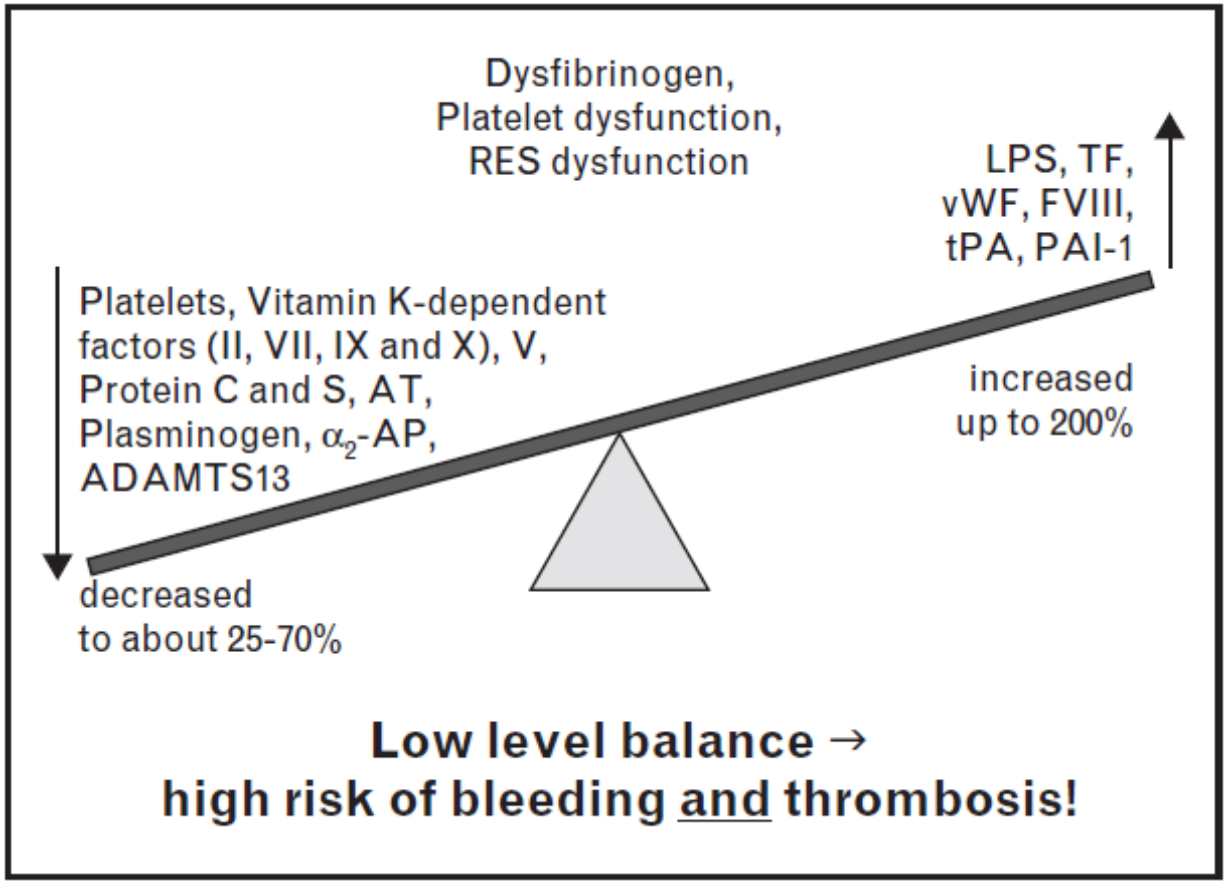
Speciális helyzetek I. – Cirrhotikus beteg, urémiás beteg

Fazakas János, Smudla Anikó

Semmelweis Egyetem, Transzplantációs és Sebészeti Klinika

Hemostasis in Liver Disease

Hemostatic changes in patients with liver cirrhosis



Coagulopathy in liver disease is more of a myth than a reality

Schaden et al. Curr Opin Crit Care 2013, 19:000–000

Hemostasis in Liver Disease

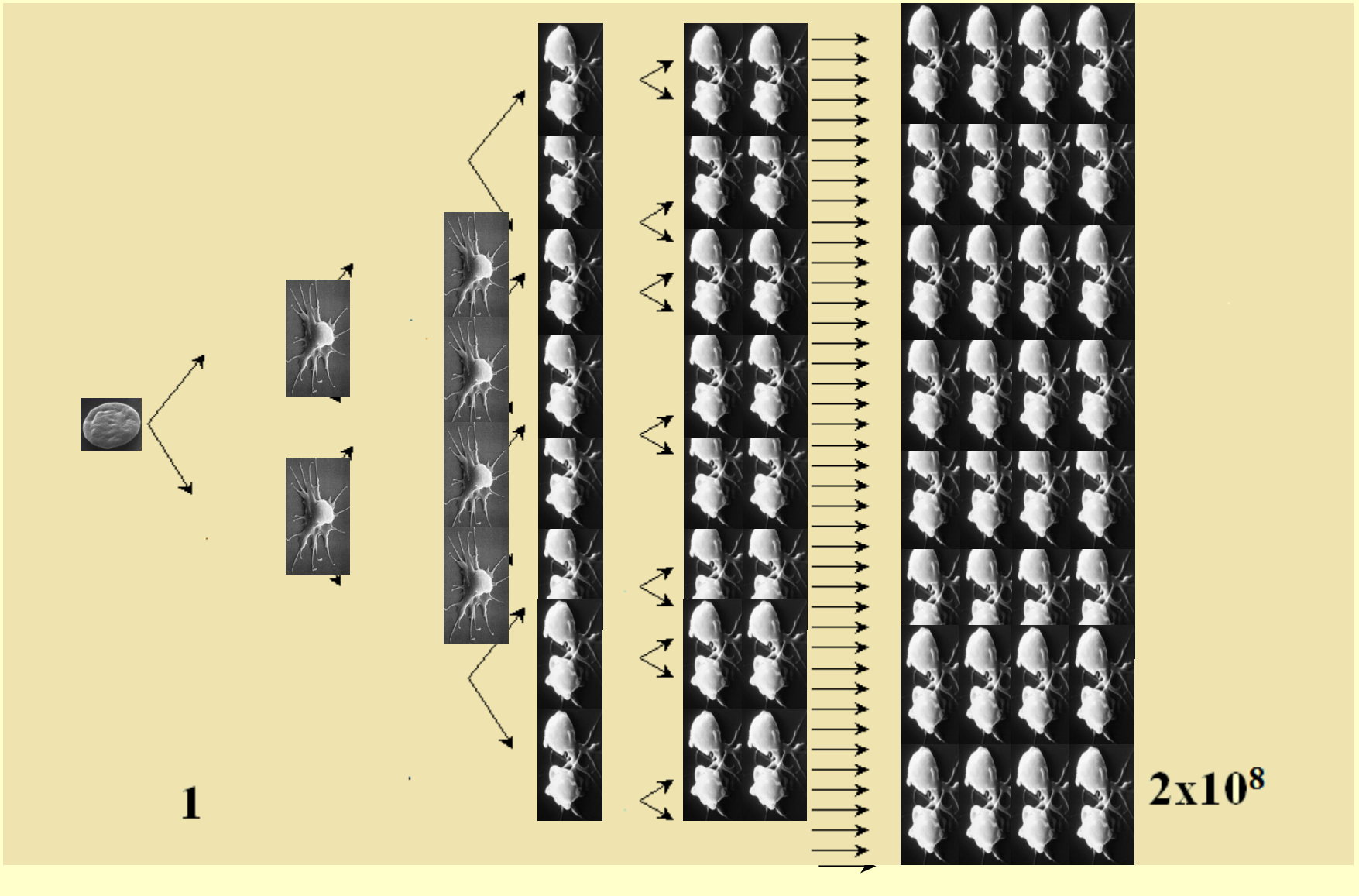
„Delicate rebalance"

Promoting bleeding		Promoting thrombosis
• thrombocytopenia + function defects • enhanced NO + PGI_2 production	Primary hemostasis	• elevated levels of VWF • decreased levels of ADAMTS (VWF protease)
• low level of II, V, VII, IX, X, XI factors • dysfibrinogenemia	Secondary hemostasis	• elevated levels of VIII factor • decreased levels of prot C, prot S, AT III • decreased levels of heparin cofactors
• low levels of $\alpha_2$antiplasmin,XIII factor • elevated tPA levels	Fibrinolysis	• low levels of plasminogen

Current Opinion in Organ Transplantation 2008, 13: 298-303

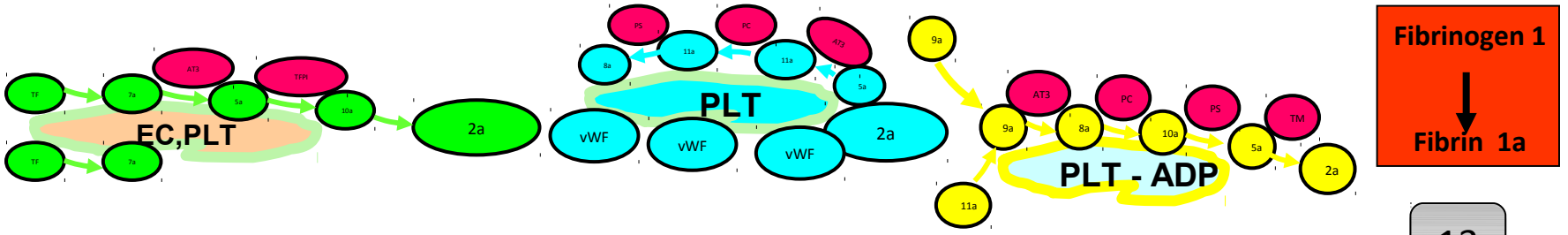
Platelet Function in Liver Disease

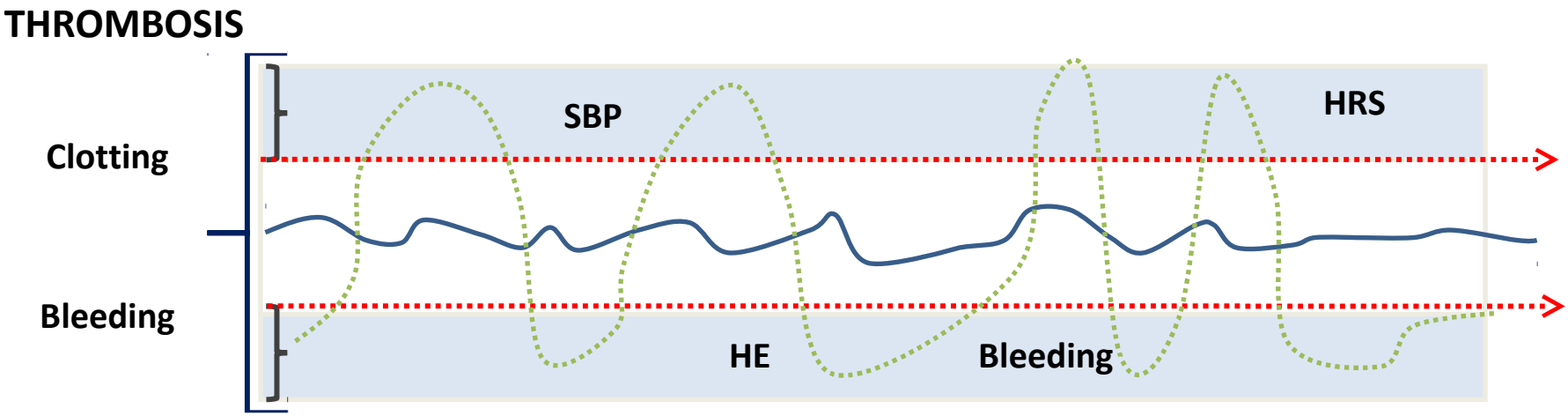
Platelets and the coagulation balance of cirrhotic patients



Coagulation Cascade and Liver Disease

Cirrhosis: a dynamic hemostatic balance = rebalance… rebalance… rebalance… rebalance…





