Laboratory diagnosis and interpretation of coagulation disorders

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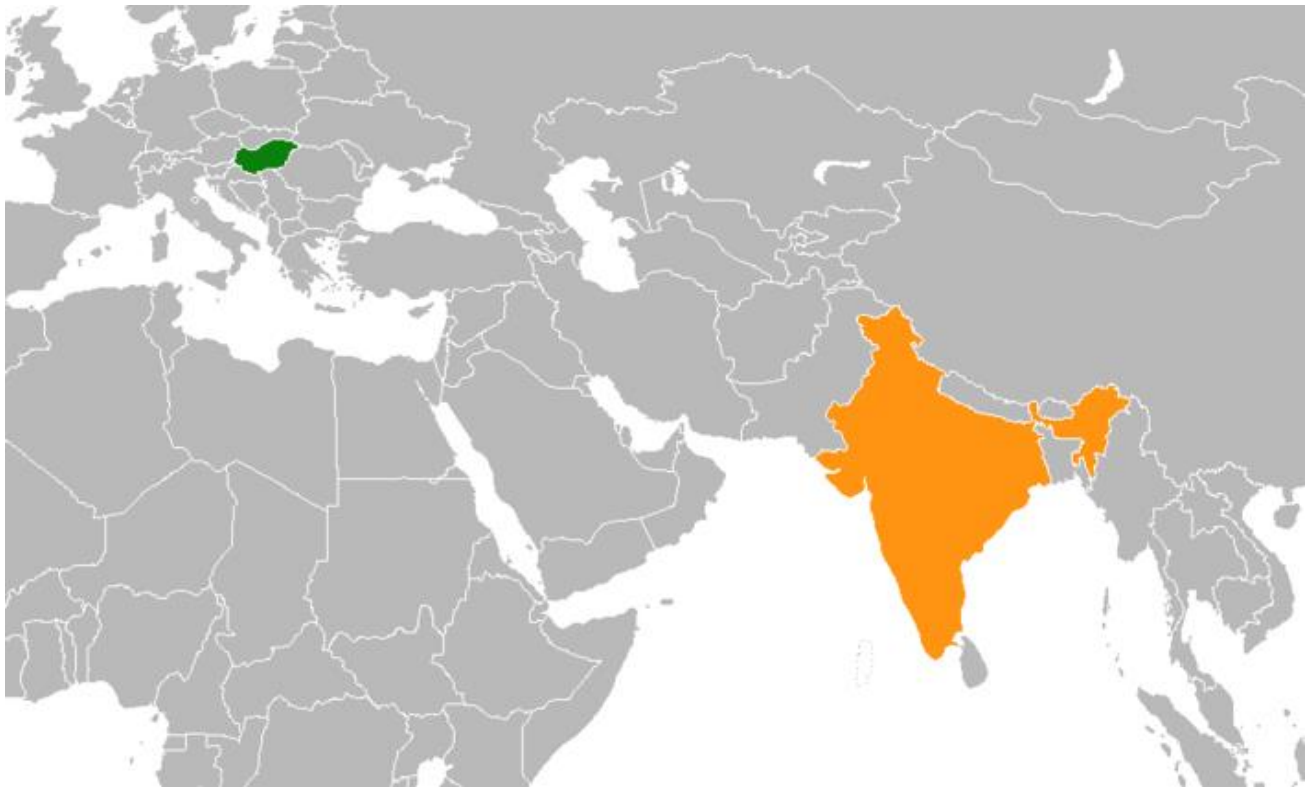
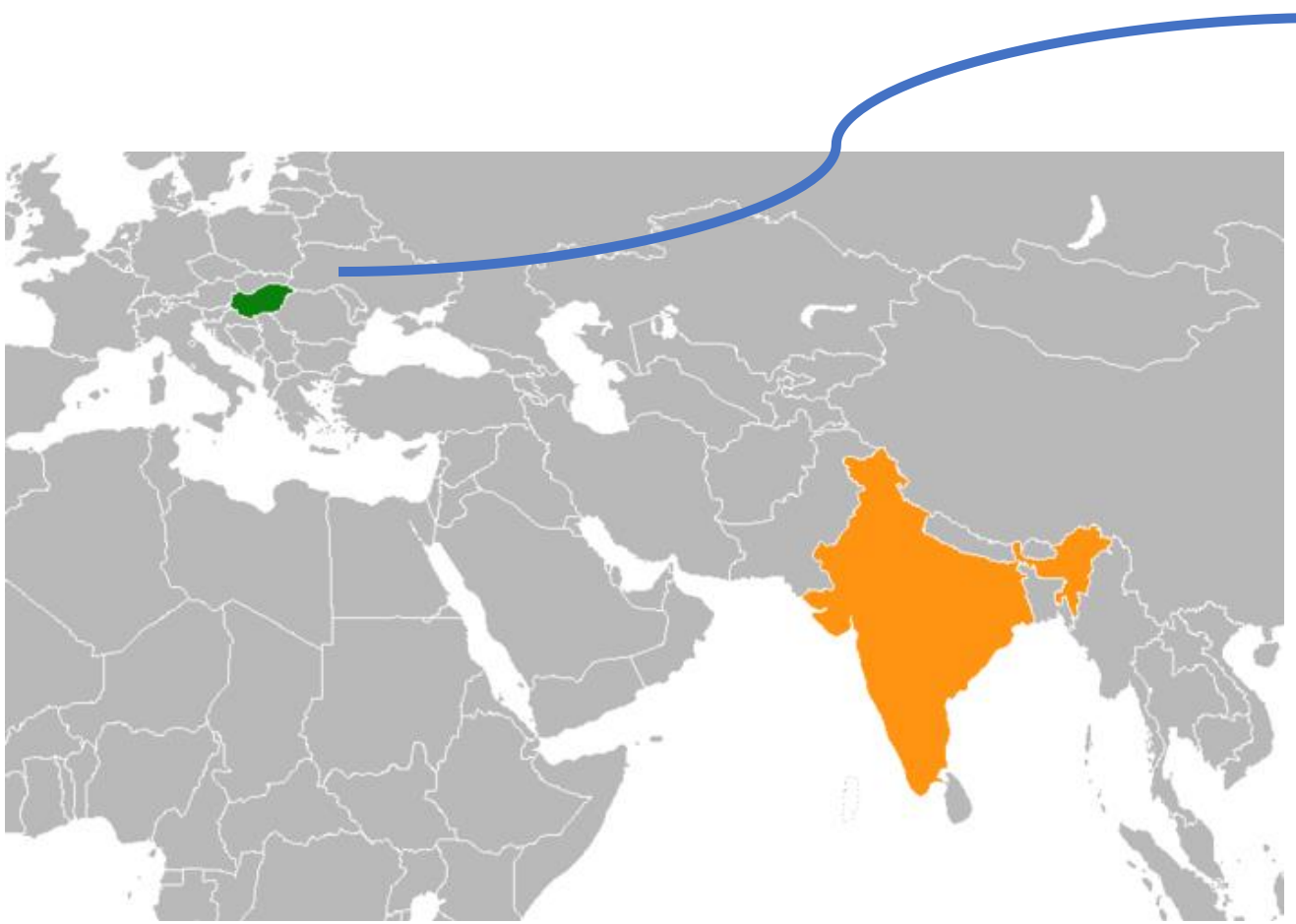
Challenges in Hematology, EHA-2022 Hyb
Under the aegis of the Mumbai Hematolo



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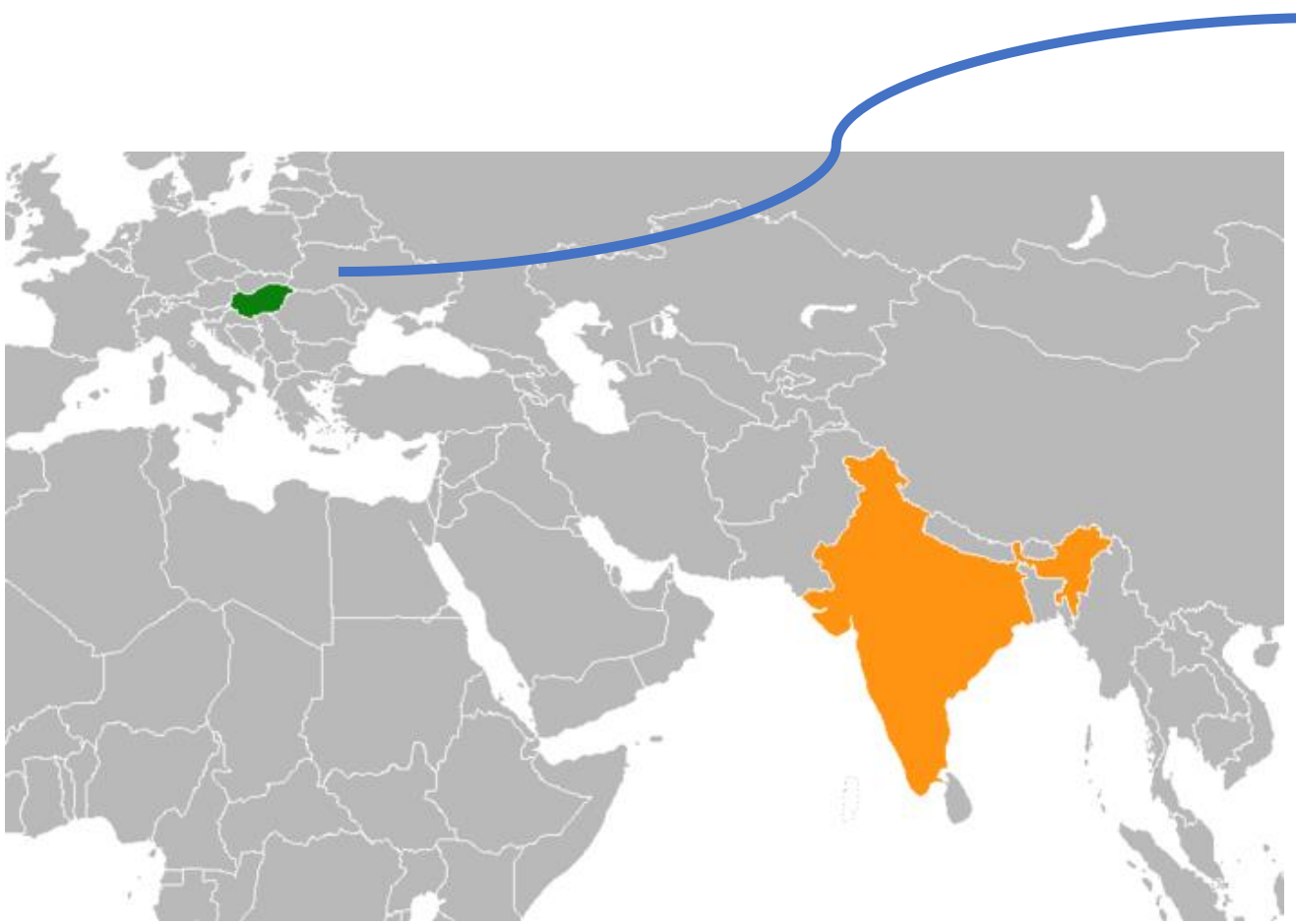


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Is interpretation needed for general laboratory results?

Usually no !

Is interpretation needed for general laboratory results?

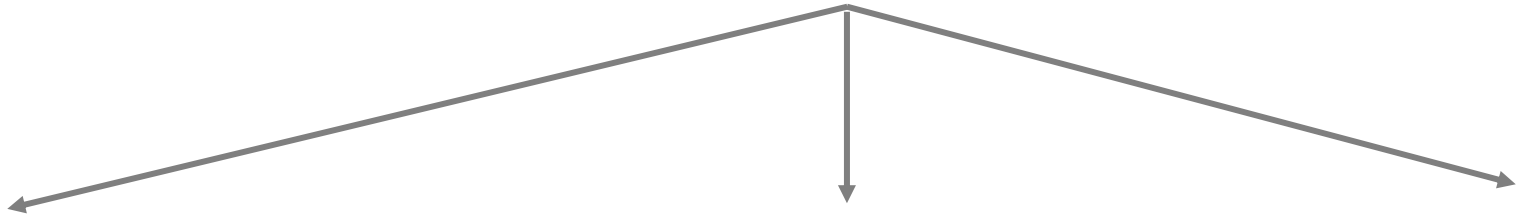
Usually no !

Is interpretation needed for laboratory results sent for evaluating coagulation disorders?

Yes, nearly always !

