Monitoring new oral anticoagulants- Practical approach

ECAT 2014

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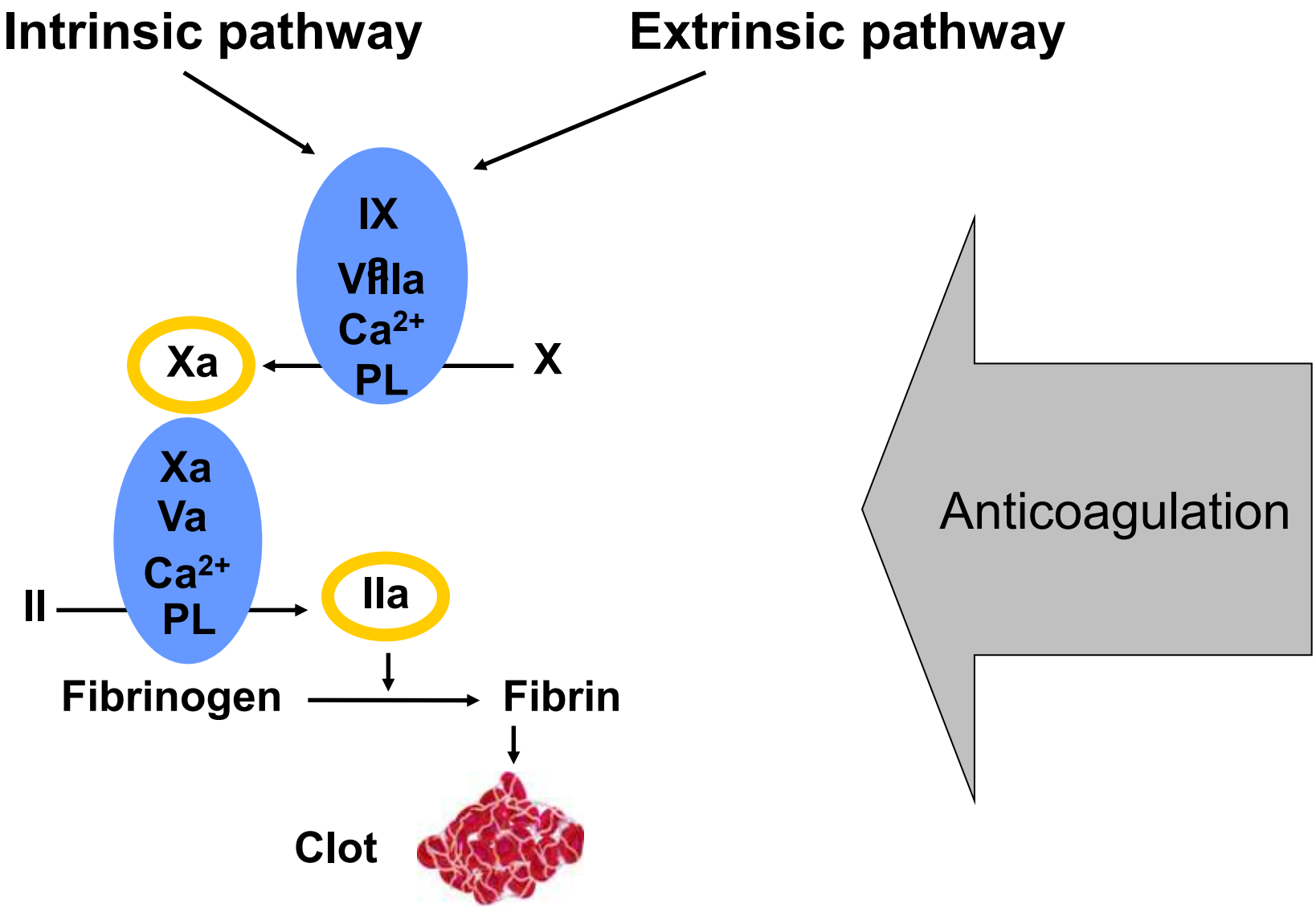
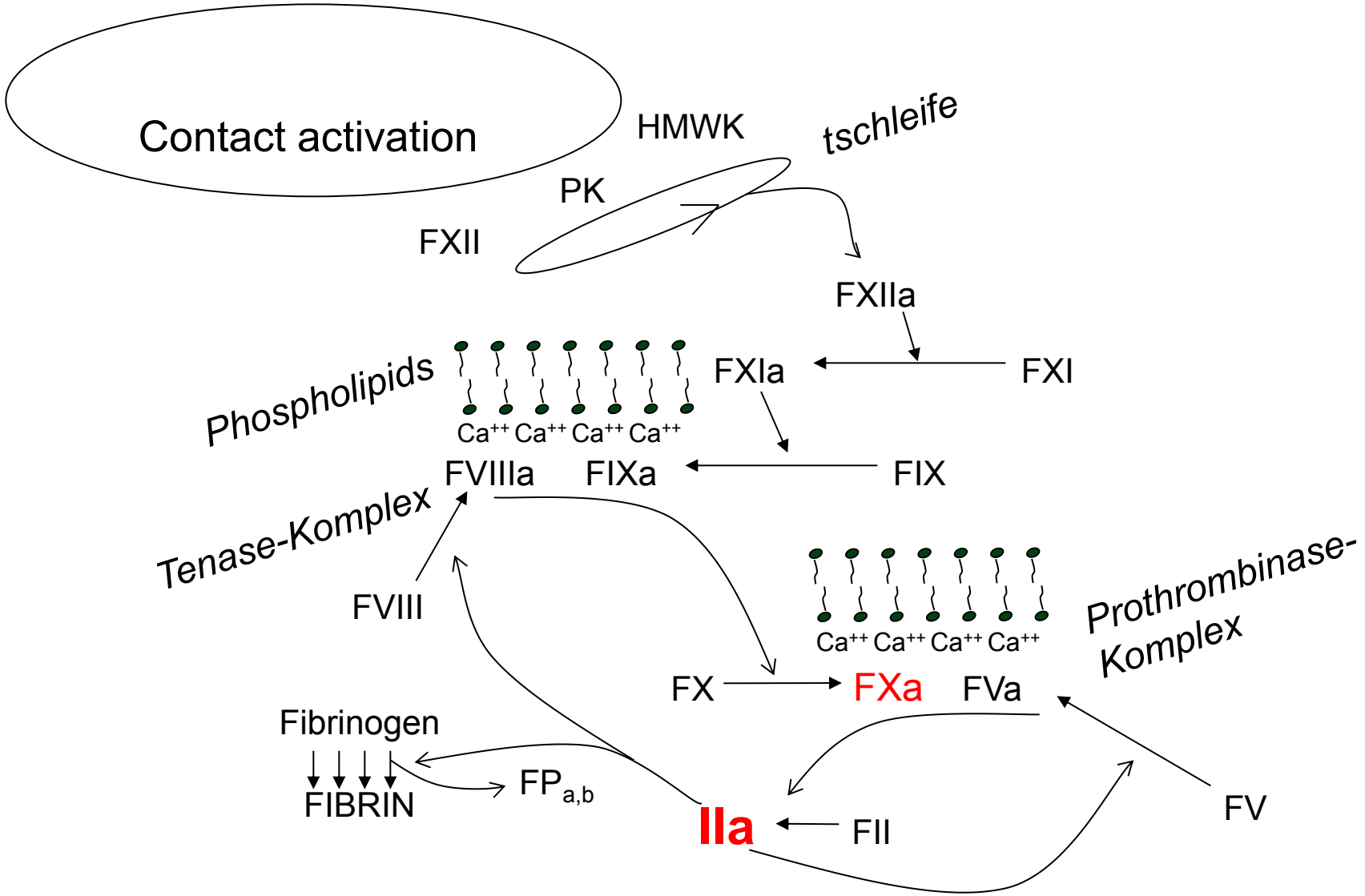

Intrinsic pathway
Extrinsic pathway
IX
VIIIa
Ca2+
PL
Xa
X
Xa
Va
Ca2+
PL
II
IIa
Fibrinogen
Fibrin
Clot
Anticoagulation

Clot test in concert



Introduction: aPTT: physiological basis of the monitoring of anticoagulants

contact activator

standardization

not part of hemostasic process

FXII, prekallikrein, kininogen

FXIa

phospholipids - Ca^{++} - FIXa -FVIIIa

acute phase reaction

phospholipids - Ca^{++} - **FXa** - FVa

FIIa □ fibrin □ detection of clotting

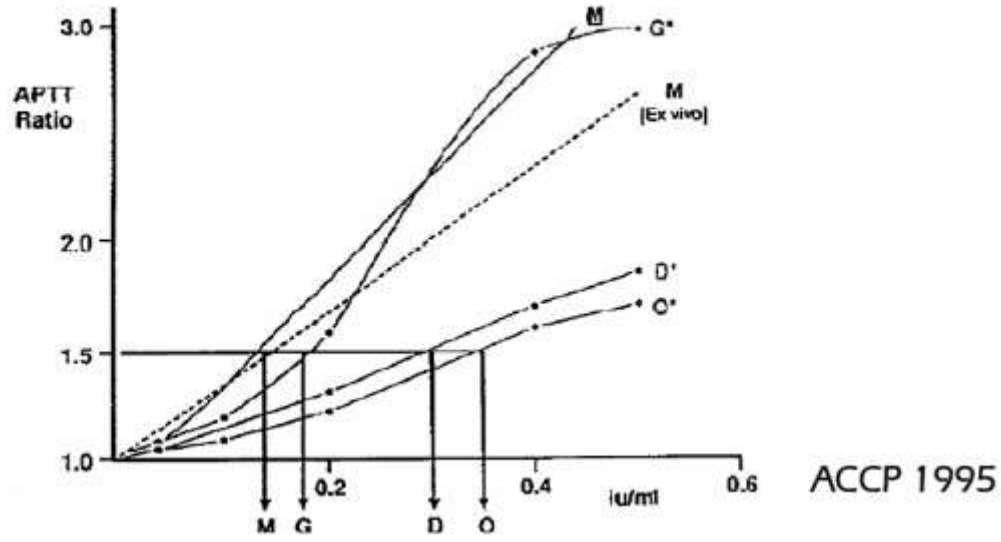
main action of direct / indirect anticoagulants

> 300 aPTT methods (combinations instrument – reagents)

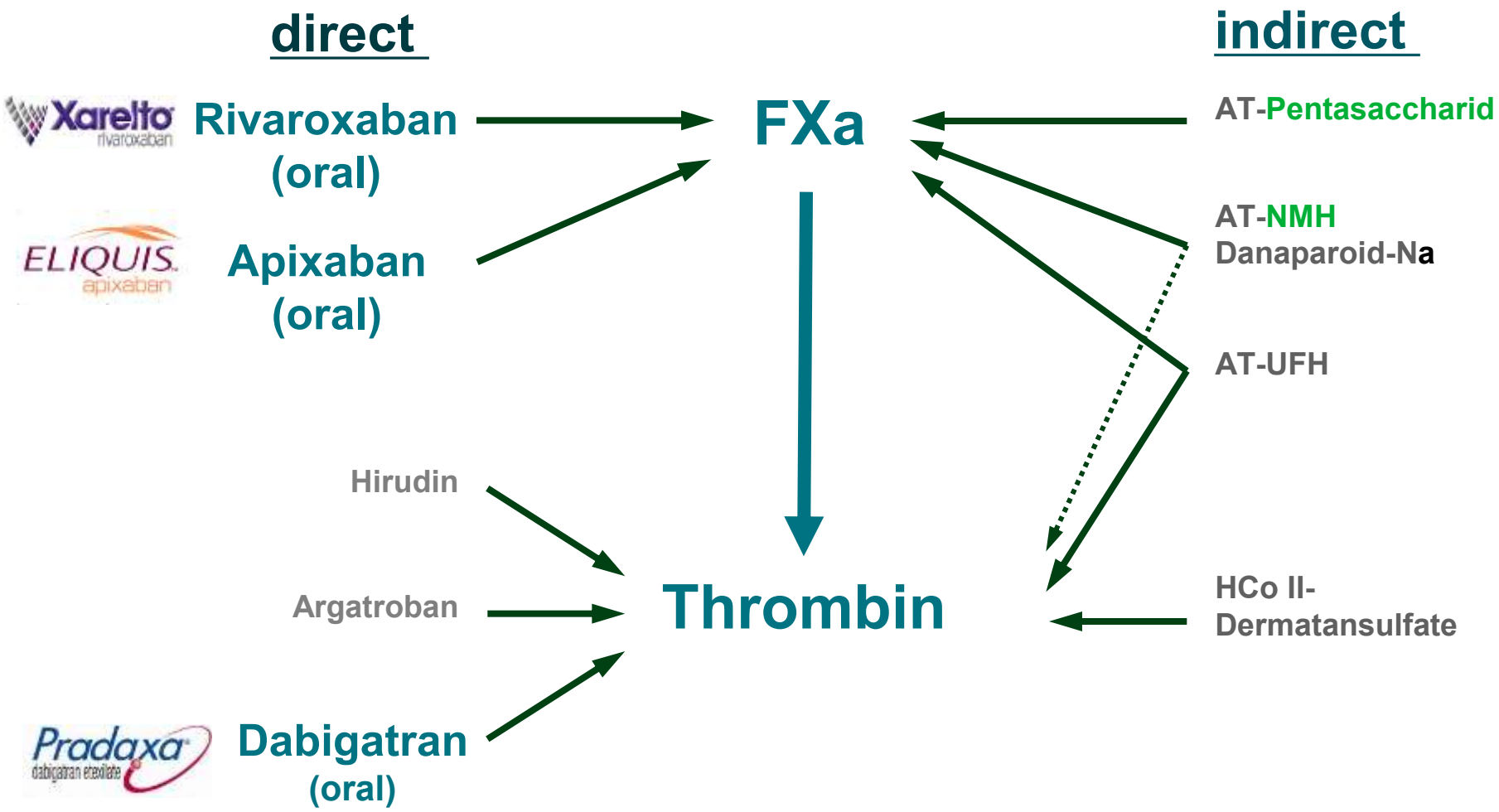
0,3 IU heparin (aXa activity) → aPTT: 48-108 sec

therapeutic ranges (0.3-0.7 IU /ml) → aPTT ratio: 1.6-2.7 to 3.7-6.2

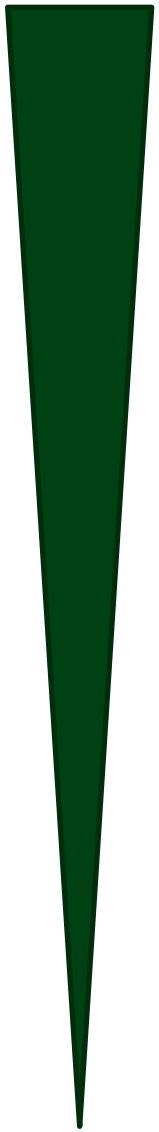
option: calibration of local combination instrument – reagent (lot?) towards heparin concentration



