Il laboratorio nella gestione delle terapie anticoagulanti

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"Old" Anticoagulant Drugs

	Unfractionated Heparin			
Mechanism	Fast acting Antithrombin-mediated IIa & Xa inhibitor			
Administration	IV			
Lab monitoring for dose-adjustment	YES, APTT or anti-FXa assay			

"Old" Anticoagulant Drugs

	Unfractionated Heparin	**LMWH**		
Mechanism	Fast acting Antithrombin-mediated IIa & Xa inhibitor	Fast acting Antithrombin-mediated Xa inhibitor		
Administration	IV	SC		
Lab monitoring for dose-adjustment	YES, aPTT or anti-FXa assay	NO (in general)		

"Old" Anticoagulant Drugs

	Unfractionated Heparin	**LMWH**	**Fondaparinux**	
Mechanism	Fast acting Antithrombin-mediated IIa & Xa inhibitor	Fast acting Antithrombin-mediated Xa inhibitor	Fast acting Antithrombin-mediated Xa Inhibitor	
Administration	IV	SC	SC	
Lab monitoring for dose-adjustment	YES, aPTT or anti-FXa assay	NO (in general)	NO	

"Old" Anticoagulant Drugs

	Unfractionated Heparin	**LMWH**	**Fondaparinux**	**VKA**
Mechanism	Fast acting Antithrombin-mediated IIa & Xa inhibitor	Fast acting Antithrombin-mediated Xa inhibitor	Fast acting Antithrombin-mediated Xa Inhibitor	Slow acting carboxylation-mediated reduction of VII, IX, X, II, PC, PS
Administration	IV	SC	SC	Oral
Lab monitoring for dose-adjustment	YES, aPTT or anti-FXa assay	NO (in general)	NO	YES, the INR

aPTT for unfractionated heparin

- Variable responsiveness of commercial aPTT
- Need to determine locally the therapeutic interval
- Affected by other variables (i.e., factor VIII)
- Simple to do and cheap

INR for VKA

- Simple to do and cheap
- Well established therapeutic interval (2.0-3.0)
- Safe and effective for the majority of patients
- Interval of validity 1.5-4.5
- Valid only for patients on VKA

The laboratory & the DOAC

- *Need for testing*
- Usefulness of measuring the effect of DOAC
- How to measure the effect of DOAC
- When to measure
- Alerting values
- DOAC Effect on the most common hemostatic parameters

Is there any need for DOAC dose-adjustment based on laboratory testing?

No!!

Clinical trials showed that fixed doses are effective and safe

…However

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The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PHD,* Thorsten Lehr, PHD,†‡ Sebastian Haertter, PHD,†
Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPHIL,§ John W. Eikelboom, MB BS,§
Michael D. Ezekowitz, MD, PHD,‖ Gerhard Nehmiz, PHD,† Susan Wang, PHD,*
Lars Wallentin, MD, PHD,¶ on behalf of the RE-LY Investigators

In some patients who are at the extremes of the concentration range and have one or more risk factors (i.e., old age, reduced creatinine clearance or low body weight),

BETTER OUTCOMES MIGHT BE ACHIEVED BY ADJUSTING THE DOSAGE

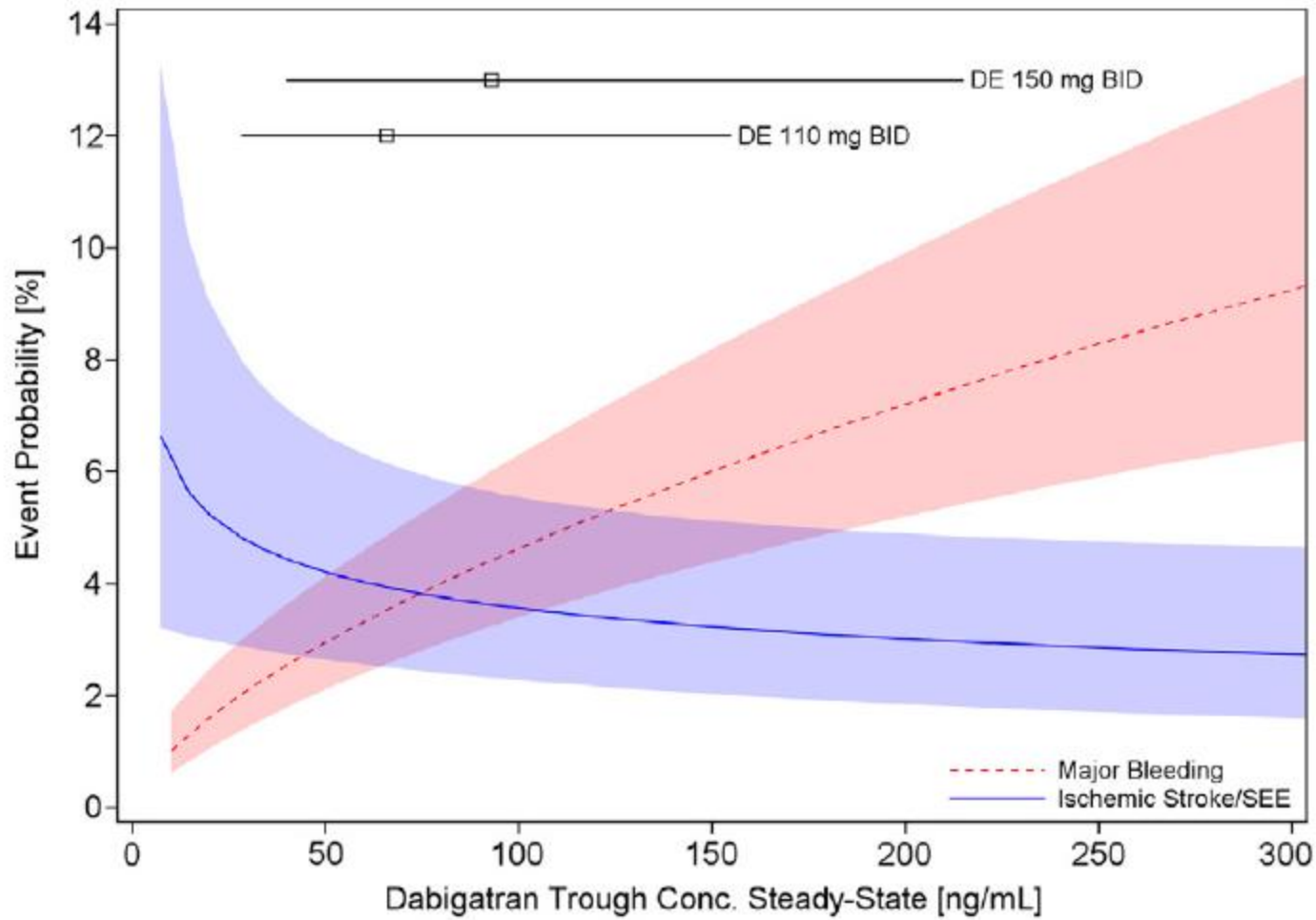

Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Cosa fare secondo lo stato dell'arte

The Laboratory & the Anticoagulants

- *Monitoring*
- Implies dose-adjustment based on test results (VKA, UFH, LMWH)
- *Measuring*
- Implies determining the anticoagulant effect (DOAC)

The laboratory & the DOAC

- Need for testing
- *Usefulness of measuring the effect of DOAC*
- How to measure the effect of DOAC
- When to measure
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Usefulness of measuring the effect of DOAC

