CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

CREMONA 10 MARZO 2017

Coagulopatie congenite: presentazione clinica e diagnosi

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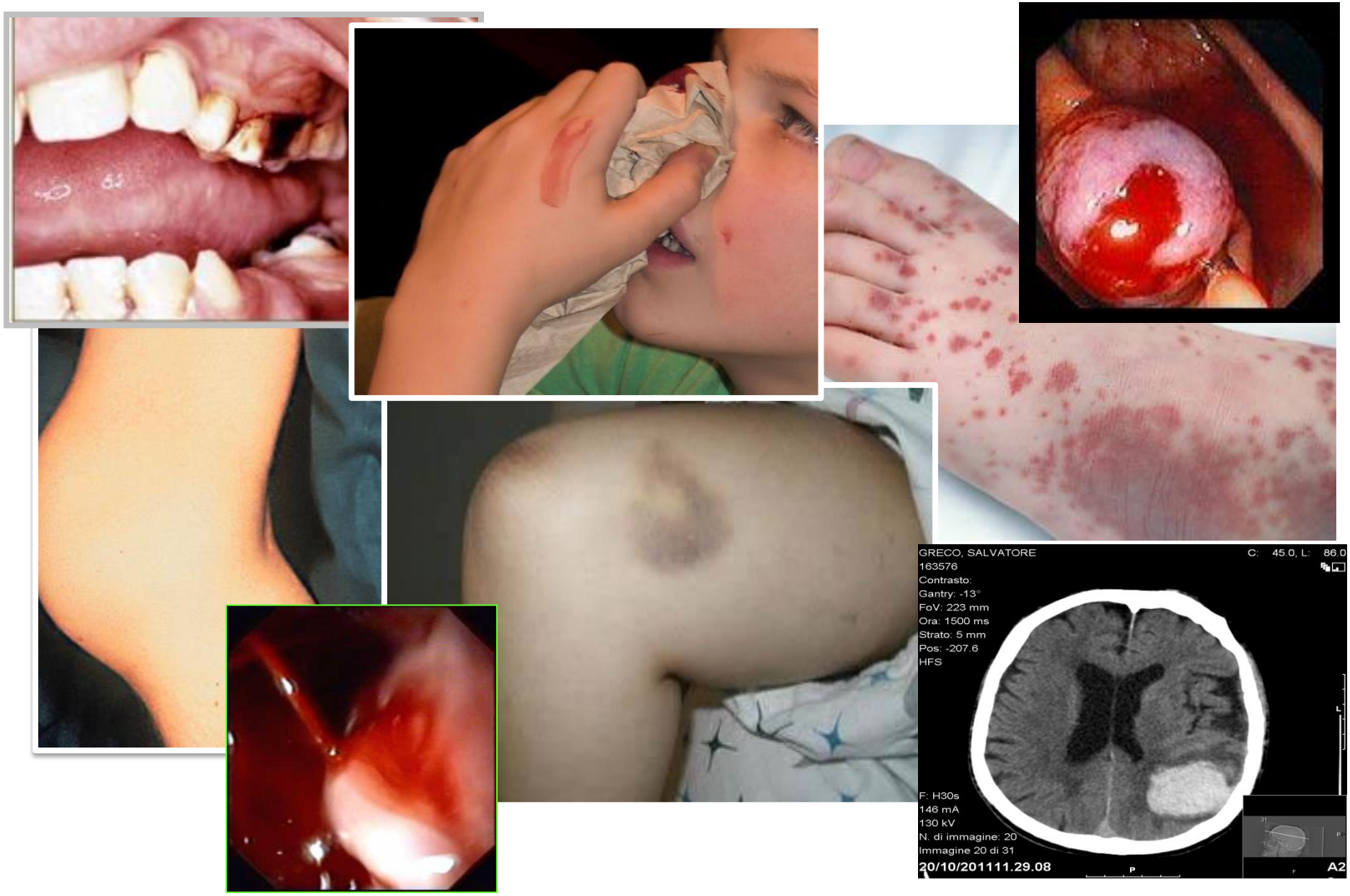
AOU Federico II, Napoli

Malattie emorragiche congenite

- Alterazioni **geneticamente determinate**
  - Familiare, sporadica
- di una proteina coinvolta direttamente nel sistema emostatico o nella regolazione della sintesi o della funzione di una o più proteine di tale sistema
- che si esprime con una **tendenza emorragica** di diverso impatto clinico
  - Esordio clinico (e diagnosi) precoce o meno

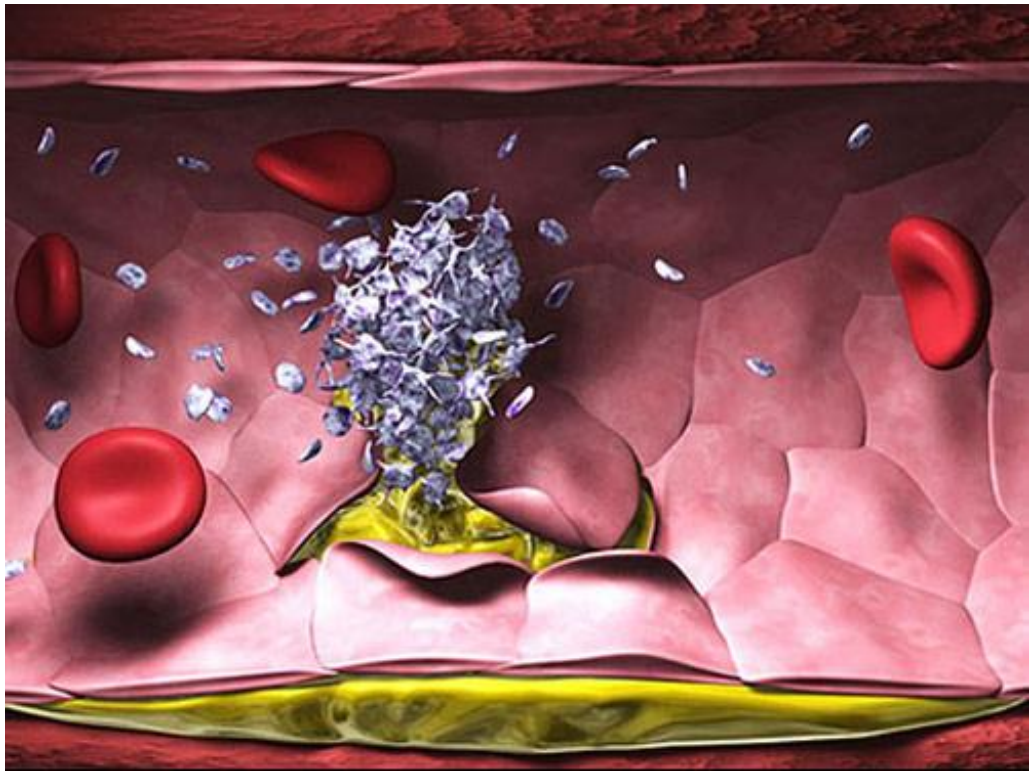
Clinical aspects of bleeding



Normal Hemostasis

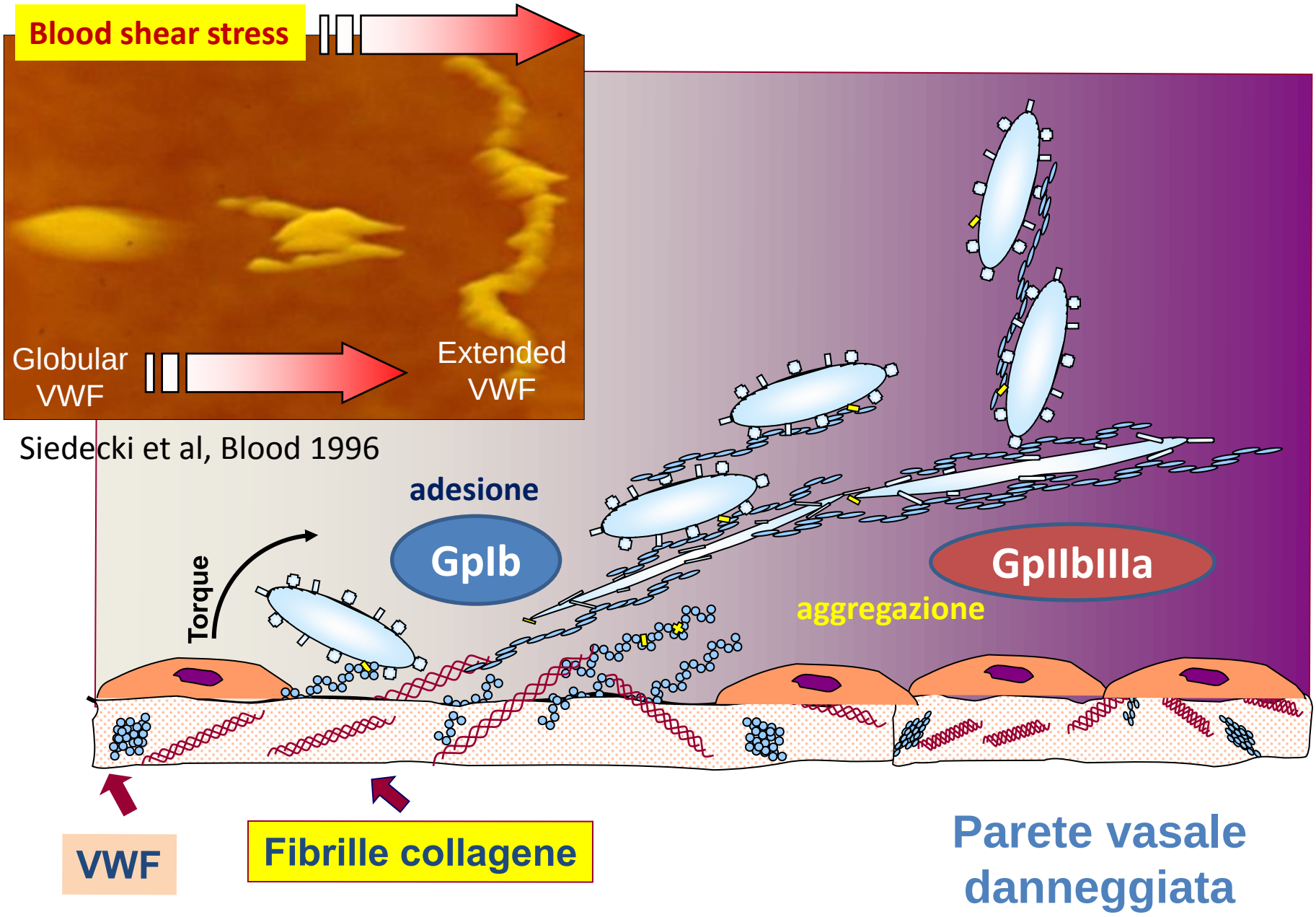
Dependent on 3 main factors:

1. Vascular endothelium
2. Platelets
3. Coagulation system

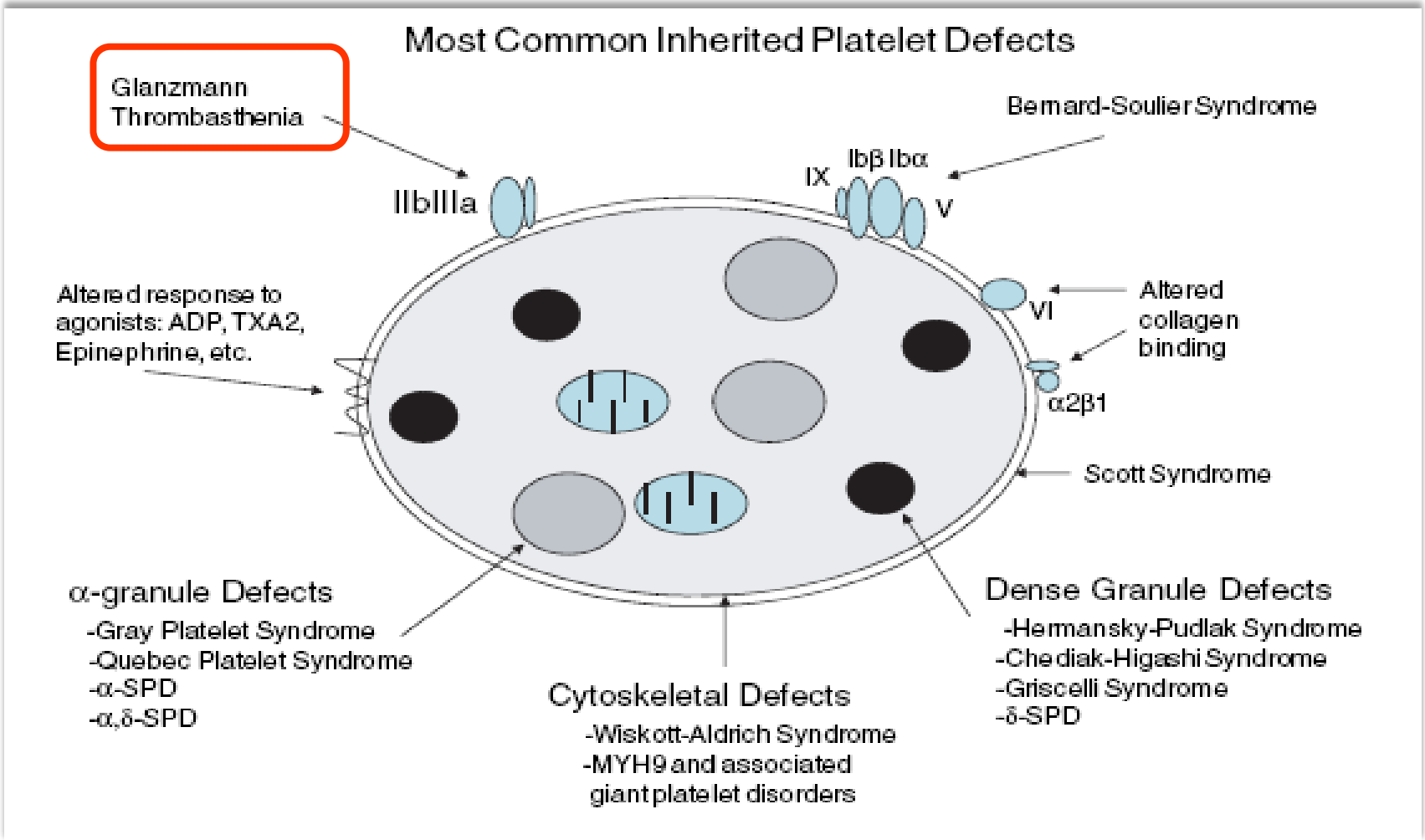


Regulation systems

VWF e fase vaso-piastrinica



Identified platelet function defects



Simon et al, Haemophilia, 2008

Bleeding pattern in

Glanzmann's Thrombastenia

64 patients, France,
+ 113 patients, literature

Menorrhagia	98%
Easy bruising/purpura	86%
55%	
GI bleeding	12%
Hematuria	6%
Hemarthrosis	3%
CNS bleeding	2%
Visceral hematoma	1%

