I Test di Laboratorio per lo Studio dell'Emostasi

Armando Tripodi
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center
Department of Internal Medicine
University of Milano

Alteration of Hemostasis

Tests to Assess the Risk of Bleeding

- Primary Hemostasis
- Fibrinolysis
- Coagulation

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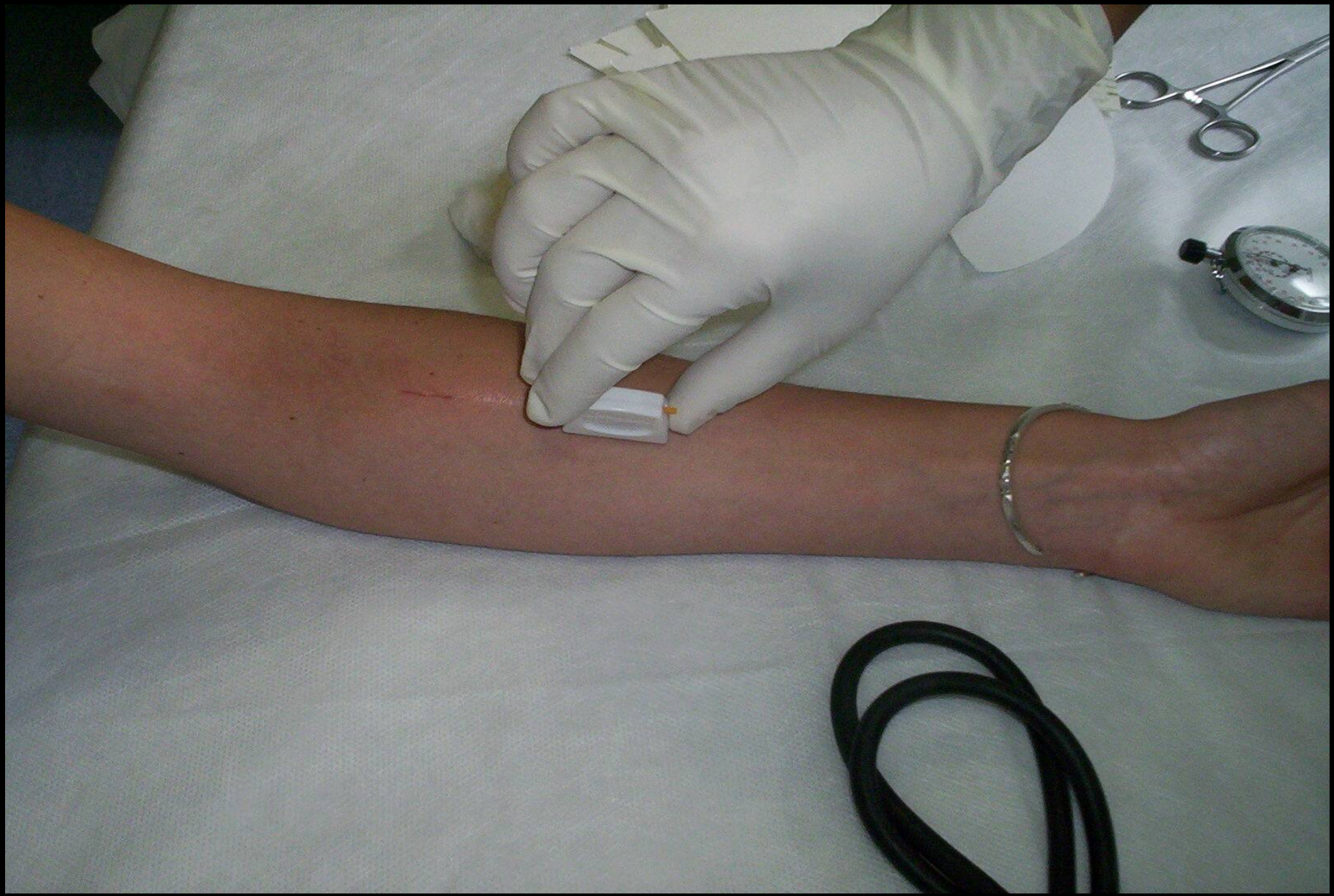
Alteration of Primary Hemostasis and Bleeding

Background

- Characterized by thrombocytopenia, thrombocytopathy or Willebrand factor defects
- This complex defect has been historically documented through the measurement of the skin bleeding time



Bleeding Time as Predictor of Bleeding

- Bleeding time has been reviewed and its value as predictor of bleeding has been questioned

- Burns et al, 1989
- Rodgers & Levine, 1990
- Lind, 1991
- De Caterina et al, 1994
- Triplett, 1989

Bleeding Time in Liver Disease

- The skin bleeding time is frequently prolonged in cirrhosis (up to 40% of patients, J Hepatol 1994; 20: 531)

Does it matter ?

Primary Hemostasis and Bleeding Time

Conclusions and Future Directions

- Defects of primary hemostasis have a causative role in the occurrence of bleeding
- But, the bleeding time is not a good predictor of bleeding and is difficult to standardize
- Laboratory methods should go beyond the bleeding time

Alternative Tests for Primary Hemostasis

- Platelet Aggregation (Born)
- Platelet Functional Assay 100 (PFA-100)
- Other devices

PFA-100 & PubMed

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Journal of Thrombosis and Haemostasis, 4: 312–319

REVIEW ARTICLE

Platelet function analyzer (PFA)-100® closure time in the evaluation of platelet disorders and platelet function

C. P. M. HAYWARD,*† P. HARRISON,‡ M. CATTANEO,§ T. L. ORTEL¶ and A. K. RAO**†† ON BEHALF OF THE PLATELET PHYSIOLOGY SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

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Journal of Thrombosis and Haemostasis, **5**: 2393–2398

ORIGINAL ARTICLE

Usefulness of PFA-100® testing in the diagnostic screening of patients with suspected abnormalities of hemostasis: comparison with the bleeding time

G. M. PODDA,* P. BUCCIARELLI,* F. LUSSANA,† A. LECCHI* and M. CATTANEO†

**Dipartimento di Medicina e Specialità Mediche, IRCCS Fondazione Ospedale Maggiore, Mangiagalli e Regina Elena; and †Unità di Ematologia e Trombosi, Ospedale San Paolo, Dipartimento di Medicina, Chirurgia e Odontoiatria, Università di Milano, Milan, Italy*

