NOAC

Role of the Clinical Laboratory in Patients receiving New Oral Anticoagulants

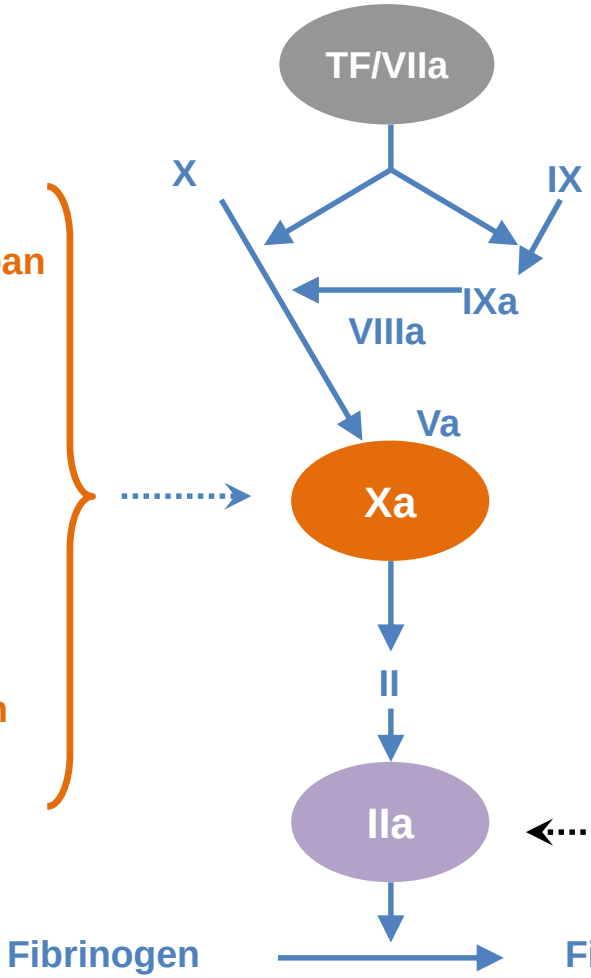
NOACs

Target a single coagulation factor

rivaroxaban
(Xarelto®)

apixaban
(Eliquis®)

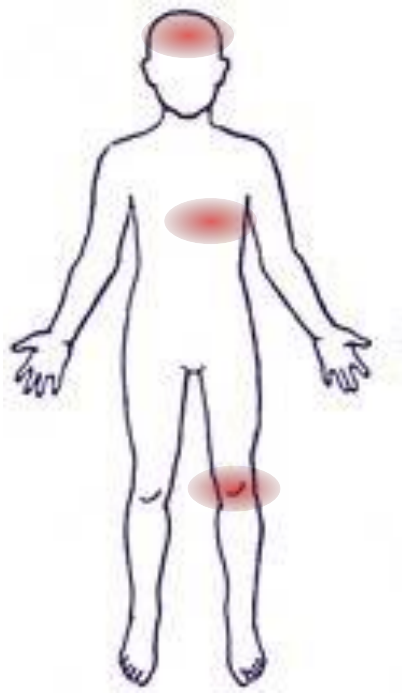
edoxaban
(Lixiana®)



dabigatran
(Pradaxa®)

Potential indications for NOACs

- VTE Prophylaxis in Major Orthopedic Surgery (MOS)
- Stroke Prevention in Atrial Fibrillation (SPAF)
- VTE Treatment (Rx)
- VTE Prophylaxis in Medical Patients (MED)
- VTE recurrence prophylaxis (REC)
- Acute Coronary Syndromes (ACS)
- Prosthetic Heart Valves (PHV)



NOACs

What are they approved for?

