Measurement of new oral anticoagulants (NOACs)

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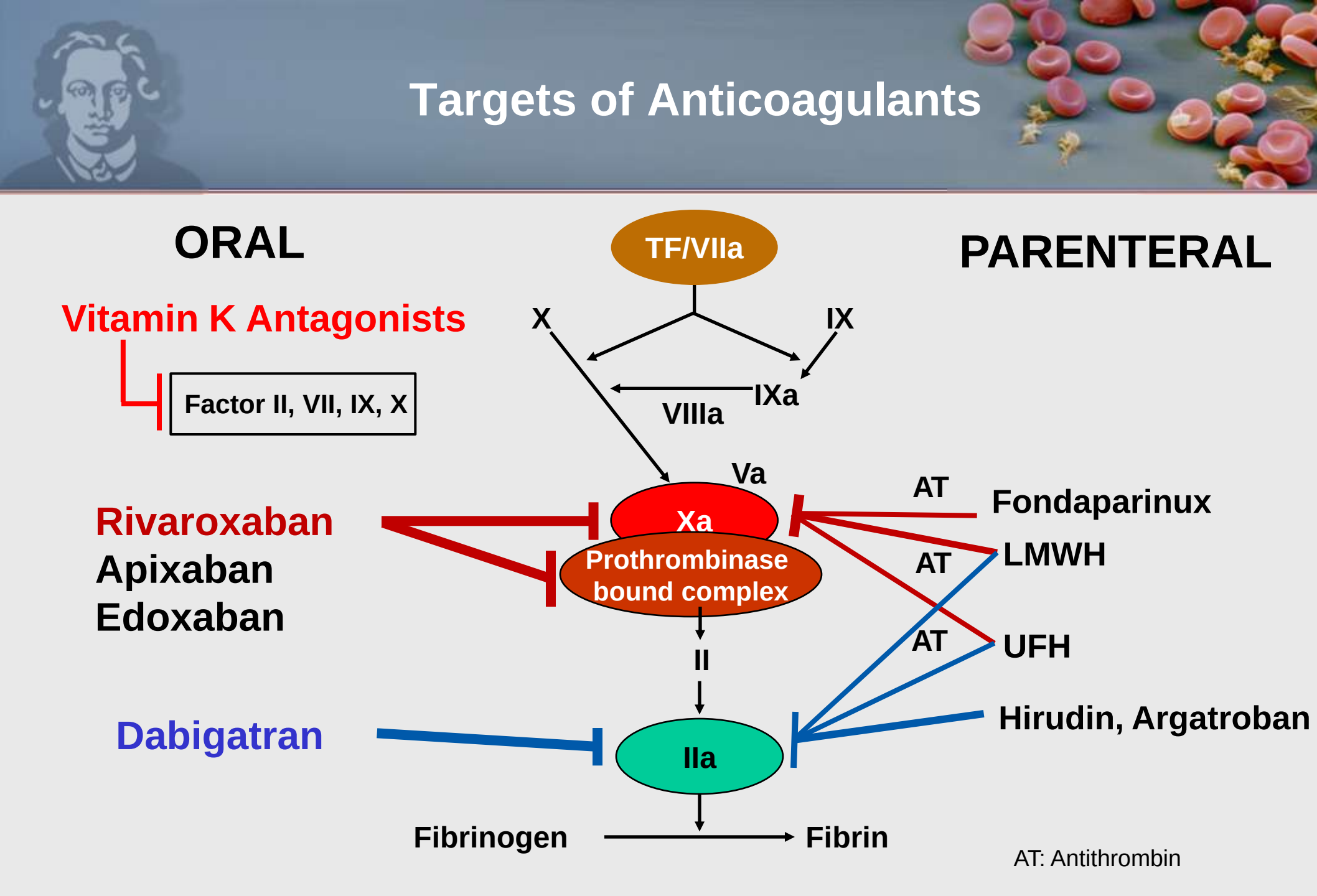
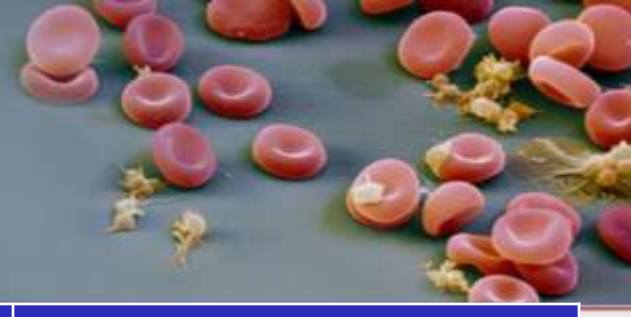
Targets of Anticoagulants