Interpretation issues:

Is the patient treated with ant



No

Yes

May be/No

Critically ill pat

Interpretation of test results involved in the exploration of the bleeding tendency

Clotting assays:

PT, APTT, fibrinogen

Mixing studies

Thrombin time

Reptilase time

Thrombin generation assays:

Plasma TGA

PRP TGA

Whole blood assays:

Platelet Function Analyzer

(PFA-100, PFA-200)

Rotem assay

ClotPro assay

Interpretation of test results involved in the exploration of the bleeding tendency

Clotting assays:

PT, APTT, fibrinogen

Mixing studies

Thrombin time

Reptilase time

Thrombin generation assays:

Plasma TGA

PRP TGA

Whole blood assays:

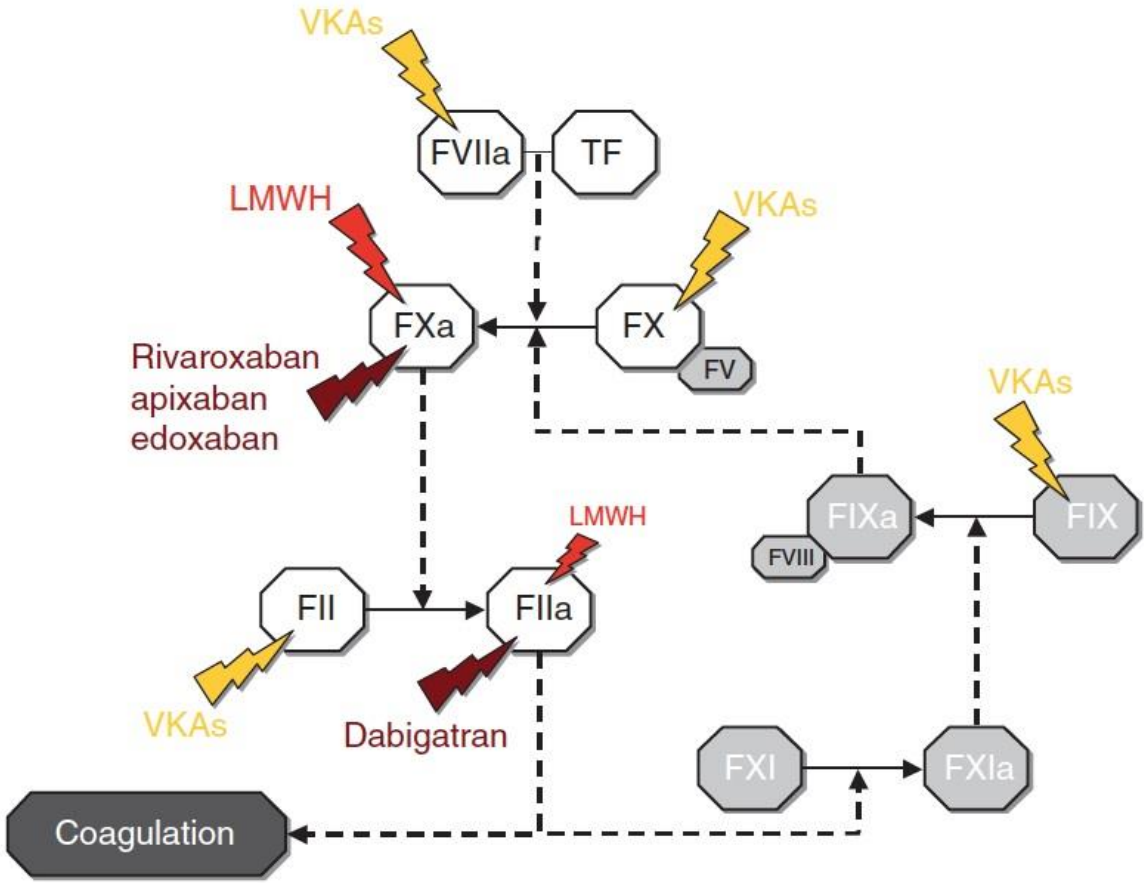
Platelet Function Analyzer

(PFA-100, PFA-200)

Rotem assay

ClotPro assay

How various anticoagulants exert their effect?



G. Lippi, CCLM 2015;53:185-197.

Pattern recognition I.

Prothrombin time:	33.1 sec		8.8 sec
INR	3,27	-	
APTT	65.7 sec		28.7 sec
Thrombin time	21.2 sec		18.2 sec

Prothrombin time:	7.9 sec		8.8 sec
INR	0.94	-	
APTT	41.0 sec		28.7 sec
Thrombin time	19.8 sec		18.2 sec

Prothrombin time:	12.6 sec		8.8 sec
INR	1.43	-	
APTT	40.8 sec		28.7 sec
Thrombin time	19.4 sec		18.2 sec

Pattern recognition I.

Prothrombin time:	33.1 sec		8.8 sec
INR	3,27	-	VKA
APTT	65.7 sec		28.7 sec
Thrombin time	21.2 sec		18.2 sec

Prothrombin time:	7.9 sec		8.8 sec
INR	0.94	-	LMWH
APTT	41.0 sec		28.7 sec
Thrombin time	19.8 sec		18.2 sec

Prothrombin time:	12.6 sec		8.8 sec
INR	1.43	-	
APTT	40.8 sec		28.7 sec
Thrombin time	19.4 sec		18.2 sec

Rivaroxaban

Pattern recognition II.

Prothrombin time:	9.0 sec		8.8 sec
INR	1.06	-	
APTT	61.0 sec		28.7 sec
Thrombin time	>100 sec		18.2 sec
TT with polybrene (20 mg/L)	18.9		

Prothrombin time:	21.5 sec		8.8 sec
INR	2.29	-	
APTT	> 200 sec		28.7 sec
Thrombin time	>100 sec		18.2 sec
TT with polybrene (20 mg/L)	>100 sec		
TT with polybrene (100 mg/L)	25.0 sec		

Prothrombin time:	10.6 sec		8.8 sec
INR	1.2	-	
APTT	52.1 sec		28.7 sec
Thrombin time	>100 sec		18.2 sec
TT with polybrene (20 mg/L)	>100 sec		

Pattern recognition II.

Prothrombin time:	9.0 sec		8.8 sec	
INR	1.06	-		UFH
APTT	61.0 sec		28.7 sec	
Thrombin time	>100 sec		18.2 sec	
TT with polybrene (20 mg/L)	18.9			

Prothrombin time:	21.5 sec		8.8 sec	
INR	2.29	-		Excess UFH
APTT	> 200 sec		28.7 sec	
Thrombin time	>100 sec		18.2 sec	
TT with polybrene (20 mg/L)	>100 sec			
TT with polybrene (100 mg/L)	25.0 sec			

Prothrombin time:	10.6 sec		8.8 sec	
INR	1.2	-		Dabigatran
APTT	52.1 sec		28.7 sec	
Thrombin time	>100 sec		18.2 sec	
TT with polybrene (20 mg/L)	>100 sec			

Vascular Health and Risk Management

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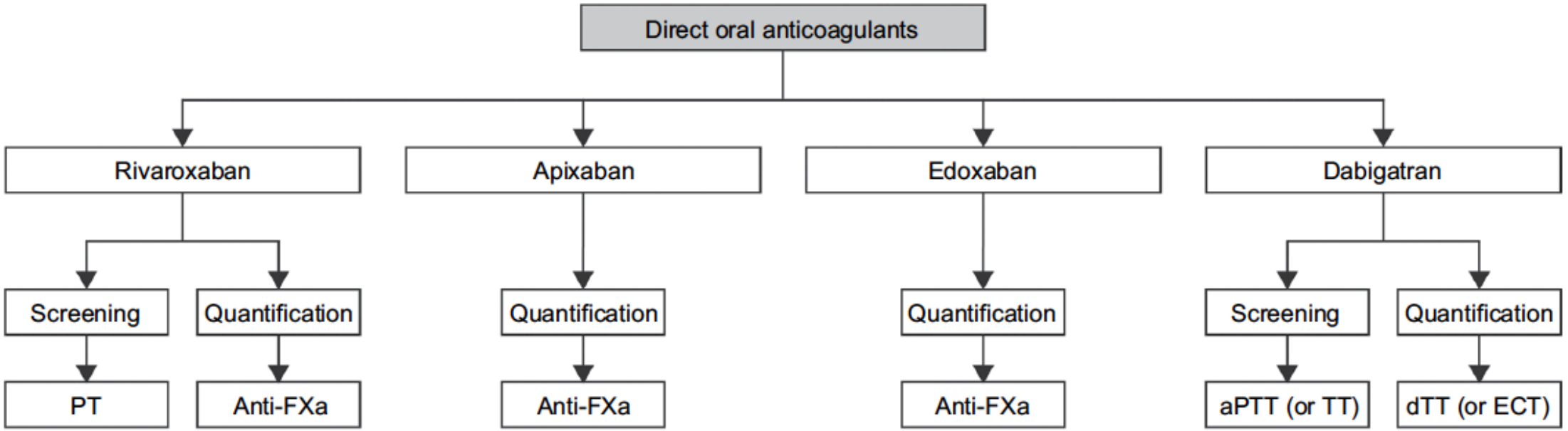
REVIEW

Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants



Ten Cate et al,

Interference of the new oral anticoagulant dabigatran with frequently used coagulation tests

Analyte	Influence of different concentrations of dabigatran in plasma				
	0.0 µg/mL	0.05 µg/mL	0.10 µg/mL	0.24 µg/mL	0.48 µg/mL
PT, %	69.0 (68/74)	63.0 (59/64)	54.0 (52/64)	41.5 (40/42)	28.0 (23/29)
INR, -	1.22 (1.2/1.2)	1.3 (1.3/1.3)	1.44 (1.4/1.5)	1.7 (1.6/1.8)	2.42 (2.4/2.4)
aPTT, s	43.0 (39.1/45.9)	57 (54.8/62.2)	76 (64.8/83.4)	90.2 (89/108)	131.5 (107.5/147.5)
Fib/Clauss <50U IIa, mg/dL	232.0 (217/239)	203.3 (174/218)	205.0 (187/222)	200.9 (158/221)	110.6 (78/121)
AT (IIa), %	94.2 (91/97)	99.4 (97/102)	97.3 (97/98)	113.2 (107/119)	123.3 (118/129)
F II, %	87.0 (82/91.5)	74.1 (72.6/78.1)	68.15 (63.7/73.5)	54 (50.6/58.5)	34.1 (33.1/35)
F V, %	74.8 (72/82)	69.3 (64/70)	72.2 (68/74)	54.8 (52/58)	42.2 (36/44)
F VII, %	80.0 (78/85)	76.0 (74/78)	78.0 (71/78)	63.0 (60/69)	62.0 (52/64)
F X, %	79.6 (75/80)	70.9 (68/75)	69.0 (67/69)	59.0 (58/63)	47.0 (43/55)
F VIII, %	64.45 (59/65.2)	41 (38/43.6)	28.85 (27.5/32.9)	12 (8.3/17)	4.0 (2/5.5)
F IX, %	72.3 (68/77)	47.7 (44/57)	33.8 (30/34)	11.9 (8/15)	5.2 (3/6)
F XI, %	69.0 (66/74)	48.4 (40/50)	29.8 (25/34)	9.4 (8/11)	5.0 (3/5)
F XII, %	91.0 (79/94)	63.0 (57/64)	54.0 (36/58)	31.0 (28/39)	16.7 (14/25)
F XIII Act, %	104 (94/118)	80.2 (79.6/80.6)	68.95 (67.5/81.5)	36 (30/38.3)	15 (15/17.6)
Prot. S clotting, %	66.0 (61/71)	116.0 (92/140)	150.0 (144/156)	250 (242/258)	>250
dRVVT Screen, s	44.4 (44/51)	81.2 (78/90)	99.1 (91/118)	147.0 (140/168)	>180
dRVVT Confirm, s	38.0 (38/38)	57.6 (57/59)	68.5 (67/72)	97.5 (96/99)	140.0 (136/150)
dRVVT Standard ratio	1.2 (1.1/1.2)	1.3 (1.3/1.5)	1.3 (1.3/1.5)	1.5 (1.4/1.6)	>1.5
dRVVT Normalized ratio	1.1 (1.1/1.1)	1.3 (1.2/1.3)	1.3 (1.3/1.4)	1.4 (1.4/1.4)	>1.5

Halbmayer et al, Clin Chem Lab Med, 2012

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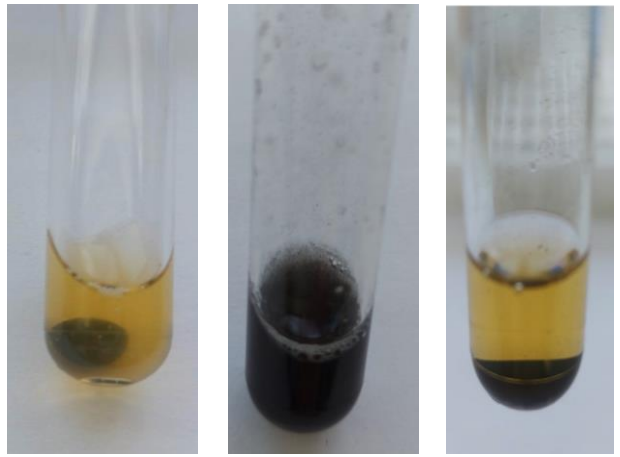
Consider using tl
DOAC stop in suc