Anticoagulants



Thrombin-Inhibition



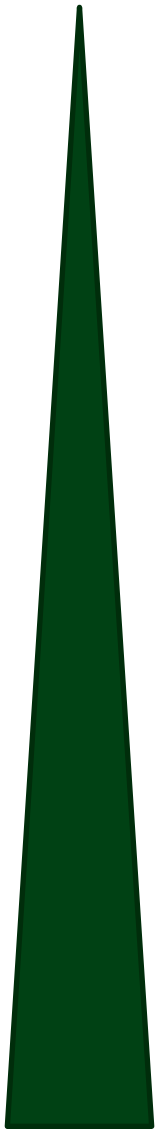
(Hirudin)
Argatroban
Dabigatran

VKA
Heparin

NMHs
Danaparoid

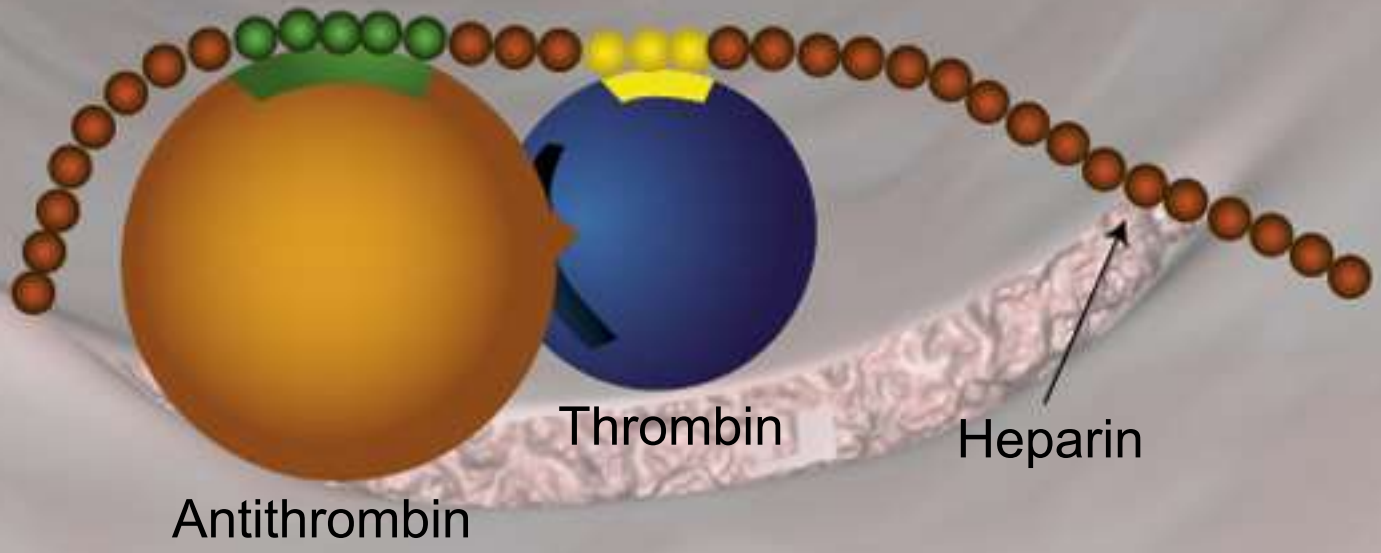
Fondaparinux

Rivaroxaban
Apixaban
(Edoxaban)

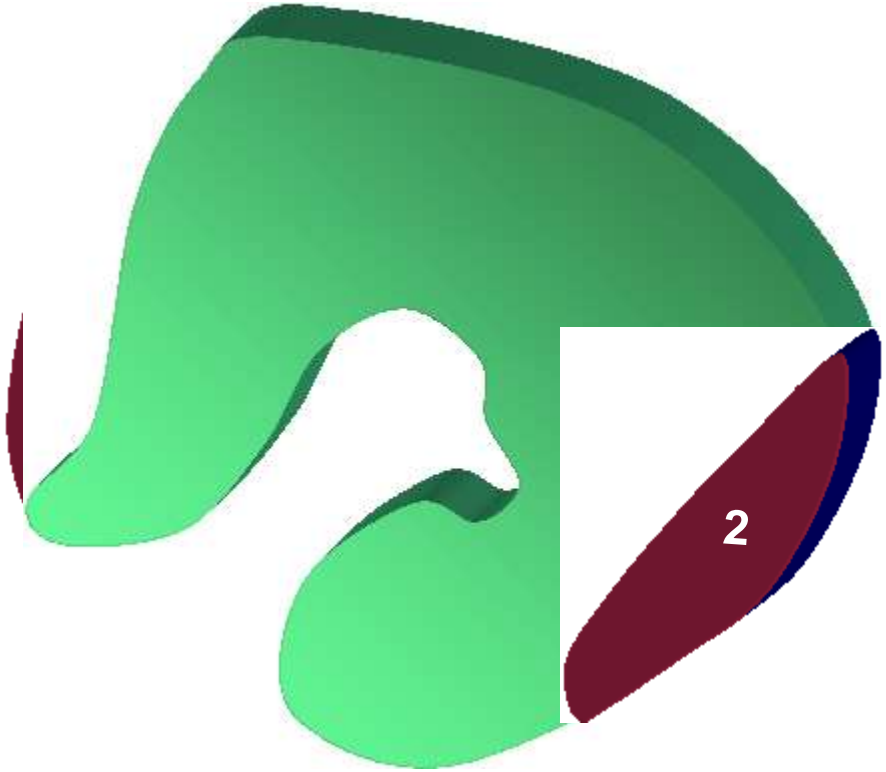


Faktor-Xa-Inhibition

Indirect thrombin inhibition
Heparin/antithrombin/thrombin complex



Direct Inhibitor

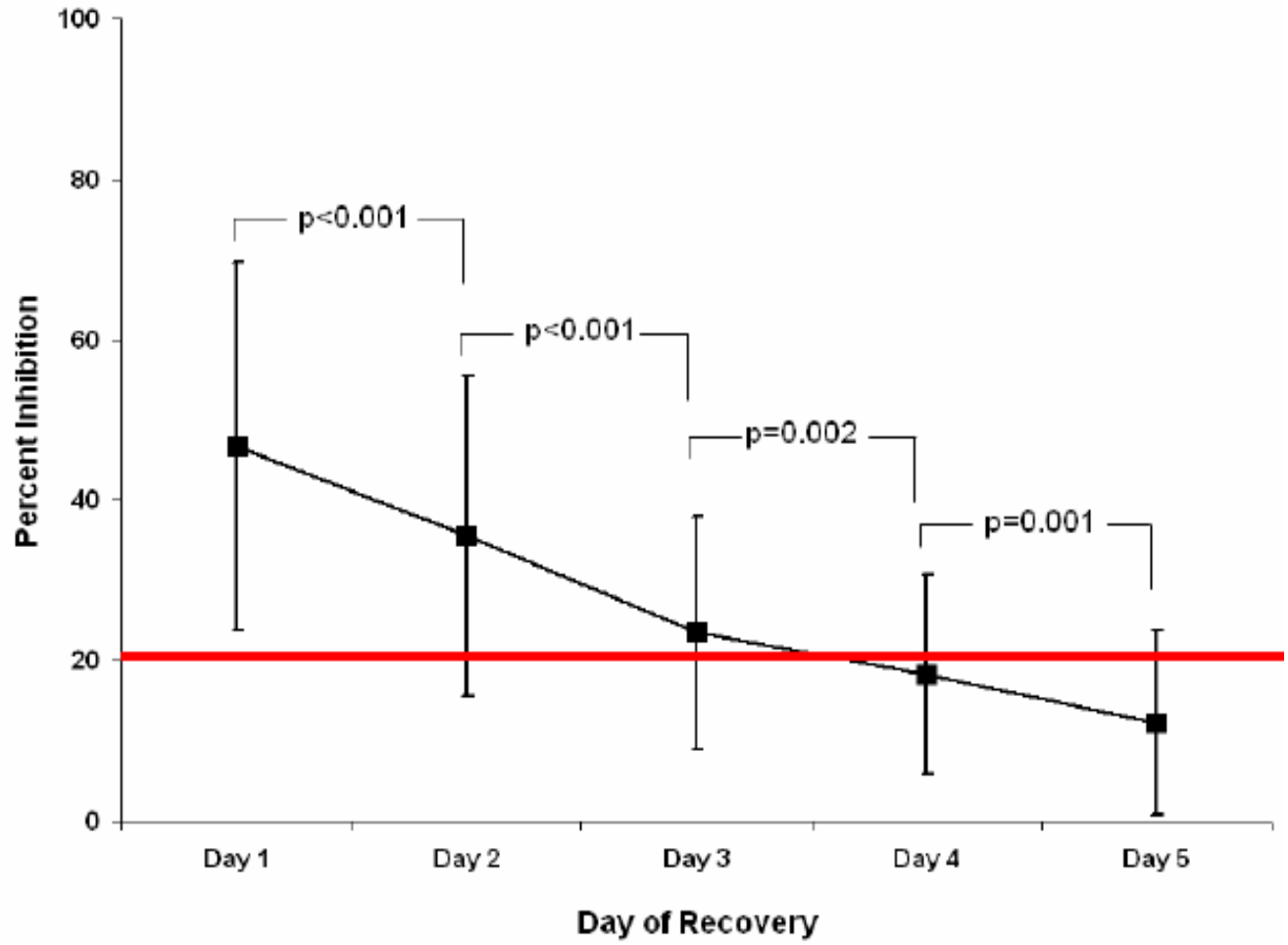


Reversible Inhibition


BRILIQUE 90 mg
ticagrelor
Efient
tablets
Dieser Patient steht unter
Antikoagulanzienbehandlung
mit Marcumar®
roche
75 mg film
Clopidogrel
WARFARIN
Abbott
ELIQUIS 2.5 mg film-coated tablets
apixaban
AGGRASTAT
R110
ASPİR
BAYER

Wiedereinsetzen der normalen Thrombozytenfunktion durch Neubildung (Clopidogrel)

Price et al (AJC 2006)



Tab. 1 Application, dynamics and pharmacological monitoring of antiaggregants and anticoagulants

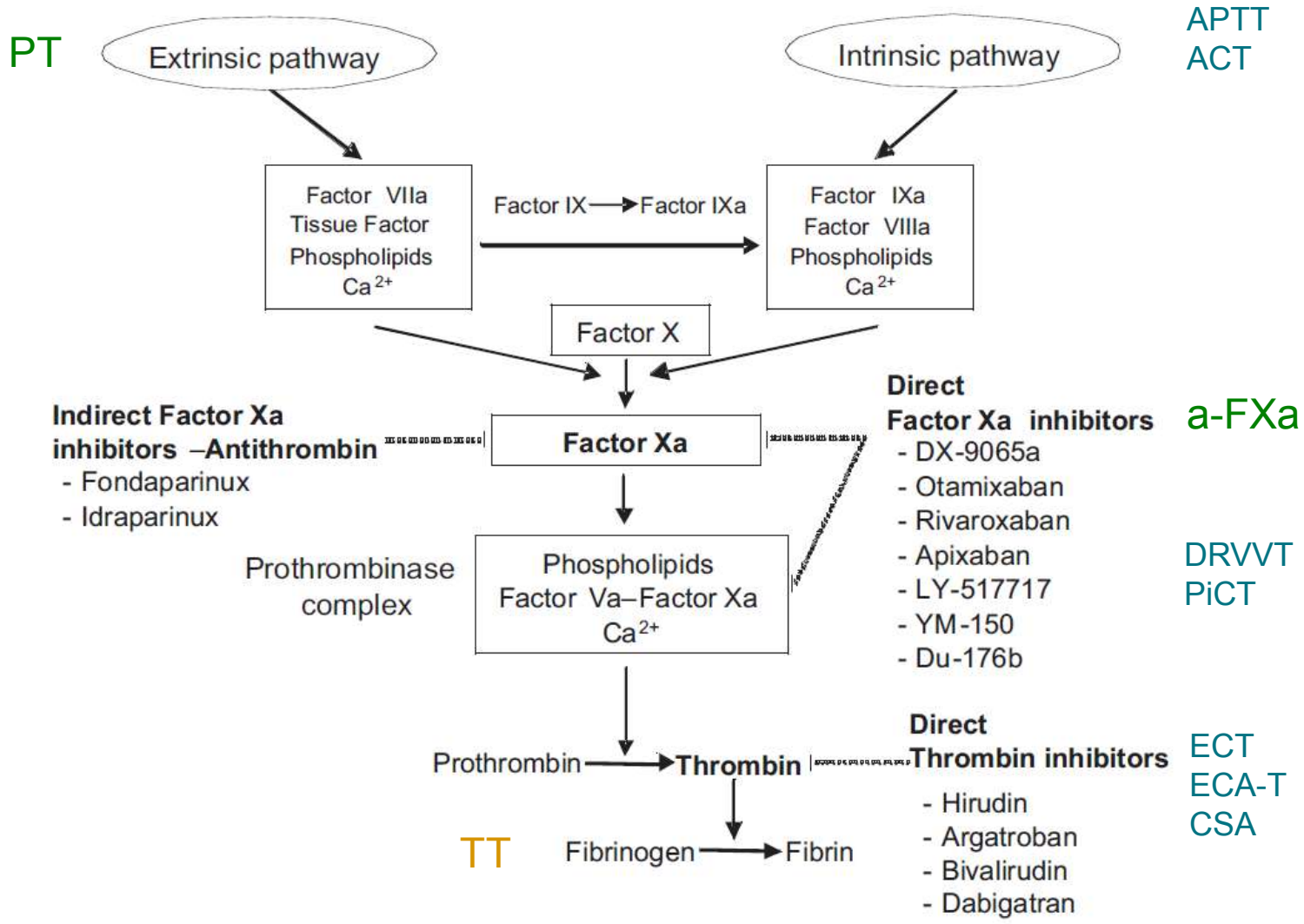
monitoring, pharmacological properties	anticoagulant or antiaggregant							
	ASS	ADP receptor blockers	VKA	DOACs (thrombin inhibitor)	thrombin inhibitors (i.v.)	DOACs (Xa inhibitors)	UFH	LMWH
pharmacokinetic (PK)	---	---	---	diluted thrombin time (ECT, anti-IIa)	ECT, anti-IIa	anti-Xa	---	anti-Xa
pharmacodynamic (PD)*	aggregation in liquid phase or on surfaces		PT, INR	aPTT (PT)	aPTT ACT	PT (aPTT)	aPTT ACT	---
rapid change in PK/PD	---	---	---	+	++	+	++	+
application	p.o. or i.v.	p.o.	p.o.	p.o.	i.v.	p.o.	i.v.	s.c. (i.v.)