- ***Required***
- At baseline (before initiation of treatment)
- Before surgical/invasive procedures
- Adverse events (hemorrhage or thrombosis)
- Make decision on thrombolytic therapy in stroke patients
- ***Useful***
- Soon before and after introducing additional drugs
- Extreme body weight
- ***Potentially useful***
- When chronic anticoagulation is achieved (1-2 weeks after initiation)
- At regular intervals during clinical visits
- Need for reversal of anticoagulation

Vantaggi/svantaggi del test prima di intervento chirurgico/manovra invasiva

Possibili opzioni prima di intervento chirurgico/manovra invasiva che preveda la sospensione del DOAC

- Sospensione del trattamento prima dell'intervento sulla base della
- *Farmacocinetica*
- *Clerance renale*
- *Conoscenza dell'ora dell'ultima somministrazione*
- Misura dell'effetto anticoagulante subito prima dell'intervento con test specifici

Sospensione del trattamento sulla base della farmacocinetica e della clerance renale

- *Vantaggi*
- Semplicità di esecuzione
- *Svantaggi*
- La clearance renale è determinata “una tantum” Stabile nel tempo??
- La clearance renale non è l’unico determinante dell’eliminazione del farmaco
- Incertezza sull’ora dell’ultima somministrazione

Conclusione

- Bisogna quindi misurare la clearance renale poco prima dell'intervento
- Quale è la differenza fra misurare la clearance renale e misurare l'effetto anticoagulante del farmaco con un test specifico?
- In quest'ultimo caso

- *Si affronterebbe il problema in maniera diretta*
- *Si disporrebbe di una prova in caso di contenzioso*

Possibili svantaggi dell'esecuzione dei test (1)

- Non c'è consenso sui test da usare
- *Falso*
- *Consenso su dTT o ECT (ECA) per dabigatran e anti-FXa per gli altri DOAC*
- I test non sono prontamente reperibili
- *Falso*
- *Tutti i test sono reperibili*
- *Facilmente eseguibili anche in emergenza*

Possibili svantaggi dell'esecuzione dei test (2)

- Mancanza di specifici cut-off
- *Vero in parte*

- Non ci sono studi ad hoc
- Ma è ragionevole ritenere che valori inferiori a 30 ng/mL siano adeguati

Possibili svantaggi dell'esecuzione dei test (3)

- Difficile organizzazione delle sale operatorie (cancellazioni di interventi)
- Eccesso di scrupolo
- Motivi difensivi
- Vero in parte
- *Non è buona pratica nascondere la polvere*
- *Meglio eliminarla*
- *Si elimina con una buona organizzazione e con molto buon senso*

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ORIGINAL ARTICLE

Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure

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Dabigatran interruption

For patients with Renal Clearance > 50 mL/min

- Last dose before
- 24h for low risk procedures
- 48h for high risk procedures

A: TRIPODI

Tests

- Activated partial thromboplastin time
- Thrombin time
- Dilute thrombin time

	All patients	Low bleeding risk	High bleeding risk
aPTT			
median (IQR), sec	32.0 (29.0-35.0)	32.0 (30.0-35.0)	30.0 (29.0-34.0)
normal (22-35 sec), n (%)††	147 (81.2)	91 (77.1)	56 (88.9)
increased (>35 sec), n (%)	34 (18.8)	27 (22.9)	7 (11.1)
TT			
median (IQR), sec	35.0 (28.0 -55.0)	40.0 (31.0-70.0)	29.0 (25.0-36.0)
normal (20-30 sec), n (%)	60 (33.1)	24 (20.3)	36 (57.1)
increased (>30), n (%)	121 (66.9)	94 (80.0)	27 (42.9)
dTT			
median (IQR), ng/mL¶	19 (19-19)	19 (19-19)	19 (19-19)
normal (<20 ng/mL), n (%)	146 (80.7)	91 (77.1)	55 (87.3)
increased (≥20 ng/mL), n (%)	35 (19.3)	27 (22.9)	8 (12.7)

Cosa fare secondo lo stato dell'arte

- Costruire linee guida ziendali, definendo le situazioni per le quali prescrivere i test
  - *Clinici (cardiologia, medicina interna, ematologia, neurologia, pronto soccorso)*
  - *Medicina di laboratorio*
- Applicare le linee guida nella pratica e verificarne periodicamente l'efficacia in termini di rapporto costo/beneficio

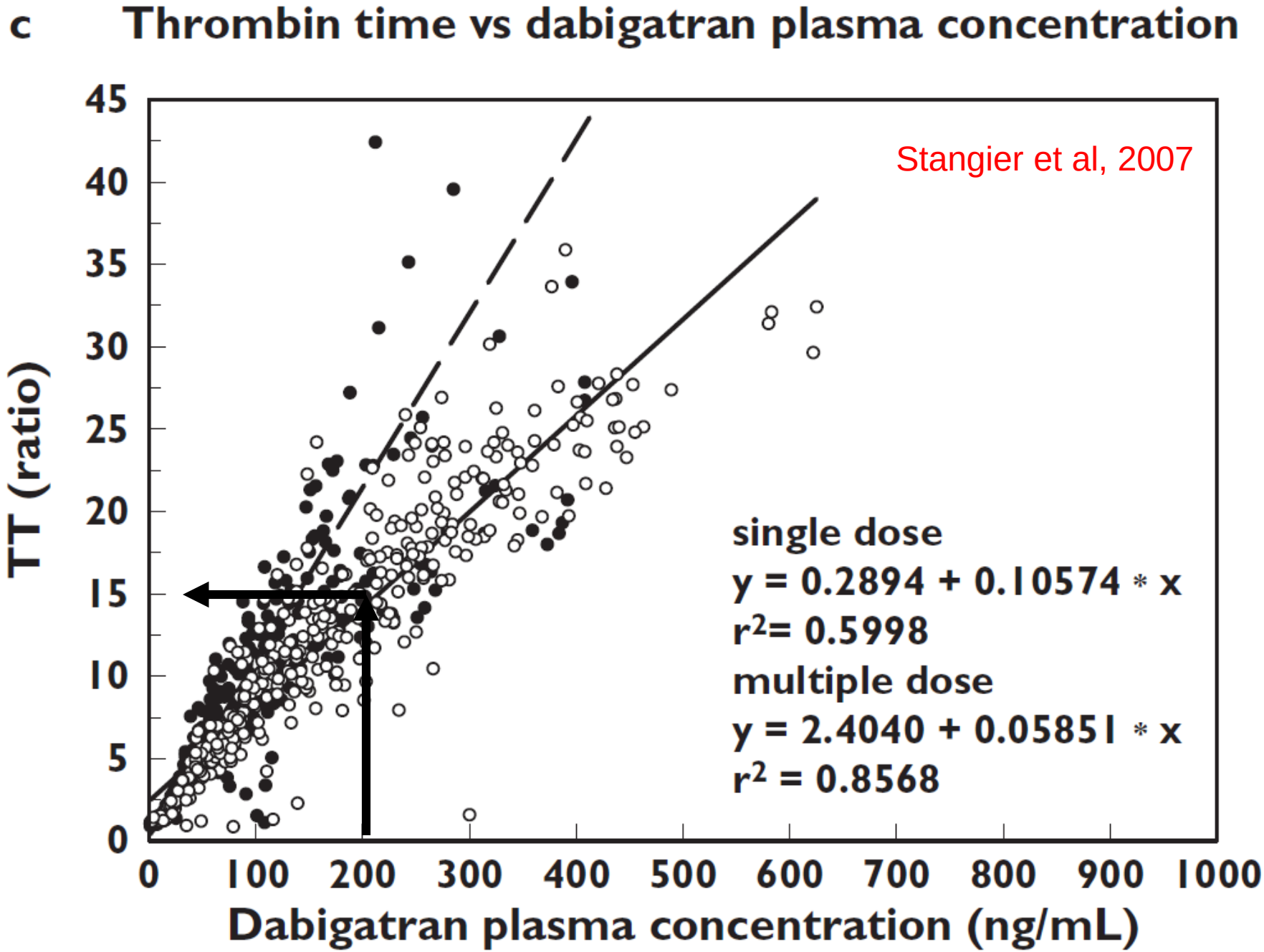
The laboratory & the DOAC

- Need for testing
- Usefulness of measuring the effect of DOAC
- *How to measure the effect of DOAC*
- When to measure
- Alerting values
- DOAC Effect on the most common hemostatic parameters