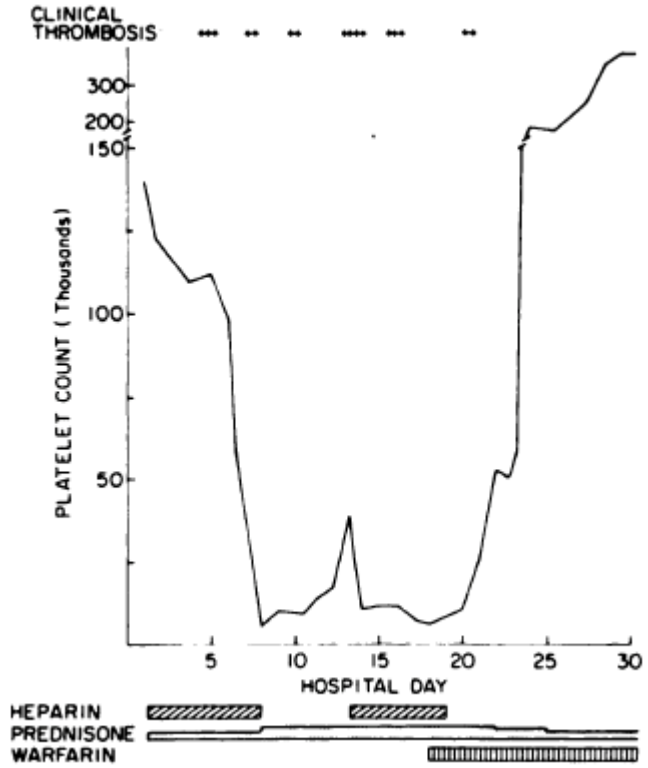


Halbmayer et al, Clin Chem Lab Med, 2012

Heparin as a cause of bleeding or thrombosis

Heparin-induced Thrombocytopenia: Confirmation of Diagnosis With In Vitro Methods

By Joseph C. Fratantoni, Robert Pollet, and Harvey R. Gralnick



Blood 1975, 45: 395-401

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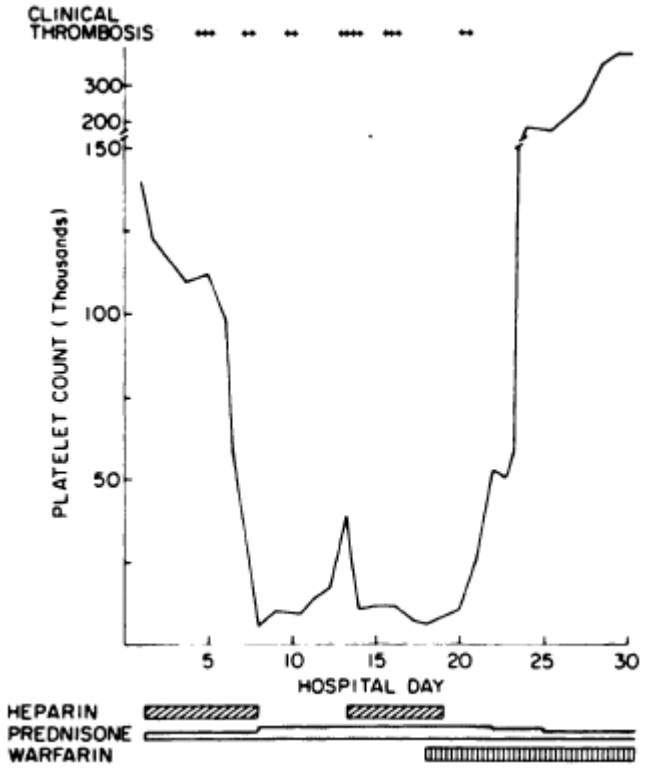

Blood 1975, 45: 395-4

4T score (pretest probability)

	2 points	1 point	0 point
Thrombocytopenia	> 50%	30-50%	< 30%
Time of platelet count decrease	5-10 days	> 10 days	< 5 days
Thrombosis or other related phenomenon	New thrombosis, Skin necrosis, anaphylaxia	Erythema, Repeated thrombosis	No
Thrombocytopenia of other cause	No	Possible	Yes

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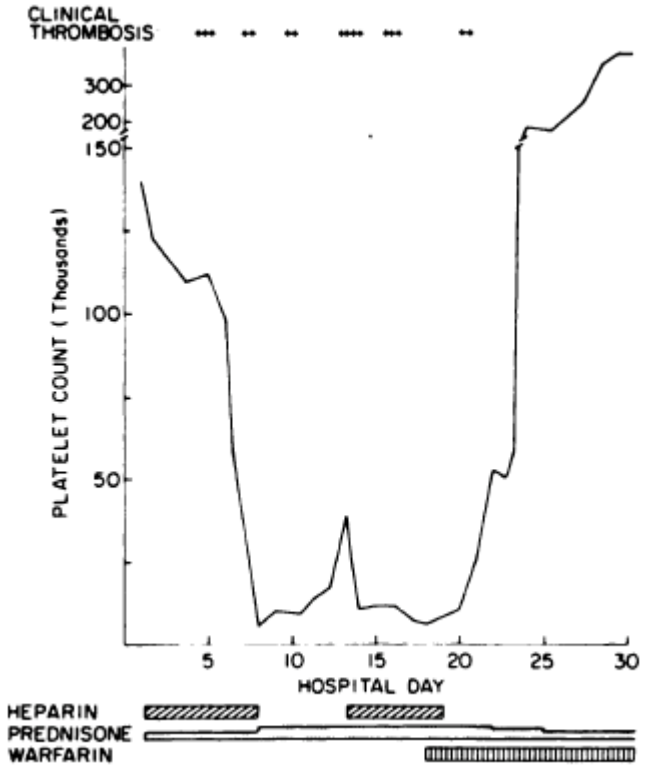

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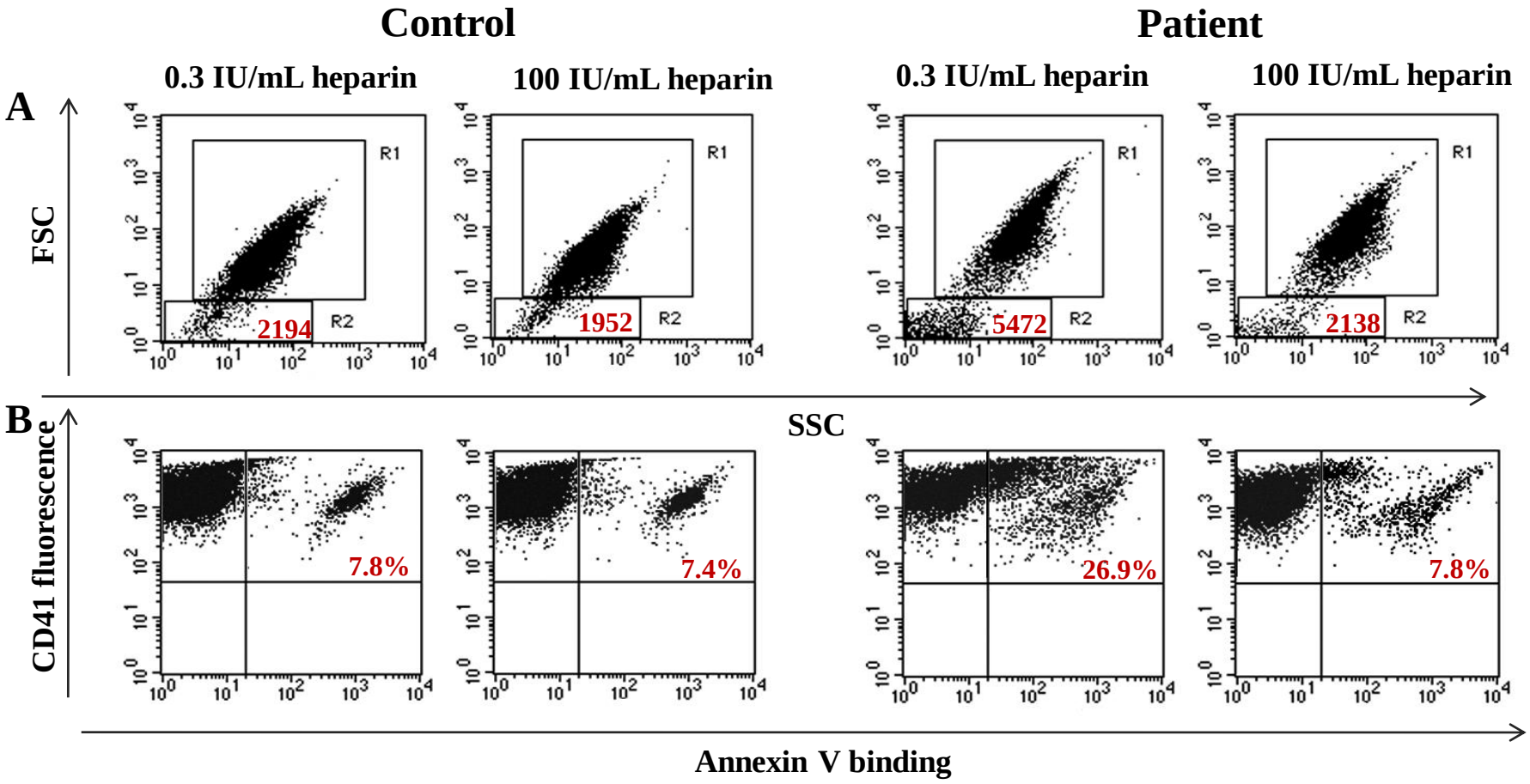
Thrombosis or other related phenomenon	New thrombosis, Skin necrosis, anaphylaxia	Erythema, Repeated thrombosis	No
Thrombocytopenia of other cause	No	Possible	Yes

HIT probability

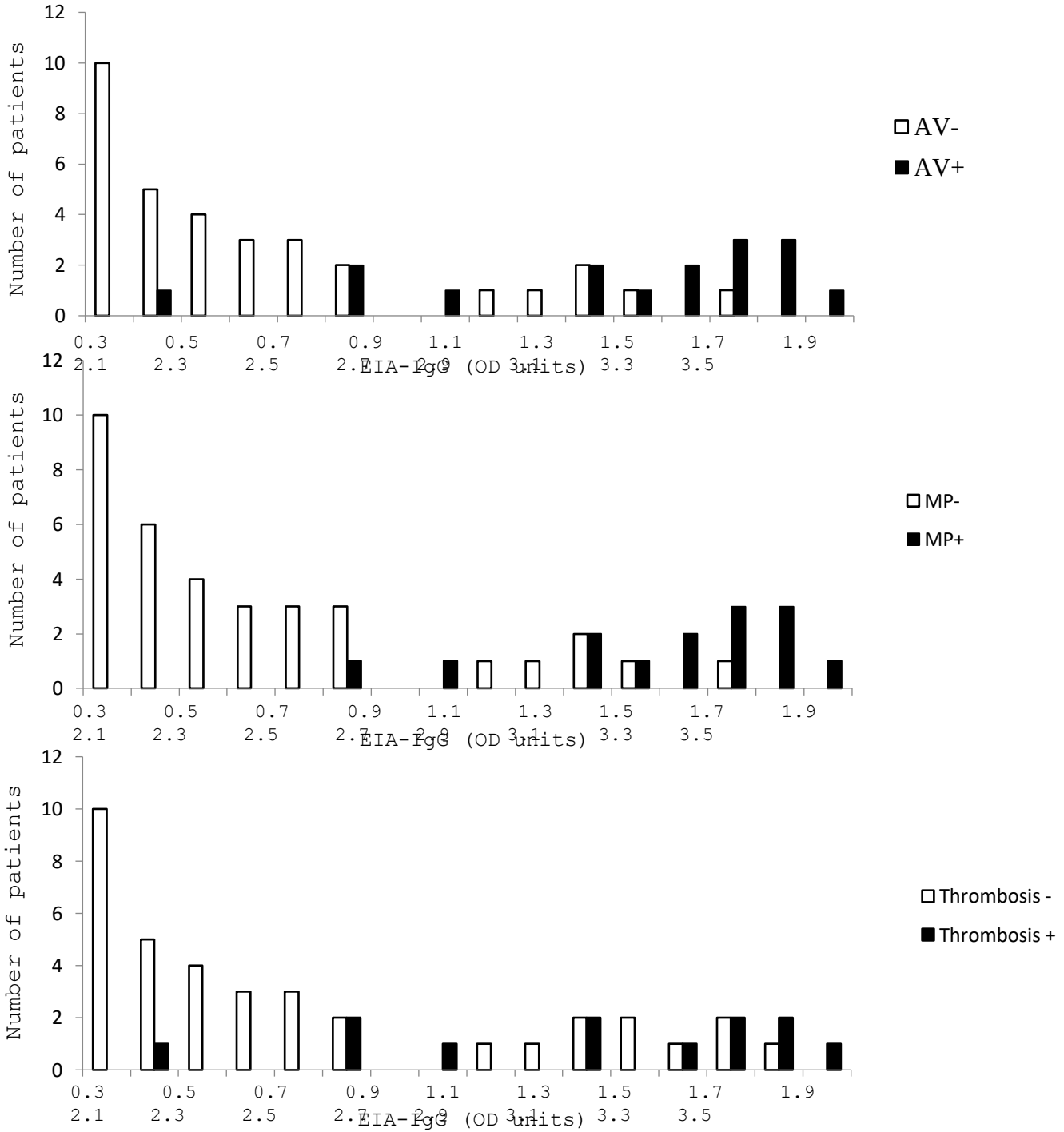
low: 0-3 points
intermediate: 4-5 points

