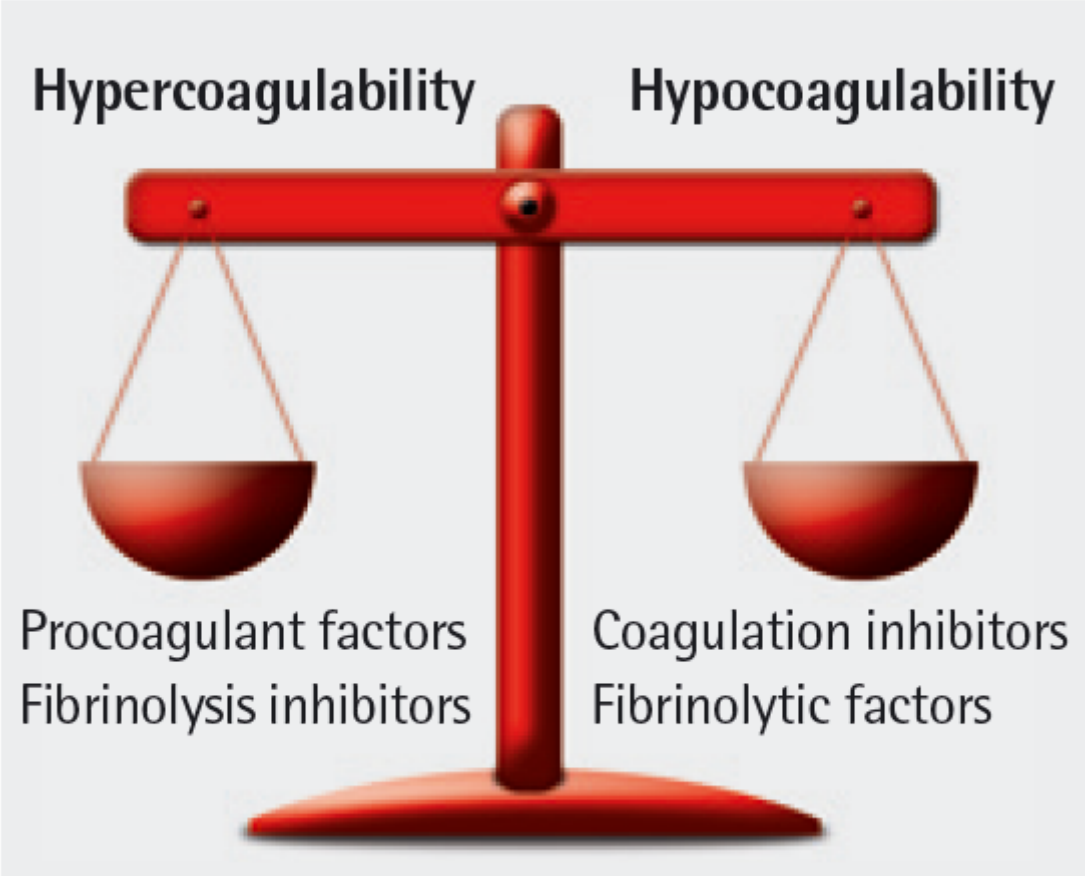
Hemosztázis: klinikai laboratóriumi vonatkozások

dr. Várnai Katalin

2016. május 17-19.

Hemosztatikus egyensúly



A hemosztatikus rendszer érzékeny egyensúlyt tart fenn a véralvadás aktiváció-gátlás és a fibrinolízis aktiváció-gátlás között.

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Hipokoagulabilitás

fiziológiásan csak ritkán fordul elő (pl. újszülöttben) , legtöbbször terápiás antikoaguláció váltja ki (pl. K vitamin antagonisták).

Hiperkoagulabilitás

- DIC (disseminated intravascular coagulopathy)
- szepszis
- tumor
- trauma
- patológiás terhesség
- tromboembólia, trombofilia
- akut kardiovaszkuláris esemény

Trombociták laboratóriumi vizsgálatai

Szűrőtesztek

- Teljes vérkép (Trombocita szám, MPV, egyéb sejtes elemek)
- Minőségi vérkép
- Alvadási szűrőtesztek (PI, APTI, TI, RI, Fibrinogén)

A trombocita működés vizsgálata

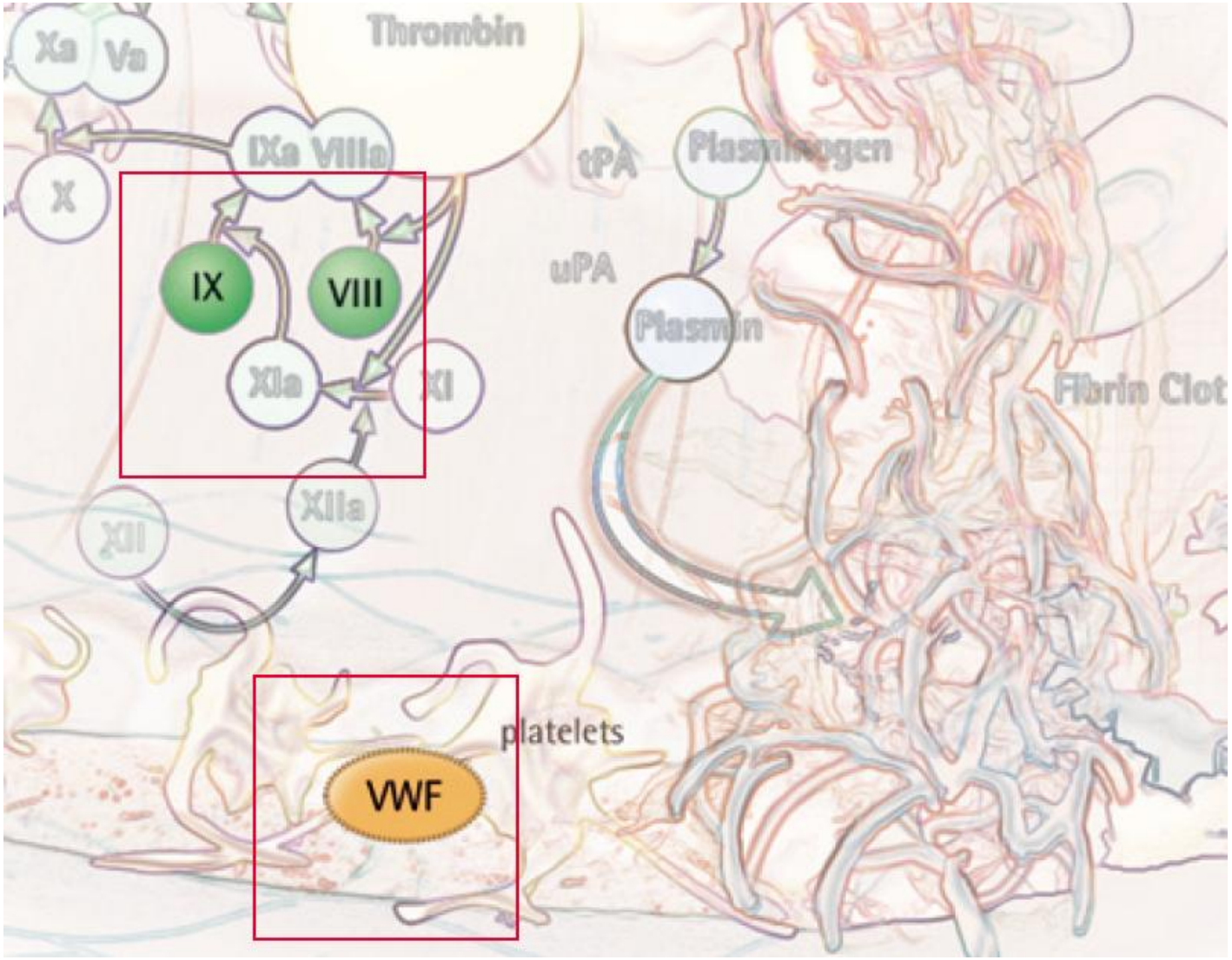
- Vérzésidő
- Trombocita aggregáció (turbidimetriás módszer, impedancia aggregometria, PFA)
- Trombocita szekréció (ATP, Ca, thromboxan, beta-thromboglobulin, serotonin)
- *Trombocita aggregáció és szekréció együttes mérése:* lumiaggregometria
- Áramlási citometria
- Alvadék retrakció
- Elektromikroszkóp
- Molekuláris genetikai vizsgálat
- ASA és clopidrogel rezisztencia

Szakmai Irányelv, Pfligler György 2013

Trombocita funkció vizsgálata – Point-of-Care

- **PFA-100**: ASA, $P2Y_{12}$, vWF (záródási idő, magas nyíróerő)
- ***VerifyNow***: ASA, $P2Y_{12}$, GPIIb/IIIa gátló (optikai detektálás, fibrinogénnel bevont gyöngy)
- ***Chrono-log Aggregometer***: ASA, $P2Y_{12}$, GPIIb/IIIa gátló (elektromos impedancia)
- ***Platelet-Mapping Assay***: ASA, $P2Y_{12}$ (TEG+kit: reptiláz, F XIIIa)

Hemofilia – amikor a hemosztatikus egyensúly hipokoagulabilitás felé billen



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Veleszületett hemofilia

Deficient factor	Prevalence in the general population	Hemostatic level required	Plasma half-life	Clinical symptoms
Inherited X-linked recessive coagulation factor deficiencies				
Factor VIII (Hemophilia A)	1:5,000 in males	25-30 %	12 hours	Joint and muscle bleeding
Factor IX (Hemophilia B)	1:30,000 in males	25-30 %	24 hours	Joint and muscle bleeding
Inherited autosomal coagulation factor deficiencies:				
VWF (von Willebrand Disease)	1:1,000 or higher	40-60 %	8-14 hours	Mucosal bleeding, menorrhagia; joint and muscle bleeding only in type 3 VWD
Factor VII	1:500,000	15-20 %	4-6 hours	Mucosal, joint and muscle bleeding
Factor V	1:1 million	15-20 %	36 hours	Mucosal bleeding
Factor X	1:1 million	15-20 %	40-60 hours	Umbilical cord, joint and muscle bleeding
Factor XI	1:1 million	15-20 %	40-70 hours	Posttraumatic bleeding
Factor XIII	1:1 million	2-5 %	11-14 days	Umbilical cord, intracranial and joint bleeding, miscarriages, impaired wound heeling
Fibrinogen	1:1 million	0.5 g/L	2-4 days	Umbilical cord, joint and mucosal bleeding, miscarriages
Prothrombin	1:2 millions	20-30 %	3-4 days	Umbilical cord, joint and mucosal bleeding

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Haemorrhagiás diathesis diagnosztikája

Szűrőtesztek

PI, APTI, TI, (RI), Fibrinogén,

Plazma faktorok

VIII/vWF komplex (VIII:C, vWF:RCo, vWF:Ag),
egyéb faktorok (II, V, VII, X, IX, XI, XII, XIII),
gátlók (kvalitatív és kvantitatív meghatározások)

Trombocita funkció

adhézió, aggregáció, „release”, prokoaguláns aktivitás

Fehérjék

Faktor Ag, vWF multimer analízis,
Diszfibrinogén struktúra, trombocita membrán protein

Molekuláris biológiai tesztek

FVIII, FIX és egyéb gének

Véralvadási szűrőtesztek

	PT *Dade® Innovin®, Thromborel® S*	APTT *Dade® Actin®; Dade® Actin® FS, Dade® Actin® FSL; Pathromtin® SL*	Platelet function *PFA-100® Analyzer*	Specific factor reagent / assay
Hemophilia A and B	Normal	Prolonged	Normal	*Factor VIII and Factor IX Deficient Plasma, Factor VIII Chromogenic Assay*
Von Willebrand disease	Normal	Normal or slightly prolonged	Prolonged	*BC von Willebrand Reagent, vWF Ag® assay*
Factor VII, X or V deficiency	Prolonged	Normal (or slightly prolonged)	Normal	*Factor VII, Factor X and Factor V Deficient Plasma*
Factor IX or XII deficiency	Normal	Prolonged	Normal	*Factor IX and Factor XII Deficient Plasma*
Factor XIII deficiency	Normal	Normal	Normal	*Berichrom® Factor XIII*
Afibrinogenemia	Not clottable	Not clottable	Normal or slightly prolonged	*Multifibren® U,* Dade® *Thrombin Reagent, Dade® Fibrinogen Determination Reagents*

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Prospective validation of a bleeding score

Patient ID:

Date of recruitment:

Sex:

Date of birth:

Epistaxis	
0	No or trivial (less than 5)
1	> 5 or more than 10'
2	CONSULTATION ONLY
3	Packing or Cauterization or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Oral cavity	
0	No
1	Reported at least one
2	CONSULTATION ONLY
3	Surgical hemostasis or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Surgery	
–1	No bleeding in at least 2 surgeries
0	Not done or no bleeding in 1 surgery
1	Reported in <25% of all surgeries
2	Reported in >25% of all surgeries, no intervention
3	Surgical hemostasis or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Muscle hematoma	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring Desmopressin or Replacement therapy
4	Spontaneous or traumatic requiring Surgical intervention or Blood transf

Cutaneous	
0	No or trivial (<1 cm)
1	>1 cm and no trauma
2	CONSULTATION ONLY

GI bleeding	
0	No
1	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia
2	Spontaneous
3	Surgical hemostasis or Blood transfusion or Replacement therapy or Desmopressin or Antifibrinolytics

Menorrhagia	
0	No
1	CONSULTATION ONLY
2	Antifibrinolytics or pill use
3	Curettage or Iron therapy
4	Blood transfusion or Replacement ther -apy or Desmopressin or Hysterectomy

Hemarthrosis	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or Replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Bleeding from minor wounds	
0	No or trivial (less than 5)
1	> 5 or more than 5'
2	CONSULTATION ONLY
3	Surgical hemostasis
4	Blood transfusion or Replacement therapy or Desmopressin

Tooth extraction	
–1	No bleeding in at least 2 extractions
0	Not done or no bleeding in 1 extraction
1	Reported in <25% of all procedures
2	Reported in >25% of all procedures, no intervention
3	Resuturing or Packing
4	Blood transfusion or Replacement therapy or Desmopressin

Post-partum hemorrhage	
–1	No bleeding in at least 2 deliveries
0	No deliveries or no bleeding in 1 delivery
1	CONSULTATION ONLY
2	Curettage or Iron therapy or Antifibrinolytics
3	Blood transfusion or Replacement therapy or Desmopressin
4	Hysterectomy

CNS bleeding	
0	Never
1	-
2	-
3	Subdural, any intervention
4	Intracerebral, any intervention

Total assigned score:

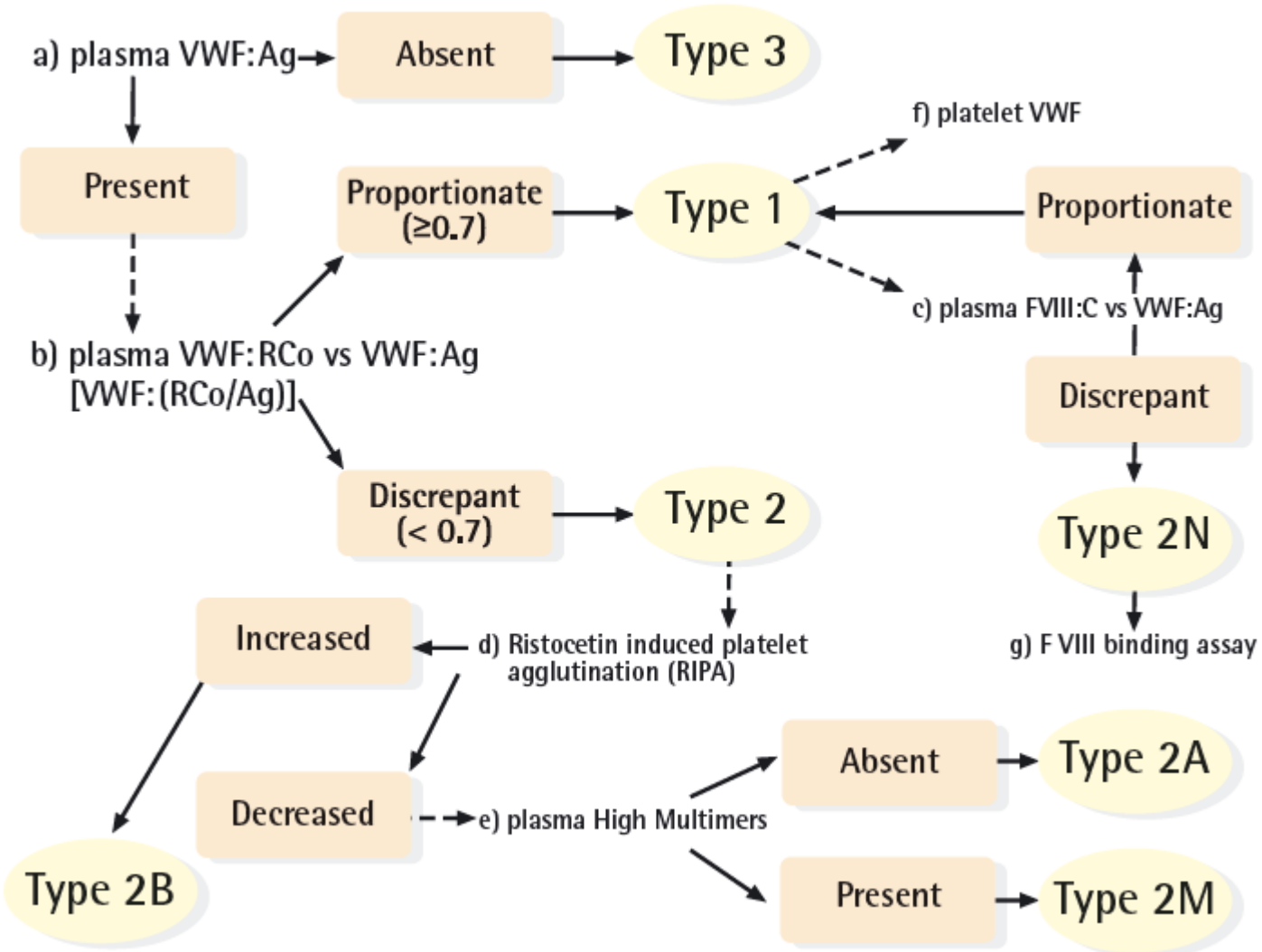
Tosetto et al. J Thromb Haemost, 2011.

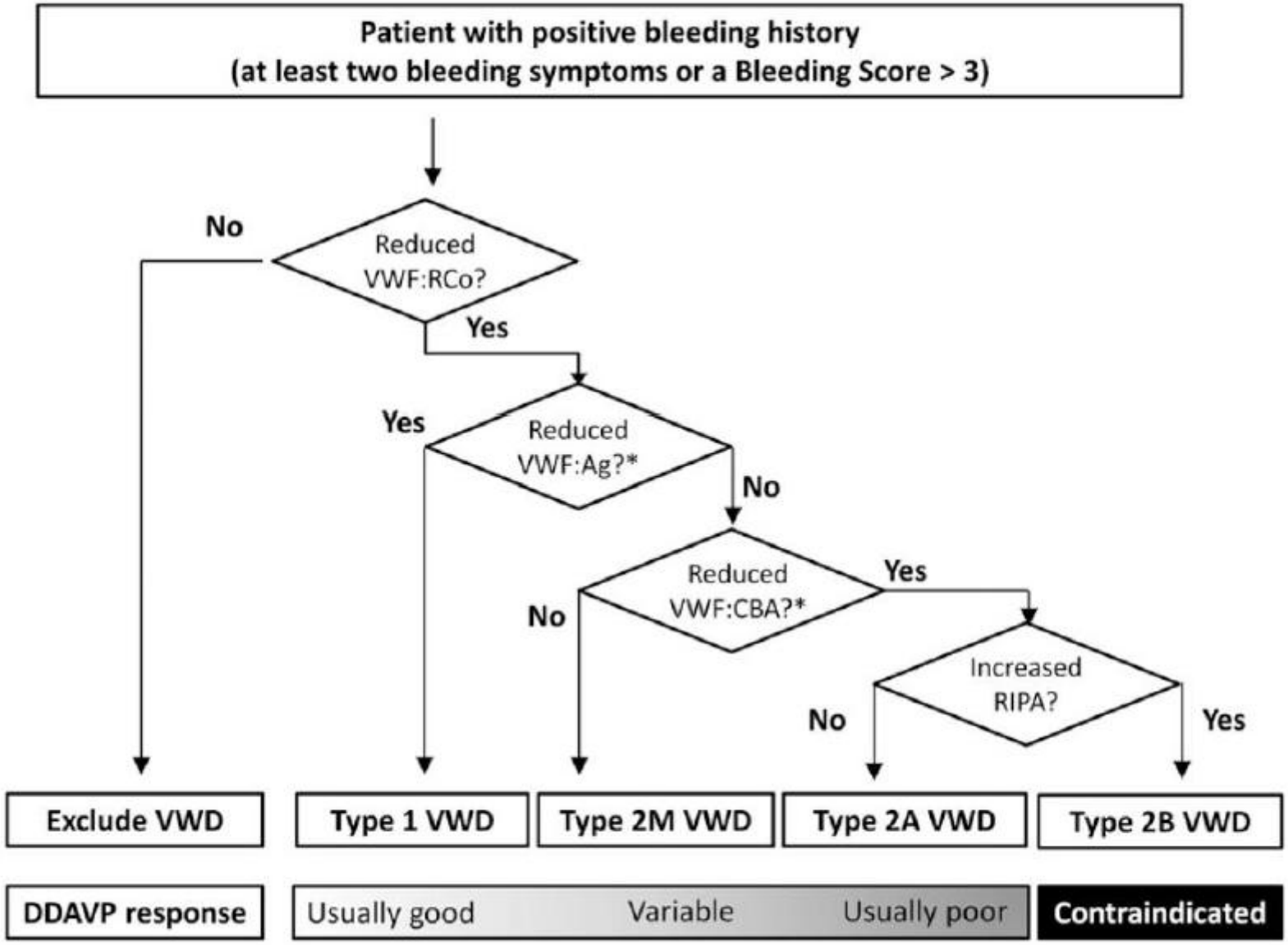
When is a bleeding history suggestive for VWD?

Bleeding score	Likelihood ratio (favouring VWD)
-3	0
-2	0.04
-1	0.10
0	0.13
1	1.60
2	2.24
3	3.00
4	15.70
≥5	∞ (well, not actually!)

Tosetto et al. J Thromb Haemost, 2006.

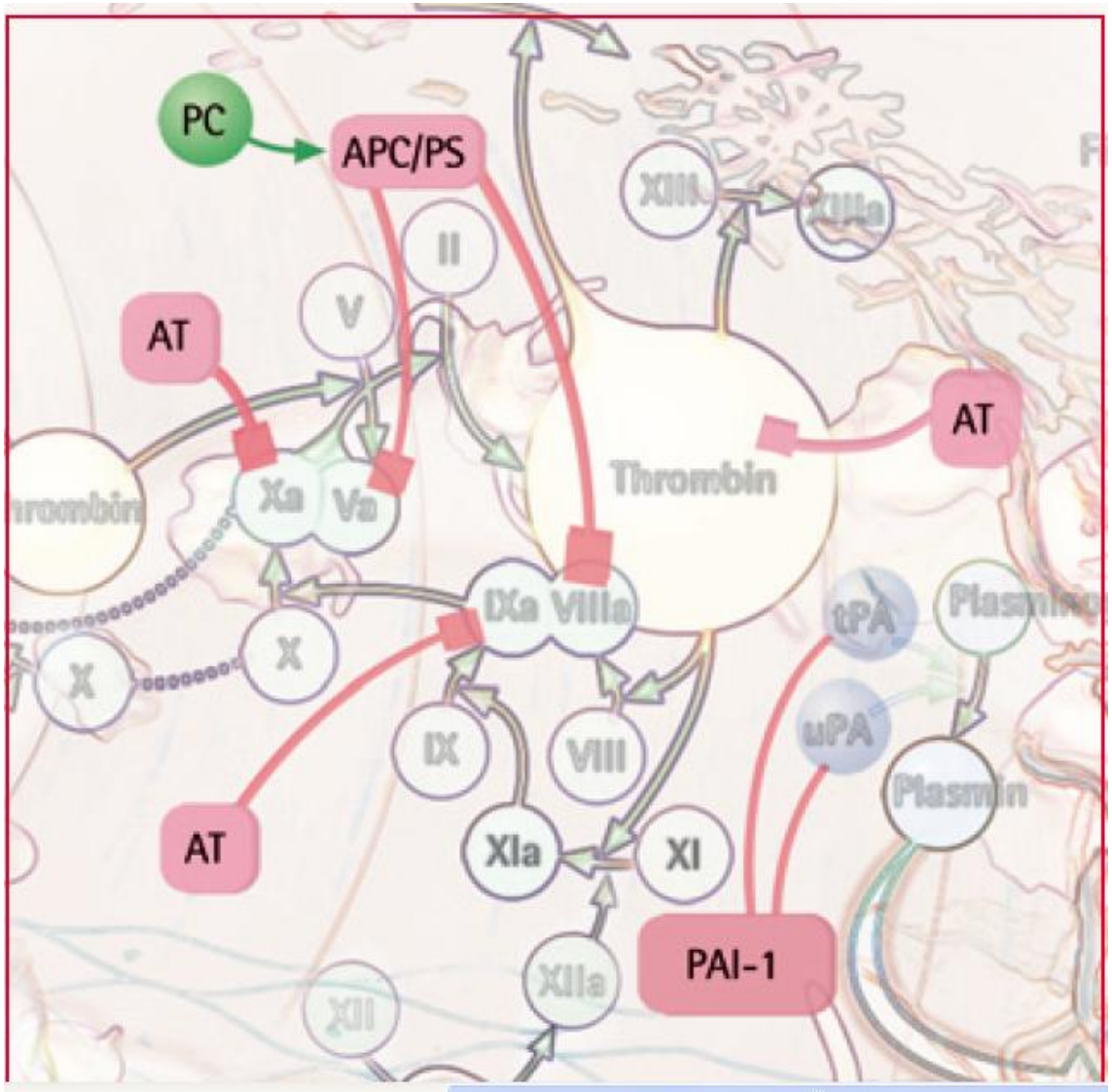
Vizsgálati algoritmus vWD diagnosztikában





Tosetto et al. Blood, 2015.

Trombofilia – hemosztatikus egyensúly hiperkoagulabilitás felé billen



Thrombózis vizsgálat

- **Szűrőtesztek**
  PI, APTI, TI, (RI), Fibrinogén, DDi
- **Temészetes gátlók és APC rezisztencia**
  AT, PC, PS, APC
- ***LA/APA***
  LA-szenzitív APTI, DRVVT; anticardiolipin IgG/IgM; anti-β2 GP I IgG/IgM
- **Plazma faktorok és fibrinolízis**
  FVIII, vWF, FII, VII, IX, XI, XII, (Plazminogén, t-PA és PAI)
- **Homocisztein**
- **Moleculáris biológiai tesztek**
  FVL, Protrombin gén (G20210A), MTHFR
- **Trombocita funkció** Sticky platelet szindróma
- **Aktivációs markerek**
  DDi, TAT, F1+2

Methodology: Guidelines LAC

- Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. **1995** Oct;74(4):1185-90.
- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. **2006** Feb;4(2):295-306.
- Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. **2009** Oct;7(10):1737-40.
- Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in H. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. **2012.**
- Clinical and Laboratory Standardization Institute (CLSI) Laboratory Testing for the Lupus Anticoagulant, H60-A, April **2014**

Katrien Devreese, Stago Webinar, 2014

Laboratory diagnosis of the APS

	Sapporo (1999)	Sydney (2006)
LAC	Screening-, mixing and confirmation test	Screening-, mixing- and confirmation test
	Interval 6 weeks	Interval 12 weeks

Wilson et al, Arthritis Rheum 1999; 42: 1309-11
Miyakis et al, J Thromb Haemost 2006; 4:295-306

Brandt et al, Thromb Haemost 1995: 74; 1185-90

Guidelines LAC

- Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. **2009,** 7:1737-40.
- Clinical and Laboratory Standardization Institute (CLSI) Laboratory Testing for the Lupus Anticoagulant, H60-A, **2014**

4 pages

academic

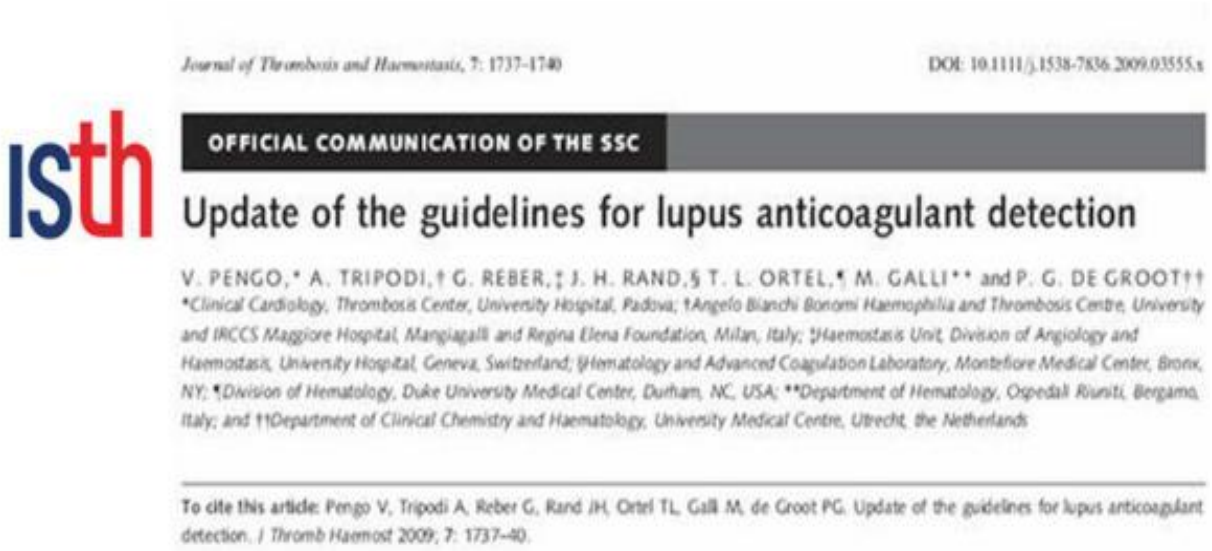
>100 pages

manufacturers and academic

Harmonise and standardise LAC testing

Lupus anticoagulant (LAC) testing

-Preanalytical conditions
-Choice of assays
-Calculation cut-off values
-Interpretation of results