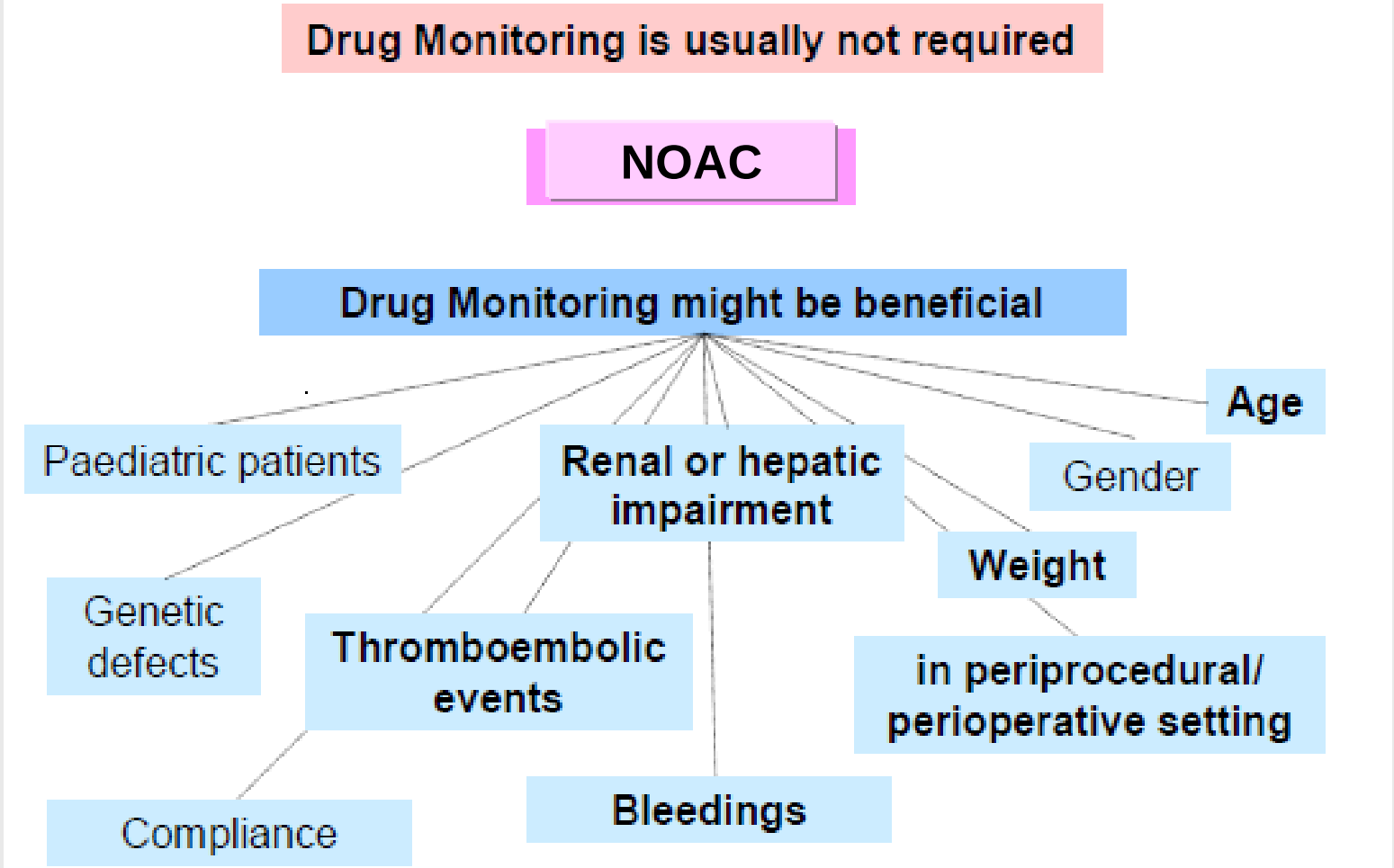


Pharmacokintic Profiles



	Dabigatran	Rivaroxaban
Direct oral inhibition	Factor IIa	Factor Xa
absolute bioavailability	6 - 7%	80 - 95%
Time for Cmax	2 - 3 h	1 – 3,5 h
Half life **($t_{1/2}$)**	14 – 17 h	7 – 11 h
Elimination	~85 % renal 20% intestinal	1/3 renal - 2/3 metabolic degradation (50 % renal /50% faecal)
Binding to plasma proteins	~35 %	~95 %
Influence of renal funktion	**CrCl ↓ ⇒ $t_{1/2}$ ↑ ↑**	**CrCl ↓ ⇒ $t_{1/2}$ ↑**
Antidot available	No	No
„Routine“-Monitoring needed	No	No

Reasons for Monitoring of NOACs

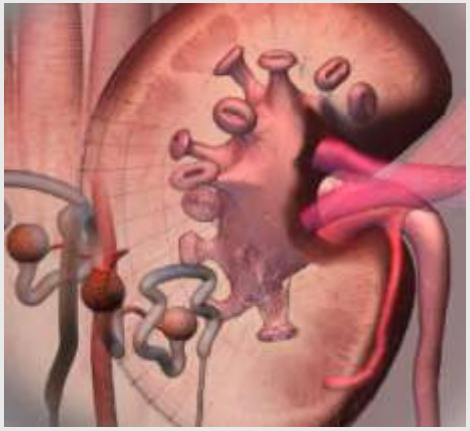


Mani H, Kasper A, Lindhoff-Last E. (Review)
Journal of Thrombosis and Thrombolysis; 2012 in press

Bleeding Risk with Dabigatran in the Frail Elderly

Harper et al, N Engl J Med 2012; 366 (9) 864-865

Report from New Zealand:
7000 patients were collected treated with dabigatran because of atrial fibrillation, auditing of bleeding episodes together with Australia: 78 bleeding episodes (44 in New Zealand)



www.schmidtwerner.de/ images/niere.jpg

4 main risk factors for bleeding:

1. **Prescription mistakes**
2. **Renal insufficiency**
3. **Old age, low body weight**
   2/3 of the patients > 80 years
4. **Complications because an antidote is missing**

Information Insert Sheet: Dabigatran, August 2011 „Trough levels“ are relevant!

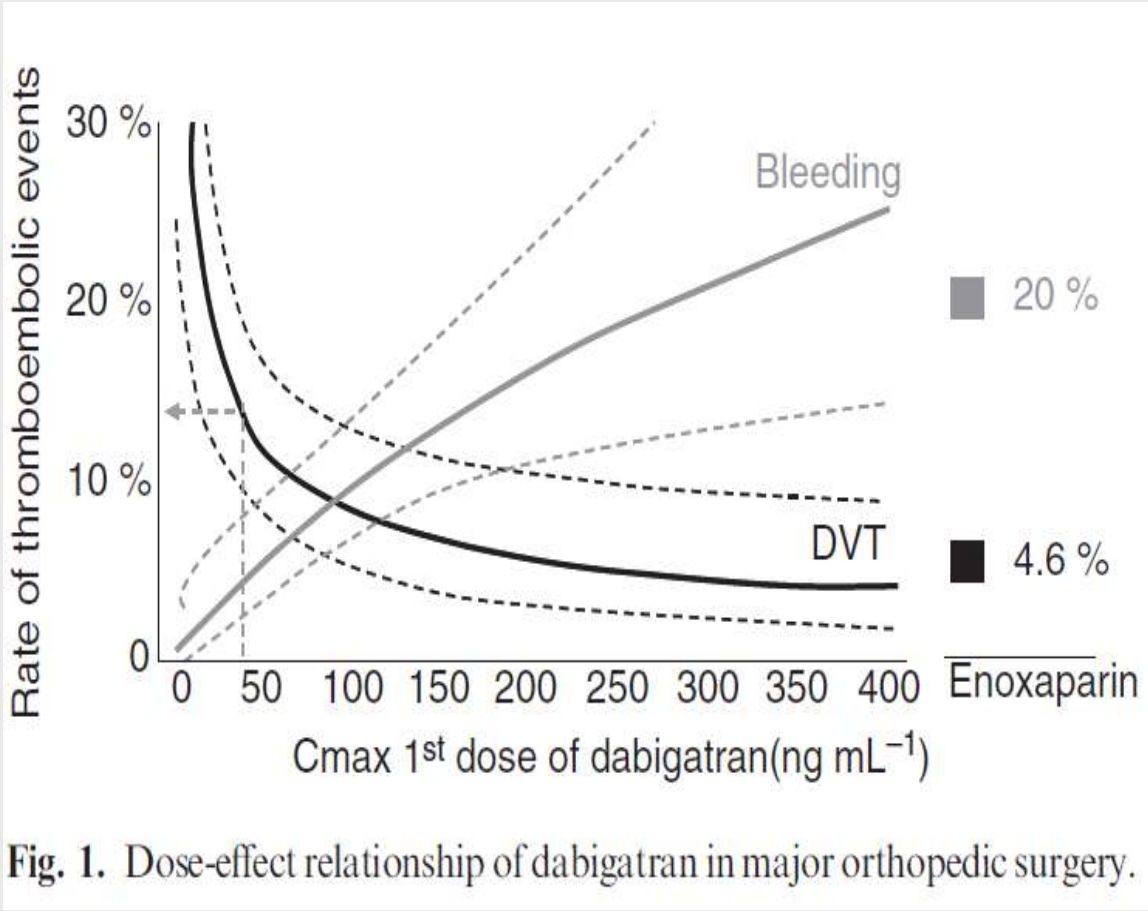


Fig. 1. Dose-effect relationship of dabigatran in major orthopedic surgery.

- **Prophylaxis after hip- or knee-replacement surgery (220mg od)**
  Bleeding risk increased:

  Dabigatran-concentration:
  > 67 ng/ml
  20-24h after intake

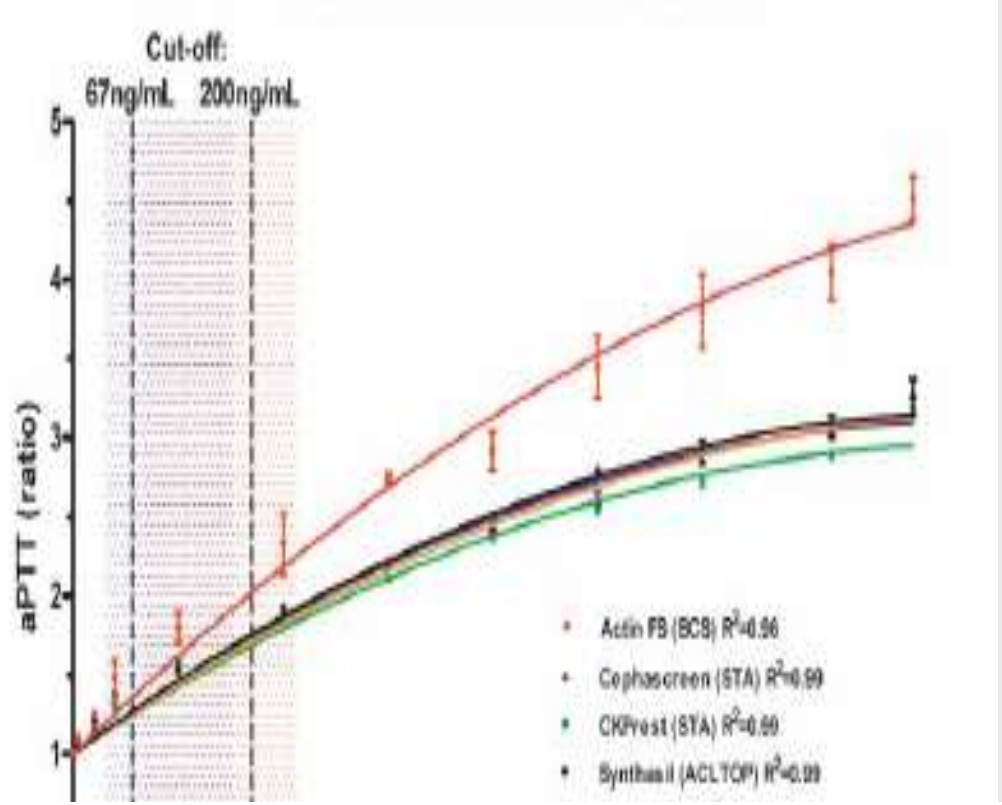
- **Therapy of atrial fibrillation (150 mg bid)**
  Bleeding risk increased:

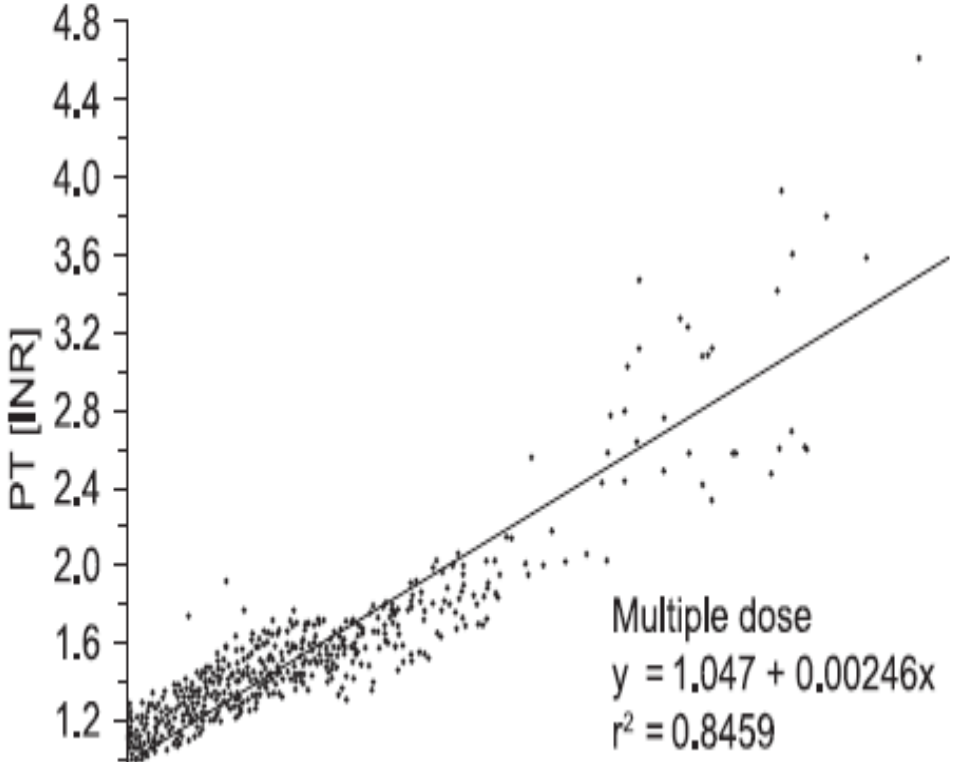
  Dabigatran-concentration:
  > 200 ng/ml
  10 – 16h after intake

Mismetti et al, J Thromb Haemost 2010; 8: 621-626;
Eriksson et al, J Thromb Haemost 2005; 3: 103-111

Monitoring, how ?