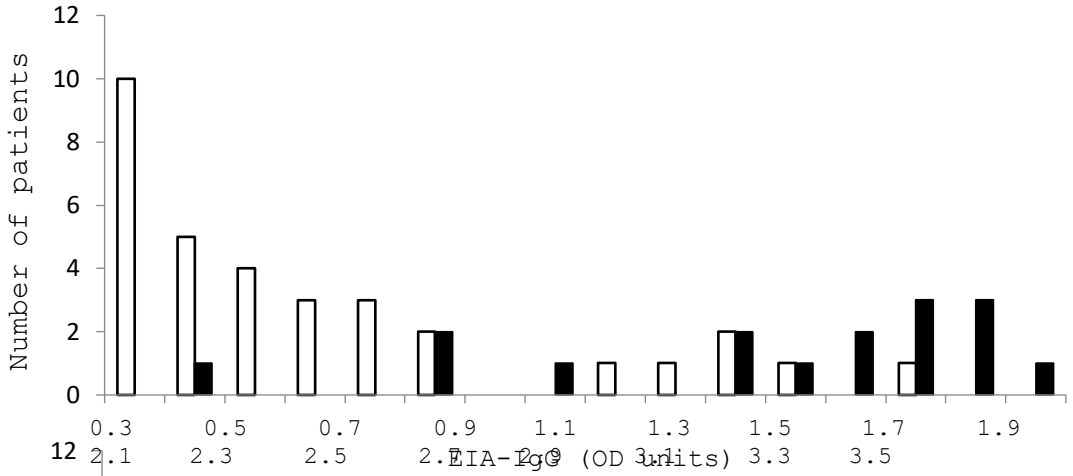
Evaluation of Flow Cytometric HIT Assays in Relation to an IgG-Specific Immunoassay and Clinical Outcome

Adrienne Kerényi,[1] Ildikó Beke Debreceni,[1] Zsolt Oláh,[2] Péter Ilonczai,[2] Zsuzsanna Bereczky,[3] Béla Nagy Jr.,[1] László Muszbek,[3] and János Kappelmayer[1*]

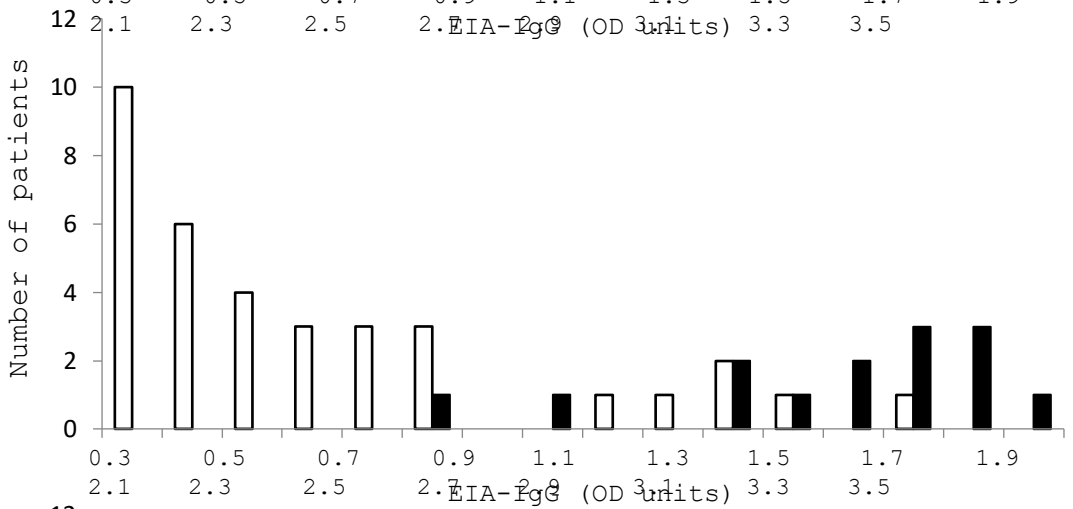


Cytometry Part B (Clinical Cytometry) 92B:390-

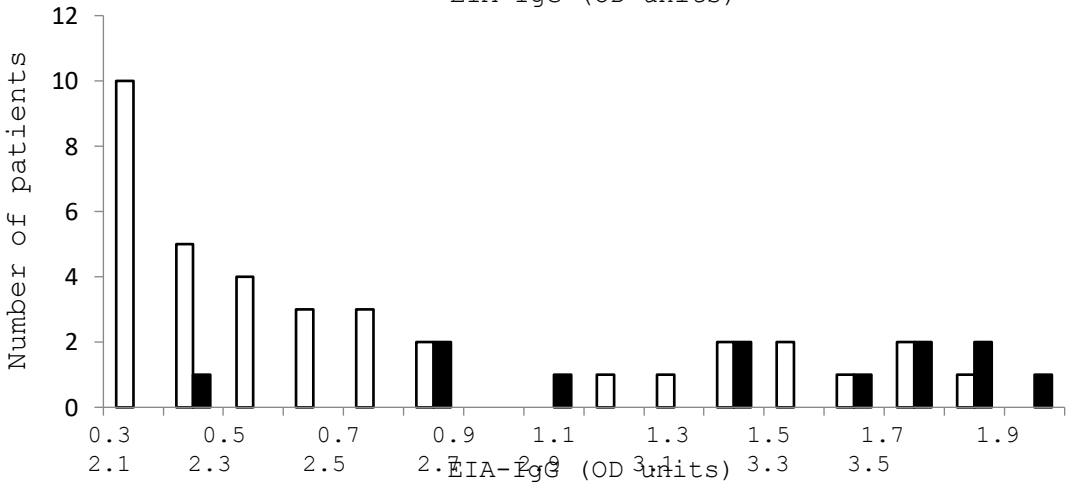

Number of patients
AV-
AV+
EIA-IgG (OD units)
Number of patients
MP-
MP+
EIA-IgG (OD units)
Number of patients
Thrombosis -
Thrombosis +
EIA-IgG (OD units)



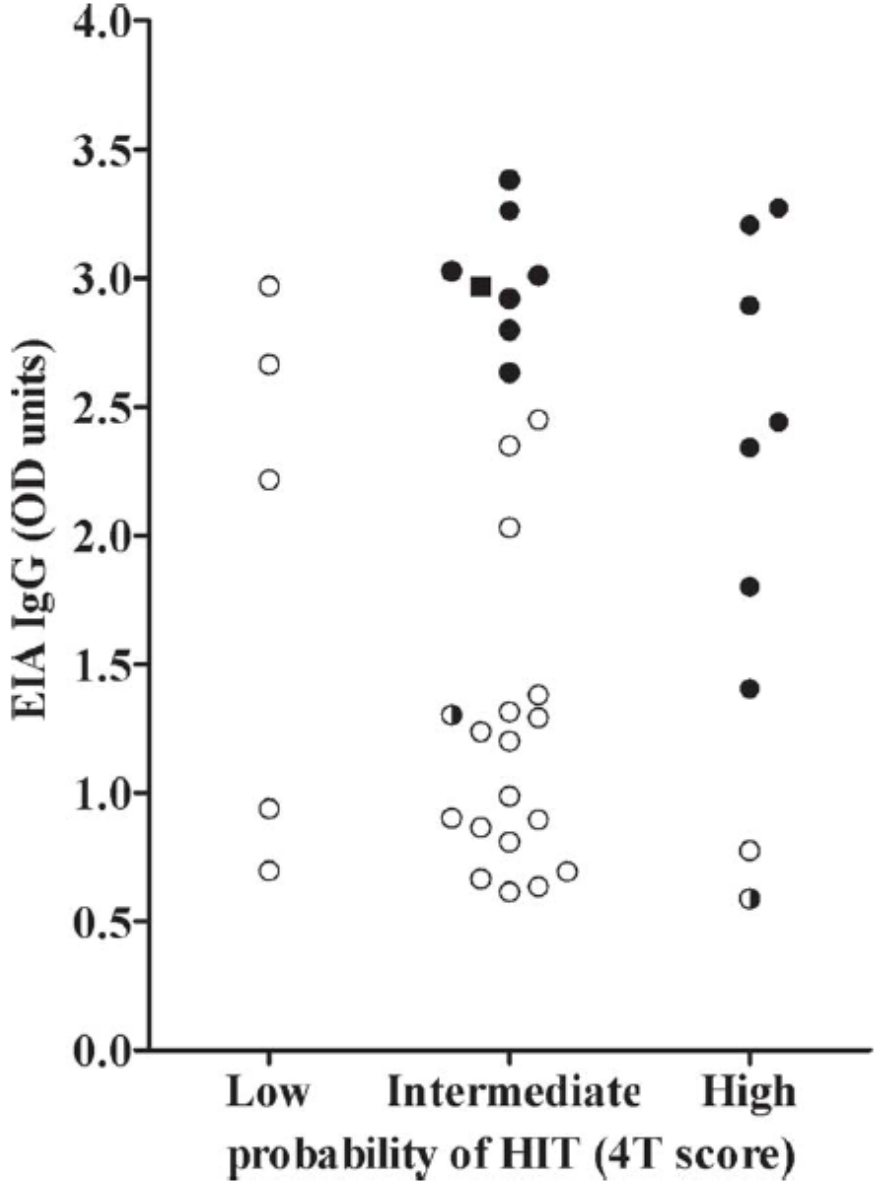
AV-
AV+



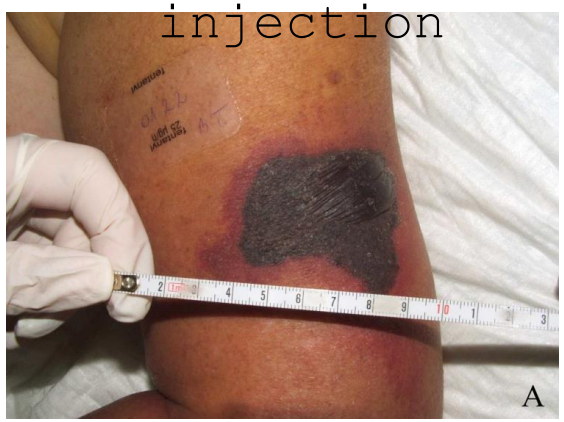
MP-
MP+



Thrombosis -
Thrombosis +



Heparin induced skin necrosis after heparin injection



Oláh et al. Platelets, 2012;23(6):495-498.

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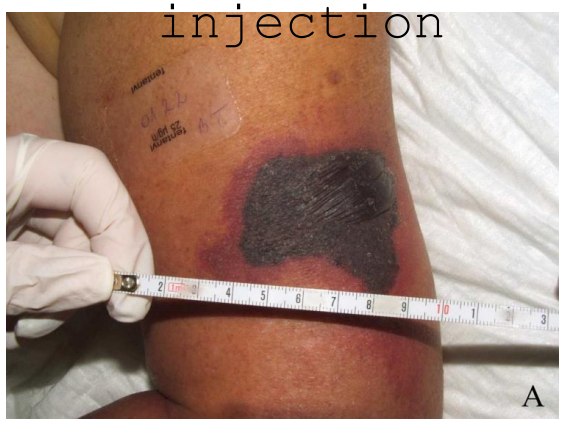
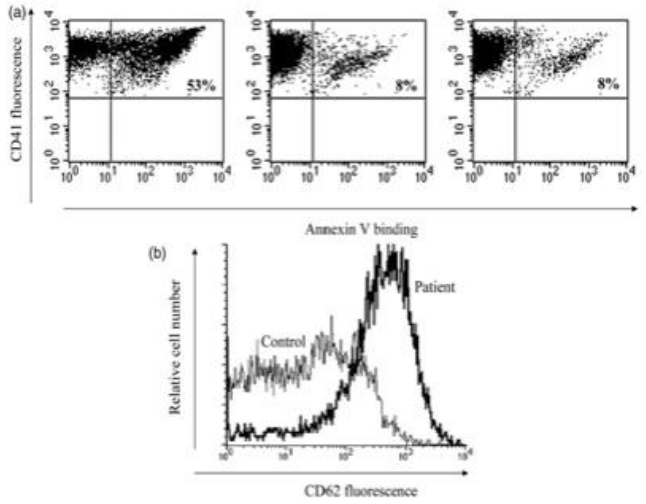
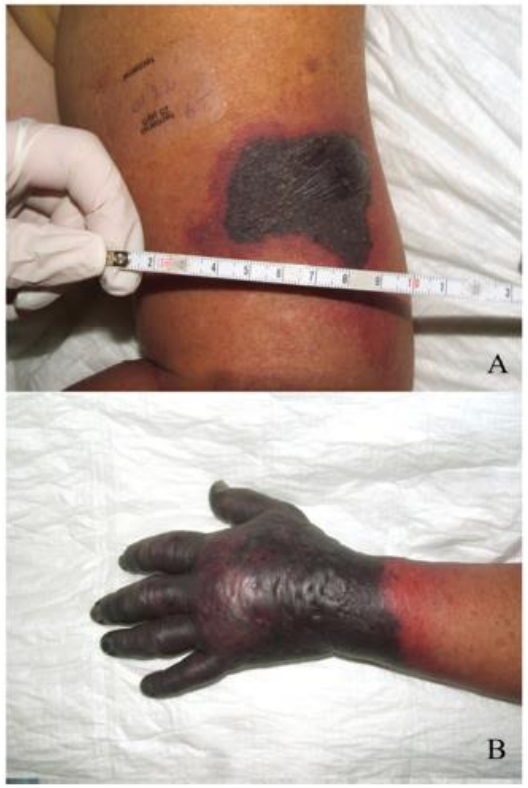


CASE REPORT

Rapid-onset heparin-induced thrombocytopenia without previous heparin exposure

ZSOLT OLAH[1], ADRIENNE KERENYI[2], JANOS KAPPELMAYER[2], AGOTA SCHLAMMADINGER[1], KATALIN RAZSO[1], & ZOLTAN BODA[1]





Oláh et al. Platelets, 2012;23(6):495-498.