George et al, Blood, 1990

382 patients, South Iran

Epistaxis	49.7%
Gingival bleed.	22.8%
Ecchymosis	14.1%
Menorrhagia	12.9%
Excessive at surgery /circumcision	6.4%
GI bleeding	4.7%
Hematoma	4.7%
Petechia/purpura	1.0%
Umbilical cord bl.	0.5%
CNS bleeding	0.3%
Hemarthrosis	0.3%

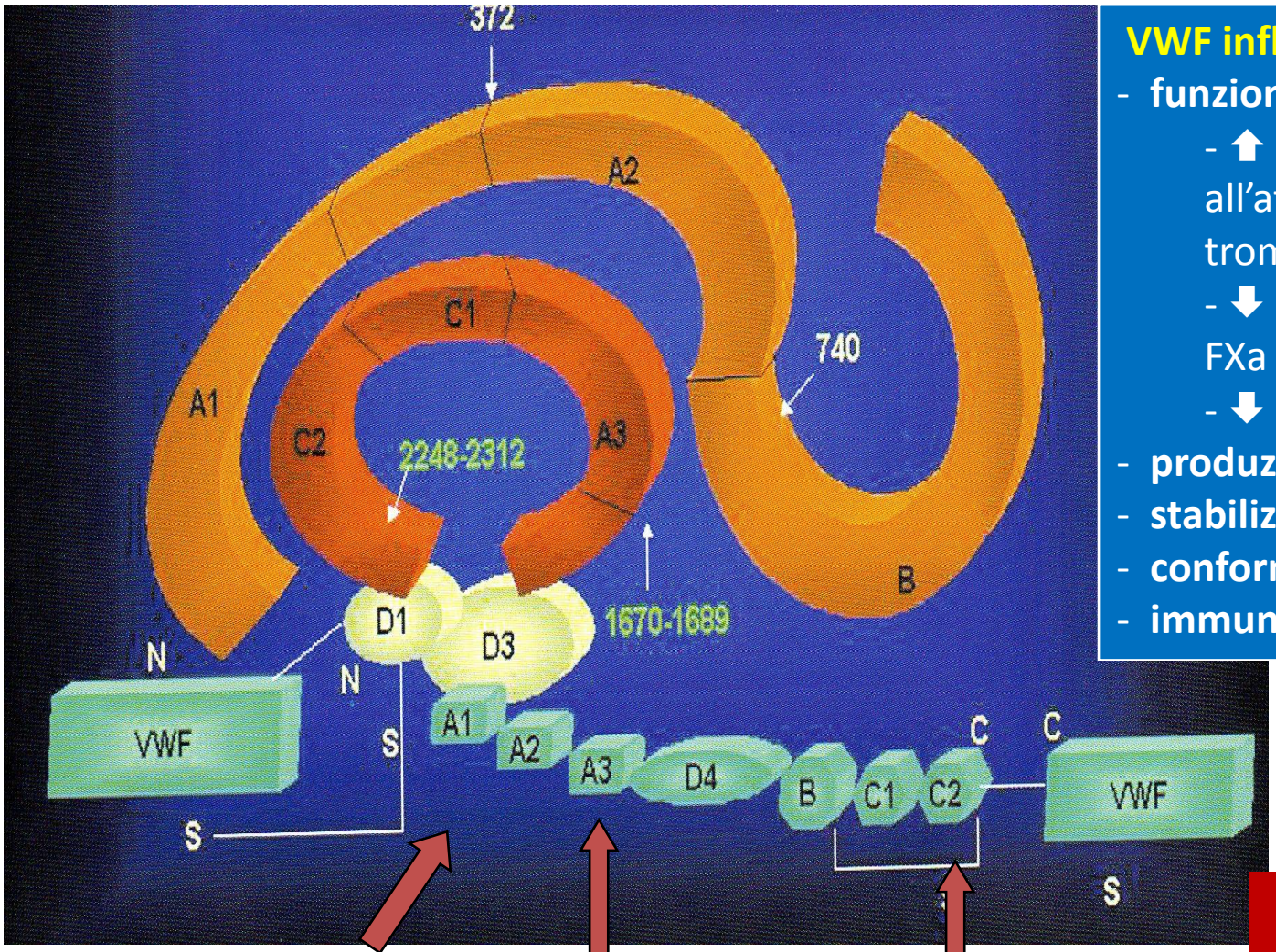
Toogeh et al, Am J Hematol, 2004

Bleeding symptoms in Italian vWD patients

Bleeding symptoms (%)	Type 1 (N=944)	Type 2 (N=268)	Type 3 (N=74)
Epistaxis	56	63	74
Menorrhagia	31	32	32
Bleeding after dental extraction	31	39	53
Hematomas	14	19	31
Bleeding after wounds	36	40	50
Gums bleeding	30	37	48
Postoperative bleeding	20	23	41
Postpartum bleeding	17	18	26
GI bleeding	5	11	18
Joint bleeding	2	5	42
Hematuria	2	4	11
C.N.S. bleeding	0.5	2	8

Federici et al, Haemophilia 2002 8, 607–621

Il complesso FVIII/VWF



VWF influenza FVIII per

- **funzione**
  - ⬆ suscettibilità all'attivazione da parte della trombina
  - ⬇ suscettibilità ad aPC e FXa
  - ⬇ binding a fosfolipidi
- **produzione**
- **stabilizzazione**
- **conformazione**
- **immunogenicità**

GP Ib

collagene

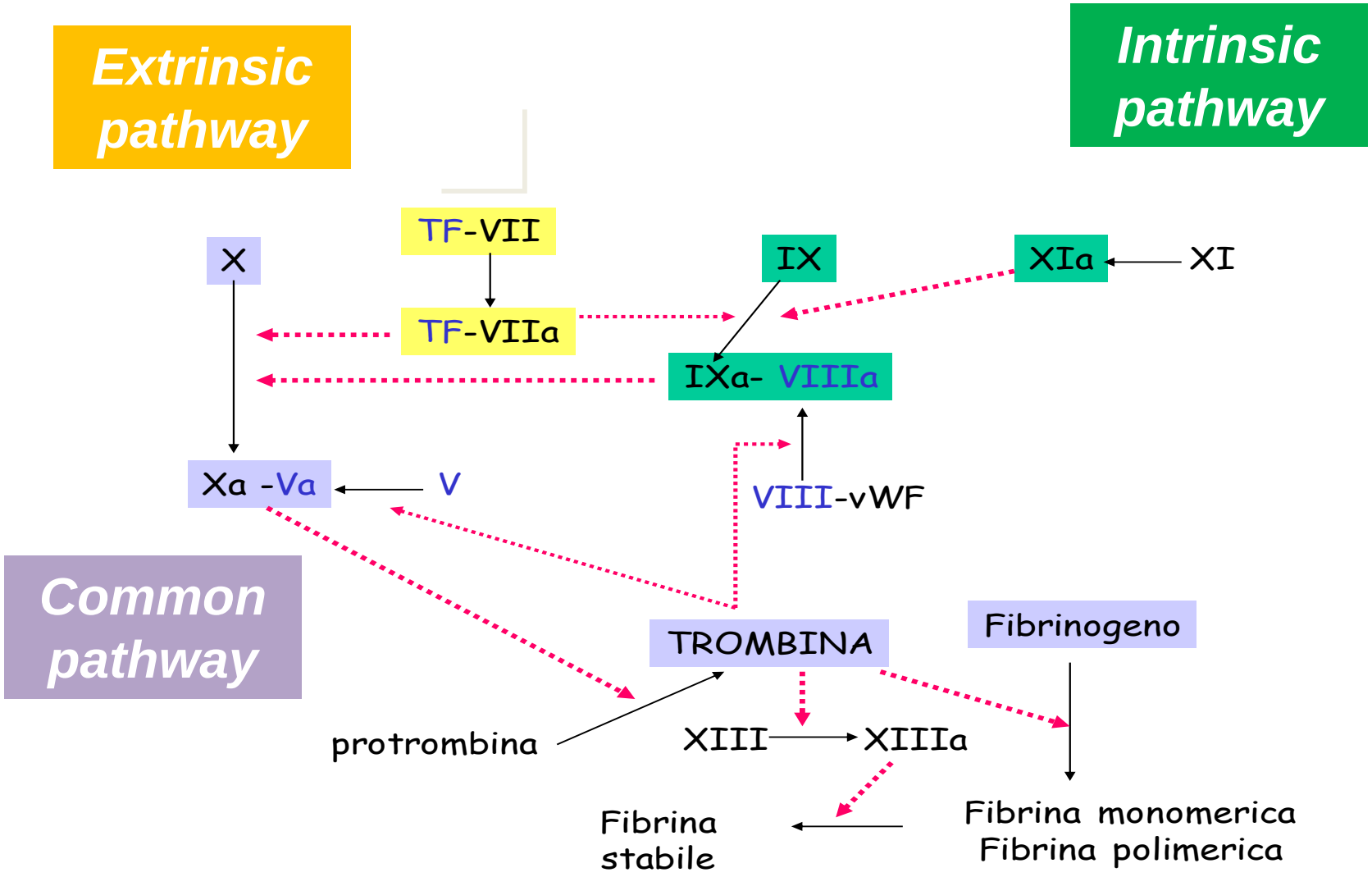
GP IIbIIIa

interazione piastrine-endotelio piastrina-piastrina

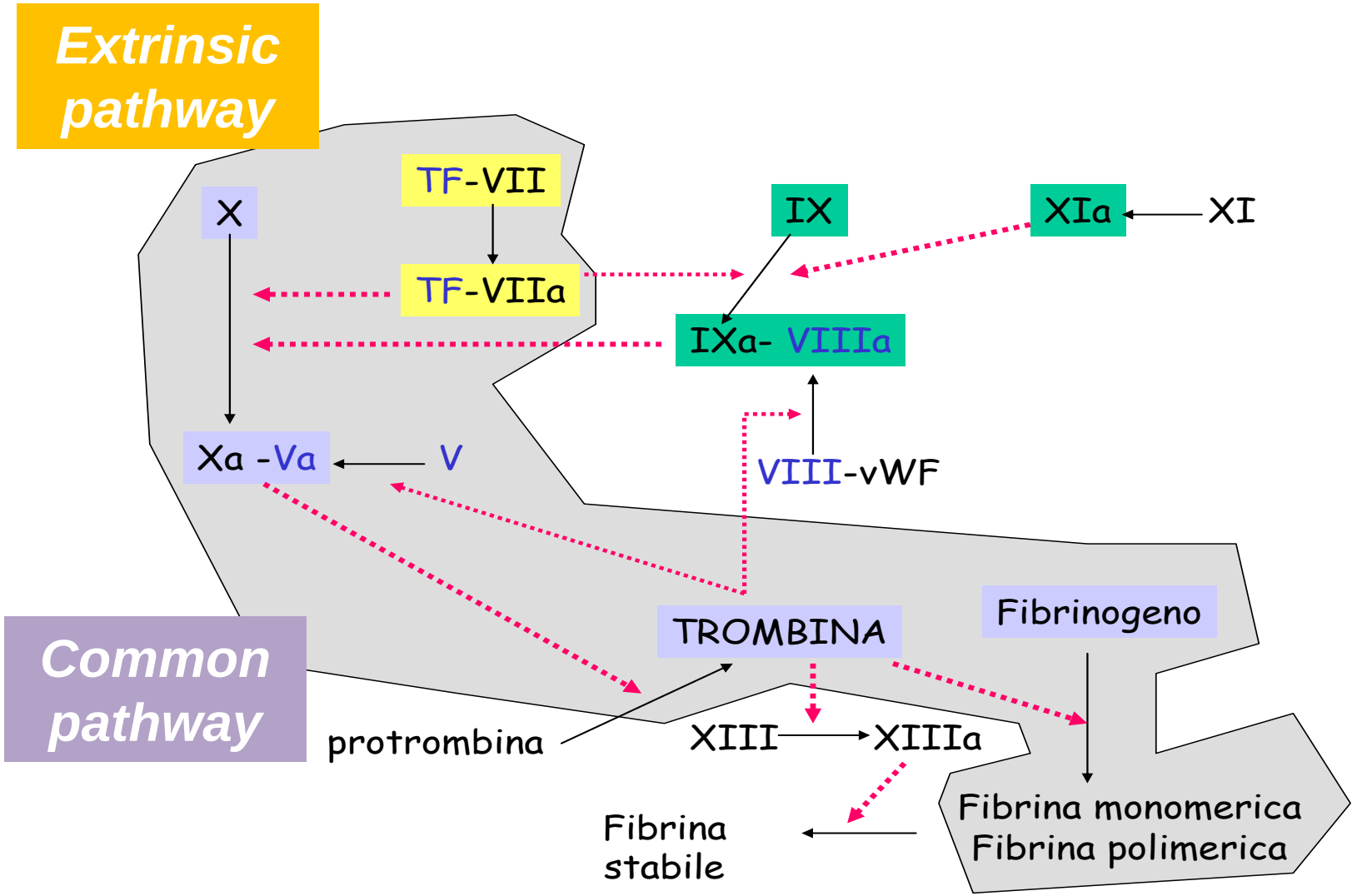
Congenital coagulation factor deficiencies

Factor	Estimated incidence	Chromosome	Inheritance
vWF (vW Disease)	1: 5000	12	Autos. Dom. (o Autos. Rec.)
F VIII (Haemofilia A)	1: 10.000	X	X-linked rec.
F IX (Haemofilia B)	1: 60.000	X	X-linked rec.
F VII	1: 500.000	13	Autos. Recess.
F X	1:1.000.000	13	Autos. Recess.
Fibrinogen	1:1.000.000	4	Autos. Recess.
F V	1:1.000.000	1	Autos. Recess.
FV+FVIII	1:1.000.000	18 (LMAN1) 2 (MFCD2)	Autos. Recess.
F XI	1:1.000.000	4	Autos. Recess.
F XIII	1:2.000.000	6 (sub. A) 1 (sub. B)	Autos. Recess.
F II	1:2.000.000	11	Autos. Recess.
VKD	1.2.000.000	2 (GGCX) 16 (VKORC1)	Autos. Recess.