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; ACT: activated clotting time; TT: thrombin time; ECT: ecarin clotting time; *see Table 2 for details with regard to DOACs and global coagulation testing

Sibbing, Spannagl Haemostaseologie 2014

NOAC - DAOC

Drug Monitoring

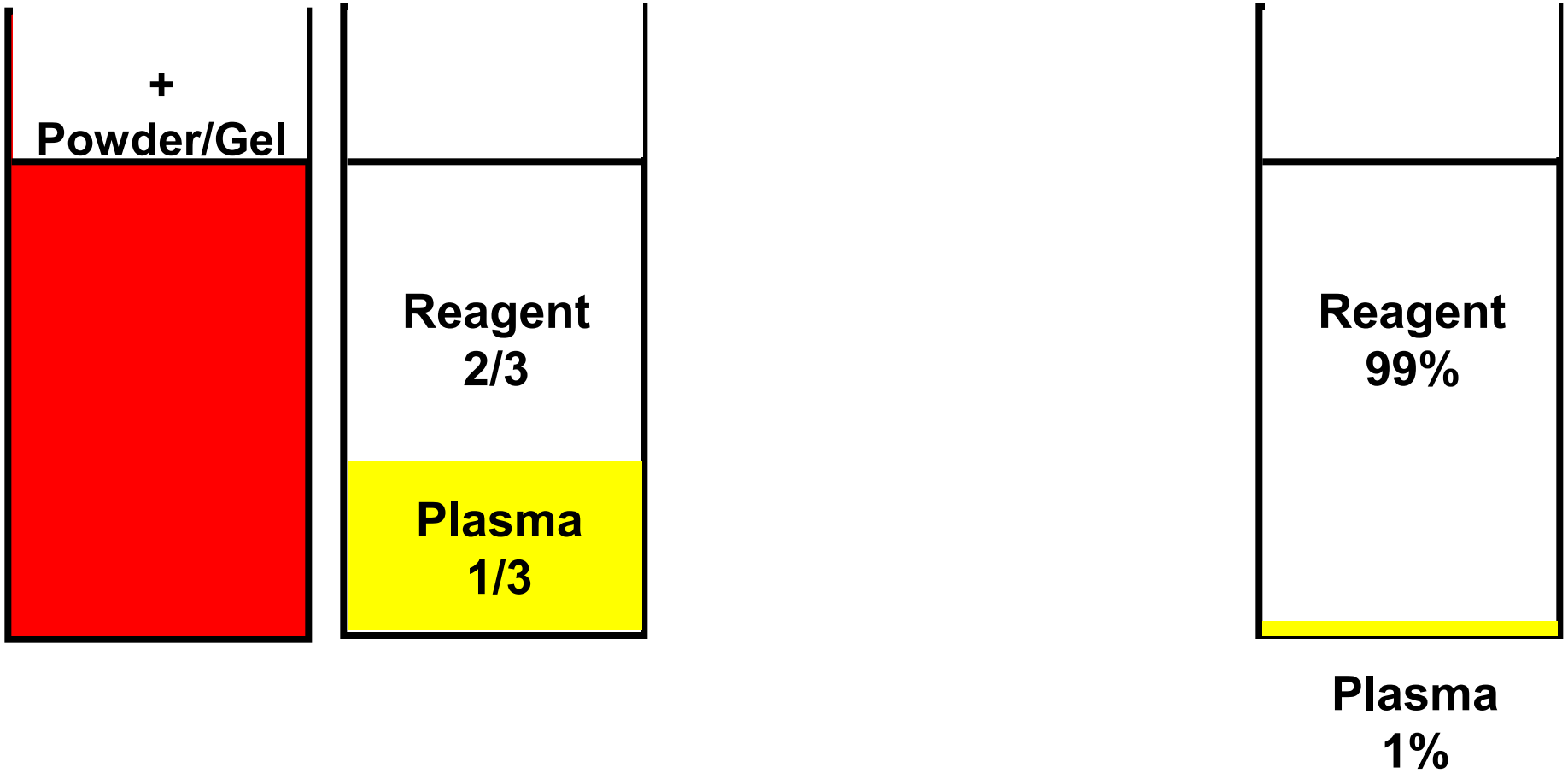


PRE/ANALYTICS - MATRIX

Whole Blood: ACT

aPTT

Anti- IIa/Xa Inhib.: Synth. Substrate



PRE/ANALYTICS - MATRIX

Whole Blood ACT

+ Powder/Gel

Reagent

aPTT dilTT

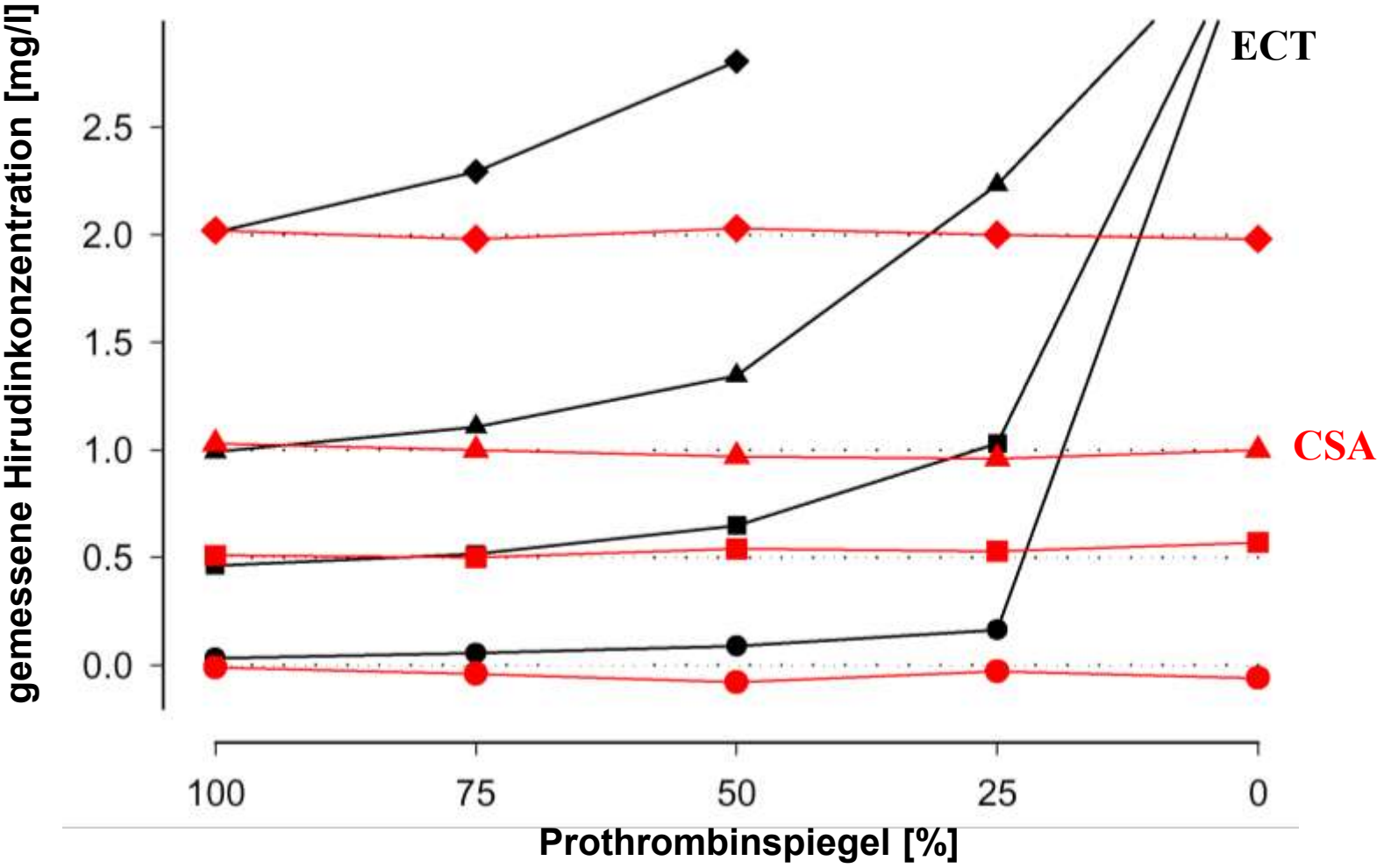
Reagent 2/3

Plasma 1/3