Russell et al. Ann. Intensive Care (2017) 7:119
https://doi.org/10.1186/s13613-017-0341-y

Annals of Intensive Care

RESEARCH Open Access

Risks of bleeding and thrombosis in intensive care unit patients with haematological malignancies

Lene Russell[1,2*], Lars Broksø Holst[1], Lars Kjeldsen[3], Jakob Stensballe[4,5] and Anders Perner[1]

Russell et al. Ann. Intensive Care (2017) 7:119
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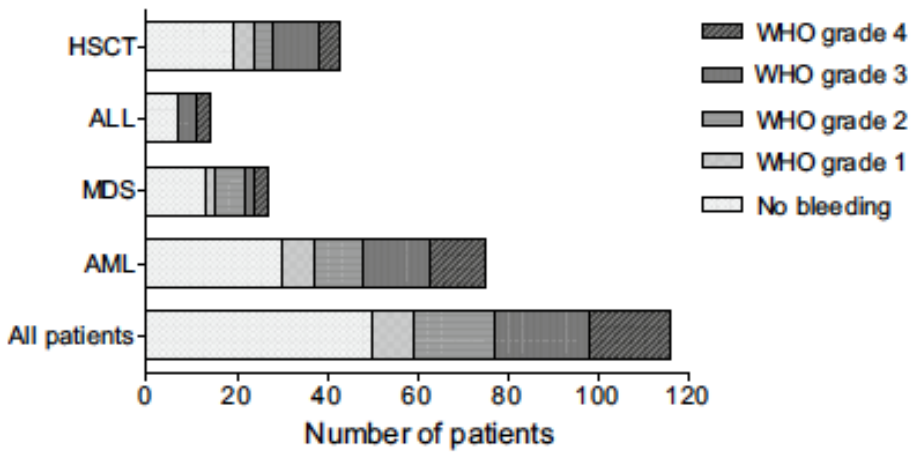

Fig. 1 Bleeding complications during ICU stay. No significant difference was seen in number of bleedings complications between the different diagnoses or in patients with haematopoietic stem cell transplantation (HSCT). *ALL* acute lymphoblastic leukaemia, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukaemia

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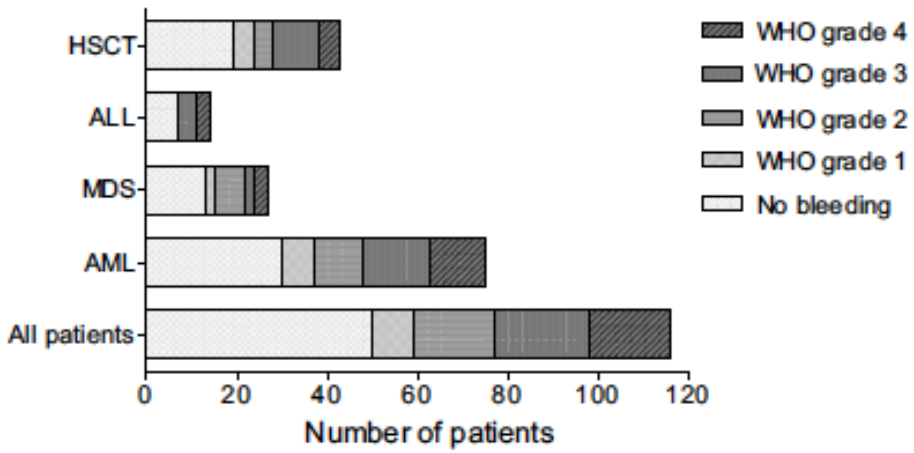
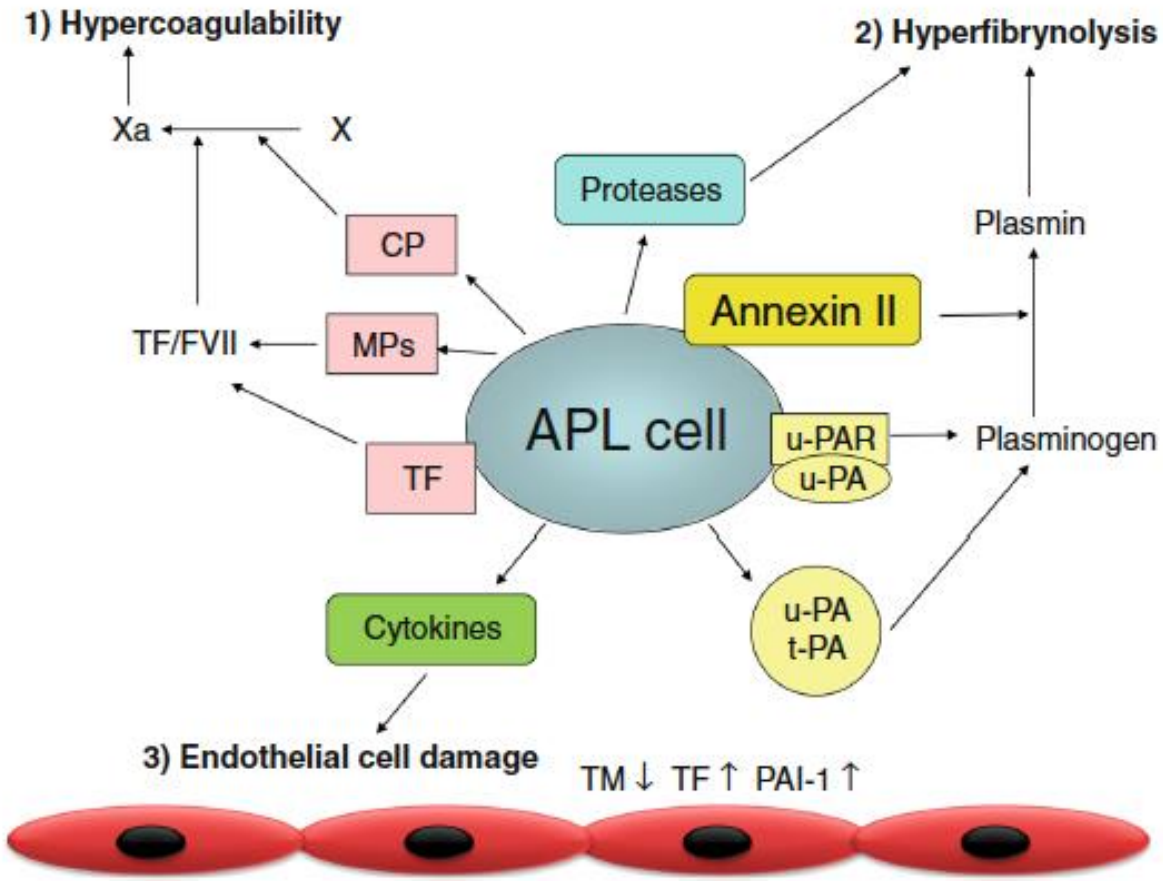


Fig. 1 Bleeding complications during ICU stay. No significant difference was seen in number of bleedings complications between the different diagnoses or in patients with haematopoietic stem cell transplantation (HSCT). *ALL* acute lymphoblastic leukaemia, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukaemia

Table 4 Thrombotic events in ICU

No. of thrombotic events—no (%)	11	(9)
Site of thrombosis		
Brain	5	
Arm, fingers, toes	2	
Liver veins	2	
Spleen (post-mortem finding)	1	
Inferior vena cava	1	
Haematological diagnosis		
AML	10	
ALL	1	
MDS	0	
Severe sepsis/septic shock—no (%)	11	(100)
Death directly related to thrombosis—no	4	
Bleeding prior to thrombotic event	3	
Bleeding after thrombotic event	3	
LMWH[a]	4	
Drugs given prior to thrombotic event		
Tranexamic acid	2	[b]
Vitamin K	2	[c]

Data are in number (%)



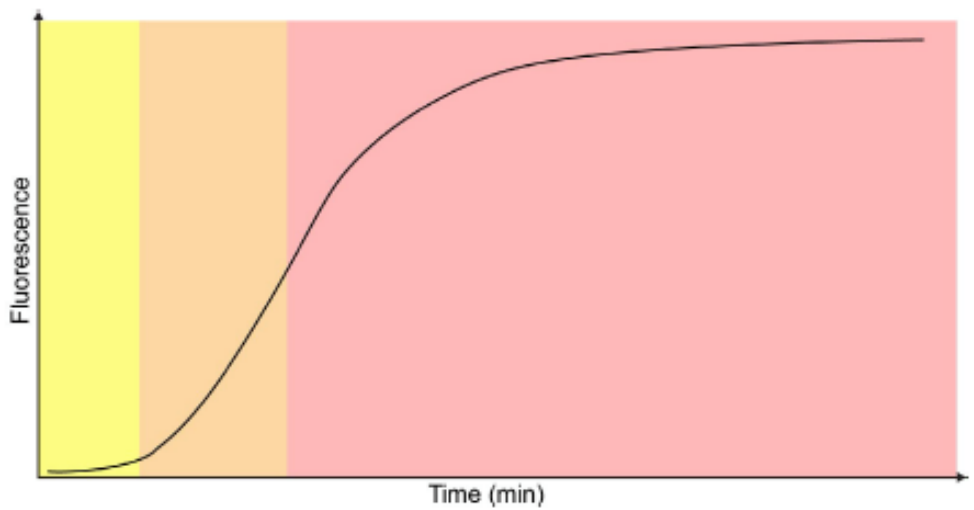
Ikezoe T. et al. Int J Hematol (2

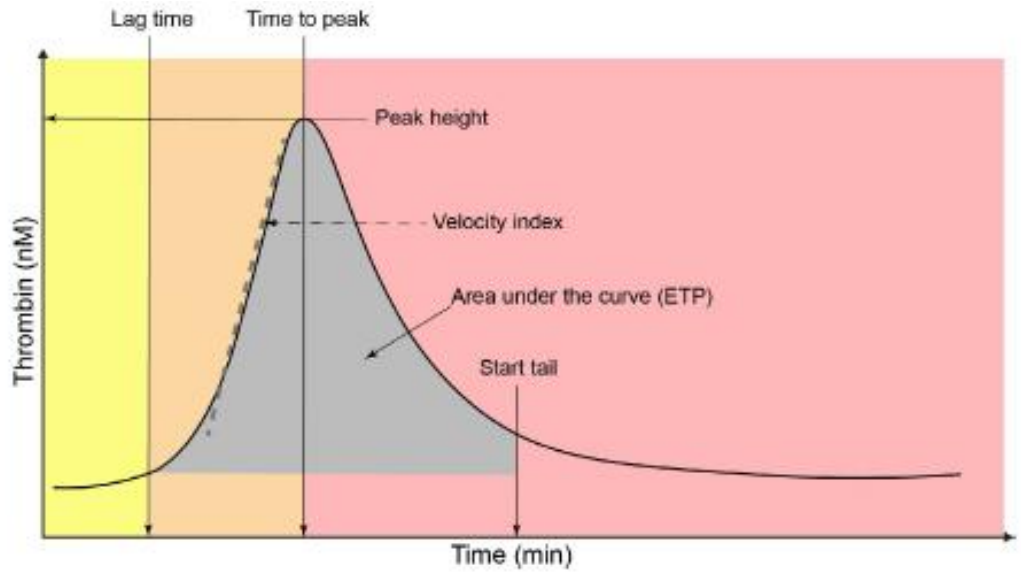
Clinical use of thrombin generation assays

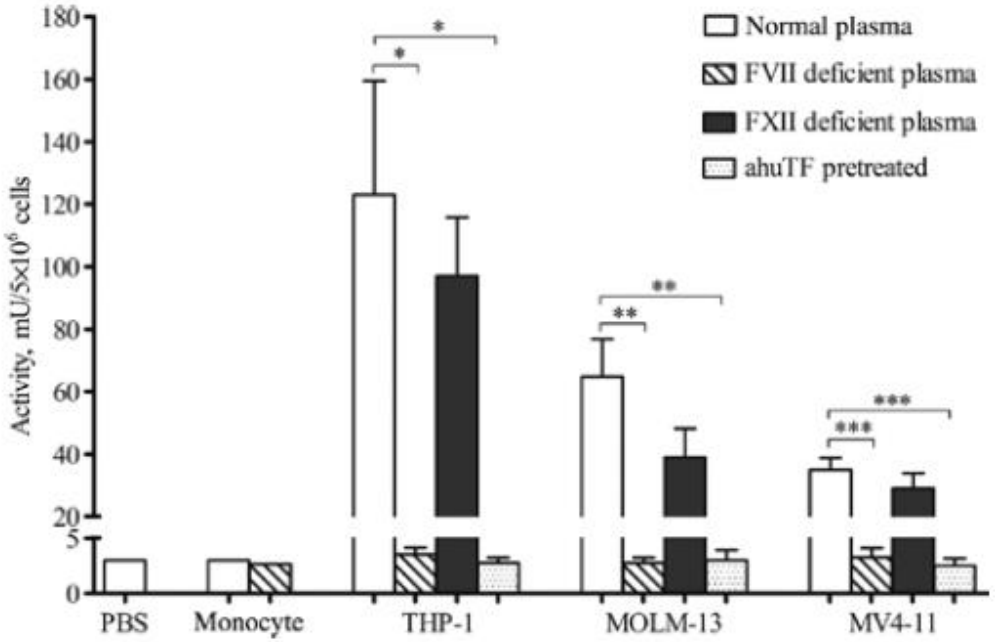
Nikolaus B. Binder[1],*,† | François Depasse[2],*,† | Julia Mueller[3],* | Thomas Wissel[3],* | Stephan Schwers[4],* | Matthias Germer[5],* | Björn Hermes[6],* | Peter L. Turecek[7]