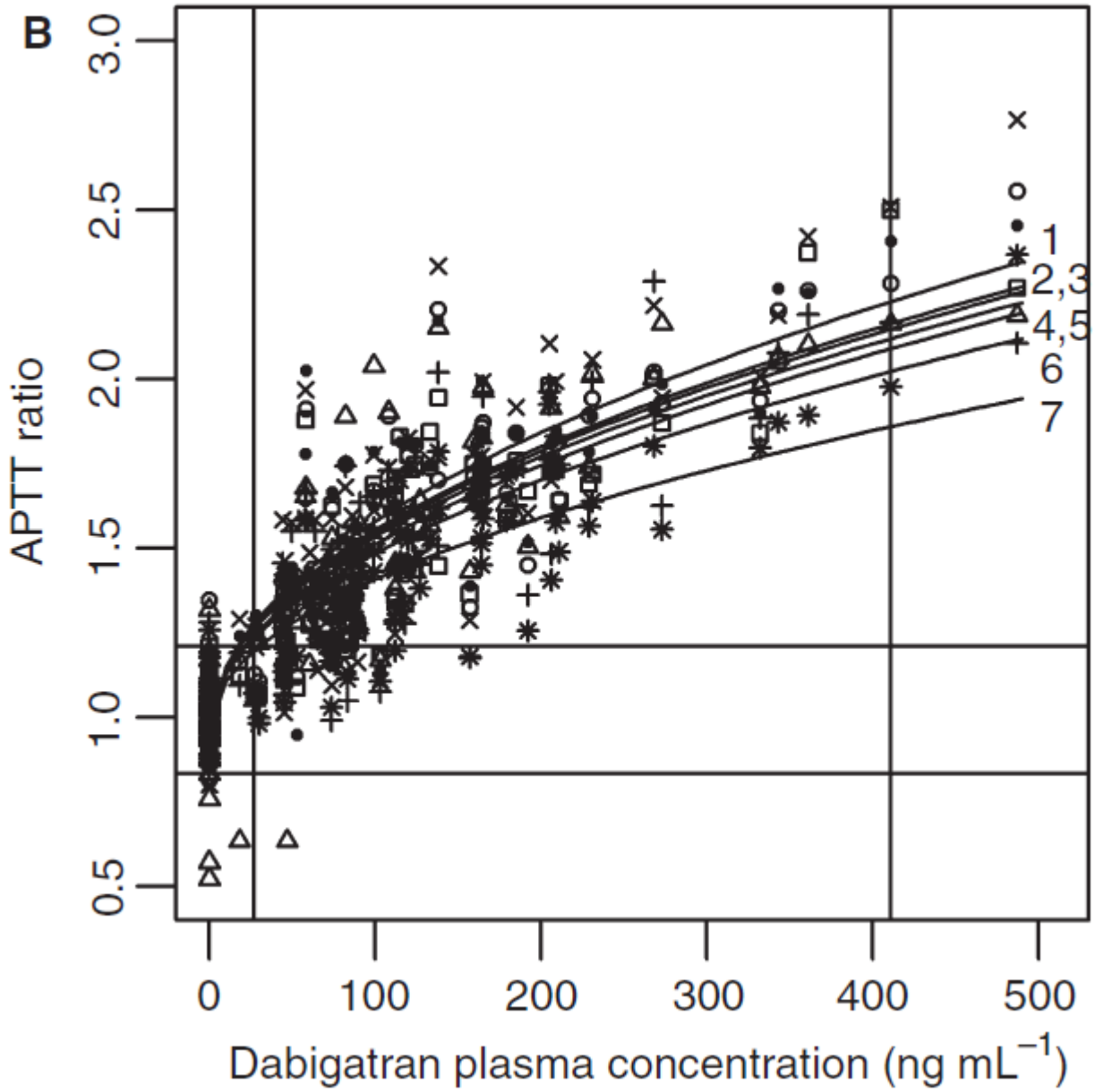
How to measure the effect of DOAC

Basic coagulation tests (i.e, PT, APTT or TT) are affected by DOAC

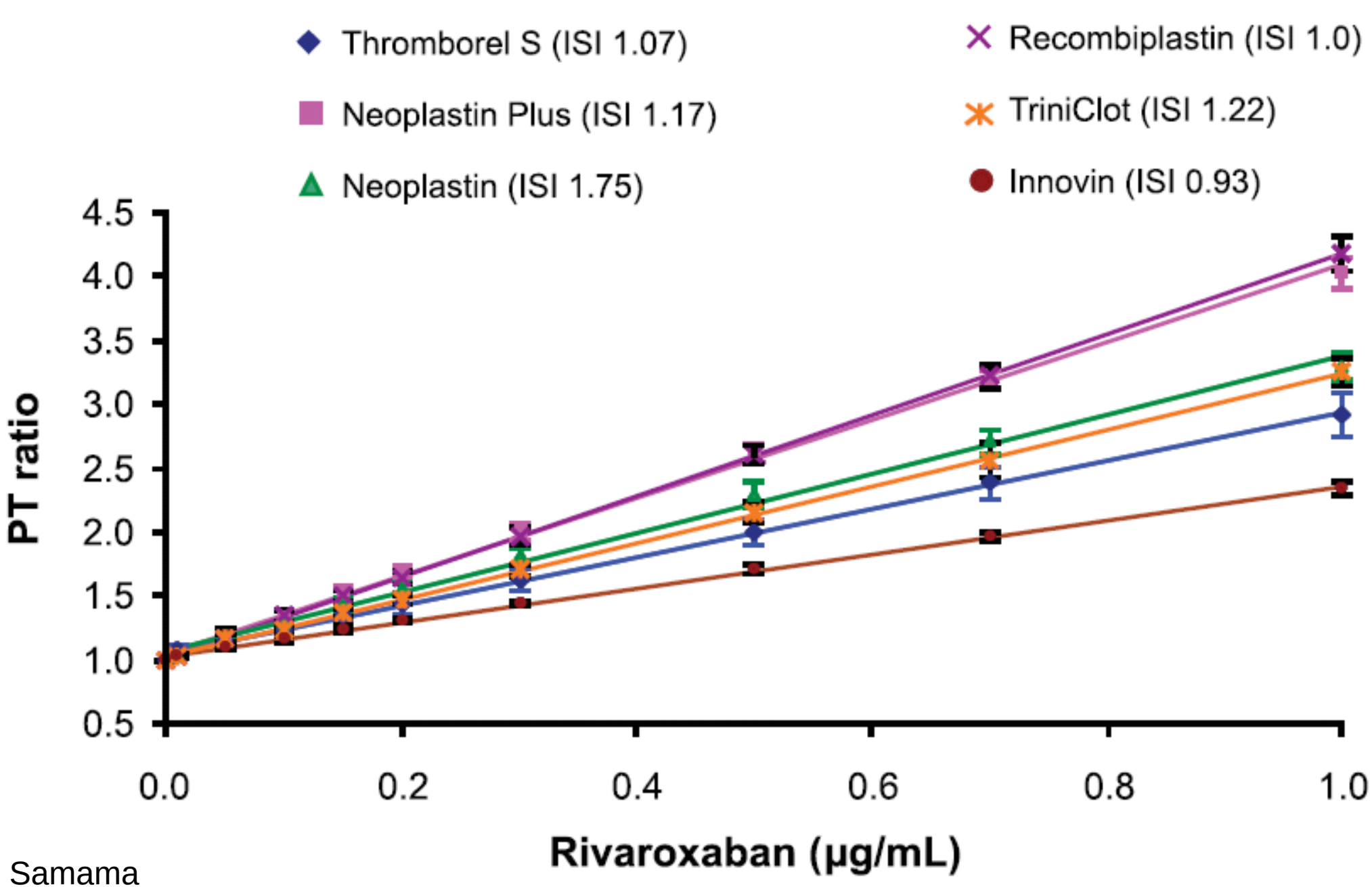
Owing to the btween-reagent variability their prolongations are not invariably related to their circulating concentrations