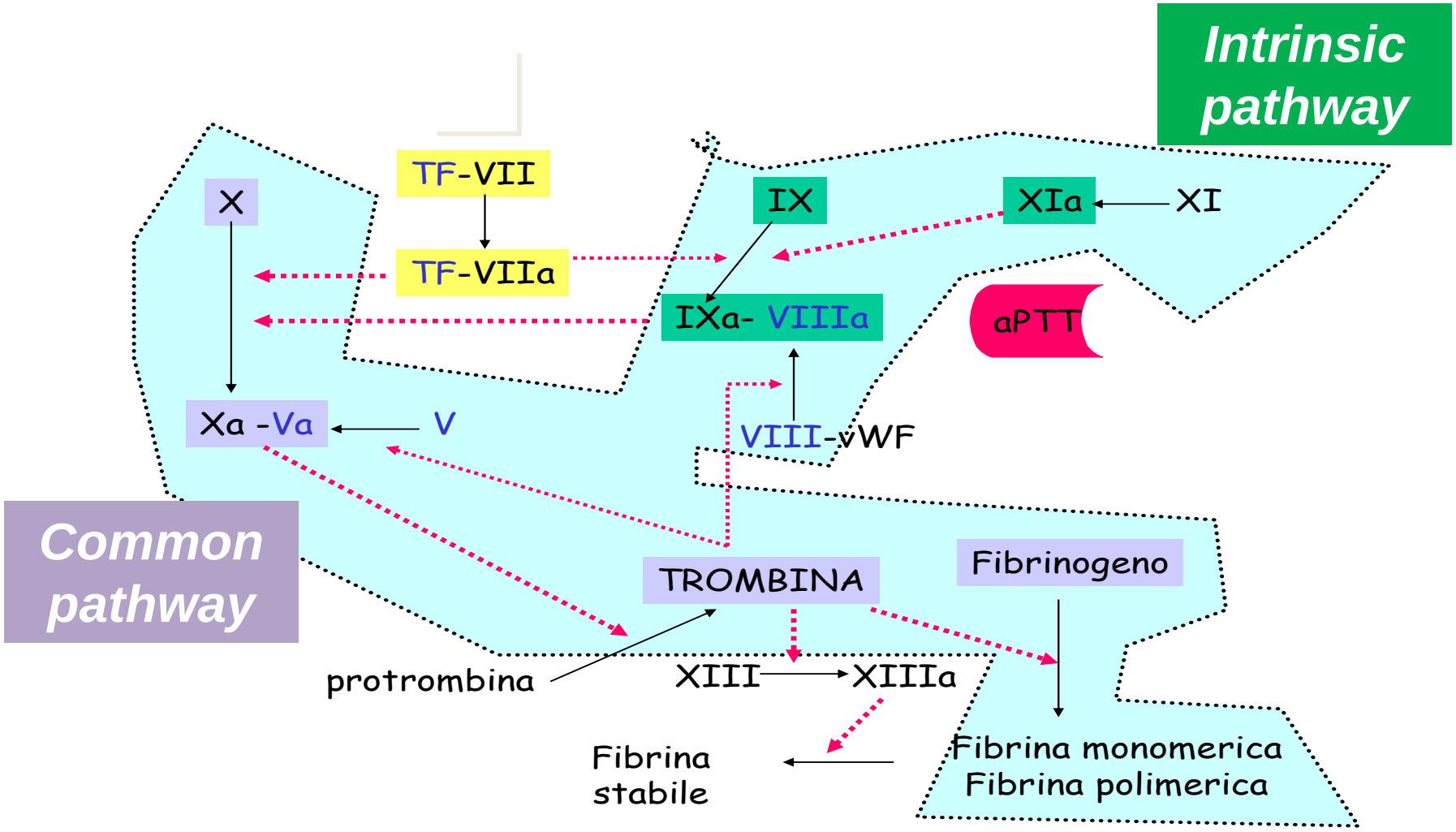
Coagulation cascade



Tempo di Protrombina - PT



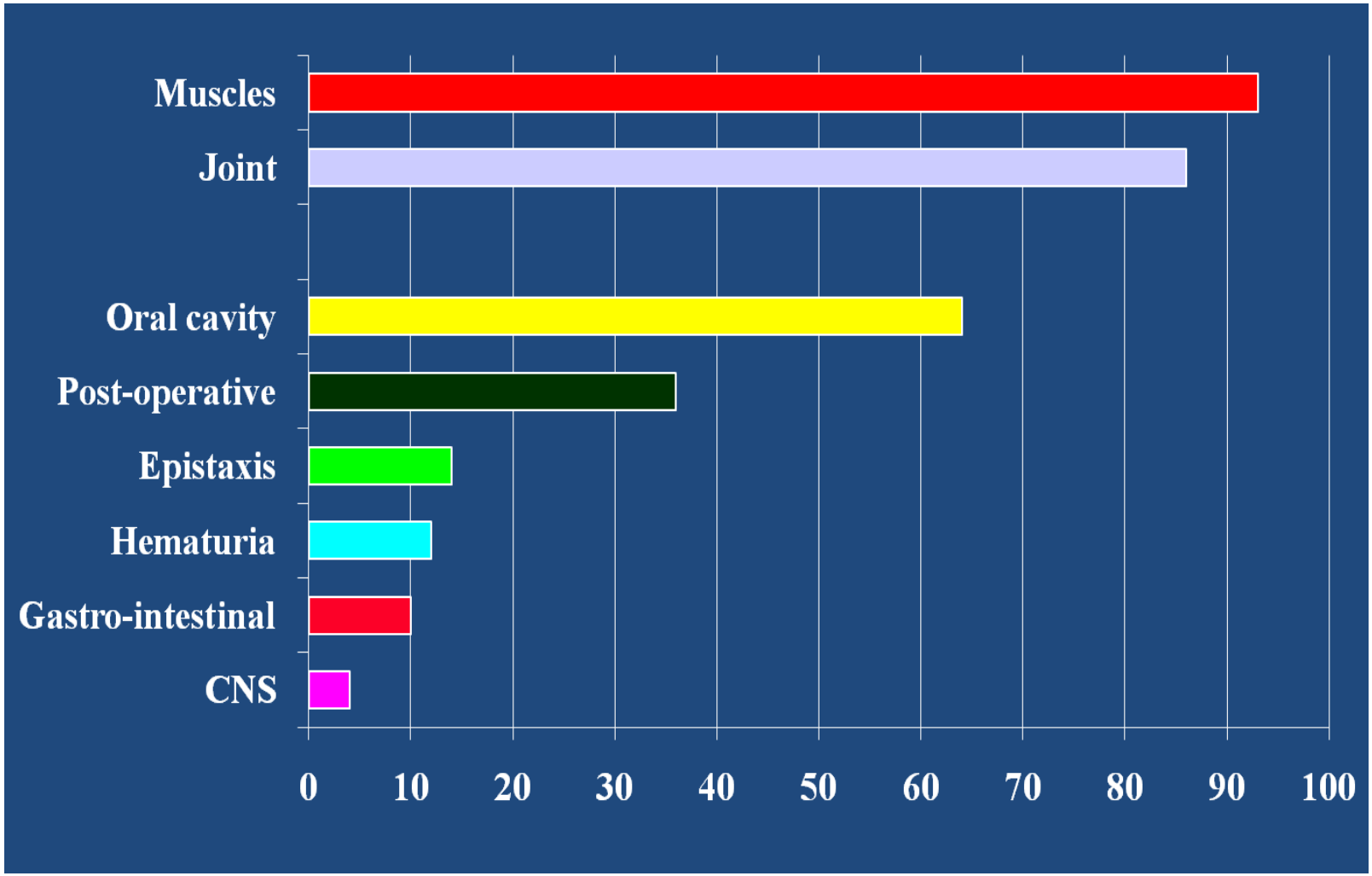
Tempo di tromboplastina parziale attivata - aPTT



I test di screening nelle coagulopatie congenite

Difetto	*APTT*	*PT*
Fibrinogeno	↑↑↑	↑↑↑
FII	↑↑↑	↑↑↑
FV	↑↑	↑↑
FVII	N	↑↑
FVIII-FIX	↑↑	N
FX	↑↑	↑↑
FXI	↑↑ o ↑↑↑	N
FXII	↑↑↑	N
FXIII	N	N

Bleeding sites in haemophilia



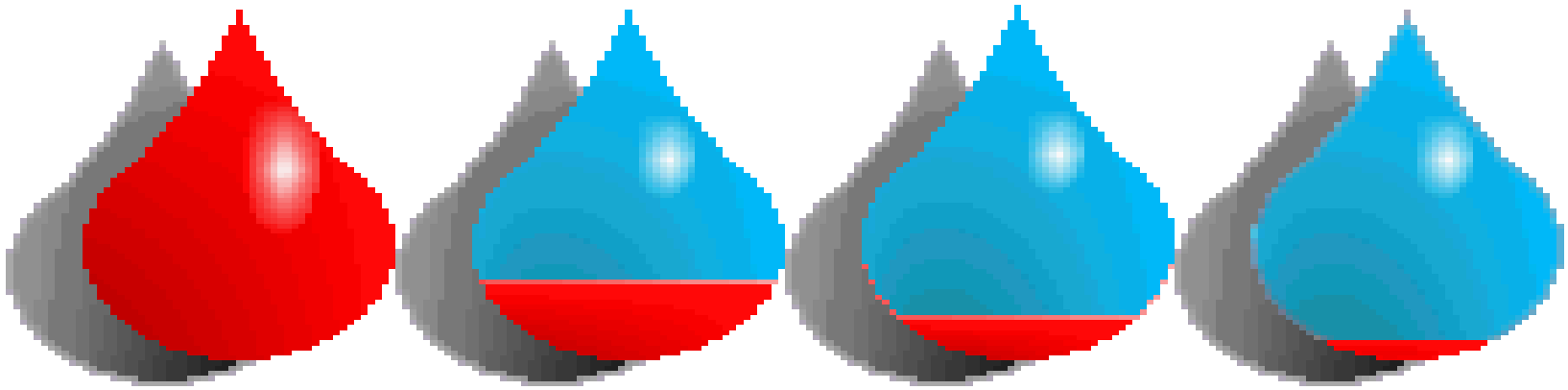
at least once in life, n=100

Lak & Peyvandi, Br J Haematol 2000

DISEASE SEVERITY

Degrees of severity in haemophilia

Factor VIII or IX activity



Normal	Mild	Moderate	Severe
	>5-40%	1-5%	<1%

Bleeding usually associated with teeth extractions, surgery, severe trauma. Often diagnosed later in life

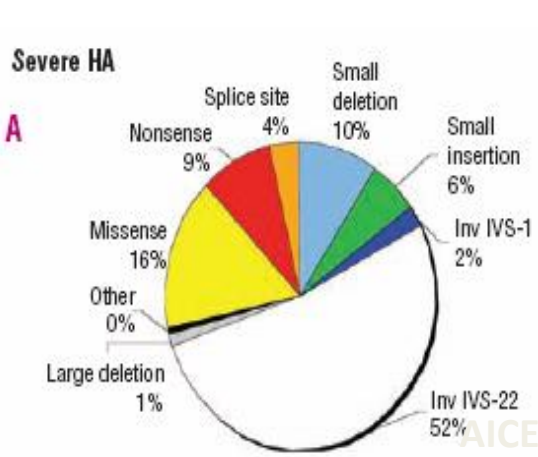
Bleeding usually associated with trauma. Rarely similar to severe haemophilia

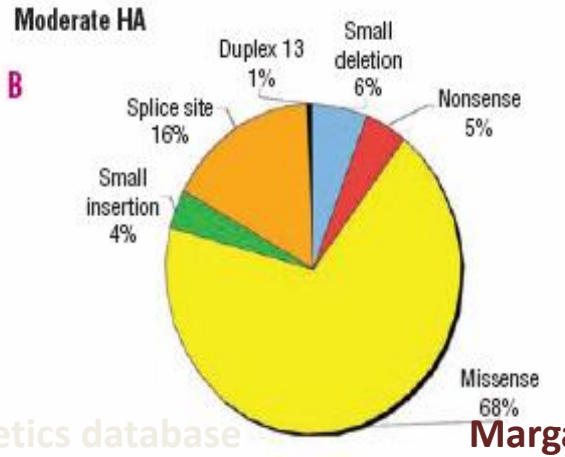
Bleeding frequent, often spontaneous (joints, muscles, any site). Usually diagnosed in first year of life.