Thrombin generation assays are versatile tools in blood coagulation analysis: A review of technical features, and applications from research to laboratory routine

François Depasse[1] | Nikolaus B. Binder[2] | Julia Mueller[3] | Thomas Wissel[3] | Stephan Schwers[4] | Matthias Germer[5] | Björn Hermes[6] | Peter L. Turecek[7]







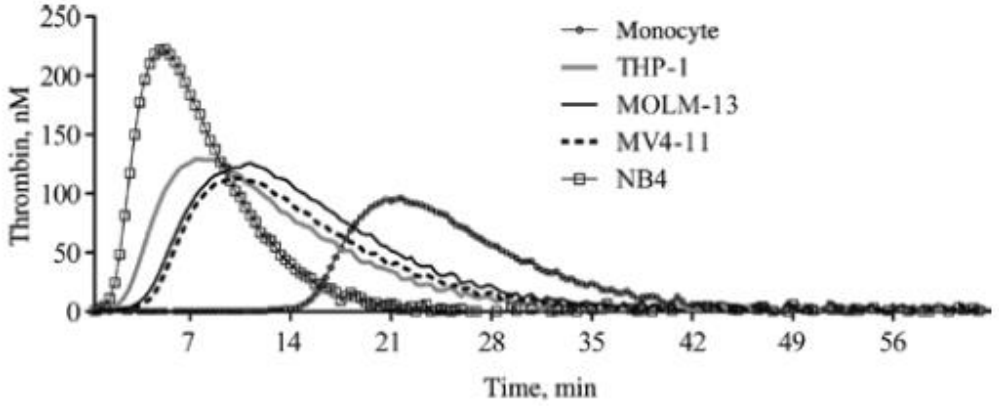
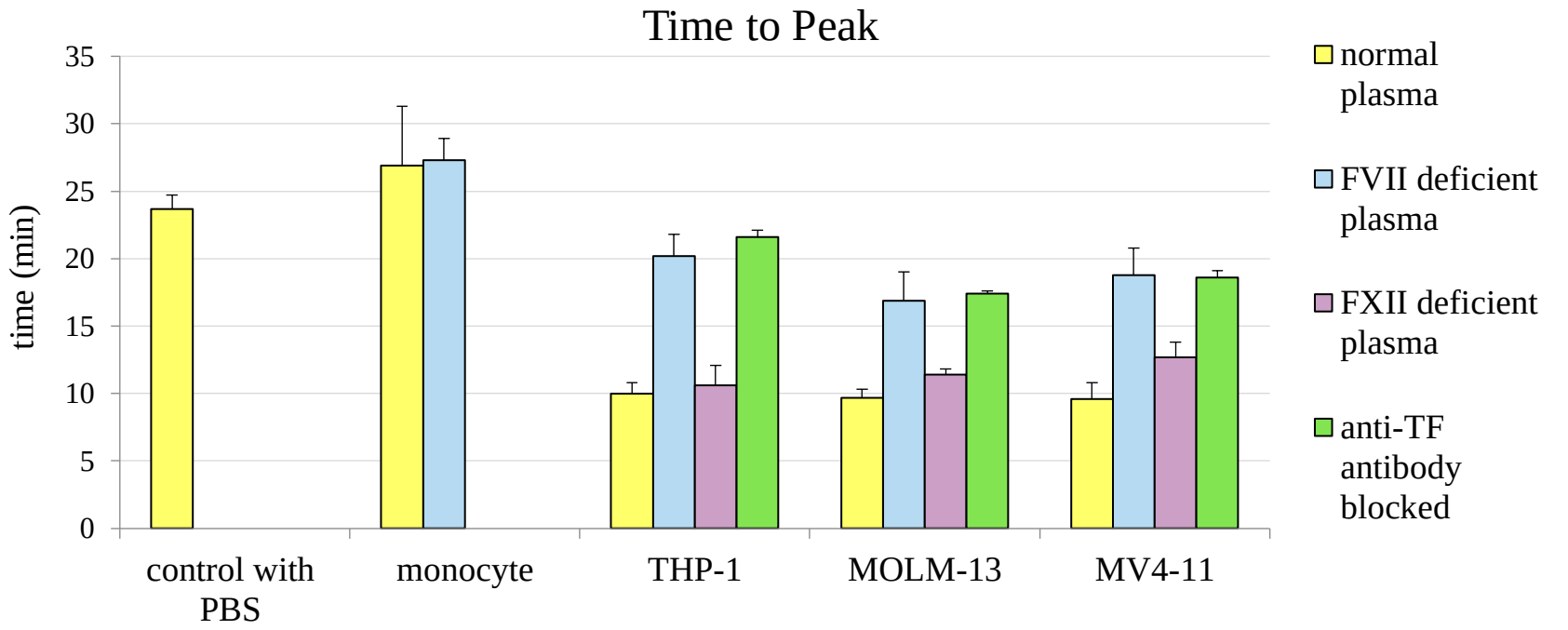
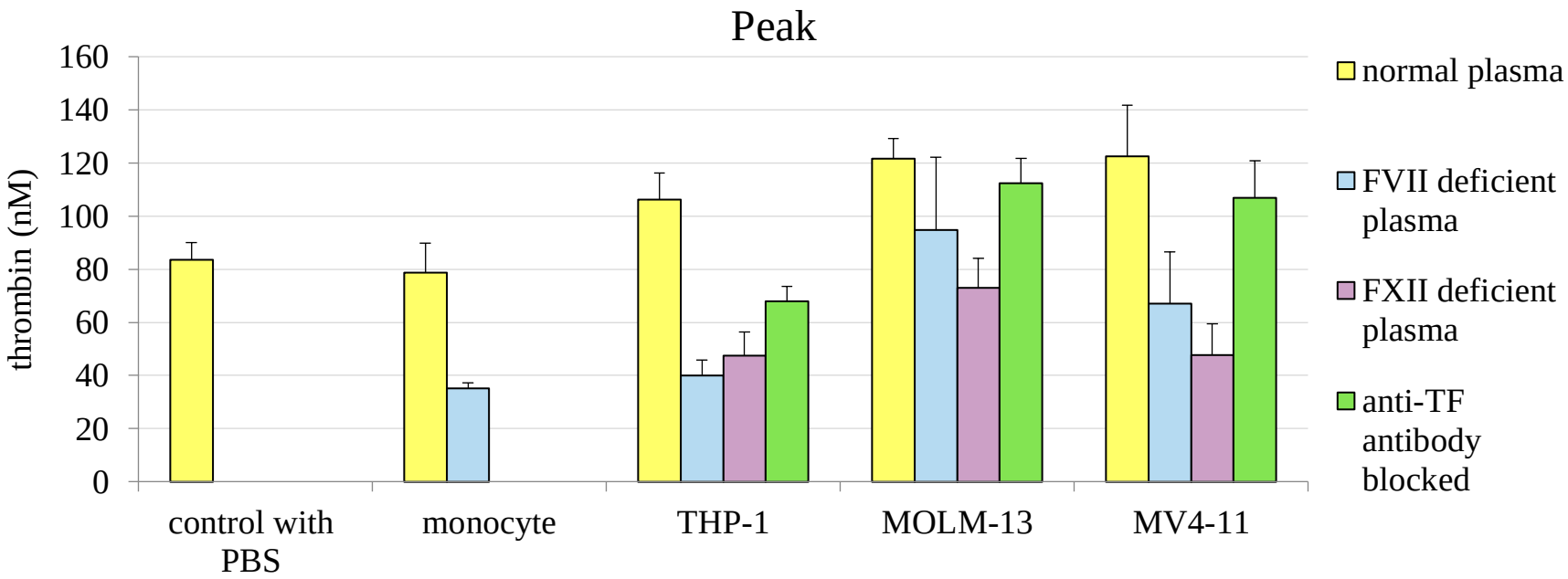


Figure 2: Representative thrombin generation curves of monocytes and leukemic cell lines.
The vertical axis represents the amount of formed thrombin by 60 min using Thrombinoscope software.

Hudák R et al. Clin Chem Lab Med: 2017, 55

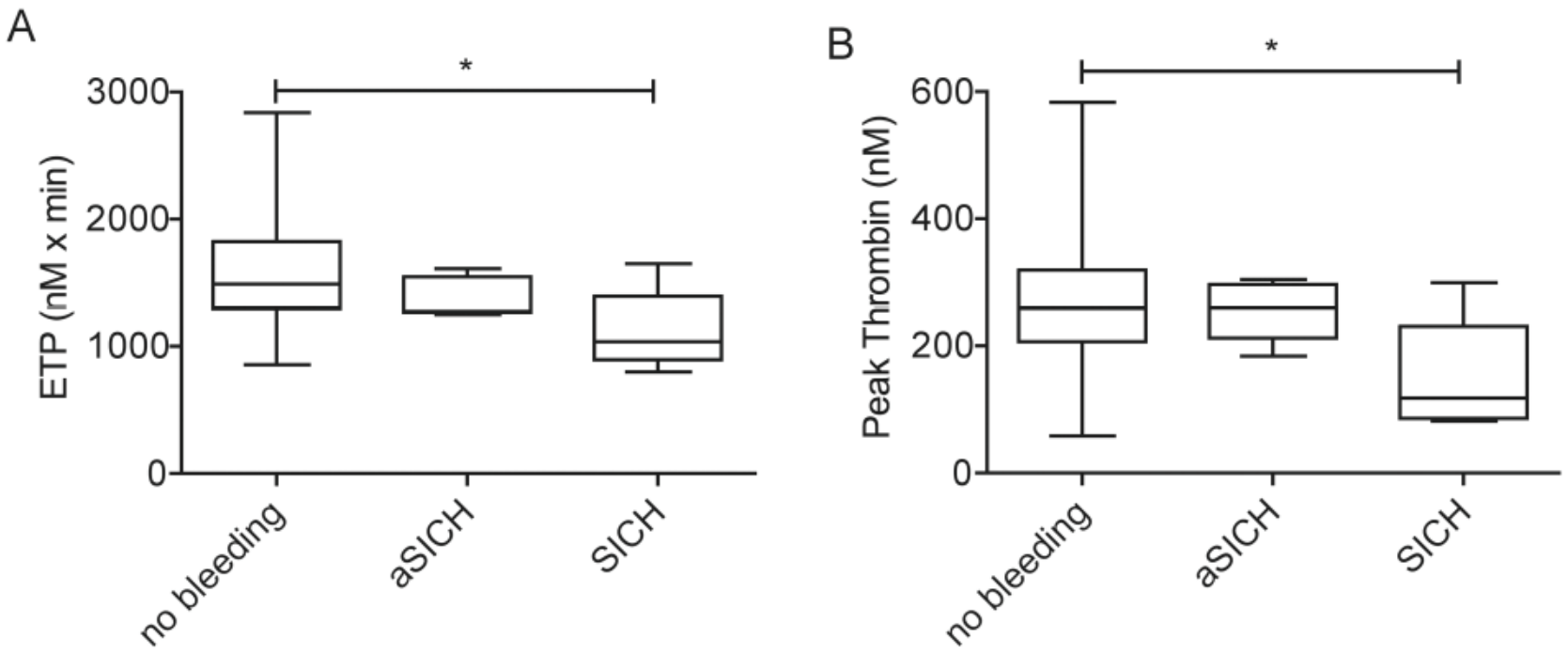

Time to Peak
time (min)
35
30
25
20
15
10
5
0
control with PBS
monocyte
THP-1
MOLM-13
MV4-11
normal plasma
FVII deficient plasma
FXII deficient plasma
anti-TF antibody blocked


Peak
thrombin (nM)
160
140
120
100
80
60
40
20
0
control with PBS
monocyte
THP-1
MOLM-13
MV4-11
normal plasma
FVII deficient plasma
FXII deficient plasma
anti-TF antibody blocked

RESEARCH ARTICLE

Low thrombin generation predicts poor prognosis in ischemic stroke patients after thrombolysis

Renáta Hudák[1], Edina G. Székely[2], Katalin R. Kovács[3], Attila Nagy[4], Gergely Hofgárt[3], Ervin Berényi[5], László Csiba[3], János Kappelmayer[1], Zsuzsa Bagoly[2]*

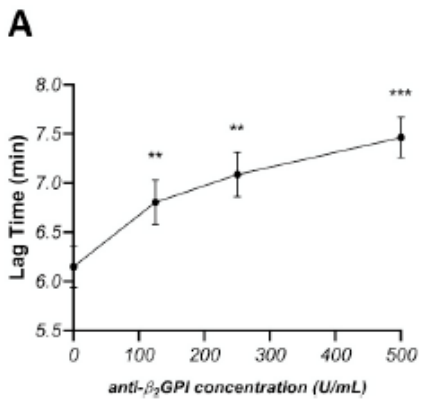


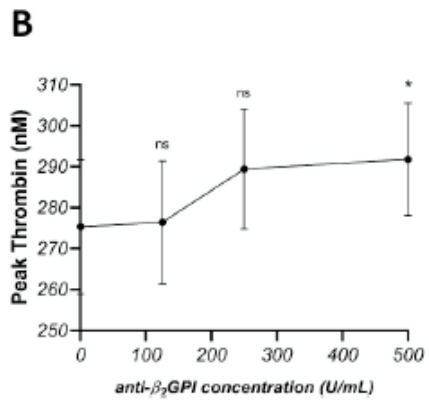
Hudák R et al, PlosOne, 2017 10.1371/jour