Influence of Dabigatran on APTT and PT



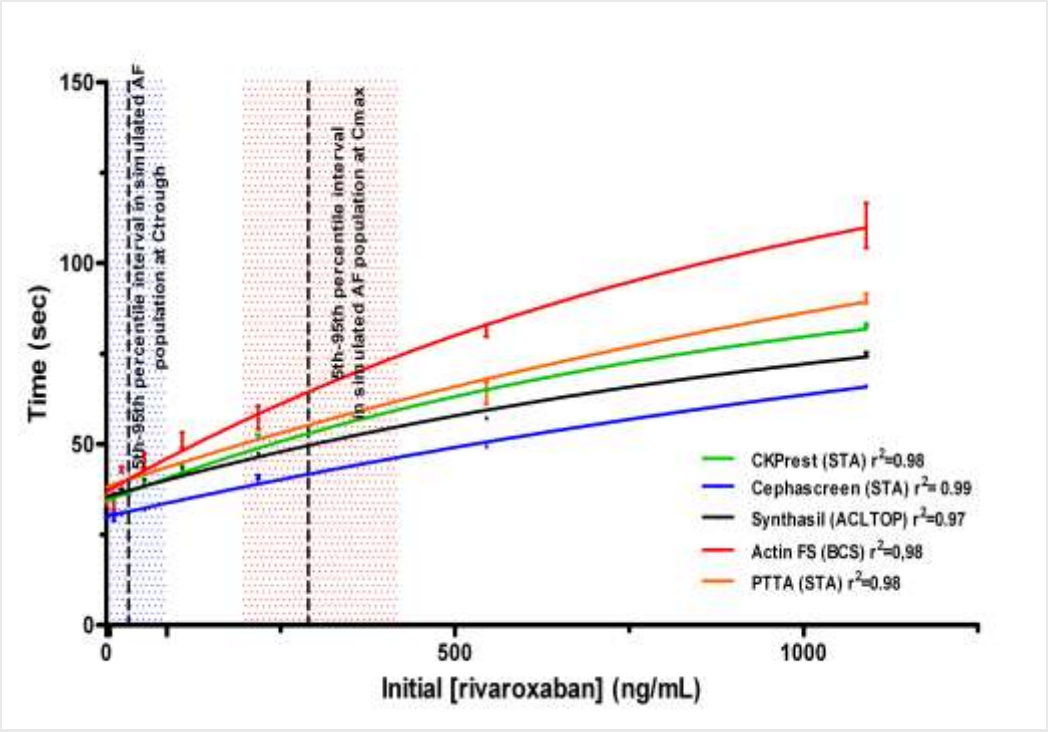


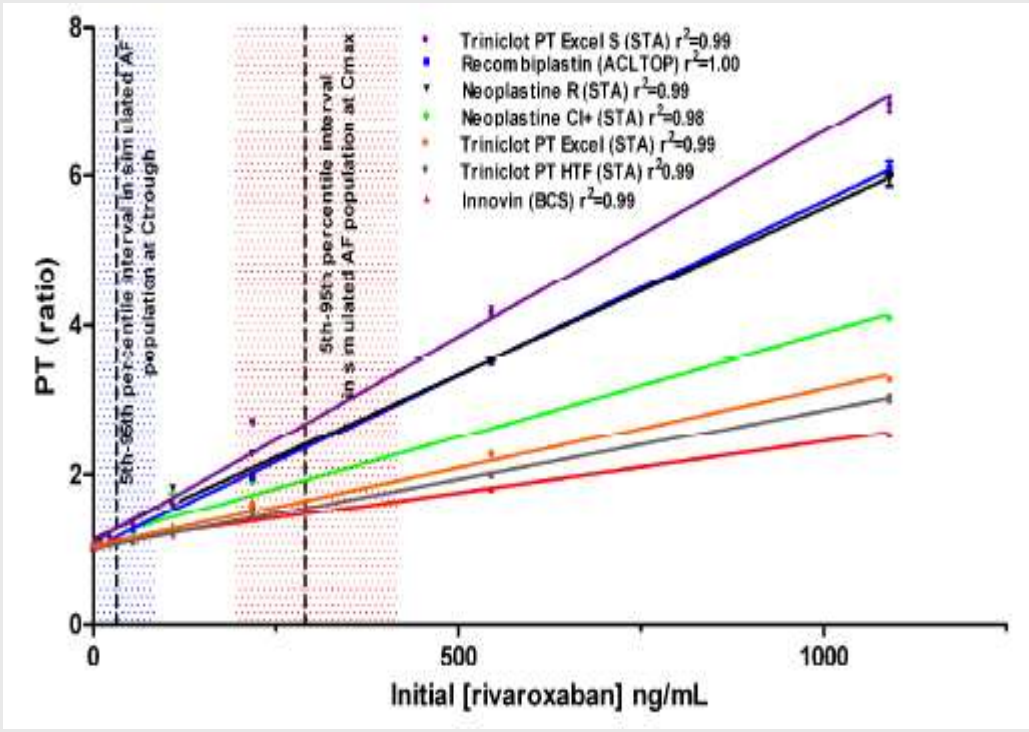
The APTT and PT are influenced by dabigatran depending on the reagents used and the concentration of dabigatran.
The APTT is more sensitive to dabigatran concentration than the PT.

Douxfils et al. Thromb Haemost 2012

van Ryn et al. Thromb Haemost 2010,

Influence of Rivaroxaban on APTT and PT (in vitro)



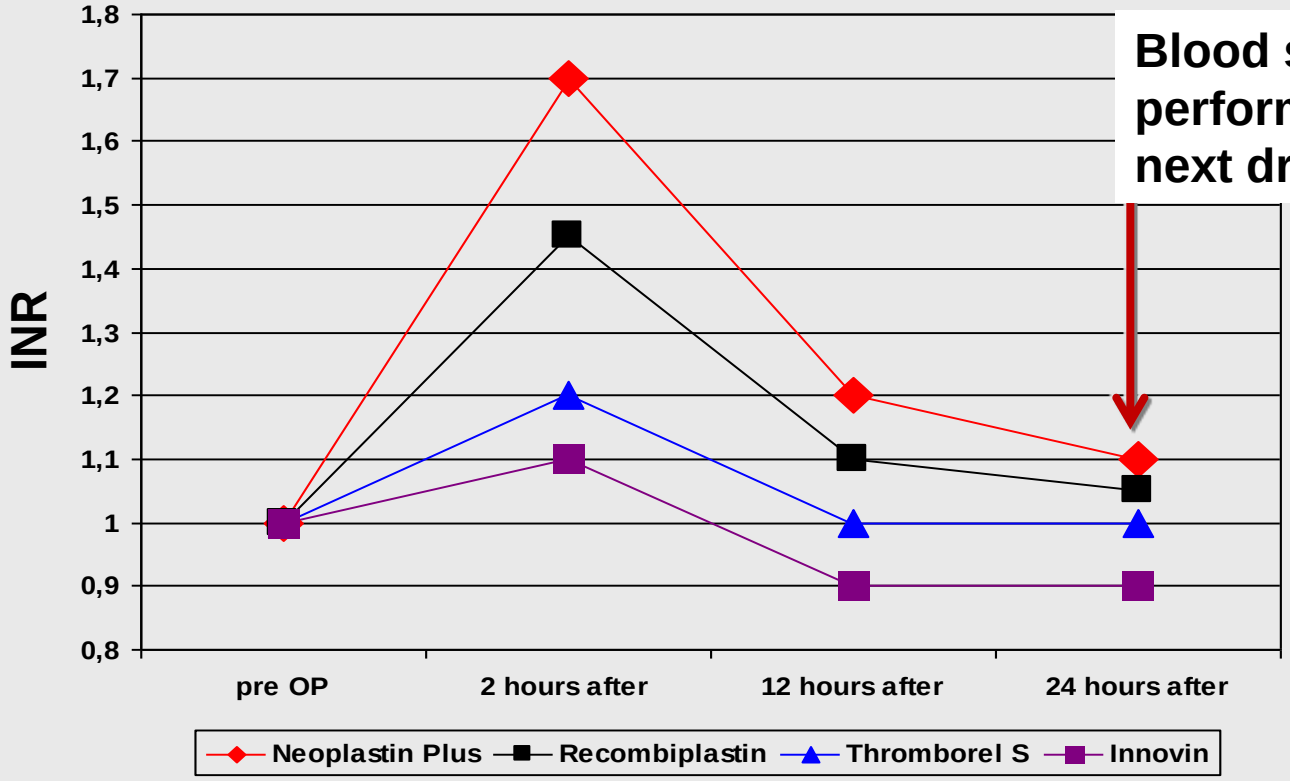


The APTT and the PT are influenced by rivaroxaban depending on the reagents used.

The PT shows a more sensitive concentration-dependent prolongation than APTT

Douxfils et al. Thromb Res 2012

Influence of Rivaroxaban on PT (ex vivo)

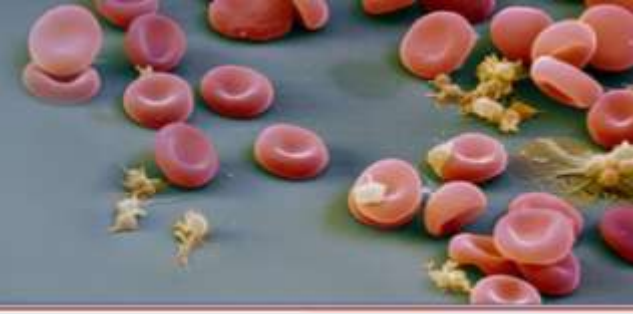


Blood sampling performed directly before next drug administration

The PT values are influenced by rivaroxaban
depending on the time of drug intake.
Neoplastin Plus is most sensitive PT reagent

Mani et al. Thromb Haemost 2011 (modified)

Monitoring of NOACs



Can the aPTT oder PT - assay be used for accurate monitoring of NOACs ?

Not useful for quantitative drug concentration measurement, due differences in sensitivity of aPTT- und PT-reagents