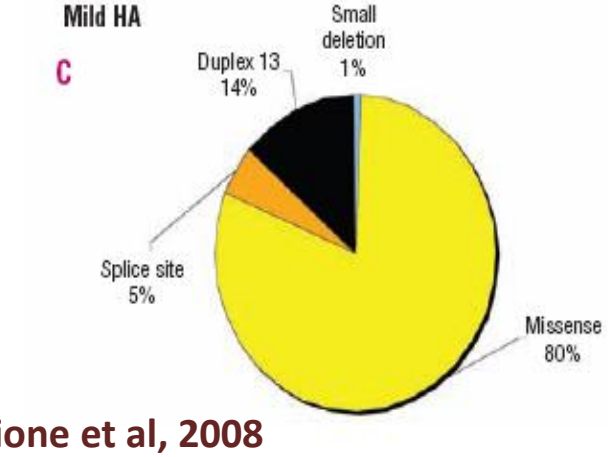
Severity of FVIII defect and type of mutations

www.geneclinics.org

Probands with Severe Hemophilia A	Probands with Mild to Moderate Hemophilia A	Genetic Mechanism
45%	0%	***FVIII* gene inversion**
45%	5-20%	**Gene deletions or rearrangements, frameshift, splice junction, nonsense or missense mutations**
10%	**80-95%**	**Missense or occasionally splicing or in-frame deletion mutations**

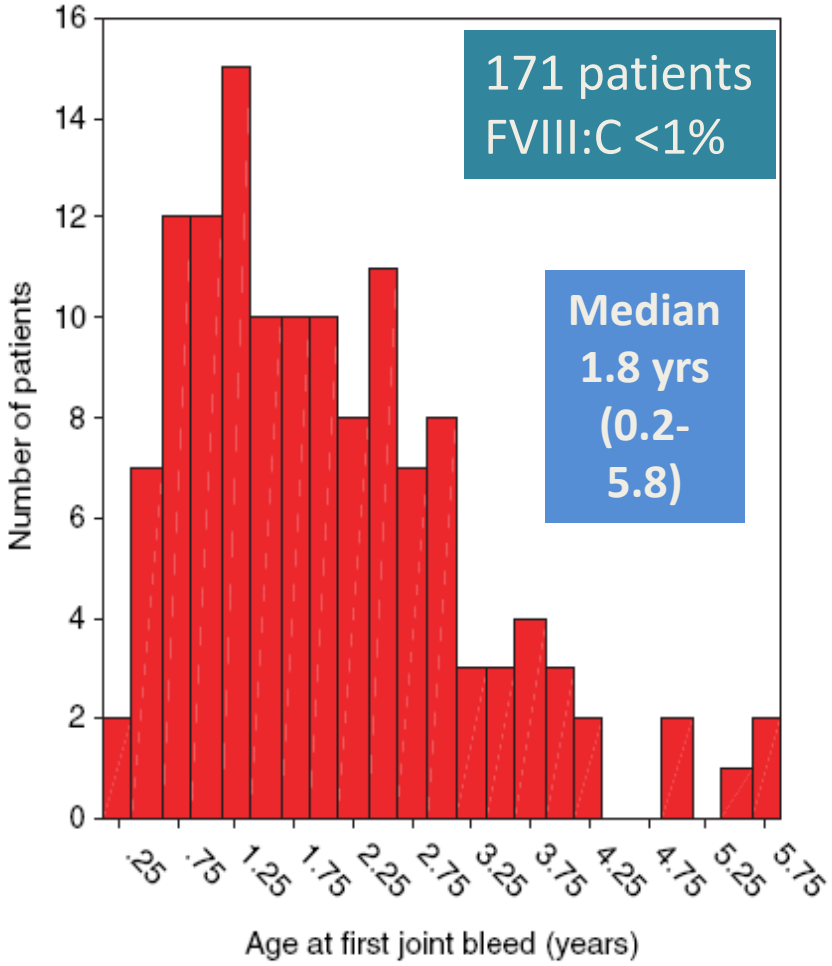


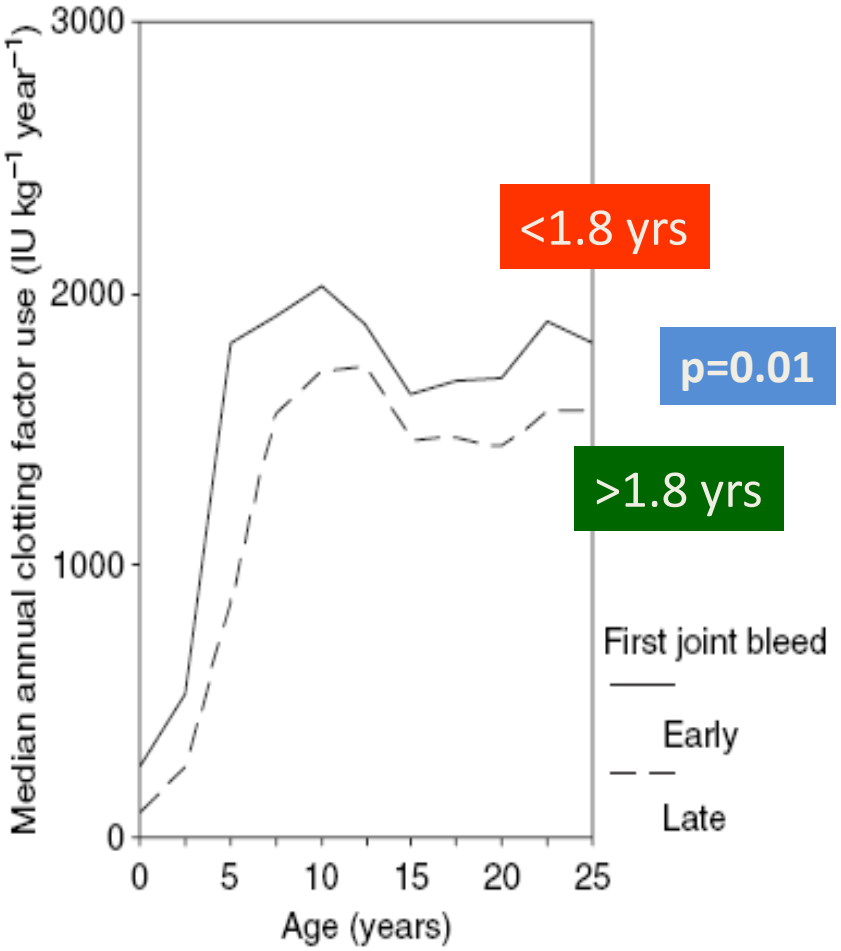




Margaglione et al, 2008

Age at first joint bleed and clinical severity

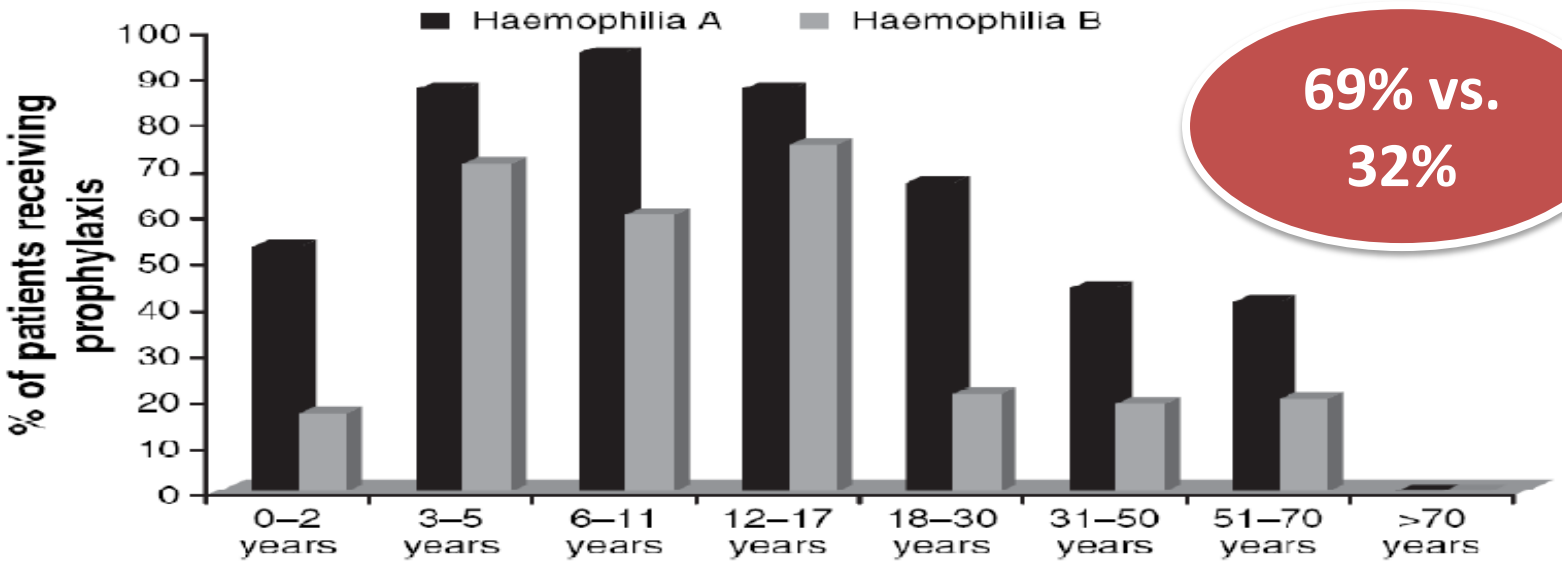




van Dijk et al, Haemophilia 2005

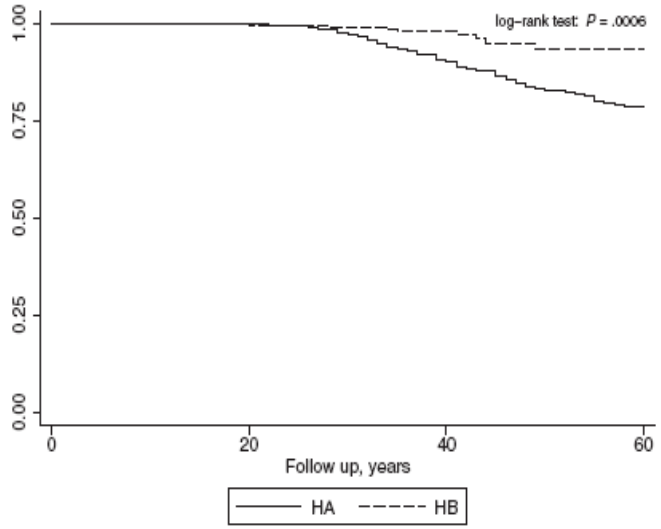
A tendency to more severe Pettersson scores was also shown in patients with earlier age at first joint bleed.

HA vs. HB: a different clinical severity?