Anti- IIa/Xa Synth. Substrate

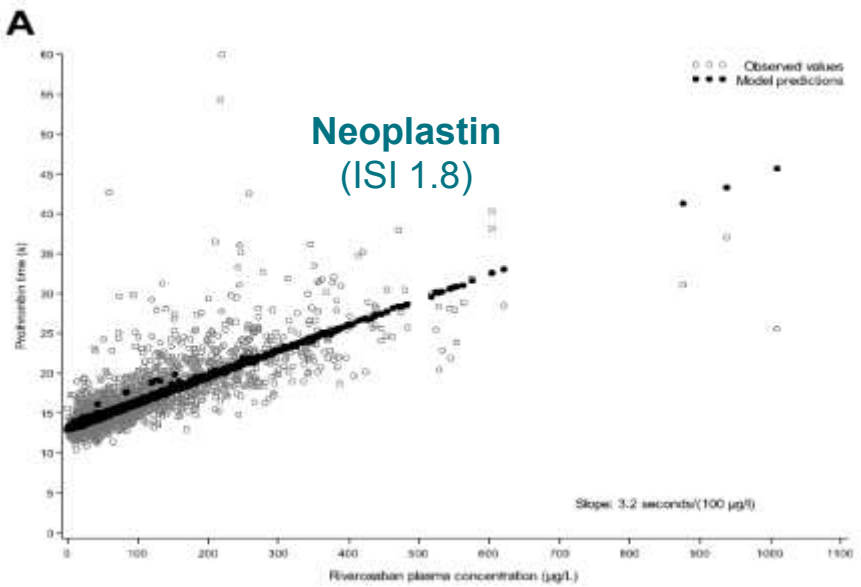
Reagent 99%

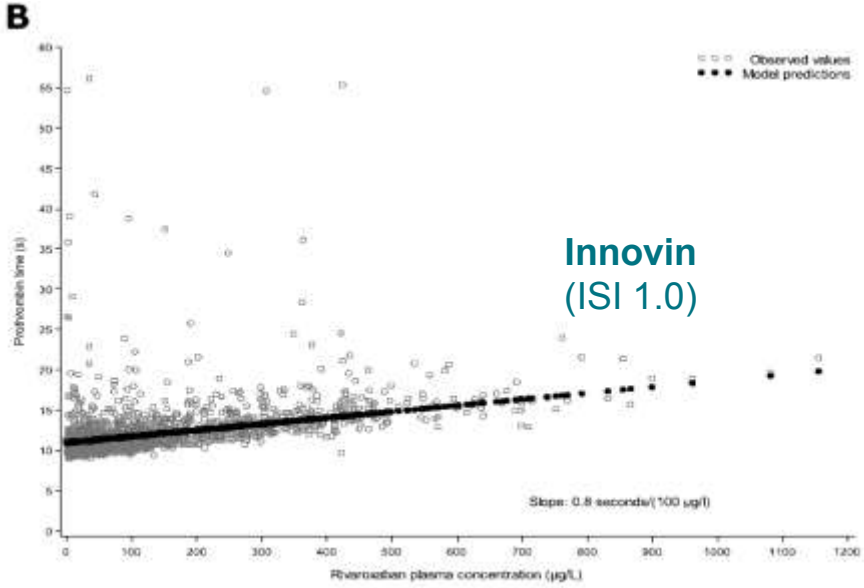
Plasma 1%



Lindhoff-Last E et al. Thromb Res 2005; 100: 55–60

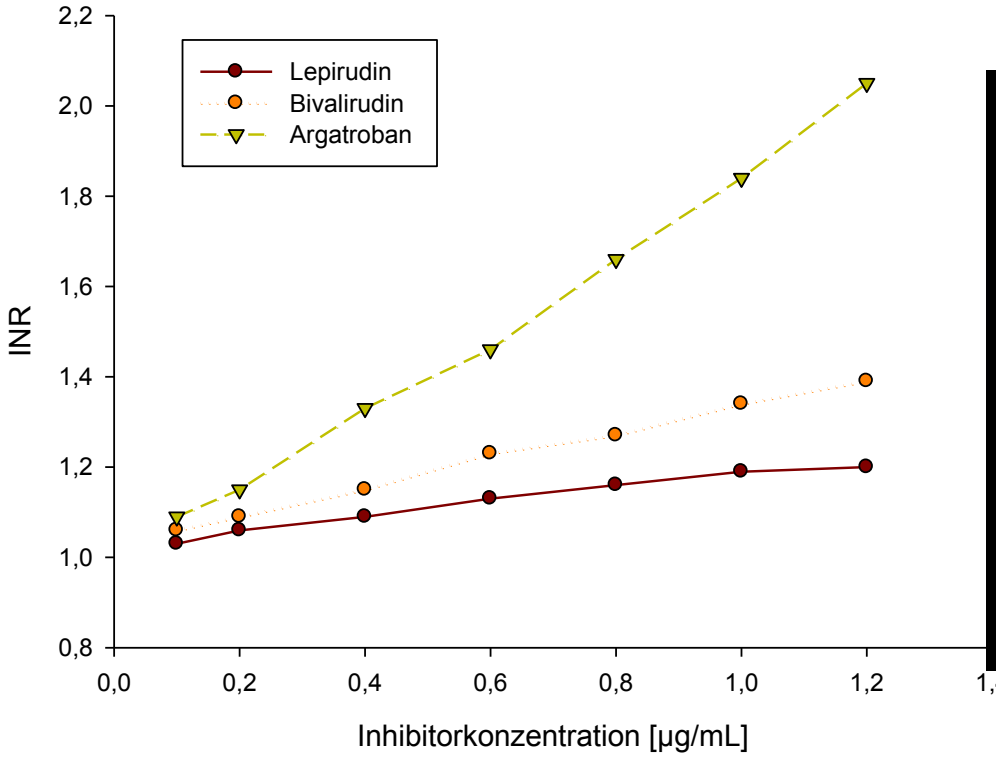
Rivaroxaban

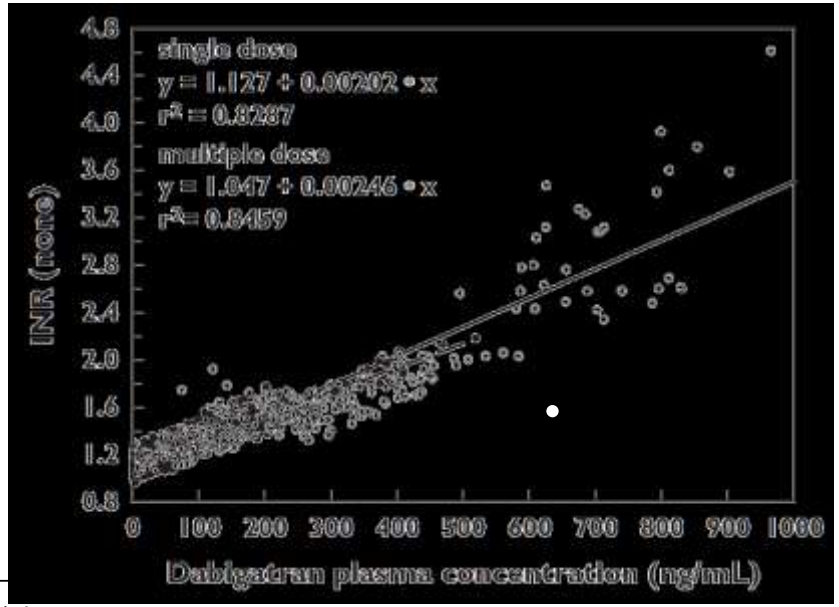




Mueck W et al. Thromb Haemost 2008; 100: 453–461

Influence of direct thrombin inhibitors on INR

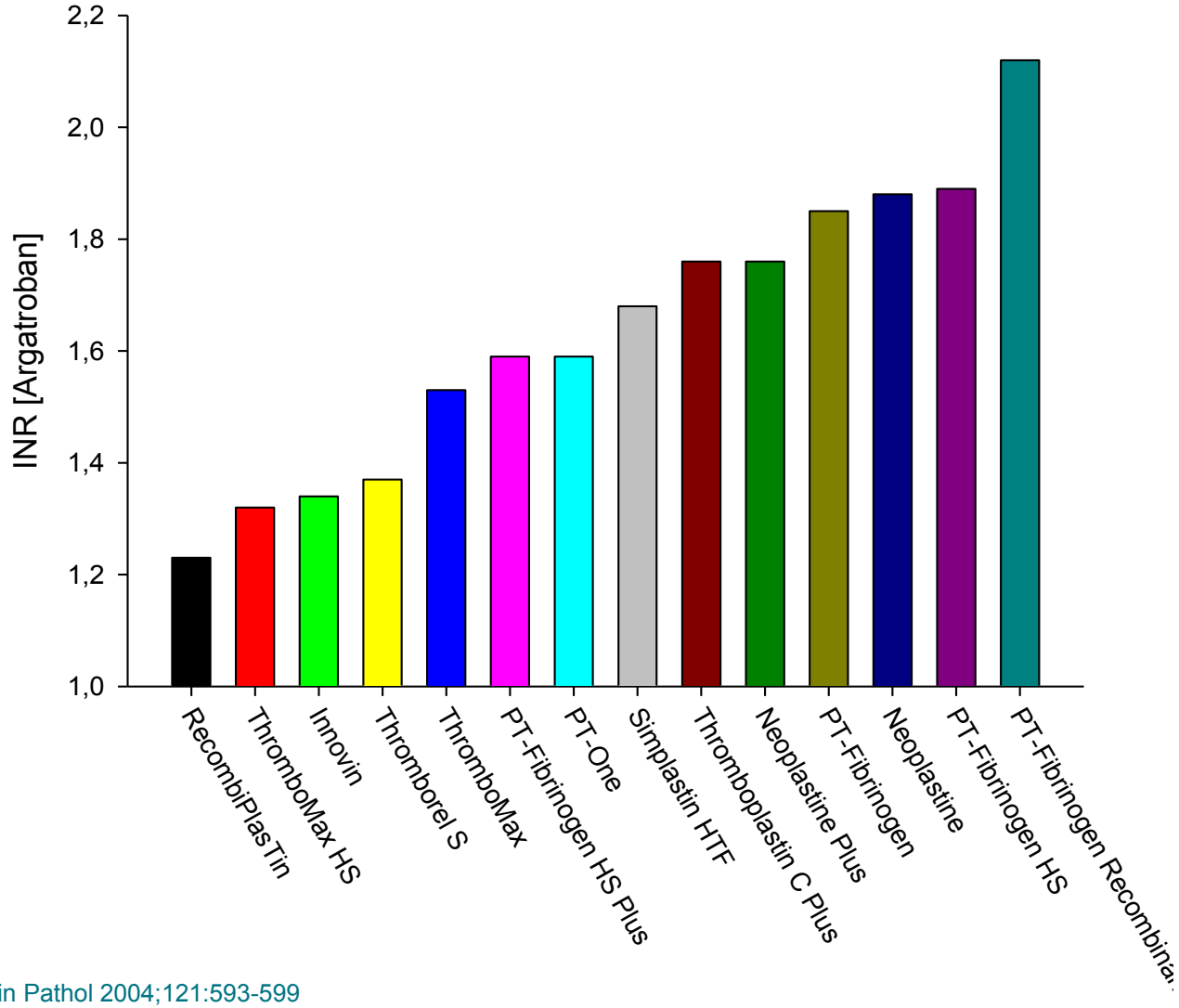




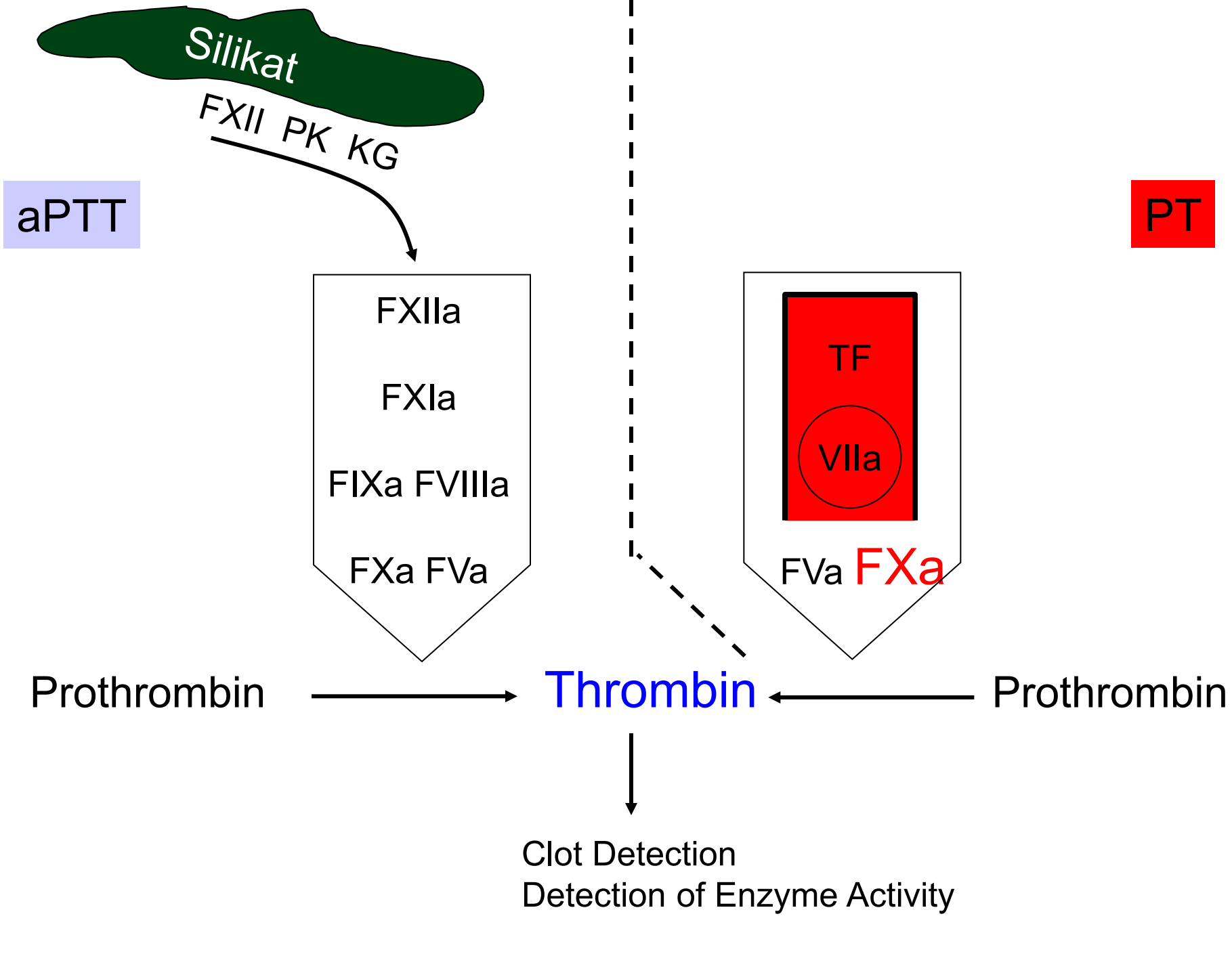
Gosselin RC et al. Am J Clin Pathol 2004;121:593-599, Stagnier et al. Br J Clin Pharmacol 2007;64:292–303