Europe	MOS	SPAF	Rx	MED	REC	ACS	PHV
dabigatran etexilate **Pradaxa®**	√	√					X
rivaroxaban **Xarelto®**	√	√	√		√	√	
apixaban **Eliquis®**	√	√				X	
edoxaban **Lixiana®**	√ *Only in Japan*						

As of April 2013, 5th

Situations requiring laboratory control

Oral direct inhibitors of factor IIa and Xa

- **Bleeding**
- Before surgery or invasive procedure
  - the patient has taken the drug
    - in the previous 24h
    - or longer if creatinine clearance is < 50 mL / min
- Identification of sub- and supratherapeutic levels in patients
  - taking other drugs known to significantly affect pharmacokinetics
  - at extremes of body weight
  - with deteriorating renal function
- Suspicion of overdose

Baglin T *et al*. Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the SSC of the ISTH. J Thromb Haemost 2013; 11: 756-60.

French GIHP* recommendation

Perioperative situations

Can I perform surgery on my patient under rivaroxaban or dabigatran?

Drug concentration

< 30 ng/mL	30 - 200 ng/mL	200 - 400 ng/mL	> 400 ng/mL
Perform surgery	• Wait 12h and **repeat drug measurement** • If surgery cannot wait, **perform surgery** • In case of **abnormal bleeding,** consider antidote (PCC or FEIBA)**	• Wait 12-24h and **repeat drug measurement** • If surgery cannot wait, **delay surgery** as much as possible • In case of **abnormal bleeding,** consider antidote (PCC or FEIBA)**	**Overdose, risk of major bleeding**

Pernot G, Abaladejo P.: GIHP recommendation, *February 2013, available at eurekapro.fr*

* Groupement d'Intérêt en Hémostase Périopératoire

*** PCC: Prothrombin Complex Concentrate - FEIBA: Factor Eight Inhibitor Bypass Activity*

Limitations of "non specific test“

Example of PT test

- **PT** is not specific
  - may be prolonged in case of factor deficiency, LA…
  - risk of drug concentration overestimation
- **PT baseline** is not always available
- Apixaban induces no / limited **PT prolongation**
- **PT prolongation** depends on reagent sensitivity

➔ **PT** is not recommended to estimate NOAC blood concentration

Limitations of “non specific test”

Example of aPTT test

- **aPTT: measures activity of various factors**
- **Anti-IIa drug (dabigatran)**
  - curvilinear dose-response
  - steep increase at low concentrations
  - normal aPTT cannot exclude significant anticoagulant level onboard
- **Anti-Xa drugs: aPTT is not sensitive enough**
  - no prolongation or minimal prolongation…

➔ **aPTT** test: “not suitable” for NOAC activity determination

Anticoagulant line

A comprehensive product portfolio

Prevention & treatment of venous thromboembolic disease

VKA	Heparins	fondaparinux	Anti-Xa	DTI
	• UFH • LMWH	• calibrator	• rivaroxaban • apixaban • edoxaban	• argatroban • dabigatran • bivalirudin