69% vs. 32%

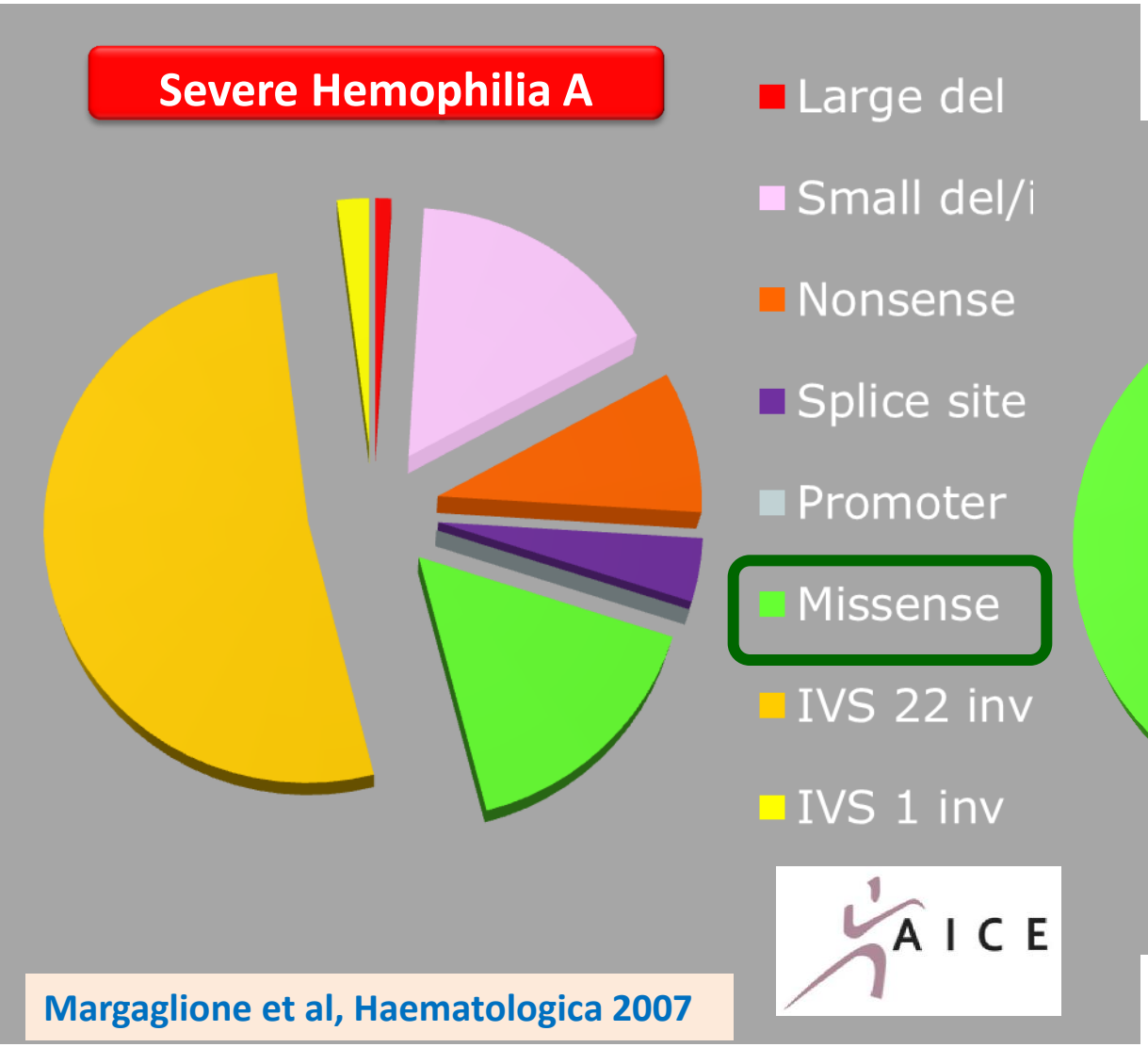
Biss et al, Haemophilia 2008



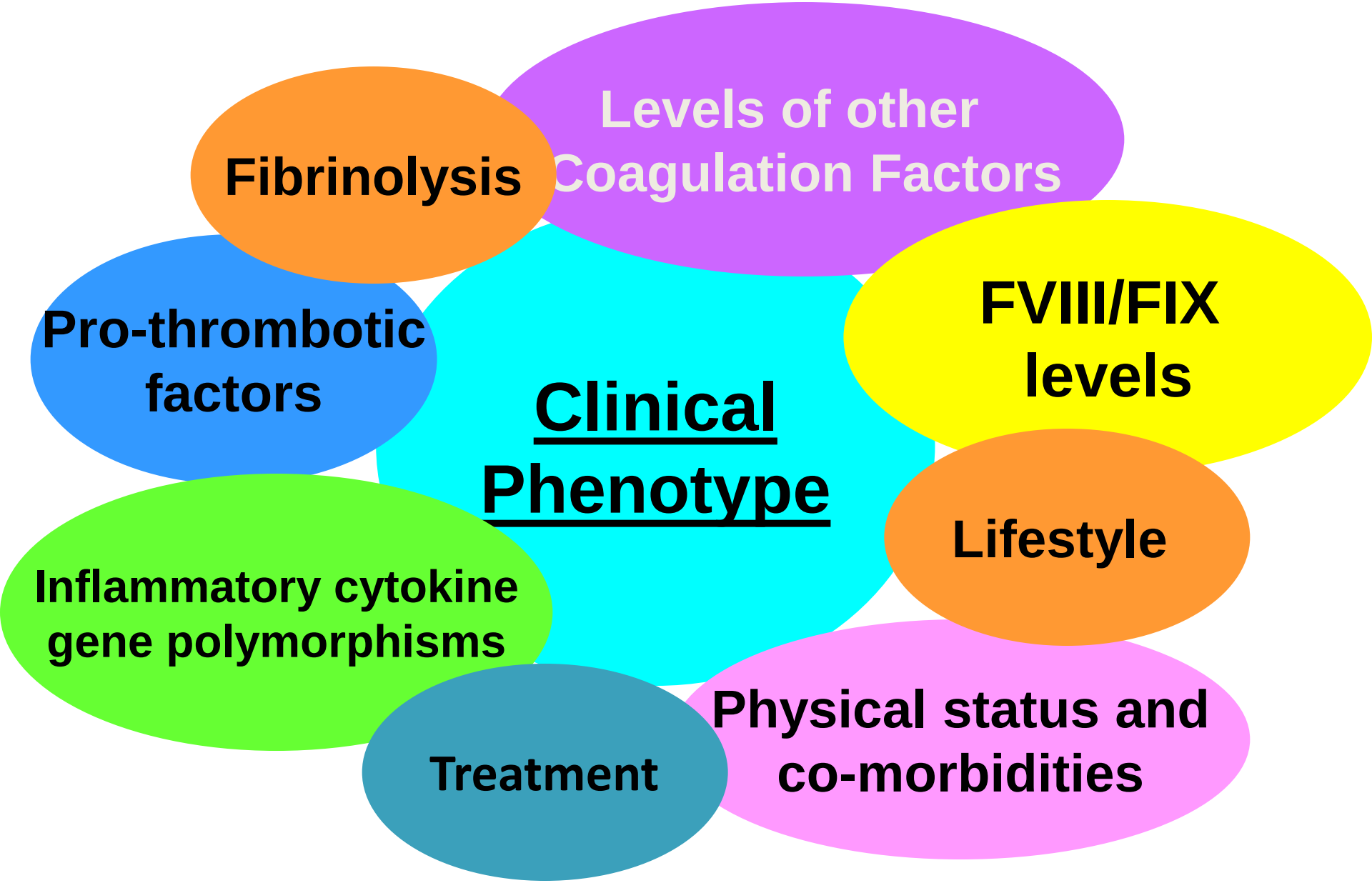
- 80-96% of reported joint arthroplasties in HA patients (literature review and Italian experience, 547 patients)
- The **3-fold higher risk of arthroplasty requirement** in HA vs. HB may reflect a different clinical severity.

Tagariello et al, Blood 2009

Type of causative gene defect in hemophilia A and B

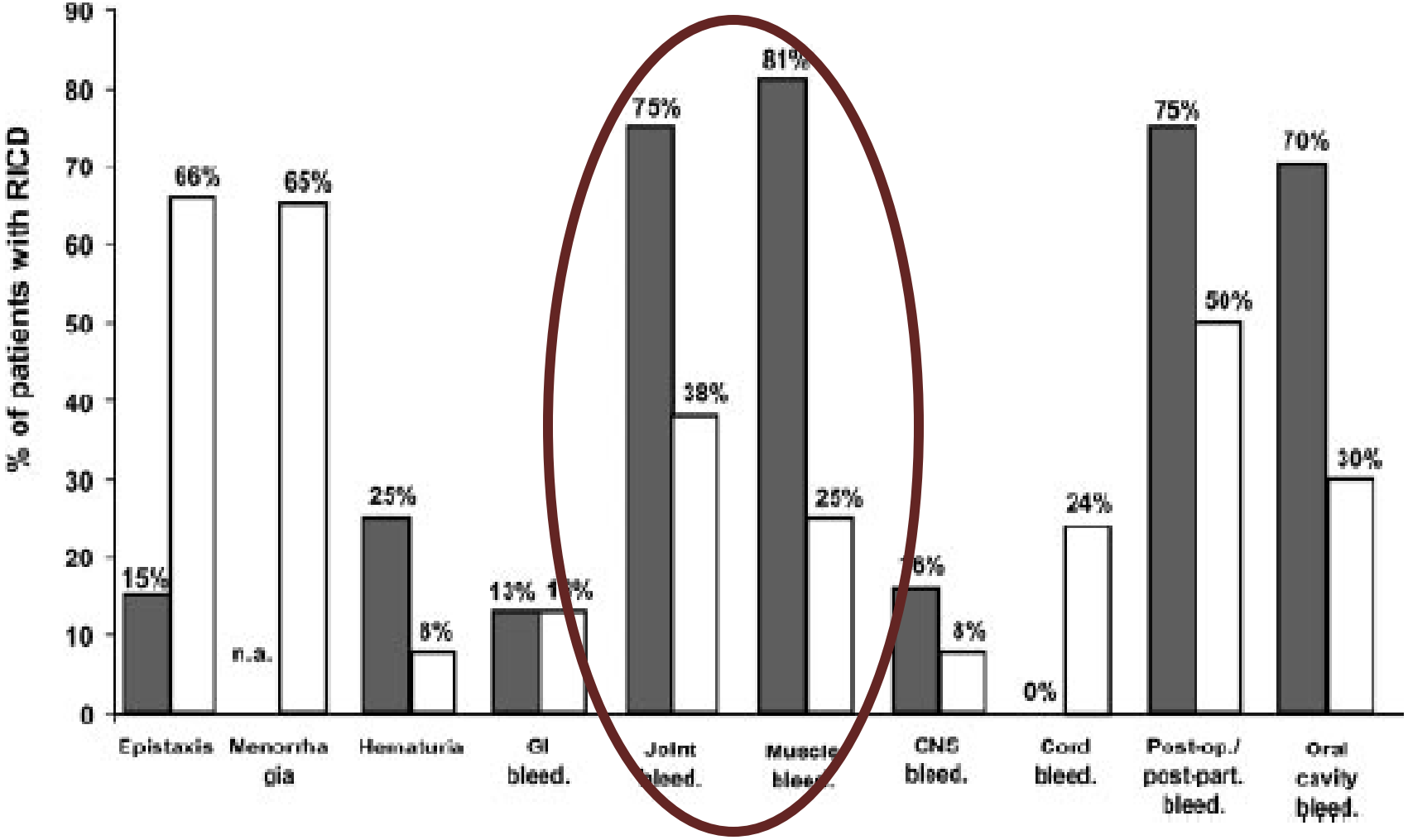


AICE



van den Berg, JTH 2007, modified

Bleeding symptoms in hemophilia vs. RCBD



Mannucci et al, Blood 2004

RBDs: the peculiarity of Afibrinogenemia and FXIII deficiency

Symptom	Afibrinogenemia	FXIII deficiency
Bleeding from umbilical stump*	75 %	73 %
Spontaneous cerebral bleeding	10 %	30 %
Miscarriage	> 50 %	> 50 %

*in these cases usually early diagnosis.

Lak et al, Br J Haematol 1999; Inbal A et al, Semin Thromb Hemost 2003

Gravità clinica o di laboratorio: RBD

Table 3 Proposal of the project on RBDs

Coagulant factor	Laboratory phenotype: Coagulant activity		
	Severe	Moderate	Mild
Fibrinogen	Undetectable clot	0.1–1g L^{-1}	> 1 g L^{-1}
FII	Undetectable activity	≤ 10%	> 10%
FV	Undetectable activity	< 10%	≥ 10%
FV + FVIII	< 20%	20–40%	> 40%
FVII	< 10%	10–20%	> 20%
FX	< 10%	10–40%	> 40%
FXIII	Undetectable activity	< 30%	≥ 30%

Table 4 Severity classification of FVII deficiency, as reported in table 1 of reference [9] *Lapecorella, Haemophilia 2008*

Severe	They had at least one of the following symptoms: GI or CNS bleeding or hemarthrosis with or without other bleeds
Moderate	Those who had three or more symptoms with the exception of GI CNS bleeding or hemarthrosis
Mild	Those who had one or two symptoms with the exception of GI CNS bleeding or hemarthrosis

CNS, central nervous system; FVIIc, factor VII coagulation activity; GI, gastrointestinal

Peyvandi et al, 2012

Factor deficiency	Beta (95% CI)	Factor activity for asymptomatic patients (95% CI)	Factor activity for Grade I bleeding (95% CI)	Factor activity for Grade II bleeding (95% CI)	Factor activity for Grade III bleeding (95% CI)
Fibrinogen, mg dL^{-1} (n = 26)	−40.22 (−54.24 to −26.19)	113.40 (22.80–204.01)	73.19 (0–164.14)	32.97 (0–126.39)	0 (0–90.61)
FV, U dL^{-1} (n = 50)	−5.96 (−10.74 to −1.19)	11.94 (0–33.73)	5.98 (0–27.71)	0.01 (0–22.72)	0 (0–18.63)
FV + VIII, U dL^{-1} (n = 18)	−9.52 (−15.07 to −3.96)	43.38 (24.90–61.86)	33.87 (15.71–52.02)	24.35 (4.87–43.82)	14.83 (0–36.98)
FVII, U dL^{-1} (n = 203)	−5.74 (−8.33 to −3.15)	24.87 (14.88–34.86)	19.13 (8.48–29.78)	13.39 (1.54–25.25)	7.66 (0–21.11)
FX, U dL^{-1} (n = 34)	−15.45 (−21.62 to −9.28)	55.91 (28.69–83.12)	40.45 (13.99–66.91)	25.00 (0–52.12)	9.55 (0–38.66)
FXI, U dL^{-1} (n = 125)	−0.35 (−4.02 to 3.32)	26.05 (13.56–38.54)	25.70 (12.97–38.43)	25.35 (11.38–39.32)	25.00 (9.03–40.97)
FXIII, U dL^{-1} (n = 33)	−14.22 (−18.18 to −10.26)	31.07 (10.83–51.31)	16.85 (0–37.13)	2.63 (0–23.71)	0 (0–10.97)

Sospetto di coagulopatia congenita grave

- Sintomi emorragici a comparsa precoce, in età infantile o neonatale (talora molto gravi - emorragia dal cordone, emorragia cerebrale)
- Emartri, ematomi muscolari, ampie ecchimosi
- Anamnesi familiare silente (disordini autosomici recessivi o emofilie de novo) o solo maschi affetti (emofilia X-linked)

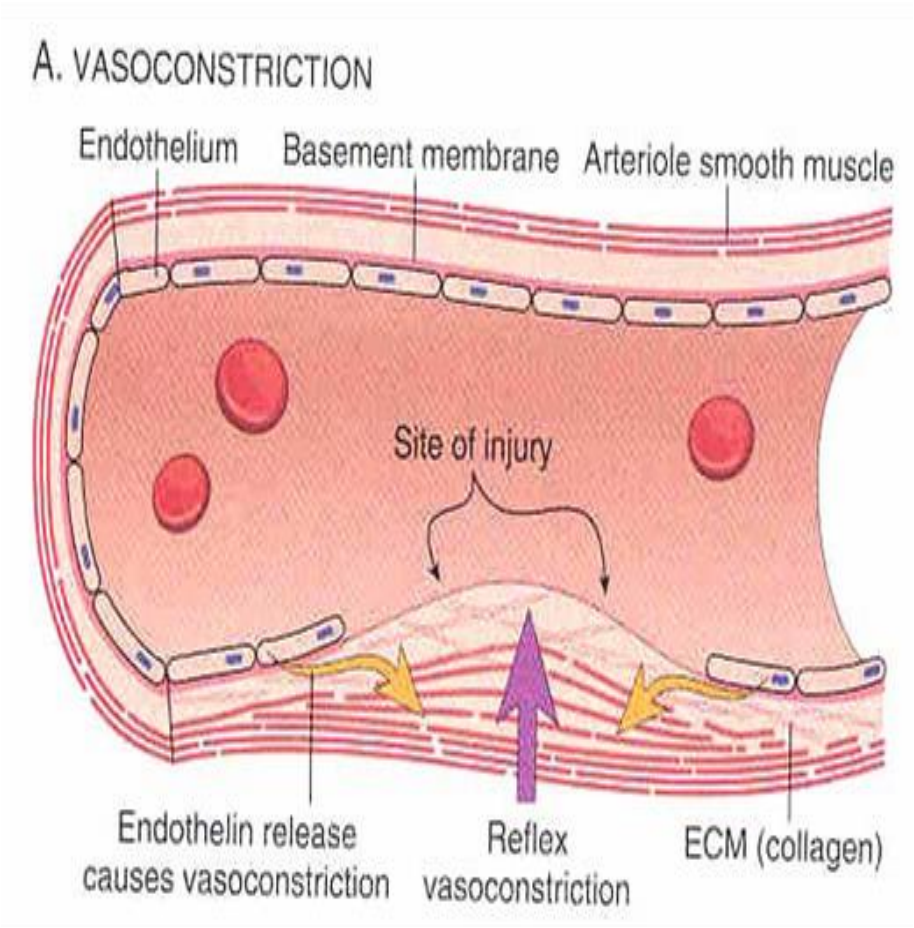
Impatto clinico delle MEC: sono tutte uguali ?