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Summary of Findings

- Although PFA-100 showed a greater sensitivity than the BT to defects of primary hemostasis including VWF, it is still unsatisfactory

  - 30% VWD and 50% PFD undetected

- In general, PFA-100 is not useful for the initial screening of patients suspected of having disorders of primary hemostasis

Alteration of Hemostasis

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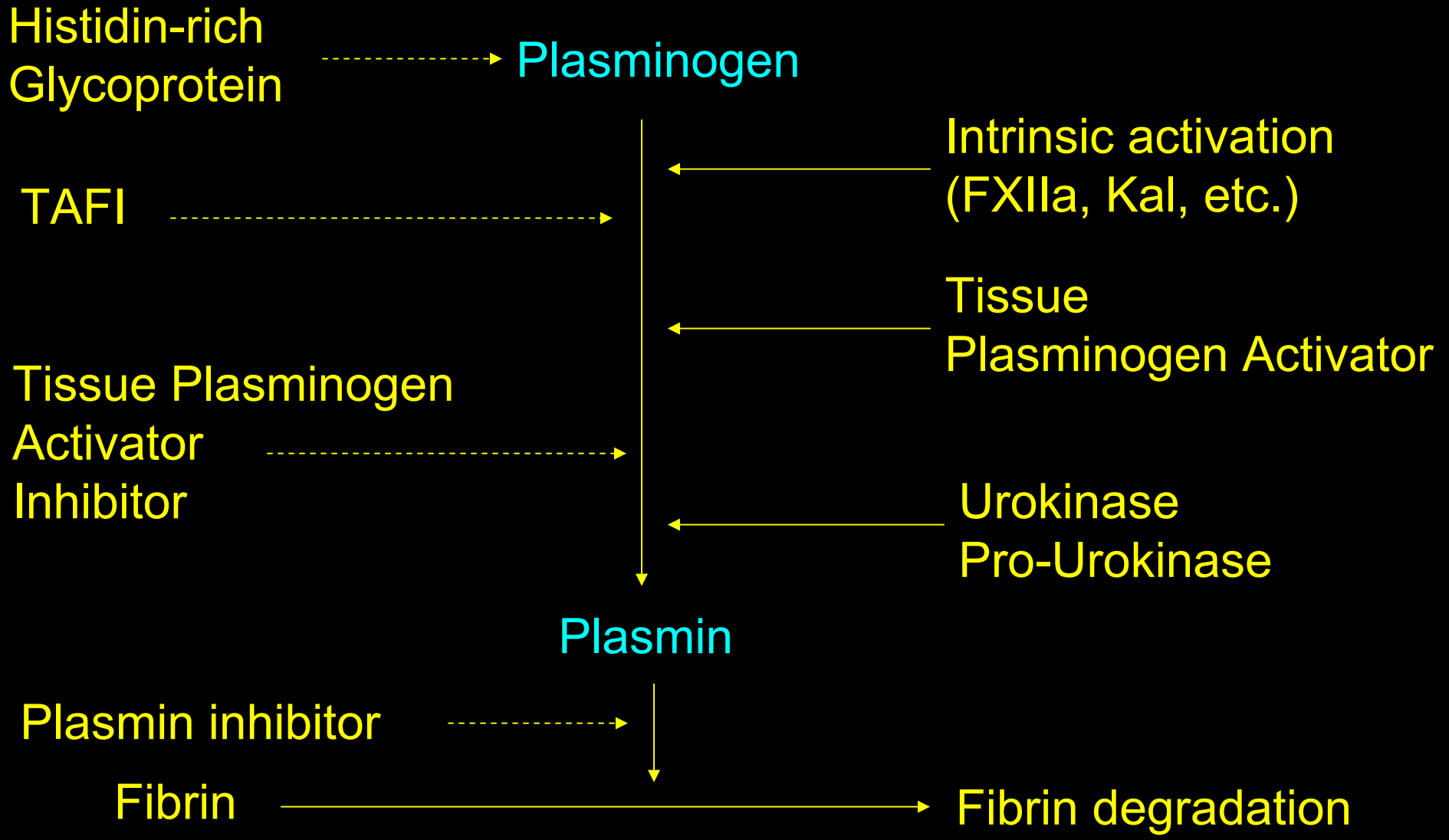
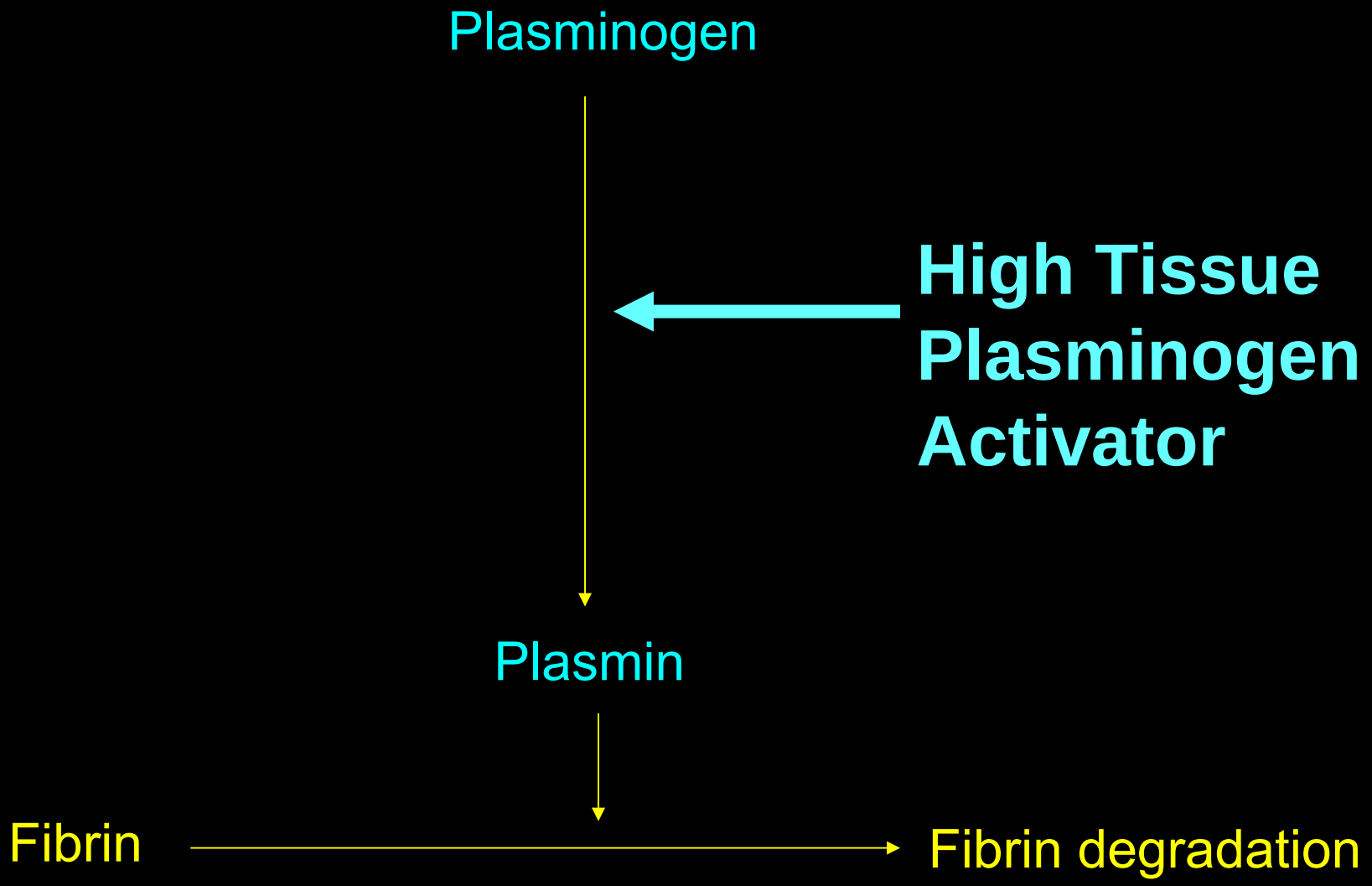
Fibrinolysis