c
Thrombin time vs dabigatran plasma concentration
Stangier et al, 2007
single dose
y = 0.2894 + 0.10574 * x
r2= 0.5998
multiple dose
y = 2.4040 + 0.05851 * x
r2 = 0.8568
TT (ratio)
0
5
10
15
20
25
30
35
40
45
0
100
200
300
400
500
600
700
800
900
1000
Dabigatran plasma concentration (ng/mL)

Commercial APTT & Dabigatran



Hawes EM et al, 2013



Samama et al, 2010

How to measure the effect of DOAC

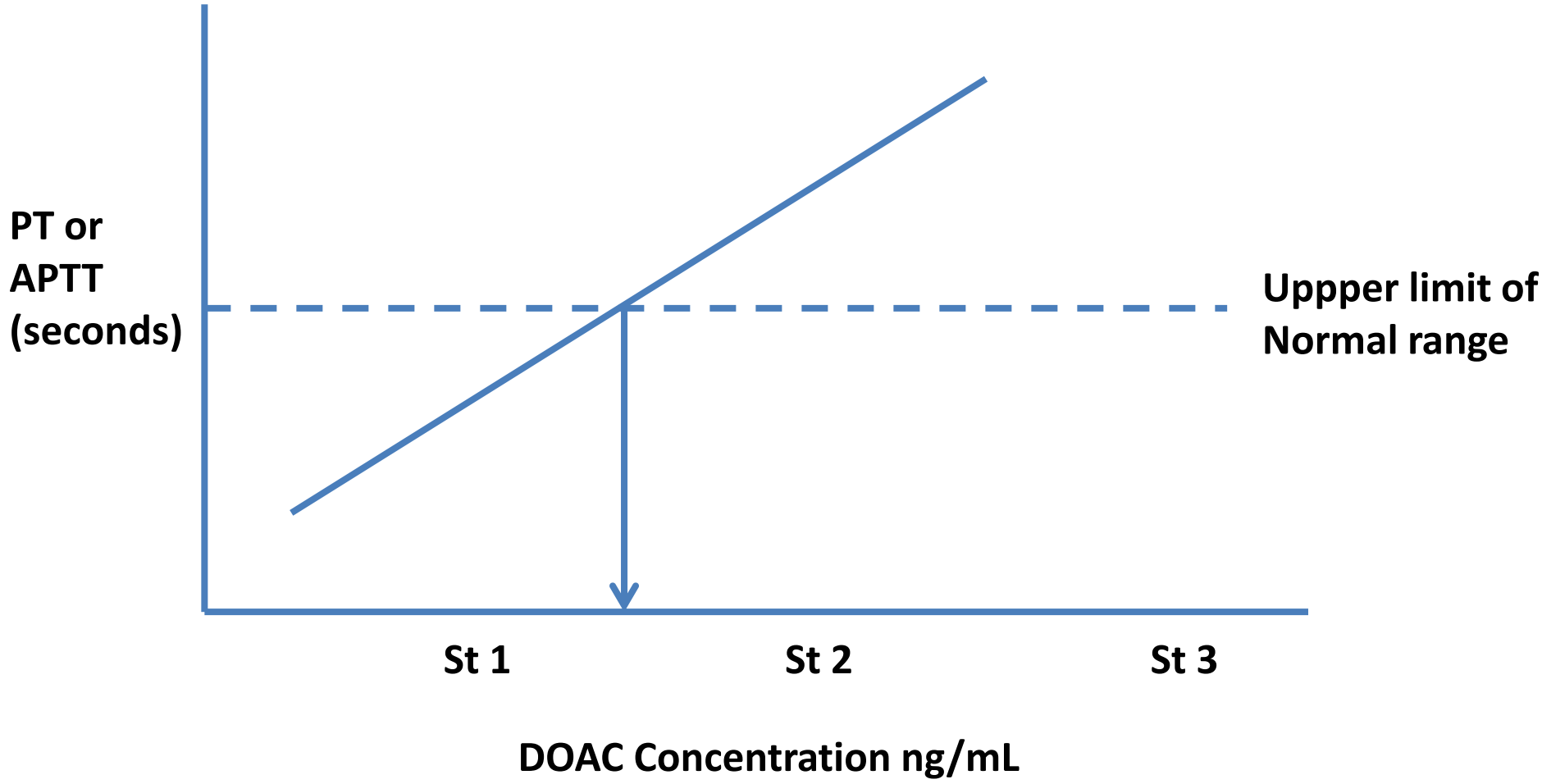
- *Dabigatran*
- *Dilute TT (or ECT)*
- *Rivaroxaban*
- *Anti-FXa or PT with a sensitive thromboplastin*
- *Apixaban*
- *Anti- FXa*

Cosa fare secondo lo stato dell'arte

- Determinare il livello di sensibilità per i DOAC del PT e APTT usati localmente
- Rendere disponibili i test specifici per i DOAC

- *dTT o ECT (dabigatran)*
- *Anti-FXa o PT con tromboplastina sensibile (rivaroxaban)*
- *Anti-FXa (apixaban)*

How to determine the responsiveness of local PT or APTT to DOAC



The laboratory & the DOAC

- Need for testing
- Usefulness of measuring the effect of DOAC
- How to measure the effect of DOAC
- *When to measure*
- Alerting values
- DOAC Effect on the most common hemostatic parameters

Laboratory & DOAC
When to measure

- DOAC reach peak value (Cmax) approximately 2 hours after ingestion
- DOAC reach Ctrough values approximately 12h (bid) or 24h (od) after ingestion
- Knowledge of timing of blood draw relatively to the last dose is essential for results interpretation

Cosa fare secondo lo stato dell'arte

Spiegare al paziente

- Quanto è importante l'adeguatezza alla terapia
- Che il rispetto dell'ora di assunzione del farmaco è molto più importante per i DOAC che per gli AVK
- L'importanza di ricordare con esattezza l'ora dell'ultima assunzione e riportarla al medico in caso di prelievo per la misura dei DOAC

Peak or trough values?