INR and argatroban therapy

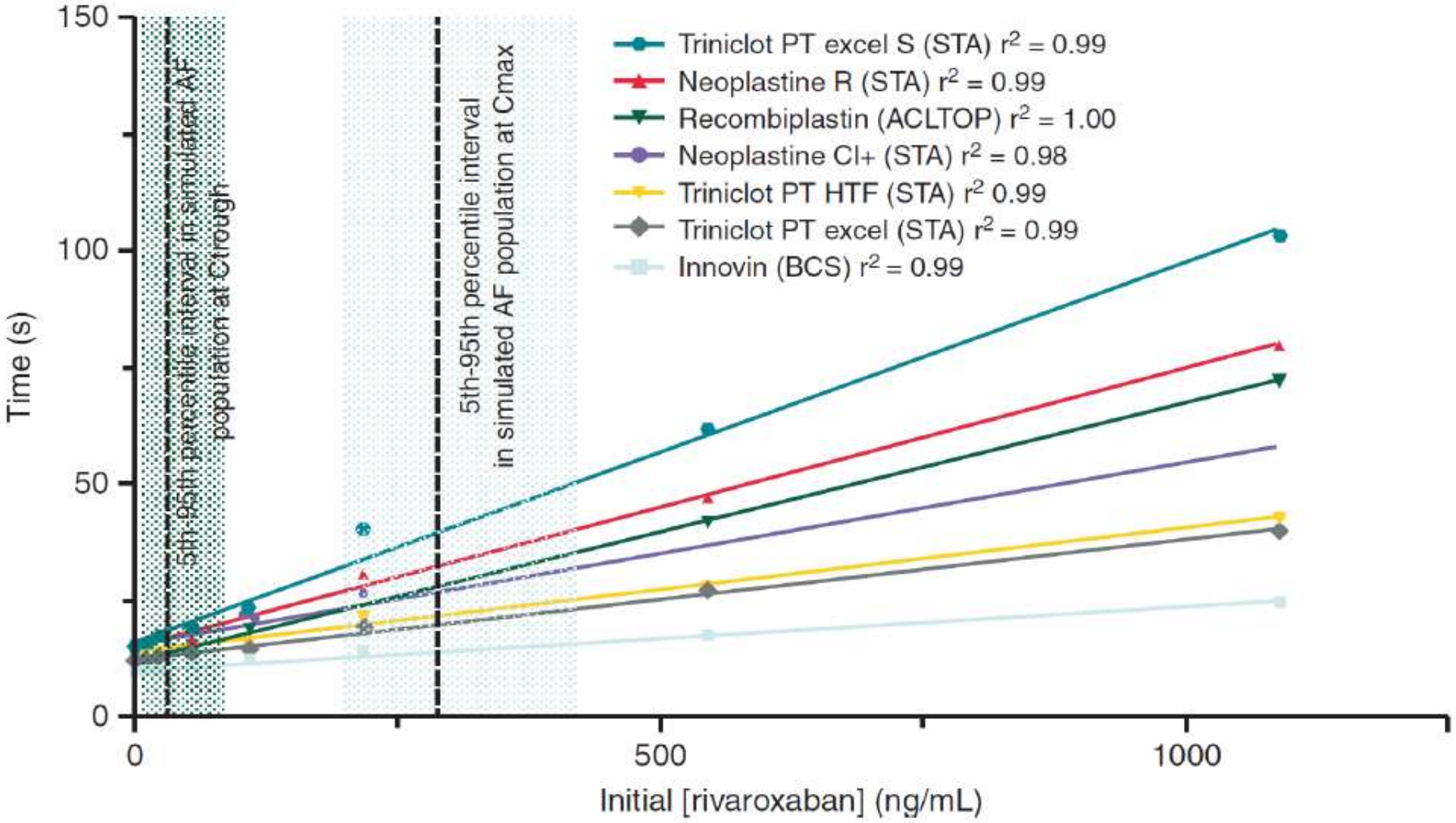
Influence of the thromboplastin



Gosselin RC et al. Am J Clin Pathol 2004;121:593-599

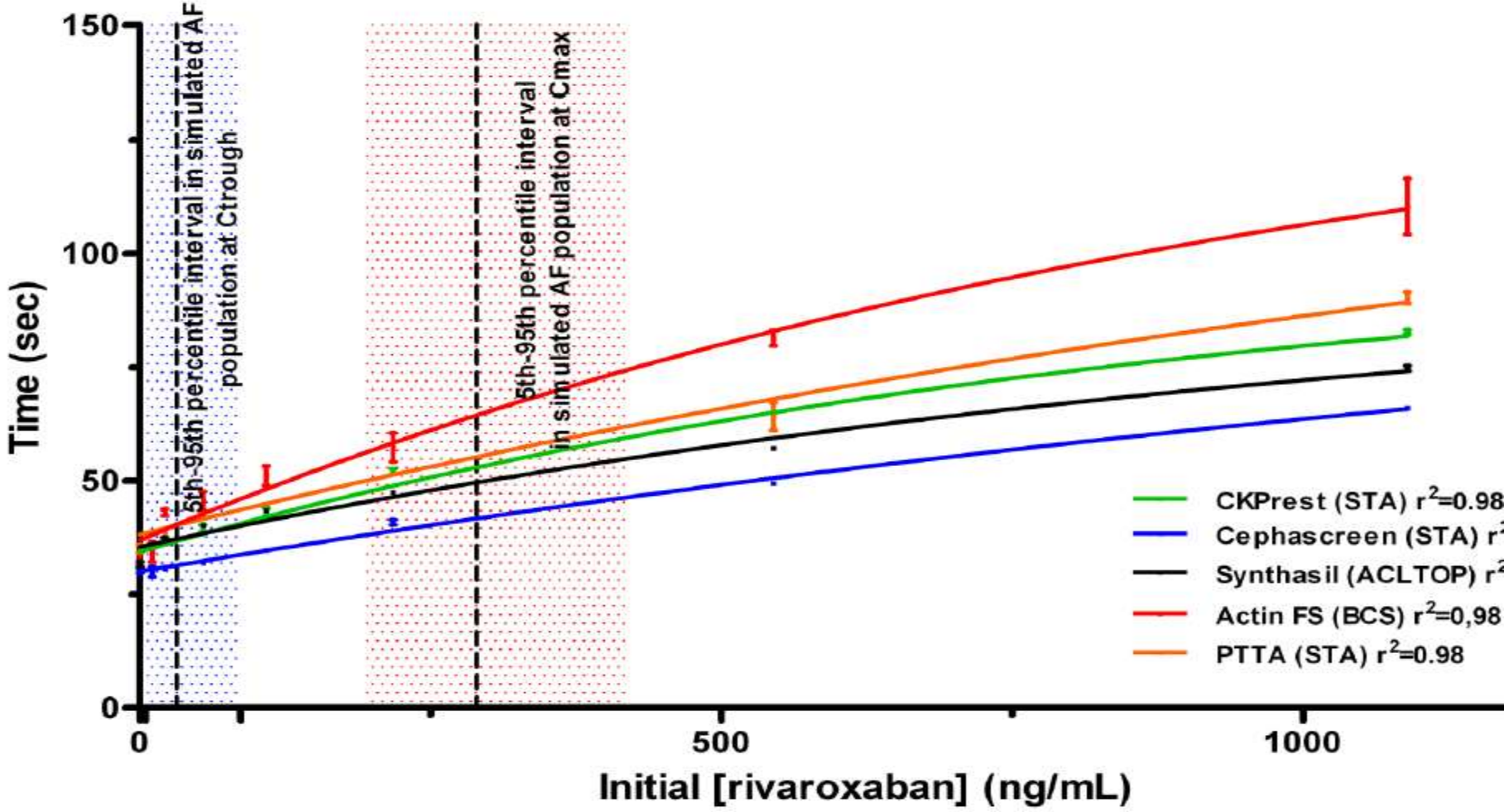

Silikat
FXII PK KG
aPTT
PT
FXIIa
FXIa
FIXa FVIIIa
FXa FVa
TF
VIIa
FVa FXa
Prothrombin
Thrombin
Prothrombin
Clot Detection
Detection of Enzyme Activity

PT and Rivaroxaban



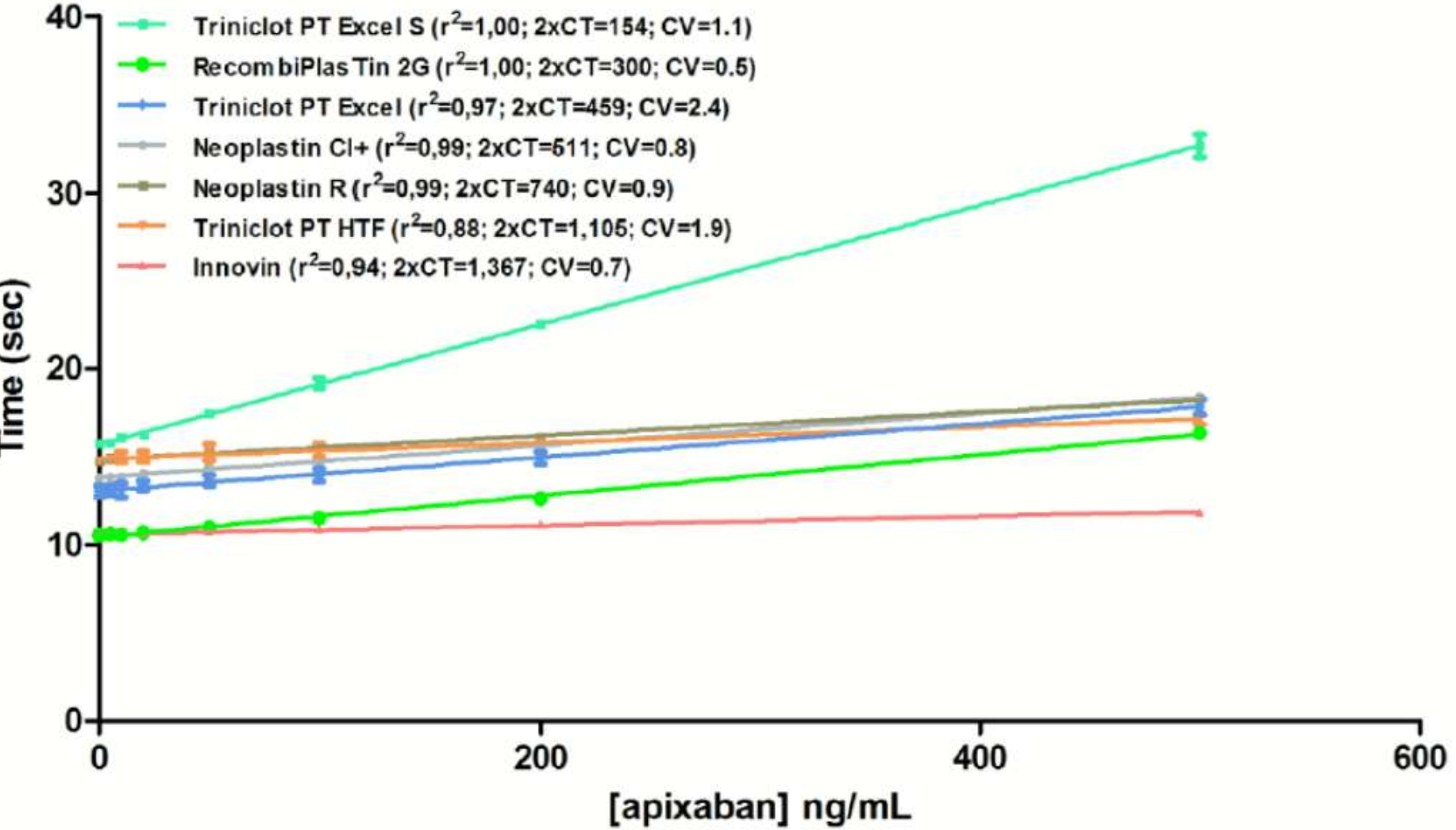
Thromb Res. 2012;130(6):956-

APTT and Rivaroxaban



Thromb Res. 2012;130

PT and Apixaban

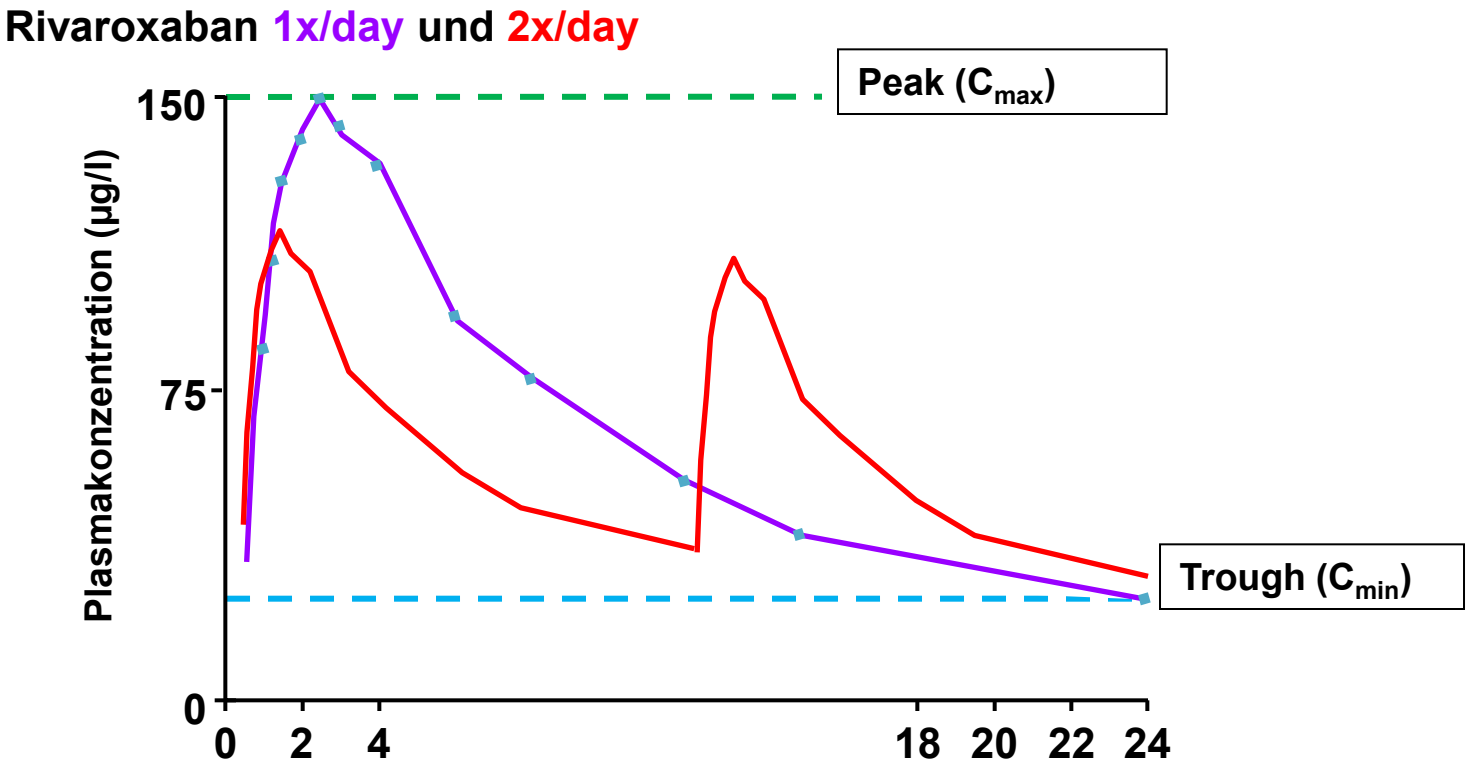


Thromb Haemost. 2013;110(2):283-94.

