!

FN = false negative result; FP = false positive result

Thank you for attention...

with greetings from Croatia

HRZZ
Croatian Science Foundation

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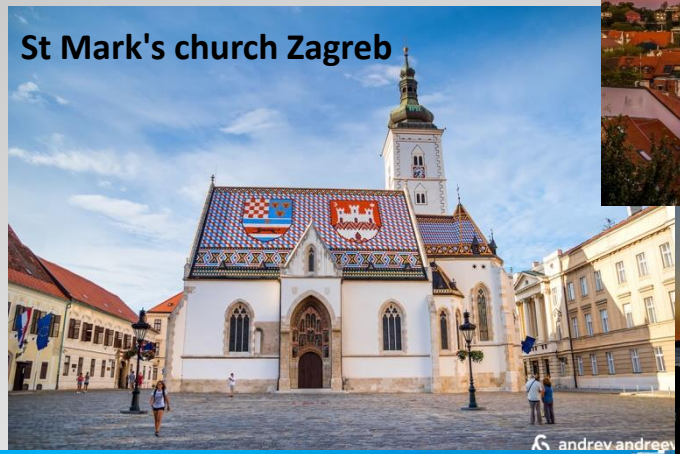
Zagreb old town


St Mark's church Zagreb


Greeting to the sun, Zadar


Dubrovnik


Plitvice lakes