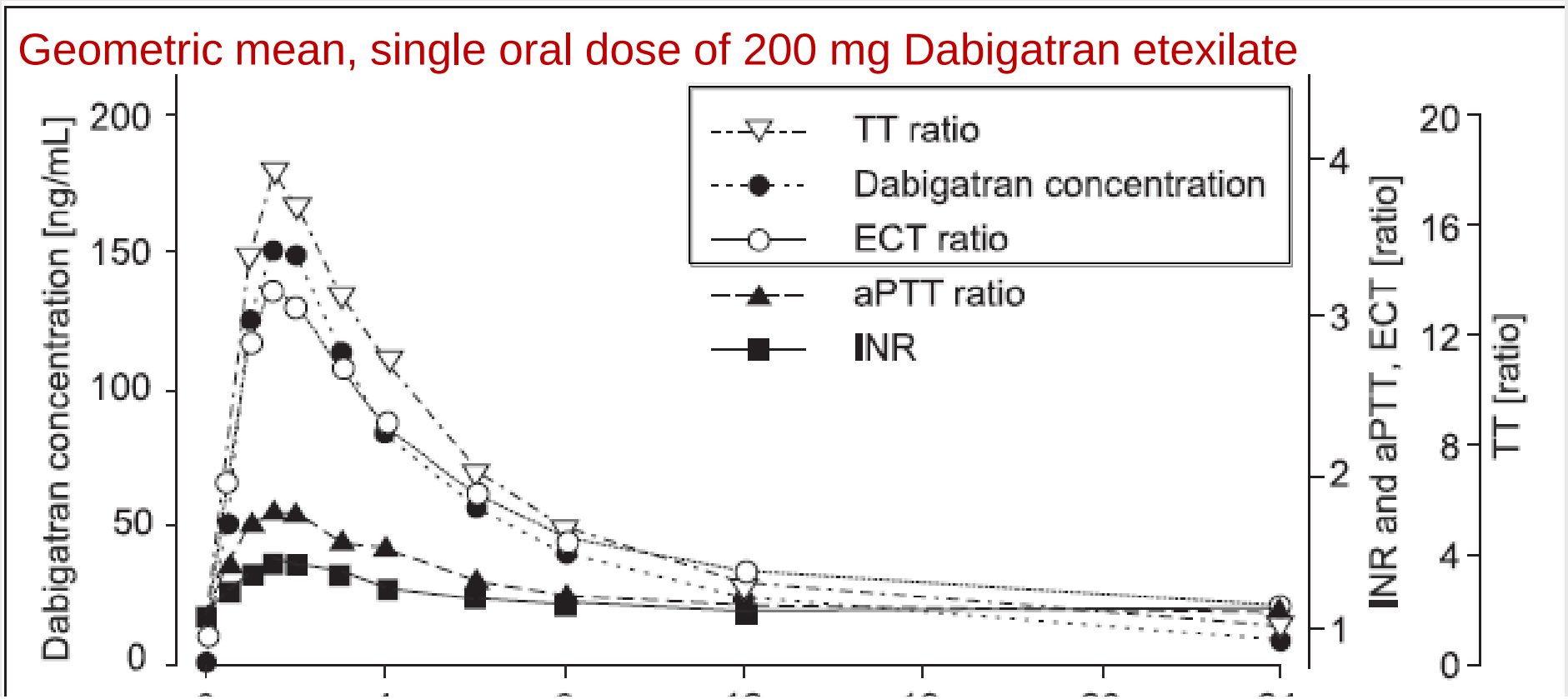
Not specific for NOACs

(Vitamin K deficiency, disseminated intravascular coagulation, coagulation factor deficiency)

Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity

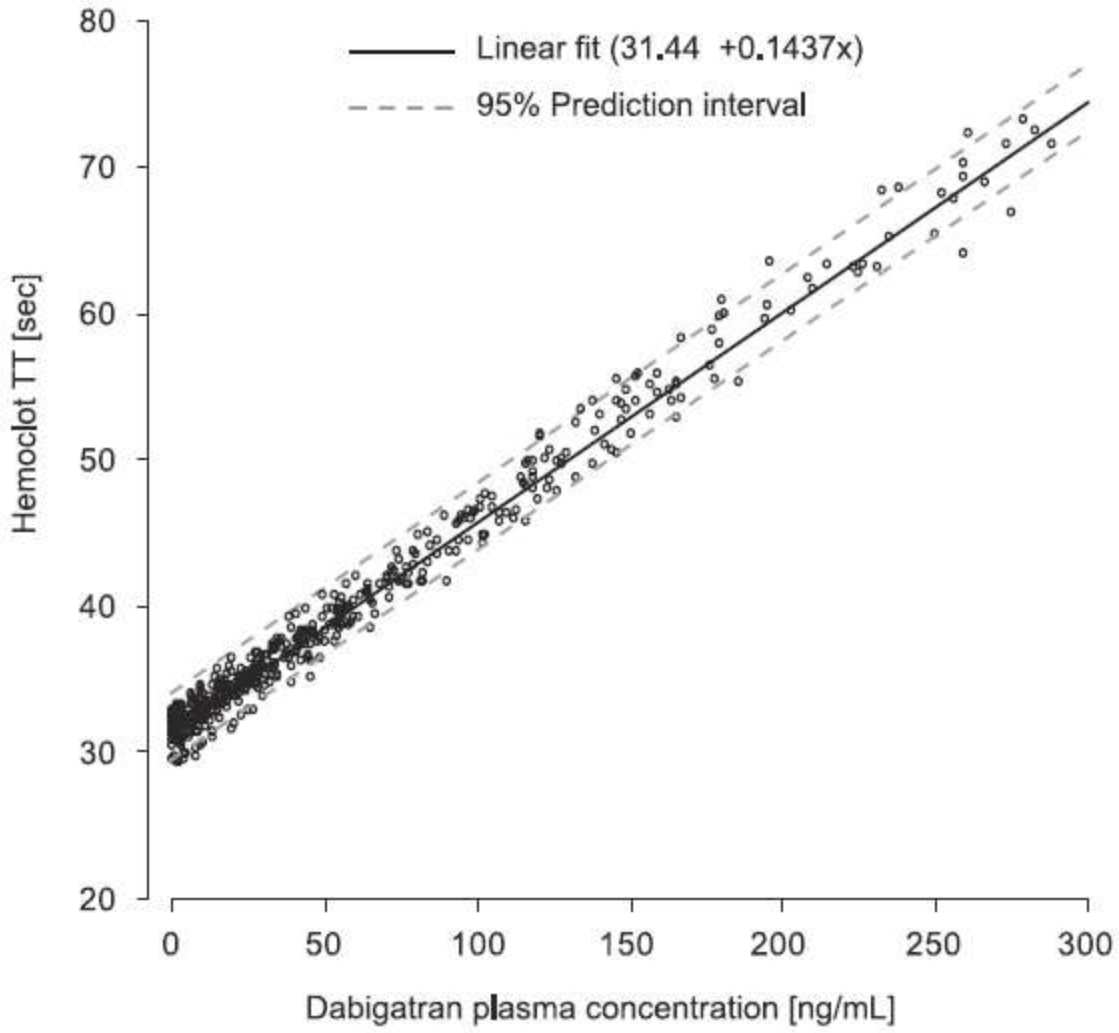
Joanne van Ryn[1]; Joachim Stangier[2]; Sebastian Haertter[2]; Karl-Heinz Liesenfeld[2]; Wolfgang Wienen[3]; Martin Feuring[4]; Andreas Clemens[4] Thromb Haemost 2010; Stangier et al Br J Clin Pharmacol 2007

Geometric mean, single oral dose of 200 mg Dabigatran etexilate



The Ecarin-Clotting-Time (ECT), a diluted thrombin time or a chromogenic Anti FIIa-assay may be used for determination of dabigatran concentrations in special clinical situations

The Hemoclot-Thrombininhibitor–Assay accurate measurement of Dabigatran-concentrations



Sensitive, diluted thrombin-time

„gold standard of monitoring for dabigatran“

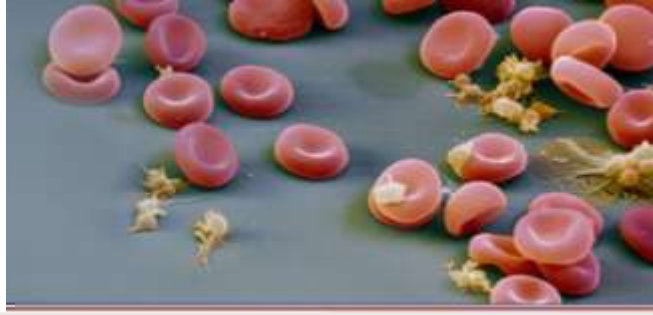
Use of human alpha-Thrombin AND Dabigatran-standards and –controls