treatments — New oral anticoagulants

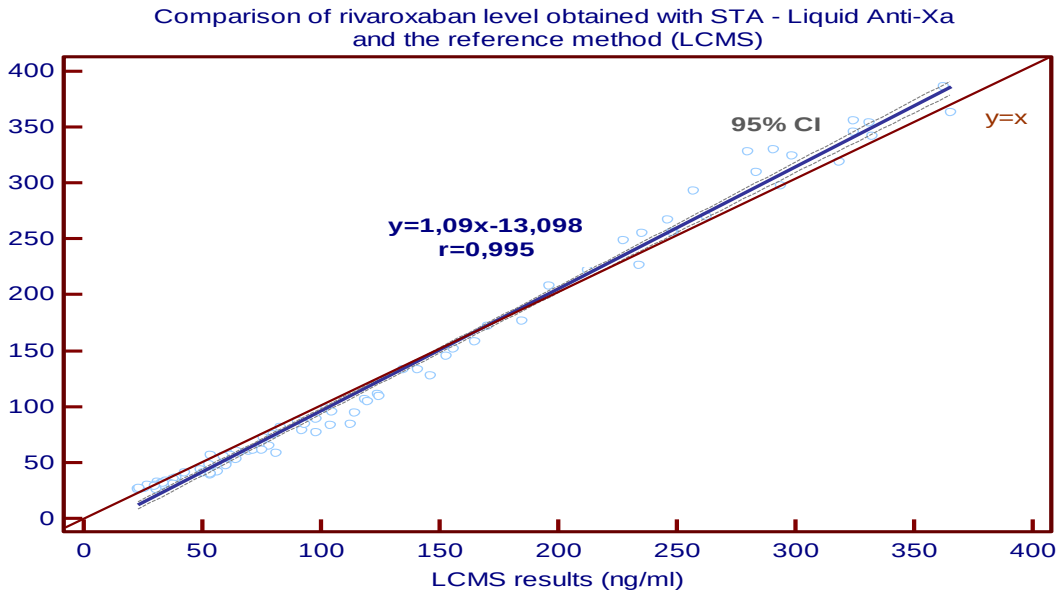
Stago ranges

PT/INR	Anti-Xa range With calibrators and specific QC	ECA range

Validation study - Results

LCMS versus STA®-Liquid Anti-Xa – rivaroxaban

- Working range: 25-500 ng/mL



Slope	1,09
Intercept	-13,08
Coefficient of correlation	0,995

➔ Very good correlation between LCMS and STA® - Liquid Anti-Xa

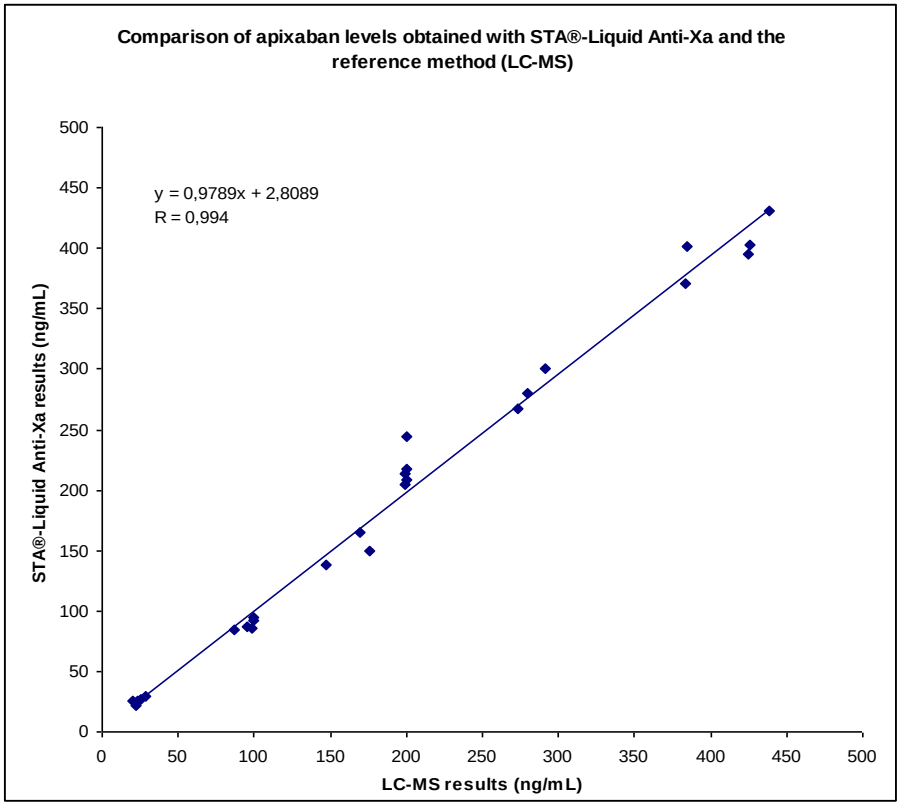
Validation study of STA-Rivaroxaban Cal & Ctrl (Saint Etienne University Hospital, 2012