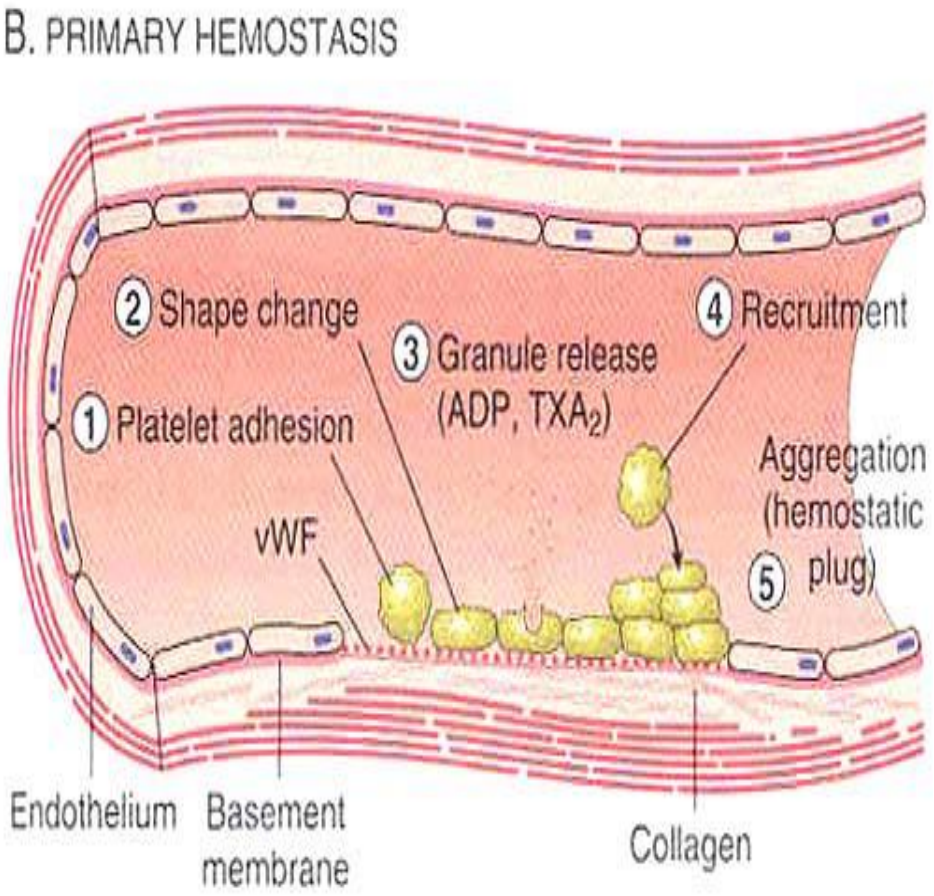
- Fase di contatto (FXII, PK, HMWK) → **asintomatici**
- FXI → Clinica eterogenea
- FV, FVII, FX → Tendenza emorragica moderata/grave
- FVIII, FIX → Sindromi emofiliche, correlazione tra clinica e gravità del difetto
- Fibrinogeno, FII, FXIII → Diatesi grave

Bleeding disorders: the tip of the iceberg?


Thank you

Fase vaso-piastrinica
Emostasi primaria

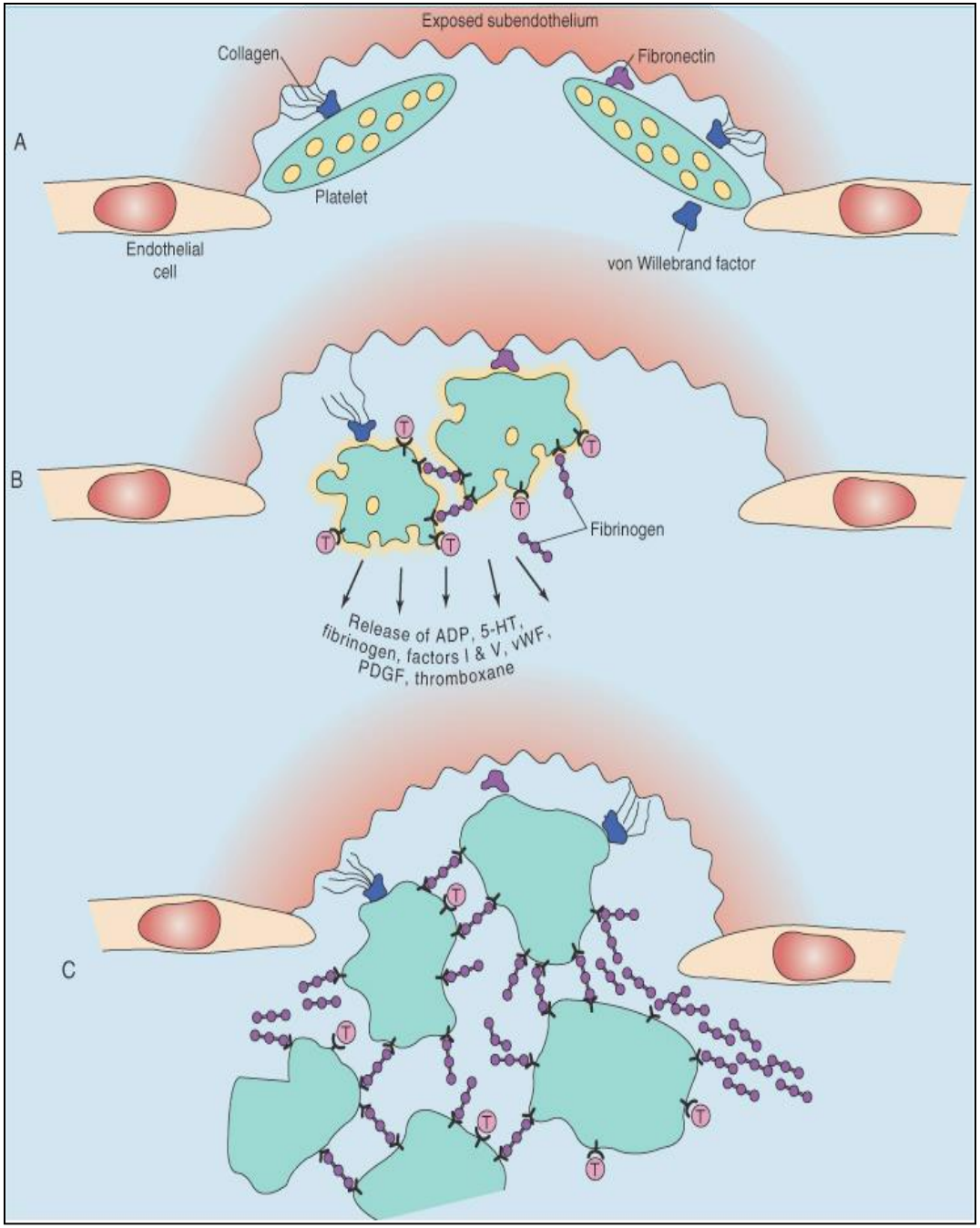




Adesione piastrinica

Attivazione e secrezione piastrinica

Aggregazione Piastrinica

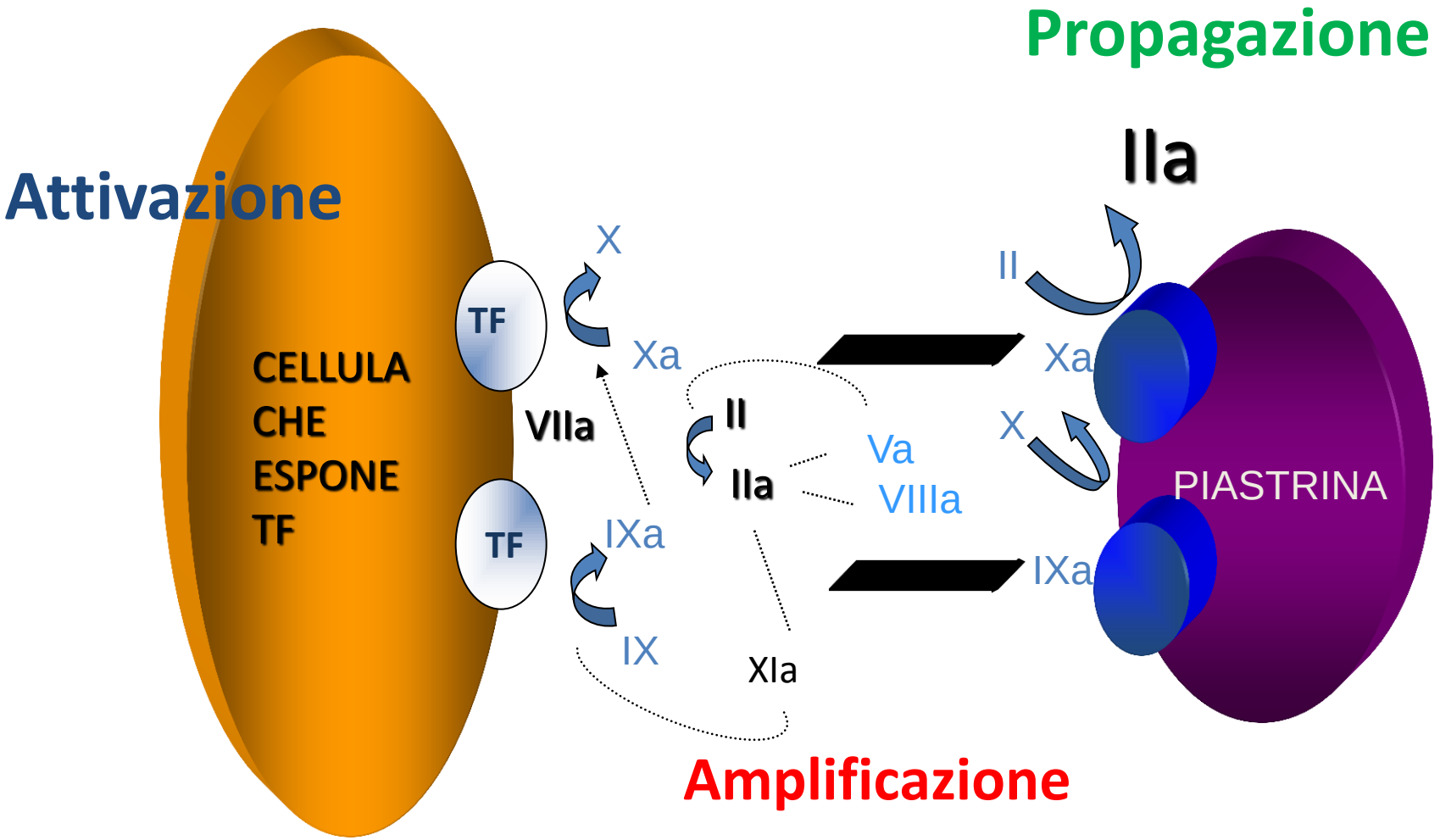


Classification of heritable platelet disorders

DISORDER	Site of gene defect	Estimated no. cases UK	Worldwide
Severe disorders of platelet function			
Wiskott-Aldrich Syndrome	WAS	<100	<1000
Glanzmann thrombasthenia	ITGA2B, ITGB3	<100	<1000
Bernard-Soulier syndrome	GP1BA, GP1BB, GP9	<100	<1000
Disorders of receptors and signal transduction			
Platelet cyclooxygenase deficiency	Unknown	<10	<100
Thromboxane synthase deficiency	Unknown	<10	<100
Thromboxane A2 receptor defect	TBXA2R	<10	<100
ADP receptor defect (P2Y12)	P2RY12	<10	<100
Disorders of the platelet granules			
Idiopathic dense-granule disorder (δSPD)	Unknown	<100	<1000
Hermansky-Pudlak syndrome	HPS1, AP3B1, HPS3, etc.	<100	>1000
Chediak-Higashi syndrome	LYST	<100	<1000
Paris-Trousseau/Jacobsen syndrome	11q23 deletion	<10	<100
Grey platelet syndrome	Unknown	<10	<100
Idiopathic α and dense-granule SPD	Unknown	<100	<1000
Disorders of phospholipid exposure			
Scott syndrome	ABCA1	<10	<10