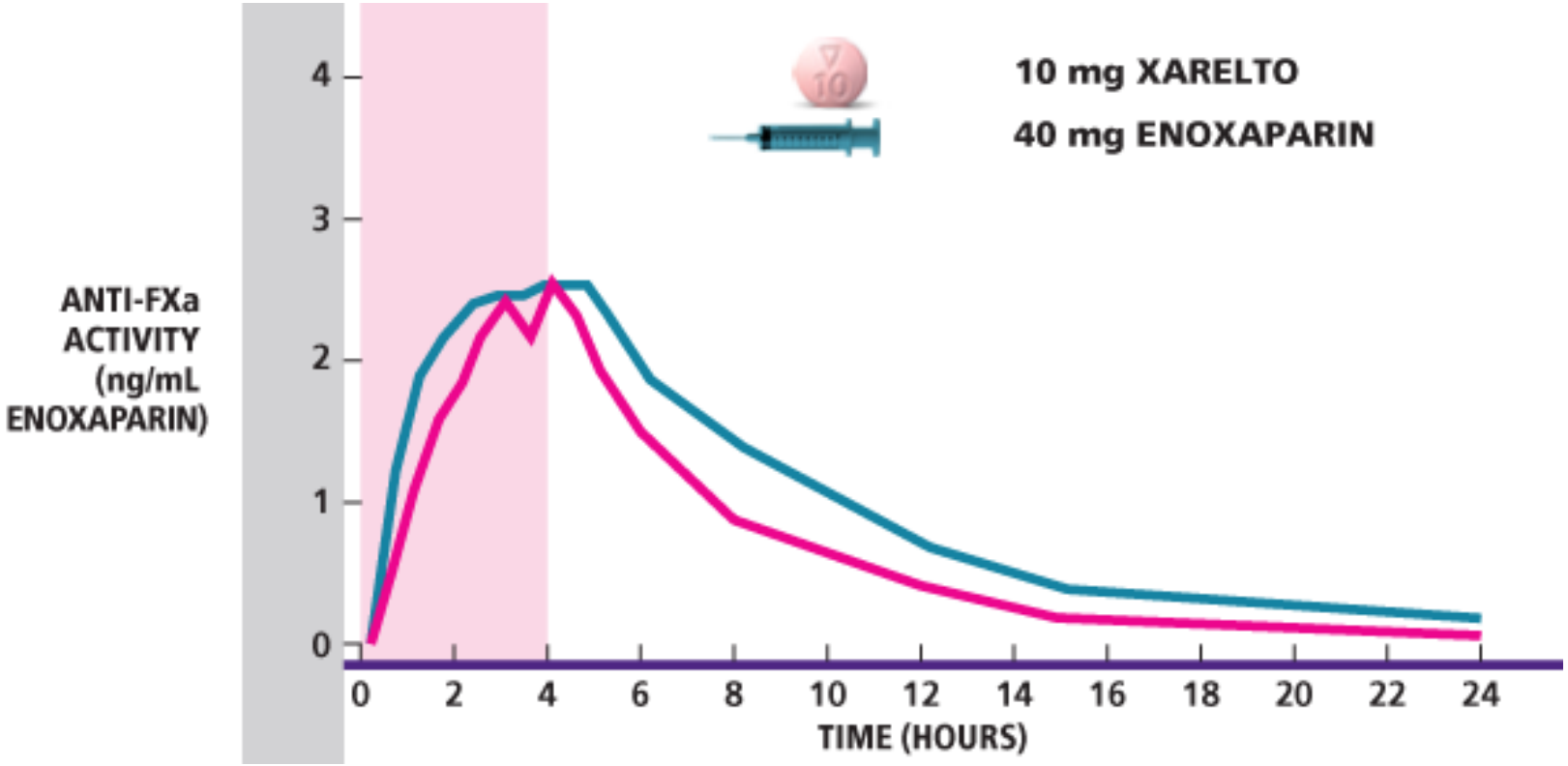
DOACs : Clotting Tests

	Dabigatran	Rivaroxaban	Apixaban
TPZ (sek/%/INR))	↑ - ∅	↑ - ∅	↑ - ∅
aPTT	↑ - ∅	↑ - ∅	↑ - ∅
Thrombinzeit	↑	-	-
Fibrinogen n. Clauss	↓ - ∅	-	-

Rivaroxaban PK
Peak-Trough

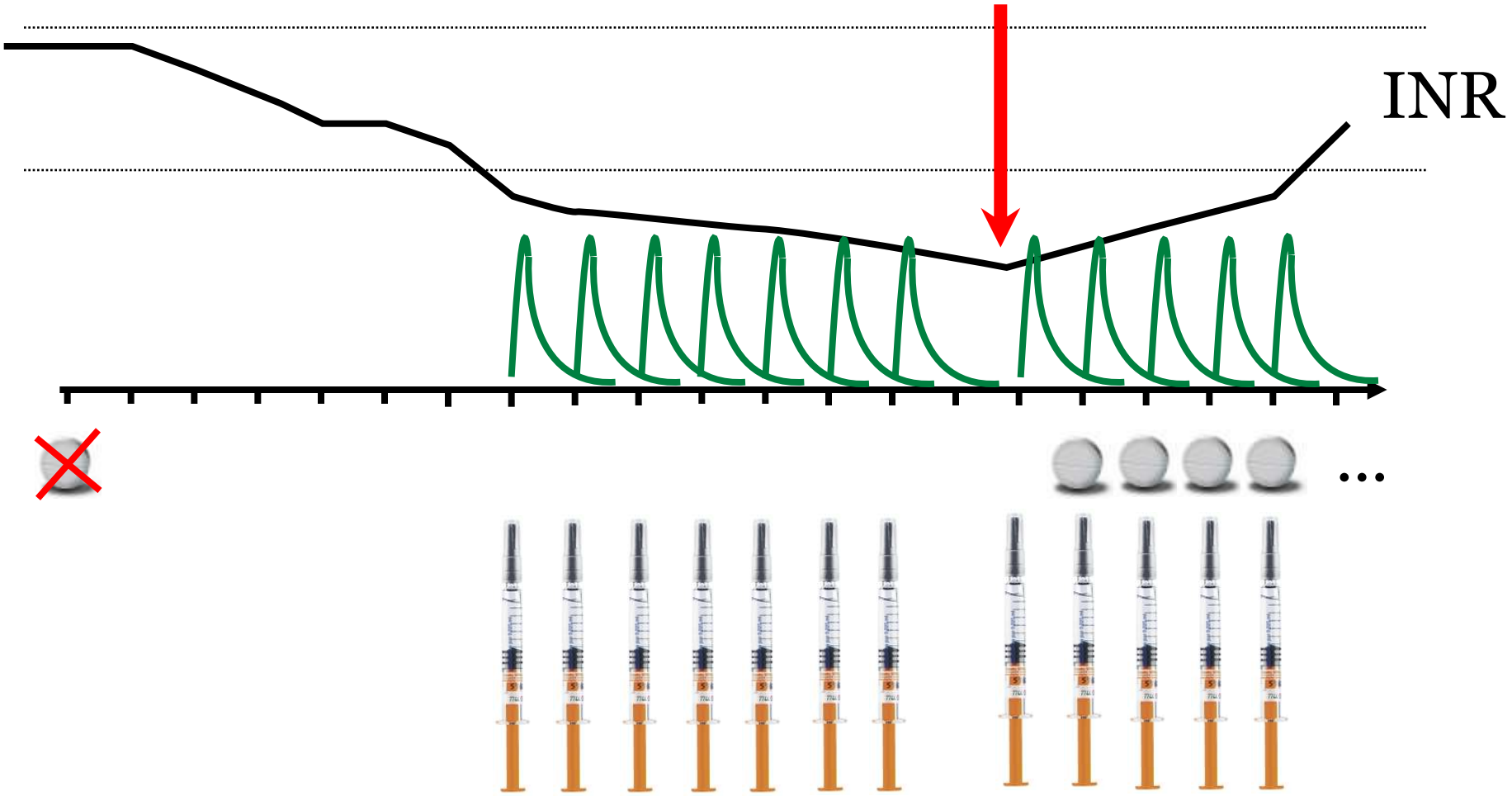


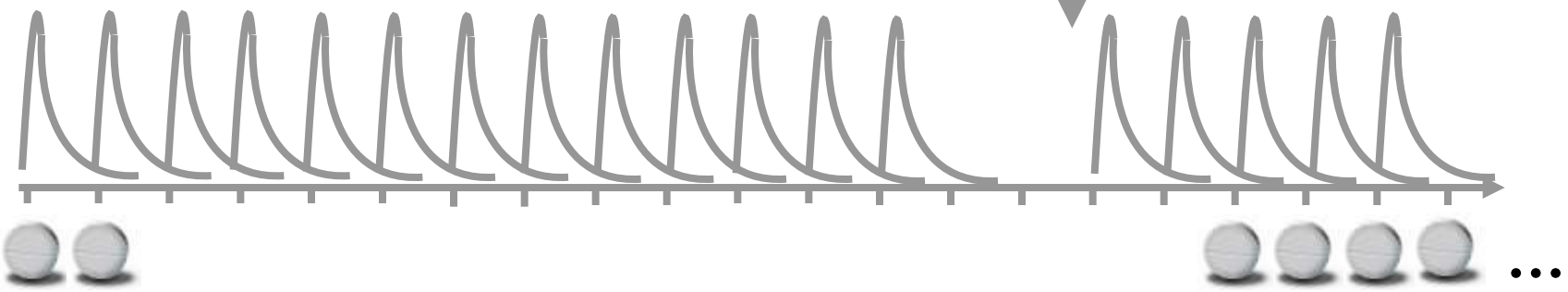
Similar PK LMWH NOAC



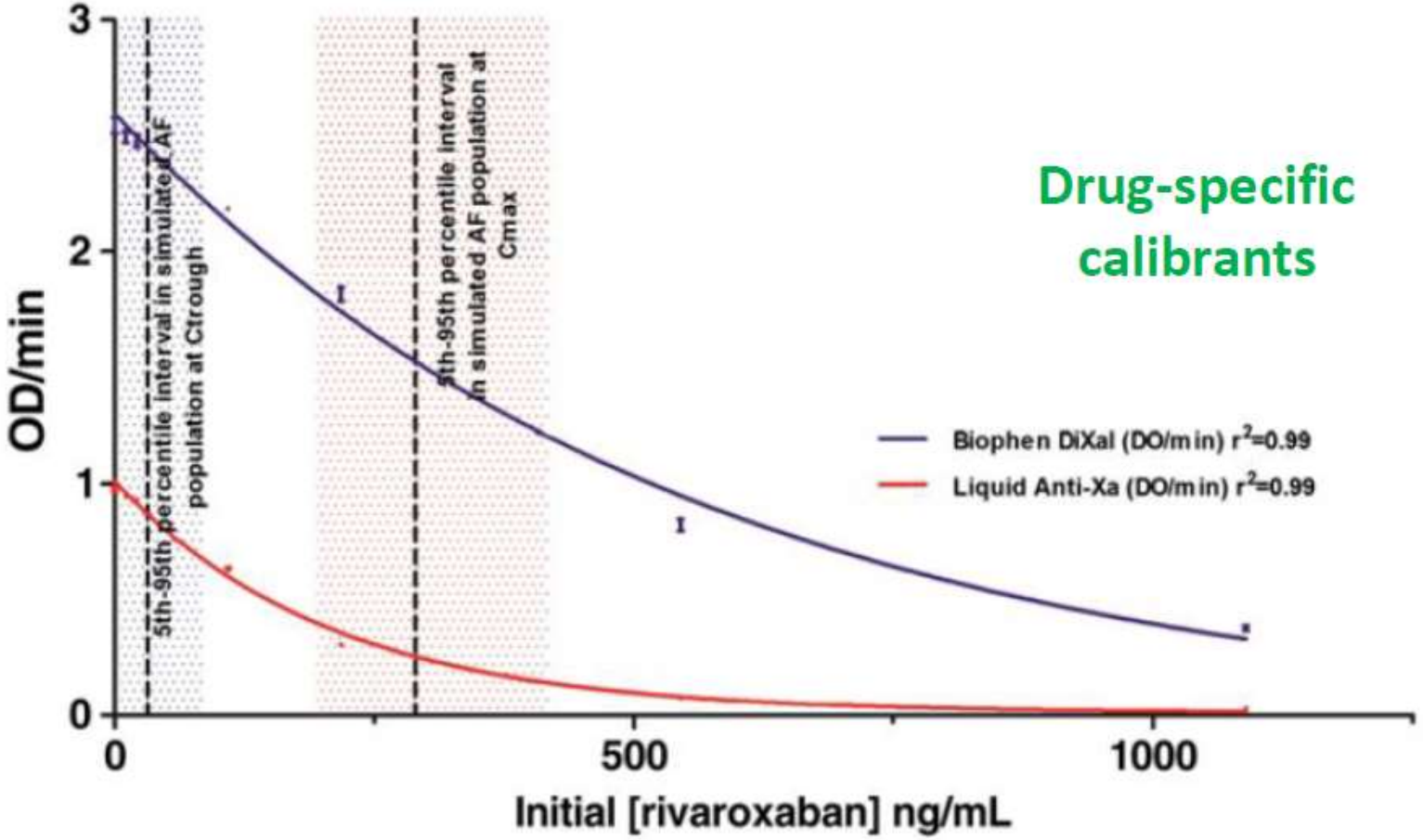
=> By the time the clinician gets the results, everything may have changed…

„Bridgen“





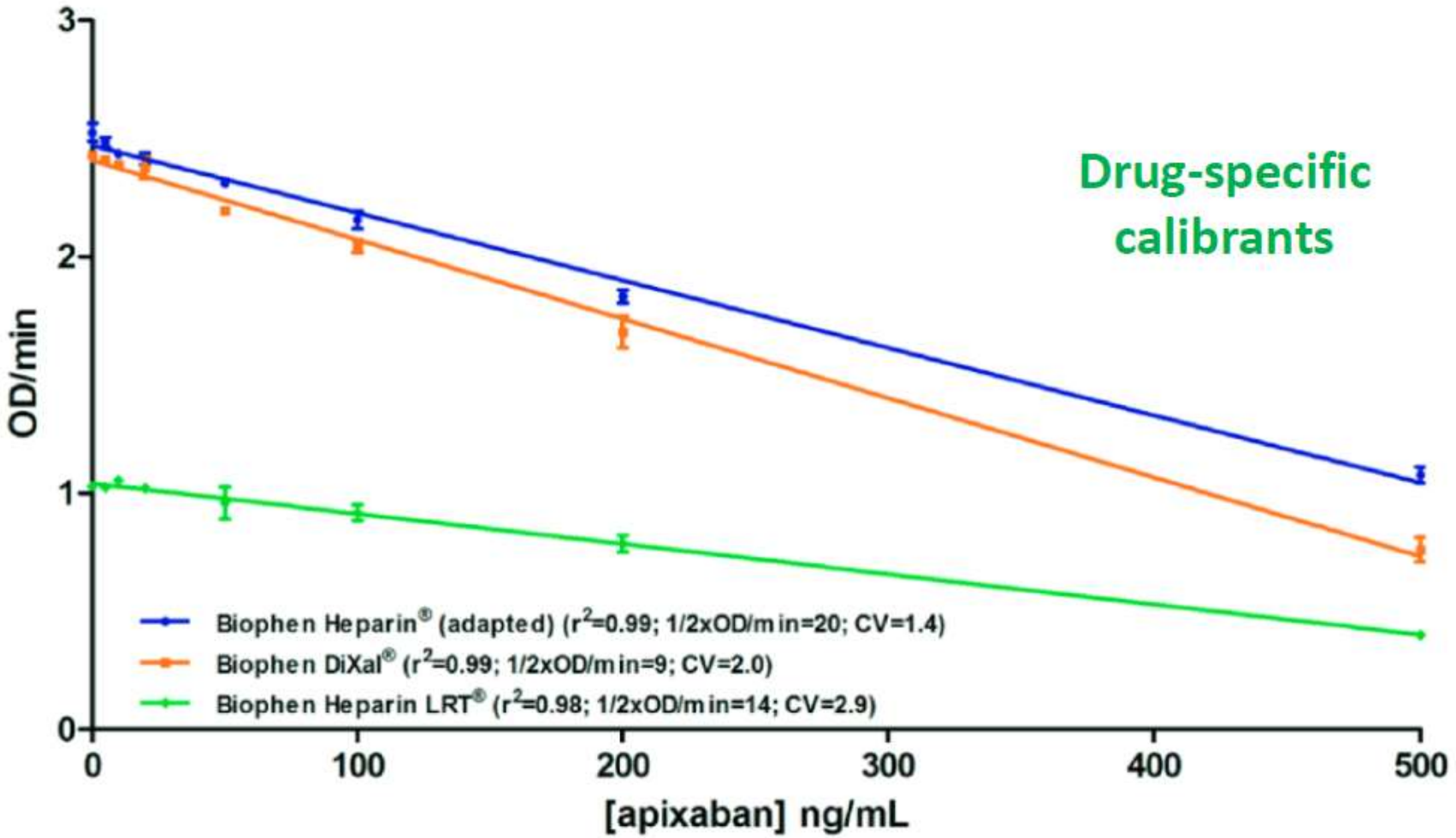
Anti-Xa assay for Rivaroxaban



Drug-specific calibrants

J Thromb Haemost 10:1433–1436.