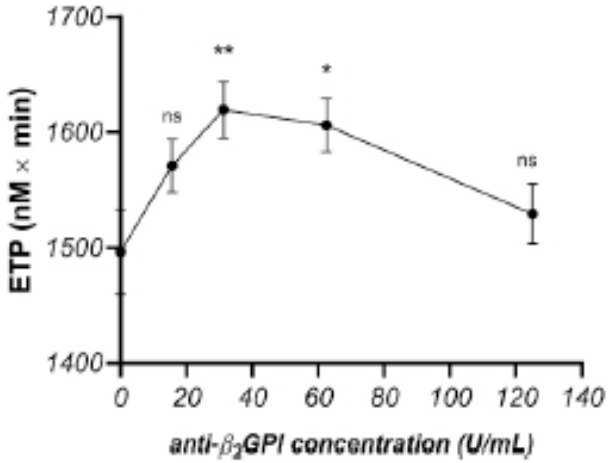
Anti-β_2-glycoprotein I autoantibodies influence thrombin generation parameters via various mechanisms

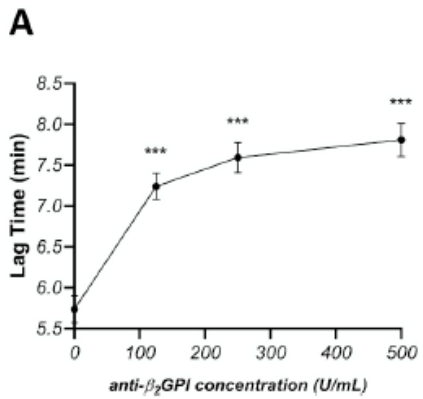
Thrombosis Research, 20

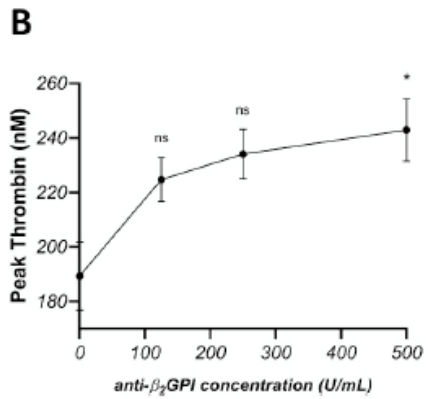
Gábor Szabó [a,b], Ildikó Beke Debreceni [a], Tünde Tarr [c], Pál Soltész [d], Bjarne Østerud [e], János Kappelmayer [a,*]

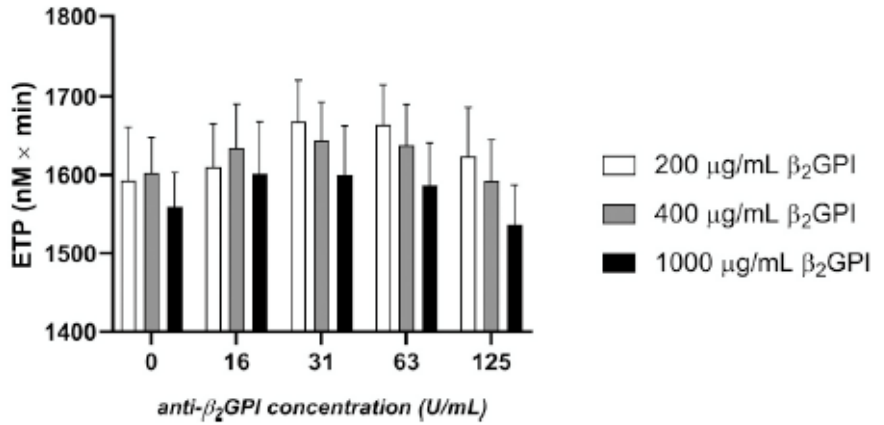












Easy to diagnose congenital coagulation disorders:

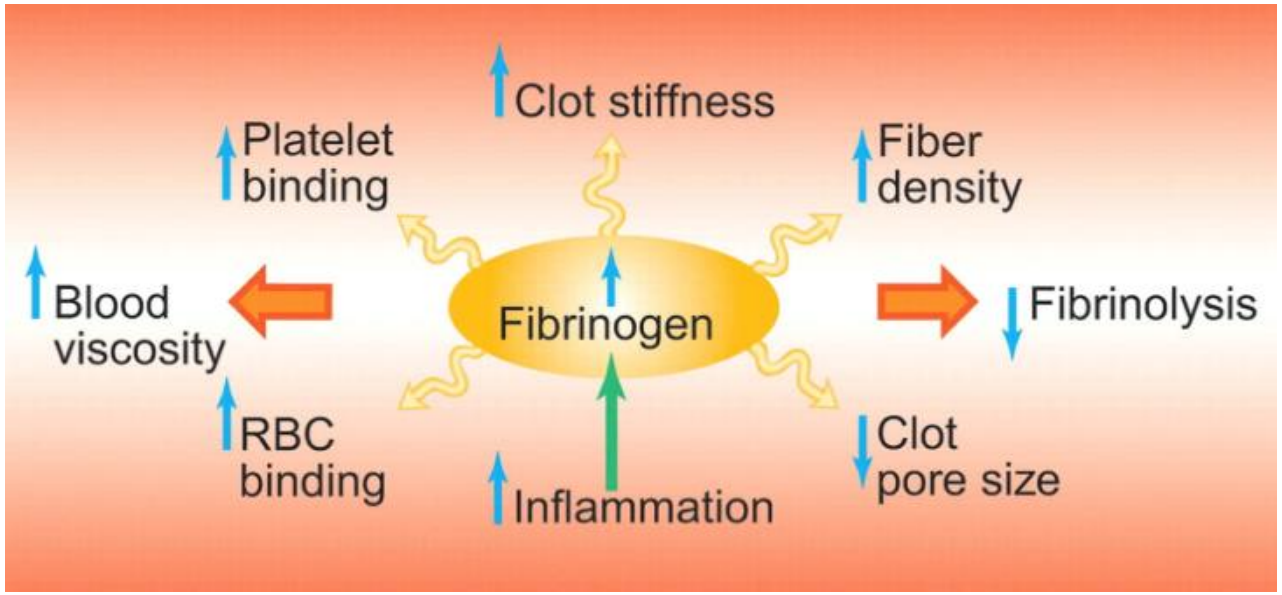
	PT	APTT
FVIII deficiency	Normal	Prolonged
FIX deficiency	Normal	Prolonged
FVII deficiency	Prolonged	Normal
FXII deficiency	Normal	Prolonged

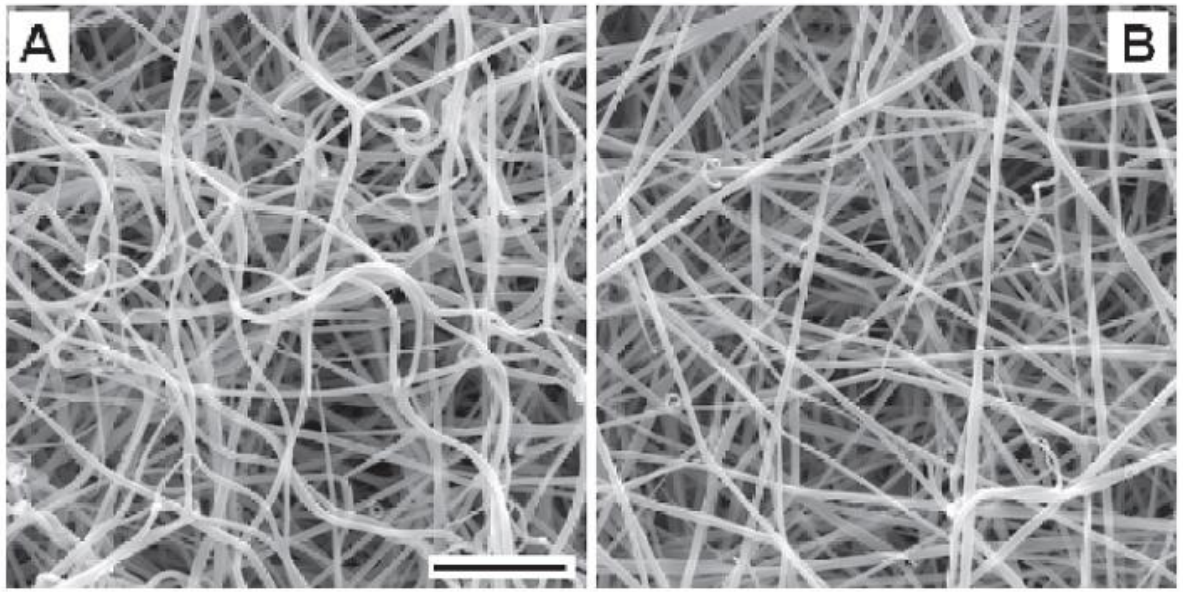
Easy to diagnose congenital coagulation disorders:

	PT	APTT
FVIII deficiency	Normal	Prolonged
FIX deficiency	Normal	Prolonged
FVII deficiency	Prolonged	Normal
FXII deficiency	Normal	Prolonged

More complicated cases:

- Patients with very rare factor deficiencies
- Patients with inhibitors
- Patients with nonfunctional coagulation factors





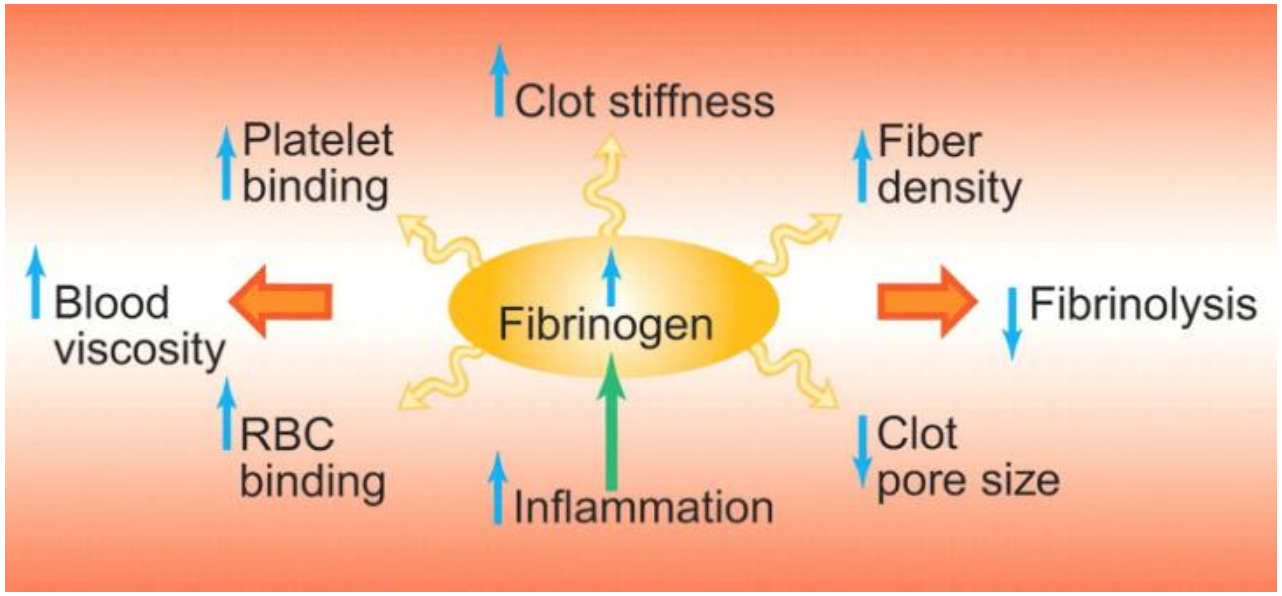
Duval C. et al Thromb Haemost, 2014

Fibrinogen methods:

activity

antigen

mass



Fibrinogen pathology:

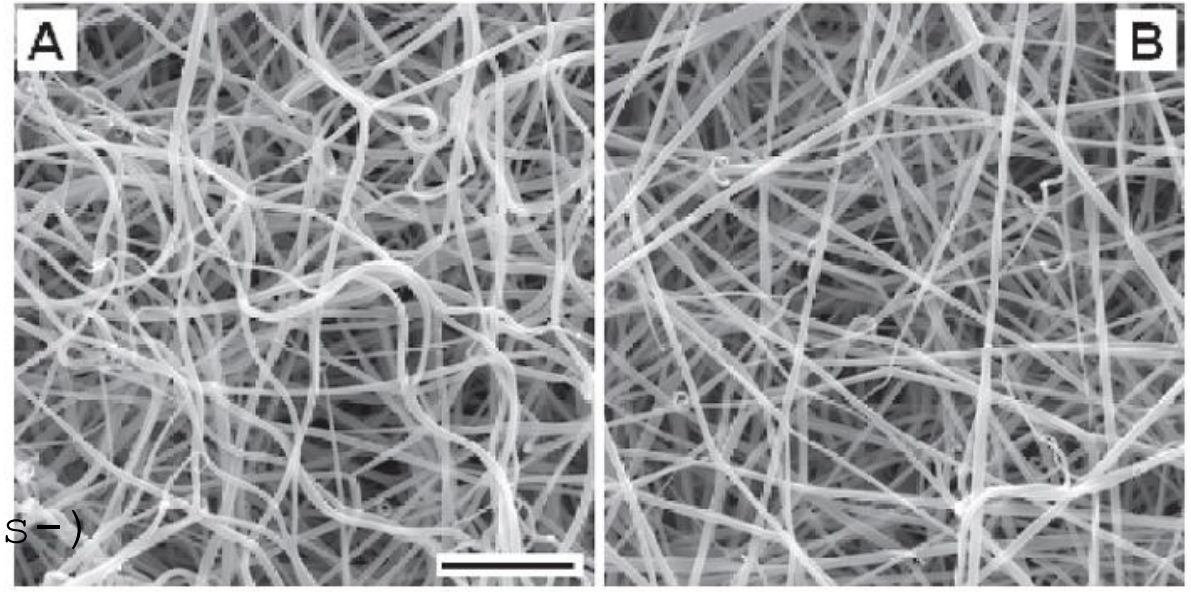
elevated

absent (a-)

decreased (hypo-)

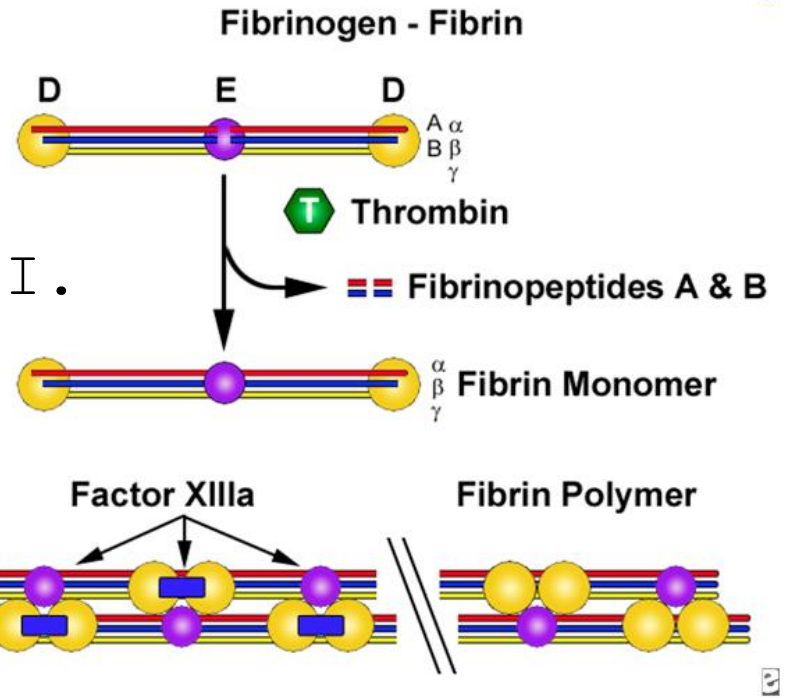
non-functional (dys-)

combined (hypodys-)



Duval C. et al Thromb Haemost, 2014

Pathophysiology of dysfibrinogenemia



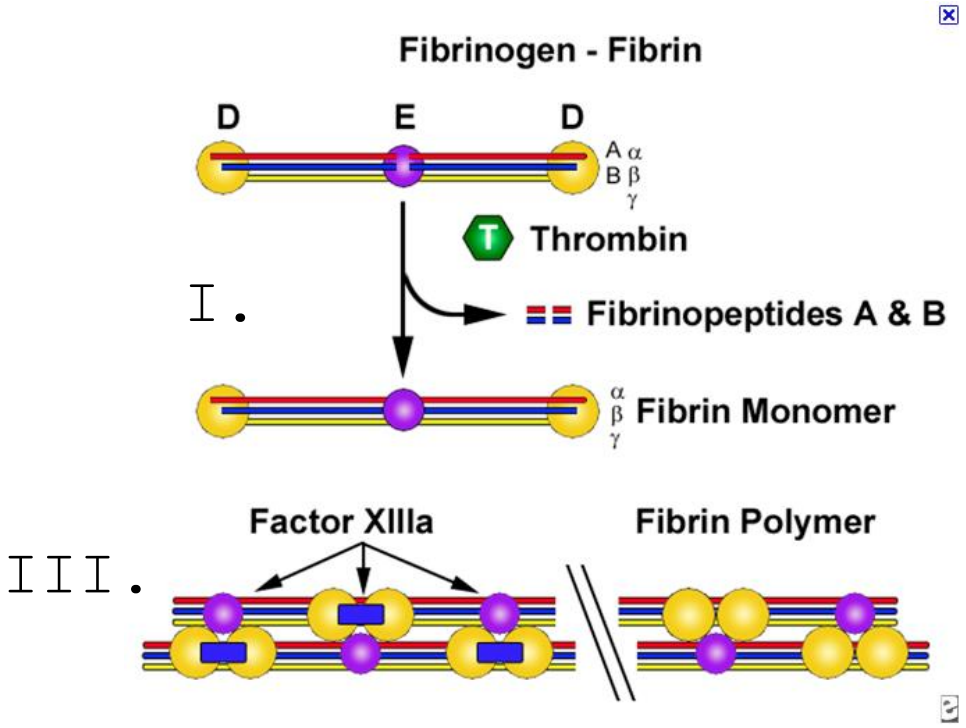
Causes of dysfibrinogenemia:

I. Disturbance of fibrinogen-fibrin conversion

II.Disturbance of fibrin polymerisation

III. Other rare diseases

Pathophysiology of dysfibrinogenemia



Diagnosis and Management of Dysfibrinogenemia

Susan E. Shapiro, MD, PhD, MRCP, FRCPath
Oxford Haemophilia and Thrombosis Centre
Oxford University Hospitals NHS Foundation Trust
NIHR Oxford Biomedical Research Centre
Oxford, United Kingdom

H&O How is HD diagnosed?

SS The initial workup should include fibrinogen assays (activity and concentration) and measurement of the prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and reptilase time (RT). Genetic analysis should be used to confirm the diagnosis.

Causes of dysfibrinogenemia:

I. Disturbance of fibrinogen-fibrin conversion

II.Disturbance of fibrin polymerisation

III. Other rare diseases

Clinical Advances in Hematology & Volume 16, Issue 9 September 2018

Should there be an algorithm of the laboratory investigation in dysfibrinogenemias ?

Our own cases at the Department of Laboratory Medicine, University of Debrecer

Patients	Symptoms	Thrombin time (sec)	Reptilase time (sec)	Clauss Fbg (g/L)	Fbg antigen (g/L)
Case 1	No symptom	57.8	75.9	1.3	2.4
Case 2	No symptom	31.0	32.2	2.02	3.26
Case 3	No symptom	41.6	not done	1.03	2.25
Case 4	Thrombosis	36.5	42.3	2.78	7.0
Case 5	Thrombosis	29.8	33.2	< 0.5	1.38
Case 6	Bleeding	80.4	>100	< 0.5	3.56
Case 7	Bleeding	48.0	>100	0.44	3.01
Case 8	Bleeding	40.7	42.5	0.55	2.8

A 19-year-old man was referred to our haemostasis laboratory with a severe bleeding.

Bleeding tendency began in infancy when he was hospitalized due to a prolonged haemorrhage of the umbilical stump. At the age of five, he was treated with subdural haematoma. Further symptoms were recurrent subcutaneous bleeding, intramuscular haematomas of both thighs and haemarthroses in the knees and repeated haemorrhages from the gum. He has had up to five major bleeding events per year.

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The bleeding episodes were treated with fresh frozen plasma. Administration of plasma always stopped the bleeding, although that was given to him on experimental basis without the recognition of the exact diagnosis.

All coagulation screening tests (PT, APTT, TT, fibrinogen) were normal and only a mild platelet

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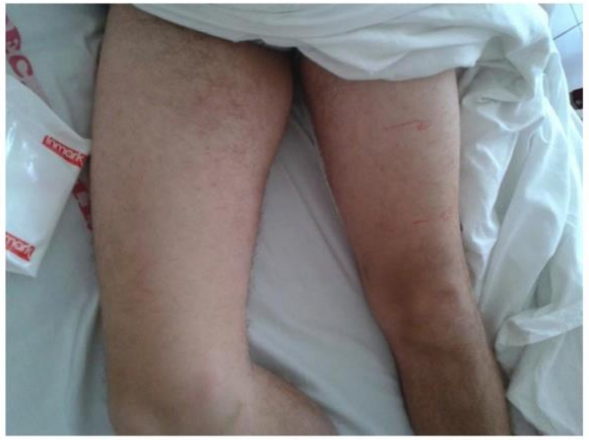
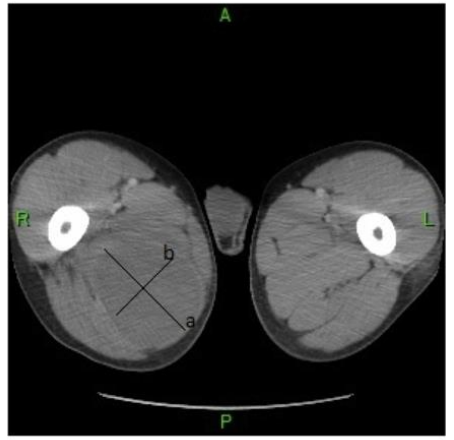
All coagulation screening tests (PT, APTT, TT, fibrinogen) were normal and only a mild platelet

Computed tomography (CT) described a huge intramuscular haematoma in the proximal and mediodorsal region of the right thigh with diameters of 7.7, 8

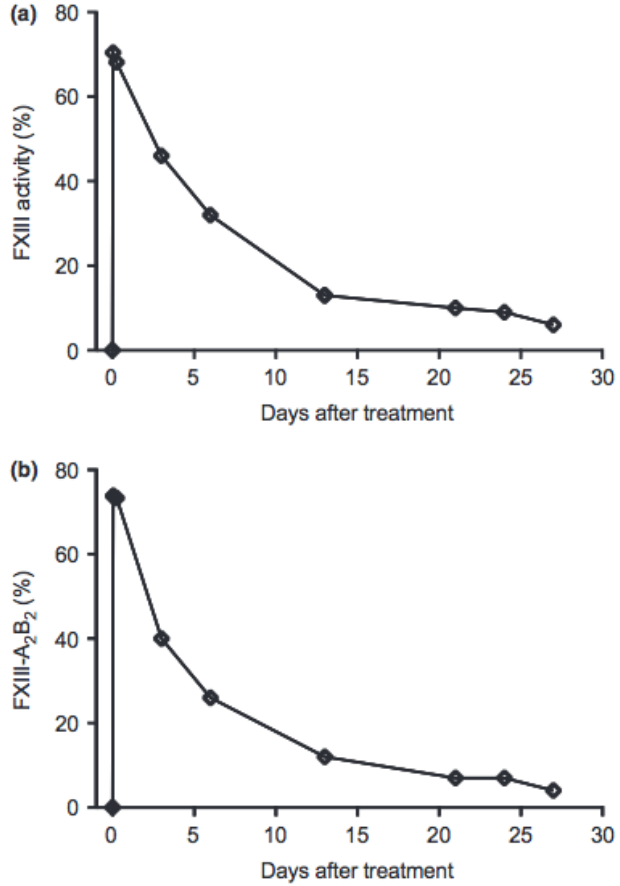




The use of recombinant factor XIII in a major bleeding episode of a patient with congenital factor XIII deficiency – the first experience

A. ÁROKSZÁLLÁSI,* A. KERÉNYI,† É. KATONA,‡ Z. BERECZKY,‡ L. MUSZBEK,‡ Z. BODA* and Á. SCHLAMMADINGER*

*Thrombosis and Haemostasis Centre, Institute of Medicine, University of Debrecen; †Institute of Laboratory Medicine University of Debrecen; and ‡Clinical Research Centre, University of Debrecen, Debrecen, Hungary



	Patient	Reference interval
Plasma		
FXIII activity	<1.0%	69-143%
FXIII-A2B2	<0.1%	67-133%
FXIII-A	<0.1%	67-133%
FXIII-B	33.5%	64-136%
Platelet		
FXIII activity	<2.0%	na
FXIII-A	<0.1%	67-133%

During a five-month prophylactic rFXIII substitution the pharmacokinetics was similar (pre-dose FXIII activity varied between 4-6%) and the patient was exempt of bleeding symptoms. As demonstrated by mixing studies carried out on

Coagulation assay puzzles:

- Use all coagulation screening assays in bleeding/thrombotic ca
- Utilize methods for assessing global hemostasis
- Be aware of the interfering factors

- Interference of anticoagulants (DOAC)
- Anticoagulants eliciting life-threatening thrombosis (HITT)
- Which patient is prone to bleeding ? FXII or FXIII deficiency

Acknowledgement

- László Muszbek

- Zsuzsa Bereczky
- Zsuzsa Bagoly
- Adrienne Kerényi

- All members of our Haemostasis Unit