Journal of Thrombosis and Haemostasis, 7: 1737–1740 DOI: 10.1111/j.1538-7836.2009.03555.x

ISth

OFFICIAL COMMUNICATION OF THE SSC

Update of the guidelines for lupus anticoagulant detection

V. PENGO,* A. TRIPODI,† G. REBER,‡ J. H. RAND,§ T. L. ORTEL,¶ M. GALLI** and P. G. DE GROOT††
*Clinical Cardiology, Thrombosis Center, University Hospital, Padova; †Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, University and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy; ‡Haemostasis Unit, Division of Angiology and Haemostasis, University Hospital, Geneva, Switzerland; §Hematology and Advanced Coagulation Laboratory, Montefiore Medical Center, Bronx, NY; ¶Division of Hematology, Duke University Medical Center, Durham, NC, USA; **Department of Hematology, Ospedali Riuniti, Bergamo, Italy; and ††Department of Clinical Chemistry and Haematology, University Medical Centre, Utrecht, the Netherlands

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Katrien Devreese, Stago Webinar, 2014

Guidelines for Antiphospholipid Syndrome detection

British Journal of Haematology, 2012, 157, 47–58

Clinical criteria:

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous or small vessel thrombosis

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation

(b) One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency

(c) Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Guidelines for Antiphospholipid Syndrome detection

British Journal of Haematology, 2012, 157, 47–58

Laboratory criteria:

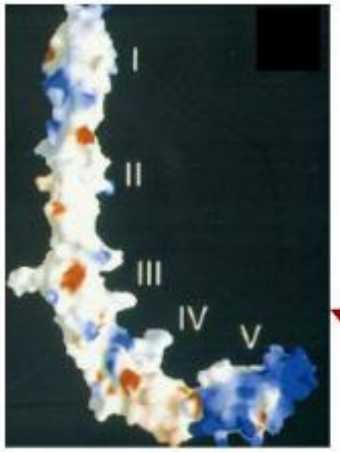
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart
2. Anticardiolipin (aCL) antibody of immunoglobulin (Ig)G and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40GPL units or MPL units, or > the 99th percentile), on two or more occasions, at least 12 weeks apart
3. Anti-b2–glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th centile), present on two or more occasions at least 12 weeks apart

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met

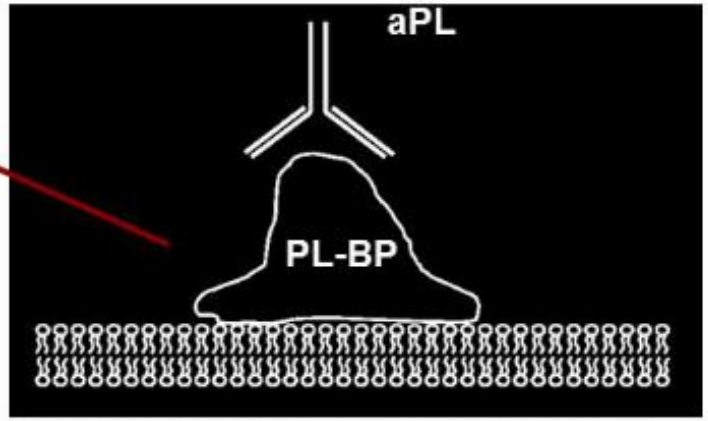
Antiphospholipid antibodies

cofactor requirement:

phospholipid binding plasma proteins

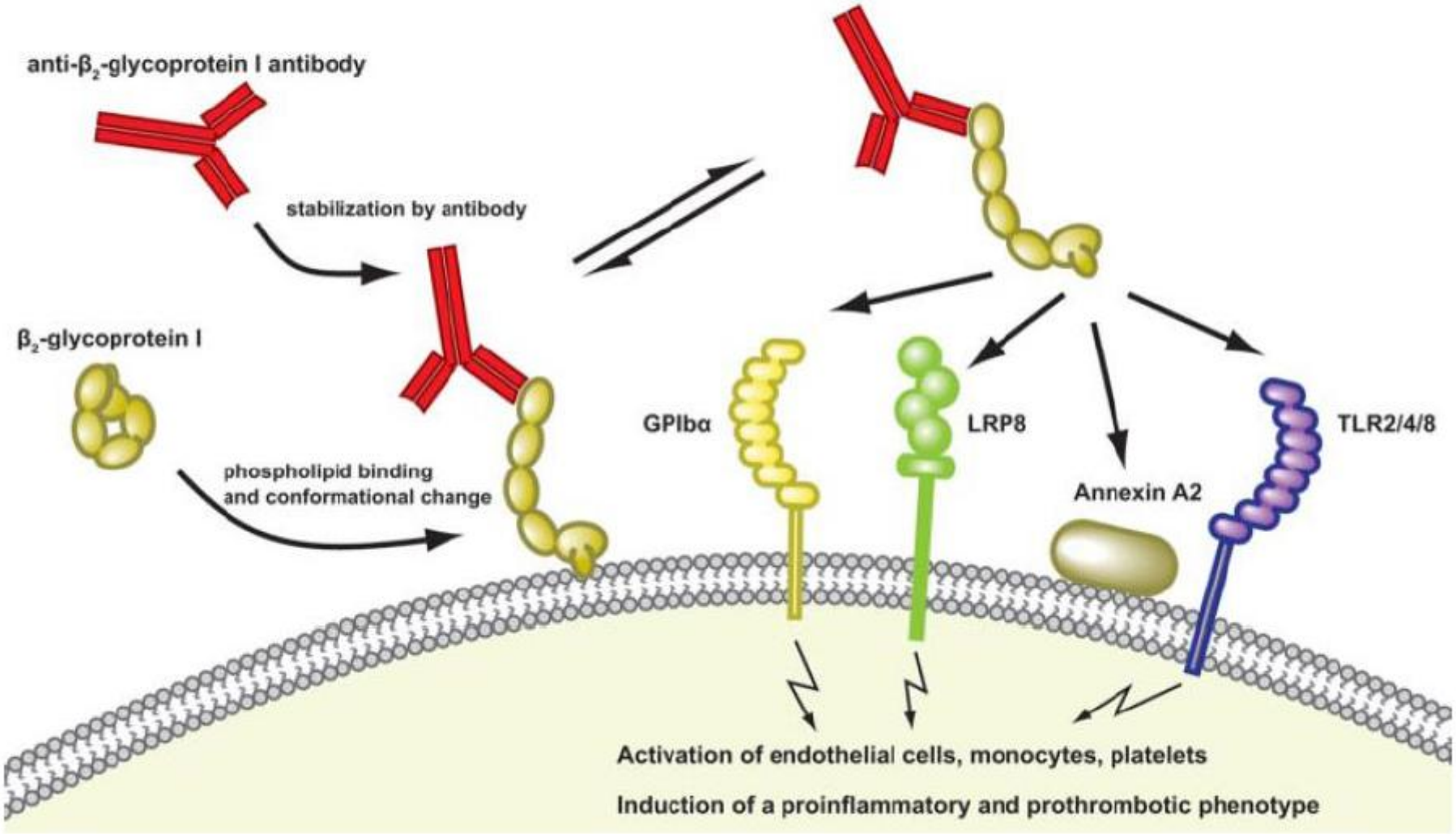


-ß2 glycoprotein I (ß2GPI)
-prothrombin
-combination



(Mc Neill et al 1990, Galli et al 1990, Matsuura et al, 1990)

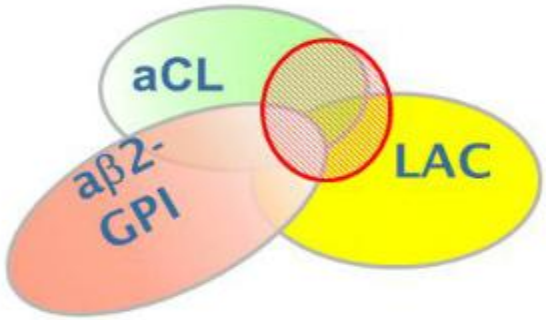
Antibody-B2gpI complexes



de Groot PG , Urbanus RT. BLOOD 2012.

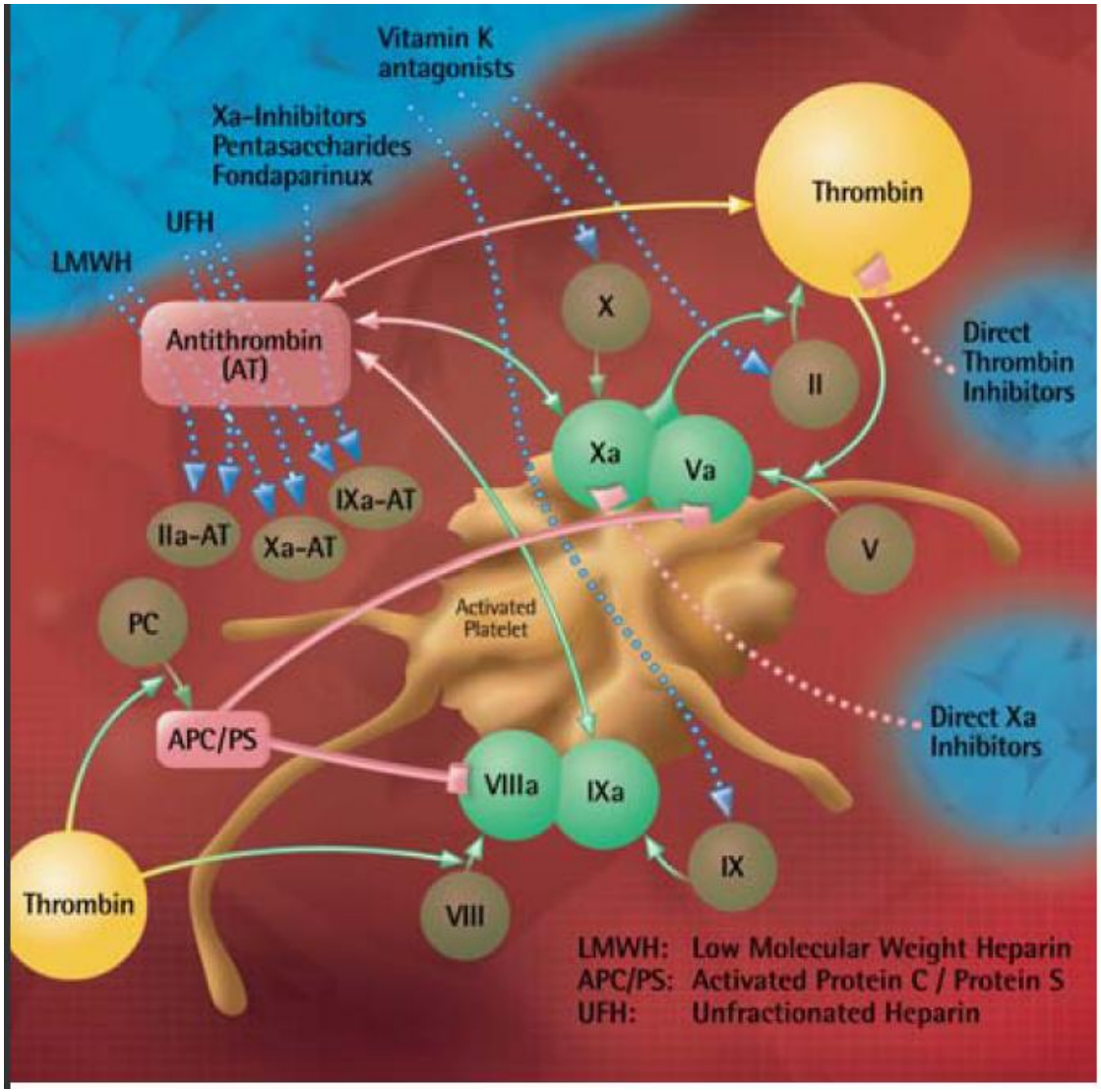
Laboratory diagnosis of the APS

- Perform all three assays: LAC, aCL, aß2GPI
- Follow the guidelines
- Participate in EQC
- Antibody profiles
  LAC, aCL, ß2GPI antibodies



Katrien Devreese, Stago Webinar, 2014

Antikoagulánsok



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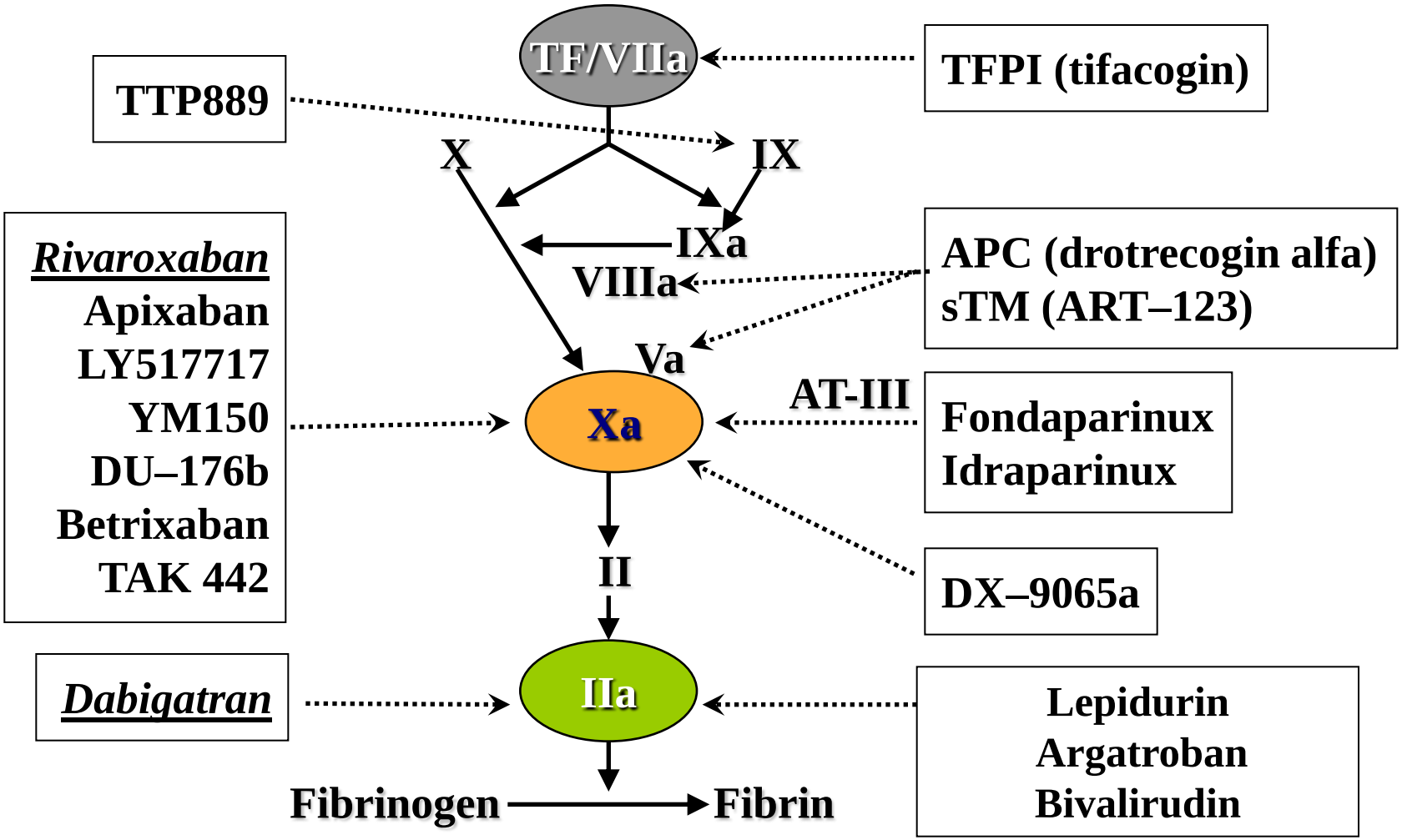
Új antikoagulánsok



Weitz JI. *J Thromb Haemost*. 2007;(5 Suppl 1):65-67.