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Antithrombotic Therapy

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

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Michael D. Ezekowitz, MD, PHD,‖ Gerhard Nehmiz, PHD,† Susan Wang, PHD,*
Lars Wallentin, MD, PHD,¶ on behalf of the RE-LY Investigators

Conclusions: Dabigatran trough values are associated with bleeding events

The laboratory & the DOAC

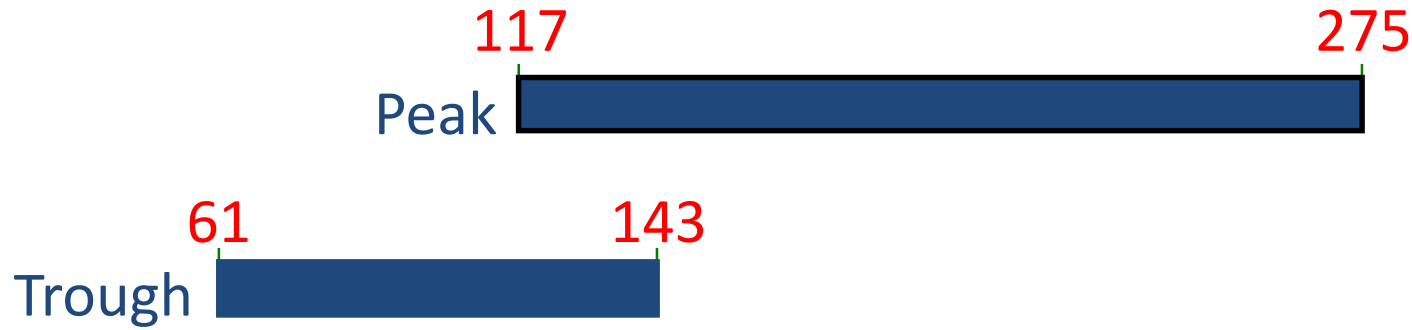
- Need for testing
- Usefulness of measuring the effect of DOAC
- How to measure the effect of DOAC
- When to measure
- *Alerting values*
- DOAC Effect on the most common hemostatic parameters

Alerting values

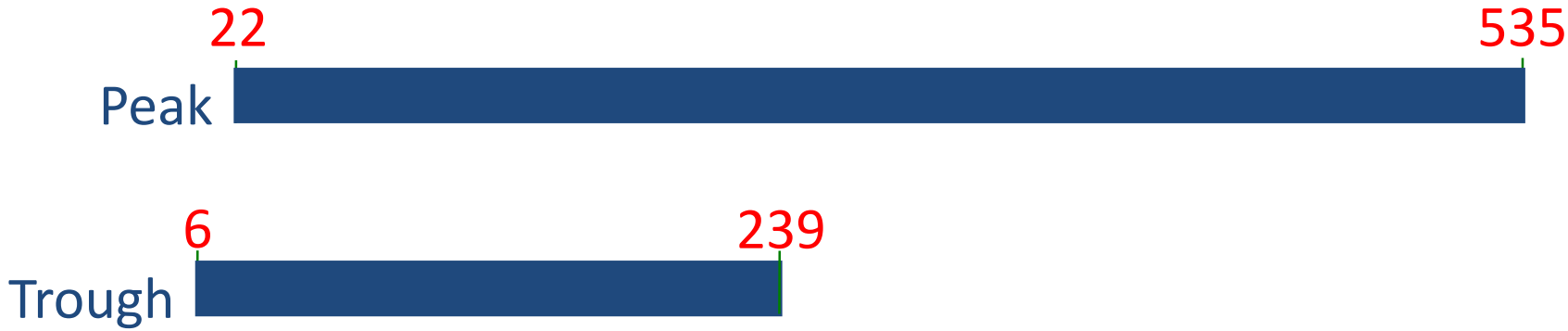
Owing to the interindividual variability and limited clinical experience, no accurate alerting values are currently known

Inter-individual variability plasma concentrations *[ng/mL (min-max)]. Data from clinical trials*