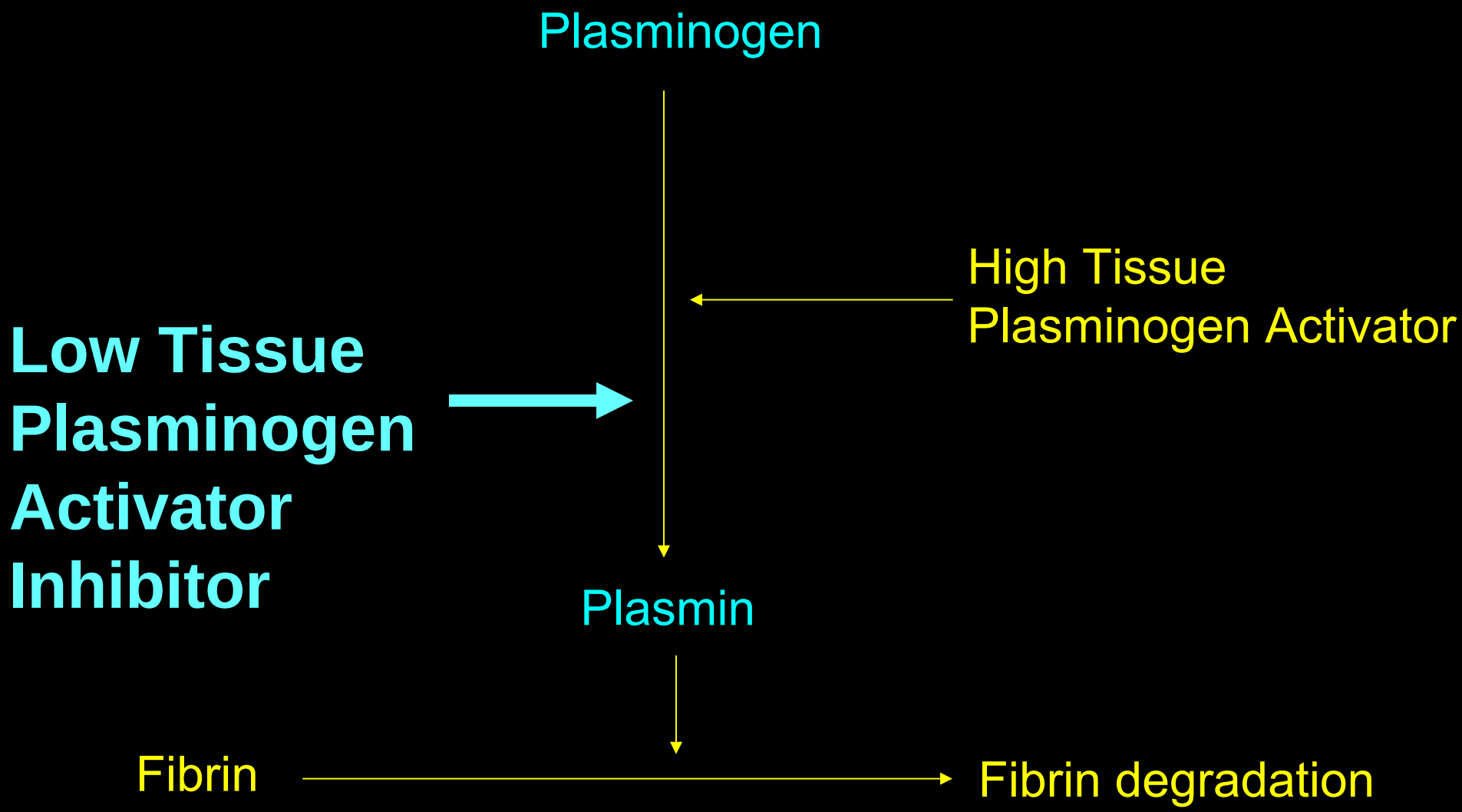
Alteration of Fibrinolysis and Bleeding



Emorragie da aumentati livelli di Attivatore del Plasminogeno

Autore	Sintomi
• Booth et al, 1983	• Emorragie post-traumatiche
• Aznar et al, 1984	• Emorragie post-traumatiche (familiari)