- ***Kell-e mérni a NOAC antikoaguláns hatását,***
- Hogyan
- Mikor
- Alarm érték
- Rutin hemosztázis paraméterekre gyakorolt hatásuk

Kötelező:

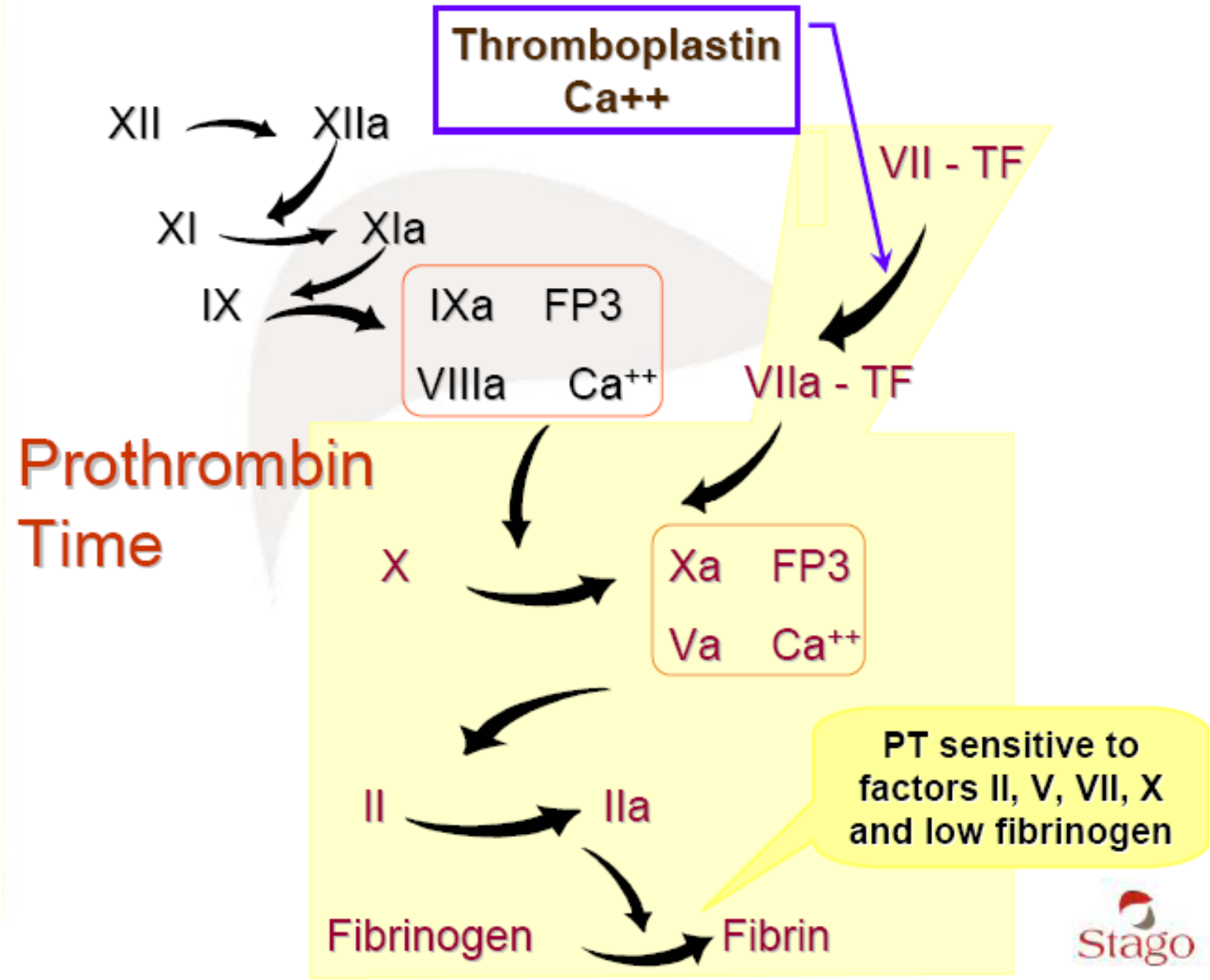
- sürgős invazív beavatkozás,
- trombolízis indikációja (stroke),
- súlyos trauma,
- kezelés alatt fellépő vérzés és/vagy TE,
- veseelégtelenség,
- mérgezés, túladagolás gyanúja

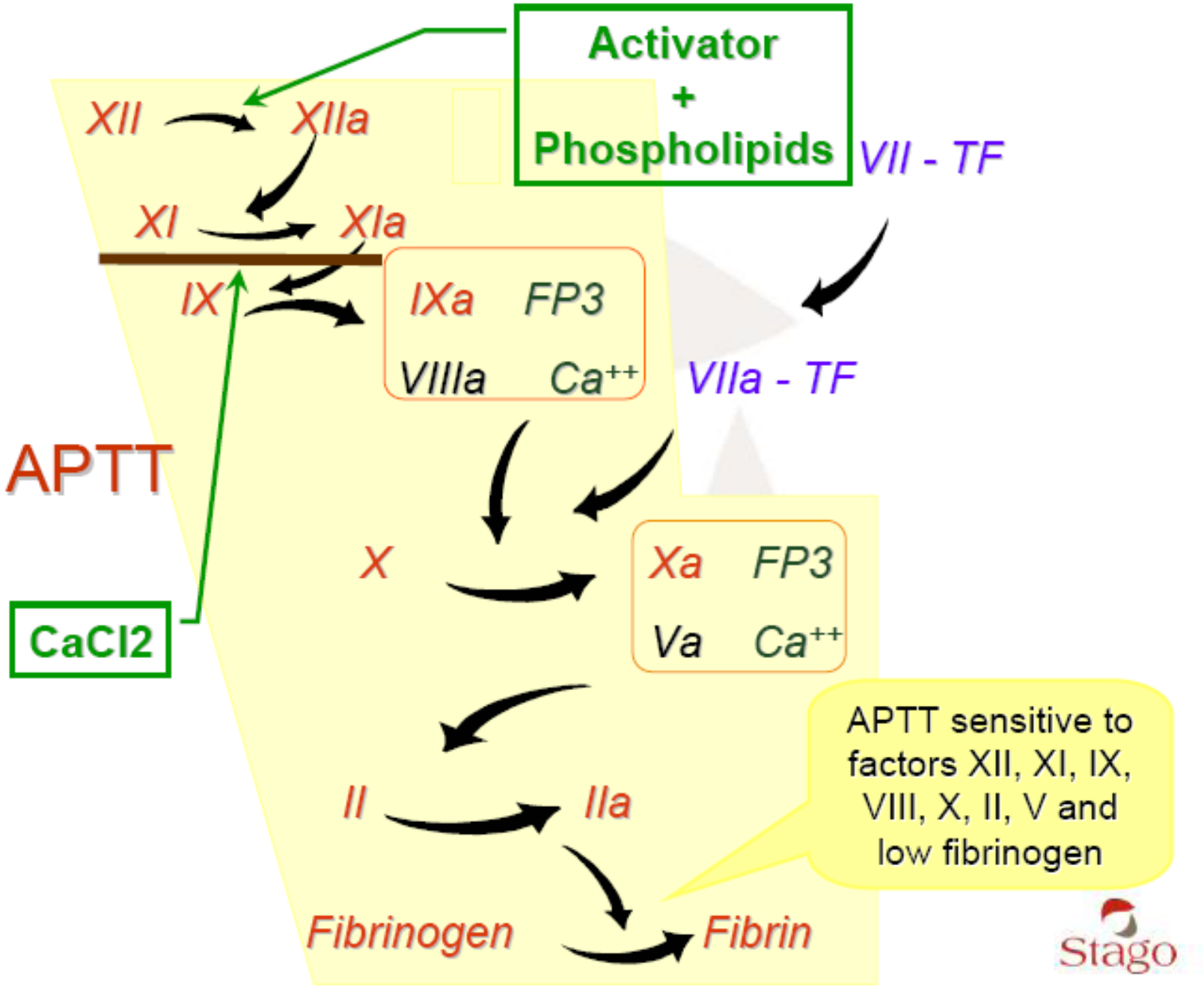
Ajánlott:

- terápia elkezdése után 1-2 héttel,
- egyéb gyógyszer bevezetése előtt/után,
- extrém testsúly,
- antikoaguláns váltása

- Kell-e mérni a NOAC antikoaguláns hatását,
- ***Hogyan***
- Mikor
- Alarm érték
- Hemosztázis paraméterekre gyakorolt hatásuk

NOAC az alap koagulációs szűrőtesztek (PI, APTI, TI) eredményeit befolyásolja!


Thromboplastin
Ca++
XII
XIIa
XI
XIa
IX
IXa FP3
VIIIa Ca++
VII - TF
VIIa - TF
Prothrombin Time
X
Xa FP3
Va Ca++
II
IIa
Fibrinogen
Fibrin
PT sensitive to factors II, V, VII, X and low fibrinogen
Stago


Activator
+
Phospholipids
XII
XIIa
XI
XIa
IX
IXa FP3
VIIIa Ca++
VII - TF
VIIa - TF
APTT
CaCl2
X
Xa FP3
Va Ca++
II
IIa
Fibrinogen
Fibrin
APTT sensitive to factors XII, XI, IX, VIII, X, II, V and low fibrinogen
Stago

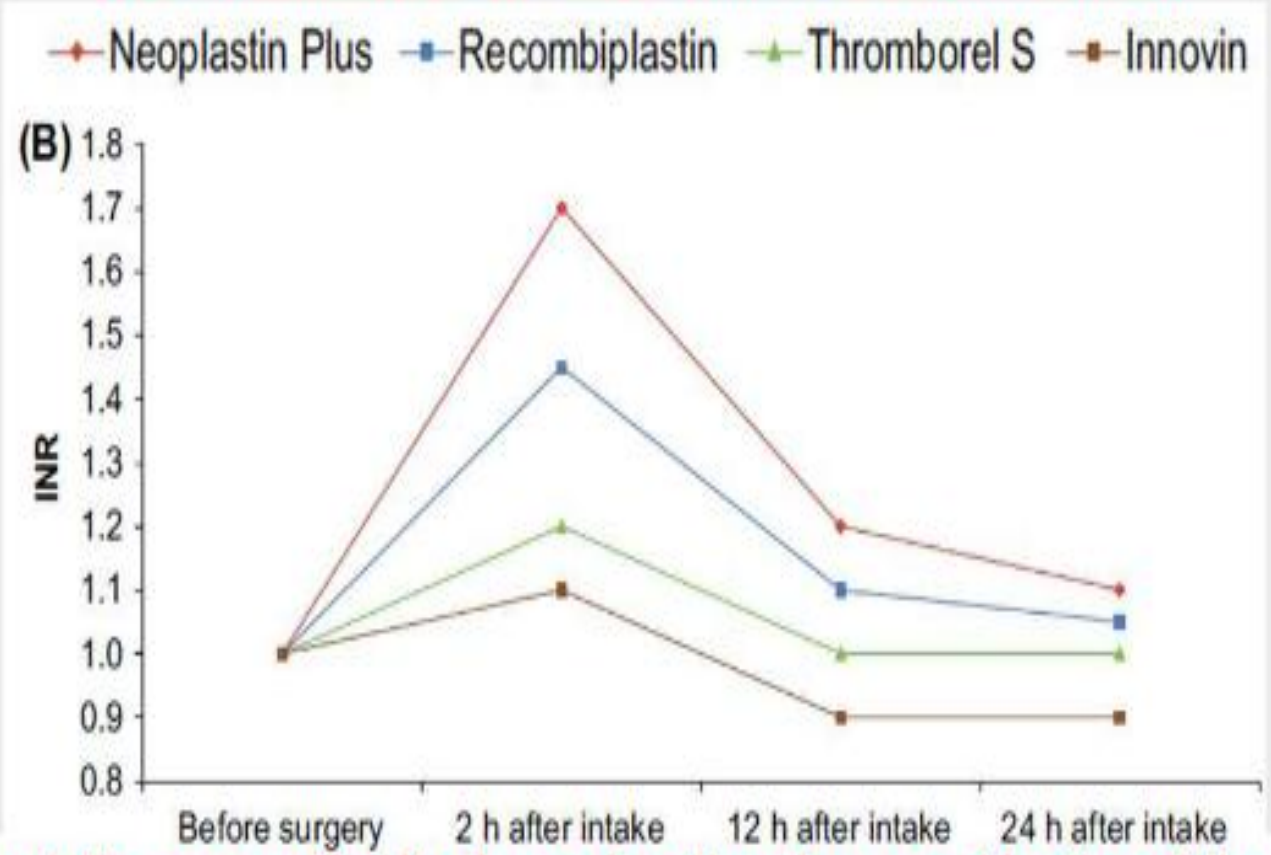
Rivaroxaban

- ***anti-Xa faktor kromogén-meghatározás***
  (PI szenzitív tromboplasztin)