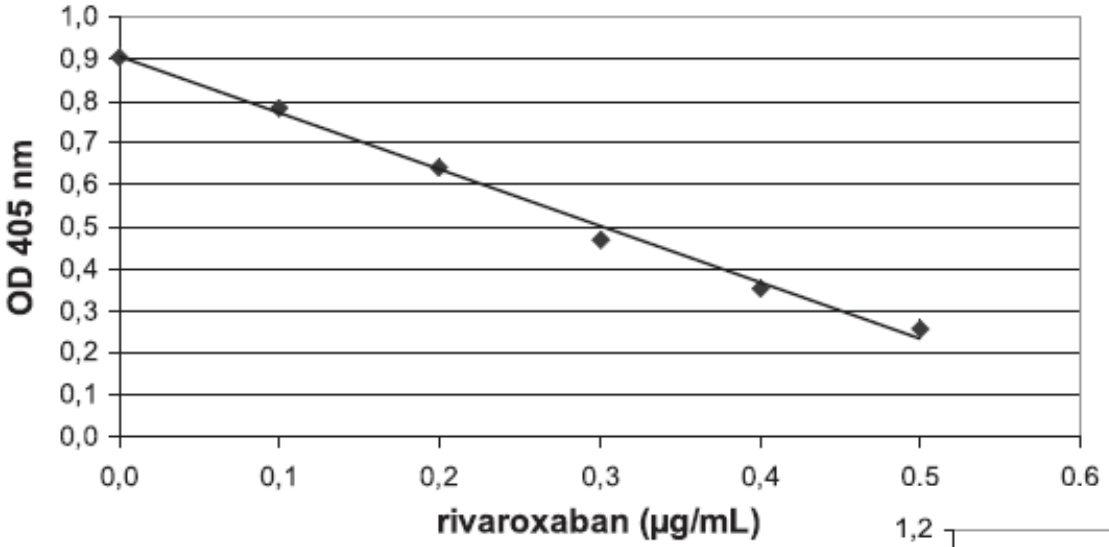
Stangier et al, Abstract, Thromb Haemost 2009; 7 (Suppl2): 978;
van Ryn et al, Thromb Haemost 2010;
Avecilla et al. Am J Clin Patho. 2012;
Douxfils et al, Thromb Haemost 2012;

An optimised, rapid chromogenic assay, specific for measuring direct factor Xa inhibitors (rivaroxaban) in plasma

Meyer Michel Samama[1,2]; Jean Amiral[3]; Céline Guinet[2]; Elisabeth Perzborn[4]; François Depasse[2]

Thromb Haemost 2010; 104: 1078-1079

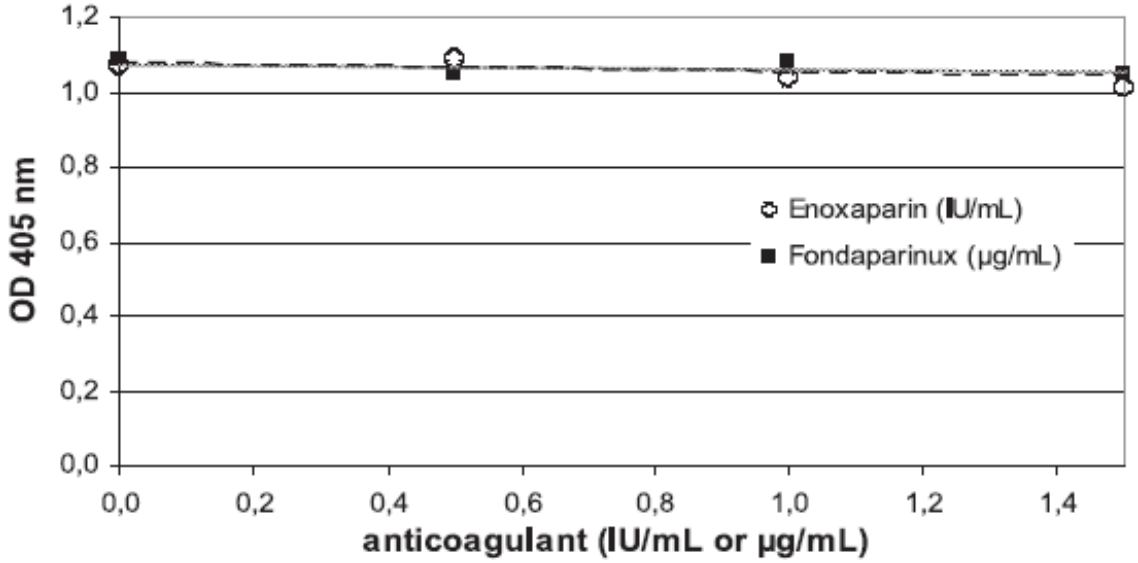




Plasmaconcentrations:
0.02-0.50 µg/ml
Dilution of plasma: 1:20
CV within run: 4.2 – 6.9%
CV between run: 4.1 – 7.2%

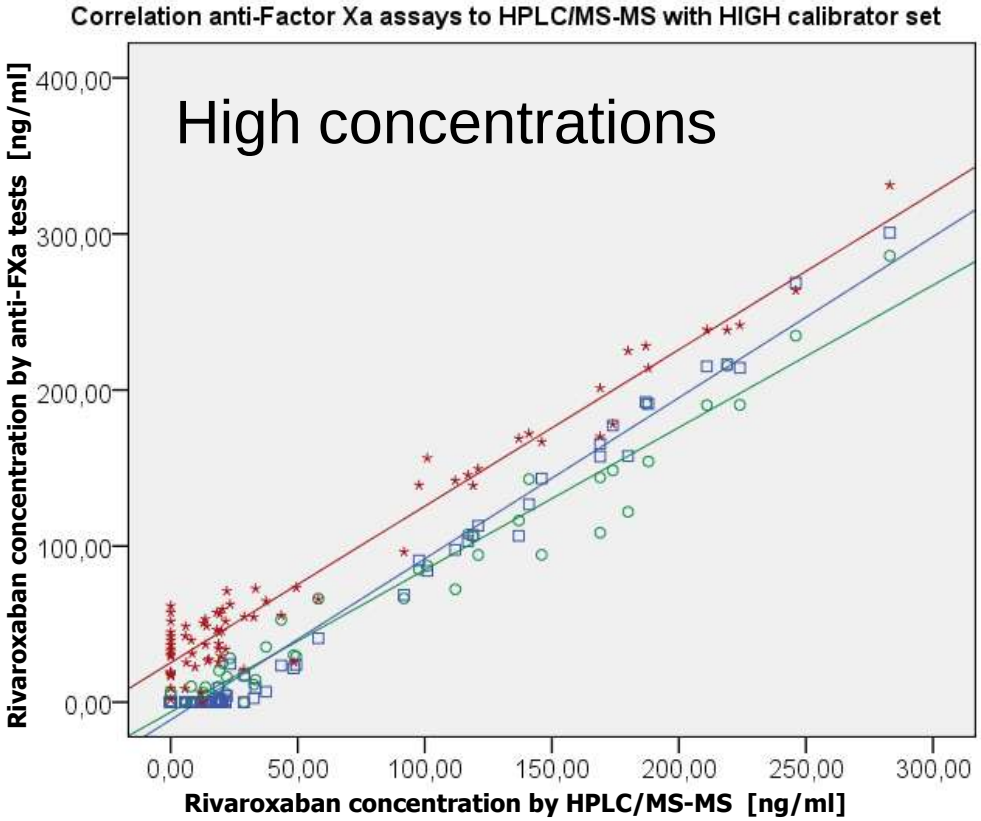
Because of pH of 7.9
no interference with
heparins or **Fondaparinux**
because of **inhibition** of
their **catalytic activity**