Evidence of normal thrombin generation in cirrhosis

despite abnormal conventional coagulation tests

PLT : 198 x10^9 versus 80 x10^9

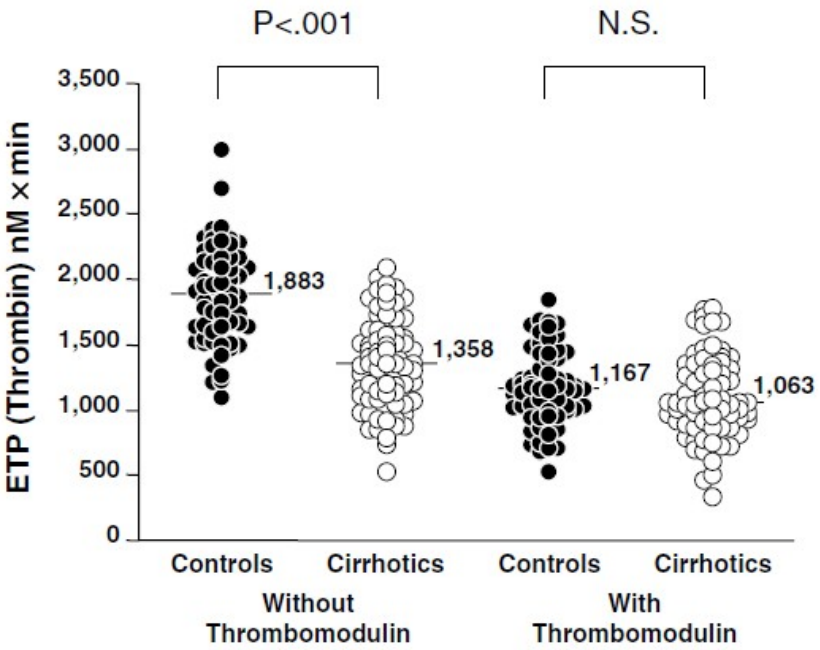


Table 3. Endogenous Thrombin Potential Values for Patients and Controls in Platelet-Free Plasma

	Endogenous Thrombin Potential (nmol/L)	
	Without Thrombomodulin	With Thrombomodulin
Patients (n = 87)	1,398 (630–2,517)	866 (175–1,939)
Controls (n = 62)	1,872 (982–2,682)	795 (75–1,473)
P value (patients vs. controls)	<.001	.08

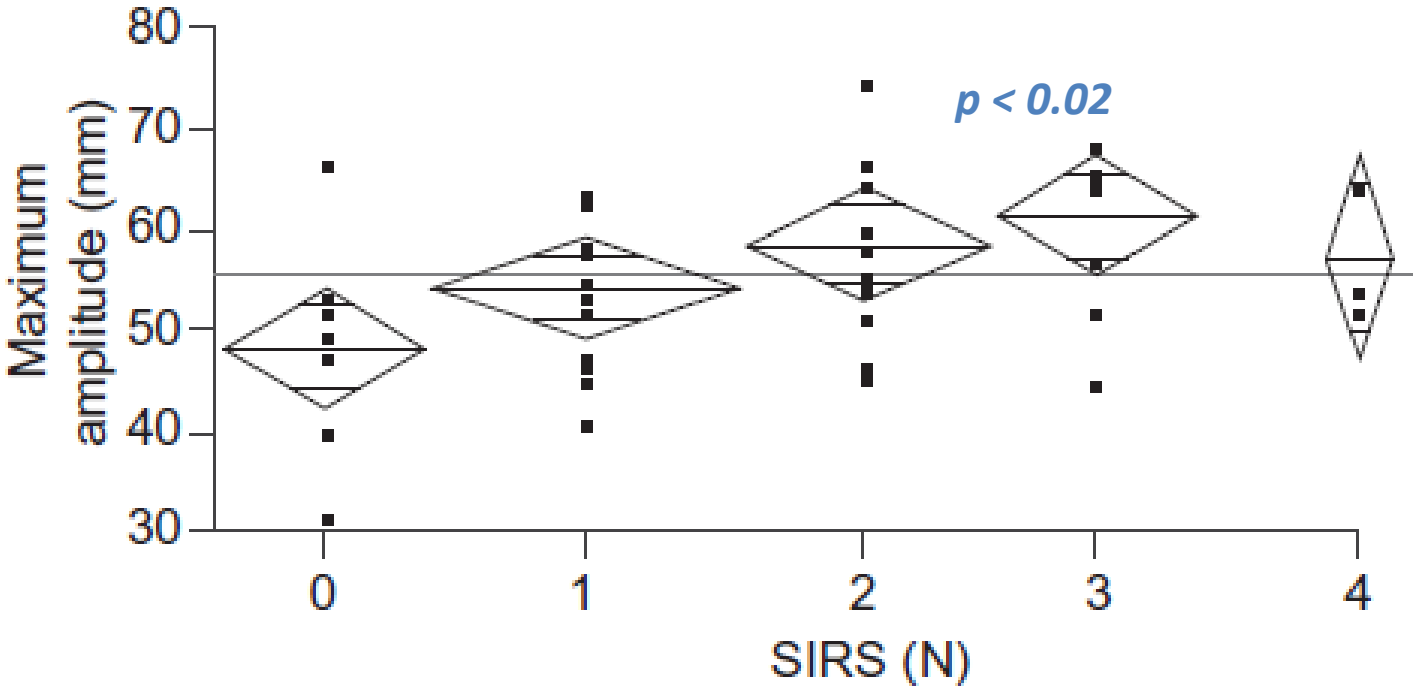
NOTE. All values other than *P* values are expressed as the median (range).

„severe thrombocytopenia may limit thrombin generation in patients with cirrhosis"

Tripodi et al. Hepatology, 2007, 46: 727-733

Coagulation Cascade and Liver Disease

Maximum amplitude of clot formation according to the number of SIRS



Inflammation and a dynamic hemostatic balance

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

Stravitz et al. Journal of Hepatology 2012 vol. 56: 129–136

Hyperfibrinolysis in Liver Disease

Hyperfibrinolysis in Liver Disease

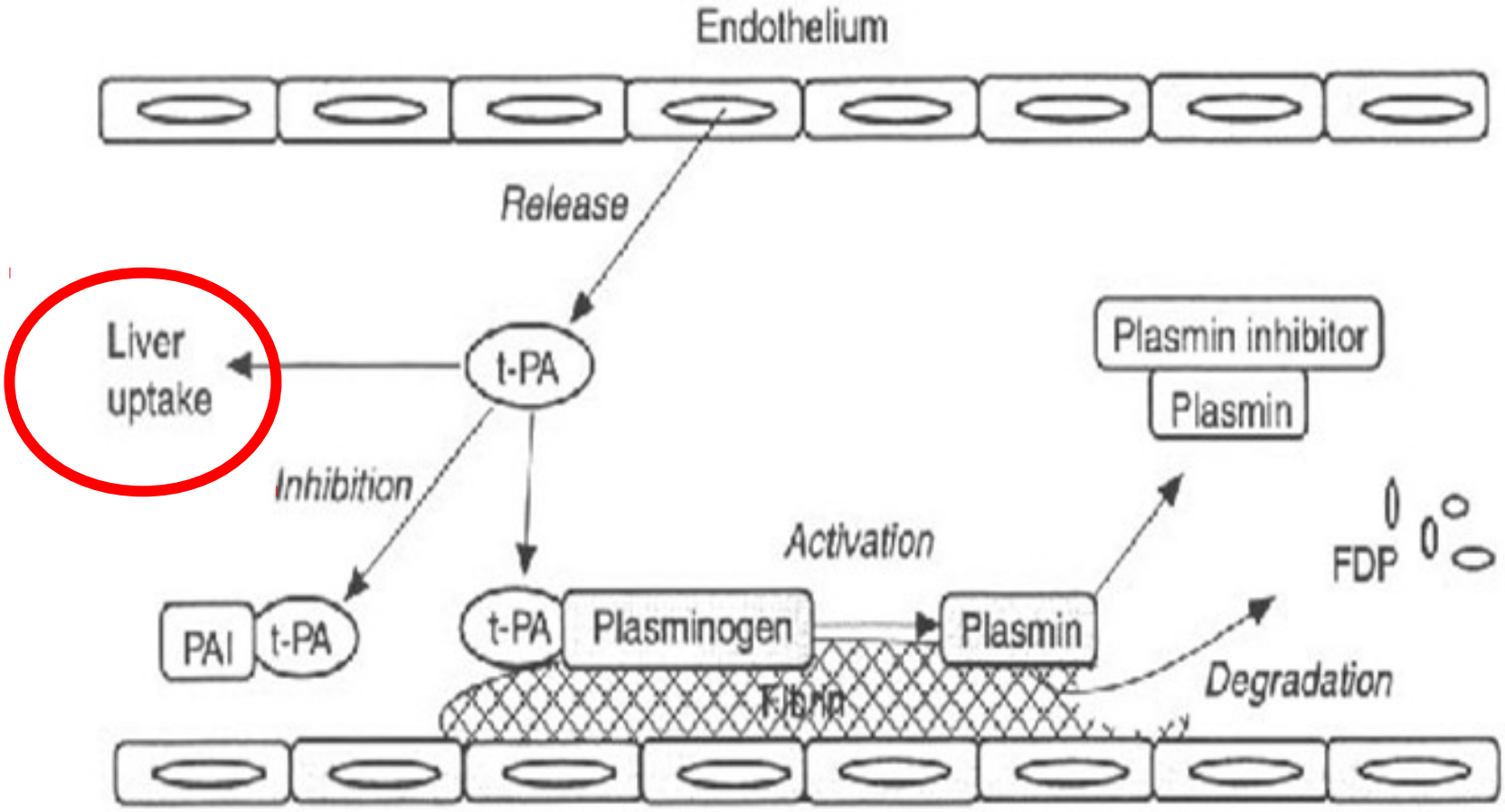


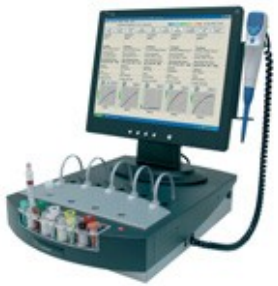
Figure 1. Schematic overview of the fibrinolytic system

http://www.mjhid.org/article/view/5283

Dynamics of coagulation – TEG; TAG

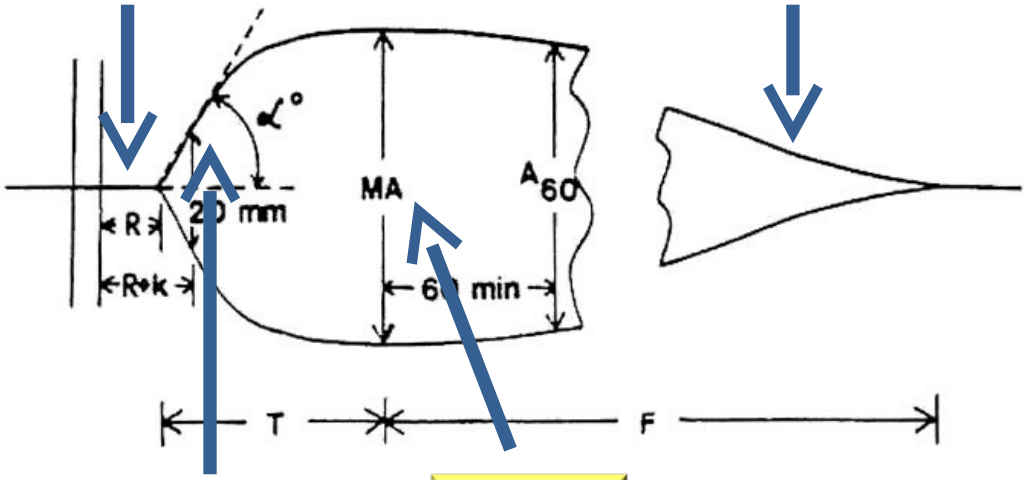
Thromboelastogram

whole blood hemostasis test



Coagulation factors
Anticoagulants
FDPs

Fibrinolytic enzymes
Fibrinolysis inhibitors
tPA, F XIII



Fibrinogen

Platelets
F XIII

Multiplate

platelet function analysis on impedance aggregometry

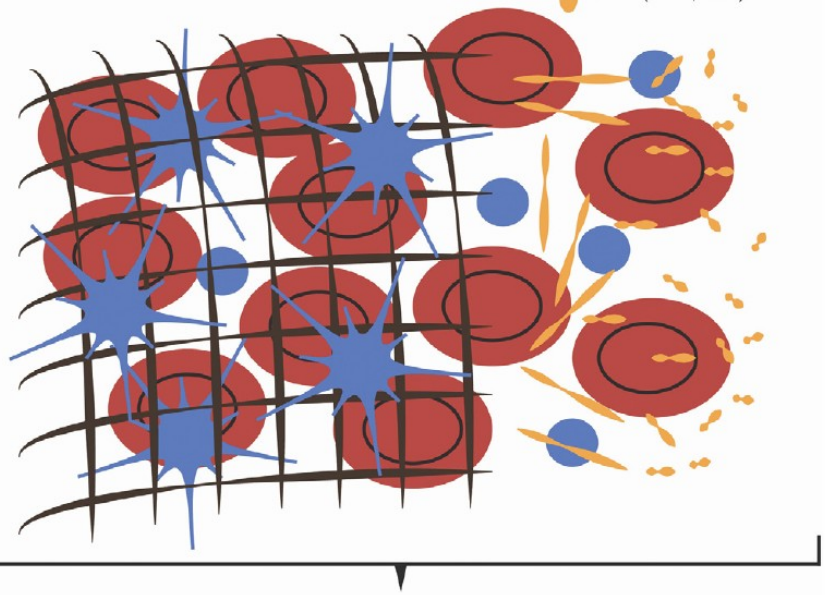
	ASPItest	ADPtest
no platelet inhib.	102 U	89 U
aspirin	17 U	134 U
clopidogrel	89 U	31 U
aspirin + clopidogrel	8 U	17 U