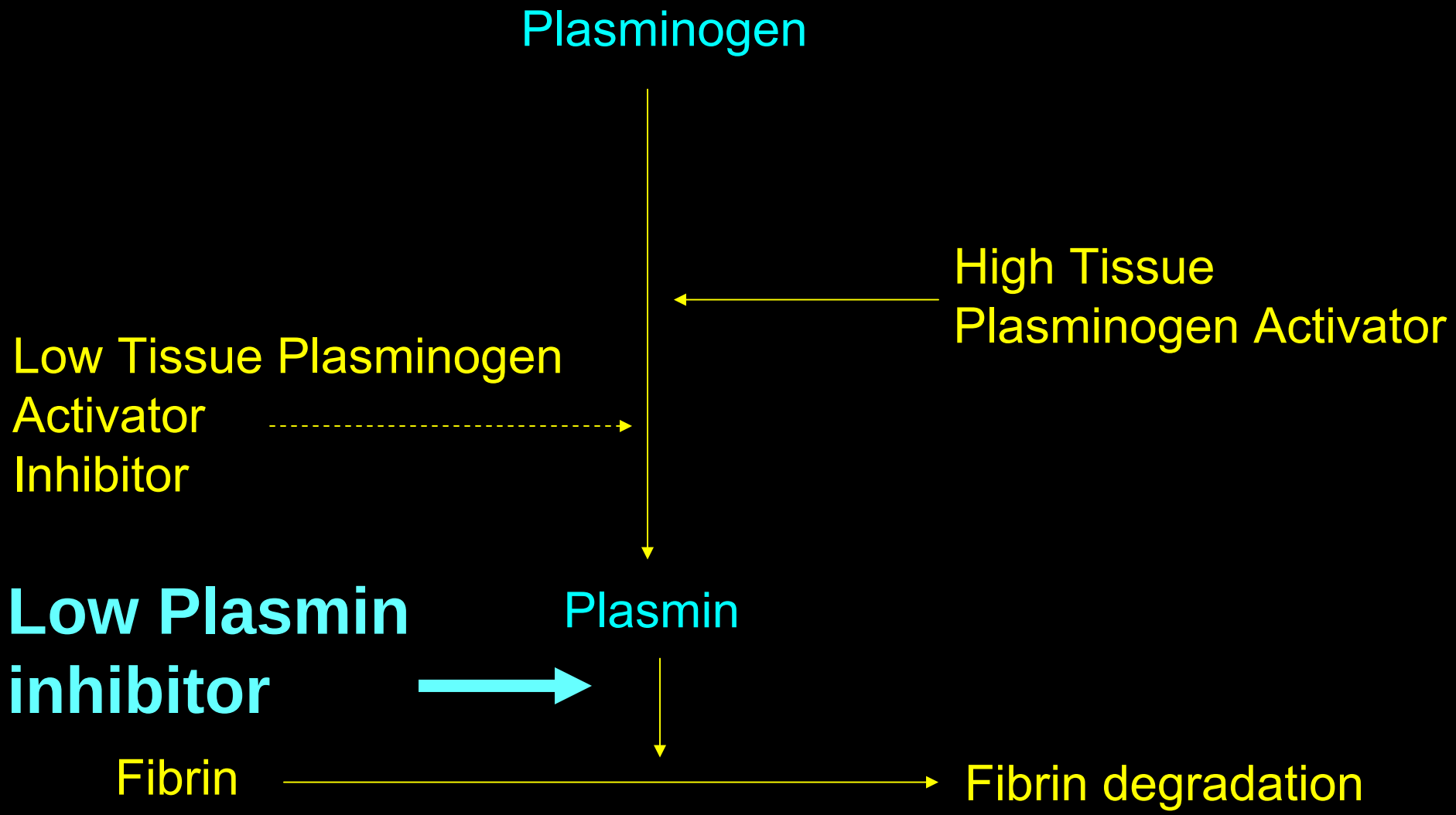
Alteration of Fibrinolysis and Bleeding



Emorragie da ridotti livelli di Inibitore del Plasminogeno

Autore	Sintomi
Schieef, 1989	Emorragie post-traumatiche
Dieval, 1991	Epistassi, emorragie tardive post-operatorie
Lee, 1993	Emorragie tardive post-operatorie (familiari)
Stankiewicz, 1991	Emorragie post-operatorie

Alteration of Fibrinolysis and Bleeding



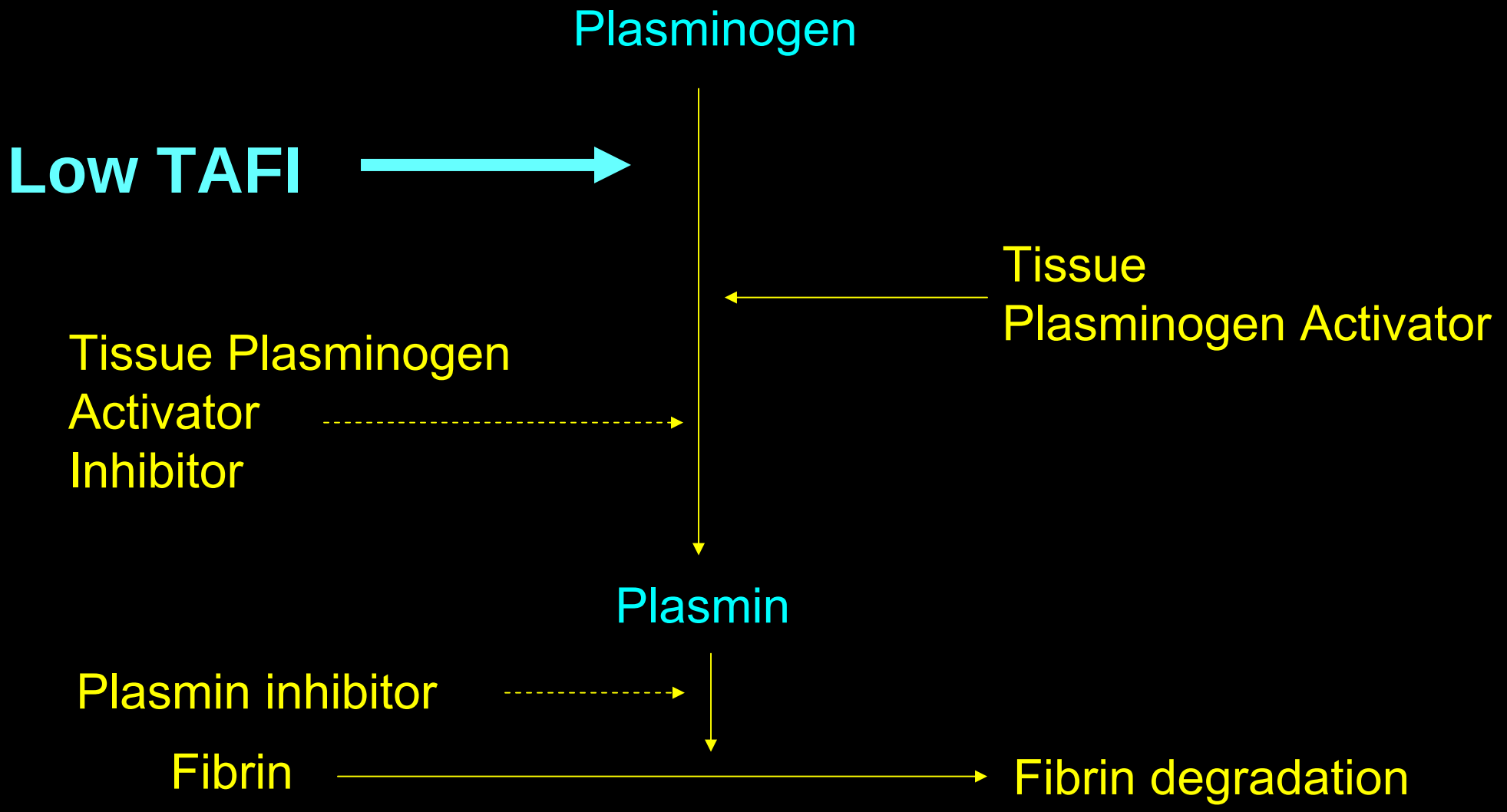
Congenital Deficiency of Plasmin Inhibitor