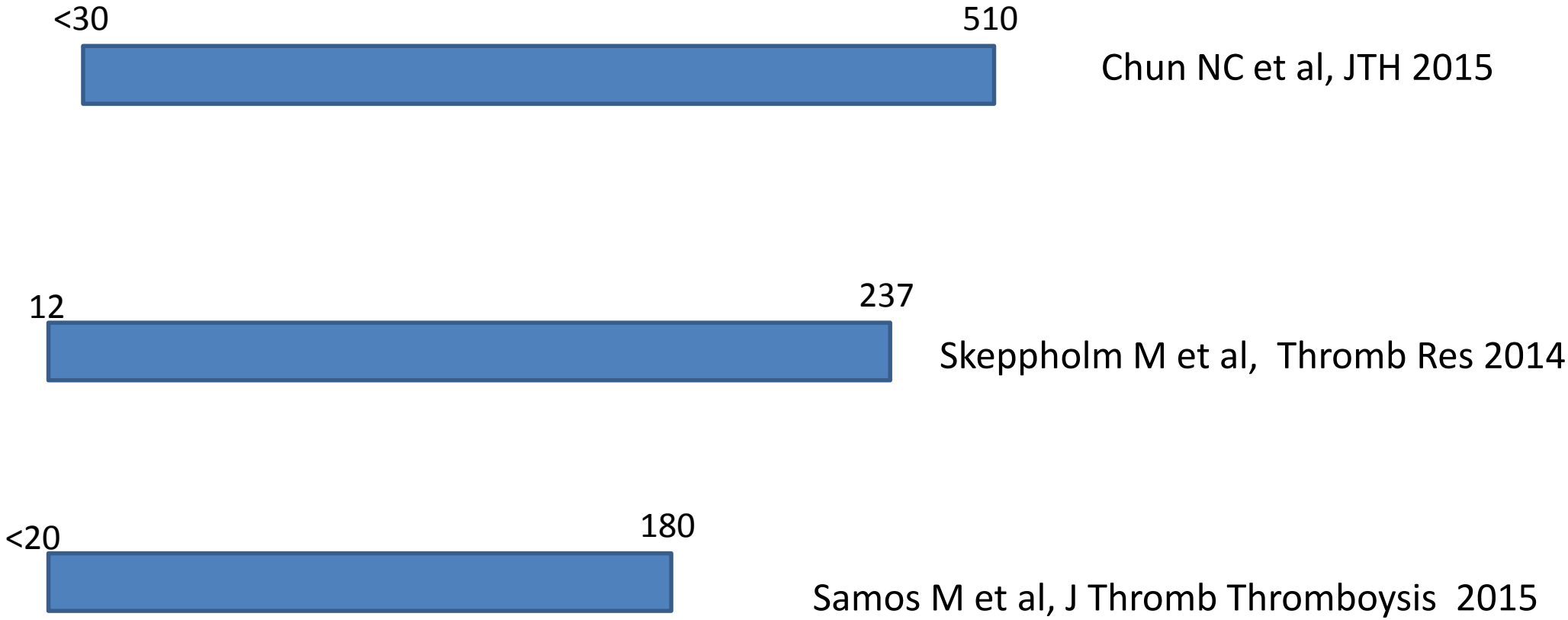
Dabigatran



Rivaroxaban



Inter-individual (trough levels) Dabigatran variability. Data from real life



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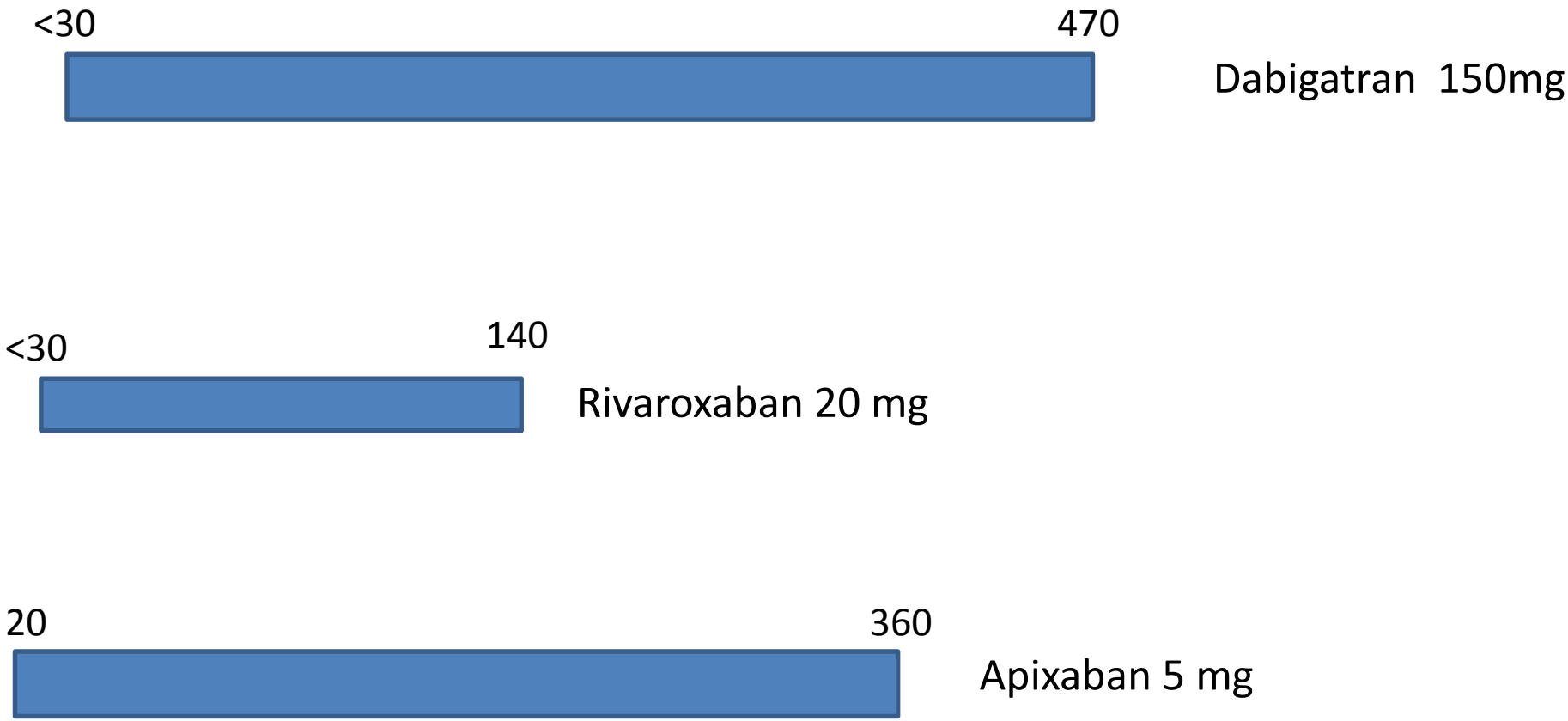

S. TESTA et al, 2015

Cosa fare secondo lo stato dell'arte

- Refertare il valore di concentrazione dei DOAC in ng/mL
- Riportare i valori attesi di concentrazione per i DOAC
- Aggiornare i valori attesi sulla base del progresso delle conoscenze

The laboratory & the DOAC

- Need for testing
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- How to measure the effect of DOAC
- When to measure
- Alerting values
- *DOAC Effect on the most common hemostatic parameters*

DE GRUYTER

Clin Chem Lab Med 2015; 53(2): 265–273

Armando Tripodi*, Lidia Padovan, Sophie Testa, Cristina Legnani, Veena Chantarangkul, Erica Scalambrino, Silvia Ludovici, Laura Bassi and Flora Peyvandi

How the direct oral anticoagulant apixaban affects hemostatic parameters. Results of a multicenter multiplatform study