Coagulation in Liver Disease: A Guide for the Clinician

Primary Hemostasis
Activated platelets and thrombin burst. Measured by platelet count, vWF, platelet function analysis, and bleeding time.

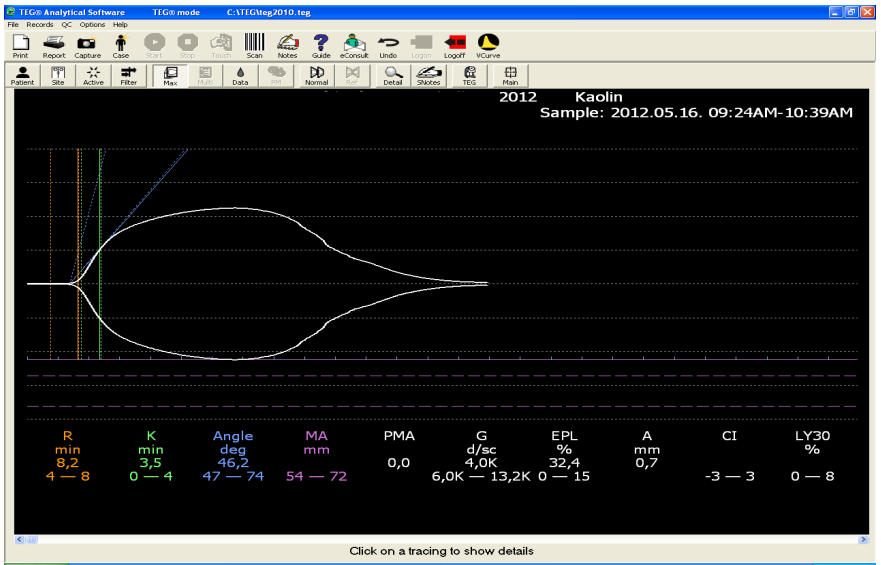
Coagulation: Intrinsic and Extrinsic Pathways
Builds the fibrin mesh. Measured by PT/INR, aPTT and specific factor levels.

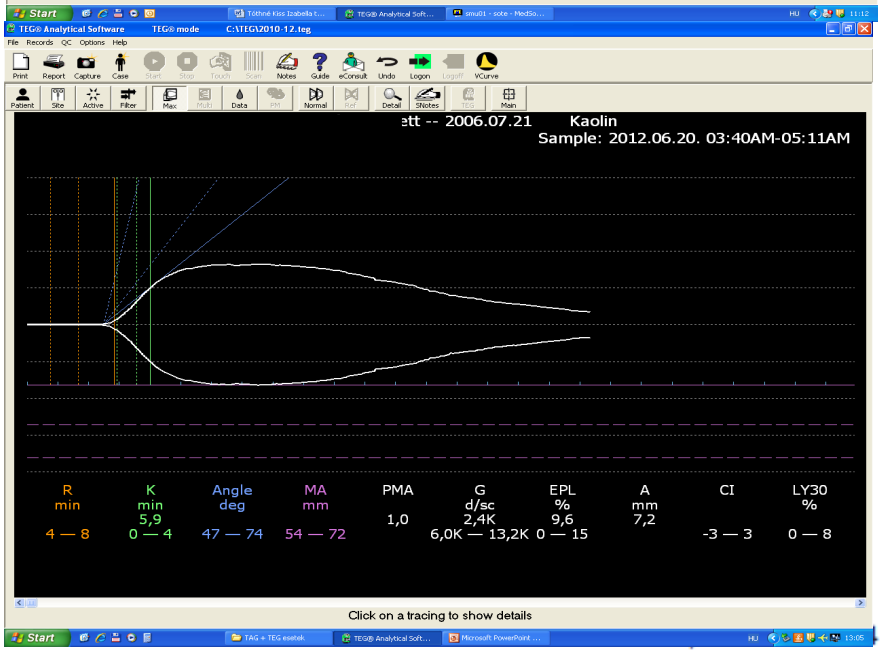
Fibrinolysis
Controls propagation of the fibrin mesh and dissolves clot when hemostasis is achieved. Measured by fibrinogen level, protein C and S levels, antithrombin III level, euglobulin lysis time, and anticoagulant levels (PAI-1, TAFI).



Estimated Thrombin Potential
Measure of ability to generate fibrin mesh. Dependent on platelet levels, platelet function, procoagulant levels, and antithrombin/protein C activity.

Whole Blood Clotting Assays
Thromboelastography, ROTEM, sonorheometry. Assessment of overall hemostasis activity including primary hemostasis, coagulation, and fibrinolysis.





Intenzív osztály: Májbeteg; Thr: 29 G/L

Multiplate® platelet function analysis - V2.03.11

The temperature of the measurement block: 37.1°C, within specified range

18. Apr. 2013, 11:35:02

F1 : Auto Pipette | F2 : Start timer | F3 : Start test | F4 : Enter ID | F5 : Change ID | T : Select test | F6 : Print | F7 : Clear channel | F8 : Screen shot | F9 : Curve mode

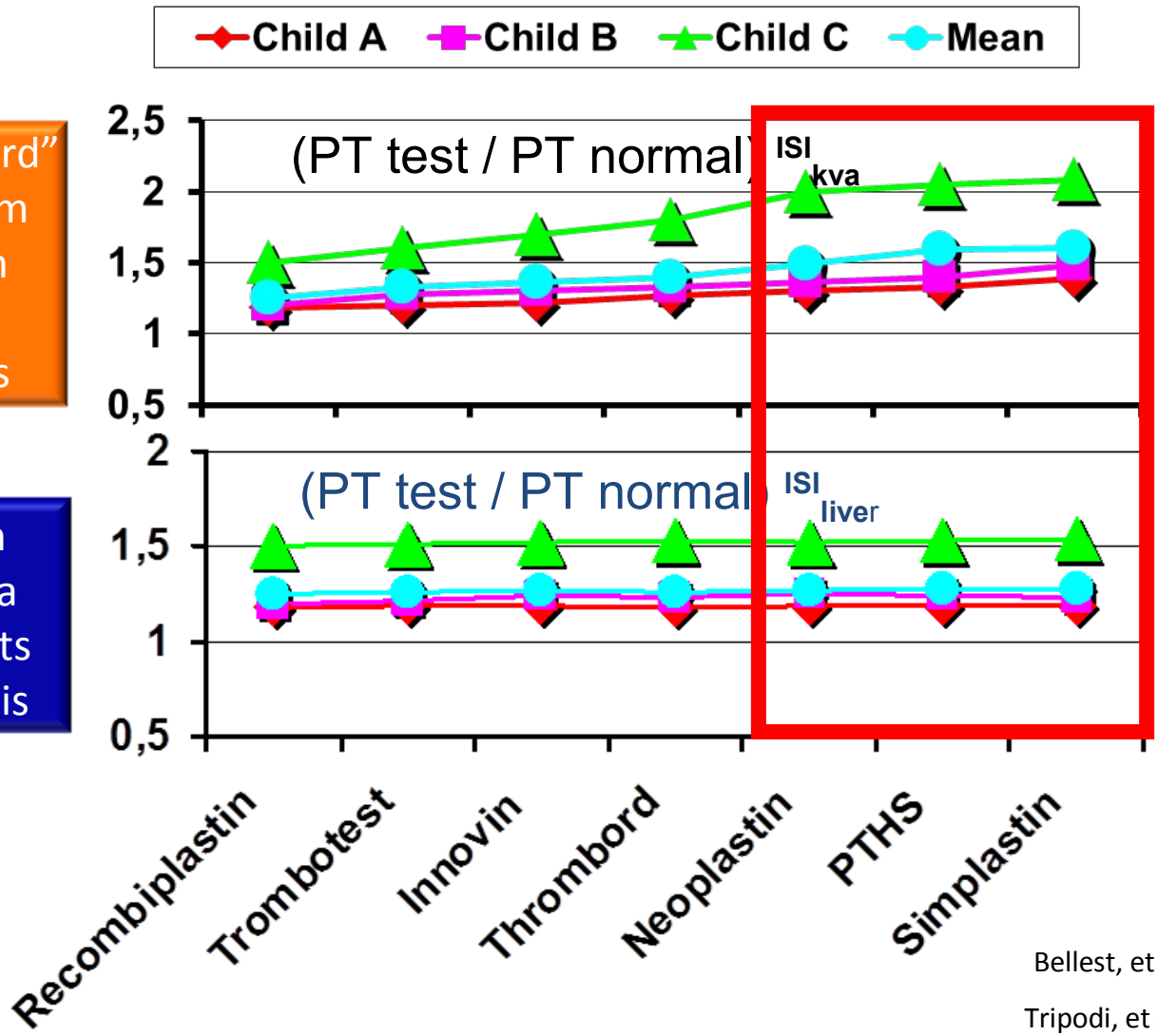
Channel 1	Channel 2	Channel 3	Channel 4	Channel 5
Patient ID :	Patient ID :	Patient ID :	Patient ID :	Patient ID :
Magusics Szilvia	Magusics Szilvia	Magusics Szilvia	Magusics Szilvia	Magusics Szilvia
Test name :	**Test name :**	**Test name :**	**Test name :**	**Test name :**
ASPItest (Hirudin blood), V1	ADPtest (Hirudin blood), V1	RISTO high (Hirudin blood), V1	TRAPtest (Hirudin blood), V1	COLtest (Hirudin blood), V1
Start : / Runtime :	Start : / Runtime :	Start : / Runtime :	Start : / Runtime :	Start : / Runtime :
18. Apr. 2013, 11:15 / 6'00"	18. Apr. 2013, 11:16 / 6'00"	18. Apr. 2013, 11:16 / 6'00"	18. Apr. 2013, 11:16 / 6'00"	18. Apr. 2013, 11:16 / 6'00"
Area under the curve :	**Area under the curve :**	**Area under the curve :**	**Area under the curve :**	**Area under the curve :**
49 U (75 - 136)	**16 U (53 - 122)**	**15 U (90 - 201)**	**56 U (94 - 156)**	**29 U (46 - 117)**
Aggregation :	Aggregation :	Aggregation :	Aggregation :	Aggregation :
RUO: 102.4 AU	RUO: 37.5 AU	RUO: 51.4 AU	RUO: 97.9 AU	RUO: 81.4 AU
Velocity :				
RUO: 12.3 AU/min.				
CC=0.997, DIF=3.862%	CC=0.998, DIF=0.912%	CC=0.994, DIF=1.987%	CC=1.000, DIF=0.797%	CC=0.998, DIF=2.207%
All / 200 AU	200 AU	200 AU	200 AU	200 AU

Thr: 29 G/L → DDAVP: 0,3 mg/kg vagy 5-10 ml/kg Thr

INR kva versus INR liver

„WHO standard" plasmas from patients on vitamin K antagonists

Calibration with plasma from patients with cirrhosis



INR kva

Δ A-B=0.3

ΔC=0.5

„healthy test"

INR liver

Δ A-B=0.01

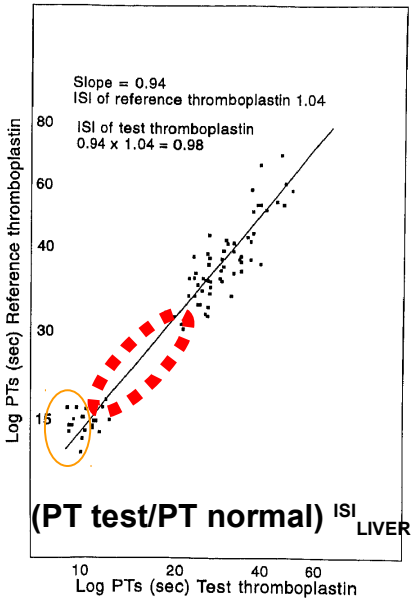
Δ C=0.02

Bellest, et al. Hepatology, 2007; 46:528-34.