- Homozygotes

  Severe hemophilia-like bleeding tendency since childhood; rebleeding from wounds
- Heterozygotes

  About 20% of patients have a mild bleeding tendency (easy bruising, oozing from dental extractions)

Alteration of Fibrinolysis and Bleeding



Hyperfibrinolysis and Cirrhosis

- Deficiency of TAFI in cirrhotics ***is not associated*** with increased plasma fibrinolysis

  Lisman T et al. Gastroenterology 2001; 121: 131

- Deficiency of TAFI in cirrhotics ***is associated*** with increased plasma fibrinolysis

  Colucci M, et al, Hepatology 2003; 38: 230

Fibrinolysis and Bleeding
Conclusions and Future Directions

- Measurements of individual plasmatic components of the fibrinolytic pathway are unlikely to help, especially in acquired coagulopathies
- Simple global tests should be developed and investigated in clinical trials

Alteration of Hemostasis

Tests to Assess the Risk of Bleeding

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- Coagulation

Alteration of Coagulation and Bleeding
Background

- Characterized by an impaired synthesis/consumption of coagulation factors
- This complex defect can be documented through the measurement of coagulation factors, or through the prolongation of PT & APTT

The Paradigm of Abnormal Coagulation Tests & Bleeding

- The concept of a causal relationship between abnormal coagulation and bleeding is widely accepted
- Common practice of screening patients with hemostasis tests
- Treating patients with abnormal values in order to correct identified abnormalities prior to potentially hemorrhagic procedures

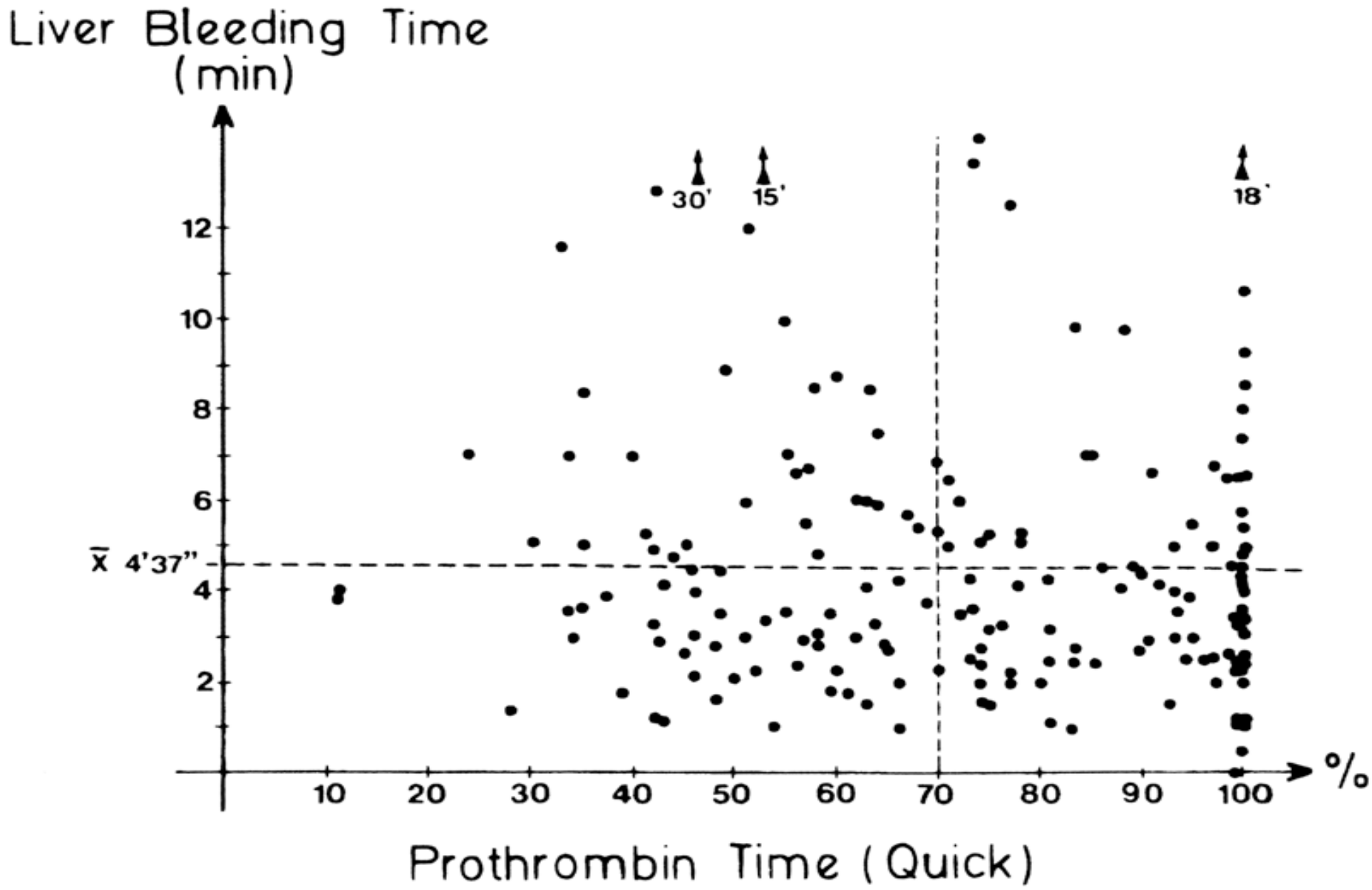
Poor Correlation of Global Hemostasis Tests and Bleeding in Cirrhosis