- PI sec
  - Ratio (beteg/normál plazma)
  - **INR nem!**

- Anti-FXa (ng/ml)
  - gyógyszer koncentráció (20-660 ng/ml) kalibrációs görbe alapján

Xarelto® 10mg od
(prophylactic dose after knee- or hip-replacement surgery)



Coagulation assay results depend on the pharmacokinetics of the drug and therefore change during the day

Lindhoff-Last et al, Ann Med 2013; 45 (5-6): 423-429

Rivaroxaban

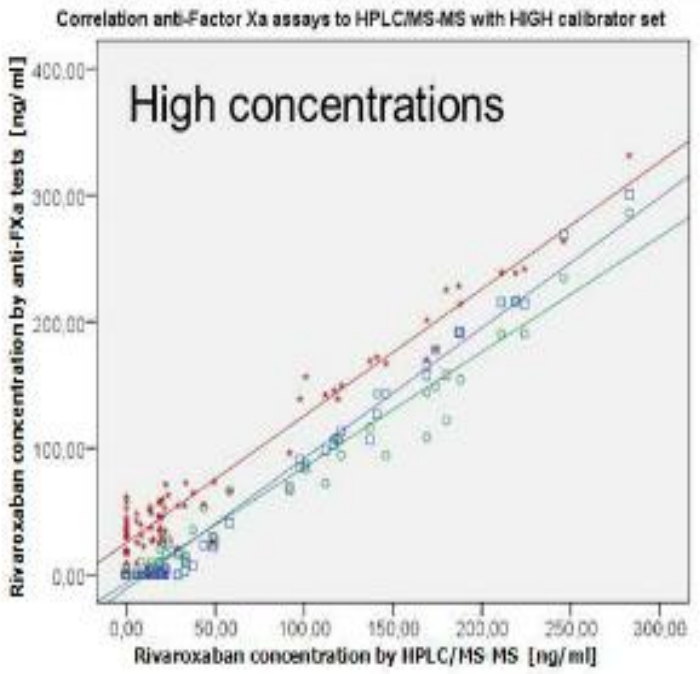
- anti-Xa faktor kromogén-meghatározás (PI szenzitív tromboplasztin)

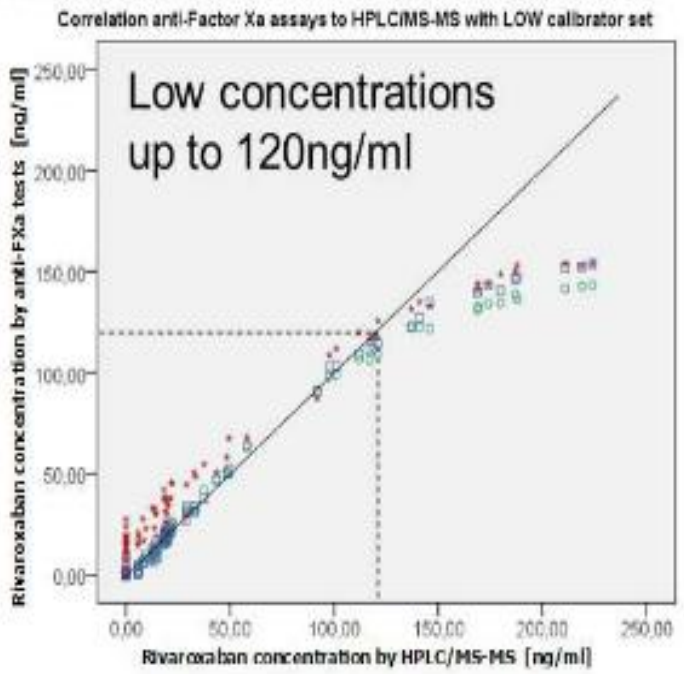
- PI sec
  - Ratio (beteg/normál plazma)
  - **<u>INR nem!</u>**

- ***Anti-FXa (ng/ml)***
  - gyógyszer koncentráció (20-660 ng/ml) kalibrációs görbe alapján

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

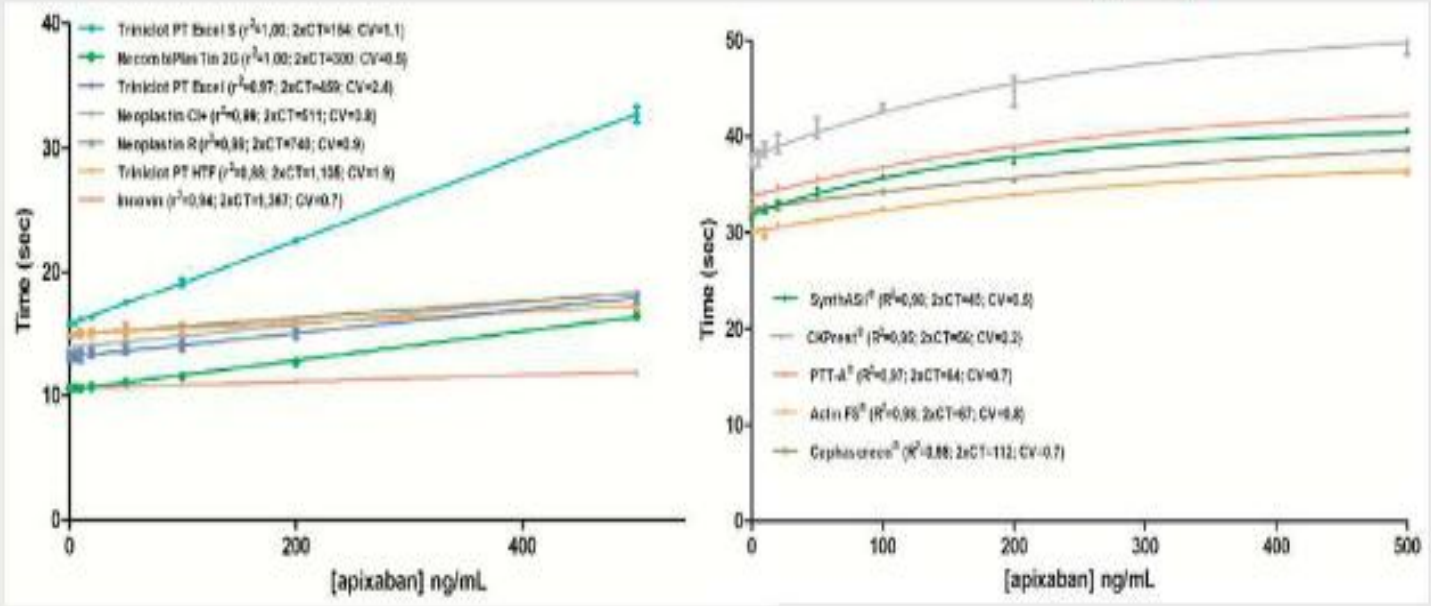
Mani, Lindhoff-Last et al, Thromb Haemost 2012; 108 (1): 191-198





E. Lindhott-Last, Stago Webinar

Apixaban in vitro data



Apart from one PT-reagent (Triniclot PT Excel S) hardly any change in PTs and aPTTs with increasing concentrations of apixaban

Douxfils et al, Thromb Haemost 2013; 110: 283-294

E. Lindhott-Last, Stago Webinar

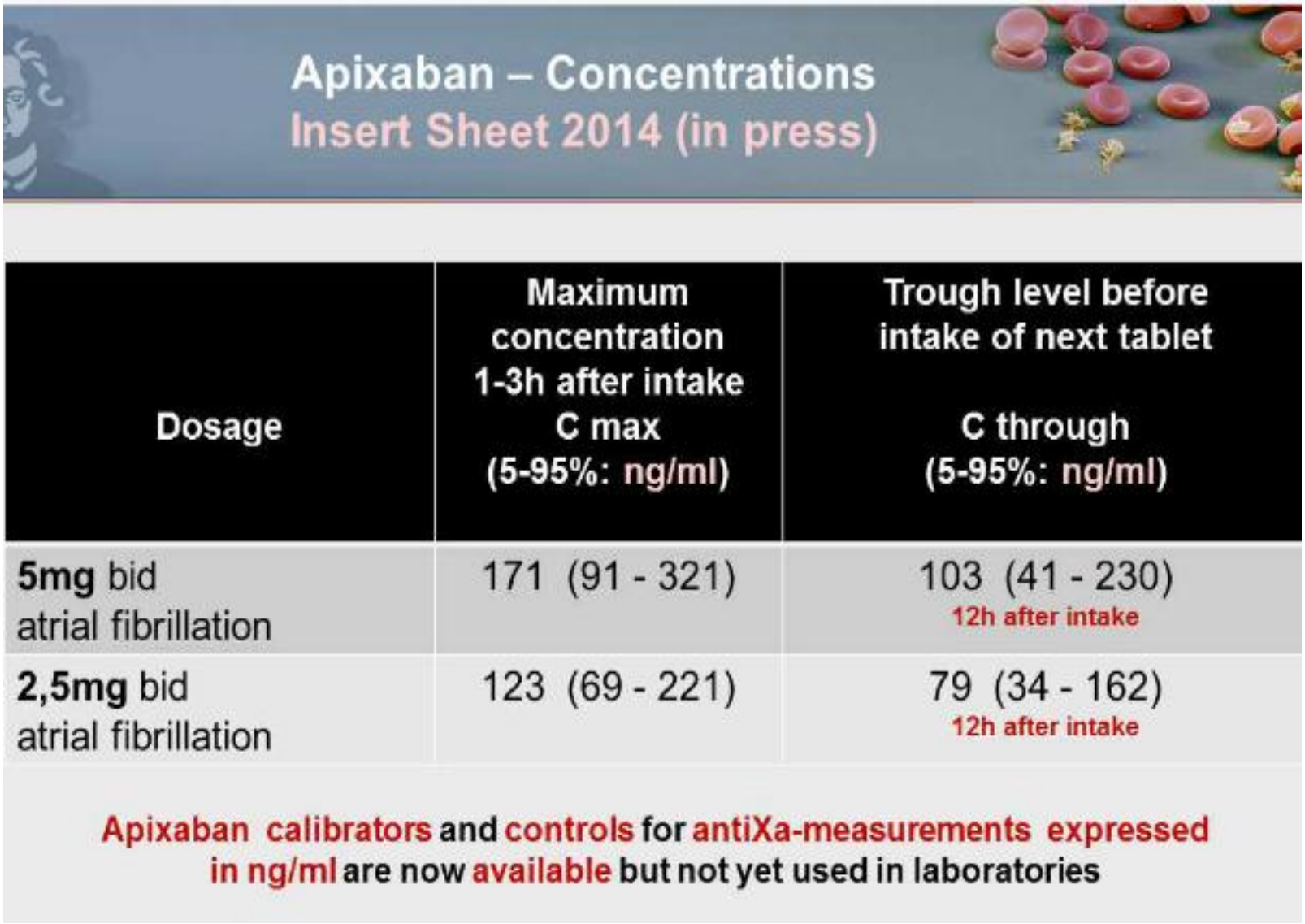
Apixaban – concentrations
Insert sheet Europe 2012
(Rotachrom-Heparin-assay, calibrator LMWH)

Dosage	Maximum concentration 1-3h after intake C max (5-95%: U/ml)	Trough level before intake of next tablet C through (5-95%:U/ml)
5mg bid atrial fibrillation	2.55 (1.36 – 4.79)	1.54 (0.61 – 3.43) 12h after intake
2,5mg bid atrial fibrillation	1.84 (1.02 – 3.29)	1.18 (0.51 – 2.42) 12h after intake

LMWH was used for calibration,
antiXa Units might confuse clinicians,
because results are much higher compared to LMWH

accurate measurements with HPLC/MS is possible

Delavenne et al, J Pharm Biomed Anal 2013; 78-79: 150-153



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Dabigatran

- ***Hígított TI vagy ECT, ECA***

-Ratio (beteg/normál plazma)

-gyógyszer koncentráció kalibrációs görbe alapján

Dabigatran – which assays may be useful ?

aPTT ?

different sensitivities of reagents

Douxfils et al, Thromb Haemost 2012

aPTT can be normal in spite of therapeutic dabigatran levels

Hawes et al, J Thromb Haemost 2013

aPTT begins to plateau with dabigatran-conc. at 200ng/ml

Hapgood et al, Thromb Haemost 2013

ECT or ECA

- Direct correlation with dabigatran-plasma-concentrations
- *3-4-fold prolonged ECT at trough levels*
- *Increased bleeding tendency*

TT

- *normal TT*
- *Absence of clinical relevant dabigatran concentrations*

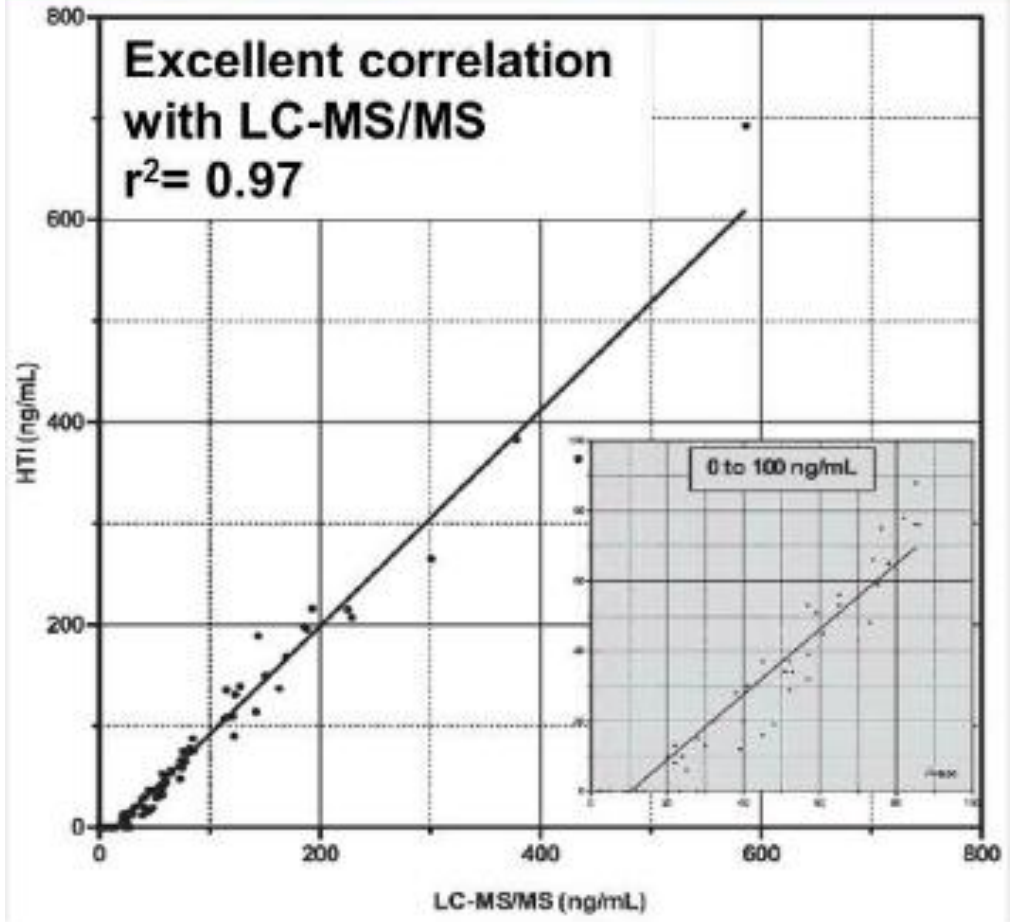
Dabigatran

- Hígított TI vagy ECT, ECA

  -Ratio (beteg/normál plazma)