Tripodi, et al. Hepatology, 2007; 46:520-27.

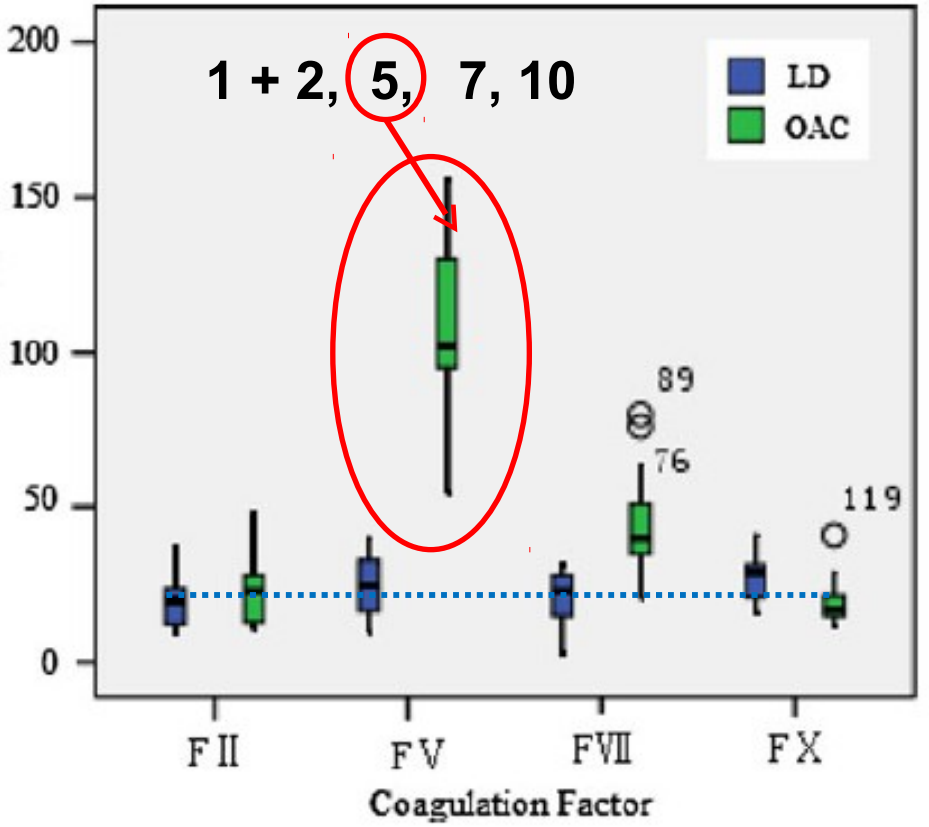
Assessment of validity of INR system for patients with liver disease associated with viral hepatitis

J Thromb Thrombolysis (2010) 30:84–89



2, 7, 9, 10

1 + 2, 5, 7, 10



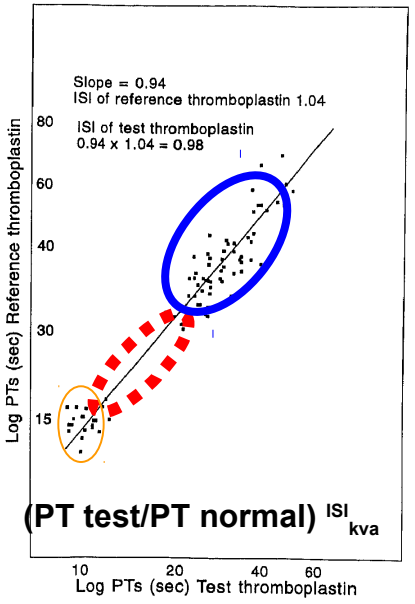


Fig. 2 Coagulant activities of factors II, V, VII, and X for 15 patients with liver disease and 15 patients on warfarin. *LD* liver disease, *OAC* oral anticoagulant

Review Article

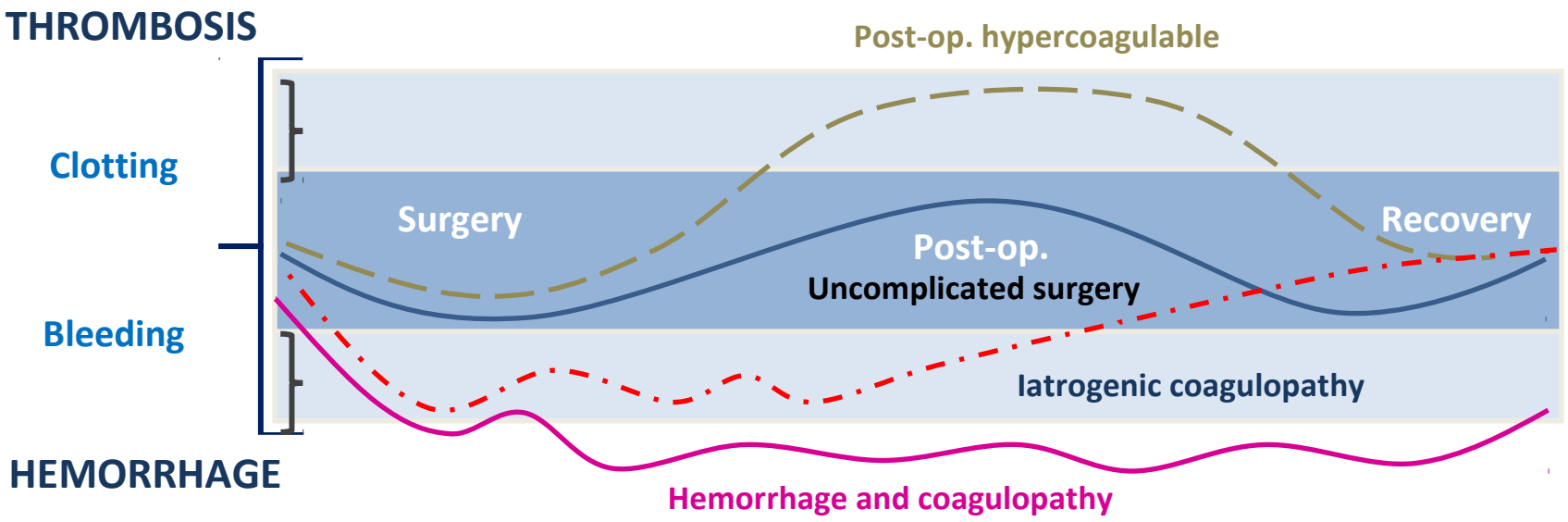
Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis

Table 1: Therapeutic options in coagulopathy in decompensated liver cirrhosis.

Agent	Utility in specific situations	Comment
Red blood cell transfusion	Bleeding patients	Transfusion should be minimum, not allowing Hb to exceed 8 to 9 mg%
Vitamin K	Every patient	May not be useful if patient has no deficiency
Fresh frozen plasma	Questionable in bleeding patients	May be used in bleeding patients when volume expansion is not a concern
Platelets	Count less than 50.000	Limited data
Cryoprecipitate	In bleeding patients	Limited data
Prothrombin complex concentrate	In bleeding patients	Limited data
Desmopressin	In bleeding patients	Efficacy unproved
Aprotinin, transexamine acid, and epsilon amino caprioric acid	Patients with hypofibrinogenemia Fibrinogen less than 100/dL	Can induce thrombosis
Recombinant factor VII	In placing ICP devices, bleeding after surgery, massive variceal bleed	Can induce thrombosis
Topical agents—cyanoacrylates, fibrin glue, and thrombin	Topical heamostasis and localized bleeding	Extremely expensive and limited data
Reduction in the portal pressure, maintaining low CVP by volume contraction (phlebotomy/diuresis)		
Surgical techniques—vascular clamping, ultrasonic/hydrojet dissectors, and thermal techniques (aarton plasma coagulator, radio frequency ablators)		

Prevention and Treatment Guidelines for Bleeding During Surgery

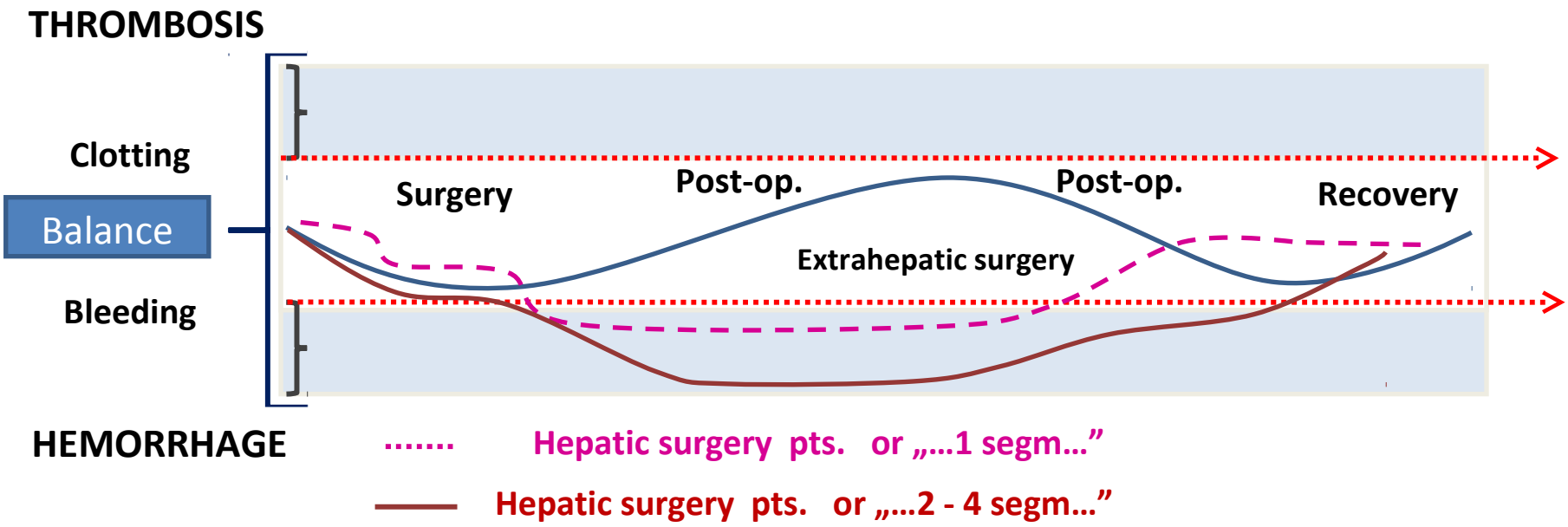
Thrombosis and hemorrhage risk associated *extrahepatic surgery*