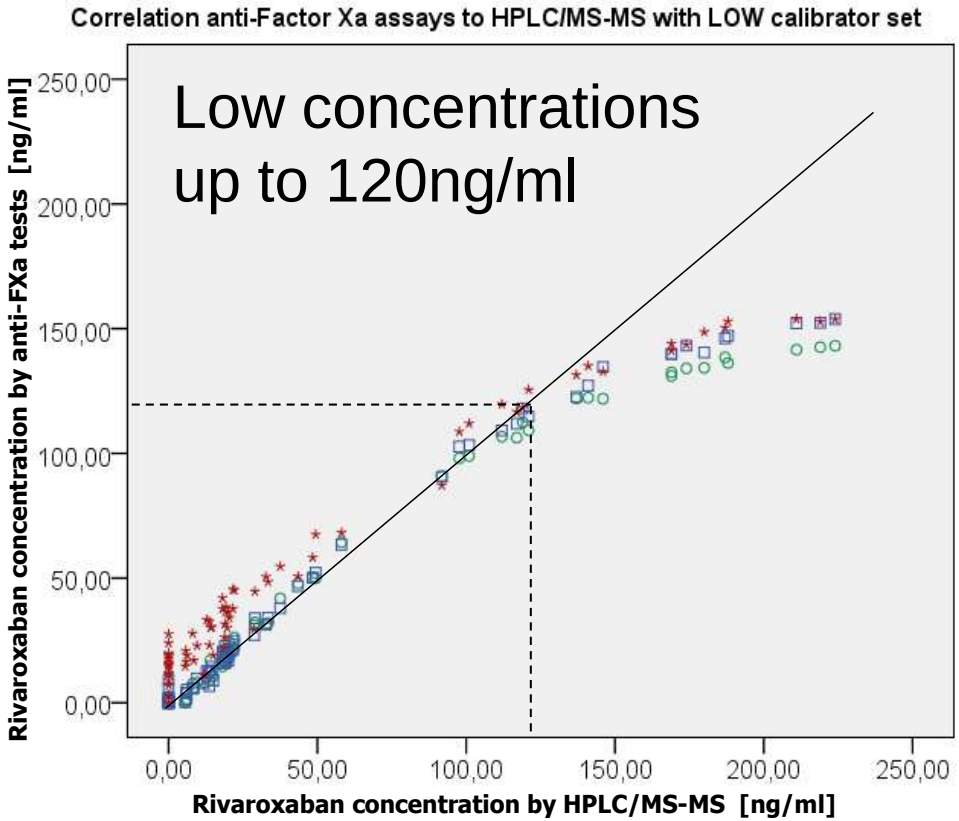
Specific for Rivaroxaban



Rivaroxaban: AntiXa-measurements: excellent correlation with HPLC-MS/MS

Mani, Lindhoff-Last et al, Thromb Haemost 2012; 108 (1): 191-198

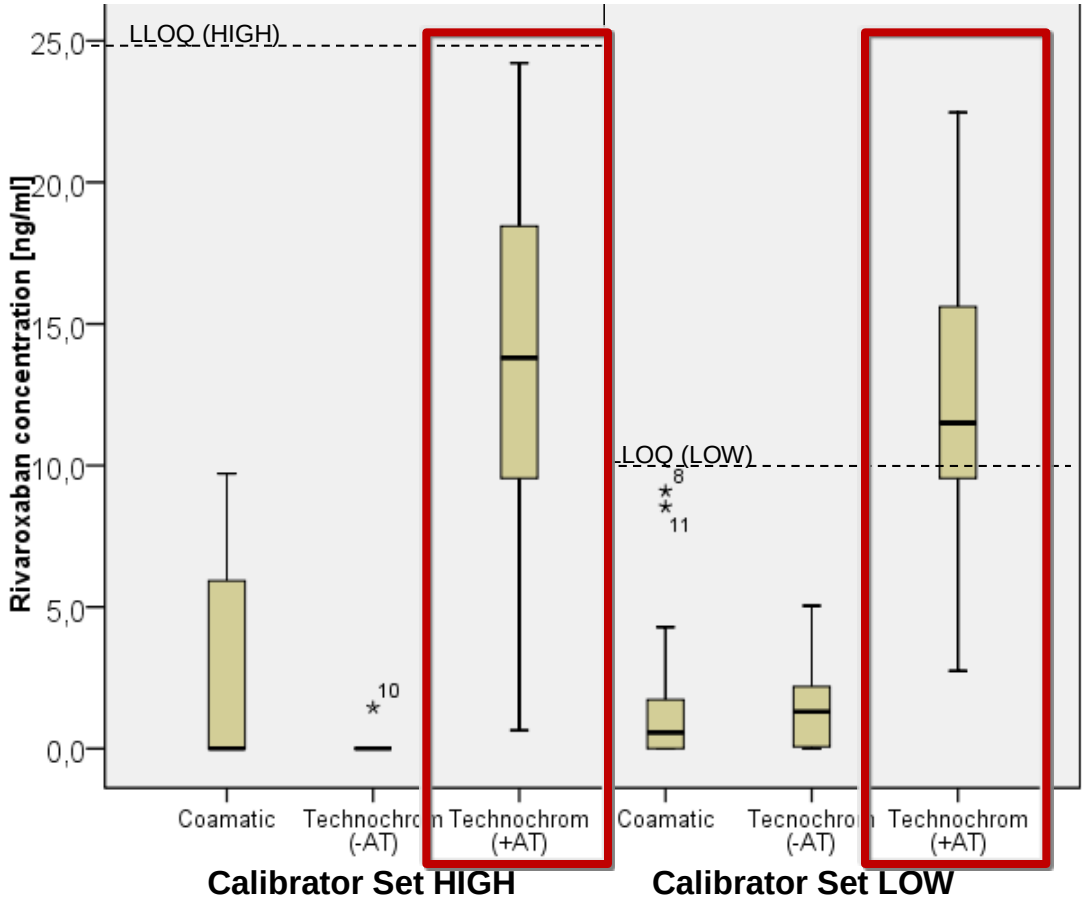




O	COAMATIC® Heparin assay (AT-)	$R^2 = 0.965$	O	COAMATIC® Heparin assay (AT-)	$R^2 = 0.966$
□	Technochrom® anti-Xa(AT-)	$R^2 = 0.981$	□	Technochrom® anti-Xa(AT-)	$R^2 = 0.973$
*	Technochrom® anti-Xa(AT+)	$R^2 = 0.953$	*	Technochrom® anti-Xa(AT+)	$R^2 = 0.960$

„Negative-control“:
AntiXa-Rivaroxaban-measurement in 20 Rivaroxaban-naive probands