Review of the Literature

- Ewe K. Dig Dis Sci 1981; 26; 388-93
- Segal JB & Dzik WH. Transfusion 2005; 45:1413-25
- Boks AL, et al. Hepatology 1986; 6: 79-86
- Diaz LK &Teruya J. New Engl J Med 2001;344:2030
- Grabau CM et al. Hepatology 2004;40:484-8
- Terjung B et al. Digestion 2003; 67: 138-45
- Mc Gill DB et al. Gastroenterology 1990; 99: 1396-1400

Bleeding Assessed during Laparoscopic Liver Biopsy does not Correlate with Indices of Peripheral Coagulation

Ewe K. Dig Dis Sci 1981; 26: 388


Liver Bleeding Time
(min)
30'
15'
18'
12
10
8
6
x̄ 4'37"
4
2
10
20
30
40
50
60
70
80
90
100
%
Prothrombin Time (Quick)

Why Conventional Coagulation Tests are not Correlated with Bleeding in Cirrhosis ?

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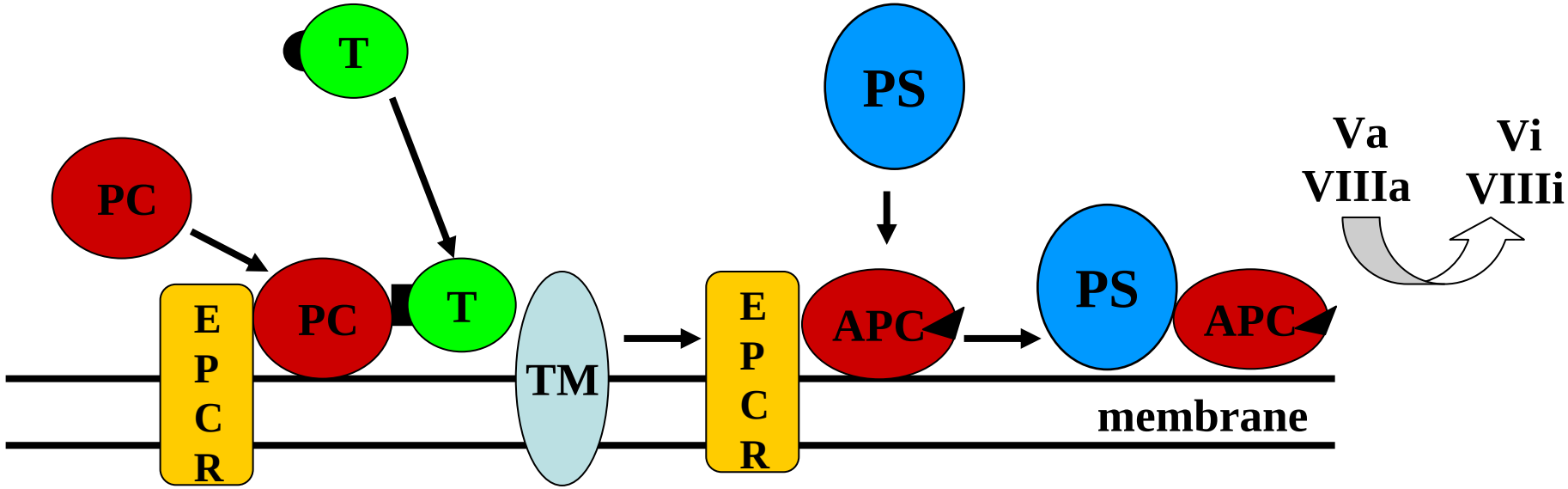
Coagulation in Liver Disease

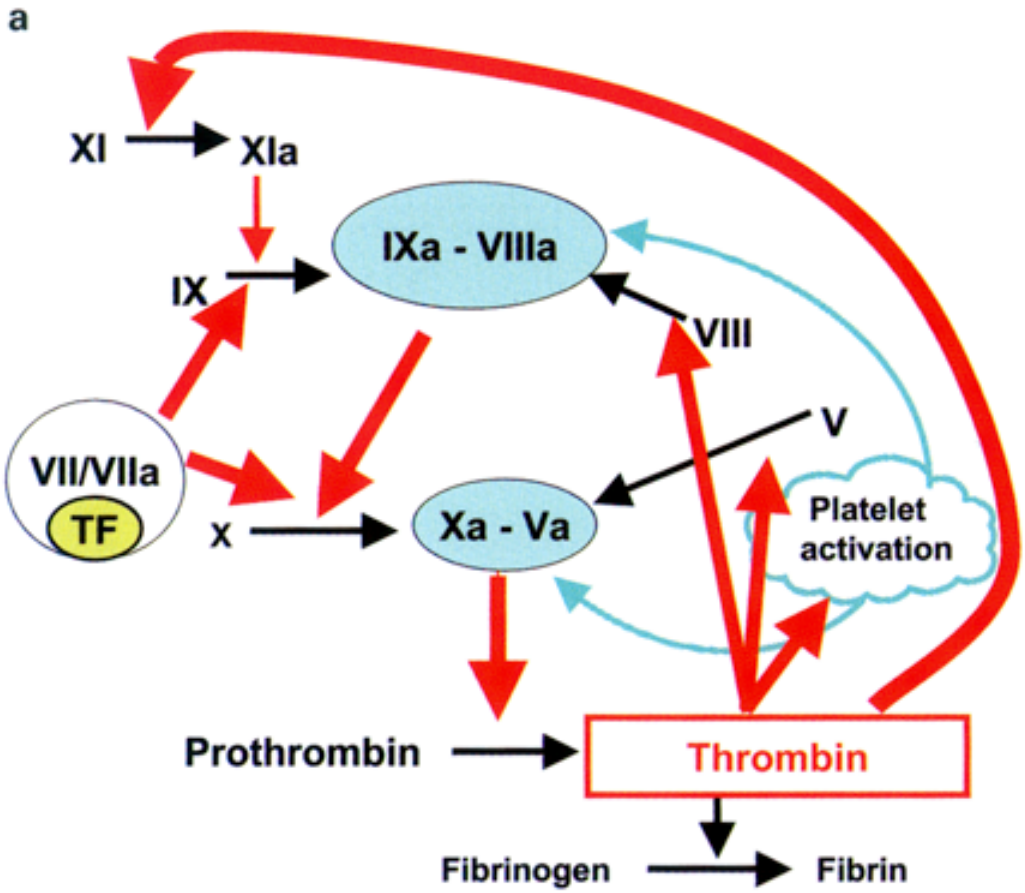
Considerations on the Suitability of Conventional Coagulation Tests