Adapted from Levy, Anesth Analg

Prevention and Treatment Guidelines for Bleeding During Liver Surgery

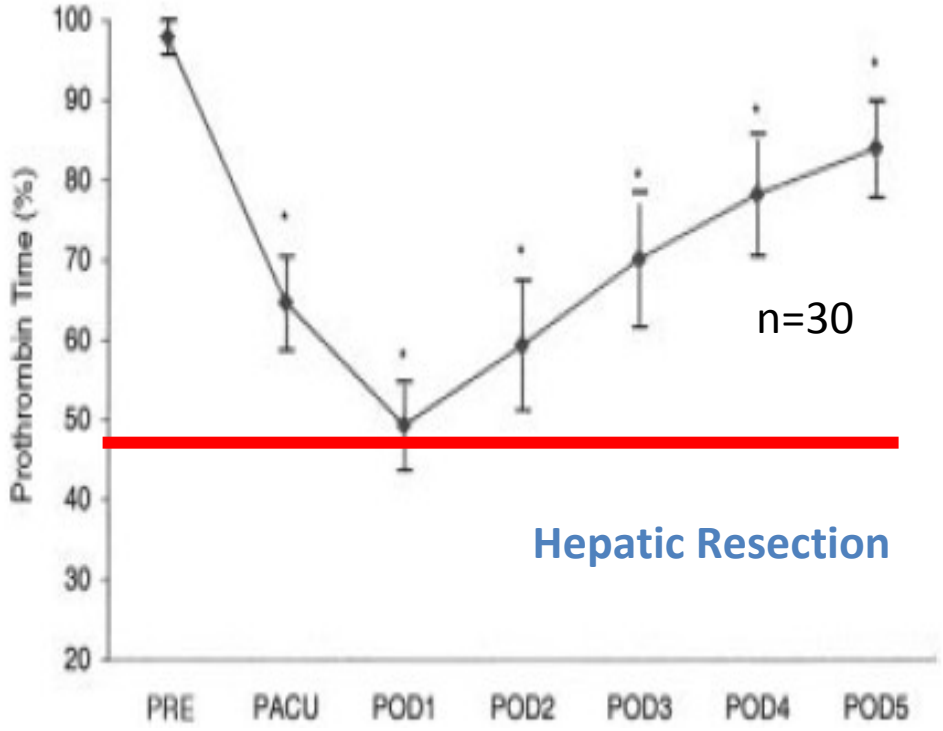
Thrombosis and hemorrhage risk associated *hepatic surgery*



Adapted from Levy, Anesth Analg

Prevention and Treatment Guidelines for Bleeding During Liver Surgery

Thrombosis and hemorrhage risk associated *hepatic surgery*



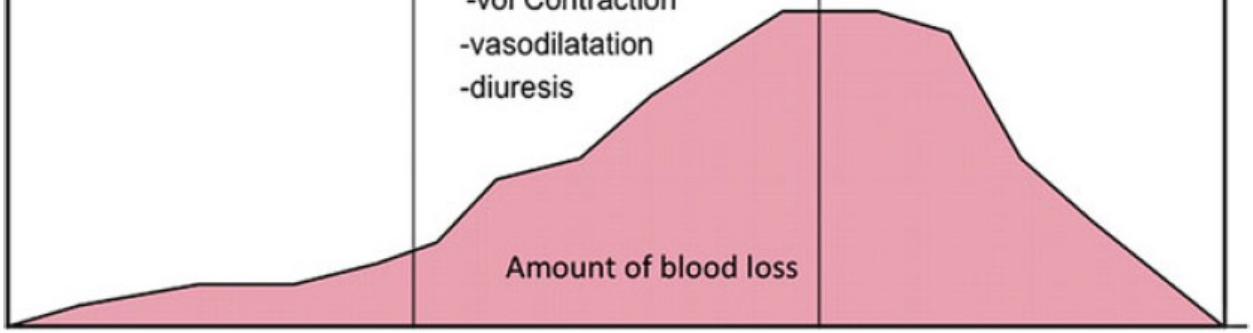
A. Siniscalchi / Liver Transpl 10 (2004) 1144 -1149

Prevention and Treatment Guidelines for Bleeding During Liver Surgery

Thrombosis and hemorrhage risk associated ***hepatic surgery***

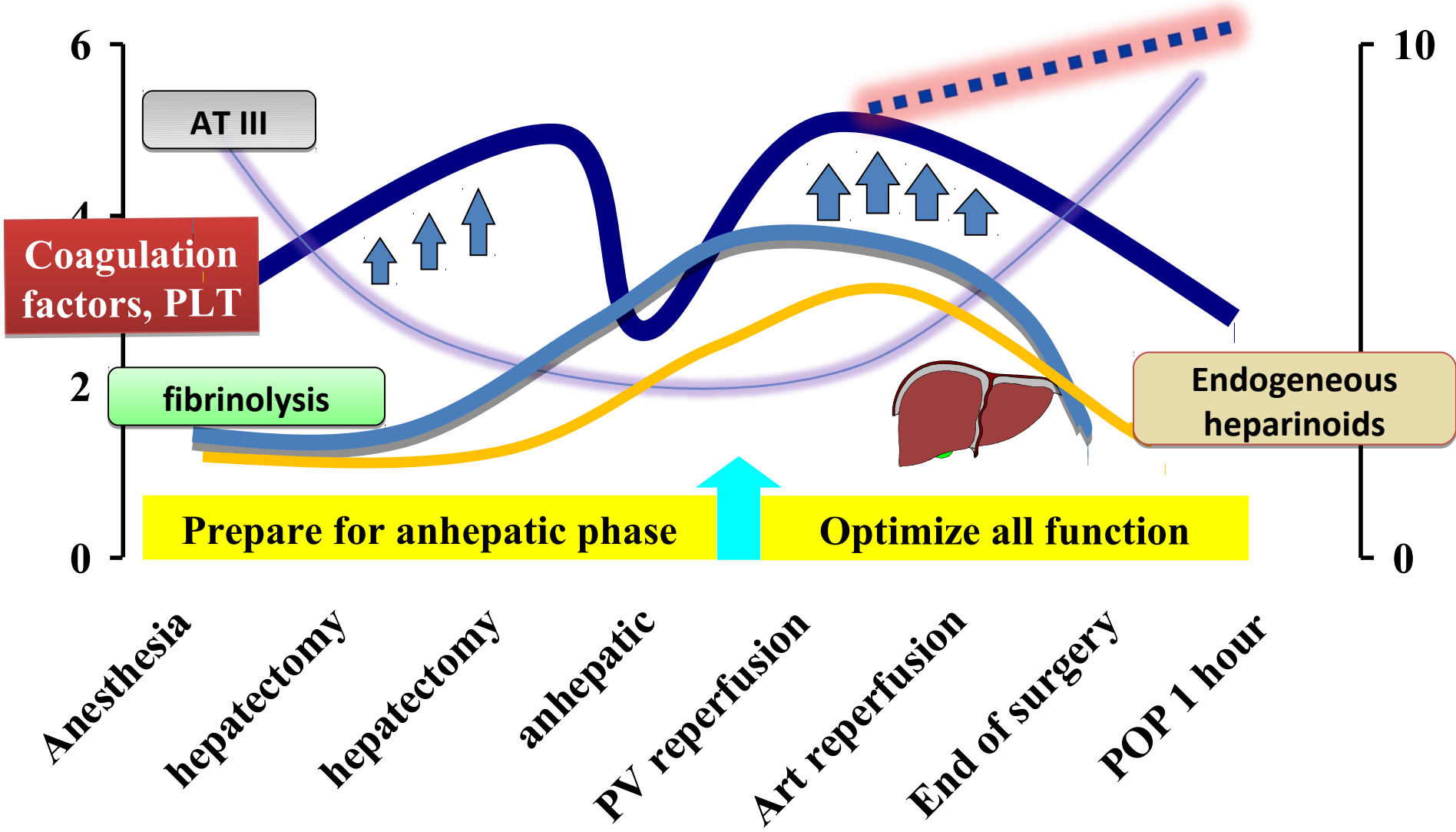
Management of Coagulopathy During Hepatic Resection

Stage 1	Stage 2	Stage 3
Dissection: -Correct anatomical ID -Blood products: Platelets, FFP, etc. -Minor blood loss	Parenchyma transection: - Technique -vasc clamping -use of dissection devices -Lower CVP -vol Contraction -vasodilatation -diuresis	Resection surface: -Hemostasis -Biliostasis -Topical agents -Antifibrinolytics -rFVIIa