  -***gyógyszer koncentráció kalibrációs görbe alapján***

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



Sensitive, 8-fold diluted thrombin-time

human alpha-Thrombin + dabigatran-calibrators (40 – 500ng/ml) and –controls

accurate determination ≥ 50ng/ml dabigatran compared to LC-MS/MS

Stangier et al, Abstract, Thromb Haemost 2009;
van Ryn et al, Thromb Haemost 2010;
Avecilla et al. Am J Clin Patho. 2012;
Douxfils et al, Thromb Haemost 2012;
Douxfils et al, Thromb Haemost 2013

E. Lindhott-Last, Stago Webinar

- Kell-e mérni a NOAC antikoaguláns hatását,
- Hogyan
- ***Mikor***
- Alarm érték
- Hemosztázis paraméterekre gyakorolt hatásuk

NOAC - farmakokinetikai adatok

paraméter	Rivaroxaban	Apixaban	Dabigatran
Támadáspont	F IIa (trombin)	F Xa	F Xa
Cmax (óra)	***2,5-4***	***3***	***2***
Féléletidő	***9-13 óra***	***8-11 óra***	***12-14 óra***
Biológiai hozzáférhetőség	80-100%	50-80%	6-8%
Renális kiválasztás	66% vese (fele inaktív)	25%	80%
Meghatározás	Anti-FXa (Rivaroxaban kalibráció)	Anti-FXa (Apixaban kalibráció)	Hígított TI ECT
Interakciók	P-GP gátló CYP 3A4 gátló	P-GP gátló CYP 3A4 gátló	P-GP gátló
Antidótum	(PRT-064446)	nincs	nincs

NOAC mérés

- C_{max} (csúcs): kb. 2 óra bevétel után
- C_{min} (völgy): 12 óra (bid) vagy 24 óra (od)
- vérvétel és a NOAC utolsó bevétele közti idő ismerete döntő az eredmény értékeléséhez

Csúcs- vagy völgykoncentráció?

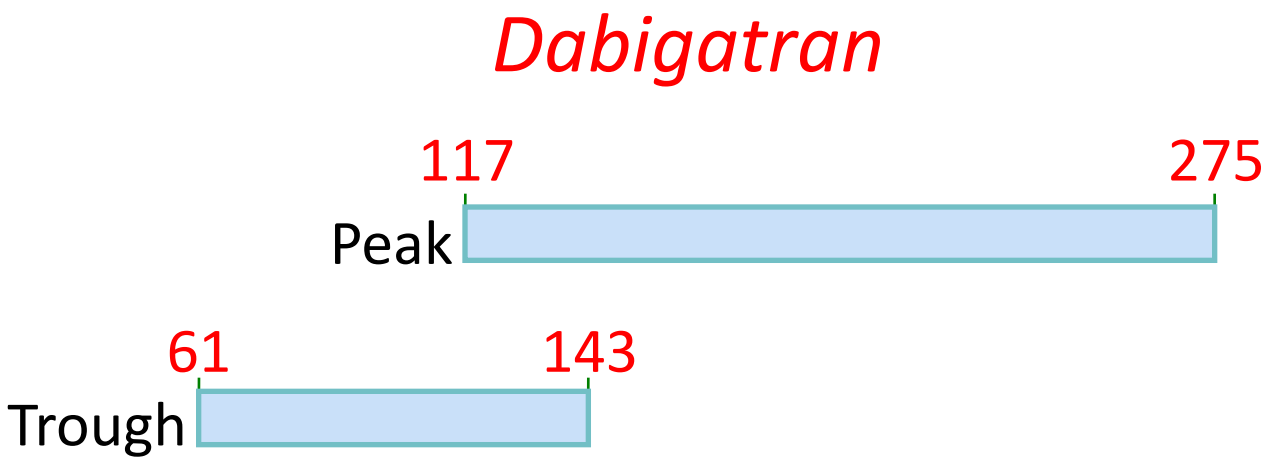
C_{min} „küszöbkoncetráció” és vérzés kockázat kapcsolata

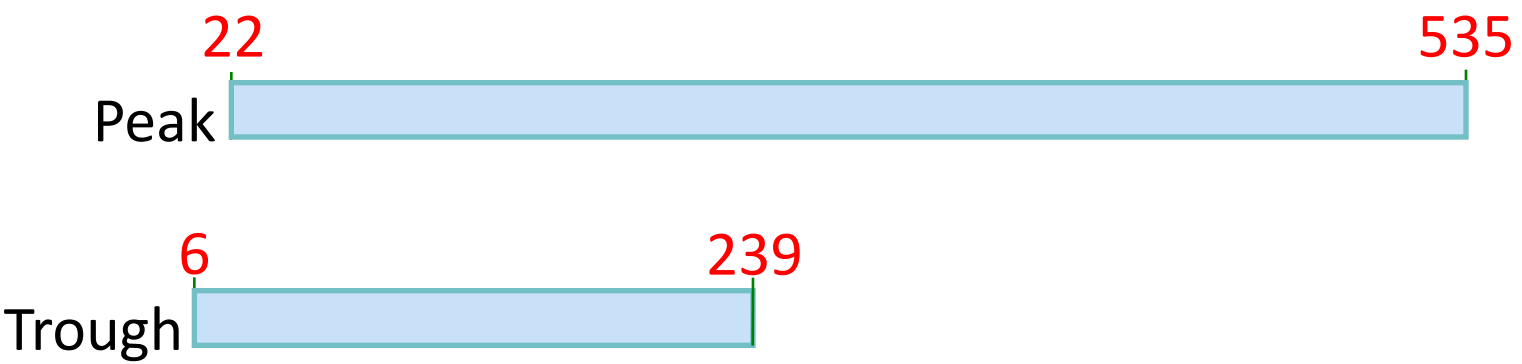
Antikoaguláns váltás

- VKA → dabigatran: INR≤2,
- Dabigatran → VKA: (normál kreat-Clear.) 3 nap
- VKA → rivaroxaban: INR<3 (AF), <2,5 (VTE)
- Rivaroxaban → VKA: kettő együtt INR 2 eléréséig
- LMWH → rivaroxaban: következő inj. előtt 2 órával
- Rivaroxaban → LMWH: rivaroxaban helyett LMWH

- Kell-e mérni a NOAC antikoaguláns hatását,
- Hogyan
- Mikor
- ***Alarm érték***
- Hemosztázis paraméterekre gyakorolt hatásuk

Plasma Concentration *[ng/mL (min-max)]* **at Steady State**





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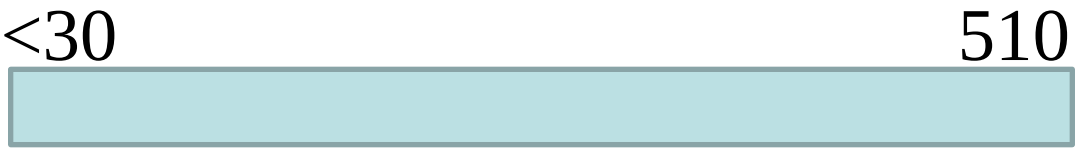
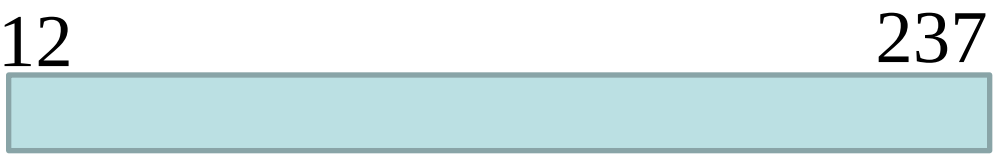
Real life dabigatran inter-individual variability (trough levels)



Chun NC et al, JTH 2015



Skeppholm M et al, Thromb Res 2014

Samos M et al, J Thromb Thromboysis 2015

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Ex vivo concentrations of rivaroxaban and dabigatran

Table 2 Concentration levels (Mean and range) of Dabigatran and Rivaroxaban at different doses and time points

Drug	Dose and regime	Concentration-maximum (2–4 h after drug intake) C max (ng/ml)	Trough levels before next drug intake at steady state C through, ss (ng/ml)		Bleeding risk Increased at trough levels
Dabigatran	220 mg od Prophylaxis	183 (62–447)	37 (10–96)	24h after intake	>67 ng/ml
	150 mg bid Therapy	184 (64–443)	90 (31–225)	12h after intake	>200 ng/ml
Rivaroxaban	10 mg od Prophylaxis	120 (90–190)	10 (3–25)		Not defined
	20 mg od Therapy	249 (184–343)	44 (12–137)		Not defined

AntiXa-assays with rivaroxaban–calibrators and –controls and a diluted TT-assay (Hemoclot assay) with dabigatran-calibrators and –controls are already commercially available

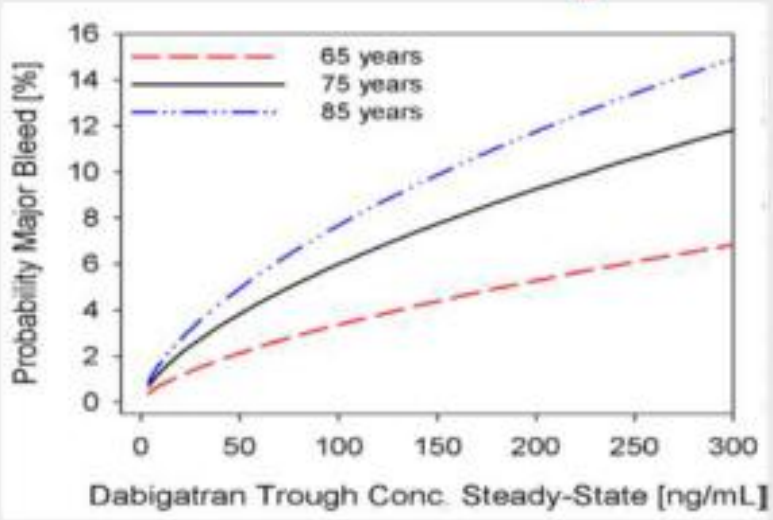
Mani H, Kasper A, Lindhoff-Last E. J Thromb Thrombolysis; 2013; 36 (2): 187-194

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

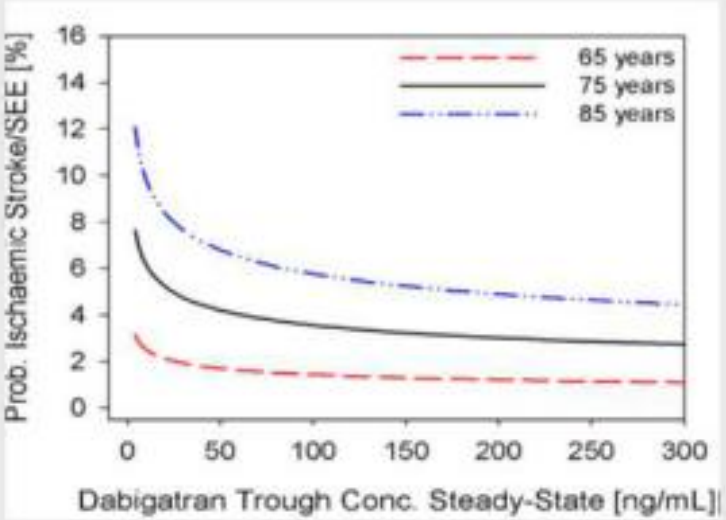
Reilly et al, JACC 2014

Measurement of plasma-concentrations in 9183 patients of the RELY-study
Probability of clinical outcomes versus Dabigatran trough plasma concentration