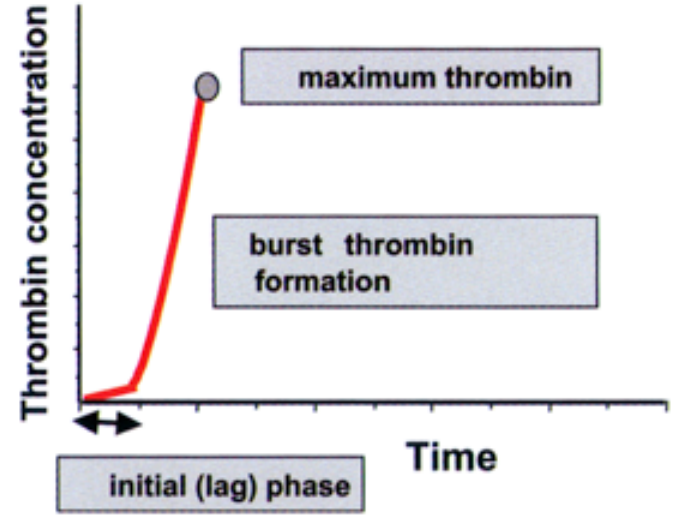
- Global coagulation tests (PT & APTT) might be inadequate to reflect the coagulation balance as it occurs in vivo especially in acquired coagulopathies (cirrhosis)
- Reduction of protein C, antithrombin and TFPI parallels that of pro-coagulants
- Protein C is activated to a limited extent in the absence of thrombomodulin

PROTEIN C Activation



It should be noted that plasma and reagents needed to perform PT & APTT do not contain TM





PT & APTT are responsive only to procoagulant factors

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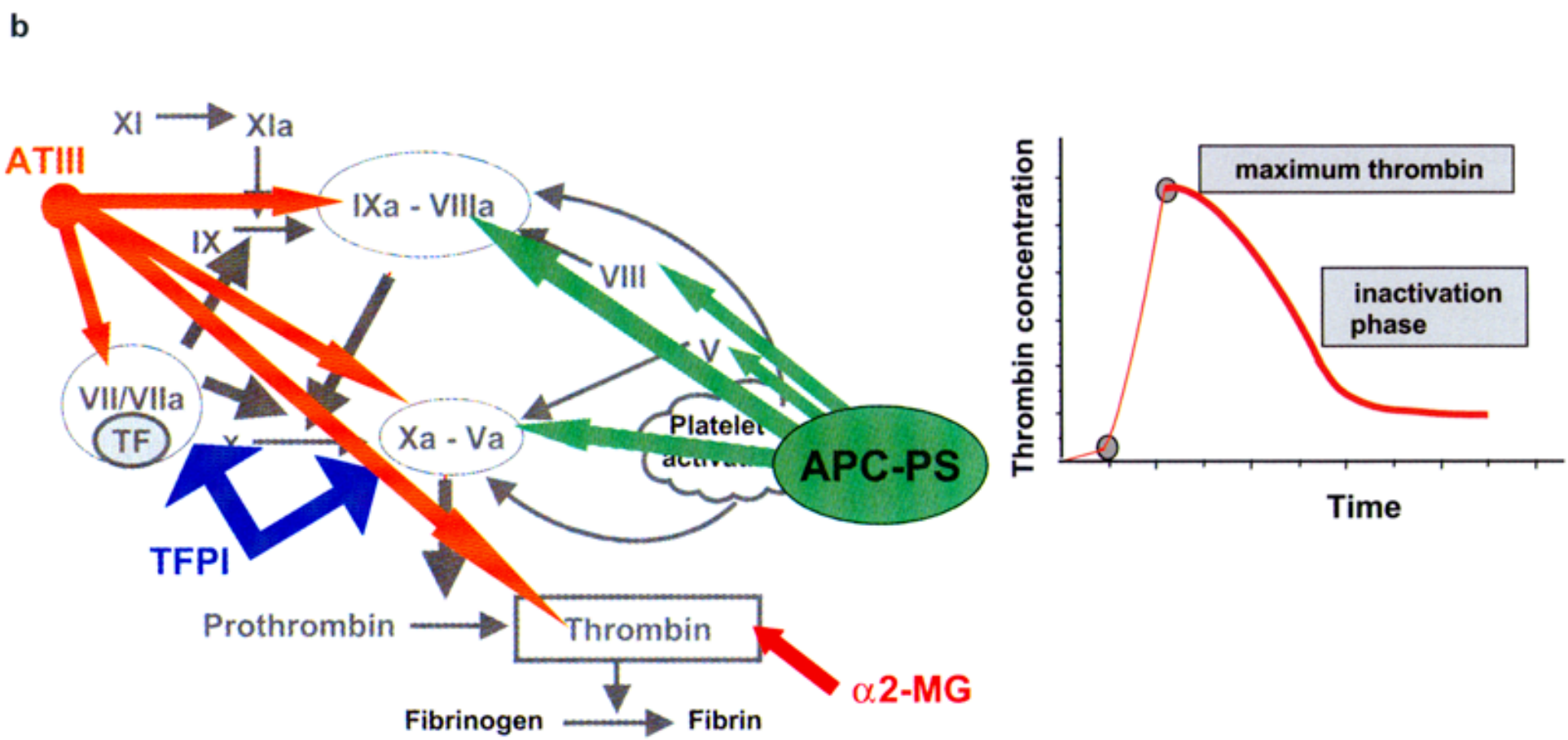