Map of hemostasis

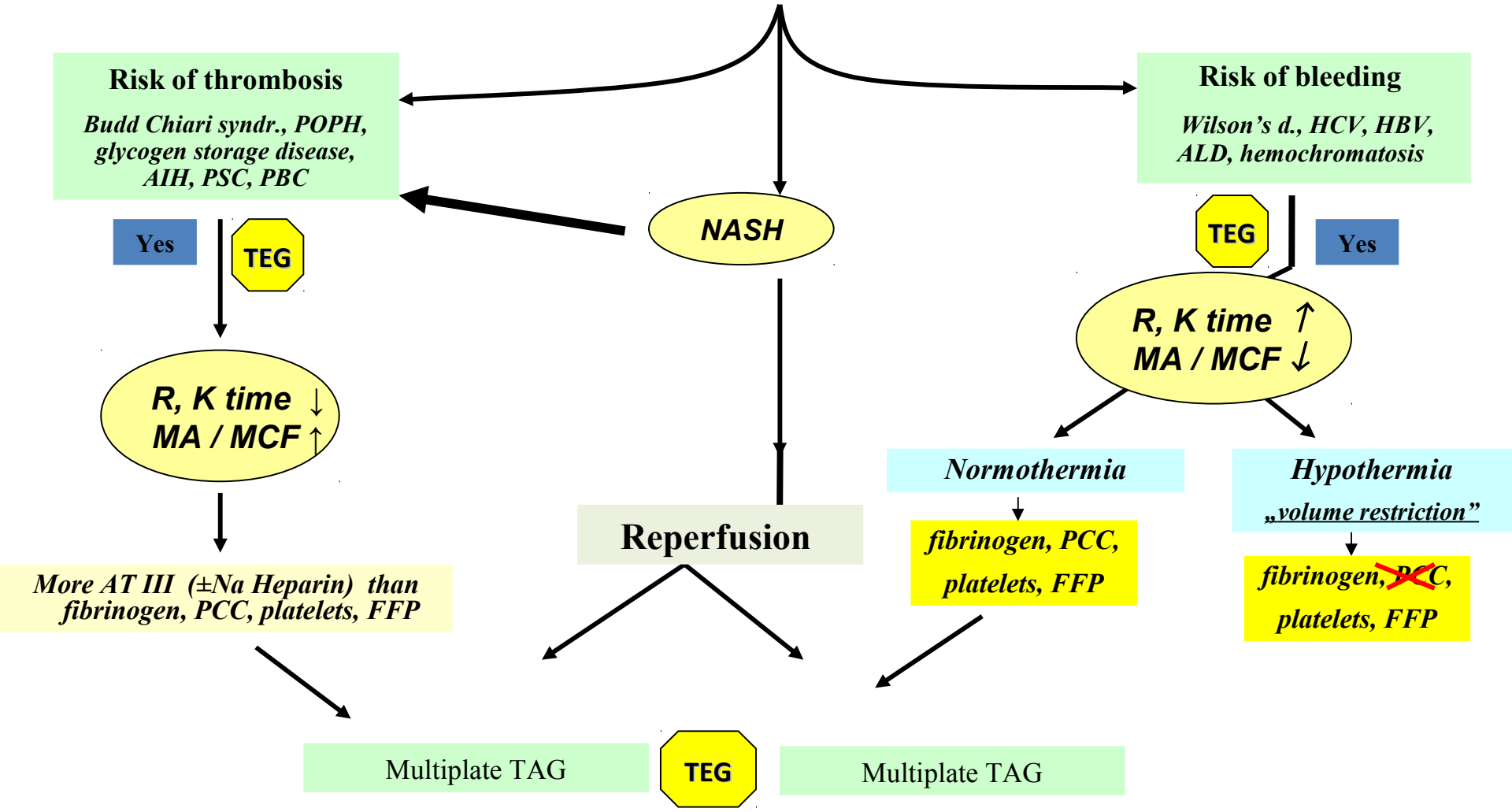
during liver transplantation



ESDL etiology and coagulation profile

PLT, INR, APTI, coagulation factors
Plasminogen, *t PA, PAI 1*, PAI 2

ATIII, protein S, protein C
α2-antiplasmin, α2 -macroglobulin

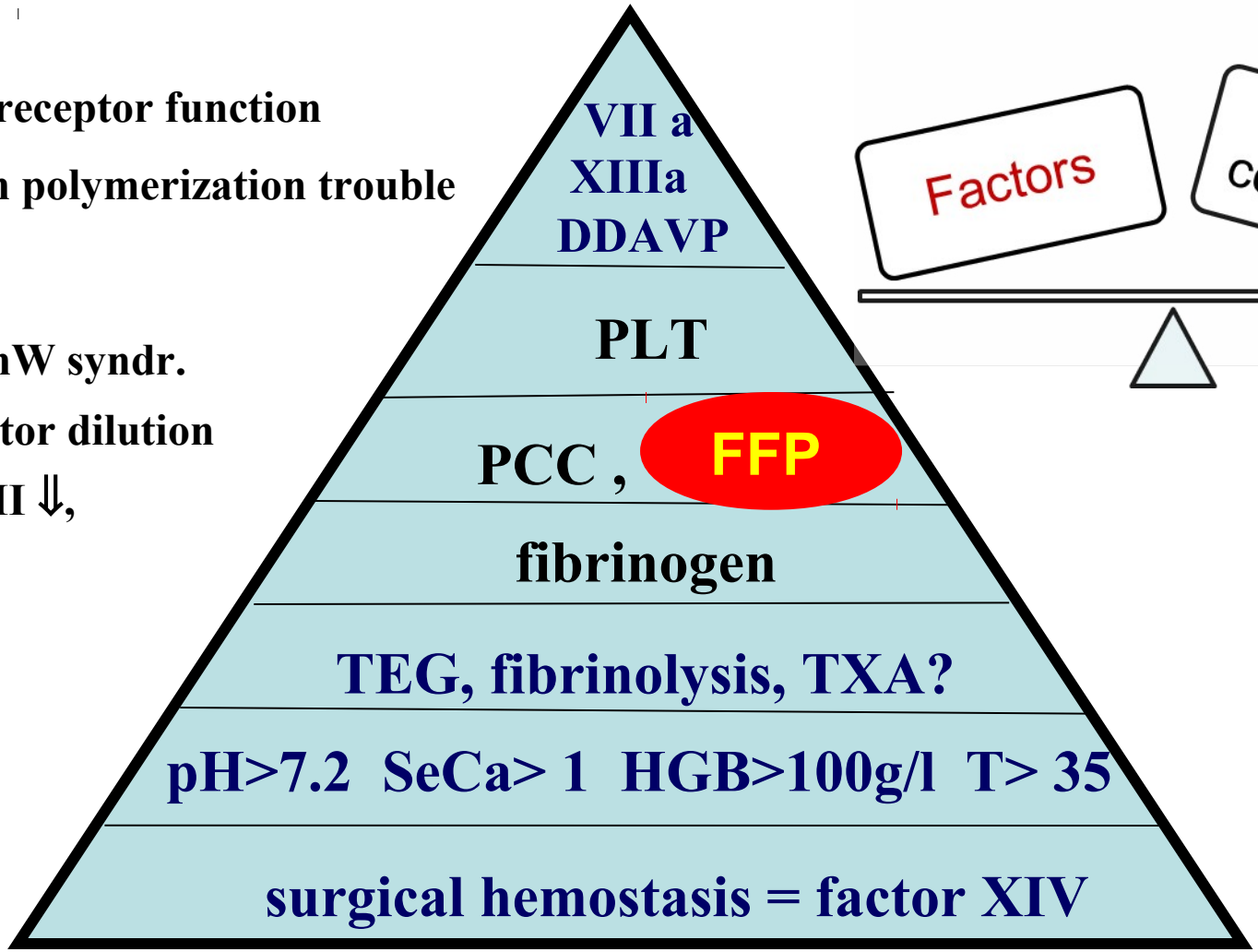


Fibrinogen < 1g/l | V < 20% | VII < 20% | PLT < 50.000

„initiation – amplification - propagation”

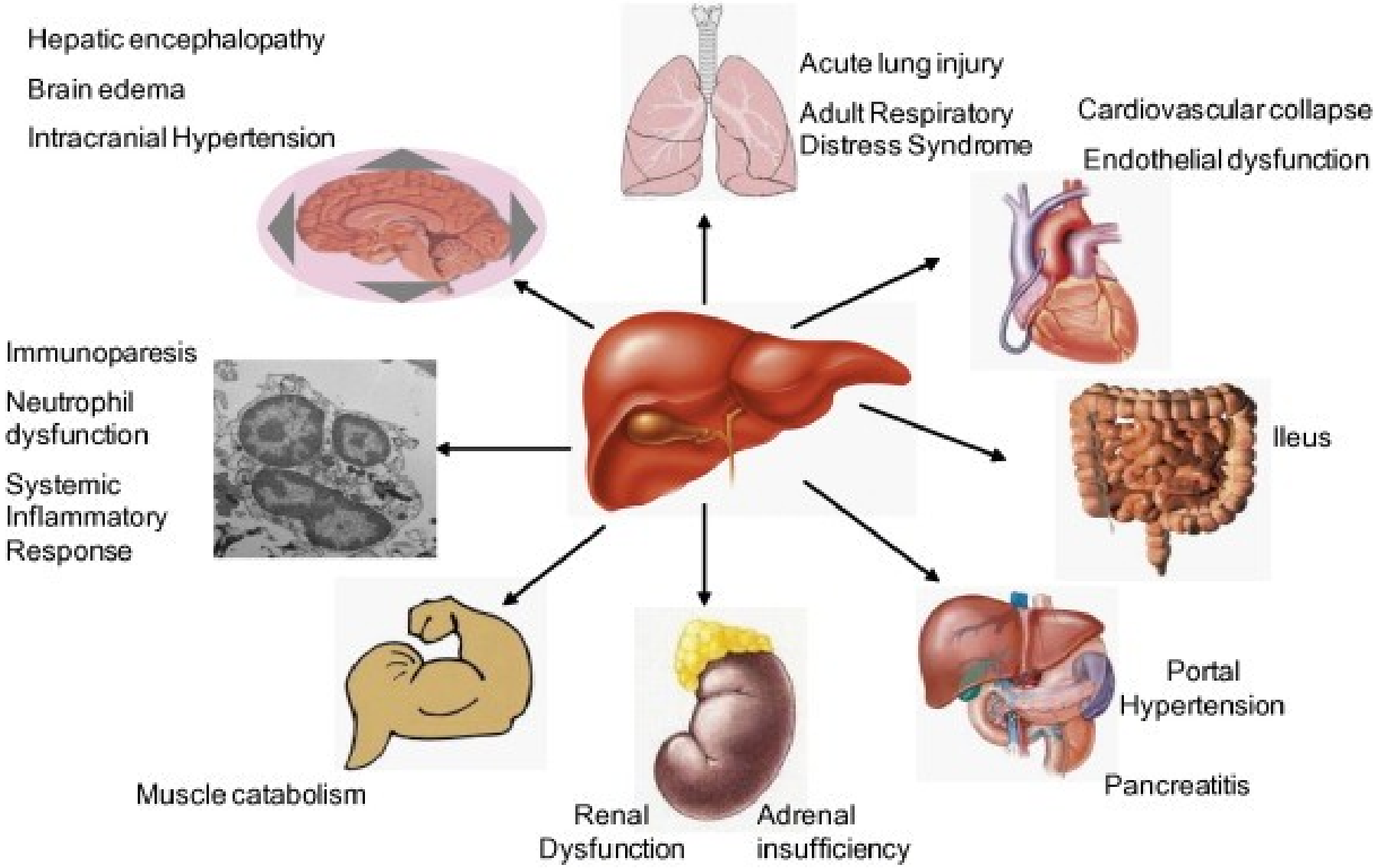
- G $_{2a/3b}$ receptor function
- fibrin polymerization trouble

- vonW syndr.
- factor dilution
- VIII ⇓,

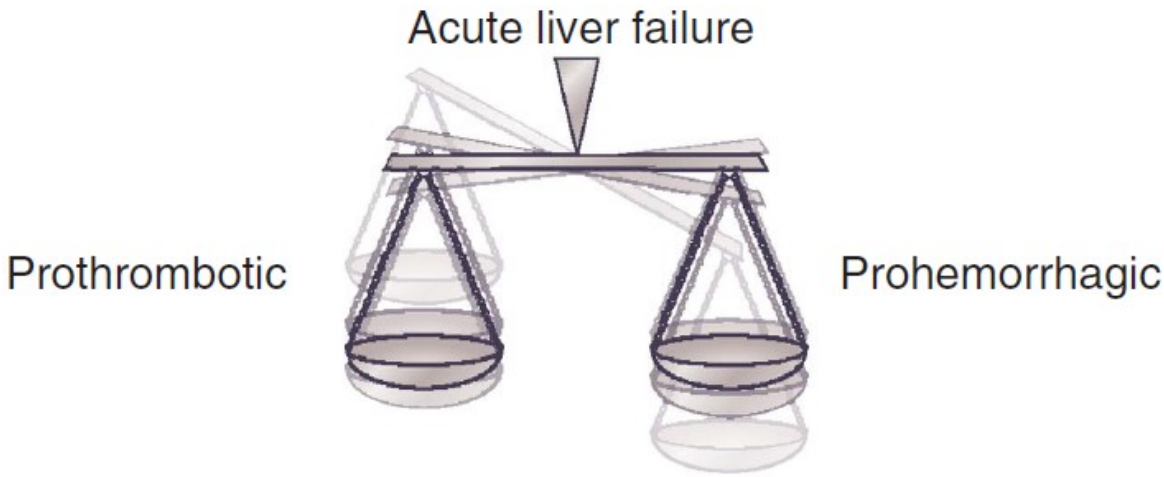


adapted from Görlinger

Systemic Manifestations of Acute Liver Failure



Paradoxical and balanced coagulation state in patients with ALF

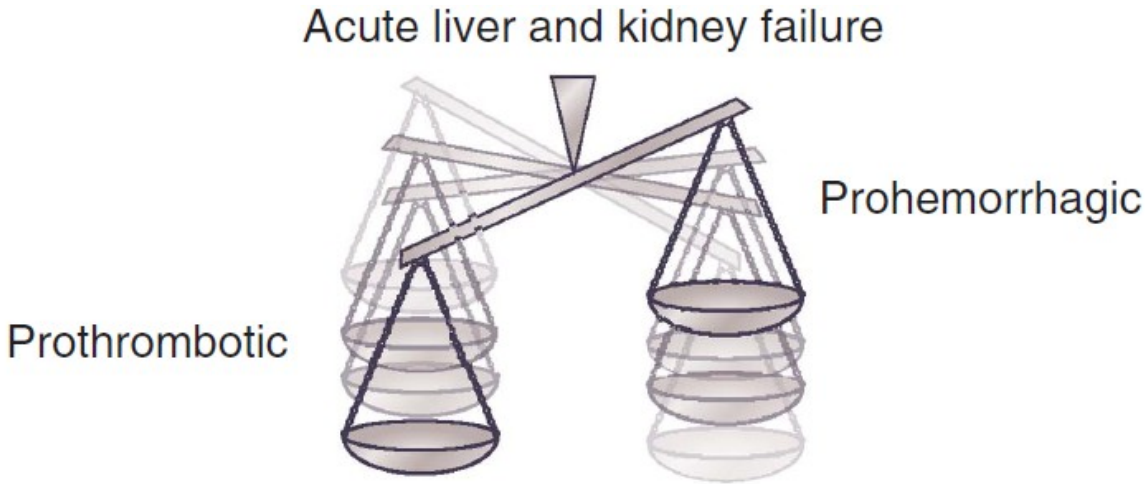


- ↑ Levels of VW F
- ↑ Levels of FVIII
- ↓↓ Levels of natural anticoagulants
- ↓ Levels of plasminogen

- ↓↓ Levels of coagulation factors
- ↑↑ Production of NO, prostacyclin
- ↓ Platelet count
- Dysfibrinogenemia