Methods

A pooled normal plasma was added with increasing amounts of apixaban

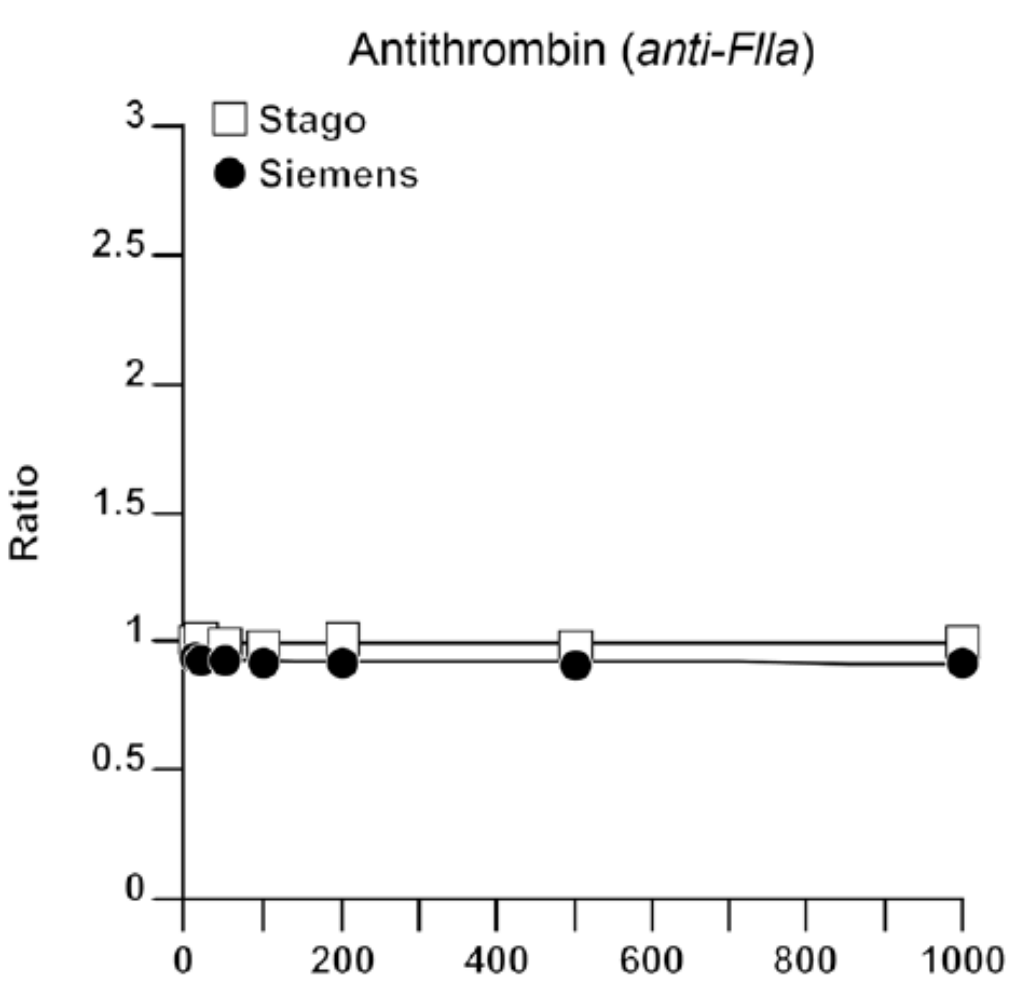
Assessment of effect

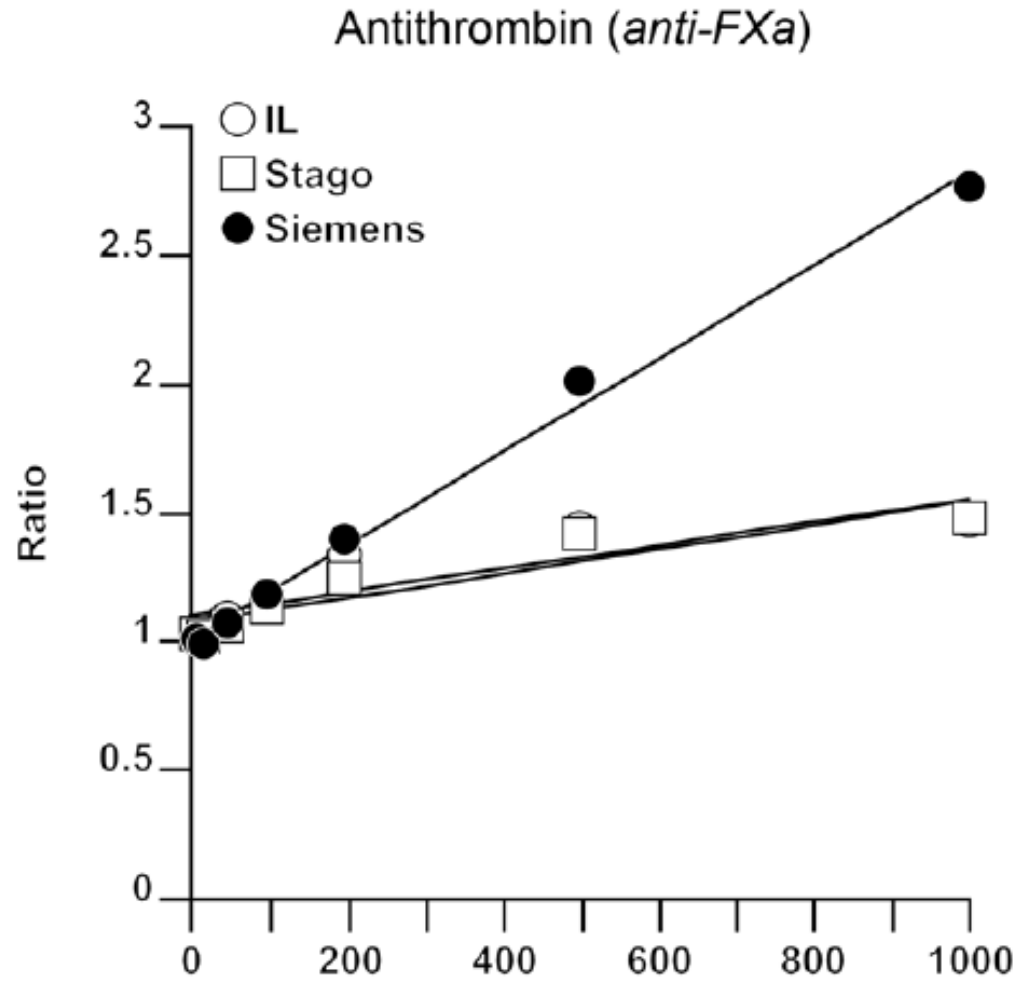
Results for each parameter obtained for each apixaban plasma concentration were divided by results obtained at 0 ng/mL

Interpretation

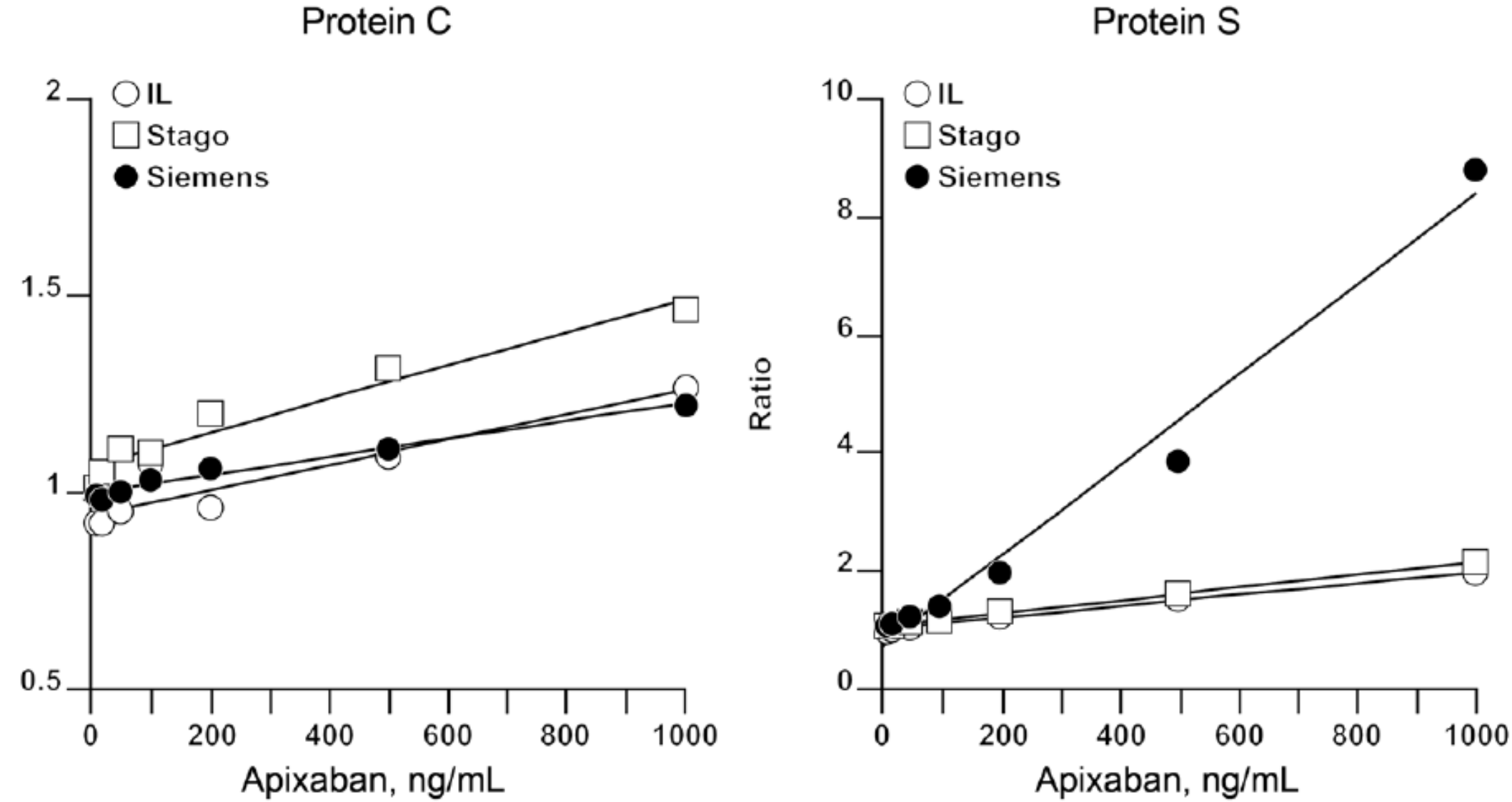
Ratio higher or lower than “unity” means over- or under-estimation, respectively