Anti-Xa assay for Apixaban



Thromb Haemost. 2013;110(2):283-94.

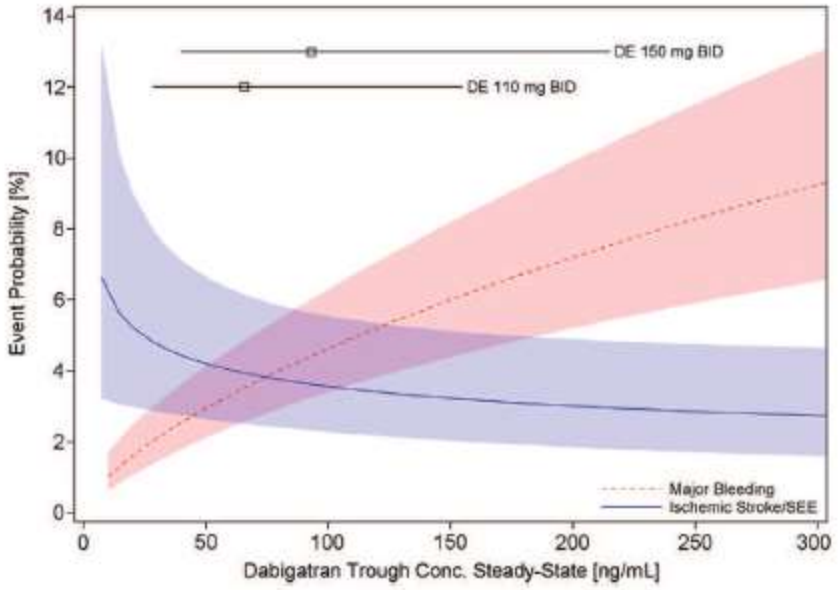
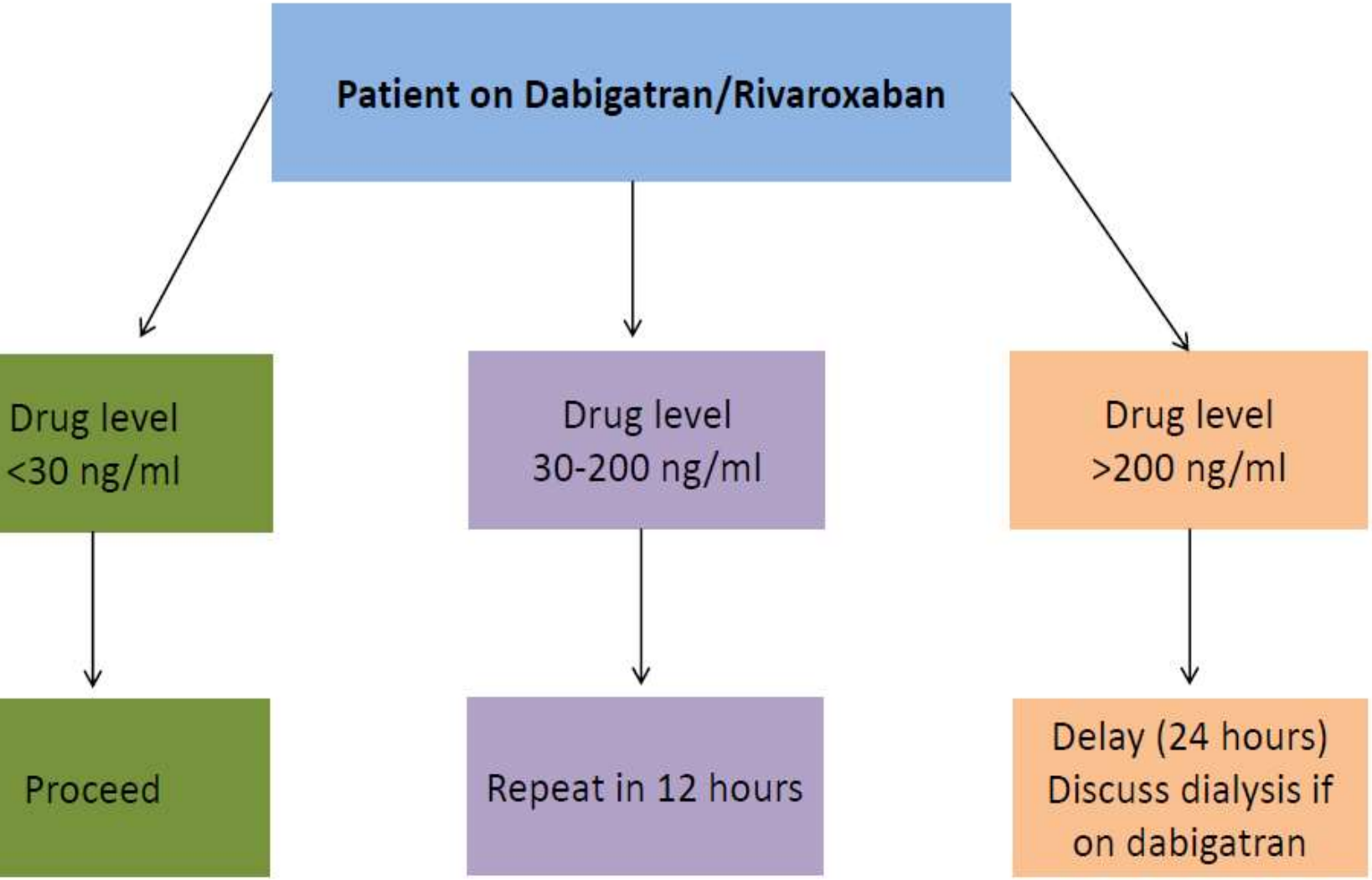
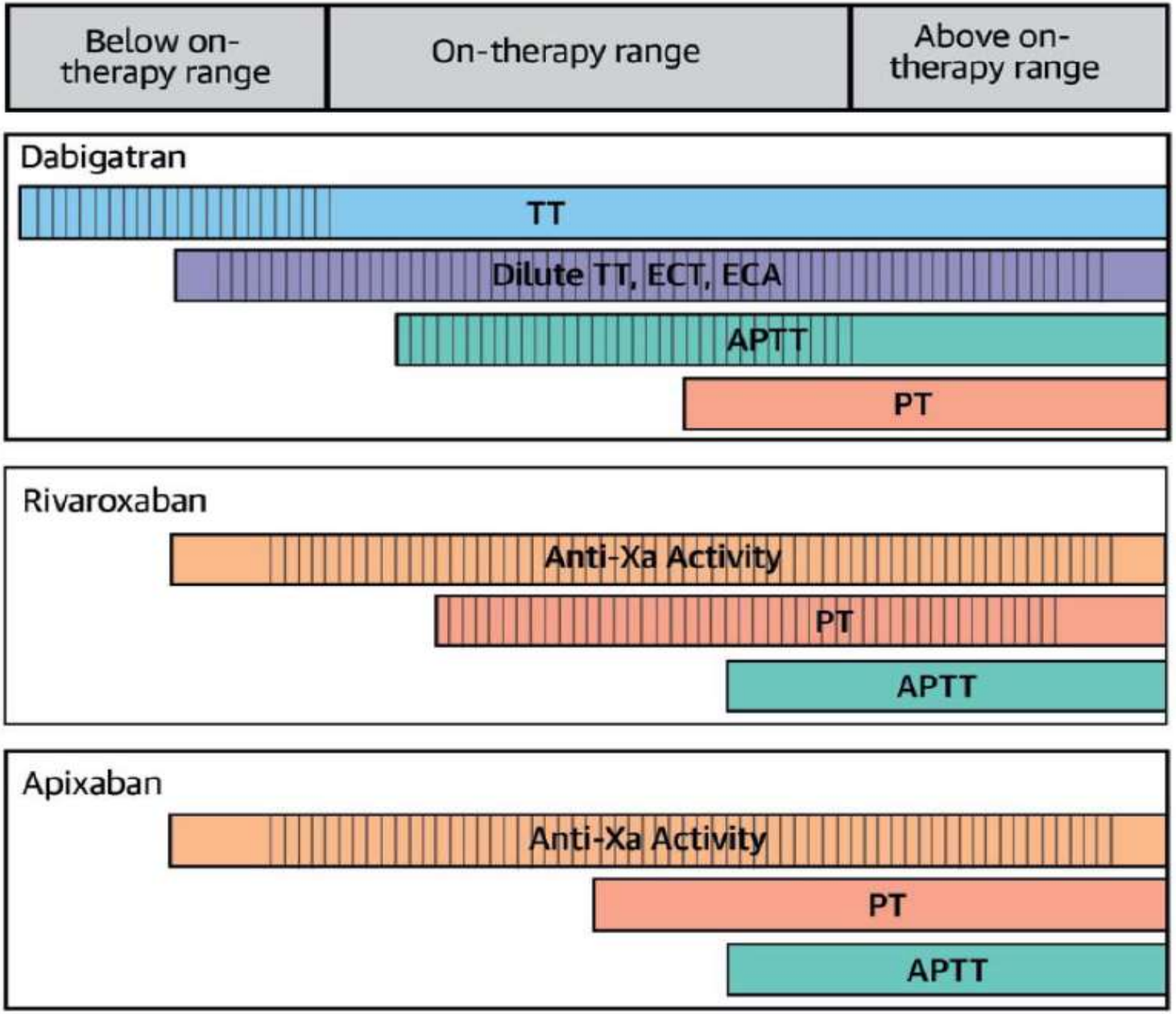


Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).