Kidney International (2013) **84,** 22–24. doi:10.1038/ki.2013.121

Para Hemostasis in acute liver and kidney failure: nothing is as it seems te in

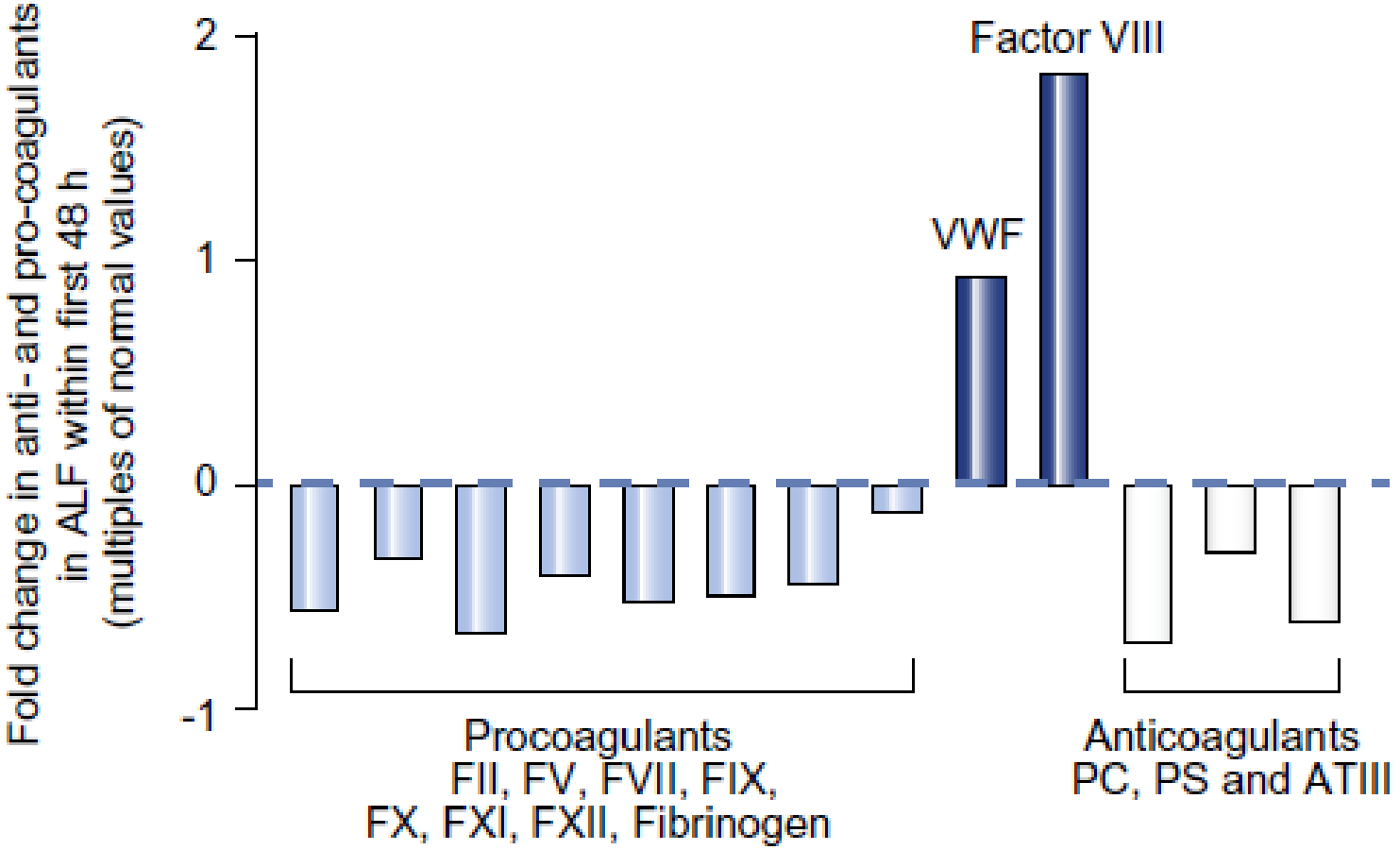


- ↑ Levels of FVIII
- ↓↓ Levels of natural anticoagulants
- ↓ Levels of plasminogen
- ↑↑ Levels of VWF
- ↑ Levels of tissue factor
- ↑ Level of microparticle activity
- ↑↑ Thrombin generation

- ↓↓ Levels of coagulation factors
- ↑↑ Production of NO, prostacyclin
- ↓ Platelet count
- Dysfibrinogenemia
- Platelet dysfunction

Kidney International (2013) **84,** 22–24. doi:10.1038/ki.2013.121

Reduced procoagulants and anticoagulants at admission to ICU with ALF



Journal of Hepatology 2012 vol. 57 j 780–786

Relative changes in thrombin generation parameters of ALF patients compared to healthy controls at admission

	Median + IQR	
TG parameters	Healthy controls	ALF patients
ETP (nM.min)	1602 (1289-1891)	932 (608-1211)***
ETP + P (nM.min)	488 (300-572)	724 (461-996)**
ETP%	29 (22-36)	84 (65-97)***
Lag-time (sec)	2.5 (2.3-2.8)	3.4 (2.8-4.2)**
Time-to-peak (min)	5.8 (5.2-6.1)	4.6 (4.0-5.7)*
Peak height (nM)	278 (221-319)	132 (98-198)***
Slope (velocity index) nM.min	91 (69-110)	122 (39-195)*
Microparticles (PPL assay) sec	68 (55-73)	56 (45-70)*
Microparticles (activity assay) nM	4.0 (3.2-5.3)	16 (11-26)***

ALF: no correlation between PT/PTR and thrombin generation

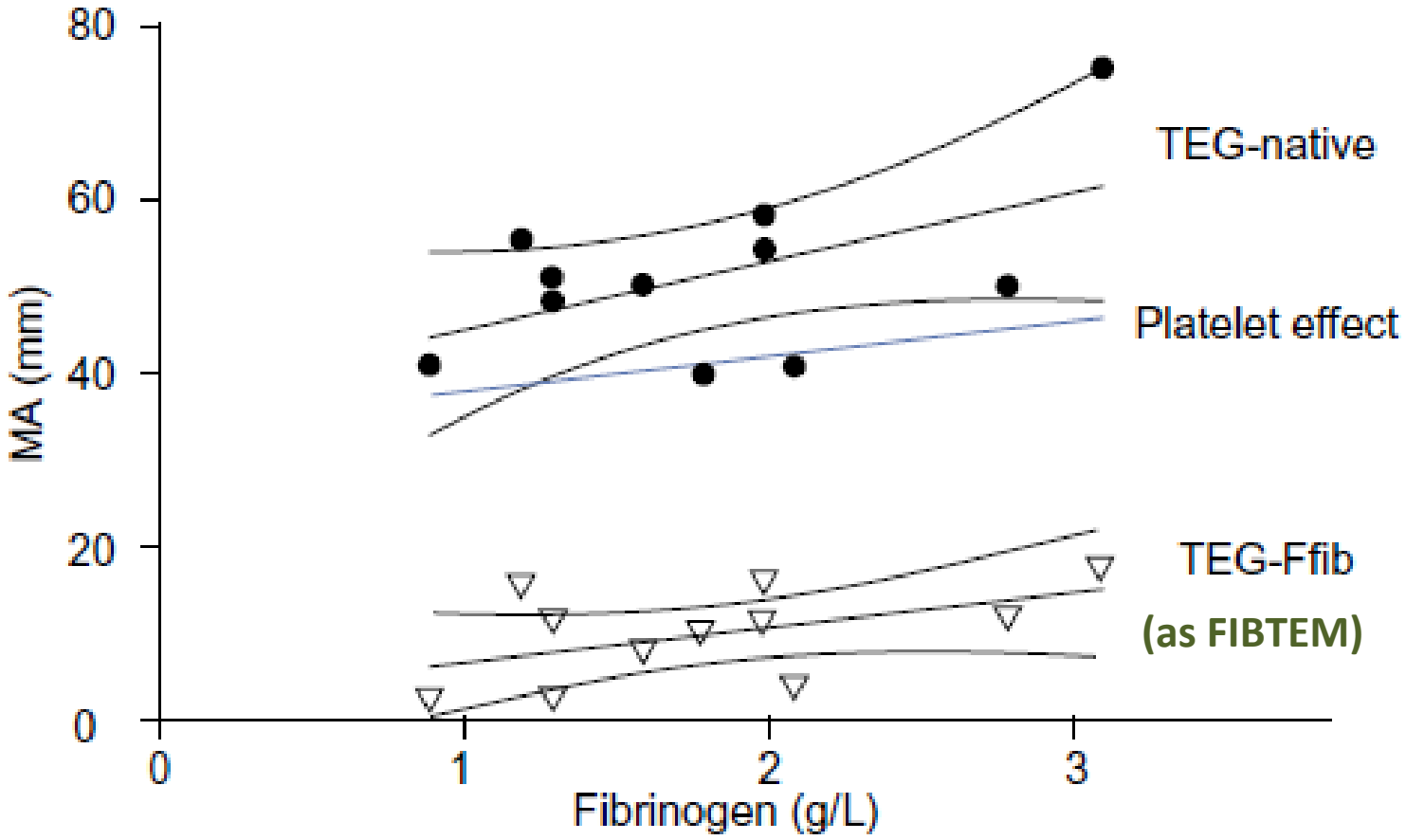
1.endogenous thrombin potential lower (total amount and peak as well)

2.relative protein C deficiency in ALF patients, in the presence of Protac ETP

3.ALF pts generated thrombin faster

Journal of Hepatology 2012 vol. 57 j 780–786

Correlation between fibrinogen and TEG native versus functional fibrinogen



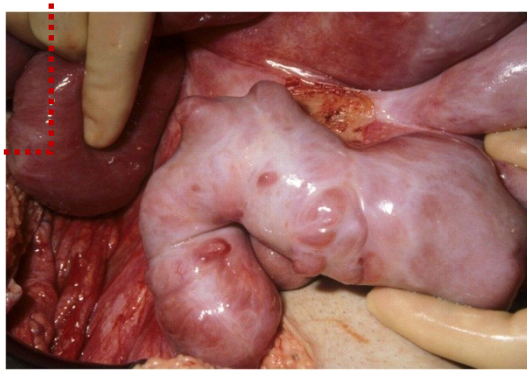
Journal of Hepatology 2012 vol. 57 j 780–786

Urémiás beteg

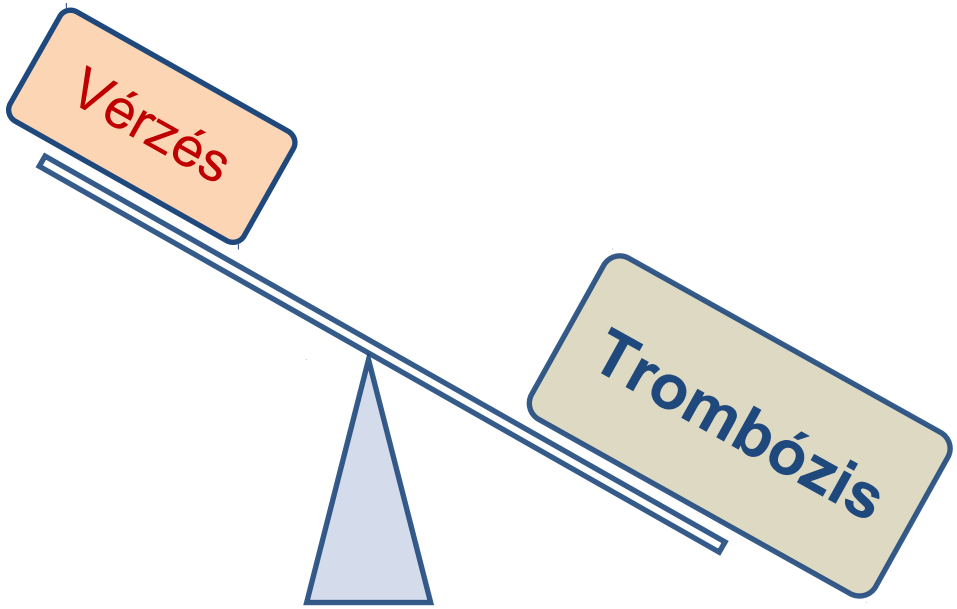
- HD, CAPD, urémia (preHD vagy 2 HD között)
  - Na-heparin, LMWH, citrát, kumarin

Hemostasis in chronic renal failure

	HD	CAPD
Fibrinogen	↑	↑↑
F II activity	↓	↑
F VII activity	↑	↑
FVIII activity	↓	↑
F IX activity	↓	↑
F X activity	↓	↑
F XII activity	↓	↑
Protein C activity	↓	↔
Protein S activity	↓	↑
antithrombin	↓	↔
vWF	↑	↑
thrombomodulin	↑	↑
TF	↑	↑
TFPI	↑	↑
F1+2	↑	↑
TAT	↑	↑
PAP	↑	↑
t-PA	↑	↓
PAI-1	↓	↑
TAFI	↔	↑



Urémiás beteg



- HD, CAPD, urémia (preHD vagy 2 HD között)
  - Na-heparin, LMWH, citrát, kumarin

Venous Thromboembolism in Patients with Renal Insufficiency: Findings from the RIETE Registry

10,526 patients

Table 3 Multivariate Analysis on the Risk of Developing Fatal Pulmonary Embolism

Variables	Odds Ratio (95% CI)	*P* Value
Symptomatic PE	17 (8.8-34)	<.001
Renal function		<.001
CrCL > 60 mL/min	Reference	-
CrCl 30-60 mL/min	2.0 (1.2-3.4)	.008
CrCl < 30 mL/min	5.2 (3.4-7.8)	<.001
Immobility ≥ 4 d	2.4 (1.7-3.4)	<.001
Cancer	2.0 (1.4-2.9)	<.001
Initial therapy, UFH	1.9 (1.2-3.0)	<.001
Inpatients	1.5 (1.0-2.1)	.027

PE = pulmonary embolism; CrCl = creatinine clearance; UFH = unfractionated heparin; CI = confidence interval.