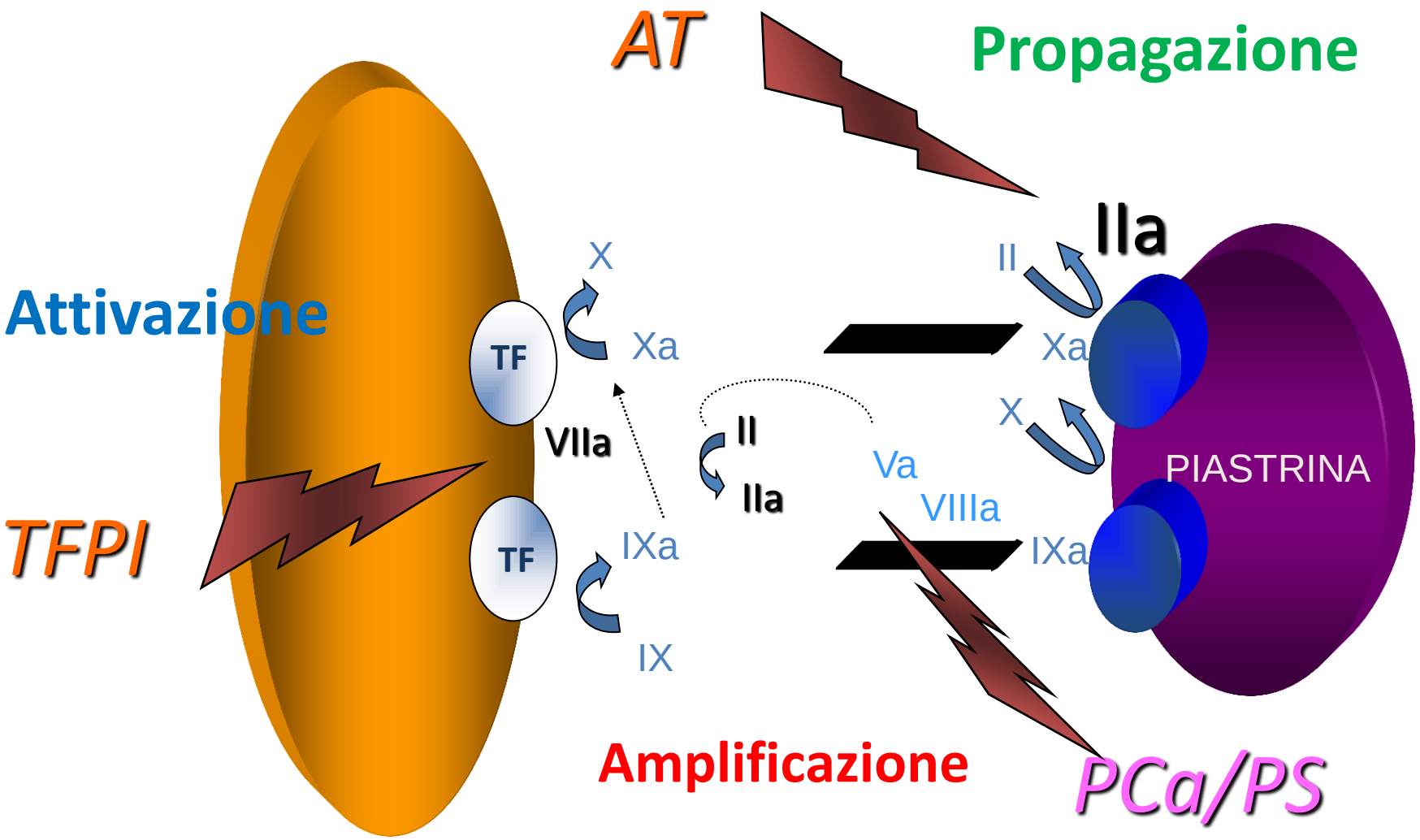
Bolton-Maggs et al, UKHCDO, Br J Haematol, 2006

Il modello cellulare della coagulazione

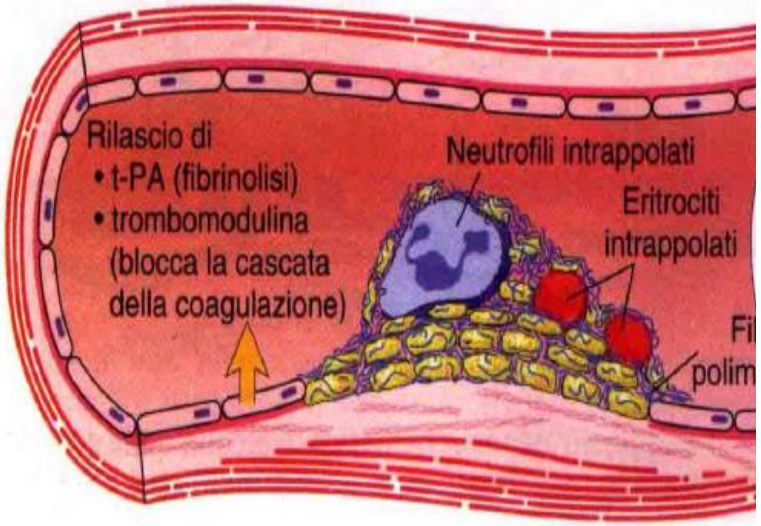


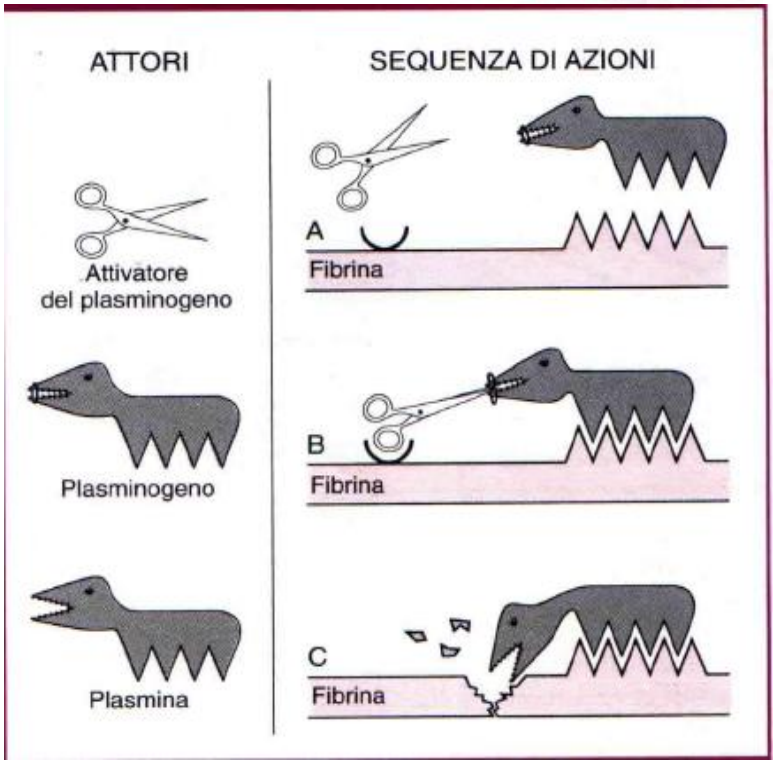
Hoffman, Blood Rev, 2003, mod.

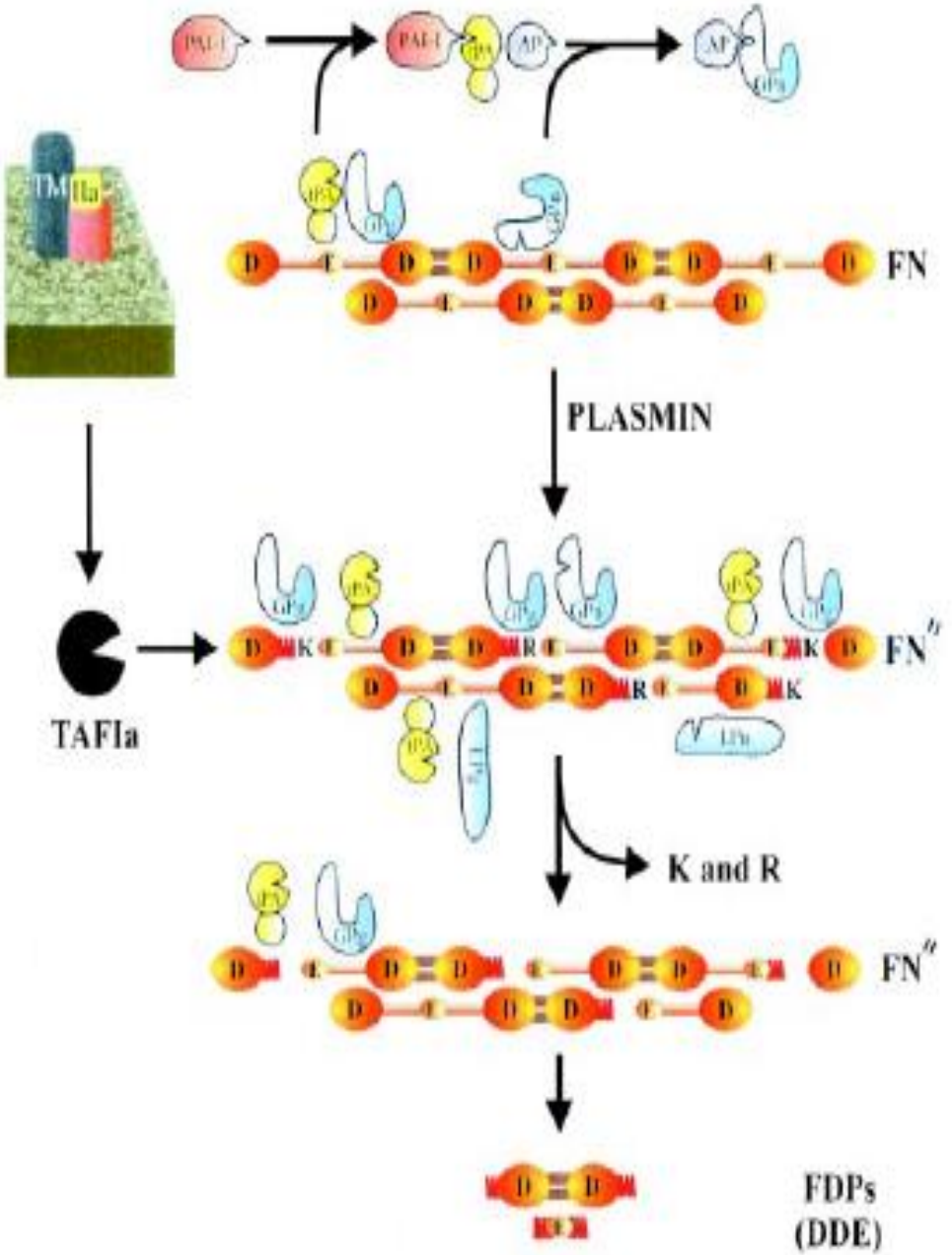
Meccanismi di controllo: gli anticoagulanti naturali