Validation study - Results

LCMS versus STA®-Liquid Anti-Xa - apixaban

- Working range: 20-800 ng/mL

Slope	0.9789
Intercept	+2.8089
Coefficient of correlation	0.994

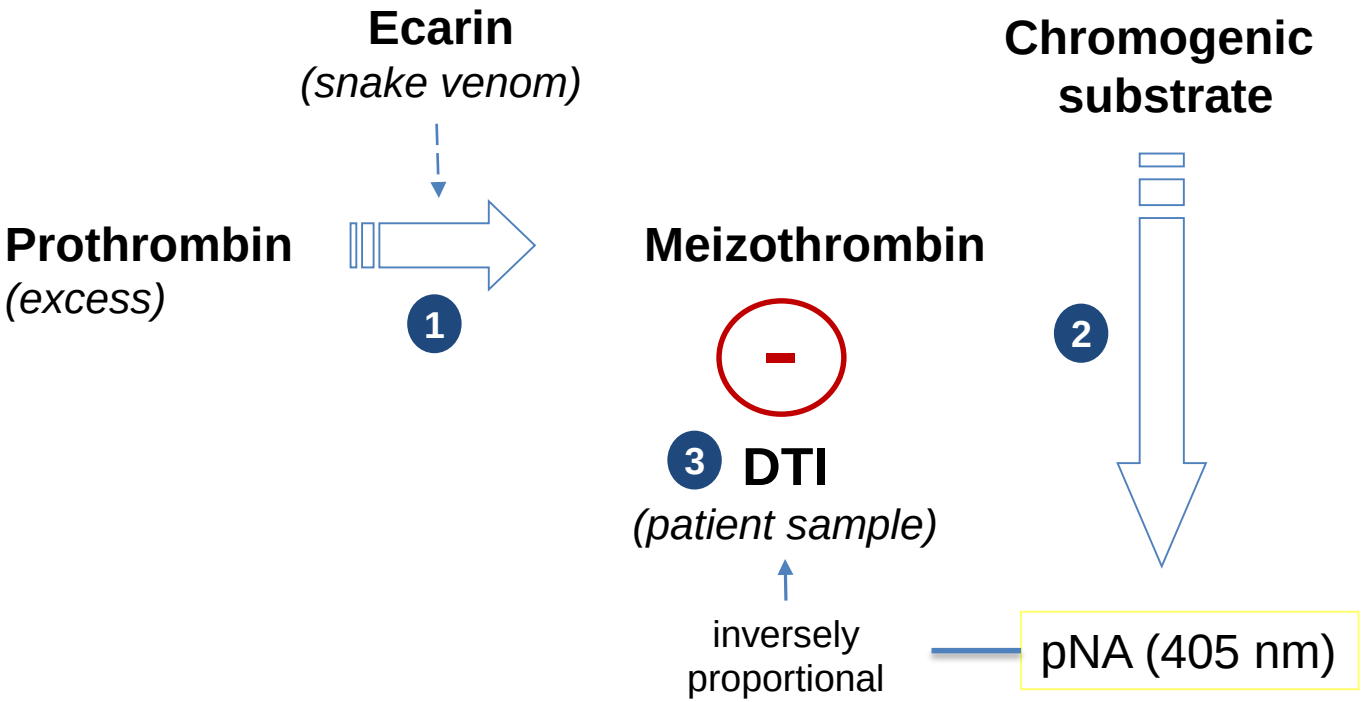


➔ Very good correlation between LCMS and STA® - Liquid Anti-Xa

Internal Stago data (Research and Development)

Anti-IIa range: ECA line

Principle



➔ **Chromogenic** assay derived from the Ecarin Clotting Time (ECT)
➔ allows the **exact DTIs concentration measurement**
➔ **No influence** of coagulation factors or inhibitors of the sample

Ecarin Clotting Time (ECT) *vs* Ecarin Chromogenic Assay (ECA)

ECT

- Clotting test
- Reference assay, but sensitive to
  - Factor II
  - Fibrinogen level
- Not standardized
- Not commercially available

ECA

- Chromogenic assay
- NOT sensitive to factor levels
- Standardized, fully automated
- CE marked

Conclusion

- NOAC do not require routine monitoring
  - but **measurement can be helpful** in special populations and/or in special clinical situations
  - **PT and APTT are not relevant** for accurate drug concentration assessment

- Stago offers a **comprehensive portfolio** for NOAC plasma concentration measurement
  - using **specific assays** along with **dedicated calibrators and controls** (STA®-Liquid Anti-Xa + dedicated Cal & Crl / ECA line + dedicated Cal & Ctrl)