Table 5 Multivariate Analysis on the Risk of Developing Fatal Bleeding

Variables	Odds Ratio (95% CI)	*P* Value
Immobility ≥ 4 d	3.3 (1.5-7.3)	.003
Cancer	2.7 (1.2-6.0)	.015
Renal function,	-	.002
CrCL > 60 mL/min	Reference	-
CrCl 30-60 mL/min	1.4 (0.3-5.9)	.677
CrCl < 30 mL/min	5.0 (2.0-12)	<.001

CrCl = creatinine clearance; CI = confidence interval.

CONCLUSIONS: Patients with VTE who have renal insufficiency had an increased incidence of both fatal PE and fatal bleeding, but the risk of fatal PE far exceeded that of fatal bleeding. Our data support the use of full-dose anticoagulant therapy, even in patients with a CrCl less than 30 mL/min. © 2006 Elsevier Inc. All rights reserved.

The American Journal of Medicine (2006) 119, 1073-1079

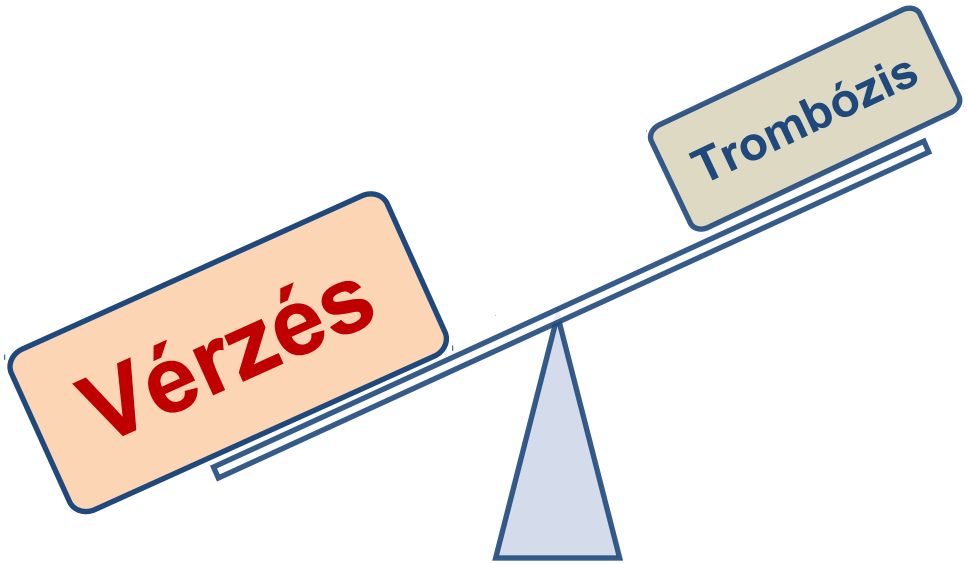
Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function

Table 2 Markers of the Tissue Factor Pathway, Natural Inhibitors and Thrombin Generation in Healthy Controls and Patients

	HC	CKD	Dialysis	*P*-Value
TF (pg/mL)	101 ± 114	234 ± 157*	334 ± 79*†	<0.0001
TFPI (U/mL)	1.2 ± 0.4	1.1 ± 0.3	1.5 ± 0.9†	<0.05
FX (%)	148 ± 42	126 ± 33*	144 ± 38	<0.05
FVIIc (%)	113 ± 11	133 ± 30*	128 ± 21*	0.001
F_{1+2} (nmol/L)	1.3 (1.0–1.5)	1.8 (1–3)	1.9 (1.6–3.3)*	<0.05
TAT(μg/L)	3.0 (2.1–4.2)	3.2 (1.7–7.9)	3.5 (1.5–8.7)	0.64
PC (%)	93 ± 12	98 ± 25	104 ± 27	0.15
PSt (%)	98 ± 19	109 ± 27	122 ± 35*	0.006
PSf (%)	100 ± 29	95 ± 30	108 ± 40	0.3
PSf/PSt	1.0 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.03
ATIII (%)	110 ± 31	91 ± 27*	85 ± 35*	0.007

Thrombosis Research (2008) **123**, 374–380

Urémiás beteg



- HD, CAPD, urémia (preHD vagy 2 HD között)
  - Na-heparin, LMWH, citrát, kumarin

Uremic Bleeding: Pathophysiology, Diagnosis, and Management

Table 1. Clinical Presentations of Uremic Bleeding*

Petechiae, purpura, ecchymoses
Epistaxis
Bleeding after invasive procedures (eg, surgery, catheter placement, biopsy)
Hemorrhagic pericarditis (eg, pericardial tamponade)
Hemorrhagic pleural effusion
Gastrointestinal hemorrhage
Intracranial bleeding (eg, from a subdural hematoma or subarachnoid hemorrhage)
Retroperitoneal bleeding (spontaneous or occurring after invasive radiology)
Spontaneous subcapsular hematoma of the liver
Ocular hemorrhage
Uterine hemorrhage

*Arranged in approximate order of frequency.

Table 2. Factors Involved in the Uremic Bleeding Tendency

Factors related to the vessel wall
Decreased production of the largest multimers of von Willebrand's factor
Enhanced nitric oxide production
Enhanced prostacyclin production
Factors related to platelets
Abnormal mobilization of calcium ions in platelets
Defective activation of glycoprotein IIb-IIIa receptors
Defective cyclooxygenase activity (reduced ability to generate thromboxane A_2)
High levels of cyclic adenosine monophosphate
Low levels of serotonin and adenosine diphosphate
Factors related to the blood
Anemia
Altered blood rheology (ie, deranged radial transport of platelets)
Altered transfer of adenosine diphosphate from erythrocytes to platelets
Uremic toxins (eg, guanidinosuccinic acid, phenol, phenolic acid, urea)

Uremic Bleeding: Pathophysiology, Diagnosis, and Management

Therapies for uremic bleeding

- **HD-CAPD**
  - Toxin removal → Platelet function improve
- **Anemia correction: RBC or rhEPO**
  - Static plasma and Platelets
- **DDAVP**
  - 0.3 μg/kg → vWF release↑ for 4-8 hours
- **Conjugated estrogen**
  - GI bleeding, Intracranial bleeding
  - 25 mg per oral → normal BT 3-10 days
- **Platelet transfusion**
- **TXA only in acute setting**

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Coagulopathy and renal disease

Point-c…ng time p…ent in ura…his setting…

We sug… be used in uraemia. **2C**

1185 Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; **3**:138–153.

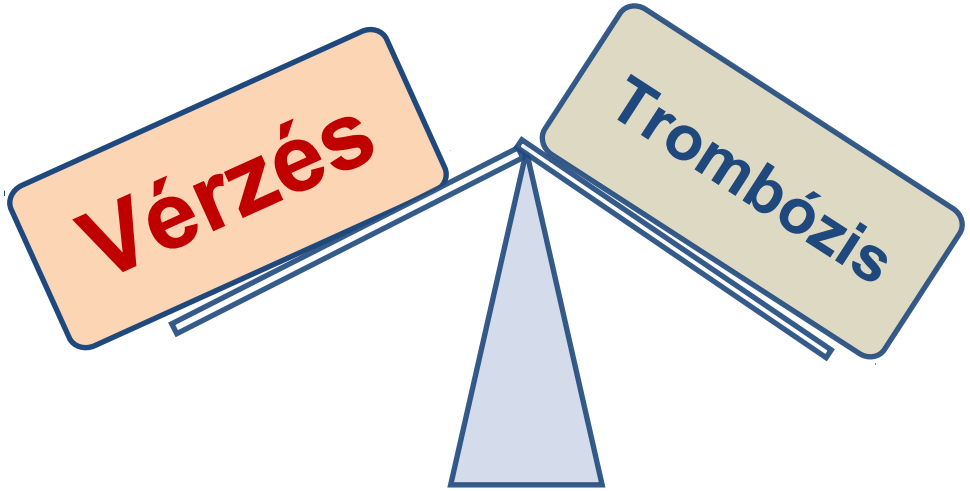
1186 Zupan IP, Sabovic M, Salobir B, Ponikvar JB, Cernelc P. Utility of in vitro closure time test for evaluating platelet-related primary hemostasis in dialysis patients. *Am J Kidney Dis* 2003; **42**:746–751.

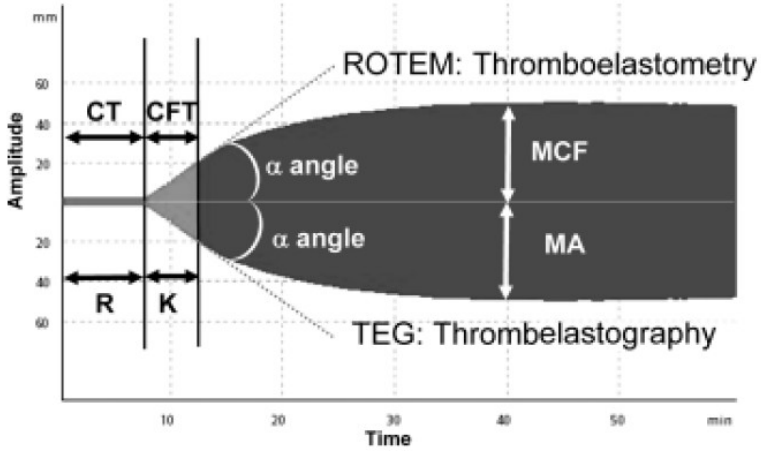
1187 Islam N, Fulop T, Zsom L, *et al.* Do platelet function analyzer-100 testing results correlate with bleeding events after percutaneous renal biopsy? *Clin Nephrol* 2010; **73**:229–237.

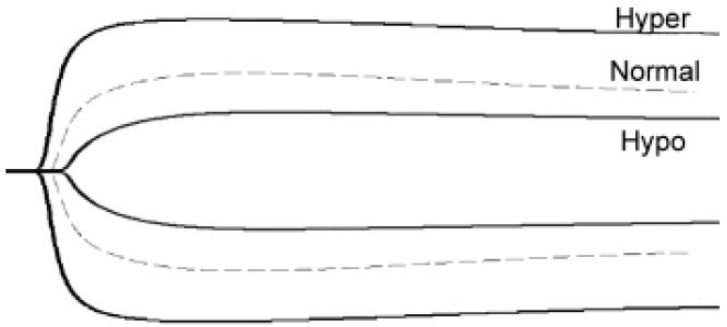
We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. **2C**

There is no evidence to support use of rFVIIa in this setting.

Amikor POC eszköz nélkül nem megy…







„ne csak a számokat kezeljük”

dr. Fazakas J.