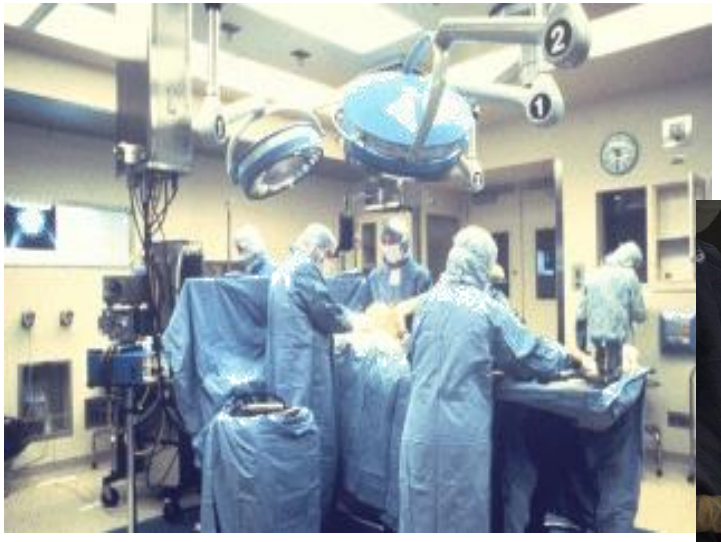


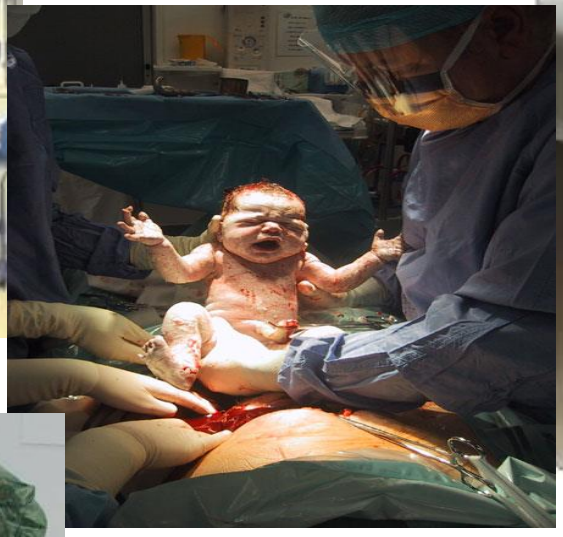
D. TROMBO E FATTORI ANTITROMBOTICI

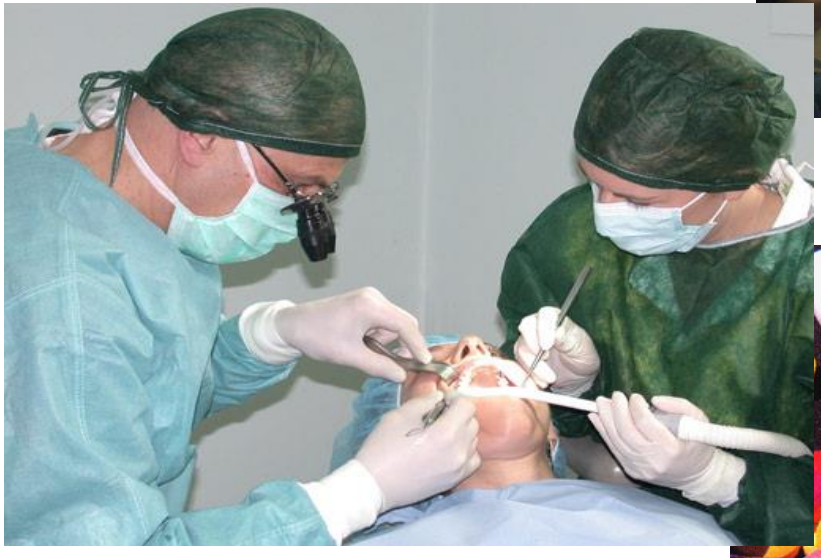


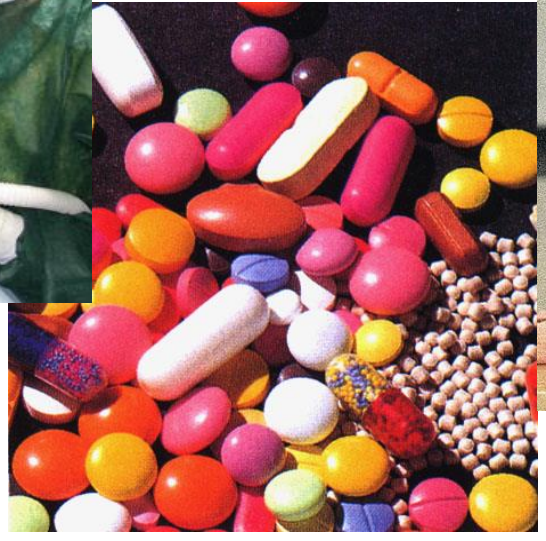


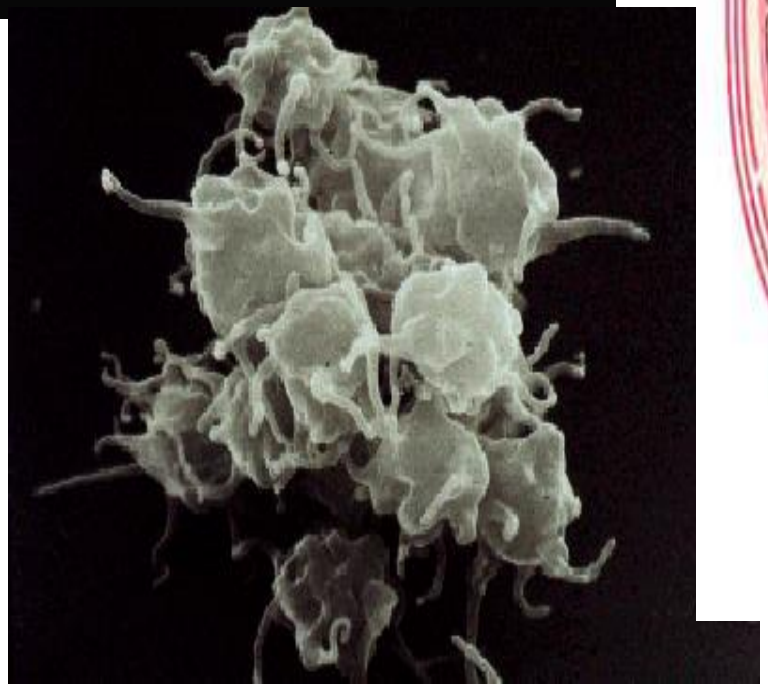




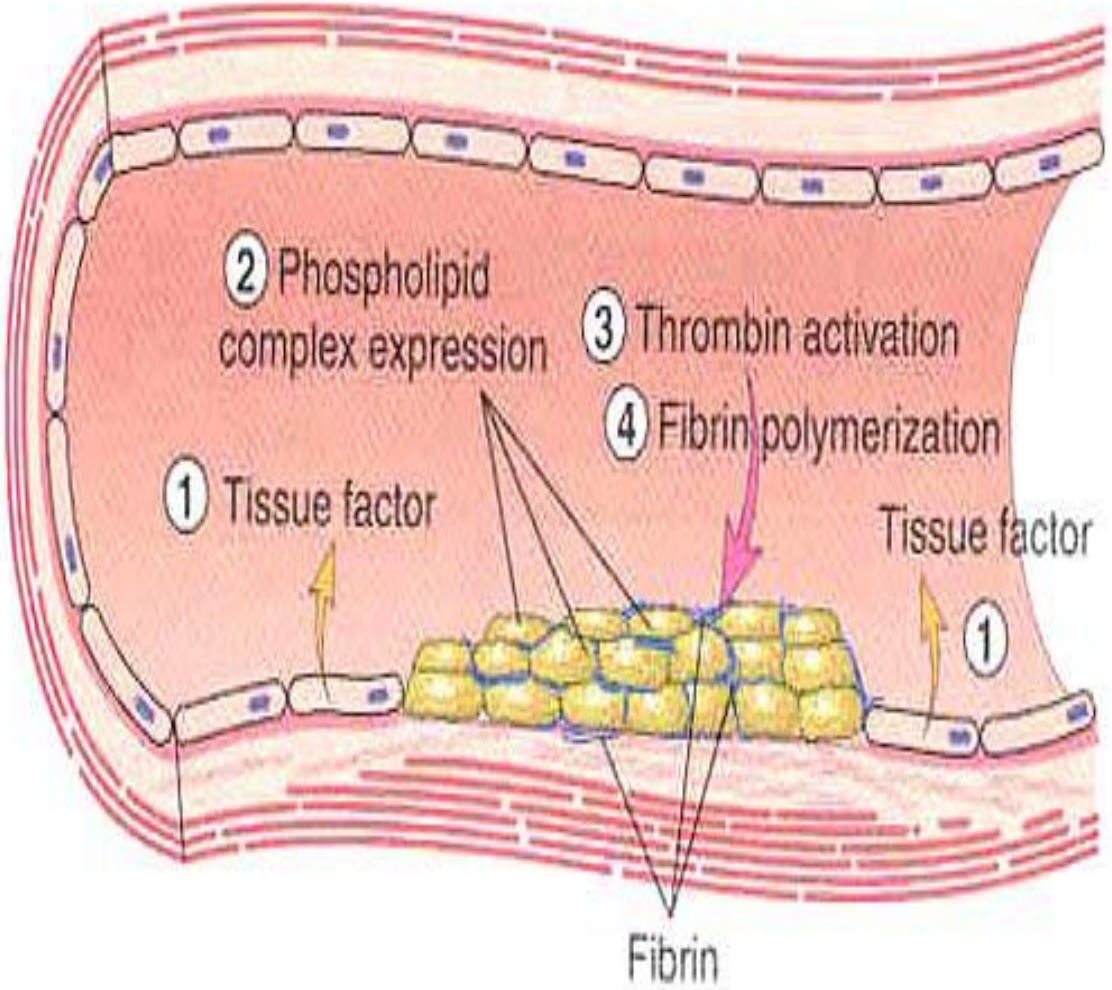








C. SECONDARY HEMOSTASIS



Bleeding pattern in haemophilia

In young **severe** patients treated **on-demand**:

- Median number of joint bleeds/yr : 16.5
- Median progression of orthopedic joint score/yr: 0.5

Aledort et al, J Intern Med 1994

- 3-10% of severe patients have mild bleeding tendency and do not develop significant arthropathy

Aledort et al, J Intern Med, 1994; Molho et al, Haemophilia, 2000; Aznar et al, Haemophilia 2000

- 12% of **moderate** patients need long-term prophylaxis in the Netherlands

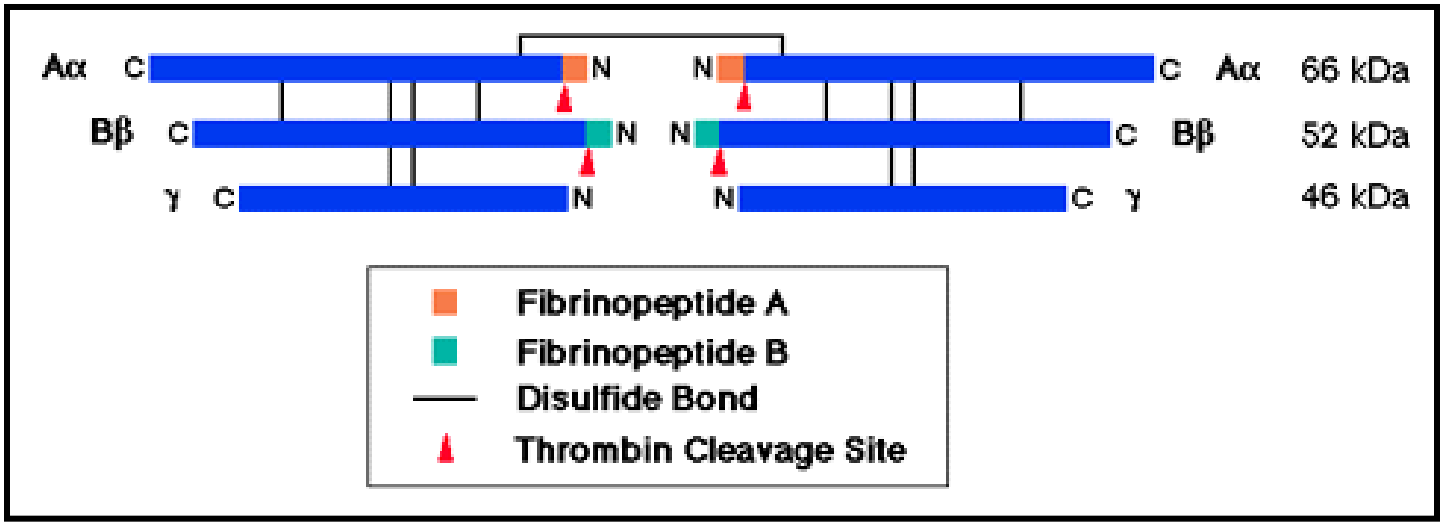
Plug et al, Blood 2004

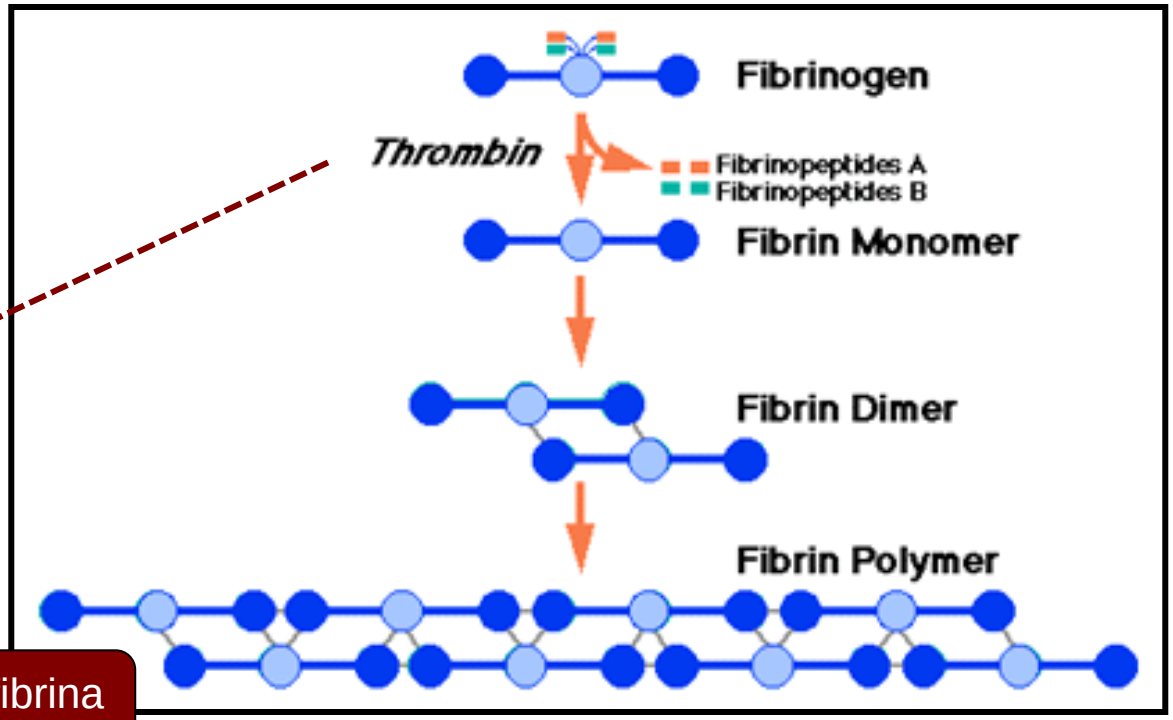
Biological severity = clinical severity ? the Hemophilia Severity Score (HSS)

3 components:

- **Bleeding Score (BS)**: average of annual number of joint bleeds over 10 years / 20 (the maximum number of annual bleeds in a typical severe patient).
- **Joint score (JS)**: last orthopedic joint score / 86 (maximum possible score).
- **Factor score (FS)**: average of 10-yr annual use of concentrates (kIU), normalized by dividing by the mean patient body weight and by 6 kIU/Kg (approximately the maximum consumption of regular prophylaxis).

Schulman et al, JTH 2009





FXIII

FXIIIa

Stabilizzazione della fibrina (legami covalenti Lys-Gln