Effect of apixaban on Antithrombin

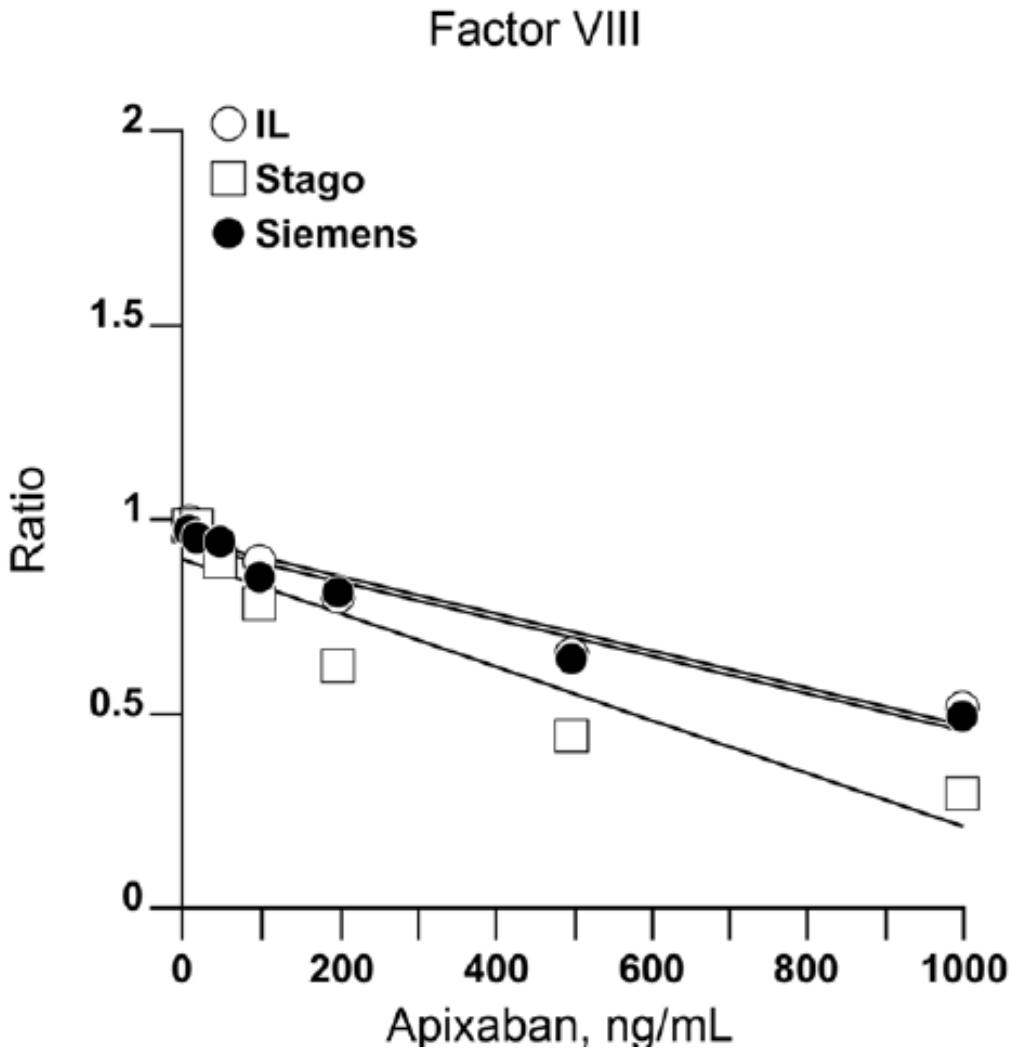


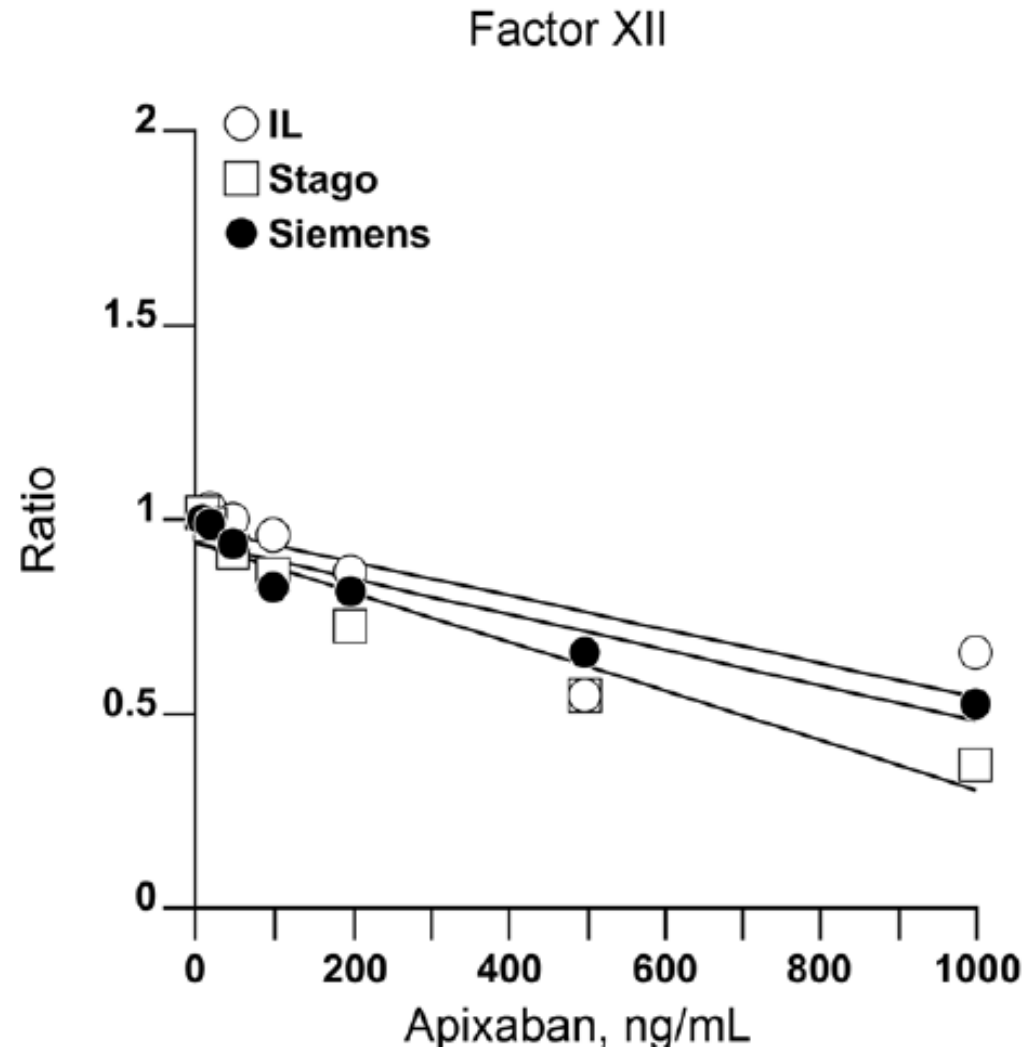


Effect of apixaban on PC or PS



Effect of apixaban on factor assays





DOAC effects on the most common hemostatic parameters

• Antithrombin	• *Overestimation*
• Fibrinogen	• *Underestimation with dabigatran*
• APC-resistance	• *Underestimation*
• Factor assay	• *Underestimation*
• Protein C/S anticoagulant activity	• *Overestimation*
• Lupus anticoagulants	• *Difficult interpretation*
• Factor XIII	• *Underestimation with dabigatran*

Cosa fare secondo lo stato dell'arte

- Spiegare ai clinici prescrittori che i più comuni test dell'emostasi potrebbero essere influenzati in maniera significativa dai DOAC
- Meglio prescriverli a qualche giorno di distanza dalla dalla sospensione dei DOAC
  - Due-tre giorni sono sufficienti in caso di normale funzione renale

Conclusions on Lab testing & DOAC

- Although DOAC do not require dose-adjustment based on lab testing, assessment of anticoagulant effect is useful in many circumstances
- Specific lab testing should be used

- *dTT or ECT (dabigatran)*
- *Anti-FXa or PT with sensitive thromboplastins (rivaroxaban)*
- *Anti-FXa (apixaban)*

- Caution should be exerted when interpreting results of hemostatic parameters in patients on DOAC