Major Bleeding
trough conc. > 210ng/ml:
2-fold increased bleeding risk



Ischaemic stroke/SEE
trough conc. < 28ng/ml:
+ 50% increased stroke risk



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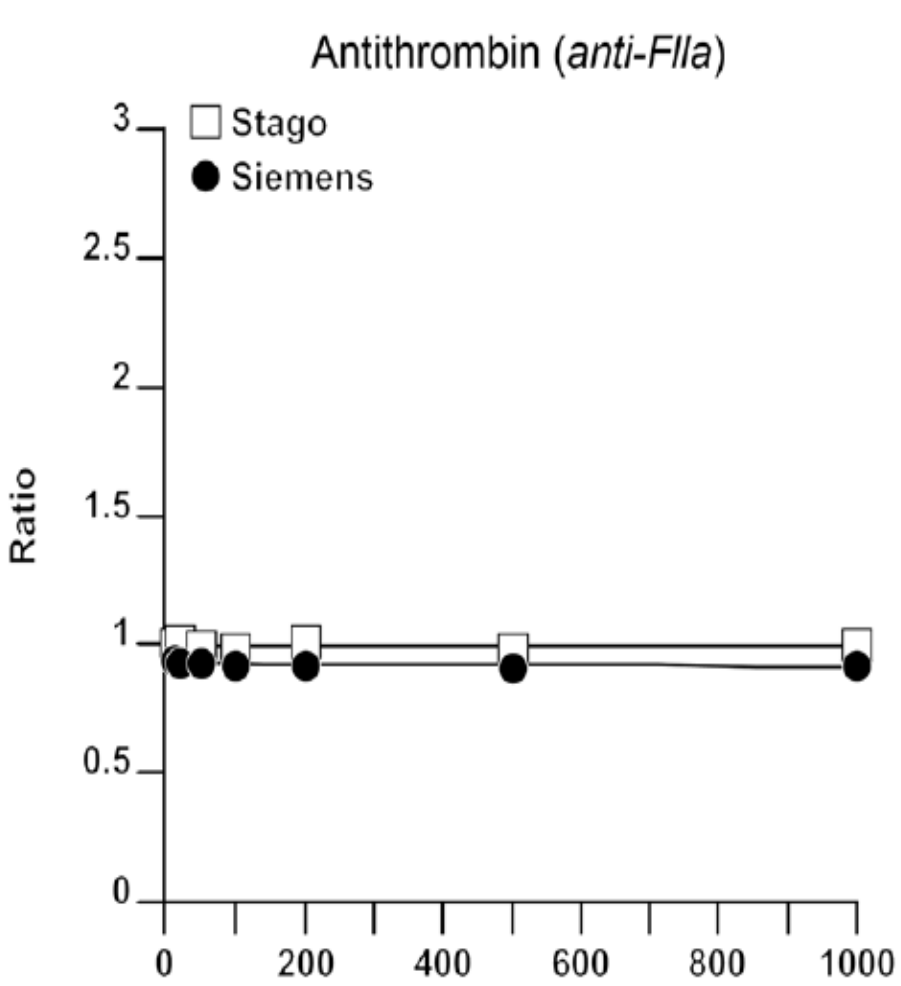
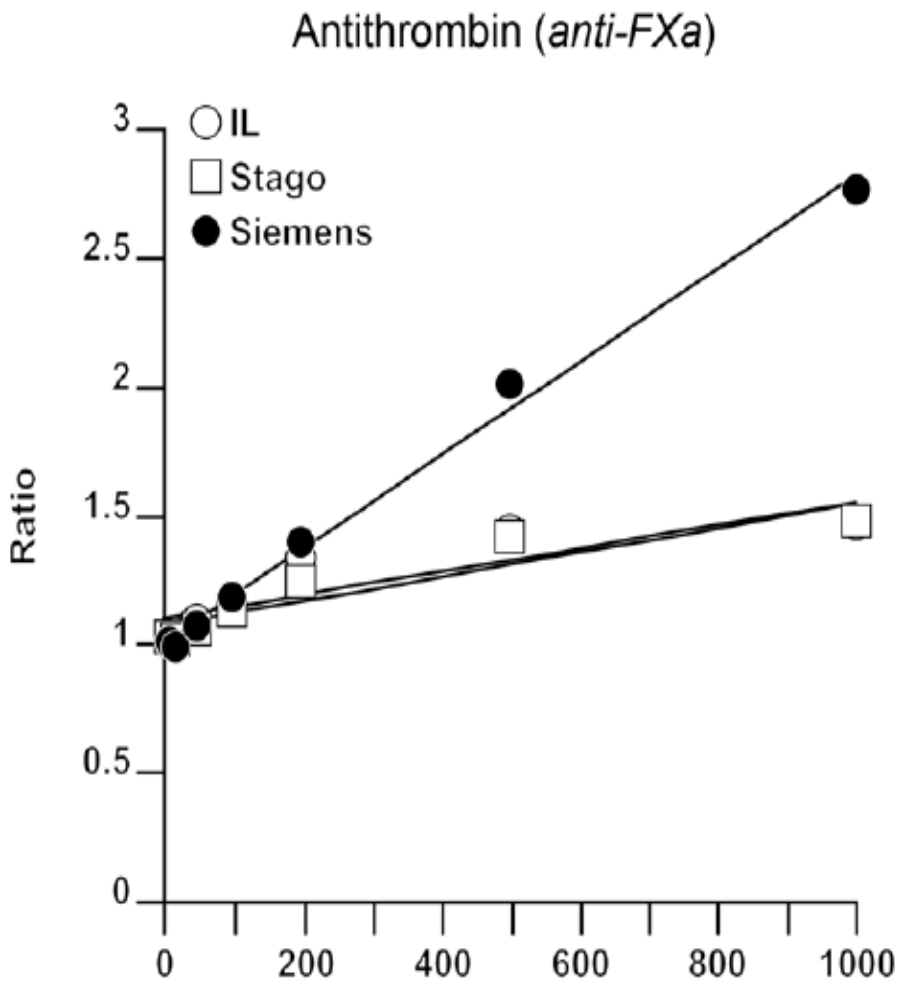
- Kell-e mérni a NOAC antikoaguláns hatását,
- Hogyan
- Mikor
- Alarm érték
- ***Hemosztázis paraméterekre gyakorolt hatásuk***

Effect of apixaban on Antithrombin





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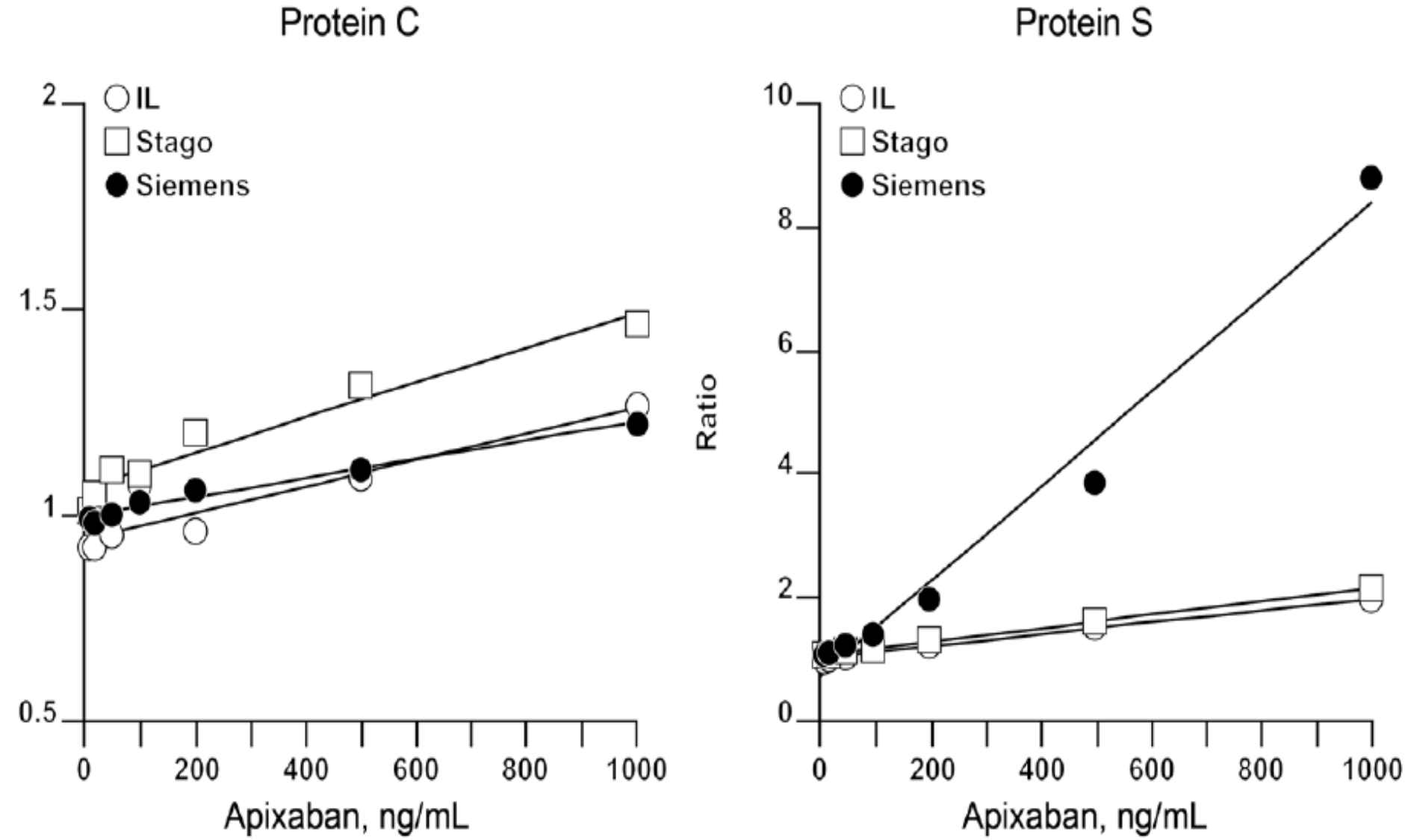
Effect of apixaban on PC or PS



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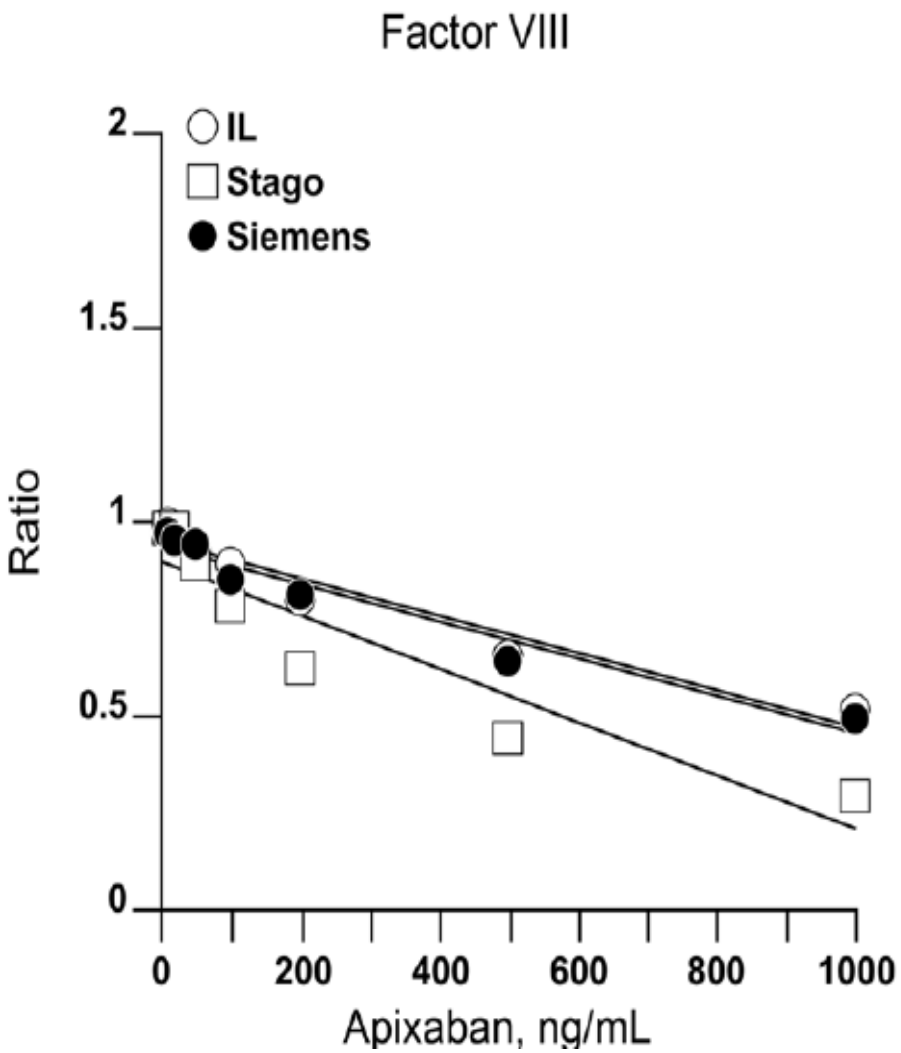
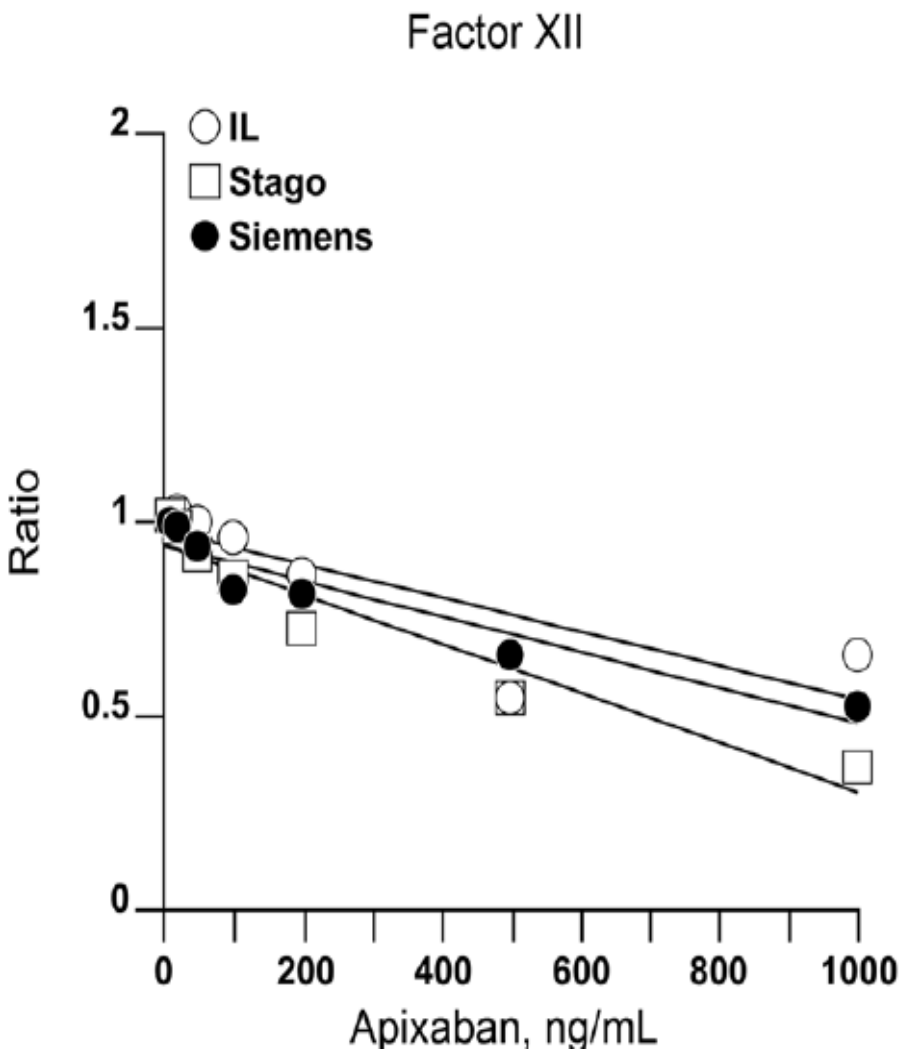
Effect of apixaban on factor assays





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NOAC hatása a leggyakoribb hemosztázis paraméterekre

• Antitrombin	• ***magasabb***
• Fibrinogén	• ***alacsonyabb (dabigatran)***
• APC-rezisztencia	• ***alacsonyabb***
• Factor assay	• ***alacsonyabb***
• Protein C/S aktivitás	• ***magasabb***
• Lupus antikoaguláns	• ***bizonytalan értékelés***
• Faktor XIII	• ***alacsonyabb (dabigatran)***

NOAC összefoglalás

- NOAC *nem igényel laboratóriumi mérés* alapján dózis illesztést, antikoaguláns hatás ismerete speciális eseteknél nélkülözhetetlen
- NOAC alkalmazásakor a *hemosztázis paramétereinek értékelés*énél nagy gonddal kell eljárni
- *A gyógyszer utolsó bevétele időpontjá*nak ismerete nagyon fontos
- A *„völgykoncentráció”* jelzi a vérzés kockázatát.
- *Invazív beavatkozás előtt 24 órával* fel kell függeszteni a gyógyszer bevételét.
- *Vérzés* mértékétől függően: következő adag kihagyása, hosszabb felfüggesztés, helyi vérzéscsillapítás, szupportív terápia, volumenpótlás, transzfúzió, PCC

- While PT and aPTT are excellent screening test for the identification of clotting factor deficiencies, suitable screening tests for the identification of thrombophilia defects are not (yet) available.
- The calibrated automated thrombogram (CAT) assay in plasma is a versatile tool to investigate patients with hypo- or hyper-coagulable phenotypes because of
- 1) the use of low tissue factor which permits exploration of the amplification phase of clotting;
- 2) the potential for the inclusion of cofactors of the natural anticoagulant systems not usually present in the circulating blood.