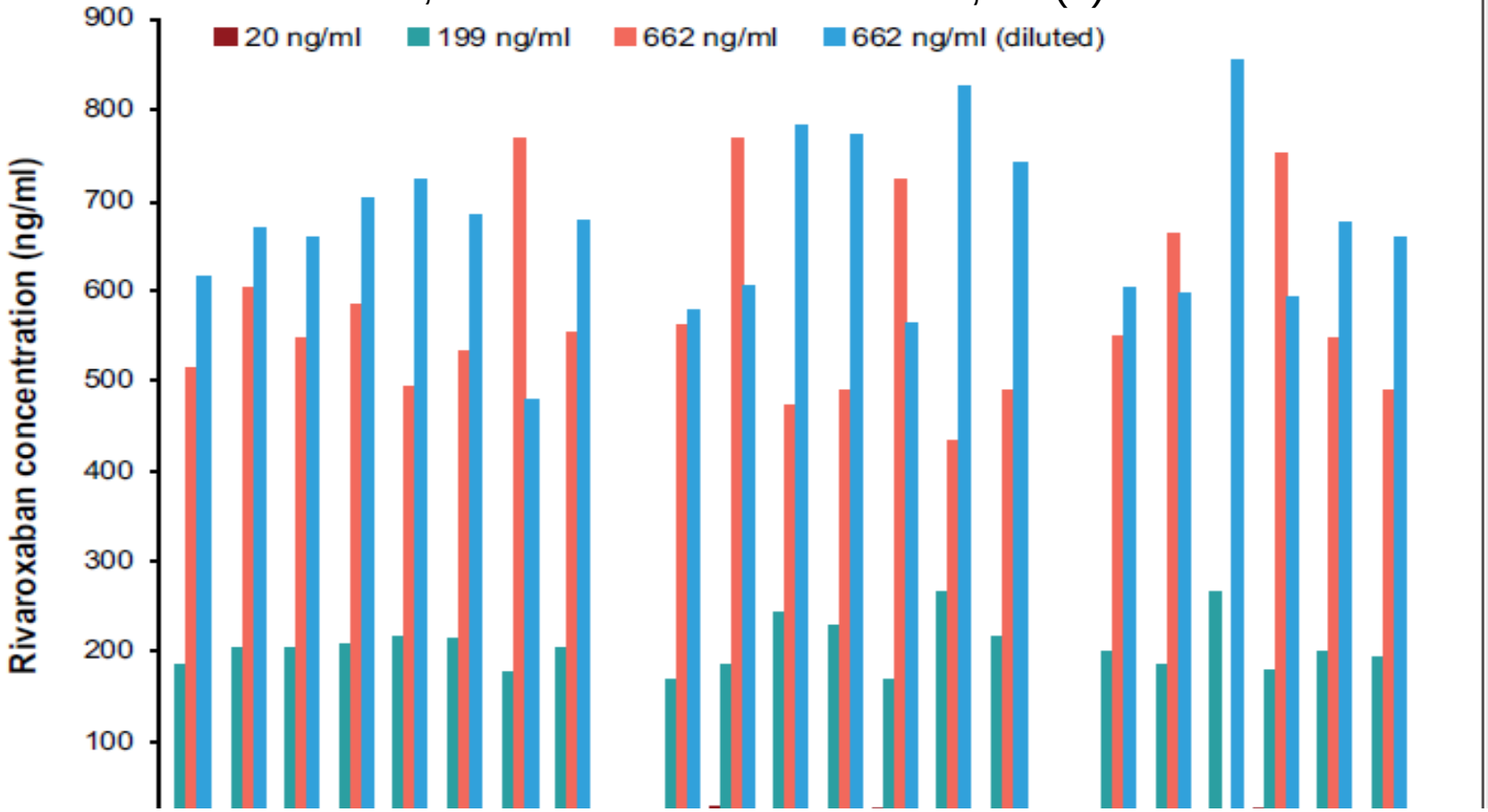
Low range: Falsly high antiXa-measurements with exogenous addition of antithrombin



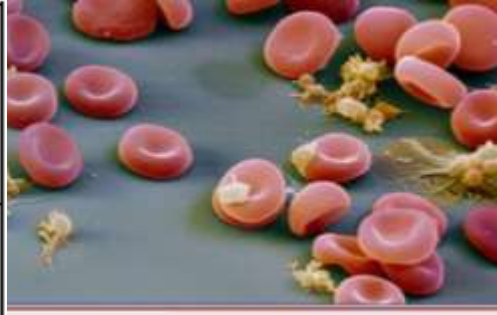
Mani, Lindhoff-Last et al, Thromb Haemost 2012; 108 (1): 191-198

International multicenter in vitro study for measurment of anti-Xa-activity (n=24 laboratories, USA and Europe)

Samama et al, Thromb Haemost 2012 Feb;107(2):379-87



Lyophylised rivaroxaban-calibrators and controls:
Comparable rivaroxaban-concentrations worldwide (20 – 660ng/ml)



	Direct Thrombin Inhibitors		Direct FXa Inhibitors	
	Influence	Useful for Monitoring	Influence	Useful for Monitoring
PT in sec	⬆	no	⬆(⬆)	**yes (*qualitative*, if sensitive)**
APTT	⬆⬆	**yes (*qualitative*, if sensitive)**	⬆	no
Thrombin time (TT)	⬆⬆⬆	**yes (*qualitative*, very sensitive)**	no	no
Diluted thrombin time	⬆⬆	**yes (*quantitative*, preferable)**	no	no
Activated Clotting Time	⬆	in question	⬆	in question
Ecarin Clotting Time	⬆⬆	yes (quantitative, but not widespread)	no	no
Chromogenic anti-Xa assay	no	no	⬆⬆	**yes (*quantitative*, preferable)**
Chromogenic anti- IIa assay	⬆⬆	yes (quantitative, but not widespread	no	no

Mani H, Kasper A, Lindhoff-Last E. (Review) Journal of Thrombosis and Thrombolysis; 2012 in press

Coagulation tests thresholds that may be associated with an increased risk of bleeding

Test at trough value	Dabigatran
Diluted Thrombin Time	> 200 ng/ml
Ecarin Clotting Time	> 3-fold upper limit of normal
aPTT	> 2-fold upper limit of normal

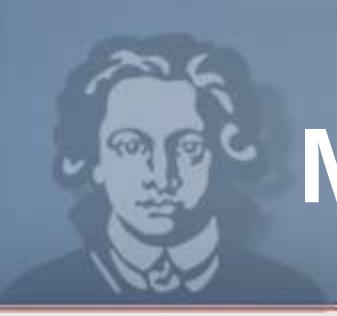
Test at trough value	Rivaroxaban
Anti FXa-assay	?
PT	?

- **Clinical Relevance has to be proven !**
- **Until then: Tailoring drug dosage according to drug-levels is of uncertain value!**

(for rivaroxaban):
Through values has to be defined to exclude accumulation

Residual levels has to be defined for invasive elective surgery

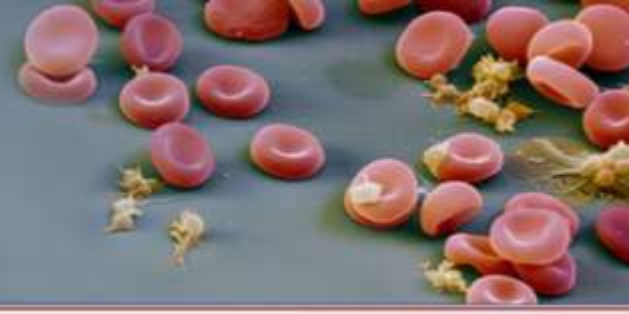
Peak levels has to be defined for reversing action in situation as **life-threatening bleeding**



Measuring NOAC- future needs?

- **Threshold values of drug concentrations and the degree of prolongation that is critical, need to be defined.**
- **Bedside-Monitoring is urgently needed for effective management of emergency situations as:**
- **Life-threatening bleeding, i.e. polytrauma, intracranial bleeding, before emergency operations: Factor concentrate (i.e. PCC) needed?**
- **Before acute PCI (heparinbolus injection yes/no?)**
- **Acute stroke: fibrinolysis possible?**
- **Specific methods are necessary to differentiate between other anticoagulants (no interference with heparins or fondaparinux) as well as between NOACs in bleeding situations**
  dabigatran: ***acute dialysis useful –***
  rivaroxaban: ***dialysis ineffective***

Conclusion



In patients with deteriorating renal function, in case of overdose, in patients with hemorrhagic or thromboembolic events during treatment with NOACs the exact drug concentration should be known.

- A **diluted thrombin time** is suitable to measure **Dabigatran-concentrations**
- **Chromogenic AntiXa-Assays** are useful to measure **Rivaroxaban-concentrations**
- Determination of **trough levels** seems to be **more appropiate**
- **Time interval between latest drug intake** and **blood sampling** is most relevant for **correct interpretation of test results**

Thank you for your attention

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