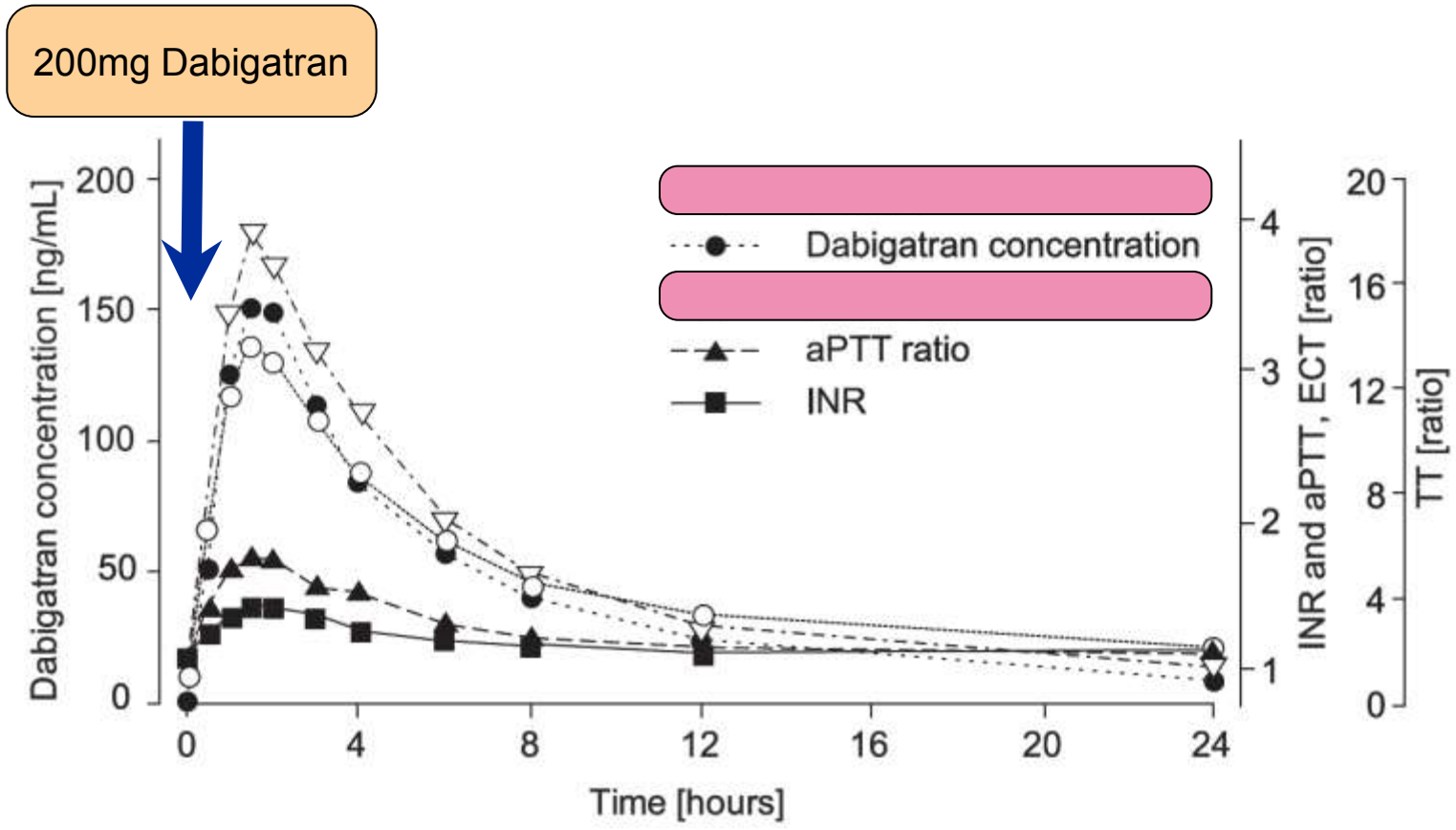


Arch Cardiovasc Dis 2013; 106, 382—393



JACC 2014;11:1128-39

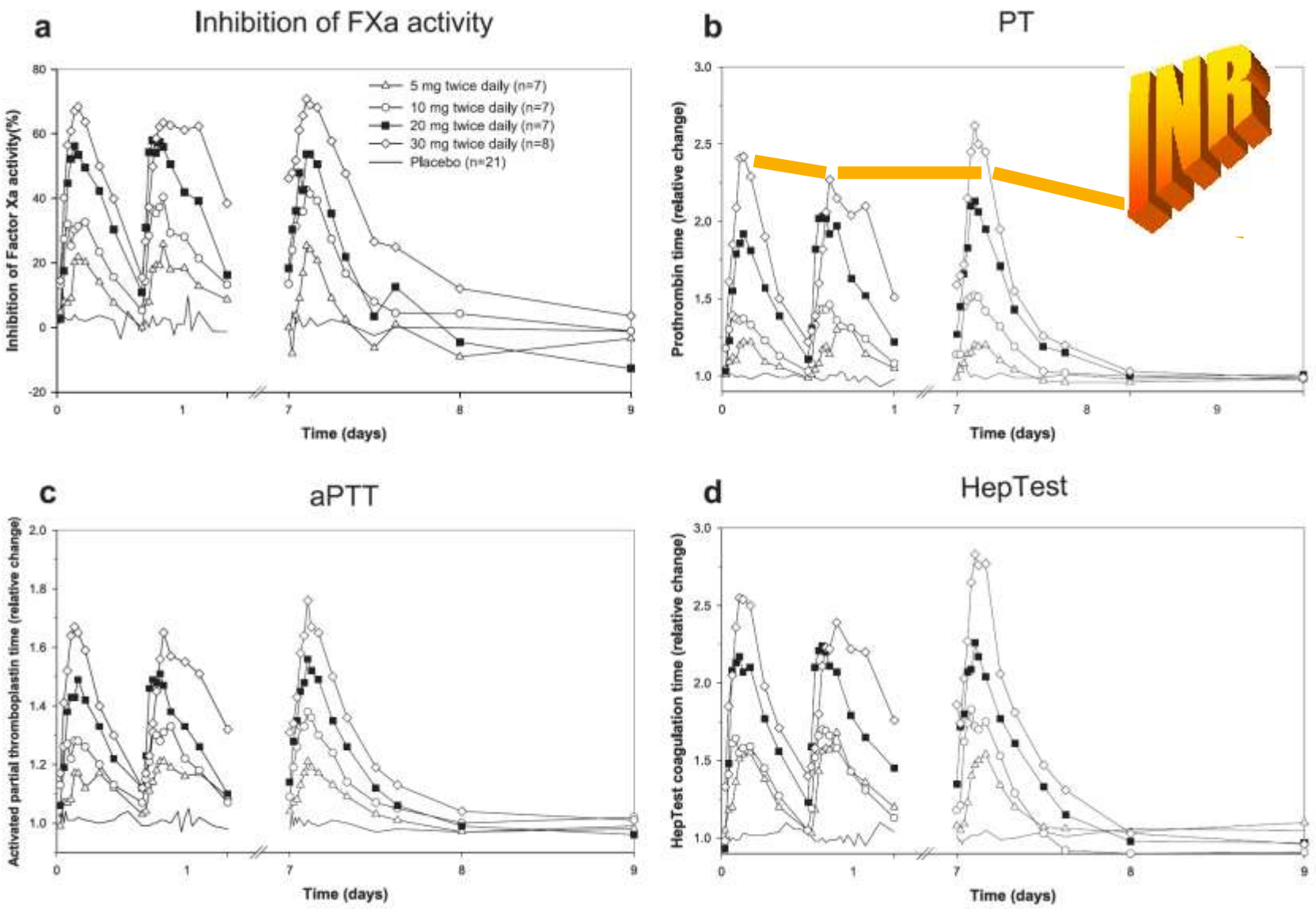
Dabigatran
Clotting Tests



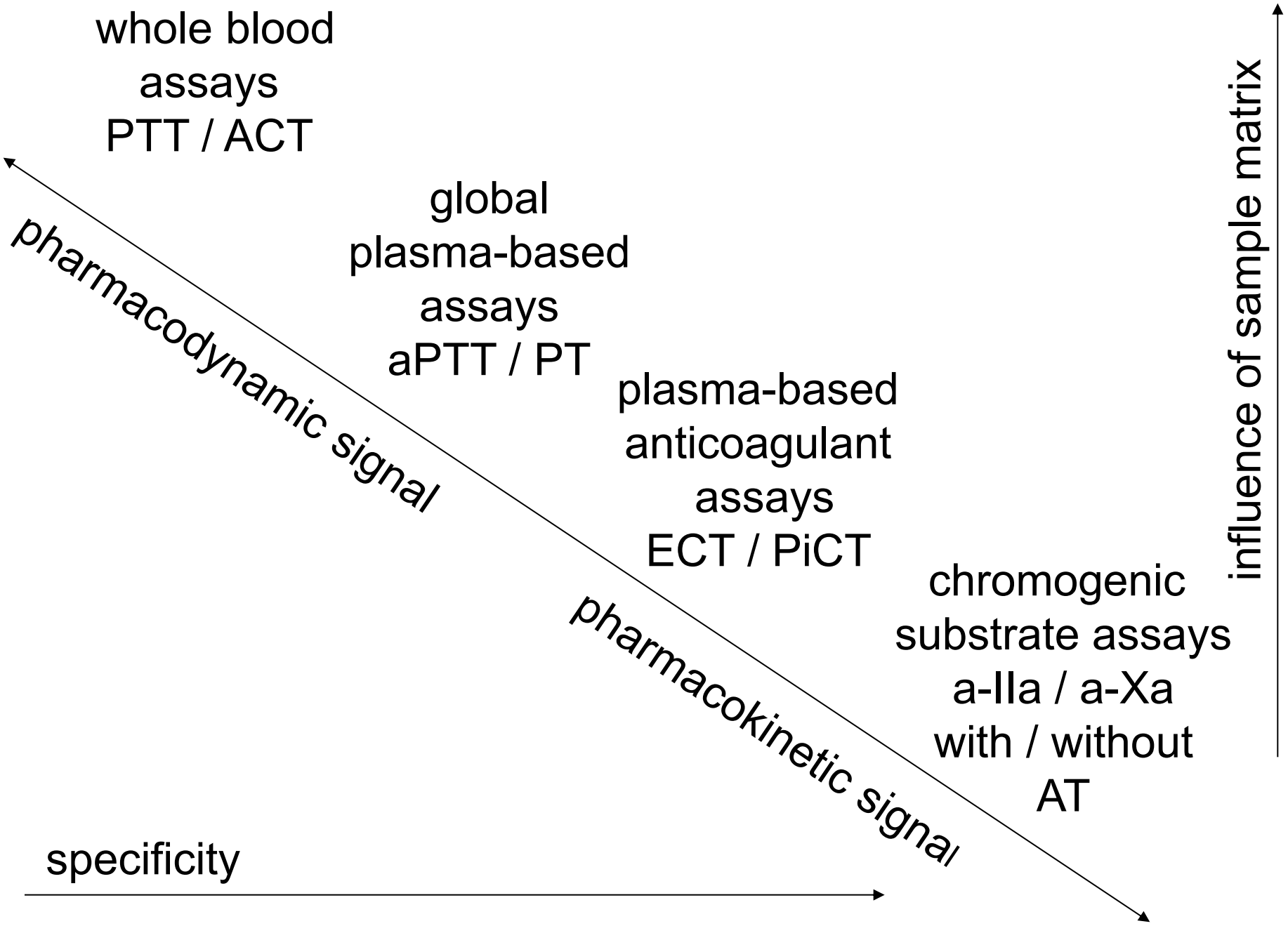
TT: Thrombin time; **ECT:** Ecarin-clotting time; **aPTT activated partial** thromboplastin time

van Ryn J et al. Thromb Haemost. 2010;103:1116-1127

Monitoring BAY 59-7939



Eur J Clin Pharmacol 2005: 61: 873–880


whole blood
assays
PTT / ACT
global
plasma-based
assays
aPTT / PT
plasma-based
anticoagulant
assays
ECT / PiCT
chromogenic
substrate assays
a-IIa / a-Xa
with / without
AT
pharmacodynamic signal
pharmacokinetic signal
influence of sample matrix
specificity

- Direct anticoagulants (IIa- and Xa-inhibitors) have a significant impact on global clotting tests. Depending on reagent composition this is evident already at low (prophylactic) plasma levels. Other test kits may be not sensitive at all.
- To evaluate patients own coagulation capacity take blood before next dosing (even postponing 6 - 8 hours may be necessary to avoid drug impact)
- In the moment no possibility to antagonize new anticoagulants in the test mixture

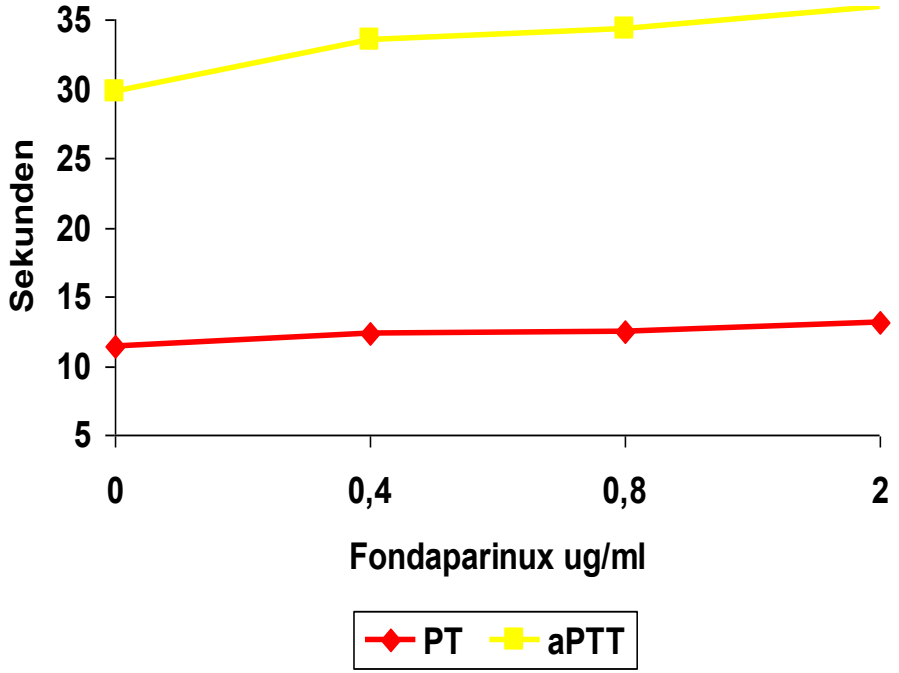
- differentiate PK and PD of old and new anticoagulants
- use certified calibrants only

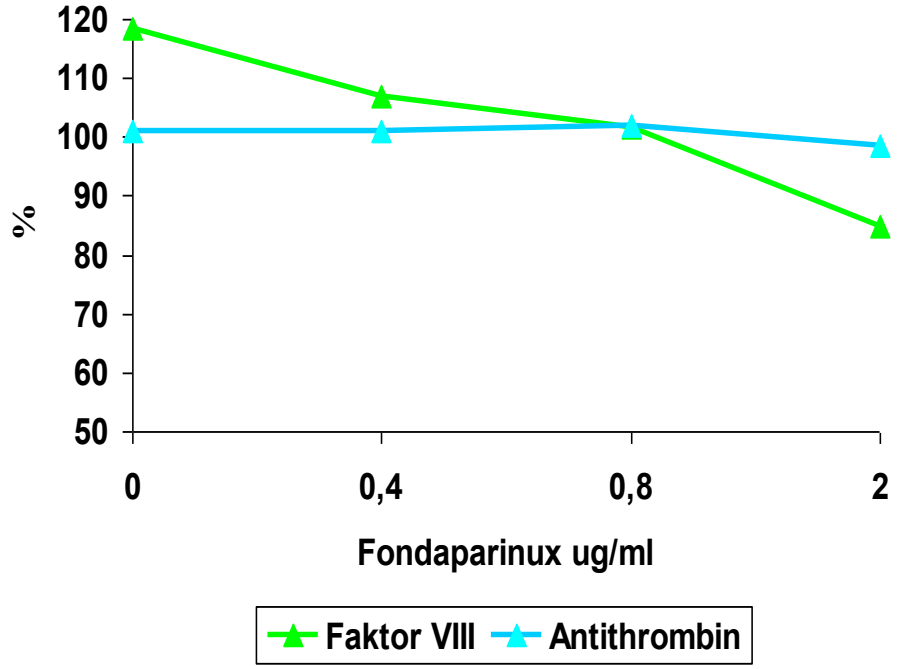
Lab and Clinics have to communicate concerning

- reagent heterogeneity, should all new compounds be measured?, which result to be reported?, be aware of PK vs PD..

NOT NEW: Anticoagulants disturb coag tests !

Smorozewska et al: Arch Pathol Lab Med 2006: 130: 1605-1611: College of American Pathologists Proficiency Testing





Thank you for Attention