…and much less to the anticoagulant factors

PT & APTT as Tools to Investigate the Balance of Coagulation

- Suitable to investigate congenital deficiencies of pro-coagulants
- Unsuitable to investigate congenital deficiencies of anti-coagulants
- Unsuitable to investigate acquired deficiencies of **both** pro- and anti-coagulants

PT & APTT as Tools to Investigate the Balance of Coagulation

- PT & APTT can tell us whether a patient is deficient in one or more procoagulant factors
- ….but not whether this deficiency is counterbalanced by a concomitant deficiency of the anticoagulant factors

Cirrhosis as a Model

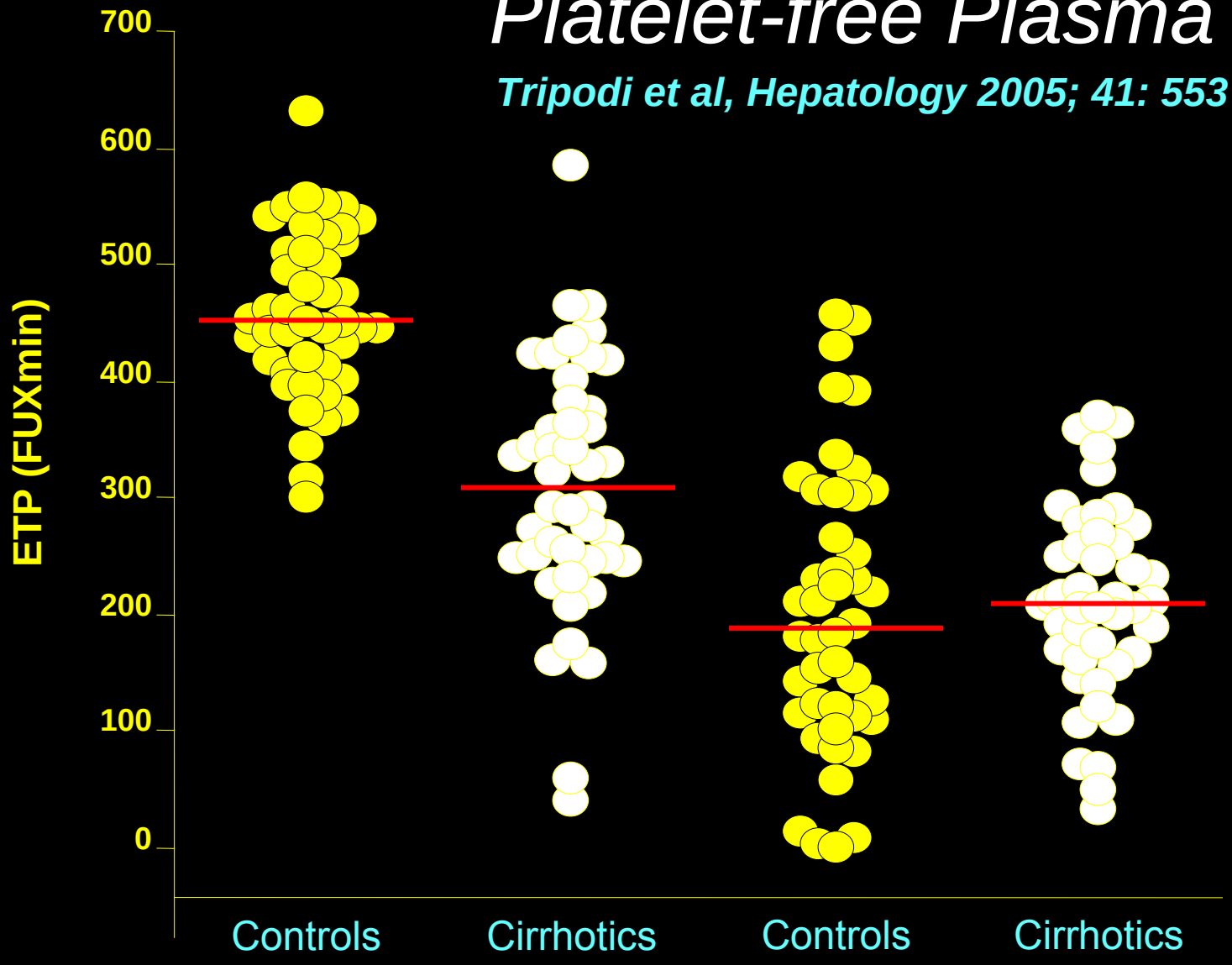
Hemostatic Parameters in Patients with Cirrhosis and Controls (n=44)

Tripodi et al, Hepatology 2005; 41: 553

Parameter	Patients Median	Controls Median	P value
PT ratio	1.26	0.99	P<0.001
APTT ratio	1.31	0.99	P<0.001
Protein C (%)	39	105	P<0.001
Antithrombin (%)	52	101	P<0.001
Factor II (%)	49	105	P<0.001
Factor VIII	132	124	P=0.14

Platelet-free Plasma

Tripodi et al, Hepatology 2005; 41: 553



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Thrombin generation in Cirrhosis
Conclusions

- Coagulation in cirrhosis is not abnormal when assessed with global tests reflecting the function of **both** pro- and anti-coagulants
- The findings question the usefulness of traditional coagulation tests in assessing hemorrhagic risk in cirrhosis (and acquired coagulopathies)
- Global tests reflecting the function of all components of coagulation system should be designed and investigated in clinical trials

Conditions Underlying Bleeding in Liver Disease

- Portal Hypertension
- Endothelial dysfunction
- Renal failure
- Bacterial infections

Value of Conventional Global Tests

- Uncertain
  - Acquired coagulopathies
- Certain
  - Congenital coagulopathies
  - Control of therapies

The Future

- Functional assays mimicking as much as possible in vivo hemostasis
  - Global tests
  - Plasma, platelet & blood cells
  - Protein C & antithrombin activators

Thrombin Generation Tests ?

Desirable Features of the Thrombin Generation Test

- Low tissue factor
- Platelet-rich plasma (possibly whole blood)
- Synthetic fluorogenic substrate