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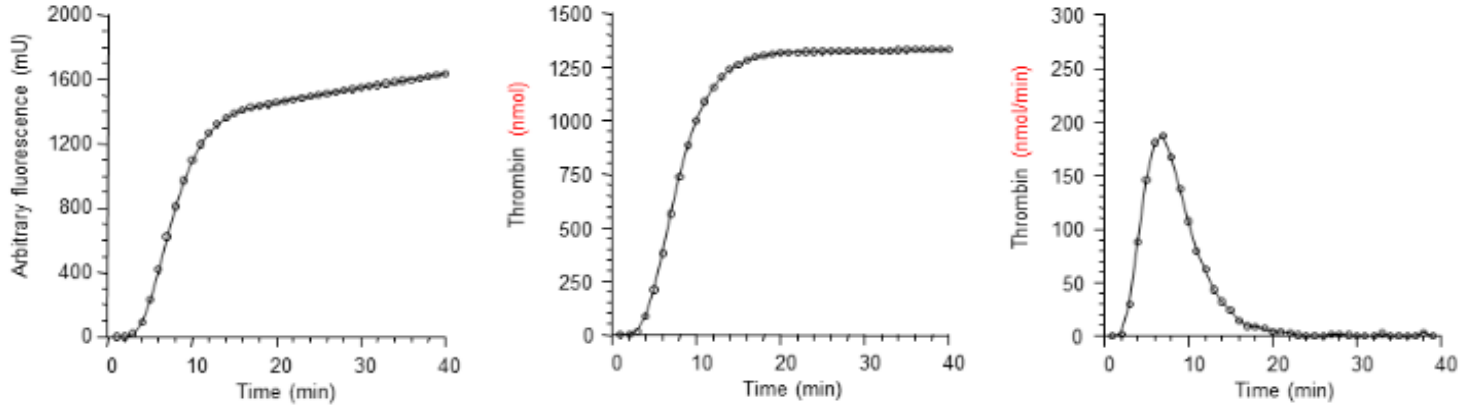
The thrombograph

PPP + Ca2 +TF + PL +
Fluorogenic substrate

Correction for:
α_2-M-thrombin complex
inner filter effect
substrate consumption

First derivative
(calibrated thrombograph)



Hemker HC & Kremers R. Thromb Res 2013;131:3–11

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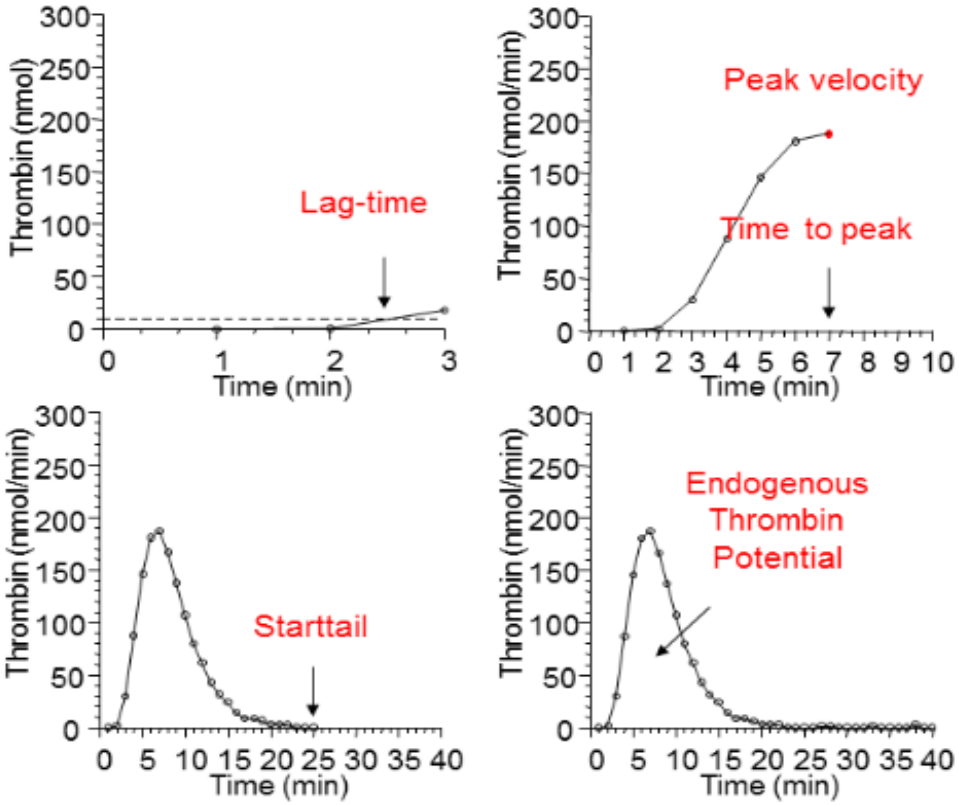
Traditional CAT parameters



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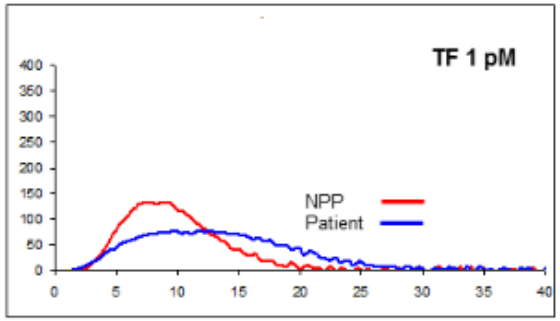
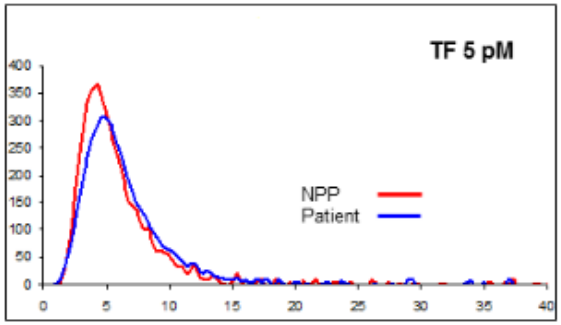
Our modification of CAT

- To simulate the clotting status within the microcirculation we have developed and validated a modification of the thrombin generation test (CAT) in platelet-poor plasma using an intermediate tissue factor (TF) concentration (3 pmol) in the presence of 5 nmol/L thrombomodulin and 116 nmol/L fondaparinux (TMF).

Factor XI deficiency (3%)





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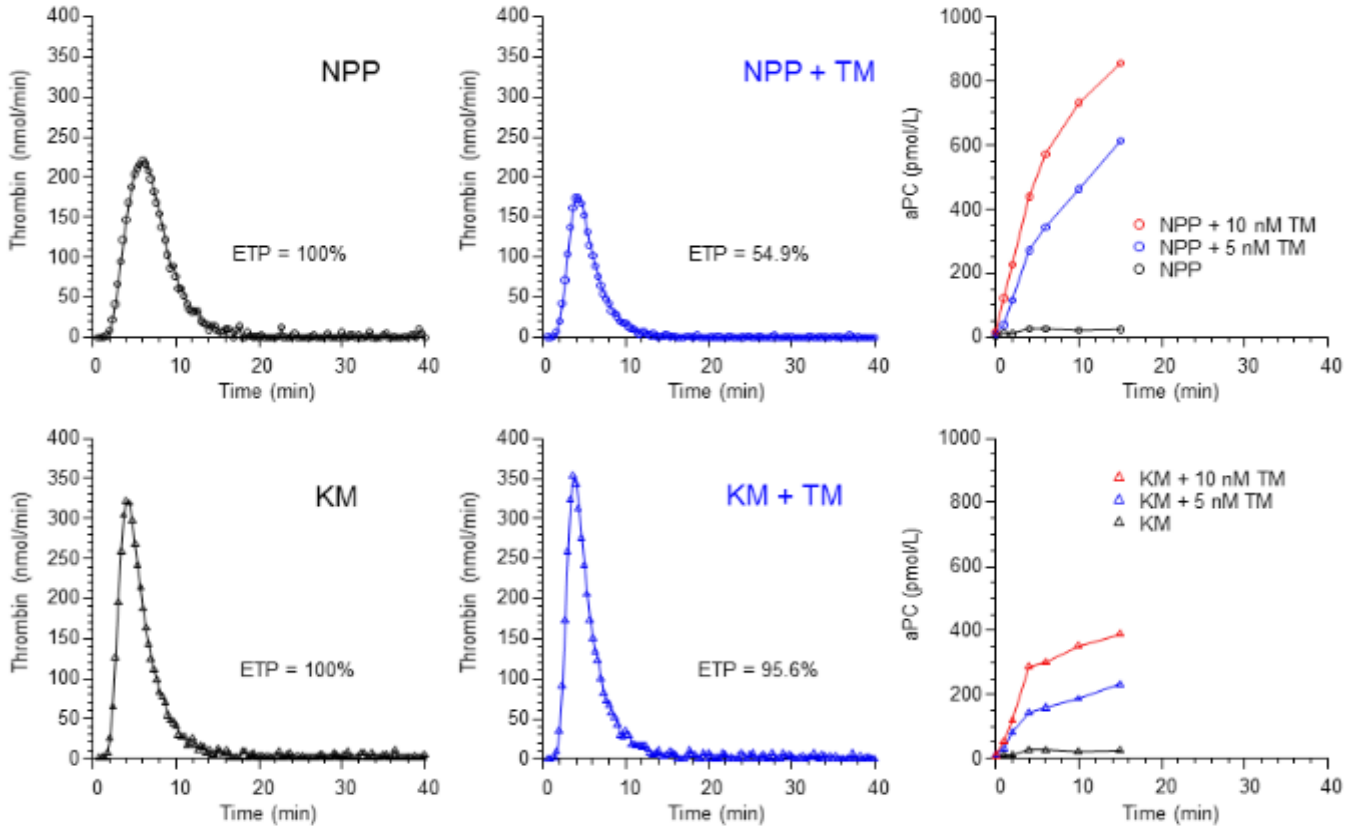
Heterozygous protein C deficiency



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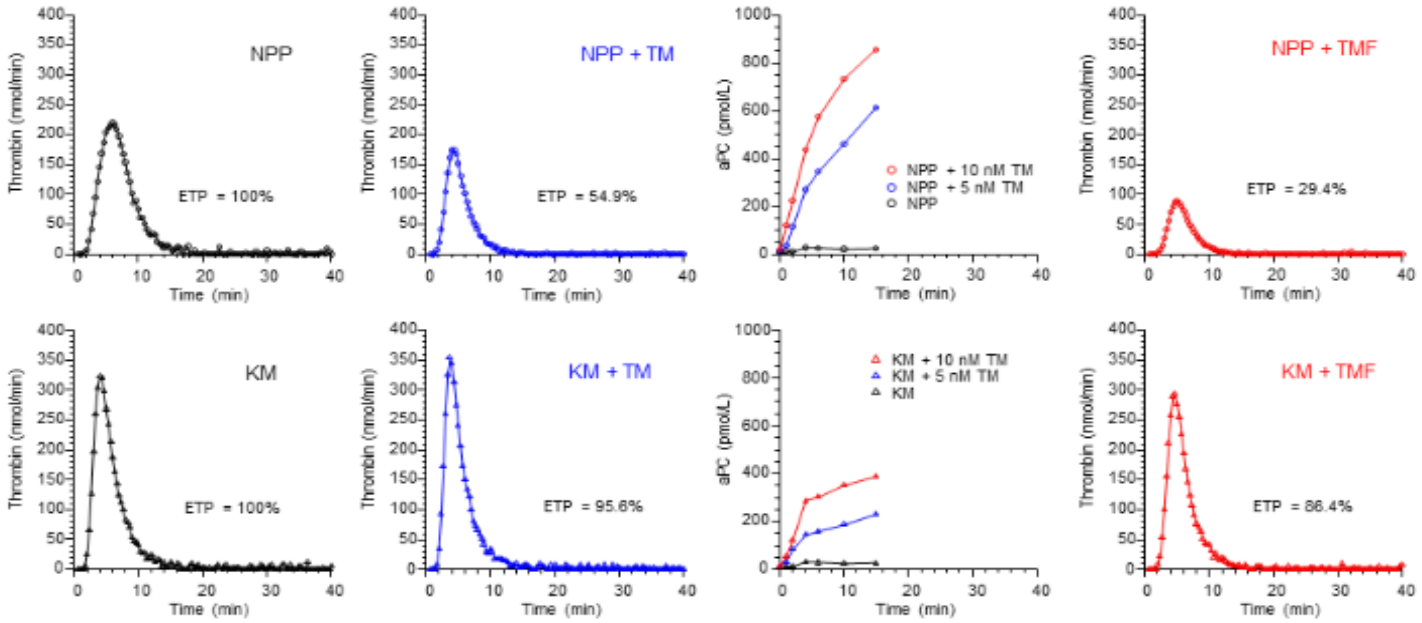
Heterozygous protein C deficiency



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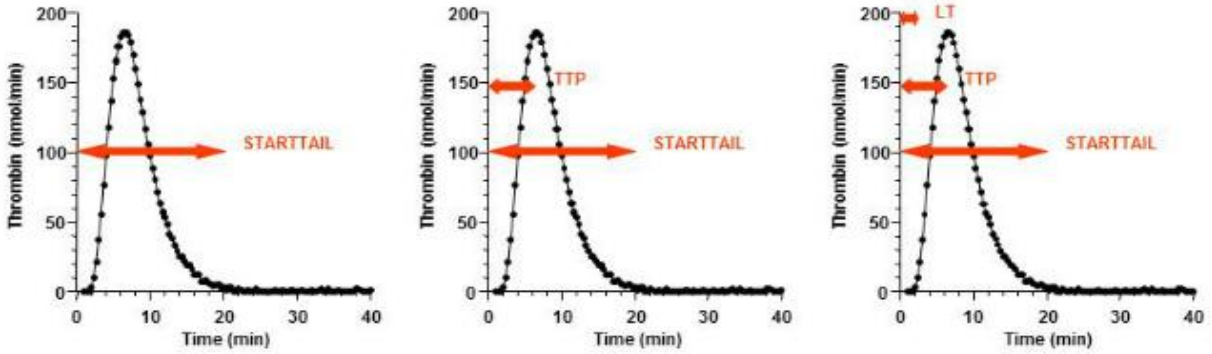
Choosing parameters



Parameters	Ratios
Lag time (min)	Lag time Ratio (NPP/PP)
Peak (nM/min)	Peak Ratio (PP/NPP)
Acceleration [Peak/(TTP-LT), nM/min^2]	Acceleration Ratio (PP/NPP)
True Tail (Starttail-TTP, min)	True tail Ratio (PP/NPP)
ETP (nM)	ETP Ratio (PP/NPP)

Ratios > 1 indicative of hypercoagulability

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Köszönöm a figyelmüket